Catheter-Related Infection: An Update on Diagnosis, Treatment, and Prevention

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ABSTRACT

Catheter-related infection (CRI) accounts for a large percentage of nosocomial infections, and related bacteremia is a common complication. Bacteremia arises in approximately 1 of 15 episodes of CRI and causes considerable morbidity and occasional mortality, as well as increased medical costs. The diagnosis of CRI and catheter-related bacteremia (CRB) is still a challenge for practitioners treating catheterized patients. Semiquantitative tip culture by the roll-plate method is the cornerstone for diagnosis of CRI in routine practice. However, there is a great deal of interest in the alternative methods for diagnosing CRI without catheter withdrawal, since treatment of the patient can be successfully completed with the infected device maintained in place. The conservative management of CRI includes perfusion of antibiotics through the infected catheter and the antibiotic-lock technique (ALT). Catheter-related infection prevention is accomplished mainly by strict adherence to hygienic practices in insertion and manipulation of the catheter. However, knowledge of the pathophysiology of CRI has led to the development of new sophisticated catheters and hubs that incorporate mechanical and antibacterial barriers.

Key Words: catheter-related bacteremia, nosocomial infection, sepsis


Infection due to intravascular catheterization is one of the leading mechanisms of hospital-acquired infection. Catheter-related infection (CRI) accounts for a large percentage of nosocomial infections, and related bacteremia is a common complication. More than 850,000 episodes of CRI are diagnosed yearly in the United States, and the number of episodes of catheter-related bacteremia (CRB) is estimated to be higher than 50,000 per year. Without doubt, these rates are increasing as more and more catheters are used in medical treatments.

Catheter-related bacteremia is the third most frequent cause of nosocomial bacteremia, with an incidence of 20 to 30%. The emergence of CRB is directly related to the duration of catheterization and ranges from 0.02 to 0.66 episodes of bacteremia per 100 days, according to the series and the type of catheter used. Catheter-related bacteremia causes considerable morbidity and occasional mortality, as well as high medical costs, derived from diagnosis, treatment, and mainly, prolongation of the patient's in-hospital stay.

The main approach to this problem is prevention. This review discusses the diagnosis and treatment of CRB and the latest trends in prevention based on the pathophysiology of the disease.

PATHOPHYSIOLOGY OF CATHETER-RELATED INFECTIONS

Catheter-related bacteremia is the final link in a chain of events that begins with the simple colonization of a segment of the catheter by bacteria or fungi. These microorganisms grow and multiply, favored by local factors that interfere with the patient's immunologic defenses (e.g., sheets of fibrin adhering to the catheter walls) and the structure and make-up of the catheter itself. Because the device is in intimate contact with the systemic circulation, it is understandable that catheter infection is often associated with bacteremia, particularly when the catheter is in use. The dissemination of microorganisms from the infected catheter through the bloodstream can provoke a systemic inflammatory response that may give rise to a process of severe sepsis and the appearance of distant septic metastases.

Microorganisms colonize the catheter by various routes. Migration from the catheter-skin interface over the external surface, or from the hub over the internal surface of the device to the catheter tip are the most common. Other pathways include hematogenous seeding from a distant focus of bacteremia (including other catheters) and contamination of the infusates. Approximately 50% of CRIs originate from the skin, 40% from the contaminated hub, and 10% from other pathways. This distribution reflects duration of catheterization, type of catheter used, adherence to preventive measures, and the patient population studied.
MICROORGANISMS

Coagulase-negative staphylococci and Staphylococcus aureus are the pathogens most frequently found in CRI. They arise from the cutaneous flora of the patient or the hands of medical personnel. Gram-negative bacilli are the second most common group of pathogens responsible for CRI. They are involved in cases acquired in special care units and hemodialysis wards, and are common in neutropenic patients.12 Enterobacter spp, Pseudomonas cepacia, Stenotrophomonas maltophilia, and Citrobacter freundii should alert the clinician to check for contaminated infusates, disinfectants, or medical devices other than the catheter.13 Fungal etiology is usually related to catheters used for parenteral nutrition. Other microorganisms, such as Bacillus licheniformis,14 Stomatococcus mucilaginosus,15 Mycobacterium spp,16 and Malassezia furfur,17 also have been implicated in CRI cases.

DIAGNOSIS

Catheter-related infection should be suspected when there is unexplained fever in a catheterized patient. Clinical suspicion is reinforced if fever can be linked to manipulation of the device, or if there are local inflammatory signs. In this situation, the device is usually removed and the tip cultured to determine if it is the source of the infection. Positive culture demonstrates catheter infection. When blood cultures performed at the same time are positive for the same microorganism found in the catheter, CRB is diagnosed. In epidemiologic studies and studies investigating the pathophysiology of catheter infection, molecular typing of catheter and blood isolates should be carried out to definitively establish the source of bacteremia.

Catheter culture is the reference method for diagnosing CRI. However, routine catheter withdrawal in case of possible CRI implies a rate of between 70 and 80% of devices with negative cultures that have been unnecessarily removed.18 For this reason, and because an infected catheter does not always have to be withdrawn for treatment,19-25 alternative methods for diagnosing CRI have been developed. Some of the methods used for culturing the device, and the strategies that have been developed to demonstrate catheter infection without catheter removal are listed in Table 1.

Maki et al were the first to describe a reliable method for microbiologic diagnosis of catheter infection.26 Their roll-plate method established a value of 15 colony-forming units (CFU) as indicative of infection and showed a good correlation with CRB episodes. Since this method is easy to perform and is reproducible in any laboratory, it has become the reference standard for diagnosis of CRI. However, the cutoff described (15 CFU) should be used only as a guide: differences in the shape, size, and materials that make up the catheter, the large variety of microorganisms able to adhere to these materials, the type of patient catheterized, and the possibility that the patient might have received antibiotics for other reasons at the time of catheter withdrawal, are all variables that can affect this criterion. Since its description in 1977, the technique has not been validated according to these variables.27 Moreover, the method described by Maki and colleagues cannot detect infections of endoluminal origin, since the roll-plate technique investigates only the external surface of the catheter.

Other quantitative methods evaluate both the external and internal surfaces of the device. Cleri et al, using successive flushings of the catheter lumen with culture broth, established a value of more than 1000 CFU/mL as indicative of catheter infection.28 Brun-Buisson et al described a quantitative culture technique simpler to perform than Cleri's that consists of introducing the segment of catheter to be studied in a tube with 1 mL of sterile distilled water and agitating.29 Using a cutoff point of 10^5 CFU/mL, they obtained a sensitivity of 97.5% and a specificity of 88% for diagnosing catheter infection, and 100% sensitivity and specificity for diagnosing CRB. Sonication of the catheter submerged in 10 mL of culture broth did not substantially improve the diagnostic performance of the earlier quantitative techniques.30

The quantitative methods mentioned so far do not establish whether a catheter infection is produced by the endoluminal, or the exoluminal route. These techniques do not differentiate between the two surfaces. In 1985, Lihares et al described a modification of the quantitative method of Cleri that permits this differentiation.6 The authors rinsed the internal surface of the catheter with 2 mL of culture medium and then plated serial dilutions of 0.1 mL of the medium to quantify endoluminal colonization. Subsequently, the catheter was cultured according to the technique described by Maki et al to determine exoluminal colonization.36 This labor-intensive method has a sensitivity of 100% and is of interest in studies con-
cerning the pathophysiology of CRL.6 Using this technique, the same authors demonstrated the importance of contamination of the hub in the pathogenesis of CRI.7

All the methods so far described require a waiting interval of 18 to 24 hours before results are obtained. Several quick techniques, based on microscopic study of withdrawn catheters stained by the Gram stain or acridine orange methods, have been developed for early diagnosis of infected catheters.31,32 The presence of one microorganism per 20 fields observed in the microscope is considered to be positive. These rapid methods require experienced technicians and are laborious. They are also less sensitive and specific. Moreover, they can be performed only on transparent plastic catheters with thin walls.

Swab culture from the skin or the catheter hub is highly predictive that the catheter is not infected when results are negative.33-35 Thus, removal of many catheters can be avoided. However, since positive colonization of the skin does not ensure that the catheter is the origin of sepsis, the positive predictive value of superficial swab cultures is lower.36 Gram stain of superficial swabs prior to culture permits quick diagnosis of catheter infection and can point to its etiology. In a preliminary study using this rapid technique in patients admitted to the intensive care unit with suspected CRB, sensitivity was 77%, specificity 86%, positive predictive value 51.2%, and negative predictive value 97.8%.34 Negative Gram stain from two swabs virtually rules out the catheter as the origin of infection 24 hours before culture results are available.

Another method for diagnosis of CRB and for identifying an infected catheter without catheter removal involves obtaining quantitative blood cultures through each catheter placed in the patient, and comparing the results with a peripheral blood culture obtained by direct venipuncture.37-50

Wing et al were the first to propose the usefulness of quantitative blood culture in the diagnosis of CRI.57 Later works have confirmed this hypothesis in a large number of patients and infected catheters.39-51 These studies have established that a finding of colony-forming units per milliliter of catheter blood that is 4 to 10 times the number found in peripheral blood is indicative of CRB. The author applied this method during the course of 67 episodes of fever in catheterized patients (107 devices). Seventeen episodes of CRI were diagnosed, and the catheter responsible for the infection was identified in all but one of the cases. A differential value higher than or equal to four times the number of colony-forming units per milliliter between catheter and peripheral blood cultures diagnosed CRI, and the infected device was identified with a sensitivity of 94% and a specificity of 100%.49 More than 100 CFU/mL in a quantitative transcatheter blood culture also is highly suggestive of CRI.45,49 Both culturing of superficial swabs (skin and hub) and quantitative blood cultures are useful for diagnosing CRB without catheter withdrawal. Moreover, in a patient with several intravascular catheters, quantitative blood cultures can determine which one is the origin of sepsis. As an additional advantage, quantitative blood cultures obtained through the catheter can be used to monitor the effectiveness of the antibiotic treatment being administered to the patient.

Rushforth et al described a method that results in quicker diagnosis of CRB than analyses based on quantitative blood culture.52 Using acridine orange stain of the leukocyte layer obtained by centrifuging blood extracted through the catheter, these authors obtained a sensitivity of 87% and a specificity of 94% as compared to the corresponding quantitative blood cultures. Detection of bacteria denoted a positive result, and a duplicate cytospin preparation was Gram stained to characterize the bacteria.

Markus and Buday proposed a method using an endoluminal brush to identify an infected central venous catheter in situ.53 The brush, composed of plastic bristles affixed to a stainless steel wire, collects fibrin as it is passed in and out of the device. However, this may be a complex and expensive method, and there is still too little experience to recommend its use.

A recent meta-analysis of diagnostic methods for catheter-related bloodstream infection showed that quantitative culture is the most accurate method for catheter segment culture, and that unpaired quantitative catheter blood culture is the single most cost-effective test, especially for long-term catheters.54

TREATMENT

Conventionally, treatment involves simply withdrawing the catheter; however, this maneuver raises practical problems in central catheters of long duration, in catheters that must be implanted and withdrawn in the operating room, and in patients with no other vascular access. To overcome these problems, several studies have demonstrated that these infections may be treated successfully without catheter removal, even in immunocompromised patients.6 However, it is advisable to withdraw the catheter in cases of septic shock, pulmonary embolism, purulent thrombophlebitis, and infection of the subcutaneous tunnel extending more than 2 cm proximally from the catheter exit site.51,55 Persistently positive blood cultures after 48 hours of appropriate antibiotics should prompt catheter removal.56

In the majority of cases, catheter withdrawal alone is enough to cause fever and symptoms of infection to disappear. If the patient shows signs of severe sepsis (e.g., alterations in general condition, hypotension, shock) or when other catheters or prosthetic material (e.g., pacemakers, cardiac or joint prostheses) are present, empiric antibiotic treatment that covers the majority of organisms implicated in catheter sepsis, mainly staphylococci and gram-negative bacilli, should be initiated.
Treatment will vary in each hospital according to the rate of methicillin resistance and the spectrum of gram-negative bacilli causing the catheter sepsis. Table 2 lists some of the antibiotics that can be used. In each specific case, the duration of antibiotic treatment for catheter sepsis depends on the intensity of the initial bacteremia, the clinical condition of the patient, possible metastatic complications, and the microorganism responsible. In general, antibiotic treatment is administered for 7 to 15 days. In infections by *S. aureus* or *Streptococcus faecalis*, treatment is prolonged for 15 days, to avoid the appearance of late-emerging septic metastases, mainly endocarditis and osteomyelitis. In *Candida* spp infections amphotericin B should be administered until an accumulated dose of 300 to 500 mg is reached. Fluconazole is a good alternative for treating candidiasis due to susceptible species. Other noncandidal yeast catheter infections could be appropriately treated by a combination of amphotericin B and catheter removal, although catheter withdrawal is not always mandatory. Data from the Sloan-Kettering Memorial Cancer Center (New York) suggest that catheter removal is not always necessary for a favorable outcome of candidemia. In a prospective randomized study conducted by Anaisse et al, removal of central venous catheters from patients with candidemia did not improve outcome. In an in vitro study, a higher concentration of liposomal amphotericin B than amphotericin B was required to produce a similar effect in reducing the number of yeasts adhering to the surface of plastic catheters. Infection due to filamentous fungi arising in neutropenic patients should prompt catheter removal. When there is purulent thrombophlebitis, surgical resection of the affected vein and heparinization can be considered.

Treatment of catheter-related sepsis (CRS) while maintaining the catheter in place involves sterilizing the catheter and treating the sepsis. Several strategies have been designed to achieve this, always adapted to the particular situation of each patient; that is, taking into account the number and type of catheters in place and their purpose. Sepsis should be treated by systemic administration of antibiotics through the infected route or a separate route, while the infected catheter is subjected to continuous perfusion of antibiotics or the antibiotic-lock technique (ALT). The ALT consists of filling and closing the catheter lumen with an antibiotic solution that acts locally, sterilizing the device. With this method, a high continuous local concentration of antibiotic may be applied and systemic toxicity and the need to monitor serum drug levels can be avoided. Moreover, since the catheter is closed, there is no chance of distant dissemination of microorganisms, as may occur with continuous perfusion. The ALT in association with systemic administration of antibiotics at the end of each dialysis obviated catheter withdrawal in a series of patients in end stage renal failure. This strategy was cost effective and was not associated with long-term infectious complications. In other settings, such as in pediatric patients, ambulatory parenteral nutrition, or acquired immunodeficiency syndrome (AIDS), the ALT with or without concomitant administration of systemic antibiotics has proven to be efficacious without catheter removal. Some authors administered systemic antibiotics during the first 2 or 3 days and subsequently use only the ALT. This depends on the clinical setting and patient condition. Many questions remain to be resolved, including appropriate concentration of intracatheter antibiotics, duration of the ALT, and the role of heparin-lock in association with antibiotics.

<table>
<thead>
<tr>
<th>Table 2. Antibiotics Used in Treatment of Catheter-Related Sepsis</th>
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<tr>
<td><strong>Empiric</strong></td>
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<tr>
<td>Glycopeptide plus aminoglycoside</td>
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<tr>
<td>Glycopeptide plus aztreonam</td>
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<td>According to microbiologic findings</td>
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<tr>
<td>Cloxacillin*</td>
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<td>200 mg/kg/day/IV</td>
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<tr>
<td>Ampicillin</td>
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<td>200 mg/kg/day/IV</td>
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<td>Vancomycin</td>
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<td>30 mg/kg/day/IV</td>
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<td>Telopenptomycin</td>
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<td>8 mg/kg/day/IV</td>
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<td>Aztreonam</td>
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<td>3 g/day/IV</td>
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<td>Gentamicin</td>
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<td>3 mg/kg/day/IV</td>
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<td>Ciprofloxacin</td>
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<tr>
<td>400–600 mg/day/IV</td>
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<td>Amphotericin B</td>
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<td>0.5–1 mg/kg/day/IV</td>
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<tr>
<td>Fluconazole</td>
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<td>200–400 mg/day/IV</td>
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*Offering broad antibiotic coverage, including methicillin-resistant staphylococci and gram-negative bacilli.

Especially indicated in patients with renal insufficiency.

Or other penicillinase-resistant penicillins.

**PREVENTION**

Catheter-related infection is a preventable nosocomial infection. Published guidelines have promoted practices aimed at the prevention of CRI. Of these, certain easy-to-perform rules for hygiene have proven effective. The use of sterile barriers during catheter insertion is of utmost importance for avoiding early CRI. This involves wearing sterile gloves, a mask, a gown, and a cap, and using a large drape during insertion of a central venous catheter (CVC). The patient's skin should be carefully disinfected. In centers with high rates of CRI, teams of health care workers trained in catheter insertion and maintenance could be cost-effective. Peripherally inserted CVCs are less prone to be infected than centrally implanted ones. Subclavian catheters have a lower rate of infection than jugular or femoral catheters. Multilumen catheters are more susceptible to infection than monolumen catheters, probably because they are subject to more manipulation.
There is some controversy about the type of dressing at the catheter exit site. Changing the infusate tubing and dressing at the insertion site every 24 hours is no more protective than changing them every 72 hours. There is some controversy about the type of dressing at the catheter exit site. Changing the infusate tubing and dressing at the insertion site every 24 hours is no more protective than changing them every 72 hours.72,73 Periodic catheter removal is not sustained in terms of prevention of catheter infection and involves additional risks and cost. Central venous catheter exchange over a guide wire may protect against the mechanical complications of catheter insertion but it does not avoid colonization of the new catheter and could increase the risk for bloodstream infection.74

Subcutaneous tunnelling of the catheter has been used to make exoluminal colonization more difficult. Use of this strategy alone fails in prolonged catheterization, where infection is produced mainly by the endoluminal route.75 The use of a silver-impregnated subcutaneous collagen cuff provides both an antimicrobial and a mechanical barrier to microorganism migration from the skin. Again, this is protective in catheters of short-term use, but fails with long-term central venous catheters.76,77

Since initial colonization of the hub is an important event in the pathogenesis of CRS, a new hub model has been designed to protect against hub colonization.78 The model has a female component that consists of a plastic cylinder, with latex rubber closures at both ends, which limits a chamber containing 0.2 mL of 3% iodinated alcohol. The male component is a 18- to 20-gauge needle that connects to the female component on one side and attaches to the infusion tube on the other side. When the two portions are connected, the needle passes through the antiseptic chamber and is sterilized by contact with the antiseptic solution. This new hub model reduced CRS fourfold in a population of patients with long-term CVCs for parenteral nutrition.79 Trials assessing its efficacy in terms of cost benefits are ongoing.

Coating catheters with antimicrobial agents that are released on both the internal and external surfaces, is feasible for preventing CRI. Several promising studies using antibiotic-impregnated catheters have shown the efficacy of this method. The antimicrobial coated on the catheter has to provide broad-spectrum antibacterial activity and remain stable for a long period of time. Recently, two works have provided additional evidence to support the clinical applicability of antiseptic or antimicrobial coating of catheters. Use of central venous catheters coated with chlorhexidine-silver sulfadiazine was associated with a 44% reduction in catheter colonization and a 79% reduction in the rate of CRB.80 Use of CVCs coated with minocycline and rifampin was also associated with significant reductions in the rates of catheter colonization and CRB compared with noncoated catheters.81 The beneficial effects of these catheters were more evident in the first 10 days of catheter use. These two studies did not report adverse events related to impregnated catheters. It seems clear that impregnated catheters decrease overall rates of infection and, in turn, reduce cost. However, more experience is needed in various clinical circumstances and in each particular institution before use of impregnated catheters can be generally recommended.

A more economic approach is to periodically flush the catheter with an antibiotic solution.82 This preventive measure is useful in settings with a high rate of CRI caused by the same microorganism. There is some concern about the potential emergence of resistant microorganisms when antimicrobial agents are used to prevent CRI, and isolates obtained from catheterized patients should be strictly monitored.

Catheter infection is still an important cause of nosocomial infection. From the cost-benefit point of view it is important to adopt appropriate measures for hygiene during insertion and manipulation of these devices and to consider diagnosis and treatment of CRB without catheter withdrawal.

REFERENCES


