Intravascular Catheter-Related Infections

New Horizons and Recent Advances

Issam I. Raad, MD; Hend A. Hanna, MD, MPH

Background: Central venous catheters have become essential devices for the management of critically and chronically ill patients; however, their use is often complicated by catheter-related bloodstream infections (CRBSIs), many of which could be prevented.

Methods: This report is based on a literature review of more than 100 published articles in intravascular catheter-related infections. This review focuses on the most recent advances in the methods of diagnosis of CRBSI as they relate to its pathogenesis and on novel preventive techniques and approaches to management.

Results: Catheter-related bloodstream infections may be diagnosed by different methods, including simultaneous quantitative blood cultures, with the central blood culture yielding at least 5-fold colony-forming units greater than the peripheral blood culture, and simultaneous blood cultures, whereby the catheter-drawn blood culture becomes positive at least 2 hours before the peripheral blood culture. Novel preventive techniques include the use of ionic silver, an anticoagulant/antimicrobial flush solution, a new aseptic hub, and antimicrobial impregnation of catheters and dressings. Management of CRBSIs should be based on whether the infection is complicated or uncomplicated.

Conclusions: Novel technologies that have been proved to aid in the diagnosis and prevention of CRBSIs should be considered in clinical practice. The management approach should be based on the type of microorganism causing the infection and on whether the infection is complicated or uncomplicated.

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Intravascular catheter-related infections are the leading cause of nosocomial bloodstream infections and are associated with significant morbidity in critically ill patients. These infections are often difficult to diagnose, prevent, and manage, adding tremendously to the cost of health care. The cost of treating a single episode of catheter-related bloodstream infection (CRBSI) has been estimated to be in excess of $28000. However, as we proceed into the new millennium, new knowledge in the field has improved our ability to diagnose, prevent, and treat CRBSIs. This review will concentrate on the knowledge associated with catheter-related infections and the recent advances in diagnosis, prevention, and treatment of such infections.

Pathogenesis: New Findings

Catheter-related infections are often difficult to treat because they are caused by organisms often resistant to antimicrobial agents that embed themselves in a biofilm layer on the catheter surface and attach to the thrombin sheath on the surfaces of intravascular devices. Our understanding of the pathogenesis of these infections during the past decade should be the basis for appreciating new techniques and approaches involved in the diagnosis, prevention, and management of CRBSIs. The basics related to the pathogenesis are as follows.

Microbiological Features and Sources of Infections

The skin and catheter hub are the most common sources of colonization of intravascular catheters. For short-term, non-tunneled, noncuffed catheters, the skin insertion site is the major source of colonization, whereby 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 lead to bloodstream infection. For long-term catheters, such as cuffed, tunneled, silicone catheters (Hickman or Broviac),
or implantable catheters (such as ports), the lumen of the hub or the bell of the port is the major source of colonization.\textsuperscript{10,11} These sites may become contaminated through the hands of medical personnel during manipulation of the catheter. Because the skin of the patient or the hands of medical personnel are the main sources for the contamination of catheters, staphylococci, particularly coagulase-negative staphylococci, and \textit{Staphylococcus aureus} are the leading causes of CRBSIs.\textsuperscript{10,12–15} As shown in a pooled estimate derived from prospective studies published in the 1990s that used quantitative catheter cultures: Raad et al.,\textsuperscript{10} Cobb et al.,\textsuperscript{12} Timosit et al.,\textsuperscript{13} Maki et al.,\textsuperscript{14} and Kamal et al.\textsuperscript{15}

Most of the gram-negative bacilli causing CRBSIs are nonenteric organisms acquired from the hospital environment, such as \textit{Stenotrophomonas maltophilia}, \textit{Pseudomonas} organisms, and \textit{Acinetobacter} species.\textsuperscript{12–18} \textit{Candida albicans} and \textit{Candida parapsilosis} also colonize on the hands of medical personnel and are also associated with glucose-containing infusions and total parenteral nutrition.\textsuperscript{10,18} These fungal organisms are, therefore, emerging as important pathogens associated with CRBSIs.\textsuperscript{18,19} Gram-negative bacilli, such as \textit{Corynebacterium} (especially jeikeium strains) and \textit{Bacillus} species, are rarely introduced from the skin or the hub and may cause catheter-related infections.\textsuperscript{12–15,20,21}

### The Biofilm Factor

Staphylococci, \textit{Candida}, and some other microbes produce a slimy matrix rich in exopolysaccharides, resulting in the formation of a microbial biofilm.\textsuperscript{22,23} The biofilm helps these organisms adhere to and survive on the surfaces of foreign bodies in the bloodstream. The organizational structure of the biofilm is the result of communication between microbes using an elaborate system of chemical messengers composed of acyl homoserine–lactones.\textsuperscript{25} The microorganisms within the biofilm layer are resistant to the activity of antibiotics.\textsuperscript{2,23,25} Because the biofilm acts as a resistance factor to antibiotics, it is often difficult to eradicate a catheter-related infection without the removal of the catheter.

### The Thrombin Sheath Factor

Following catheter insertion, a thrombin layer or sheath covers the intravascular surface of a catheter acquired from the hospital environment. This sheath is rich in host-derived proteins, such as fibrin, fibrinogen, thrombopsondin, and laminin, that act as adhesins. Therefore, the thrombin layer that forms on the intravascular surface of a catheter actually promotes adherence of potential microbial pathogens to that surface. \textit{Staphylococcus aureus} binds strongly to fibronecin, fibrinogen, laminin, and thrombopsondin.\textsuperscript{27–31} In addition, coagulase-negative staphylococci bind to fibronecin,\textsuperscript{7} while \textit{C. albicans} binds to fibrin.\textsuperscript{32} Adhesins that allow coagulase-negative staphylococci to bind to the polymer composite of catheters have also been identified. The genes that regulate the expression of those adhesins have also been identified.\textsuperscript{33} Therefore, the difficulties in eradicating the organisms colonizing the catheter surface can be appreciated because they are attached to adhesins on the surfaces of the catheter and are covered by a protective layer of biofilm.

### Quantitative Threshold

Quantitative electron microscopic studies\textsuperscript{10} suggest that most indwelling catheters become colonized after insertion, even in the absence of symptoms. However, clinically apparent infection seems to be a function of the number of organisms exceeding a threshold as they multiply on the catheter surface because there is a quantitative relationship between the number of organisms isolated from the catheter surface and the risk for CRBSIs.\textsuperscript{34}

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Novel culture techniques that suggest a catheter infection without removal of the catheter include the following.

1. Simultaneously collected quantitative blood cultures in which the number of microbes isolated from blood obtained through a central venous catheter (CVC) is at least 5-fold greater than the number of microbes in a concurrent peripheral blood culture.42

2. Simultaneous qualitative blood cultures drawn from the CVC and the peripheral vein in which growth is detected from the blood drawn through the CVC at least 2 hours earlier than a simultaneously drawn blood culture from a peripheral vein.43,44 This method is termed differential time to positivity. This is a simple technique and, unlike quantitative blood cultures, is widely available on an international basis because many clinical microbiology laboratories have adopted the use of automated continuously monitored blood culture systems. Hence, this technique, if verified further by large, prospective, clinical studies, would constitute an easily adopted and inexpensive method for diagnosing CRBSIs without removal of the indwelling catheter.

3. Catheter-related bloodstream infections can also be diagnosed using an endoluminal brush technique that involves brushing the lumen of the catheter and using an acridine orange leukocyte cytopsin test on blood drawn through colonized catheters.45 The brush method had a sensitivity of 95% and a specificity of 84% in diagnosing CRBSIs without catheter removal. However, this method was associated with the induction of transient bacteremia in 6% of the patients in the study. More recently, Kite and colleagues46 demonstrated that acridine orange staining of blood drawn from the CVC could provide a rapid diagnosis of CRBSI. However, further studies are required to support such a finding.

Clinical data that would suggest the catheter as the source of the bloodstream infection include the following: (1) the absence of any other source for the bloodstream infection except the catheter, with the isolation of an organism often associated with CRBSIs, such as Staphylococcus epidermidis, S aureus, or C parapsilosis; and (2) local catheter infection around the catheter, such as exit site inflammation, tunnel tract inflammation, or a port pocket abscess associated with bloodstream infection.

PREVENTION: NOVEL TECHNOLOGY

New technologies that have been developed to prevent CRBSIs and have been shown in clinical studies to be efficacious in decreasing the risk of CRBSIs are the following: (1) ionic silver, (2) an anticoagulant/antimicrobial flush, (3) a new aseptic hub model, and (4) antimicrobial impregnation of catheters and dressings.

Silver Ions

Silver in its ionic form has broad-spectrum antimicrobial activity against bacteria and fungi. A silver-impregnated subcutaneous cuff has been developed and is usually placed at the interface of the skin insertion site and the proximal subcutaneous space.47 This cuff significantly decreases the risk of colonization associated with short-term catheters (mean duration of placement, <10 days).47,48 However, the silver cuff failed to prevent CRBSIs for long-term catheters with a mean duration of placement of 20 days or longer.48-51 This could be attributed to the biodegradable nature of the collagen, whereby the silver ions chelated to the cuff are released completely within 3 to 7 days. Because of its limited efficacy, the use of the attachable silver cuff is not recommended.52 More recently, a silver iontophoretic device has been developed, whereby silver ions are released through a low-voltage current going through silver wires that are attached to the intercutaneous proximal segment of the catheter connected to a small electric power source.53 This silver iontophoretic device has a long-lasting effect and prevents catheter infections in vitro and in vivo.53,54 The clinical safety and efficacy of this device have not been demonstrated.

Antimicrobial/Anticoagulant Flush Solution

Antimicrobial flush solutions, often consisting of an anticoagulant with an antimicrobial agent, have been used to fill the lumen of the catheter at least once daily.55,56 This procedure has been mostly used in long-term catheters in which the hub and luminal colonization are the leading causes of CRBSIs.55 However, this intervention could also be useful in short-term catheters. Various antimicrobial agents have been used as part of antibiotic lock or flush solutions and have been shown to decrease the risk of recurrence of infection and the need for catheter removal.57,58 Vancomycin hydrochloride, in combination with heparin sodium, has been used as a daily flush solution and has been shown to decrease the risk of catheter infection.58 Another study59 failed to show that this combination is effective in reducing the risk of CRBSIs caused by organisms attributable to lumen colonization.

More recently, Henrickson et al60 demonstrated in a prospective randomized study that either vancomycin and heparin or vancomycin, ciprofloxacin hydrochloride, and heparin flush solutions are efficacious in reducing the risk of CRBSIs. However, the Centers for Disease Control and Prevention guidelines recommend against the use of vancomycin as a prophylactic agent in the prevention of CRBSIs because it is an independent risk factor for the acquisition of vancomycin-resistant enterococci.61 In addition, prolonged use of vancomycin could lead to the emergence of staphylococci with intermediate resistance to vancomycin.62-65 A novel flush solution consisting of a combination of minocycline hydrochloride (a tetracycline active against gram-positive organisms) and EDTA has been developed.60 This combination is synergistic against resistant gram-positive and gram-negative bacteria and C albicans. It has also been shown in a clinical study60 to be highly efficacious in preventing the recurrence of staphylococcal infections in short- and long-term catheters. A more recent prospective randomized study dem-
onstrated the efficacy of this combination in preventing CRBSIs in patients undergoing hemodialysis with a long-term indwelling CVC. The combination of minocycline and EDTA had an equivalent anticoagulant activity to heparin.67 Like EDTA, citrate has been shown to have comparable anticoagulant activity to heparin in a prospective randomized study68 involving patients undergoing hemodialysis.

Aseptic Hub Model

A new anti-septic hub attachment has been developed to protect the contamination of the hub and the lumen. This model is used by attaching to the hub of the catheter and has been shown in an animal study69 to prevent catheter colonization. In addition, a clinical study70 in patients undergoing hemodialysis. In addition, EDTA had an equivalent anticoagulant activity to heparin.67 Like EDTA, citrate has been shown to have comparable anticoagulant activity to heparin in a prospective randomized study68 involving patients undergoing hemodialysis.

Antimicrobial Impregnation of Catheters and Dressings

The impregnation of catheters with antimicrobial agents, as predicted by Maki and colleagues in 1988, has proved to be the most effective technologic innovation in reducing the risk of device-related infection.47(p313) During the past decade, several studies8,13,72-74 have shown that vascular catheters impregnated with antimicrobial agents decreased the risk of catheter colonization and CRBSIs. The best-studied antimicrobial catheters are those that are impregnated with a combination of either chlorhexidine gluconate and silver sulfadiazine or minocycline and rifampin.74,75 The indications for using antimicrobial catheters are as follows: (1) units with a risk of catheter infections exceeding 3% or 3.3 per 1000 catheter days, (2) femoral or internal jugular vein insertion (which is associated with a greater risk of infection than subclavian vein catheterization8,74,79), (3) central catheters are expected to remain in place for longer than 4 days, (4) patients with burns, (5) patients with neutropenia or patients undergoing transplantation, (6) patients undergoing hemodialysis, (7) patients with short-bowel syndrome, (8) patients who would receive total parenteral nutrition, (9) patients colonized with methicillin-resistant Staphylococcus aureus, (10) patients with an open wound in the proximity of the insertion site, (11) insertion or exchange in a patient with a known infection or bacteremia, and (12) emergency insertion of the catheter. Maki and colleagues8 demonstrated that catheters coated on the external surface with chlorhexidine–silver sulfadiazine decrease the risk of colonization 2-fold and the risk of CRBSIs by at least 4-fold compared with uncoated catheters. Several studies77-80 failed to show any benefit from the use of catheters coated on the external surface with chlorhexidine–silver sulfadiazine (first-generation aseptic catheters), particularly when used for longer than 2 weeks. A recent meta-analysis75 of 12 studies showed that these catheters coated with chlorhexidine–silver sulfadiazine do decrease the risk of CRBSIs associated with short-term CVCs. In most of these studies, the semiquantitative roll-plate culture technique, which cultures only the external surface, was used without any attempt to culture the internal surface. Using the Mantel-Haenszel method, it was demonstrated that the short-term use (<2 weeks) of these catheters is associated with a decrease in CRBSIs.82 The lack of efficacy of chlorhexidine–silver sulfadiazine–impregnated catheters in situations requiring long-term catheterization of longer than 3 weeks was attributed to the reduced antimicrobial activity of the catheter over time and lack of luminal protection.82,81,82 The advantage of these catheters is that they are pre-coated and, hence, do not need to be treated at the bedside. However, there are several limitations to these catheters: (1) Only the external surface is coated.8 (2) The catheters have a short antimicrobial durability and lack efficacy with long-term use (>2 weeks).80-82 (3) There is concern about the potential anaphylaxis associated with these catheters, probably related to chlorhexidine.83-89 The risk of such a complication is low and could be genetically related because it has appeared only in Japan (which led to the banning of these catheters in that country), not in the United States.83 The US Food and Drug Administration recently approved the use of an improved version of this catheter (second-generation catheters) with added intraluminal chlorhexidine impregnation and slightly more prolonged antimicrobial activity.86

Catheters impregnated with minocycline and rifampin have the advantage of coating the internal and external surface of the catheter. These catheters were significantly superior in vitro and in an animal model to catheters impregnated with chlorhexidine–silver sulfadiazine.80 In a large, prospective, randomized, multicenter, double-blind trial,74 these catheters significantly decreased the risk of CRBSIs by more than 5-fold. In addition, they were highly cost-effective, resulting in an annual cost savings of more than $500,000 in a hospital that uses 850 CVCs per year.74 In a more recent prospective, randomized, multicenter, clinical trial,87 these catheters were shown to be 12-fold less likely to be associated with CRBSIs when compared with catheters externally impregnated with chlorhexidine–silver sulfadiazine. Concerns related to the potential for emergence of antibiotic resistance (especially to rifampin) with the use of this catheter were raised. Two large, prospective, randomized trials74,87 failed to demonstrate the emergence of antibiotic resistance. In addition, the use of such catheters in the intensive care unit of a cancer center resulted in a significant decrease in the frequency of nosocomial vancomycin-resistant enterococci–related bacteremia.88 However, a thorough investigation is required to determine the risk of emergence of resistance to rifampin and minocycline associated with long-term use of these catheters. A recent in vitro study86 sug-
suggested that the susceptibility of *S. epidermidis* to rifampin may decrease after repeated exposure of the organism to catheters impregnated with minocycline and rifampin. A novel dressing impregnated with chlorhexidine and placed around the catheter insertion site has recently been shown to reduce the risk of CRBSIs 3-fold in a prospective, randomized, multicenter study.90

**MANAGEMENT:**

**NEW APPROACH**

The most crucial question related to the management of CRBSIs is to determine whether the catheter should be removed. A new approach is to decide on catheter removal based on whether there is a low, moderate, or high risk of CRBSIs. Risk depends on the type of the organism (low or high virulence) and whether the CRBSI is complicated or uncomplicated. Hence, the following novel approach is suggested (Figure).

1. **A low-risk CRBSI** consists of an uncomplicated CRBSI caused by an organism of low virulence, which is not usually associated with deep-seated infections, such as coagulase-negative *Staphylococcus*.

2. **A moderate-risk CRBSI** consists of an uncomplicated CRBSI 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.

3. **A high-risk CRBSI** is a complicated CRBSI, often occurring in a critically ill or immunocompromised patient.

A complicated CRBSI consists of the following: (1) a CRBSI associated with hypotension or organ hypoperfusion; (2) the persistence of the fever or positive blood culture results for more than 48 hours after the initiation of appropriate antimicrobial therapy; (3) a CRBSI associated with septic thrombosis of the great vein, septic emboli, or deep-seated infections, such as endocarditis; and (4) the presence of a tunnel or port pocket infection.

For low-risk CRBSIs, the infections can be treated without removal of the catheter.91,103 At least 80% of CRBSIs caused by coagulase-negative *Staphylococcus* respond to antibiotic therapy without the removal of the catheter.100 However, in patients with a prosthetic heart valve, the catheters should be removed. For moderate-risk CRBSIs, which consist of uncomplicated infection caused by *S. aureus* and *Candida* species, the short-term catheters should be removed.93-95 In this case, transesophageal echocardiography may aid in the decision to remove the catheters in patients with CRBSIs and guide the decision of therapy.101 However, in stable patients with long-term tunneled catheters responding to antimicrobial therapy, consideration can be given to the use of antibiotic lock solution without the removal of the catheter.102,103 Several studies104-106 have shown that long-term tunneled dialysis catheters may be exchanged with guidewire in a patient with an uncomplicated suspected CRBSI and no signs of exit or tunnel tract infection. For patients with high-risk complicated CRBSIs (including those with tunnel tract infections), it is necessary to remove the involved catheter.93,97-99 The factors favoring the removal of the catheter include CRBSIs with associated hypotension or organ hypoperfusion, the persistence of fever or positive blood culture results after antimicrobial therapy, associated septic thrombosis or emboli, associated tunnel or port pocket infections, and the short-term nontunneled catheter as the culprit of bloodstream infection caused by either *S. aureus* or *Candida* species.

Vancocycin is the drug of choice for the treatment of CRBSIs caused by methicillin-resistant staphylococci. However, novel antimicrobial agents, such as linezolid or the combination of quinupristin and dalfopristin, with activity against methicillin-resistant *Staphylococcus*, may serve as alternative agents to vancomycin in the treatment of CRBSIs caused by methicillin-resistant *Staphylococcus*, particularly in patients who are either allergic to vancomycin or colonized with vancomycin-resistant enterococci.107-111 For CRBSIs caused by methicillin-sensitive staphylococcal organisms, an antistaphylococcal penicillin or a first-generation cephalosporin may be used if the patient is not allergic to β-lactam antibiotics. The treatment duration for

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**Algorithm for the management of catheter-related bloodstream infections (CRBSIs).** A prelude to appropriate management involves confirming the diagnosis of a CRBSI through simultaneous blood cultures (>5:1 of colony-forming units from blood cultures drawn through the catheter compared with the peripheral vein or differential time to positivity of ≥2 hours) or colonization of the catheter demonstrated through semiquantitative or quantitative catheter cultures with the same organism isolated from the peripheral blood culture. CVC indicates central venous catheter.
Catheter-related bloodstream infections caused by C albicans or C parapsilosis can be treated with fluconazole. However, resistant organisms, such as Candida krusei, should be treated with high-dose amphotericin B, 1.0 mg/kg per day. A prospective randomized study of 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. Extensive guidelines for the management of catheter-related infections have been recently published. These guidelines outline the management approach regarding accurate diagnosis, catheter removal, identification of complicated CRBSIs, duration of therapy, and type of antimicrobial agents to be used according to microbial cause.

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