

Central Venous Catheter - Related Infections: An Overview with Special Emphasis on Diagnosis, Prevention and Management

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Abstract

Background: The use of intravascular catheters for vascular access and haemodynamic monitoring has become a central part of modern medicine. Although CVCs have significant benefits in many clinical situations, catheter - related infection (CRI) remains a leading cause of nosocomial infections, especially in intensive care units and is associated with significant patient morbidity, mortality, and hospital costs.

There are four potential sources for CRI: the skin insertion site, the catheter hub, hematogenous seeding from a distant infection and contaminated infusate. The key factors for pathogenesis include bacterial adherence, host defence mechanisms and catheter material. Definite diagnosis of CRI necessitates removal of the catheter in most cases. However recently described techniques may allow diagnosis of CRI without catheter removal. As most CRI originate from skin insertion site and catheter hub successful preventive strategies reduce CRI.

Removal of the catheter in clinical practice for the management of CRI is still recommended in many cases but in specific situations catheter salvage may be undertaken. Regarding antimicrobial therapy, it can be administered either on an empirical basis or after a well-established microbiological diagnosis. Most of the CRI will be treated for a period of 7 to 14 days, depending on the isolated microorganisms.

Conclusion: Infection is one of the leading complications of indwelling central venous catheters. CVC infections are substantial and preventable cause of iatrogenic morbidity and mortality. Therefore the management of CRI, including accurate diagnosis, effective preventive strategies, therapeutic clinical decisions related to catheter removal must be guided by current knowledge.

BACKGROUND

Central venous catheters (CVCs) are used for the monitoring and therapy of critically ill patients. Estimates of their use in the United States alone suggest that over five million CVCs are inserted annually ^{1, 2}. Unfortunately, these devices are associated with a number of complications, amongst which infection predominates. CVCs are probably responsible for about 250,000 cases per year of nosocomial bacteremia in the United States, although some estimates are as high as 400,000 cases per year ^{3, 4}. Currently, catheter-related infection (CRI) is a major cause of patient morbidity and mortality, a reason for premature catheter removal and an explanation for the increase in cost and use of resources ^{5,6,7,8}. The appropriate management of CVCs has therefore, become a major challenge for physicians.

PATHOGENESIS

There are four potential sources for CRI:

- the skin insertion site
- the catheter hub
- hematogenous seeding from a distant infection
- contaminated infusate

The skin insertion site and the catheter hub are by far the two most important sources. Approximately 65% of CRI originate from the skin flora, 30% from the contaminated hub and 5% from other pathways ^{9,10,11}. For short-term catheters, skin contamination is the most likely mechanism

of pathogenesis, whereas for long-term catheters, hub contamination is more frequent³. Skin organisms migrate from the skin insertion site along the external surface of the catheter, colonising the distal intravascular tip of the catheter, and ultimately causing bloodstream infection. Hub contamination is more common in long-term catheters because such catheters often have to be intercepted and manipulated¹². Organisms are usually introduced into the hub from the hands of medical personnel. From this contaminated hub, the organisms migrate along the internal surface of the catheter, where they can cause a bloodstream infection¹³.

The key factors for pathogenesis include bacterial adherence, host defence mechanisms and catheter material¹⁴. Host glycoproteins, such as fibrinogen, fibronectin, collagen and laminin, adsorbed on the surface of intravenous devices, form a biofilm layer that enhances bacterial adherence to foreign material, in particular, *Staphylococcus aureus* and coagulase-negative staphylococci (CNS)¹⁴. Among factors possibly explaining the frequent colonization of catheters by staphylococci, the microbial production of mucoid exopolymeric substances and the presence of receptors to plasma proteins adsorbed onto the biomaterial surface have been considered^{14,15,16}. Finally, the material from which the catheter is made is important. The physical characteristics of the catheter, such as surface irregularities and charge difference, facilitate bacterial adherence¹⁴. Hydrophobic staphylococcal organisms adhere better to polyvinyl chloride, silicone, and polyethylene surfaces than to polyurethane or Teflon polymers^{17, 18}.

DEFINITIONS

- Catheter colonization: Growth of ≥ 15 colony forming units (semiquantative culture) or $>10^3$ (quantitative culture) from a proximal or distal catheter segment in the absence of accompanying clinical symptoms.
- Exit-site infection: Erythema, tenderness, induration, or purulence within 2 cm of the skin at the exit site of the catheter.
- Tunnel infection: Tenderness, erythema, and/or induration >2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter (e.g., Hickman or Broviac catheter), with or without concomitant bloodstream infection
- Pocket infection: Infected fluid in the subcutaneous pocket of a totally implanted intrascular device; often associated with tenderness, erythema, and/or induration over the pocket; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection, may also occur.
- Infusate-related bloodstream infection: Concordant growth of the same organism from the infusate and blood cultures with no other identifiable source of infection.
- Catheter-related bloodstream infection (CRBI): Isolation of the same organism (i.e., identical species, antibiogram) from culture of a catheter segment and from the blood (preferably drawn from a peripheral vein) of a patient with accompanying clinical symptoms of BSI and no other apparent source of infection. In the absence of laboratory confirmation, defervescence after removal of an implicated catheter from a patient with BSI may be considered indirect evidence of CR-BSI.

MICROBIOLOGY

Most of the micro-organisms implicated in CRIs arise from the skin flora. Staphylococci are the most frequently isolated pathogens in CRI, particularly coagulase negative-staphylococci (CNS), followed by enterococci, *S.aureus* and *Candida* species^{20,21,22}. Gram-negative bacilli are usually found at lower frequency and include *Pseudomonas* spp., *Enterobacter* spp. and other organisms (Table1). Of these organisms, the ratio of catheter colonization to bloodstream infection was highest for *S.aureus* followed by *C.albicans* and then CNS²³. This probably reflects the relative virulence of these organisms as pathogens on intravascular devices²¹. Concomitant with the increasing use of broad-spectrum antimicrobials, cases of CRI caused by a variety of unusual bacterial and fungal pathogens (such as *Achromobacter* sp., *Mycobacterium fortuitum*, *M.chelonae*, *Malassezia furfur*) have been reported with increasing frequency^{4, 24}.

Figure 1

Table 1: Etiology of CRI

Microorganism	Percentage
Coagulase-negative staphylococci (CNS)	30-40
<i>S.aureus</i>	5-10
<i>Enterococcus</i> spp.	4-6
<i>Candida</i> spp.	3-6
<i>Pseudomonas aeruginosa</i>	2-5
<i>Enterobacter</i> spp.	1-4
<i>Acinetobacter</i> spp.	1-2
<i>Serratia</i> spp.	<1
Others	<1-5

DIAGNOSIS

Fever and signs of sepsis, such as chills, rigors, hypotension, hyperventilation should always be considered as CRI when there is no other identifiable source of infection is present. But clinical findings are unreliable for establishing a diagnosis of CRI.

Catheter-associated infections can be considered local or systemic. Local phenomena include simple colonization or true infection that may involve exit site, or tunnel. Local inflammatory signs at the catheter's portal of entry or tunnel have a highly predictive value for infection but it's absence has a very poor negative value²⁵. Mechanical and chemical factors may also produce inflammation in the absence of infection. Systemic infections involve infection of the bloodstream. As local signs may be completely absent, clinical diagnosis of CRBI may be difficult. Therefore, microbiological techniques are necessary to identify CRBI. We will describe the most widespread diagnostic methods used, either non-conservative or conservative.

Semiquantitative culture method is the simplest and most commonly used method, in which the catheter segment is rolled across the surface of an agar plate and colony-forming units (cfu) are counted after overnight incubation²⁶. Its limitation is that it cultures organisms solely from the external surface of the catheter²⁷; intraluminal colonization, which is very important after prolonged and excessive use of the catheter hub, is not evaluated by this technique.

Quantitative culture of the catheter segment requires either flushing the segment with broth, or vortexing, or sonication it in broth, followed by serial dilutions and surface plating on blood agar^{21, 28, 29}. This technique can isolate organisms from both the internal and external surface of catheters.

The yield of ≥ 15 cfu from a catheter, by means of

semiquantitative culture, or a yield of $\geq 10^2$ from a catheter, by means of quantitative culture in the absence of signs of infection is considered indicative of catheter colonization. A yield of ≥ 15 cfu from a catheter by means of semiquantitative culture, or a yield of $\geq 10^2$ from a catheter, by means of quantitative culture with accompanying signs of local or systemic infection, is indicative of CRI².

Gram stain may be helpful for the diagnosis of local infections, but it is significantly less sensitive than are quantitative methods for the diagnosis of CRI³⁰. Another method in which acridine orange staining was used to examine catheter segments was found to be more sensitive and specific than Gram stain method³¹.

These culture and direct methods all require catheter removal, which may be problematic in certain patients. Therefore, the techniques described below have been developed to make a microbiological diagnosis possible without removing the catheter.

Quantitative blood culturing techniques have been developed as an alternative for the diagnosis of catheter-related bloodstream infection in patients for whom catheter removal is undesirable because of limited vascular access^{32, 33}. This technique compares colony counts from peripheral- versus central-line blood culture by various means. A five-to tenfold greater colony count of the same organism from the central-line culture is predictive of catheter related bloodstream infection. Among tunneled catheters, for which the method is most accurate, a quantitative culture of blood from the CVC that yields at least 100cfu/mL may be diagnostic without a companion culture of a peripheral blood sample^{31, 33}.

A recently introduced technique: The time to growth of cultures drawn through the catheter and by venipuncture of paired samples^{34, 35}. This method makes use of continuous blood-culture monitoring for positivity and compares the differential time to positivity for qualitative cultures of blood samples drawn from the catheter and a peripheral vein. In a study of differential time to positivity, a definite diagnosis of CRB could be made in 16 of the 17 patients who had a positive result of culture of culture of a blood sample from the CVC at least 2 h earlier than they had a positive result of a peripheral blood culture. This method shows a sensitivity of 94% and specificity of 91% for catheter related bloodstream infection diagnosis, and can be used for routine clinical practise in most hospitals using automatic devices for blood

cultures³⁴.

Another method which preserves catheter in place is the endoluminal brush technique. In this technique a wire brush is used to culture the endoluminal surface in situ, then the blood drawn through the catheter is Gram or acridine orange stained. It has a sensitivity of >90% and specificity of 84%_{36, 37}. However, this method is associated with a risk of transient bacteremia, cardiac arrhythmias and embolization⁹.

RISK FACTORS AND PREVENTIVE STRATEGIES

RISK FACTORS

Several host factors that predispose for CRI have been identified (Table 2)₃₈. Malignant hematologic disorders and AIDS increase the risk of CRI about four times, but the most important risk factor is neutropenia, with an 11-fold increased risk_{39, 40}. Other risk factors include prolonged catheterization, frequent manipulations, contaminated skin solutions, improper aseptic techniques during insertion and maintenance, number of catheter lumens and location of catheter^{18, 41}.

Figure 2

Table 2: Host-Related Risk Factors for CRI

Age 1 yr or younger, 60 yr or older
Neutropenia
Immunosuppressive chemotherapy
Loss of skin integrity (e.g. burns)
Severity of underlying illness
Presence of distant infection

INFUSION-THERAPY TEAM AND EDUCATION

Several medical centers have established an experienced infusion therapy team for the insertion and maintenance of catheters. Establishment of such team have shown unequivocal effectiveness in reducing the incidence of CRI and associated complications and costs_{42, 43}. Educational programs for clinical staff also result in improved care and reduced site colonization of CVCs_{44, 45}.

CATHETER SELECTION

Teflon or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene^{17, 46, 47}. Some CVCs have multiple infusion ports and their manipulation could increase

infection risk. Therefore CVCs with the minimum number of ports or lumens essential for the management of the patient should be used.

INSERTION SITE

Many factors, including patient-specific issues (pre-existing catheters, local infection, anatomic deformity), relative risk of mechanical complications (bleeding, pneumothorax), as well as the risk of infection enter into decision making regarding insertion site selection. Observational studies using multivariate analysis found that risk for infection was significantly decreased with insertion into the subclavian vein. Therefore, insertion of catheter into the subclavian vein is preferred to reduce the risk for infection. However, this risk must be weighed against noninfectious complications associated with subclavian vein insertion.

STERILE TECHNIQUE AND HAND HYGIENE

Good hand hygiene before catheter insertion or maintenance, combined with proper aseptic technique during catheter manipulation, provides protection against infection¹⁹. Full-barrier precautions during CVC insertion reduces the incidence of CRI compared with standard precautions^{13, 19}.

CUTANEUS ANTISEPSIS

As previously stated, there is a strong association between the level of colonization of the skin at the insertion site and the rate of subsequent catheter colonization and CRI₄₈. Povidone iodine has been the most widely used antiseptic for cleansing CVC-insertion site₄₉. However in some studies chlorhexidine significantly reduced the incidence of microbial colonization of catheters compared with povidone-iodine_{50, 51}. Based on the existing data chlorhexidine containing antiseptics should be preferred, where approved. But other antiseptics including tincture of iodine, 70% alcohol or povidone iodine can also be used as cutaneous antiseptics¹⁹.

CATHETER DRESSING

High levels of colonization of the insertion site correlate with increased frequency of catheter colonization and CRI^{18, 48}. Therefore, any dressing over an insertion site that promotes bacterial growth might be presumed to increase infection rates. Steril gauze or sterile, transparent, semipermeable dressings are used to cover the catheter site_{52, 53}. Transparent dressings reliably secure the device, permit continuous observation of the insertion site, do not become saturated with respiratory or other body fluids, and require less frequent changes than do standard gauze and tape

dressings¹⁹. The choice of dressing can be a matter of preference. If blood is oozing from the catheter insertion site, gauze dressing might be preferred. The catheter-site dressing should be replaced if the dressing becomes damp, loosened, or visibly soiled. Current CDC guidelines prefer to replace dressings used on short-term CVC sites every 2 days for gauze dressings and at least every 7 days for transparent dressings¹⁹.

DURATION OF CATHETERS

The practice of routinely changing catheters according to some defined time period to reduce the risk of CRI is referred to as “scheduled” replacement. There is no support from the literature that catheter replacement at sheduled time intervals will reduce the CRI rates^{54,55,56}. Thus, routine replacement of CVCs is not necessary for catheters that are functioning and have no evidence of causing local or systemic complications.

ADMINISTRATION SET AND FLUID CHANGES

Replacing administration sets no more than 72 hours after initiation of use is safe and cost effective. While blood products and lipid emulsions are more likely to sustain bacterial growth, more frequent changes of administration sets are indicated as these products have been identified as independent risk factors for CRI.

ANTIMICROBIAL/ANTISEPTIC IMPREGNATED CATHETERS AND CUFFS

Certain CVCs that are coated or impregnated with antimicrobial or antiseptic agents can decrease the risk for CRI¹⁹. Use of these catheters might be cost effective in ICU patients, burn patients, neutropenic patients, and other patients populations in which the rate of infection exceeds 3,3 per 1,000 catheters day³.

CHLORHEXIDINE/SILVER SULFADIAZINE

Two meta-analyses demonstrated that CVCs coated with chlorhexidine/silver sulfadiazine reduced the risk for CRI compared with noncoated catheters^{57, 58}. As the antimicrobial activity is waining over time , these catheters should be considered when the expected duration of catheterization is less than 2 weeks, particularly if there is a high rate of infection despite adherence to other strategies.

MINOCYCLINE/RIFAMPIN

The duration of antimicrobial activity of CVCs impregnated with minocycline/rifampin is longer than that of the

chlorhexidine/silver sulfadiazine coated catheters⁵⁹. In a multicenter randomized trial, these CVCs were associated with lower rates of CRI than chlorhexidine-silver sulfadiazine impregnated catheters⁵⁹.

PLATINIUM/SILVER

Platinium/Silver impregnated CVCs and silver cuffs attached to CVCs are other available catheters to prevent CRI but futher studies are needed to show their effectiveness in reducing CRI incidence¹⁹.

MANAGEMENT

Once the diagnosis of CRI is established or suspected, prudent decisions about the duration, type of antimicrobial therapy and the catheter's removal should be made dependent on different factors concerning the patient, the pathogen, and the catheter itself. Removal of an catheter suspected to be infected is recommended. However, there are circumstances in which removal of the catheter is diffucult or not desirable unless absolutely necessary. This is the case in patients with poor venous access, in patients for whom trying a new catheterization involves high risk (e.g bleeding diatesis) and with catheters that are surgically implanted. In hemodynamically stable patients, if no signs of metastatic infection and tunnel or port infection is present salvage of the catheter can be undertaken in case the blood gets sterile in 48-72 hours after antibiotic initiation⁹. CRI caused by CNS may be succesfully managed with the catheter in situ². Although catheter retention is associated with higher risk of the bacteremia, mortality and morbidity are not influenced by catheter removal⁶⁰. Therefore, catheter retention might be considered in patients with CRI due to CNS, provided that there is no indication for catheter removal (Table 3). Nonetheless, there is a 20% risk of bacteremia recurrence if the catheter remains in place, especially for longer than 3 weeks after initial bacteremia episode⁶¹.

Figure 3

Table 3: Indications for catheter removal

Severe sepsis or septic shock
Infective endocarditis
Peripheral embolization
Persistent bacteremia/sepsis after 72 h of antimicrobial treatment
Presence of local complications (e.g. signs of tunnel or port infection)
Relapse of infection after antibiotics have been discontinued
Infection caused by organism other than CNS

Regarding antimicrobial therapy, it can be administered either on an empirical basis or after a well-established

microbiological diagnosis. Although removal of the catheter alone may result in clinical cure in selected cases, it is generally recommended to treat CRI systemically with appropriate antibiotics^{2, 62}. Most of the CRI will be treated for a period of 7 to 14 days, depending on the isolated microorganisms^{2, 9, 60}. However, in cases of complicated CRI, the vascular catheter should be removed and the infection treated with antibiotics for at least 4 weeks^{2, 39, 60}.

COAGULASE-NEGATIVE STAPHYLOCOCCI

Most patients have a benign clinical course, but rarely do patients develop frank sepsis with a poor outcome^{63, 64, 65}. A 5-7 day course of antimicrobials should be adequate if the patient responds within 48 to 72 hours². Patients responding to antibiotic therapy after 72h and in whom the catheter is retained in place should have a 14-day course of antibiotics therapy^{2, 9}.

S.AUREUS

The catheter must definitely be removed; otherwise serious infectious complications may arise. Also failure to remove the catheter is associated with persistent bacteremia, relapses, and increased mortality^{66, 67}. Uncomplicated episodes of *S.aureus* infections should be treated with appropriate antibiotics given intravenously for at least 2 weeks². However, in cases of complicated infections or in patients with prolonged fever under appropriate antimicrobial therapy, much longer periods are needed².

GRAM-POSITIVE BACILLI

Removal of the catheter has been recommended for the successful management of such infections. Treatment should be prescribed on the basis of susceptibility tests⁶⁰.

GRAM-NEGATIVE BACILLI

Gram – negative bacilli such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *E.coli*, *Klebsiella* spp. are also relatively common causes of CRIs. Removal of the catheter is important, as failure to remove it results in significantly higher rates of treatment failure and recurrence of bacteremia^{2, 18}. Catheter removal and a 10-14 day course of antimicrobial is recommended^{2, 60}.

CANDIDA SPP.

Removal of the CVC is clearly necessary in candida associated CRI^{2, 68, 69}. Catheter retention is an independent risk factor for the persistence of candidemia and higher mortality rate^{68, 69}. Antifungal therapy should be started in all

cases. Intravenous fluconazole is the drug of choice for CRI due to *Candida* spp.². In the cases caused by *Candida* spp. not susceptible to fluconazole, treatment has to be changed to amphotericin B_{70, 71}. Therapy with antifungal agent is recommended for 14 days after last positive blood culture.

ATYPICAL MYCOBACTERIA

M.fortuitum and *M.chelonae*, have been shown to cause CRI. Catheter removal is crucial for the successful management of CRI due to these organisms. Combination of cefoxitin and amikacin is the best coverage for the treatment¹⁸.

ANTIBIOTIC LOCK THERAPY

The antibiotic-lock technique consists of instillation of the catheter lumen with an antibiotic solution over a period of 12-24 h in order to sterilize the catheter^{72, 73, 74, 75}. It has been demonstrated to be effective in eliminating CRB in several studies^{73, 74, 75}. With this method, a high local concentration of an appropriate antibiotic can be applied in the catheter lumen while avoiding systemic toxicity and the monitor serum drug levels. This technique is particularly appealing for treatment of noncomplicated CRI of intraluminal origin⁷⁶. Although the duration of antibiotic lock therapy has varied among different studies, it most often is 2 weeks^{2, 76}.

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