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# Central venous catheter-related bloodstream infections: Pathogenesis factors, new perspectives in prevention and early diagnosis

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Central venous catheterization was once extremely hazardous, but developments since the 1960s have rendered it relatively safe. With the advent of more aggressive treatment modalities requiring extended periods of central venous access, catheter-related local or systemic infections, including local site infection, catheter-related bloodstream infection (CRBSI), endocarditis, septic thrombophlebitis and other metastatic infections (e.g, lung or brain abscess, osteomyelitis and endophthalmitis) are becoming more common (1). In particular, CRBSIs rank among the most frequent hospital-acquired infections representing an important medical and economic issue. In the USA, in a recent meta-analysis of 2,573 CRBSIs, the case fatality rate was 14%, and 19% of these deaths were attributed to catheter infection (2), while the estimated cost per infection ranged from $3700 to $29000 (3, 4).

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 prevention and the diagnosis of CRBSIs.

Catheter-related infection pathogenesis is a complex interaction of several factors. The initial event is microorganism entry into the system, with subsequent colonization and multiplication. This can result in disease: local and/or systemic infection (1).

Intravascular devices can be contaminated during either non-aseptic device insertion or during non-aseptic care of every part of the line, i.e. at the connectors or the infused solutions, at the cutaneous catheter exit site, and at the catheter hub. Any manipulation of an intravenous giving set can introduce microorganisms, i.e. air entering solid bottles as they evacuate, injecting or withdrawing blood/fluid into/from any part of the system (1). Organisms can grow in most types of parenteral fluids. Nearly all aspects of intravenous fluid handling can result in contamination and infection, particularly if total parenteral nutrition is used with a long-term line (5). Isolation of *Pseudomonas* spp, *Enterobacter* spp, *Citrobacter* spp, *Klebsiella* spp, or *Serratia* spp (all multiply rapidly at room temperature in infusate solutions) should prompt consideration of contaminated intravenous fluid (1, 2). Total parenteral nutrition fluids readily support organism multiplication; *Candida albicans*, other *Candida* spp (6), *Malassezia furfur* (7) and coagulase-negative staphylococci (8) are particularly associated with lipid emulsion infusion.

Occasionally, bacteria originating from a distant focus of infection can hematogenously seed catheters (1, 2).

Although organism entry into the system can occur at any point, several studies showed that the exit site and the catheter hub are the most common routes of intravascular catheter microbial colonization. The contamination of the skin at the exit site is considered the main source of short-term, non-tunneled, non-cuffed catheter colonization (9-11). In these devices, organisms migrate along the external surface and the short subcutaneous segment of the catheter, leading to the colonization of the intravascular catheter segment, which can result in bloodstream infection. Evidence of this with short-term catheters includes the following: most episodes of CRBSI are due to skin commensals (1); any factor increasing exit site organism burden increases CRBSI rates (1, 12, 13); Gram-staining and

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other organism visualizations on infected catheters usually show organisms on the outside of the catheter (1); disinfectants used to "prep" the skin significantly affect CRBSI rates (14); molecular techniques demonstrate that in 50% of CRBSIs, organisms with identical DNA patterns are isolated from the skin exit site (15); tunneled and cuffed catheters, which provide a physical barrier to organisms, have lower infection rates (16-18).

With long-term catheters, such as tunneled, cuffed, silicone catheters (Hickman, Broviac, or Groshong), or totally implantable catheters (ports), the cuff and the skin, respectively, create a physical barrier that hinders skin organism migration on the external surface of the catheter along the catheter track. Contamination of the hub or the bell of the port, with organism entry into the device lumen, then becomes the major source of catheter colonization, that can lead to bloodstream infection (11, 19). It has been demonstrated that catheter hub colonization precedes intraluminal colonization and is predictive of CRBSI (19). In addition, a quantitative relationship between luminal colonization and catheter placement duration has been demonstrated (11). This emphasizes the protective role of the cuff after the first catheterization period (2 weeks are needed for the adhesion of the cuff to the tissue) and indicates the hub, contaminated through the hands of medical personnel during manipulation of the catheter, as the most important source of long-term catheter colonization. During prolonged catheterization, catheters are accessed many times, increasing the likelihood that CRBSI emanates from the colonized hub rather than the insertion site.

Because patients' skin or medical personnel's hands are the main source of catheter contamination, staphylococci, particularly coagulase-negative staphylococci, and *Staphylococcus aureus* are the leading causes of CRBSIs (11, 20, 21). *Candida albicans* and *Candida parapsilosis* can also colonize on medical personnel's hands or can be associated with parenteral nutrition infusion; therefore, emerging as important pathogens associated with CRBSIs (22, 23). Gram-negative bacilli leading to CRBSIs, i.e. *Pseudomanas* organisms, *Stenotrophomonas maltophilia* and *Acinetobacter* spp, are acquired in the hospital environment (20-24). Gram-positive bacilli (i.e. *Corynebacterium jeikeium* and *Bacillus* spp), although rare, can be introduced from the skin or the hub and can lead to CRBSIs (20-22, 25).

Additionally, central venous catheter colonization pathogenesis involves the formation of a thrombin sheath and/or a bacterial biofilm (26). Soon after insertion, the intravascular catheter surfaces become engulfed in a sheath rich in fibrin and, subsequently, in fibronectin, thrombospondin and laminin, that promotes the adherence of potential pathogens to that surface (27). Coagulase-negative staphylococci bind to fibronectin (28), *Staphylococcus aureus* binds to fibronectin, fibrinogen, thrombospondin and laminin (29-32), and *Candida albicans* to fibrin (33). Furthermore, *Staphylococcus aureus* and *Candida albicans* produce the coagulase enzyme that can promote the thrombogenesis process even further to enhance their adherence on the vascular catheter (29, 32). In addition, staphylococci coagulase-negative, *Candida* spp in the presence of glucose-containing fluids, and other organisms produce a slimy material rich in polysaccharides, resulting in the formation of a bacterial biofilm that helps these organisms adhere to and survive on the internal and the external surface of the vascular catheter (29, 33). Embedded biofilm bacteria are less permeable to phagocytes and antibiotics. Once the biofilm is established, antibiotic therapy acts only on the bacteria located in the upper regions of the biofilm, easily replaced by the embedded biofilm bacteria. Therefore, the difficulties in eradicating the organisms colonizing the catheter can be appreciated, because they are attached to the thrombin sheath that covers the catheter surfaces and are covered by a protective layer of biofilm. In these cases, catheter removal is often necessary to eradicate the infection. However, many catheters removed on suspicion of CRBSI or sepses are found to be not infected increasing the risk of complications and costs related to new catheter insertion

Based on pathogenetic factors, new techniques and approaches have been proposed to prevent catheter-related infections, and to facilitate a rapid CRBSI diagnosis, without catheter removal.

Strict adherence to maximal barrier precautions during central venous catheter insertion (mask, cap, long-sleeved sterile gown, sterile gloves, and large sterile sheet draper), to hand washing and to aseptic techniques during catheter management remains the cornerstone in preventing catheter-related infection (34). This requires intensive training of medical and nursing staff involved in insertion and care of central lines. Other measures can give additional protection (34).

Between the technological innovations aimed at reducing catheter colonization risk and CRBSI, catheters coated or impregnated with antimicrobial agents have proved to be the most effective (9, 35-37). Examples of tested antiseptic and/or antimicrobial include chlorhexidine, silver sulfadiazine, minocycline, rifampin and silver ions. All the clinical studies including coated or impregnated

catheters used double or triple lumen and non-cuffed catheters, which remained in place <30 days. A meta-analysis demonstrated that short-term use of catheters (<2 weeks) coated with chlorhexidine/silver sulfadiazine on the external surface reduced CRBSI risk compared with standard non-coated catheters (38). Several studies failed to show a difference in CRBSI with this catheter >2 weeks (39-42). This finding, probably, reflects the reduced antimicrobial activity of the catheter over time and lack of endoluminal protection (43, 44). The benefit for patients who receive this catheter will be realized within the first 14 days (42-44). This device should reduce the cost in a setting in which CRBSI incidence is high (>3.3/1000 catheter days) despite adherence to standard prevention strategies (9). The Food and Drug Administration in the USA has recently approved an improved version of this catheter with chlorhexidine coating both the external and the internal surface, and a more prolonged antimicrobial activity (45); preliminary studies with this second-generation impregnated catheter indicate promising results. There is concern about the potential anaphylaxis associated with the chlorhexidine component of the catheter. However, because the rare reports of anaphylactic reactions to chlorhexidine are confined to Japan, the risk of such a complication is low and probably genetically related (46). Clinical studies have not demonstrated resistance to the chlorhexidine/silver sulfadiazine catheter.

In a large, prospective, randomized, multicenter clinical trial on intensive care unit (ICU) patients, the use of catheters impregnated on both the external and internal surfaces with minocycline/rifampin was associated with a lower catheter colonization and CRBSI rate than the use of the catheters impregnated with chlorhexidine/silver sulfadiazine (47). The beneficial effect began 6 days post-catheterization, but none of the catheters were evaluated beyond 30 days. The duration of antimicrobial activity of minocycline/rifampin catheter has proved to be longer *in vivo* (~3 weeks) than that of the first generation chlorhexidine/silver sulfadiazine catheter. The more effective catheters had antibacterial agents on both their internal and external surfaces, whereas chlorhexidine/silver sulfadiazine catheters were coated only on the external surface. If the microbial killing abilities of these drug combinations are equivalent, the data suggest that the intraluminal route remains important for CRBSI pathogenesis, and emphasize the role of luminal colonization in causing CRBSI also in short-term multilumen catheters, generally used in the ICU, where catheter hubs are accessed many times. However, studies are needed to evaluate if the improved performance of minocycline/rifampin catheters results from the antimicrobial agents used or from the coating of both the external and internal surface. There are no comparative studies published using the second-generation chlorhexidine/silver sulfadiazine catheters. Concerns were raised relating to the potential for emergence of antibiotic resistance with the use of minocycline/rifampin coated catheters. Although two large, prospective studies failed to demonstrate antibiotic resistance emergence (37, 47), thorough investigation is required to determine the risk of emerging resistance to minocyclin and, especially, to rifampin associated with long-term use of these catheters. A recent *in vitro* study suggested that the susceptibility of *S. epidermidis* to rifampin decreases after repeated exposure of the organism to a catheter impregnated with this antibiotic (48). Despite their proven efficacy, antimicrobial impregnated catheters should complement rather than replace adequate aseptic practices. There will be continuing concern and a corresponding need for surveillance to detect antibiotic resistance with the new catheters. Although to date the evidence is scant, because of the potential for reducing morbidity and mortality at reasonable costs, an expanded use would be favored of effective second-generation catheters in the ICU, for neutropenic and burns patients, who are at a high risk of CRBSI.

Due to the short duration of the bactericidal activity of the antimicrobial agents coating the catheters, this technology was not employed with long-term catheters, i.e. tunneled, cuffed catheter or port. However, silver ions, which have a broad spectrum of antimicrobial activity, including bacterial, fungal and viral organisms, without cross-resistance to antibiotics, have been used for impregnating a subcutaneous collagen cuff of short- and long-term catheters (49). Long-term catheters (Hickman and Groshong) are available with also two cuffs: the first is a dacron cuff, placed in the subcutaneous tunnel anchoring the catheter to the tissues forming a mechanical barrier to skin organism entry. The second is a collagen cuff impregnated with silver ions, usually placed at the interface of the skin insertion site and the proximal subcutaneous space, which has antimicrobial function. This latter cuff by its antimicrobial activity would avoid organism migration along the subcutaneous catheter track until the dacron cuff is firmly anchored to the tissue. Although in two clinical studies this silver impregnated collagen cuff significantly decreased the risk of colonization associated with short-term catheters (mean duration of placement <10 days), it failed to

demonstrate CRBSI reduction because of the minimal number of CRBSIs observed (49, 50). In addition, the silver cuff failed to prevent CRBSI in long-term catheters with a mean duration of placement of 20 days or longer (51-53). This can be attributed to the biodegradable nature of the collagen, whereby the silver ions chelated to the cuff are completely released within 3-7 days. Furthermore, extrusion of the silver cuff from the catheter tunnel tract to the skin and minimal subcutaneous anchorage of tunneled silver-cuffed catheters have been observed, possibly because of a cytotoxic effect of the silver (54). On the basis of the available evidence this device seems not to be effective either with short-term or with long-term catheters and its use cannot be recommended.

A silver iontophoretic device recently developed, whereby silver ions are released through a low voltage current through silver wires attached to the intercutaneous proximal segment of the catheter connected to a small electric power source (55). In laboratory studies this device showed a long-lasting effect and prevented catheter infections *in vitro* and *in vivo* (55, 56). However, the clinical safety and efficacy of this device is not demonstrated.

Efficacy was recently demonstrated in a prospective, randomized, multicenter study of a chlorhexidine-impregnated sponge (biopatch) placed around the catheter insertion site (57). This dressing reduced the risk of CRBSI 3-fold. A recent randomized, controlled study on neonates reported a substantial decrease in colonized catheter tips, but failed to demonstrate a reduction in CRBSI rate (58). In addition, impregnated sponge use was associated with localized contact dermatitis in very low birth weight infants (15% of cases). Further prospective, randomized studies are necessary to evaluate whether this sponge prevents CRBSI, and to exclude the emergence of resistance.

With long-term catheters, in which the hub and luminal colonization are the leading causes of CRBSI, various antimicrobial agents, often associated with an anticoagulant, used as a part of an antibiotic lock or flush solutions at least once a day, and showed a decrease in the risk of infection recurrence and the need for catheter removal (59, 60). In one study a daily flush solution with vancomycin in combination with heparin sodium showed a reduction of catheter infection risk (61). Another study failed to demonstrate that this combination was effective in reducing CRBSI risk caused by organisms colonizing the catheter lumen (62). A recent prospective, randomized study demonstrated that either vancomycin and heparin, or vancomycin, ciprofloxacin and heparin flush solutions are effective in decreasing CRBSI risk (63). However, the Center for Disease Control and Prevention guidelines recommend against vamcomycin use as a prophylactic agent in CRBSI prevention, because it is an independent risk factor for the acquisition of vancomycin-resistant enterococci (64). In addition, prolonged vancomycin use can lead to the emergence of staphylococci with intermediate vancomycin resistance (65-69). In two studies another combination, i.e. minocycline and EDTA, showed effectiveness in the prevention of staphylococcal infection recurrence in short- and long-term catheters, and in preventing CRBSI in patients undergoing hemodialysis with a long-term catheter (70, 71). However, due to the risk of antimicrobial resistance emergence, prevention of intravascular catheter-related infections should not involve vancomycin or other therapeutic agents, and efforts should be focused on intervention i.e. full barrier precautions.

To protect hub and lumen contamination, a hub attachment containing an antiseptic chamber filled with iodinated alcohol has been proposed. This device showed the prevention of catheter colonization in an animal study (72), and a reduction in CRBSI rate 4-fold in a clinical study on patients with long-term catheters (73). However, recently another clinical trial failed to show any benefit from using this aseptic hub in reducing catheter infection risk (74). Therefore, further prospective, randomized studies are necessary to evaluate if this new technology is cost-effective and prevents CRBSIs.

Concerning CRBSI diagnosis, some conclusions can be drawn.

Blood cultures are an essential component of CRBSI diagnosis (1). Isolation of staphylococci, especially *S. aureus* or fungi from blood cultures in the presence of an intravenous device suggests catheter-related sepsis. However, with organisms such as coagulase-negative staphylococci and diphetheroids, which often contaminate blood cultures, repeated isolation of the same species is required (6). Therefore, two sets of blood cultures from two different peripheral sites should always be taken.

Catheter-drawn samples for qualitative blood cultures have been opposed by some clinicians because of the likelihood of contamination (i.e. 14% culture-positive vs 2% for samples carefully obtained by percutaneous venepunture when needles are not exchanged before inoculation of blood-culture bottles) (75, 76). Such contamination leads to over-treatment and increase of antibiotic resistance. Therefore, as blood cultures taken through central lines can yield high rates of false-positive results, they should not be done unless quantified (1, 6).

A definition of CRBSI, recently published by the Center for Disease Control in Atlanta, USA (77), is as follows: "the isolation of the same organism [identical specie(s) and antibiogram(s)] from cultures of catheter segment(s) and blood (preferably drawn from a peripheral vein) of a patient with accompanying symptoms of bloodstream infection and no other apparent source of infection". Therefore, confirmation of CRBSI requires removal of the catheter for culture.

The roll-plate semiquantitative culture method is the technique used most for culturing vascular catheters (78). However, this method cultures only the external surface of catheter; therefore, it is of limited value in long-term catheters, in which the internal surface is the predominant source of colonization and bloodstream infection (11). Other quantitative catheter culture methods are useful in establishing CRBSI diagnosis, such as the vortex, sonication, or flushing the catheter lumen with broth (79-81). Several studies and a meta-analysis showed that the sonication and the vortex quantitative techniques are superior to the semiquantitative catheter culture technique (11, 75, 82, 83). However, the semiquantitative and quantitative catheter culture methods have limitations, as they require catheter removal for CRBSI confirmation (84). In addition, just 15-20% of central venous catheters removed because infection is suspected, actually prove to be infected, and the diagnosis is always retrospective (80, 82). This results in risks and costs associated with the placement of a new catheter in a new site.

Methods have been devised to diagnose CRBSI without removing the device, especially with tunneled catheters or ports.

A quantitative blood culture of paired blood samples taken from the catheter and from a peripheral vein is predictive of CRBSI if the central blood has a colony count at least 5-fold greater than the peripheral count (85). The technique has a sensitivity of 94% and a specificity of 91% (85, 86). However, quantitative blood cultures results are not available for at least 24 hr. Furthermore, this technique is not routine in clinical practice despite its high specificity, because it is the most expensive and time consuming technique.

Blot et al described a qualitative method based on differential time to positivity (DTP) of blood cultures simultaneously collected from the catheter hub and from a peripheral vein. If growth is detected from the blood drawn through the catheter at least 2 hr earlier than simultaneously drawn from a peripheral vein, it is predictive of CRBSI (87, 88). The cut-off limit of +120 min had a specificity of 91% and a sensitivity of 94% for CRBSI diagnosis. There was not a CRBSI case with a time to positivity of the hub blood culture >24 hr (88). This simple technique allows a rapid diagnosis and, unlike a quantitative blood culture, it is widely available because many clinical microbiology laboratories use automatic devices for positive blood culture detection.

CRBSIs can also be diagnosed using an endoluminal brush technique that involves passing a brush down the catheter lumen, and using an acridine-orange leukocyte cytospin test on blood drawn through colonized catheters (87). The brush method had a sensitivity and a specificity of respectively 95% and 84% in diagnosing CRBSIs, but was associated with transient bacteremia induction in 6% of patients in the study.

Recently, Kite et al described a method based on gram and acridine-orange staining of a blood sample collected from the catheter lumen (89, 90). The gram stain has the advantage of enabling preliminary identification of pathogens, but in cases of gram-negative bacteremia, bacterial DNA deeply stained with acridine-orange can be more clearly visualized. The technique takes 30-60 min and, according to Kite et al, has a sensitivity of 96% and a specificity of 92%.

The methods proposed by Blot and Kite are so new that nearly all the evidence collected is from single research groups. Notwithstanding the exciting developments of the techniques, before either method can be routinely recommended their value requires confirmation by investigators in other settings. However, there is reason to believe that the main results of the studies by Blot et al and by Kite et al are correct. The rationale of the test by Blot is logical in that blood from an infected catheter should have a higher concentration of organisms than peripheral blood and give a positive result earlier in a continuously monitored blood culture system. That DTP can be as accurate as reported by Blot is not surprising, since paired quantitative blood cultures showed a similar accuracy when used to test catheters that had been in place for weeks and months (75). However, for shorter periods the sensitivity of paired quantitative blood cultures is not so good, and this difference can also be found with the DTP technique (75, 82). The low sensitivity with short-term catheterization can relate to the greater likelihood of extraluminal infection with short-term catheterization but of intraluminal infection with long-term catheterization (11).

The basis for the gram and acridine-orange leukocite cytospin test is also plausible. The Kite test has a threshold of about 1000 microorganisms

per ml of blood. The technique is unlikely to detect bloodstream infection unrelated to central venous catheters because many catheter blood samples from patients in this study contained more than 100,000 cfu/ml, while peripheral blood contained less than 1-250 cfu/ml (90). A positive test should be indicative of a high organism concentration in the catheter lumen and of catheter infection.
Like the DPT test, the staining method can also result in being more accurate for long-term than for short-term catheters. If confirmed as accurate by other studies, the gram and acridine-orange stain technique would be useful due to the rapid results and its ability to distinguish between different categories of causative agents. These advantages would enable therapy given at infection onset to be more specific than would otherwise be the case.
As to date the numbers on which to base a recommendation are limited, there will be ongoing debate about the relative cost-effectiveness of diagnostic techniques. This issue can be resolved by a trial in which patients are randomly assigned for management with different diagnostic strategies.

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