

# Hemodialysis catheter-related infection: prophylaxis, diagnosis and treatment

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## ABSTRACT

**Purpose:** Infectious complications associated with central venous catheters (CVCs) are a major source of morbidity and mortality among hemodialysis (HD) patients. This review aims to discuss prevention, diagnosis criteria and management of CVC-related infections in HD patients.

**Methods:** We searched Medline for articles published in the last 10 years, with the keywords “catheter,” “hemodialysis,” “infection,” “treatment,” “diagnosis,” “prophylaxis” and “adults.” Only English language articles were reviewed. We reviewed prophylaxis and surveillance protocols, diagnosis criteria, including new molecular tools, and the management of catheter-related infections, including antibiotic regimen, empiric and according to causal agents, lock therapy, catheter salvage or removal choice and treatment of complications.

**Results:** To prevent infectious complications, first of all we need to avoid using catheters. If we need CVC, adoption of prophylaxis and surveillance protocols, and antibiotic ointment at the exit site reduce infectious complications. The diagnosis of CVC-related infections should be made with drainage and/or blood cultures. Empiric systemic antibiotics should cover Gram-positive and -negative microorganisms, and final regimen should be based on culture results. In selected cases, salvage of site, by CVC exchange over wire, or salvage of catheter, using antibiotic lock, under the cover of systemic antibiotics, could be attempted.

**Conclusions:** The best approach to prevent CVC-related infection would be to avoid the use of CVC. However, in patients for whom it is impossible, the adoption of adequate prophylaxis protocols, early diagnosis and effective treatment of infectious complications are essential to improve outcomes.

**Keywords:** Central venous catheter, Diagnosis, Hemodialysis, Infection, Treatment

## Introduction

The prevalence of end-stage renal disease (ESRD) patients requiring renal replacement therapy (RRT) has increased in the last decade and it is expected that this increase will continue over the next 10 years. Hemodialysis (HD), the main modality of RRT (1, 2), depends on long-term and effective vascular access. Based on these characteristics, the vascular access of choice is the arteriovenous fistula (AVF), which should be used by at least 65% of the patients in a HD setting (3). Vascular grafts and central venous catheters (CVCs) are considered second and third options, due to the greater risk of infection, thrombosis, need of rescue procedures and the increase in mortality and hospitalization rates (1). The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that the prevalence of CVC should be below 10% in

HD facilities. In addition, it is suggested that a tunneled CVC be implanted if the intended stay is above 3 weeks (3). However, the evidence of advantages of tunneled catheters over nontunneled ones is entirely based on observational studies, and there is no randomized clinical trial comparing these two options in HD patients; therefore, it is unknown to what extent the tunneling could actually reduce the CVC complications in HD (4-6). Recent data show that 15% to 50% of ESRD patients in Europe and 60% in the United States started the HD program using a CVC (5). The tunneled CVCs are used as long-term vascular access mainly when the AVF possibilities were exhausted. Furthermore, a significant number of patients need temporary vascular access to manage acute kidney injury, during delayed AVF maturation, or as a bridge to kidney transplantation or peritoneal dialysis (5). The use of a CVC is the major risk factor for bacteremia in HD, which can result in life-threatening complications in over 10% of cases, such as septic shock, endocarditis, septic arthritis, osteomyelitis and epidural abscesses. The relative risk of hospitalization for infection and death is 2-3 times greater in patients using CVC compared to patients with AVF or vascular graft (7), with consequent increase in costs. Infection is the second leading cause of death in patients on HD (8, 9). Despite the astonishing number of CVC-related infectious complications, its use as a long-term vascular access in HD has increased. To

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some extent, it may be consequent to the current profile of HD patients, who present a greater number of comorbidities, in addition to older age, which could make it difficult for AVF creation (10).

Furthermore, the later referral of chronic kidney disease patients to a nephrologist, the difficulty of choosing among dialysis and access modalities and problems with reimbursement may contribute to the increased use of CVC (9). Considering the widespread use of CVC, the adherence to prophylaxis protocols, early diagnosis and effective treatment of CVC-related infections are fundamental to improve outcomes.

## Microbiology

The microorganisms most frequently isolated during catheter-related bacteremia episodes in HD are staphylococci and other Gram-positive cocci. According to US data, coagulase-negative staphylococci (CoNS) are found in 32% to 45% of cases (11, 12), *Staphylococcus aureus* in 22 to 29% (11, 13, 14) and enterococci in 9% to 13% of cases (11, 12). Gram-negative bacteria have been isolated in 21% to 30% of cases (11, 13). The microorganism isolated during bacteremia seems dependent on the type of vascular access. The ratio of *S. aureus* is higher with AVF or grafts, and CoNS and Gram negative bacteria are more frequent during catheter-related bacteremia (11, 13). Furthermore, patients on HD present an increased risk of multiresistant organism infections, such as methicillin-resistant *S. aureus* (MRSA) (8).

## Pathology and pathogenesis

The main risk factor associated with bacteremia in HD is the modality of vascular access, with the use of catheter associated with an increase of up to 10 times of the risk if compared to AVF (8). The catheter site of insertion is also associated with infection rates. The likelihood of bacteremia with nontunneled dialysis catheters increases exponentially and, by 4 weeks, reaches 10% for internal jugular catheters and 29% for femoral catheters (15). However, latest data obtained from acute kidney injury showed similar infection and colonization rates between femoral and jugular catheters. However, a prespecified subgroup analysis found a correlation between body habitus and the insertion site with greater risk of colonization: for patients with body mass index  $>28.2$  m/kg<sup>2</sup> the risk was higher using the femoral site, while in patients with body mass index  $<24$  m/kg<sup>2</sup>, the risk was higher with the jugular insertion (16). A systematic review comparing central venous access sites (not only dialysis CVC) and venous thrombosis, stenosis or infections, published by Cochrane Collaboration in 2012, found that subclavian and internal jugular CVC sites have similar risks for catheter-related complications in long-term catheterization (above 1 month) in cancer patients. Subclavian CVC is preferable to femoral in short-term catheterization because of lower risks of catheter colonization and thrombotic complications. In short-term HD catheterization, femoral and internal jugular CVC sites have similar risks for catheter-related complications, except that internal jugular site is associated with higher risks of mechanical complications.

No randomized controlled trial (RCT) was found comparing all three CVA routes and reporting the complications of venous stenosis (17). Despite the lack of an RCT, some observational studies found that subclavian vein catheterization is associated with central venous stenosis (18, 19), which will preclude the use of the entire ipsilateral arm for vascular access. Thus, subclavian vein catheterization should be avoided in patients with kidney disease.

Other risk factors for infectious complications are previous episodes of bacteremia, poor hygiene, skin infection next to the catheter exit site, iron overload, immunosuppression and hypoalbuminemia (8, 9). Nasal colonization with *S. aureus* has also been described as associated with catheter-related infection (8). As the CVC is frequently manipulated during HD sessions, breach in aseptic techniques may also result in infection complications. Patient characteristics such as age, gender, race and diabetes have not been associated with risk of CVC-related infections (9).

The presence of a biofilm in the catheter lumen is one of the factors that complicate the infection treatment. The biofilm is defined as a structured community of bacterial units covered by adherent material, which makes this community 100-1,000 times less sensitive to antibiotics if compared with its free form (20). Over the past decade, major advances in the understanding of biofilm formation have taken place. The bacterial quorum sensing system, a signaling cascade that changes the bacterial gene expression in response to high bacterial population density, has been elucidated. This system controls the genes that express virulence factors and antibiotic resistance, in addition to biofilm formation (21).

## Prophylaxis

The most obvious measure that would reduce the frequency of catheter-related bacteremia is to decrease the number of patients using a dialysis catheter (3). However, this goal has remained elusive in the United States and in most of the world, because of several barriers, including the late referral of patients with chronic kidney disease to nephrologists, high primary failure rate of new AVFs and frequent failure of arteriovenous grafts (22).

## Tunneled vs. nontunneled catheters

There is no RCT comparing the frequency of catheter-related bacteremia with tunneled or nontunneled HD catheters; although some previous prospective nonrandomized studies of HD patients observed a catheter-related bacteremia rate that was 2- to 3-fold greater for nontunneled compared with tunneled CVC (5, 23), a latest multicenter study of incident HD patients found that, compared with patients with AVFs, the age-adjusted relative risk for developing a bloodstream infection in patients with arteriovenous grafts was 1.69 (95% CI, 0.42-6.79); with tunneled CVC, 9.78 (95% CI, 3.53-27.11) and with nontunneled CVC, 10.54 (95% CI, 3.69-28.20) (12). Therefore, using tunneled or nontunneled dialysis catheters, skin flora can be introduced into the lumen during manipulation of the catheter and form a biofilm, which serves as a nidus for catheter-related bacteremia.

### **Aseptic protocol**

A strict prophylaxis protocol has been reported to reduce the incidence of catheter-related bacteremia substantially in an observational study. The protocol included measures such as wrapping the catheter hubs with iodine-saturated gauze for 5 minutes before removal of the catheter caps, having the dialysis nurse and patient wear masks during catheter connection and disconnection and minimizing exposure of the catheter to air (24). The 2000 KDOQI guidelines followed these recommendations (25). However, in the 2006 KDOQI update, soaking hubs with povidone-iodine is not mentioned; instead, cleansing catheter hubs with chlorhexidine is recommended (26).

### **Antibiotic ointment at the exit site**

In addition to the strict aseptic protocol, pharmacological measures may be useful for the prophylaxis of catheter-related bacteremia. One potential approach is to use an antibiotic ointment to reduce skin flora around the catheter exit site. Johnson et al (27) compared mupirocin ointment in exit site of new dialysis catheters with placebo in a randomized, open label study involving 50 HD patients, and found an 85% reduction on infection rate for mupirocin group. This benefit was entirely caused by a reduction in staphylococcal infections. Although no instances of mupirocin-resistant *Staphylococcus* species were documented in the present study, the emergence of mupirocin resistance has been documented by others (28, 29) and may limit the efficacy of this approach during long-term prophylaxis. Similar benefits were found by Lok et al (30) using polysporin (bacitracin, gramicidin, and polymyxin B) ointment in incident and prevalent patients with catheters.

### **Control of *S. aureus* nasal carriage**

A small randomized trial observed a lower frequency of infections caused by *S. aureus* in patients administered intermittent rifampin prophylaxis to reduce nasal carriage compared with the control group (31). However, rifampin-resistant *S. aureus* strains were observed in several patients during the course of the study. Similarly, Boelaert et al (32) used nasal mupirocin and observed a 4-fold decrease in frequency of *S. aureus* bacteremia compared with the historic control period.

### **Antimicrobial lock solutions**

Another pharmacological approach involves instillation of an antimicrobial solution into the catheter lumen to limit biofilm formation. Lock solutions with gentamicin/citrate or taurocholate/citrate compared with heparin resulted in 89% to 100% reduction on infection rates in randomized and nonrandomized studies in HD patients (33-35). However, the study using gentamicin citrate documented measurable plasma levels of gentamicin in the experimental group, and approximately 10% of those patients developed symptoms consistent with aminoglycoside ototoxicity (33). No instance of gentamicin-resistant infection was observed during the relatively short-term follow-up. However, the documented systemic absorption of gentamicin from the antibiotic lock raises serious concerns about the potential for selecting antibiotic-resistant infections during long-term prophylaxis. A randomized study including 291 HD patients with CVC, 98 with tunneled catheters, compared 30% trisodium citrate lock solution with a standard heparin lock (36). The frequency of catheter-related bacteremia was substantially lower in patients using the concentrated citrate lock (1.1 vs. 4.1 episodes/1,000 catheter-days). However, inadvertent instillation of concentrated citrate solution systemically has the potential of producing life-threatening hypocalcemia.

Many of the studies about lock solutions have been summarized in four recent meta-analyses (37-40), which concluded that antibiotic catheter lock solutions decrease catheter-related bloodstream infections (CRBIs) by 60%-70%. However, this result was limited by heterogeneity among studies, few large trials, likely publication bias and most studies conducted in populations with higher than expected infection rates.

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### **Coated catheters**

A randomized open label trial comparing silver-coated catheters with untreated CVC was unable to show reduction of infection rates with coating (41). However, another study evaluating nontunneled central vein triple-lumen catheters impregnated with minocycline and rifampin has been reported to decrease the frequency of bacteremia by approximately 90% compared with silver-impregnated catheters (42). This benefit was evaluated for only up to 30 days; thus, it is not clear whether it would translate to tunneled dialysis catheters used for longer periods.

### **Active surveillance**

Active collection and use of surveillance data allow facilities to know their infection rates and recognize patterns of infection that might warrant intervention. Several published reports have shown the benefit of performing surveillance in dialysis settings (14, 43, 44). These surveillance programs should survey outcomes and process measures (8). The outcome measures should include number of CRBIs, intravenous antimicrobial courses, hospitalizations, access site infections and pyrogenic reactions. The process measures should include hand hygiene adherence, CVC percentage use and adherence to CVC insertion practices.

### **Future perspectives**

The characterization of the signaling molecules and pathways that are involved in bacterial quorum system has led to the development of a number of new therapeutic targets. Natural and synthetic molecules mimic this system elements, and protective antibodies generated by vaccination against these molecules are under study as potential inhibitors of the system, with consequent inhibition of biofilm formation (45).

### **Conclusions**

There is a need for additional studies with long-term follow-up to evaluate the potential for selection of antibiotic-

resistant organisms by strategies using antibiotics. The CDC (46) and KDOQI (25, 26) recommendations for the prevention of bloodstream infections include to avoid CVC, surveillance for bloodstream infections, training of health care personnel on CVC care, hand hygiene before accessing catheter, surgical mask during catheter procedures (no recommendation in CDC), preferential use of chlorhexidine for skin antisepsis and antimicrobial ointment to CVC exit site (povidine-iodine is recommended by CDC and KDOQI recommends povidine-iodine or mupirocin). Routinely administer intranasal antimicrobials for *S. aureus* decolonization, use of antimicrobial-impregnated catheters, chlorhexidine-impregnated catheter dressings and prophylactic antimicrobial catheter locks are not recommended.

## Diagnosis

**Exit site infection:** hyperemia, induration and/or tenderness up to 2 cm from catheter exit site; may be associated with fever and purulent drainage from exit site. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture with antibiogram (47).

**Tunnel infection:** tenderness, hyperemia and/or induration that extends more than 2 cm from the exit site and along the subcutaneous tunnel. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture with antibiogram (47).

**Catheter-related bloodstream infections:** the patient usually presents an abrupt onset of fever and/or chills and may present signs and symptoms of sepsis, such as hypotension, without an obvious alternative infectious source. In this case, blood cultures should be collected before introduction of antibiotic treatment, collecting at least two samples, one from the catheter lumen and another from a peripheral vein. The culture of blood only from the catheter lumen is associated with an increased risk of false-positive results (colonization). In a study of cancer patients with central vein catheters for chemotherapy, negative catheter culture results virtually excluded the diagnosis of catheter-related bacteremia. However, when catheter culture results were positive, a clinical diagnosis of catheter-related bacteremia was made only 63% of the time (48). Before the blood culture collection, the catheter and the skin around peripheral venipuncture site should be cleaned with alcohol, iodine tincture or alcoholic chlorhexidine. The success in isolating the bacteria or fungus responsible for the bacteremia increases with greater volumes of blood and higher number of cultures collected. In adult patients, 20 to 30 mL should be collected from each site (47).

## Guidelines for the diagnosis of CRBI

**Infection Diseases Society of America (IDSA) (47):** The IDSA guidelines suggest that at least one of two microbiological methods should be used to confirm the diagnosis of CRBI: (1) quantitative blood cultures from the CVC lumen with at least three times higher number of colonies than cultures from the peripheral vein; or, (2) blood cultures from catheter

lumen with growth of microorganism at least 2 hours earlier than cultures from the peripheral vein. It is necessary to isolate the same microorganism in blood cultures from the catheter and the peripheral vein for the diagnosis of catheter-related bacteremia. However, this requirement has been challenging because of the unique circumstances of HD patients. The IDSA, considering that the priority of preserving arm veins for future fistula creation may render venipuncture impractical, agreed to accept blood cultures obtained from the catheter and blood line connected to the CVC (instead of peripheral vein venipuncture) when peripheral vein samples are not possible.

**CDC's National Healthcare Safety Network (CDC-NHSN) (49):** The CDC-NHSN criteria for CRBI include (1) identification of an organism unrelated to another infectious site in one or more blood cultures; (2) the presence of at least one of the following signs and symptoms: fever, chills or hypotension; frequent skin contaminants (diphtheroids [*Corynebacterium* spp.], *Bacillus* [except *B. anthracis*] spp., *Propionibacterium* spp., CoNS [including *S. epidermis*], viridans streptococci, *Aerococcus* spp., *Micrococcus* spp.) should be isolated in two or more blood cultures from different sites.

**Other criteria (9):** Considering that sometimes the guidelines criteria are not all fulfilled, some authors have suggested alternative classification systems, which classify bacteremia cases as definitely, probably and possibly related to CVC. A bacteremia episode would be classified as certainly associated to CVC if the blood cultures collected from catheter and peripheral vein result in the growth of the same microorganism, and the number of colonies in blood from the catheter is at least 10 times greater than that collected from peripheral vein. When the blood cultures are positive, and no alternative infectious site is identified, the bacteremia would be classified as probably catheter related. The patient who has fever which is resolved after catheter removal, with negative blood cultures, and no alternative infection site identified, is classified as having possibly catheter-related bacteremia.

## New molecular methods for diagnosis of CRBI

Although the Gram stain can identify Gram-positive cocci in grape-like clusters as staphylococci, while enterococci appear in pairs or chains, the species determination is only possible after growth of colonies, which may take 24 to 72 hours. New molecular technologies can identify the species in a few hours. Two of these techniques have become recently available: real-time polymerase chain reaction (PCR) and fluorescence in situ hybridization using peptide nucleic acid probes (PNA FISH). The real-time PCR identifies the *S. aureus mecA* gene, and determines its sensitivity to methicillin, making it possible to classify as MRSA or methicillin-sensitive *S. aureus* with 100% sensitivity and 98.5% specificity (50-52). The PNA FISH uses probes to 16S ribosomal RNA to identify organisms in the blood within 3 hours, making it possible to distinguish *S. aureus* from CoNS and *Enterococcus faecalis* from other enterococci, although this technique is not capable of determining the resistance pattern (53). However, both technologies are expensive and they are not widely available.

### CRBI complications

Echocardiogram should be considered in cases of persistent bacteremia after 72 hours of adequate antibiotic treatment. The 2005 American Heart Association guidelines for the management of valve heart disease recommended initial transesophageal echocardiography in HD patients for diagnosing and managing *S. aureus* infective endocarditis (54). Although transthoracic echocardiography can detect larger vegetations, it is less sensitive (20%-60%) and frequently can miss smaller vegetations, myocardial abscesses or other serious valve abnormalities (55).

### Management

#### Exit site infection

Treatment with topical antibiotics is indicated on the basis of exit site culture results (e.g., mupirocin ointment for *S. aureus* infection) (47). If there is no resolution of the exit site infection or if there is purulent drainage, systemic antibiotic should be used. If despite systemic antibiotic there is no resolution of the infection, the CVC should be removed (47).

#### Tunnel infection

Systemic antibiotic is indicated; the CVC should always be removed and antibiotic treatment maintained for 7 to 10 days (47).

#### Catheter-related bloodstream infection

Treatment with systemic antibiotics should be prescribed without delay, before blood culture results. The initial empiric antibiotic coverage should include Gram-positive and Gram-negative germs, with adjustment of the antibiotic regimen after isolation of the microorganisms and sensitivity pattern recognition (56) (Tab. I).

#### Initial empiric therapy of CRBI

Bacteriological data from several institutions documented a wide range of bacterial pathogens (11-14). A substantial proportion of catheter-related bacteremia is caused by Gram-negative rods, thus mandating broad-spectrum antibiotic coverage for both Gram-positive and -negative organisms pending culture results. Moreover, many staphylococcal infections in HD patients are caused by methicillin-resistant species, requiring empiric therapy with vancomycin pending sensitivity reports (8), in addition to an antibiotic with broad-spectrum Gram-negative bacterial coverage (aminoglycoside or third-generation cephalosporin) (47). Although the choice of antibiotic may be associated with personal preference, regional resistance pattern and/or hospital guidelines, it is recommended to choose an antibiotic whose pharmacokinetic profile allows doses after each dialysis, such as vancomycin, cefazolin, ceftazidime and daptomycin. Aminoglycosides may not attain adequate serum levels only with doses after dialysis, and its use is associated with ototoxicity, loss of residual

renal function, treatment failure and bacterial resistance development. However, considering its fast bactericidal effect, the administration of a single dose of aminoglycoside 1 hour before HD may be useful (57). Although the half-life of vancomycin is longer in patients with kidney disease, the advances of the dialysis technology, such as better dialyzer membrane biocompatibility and larger surface area and permeability, increase this drug removal by HD. Barth and DeVincenzo suggest a loading dose of 20 mg/kg administered at a rate of 1,000 mg/hour and maintenance doses of 500 mg administered during the last hour of each HD session (58). Side effects that may occur during vancomycin infusion, such as red man syndrome (which is often mistaken for allergic reaction), are usually solved by decreasing the infusion rate and/or administration of antihistamine drugs.

#### Antibiotic therapy of CRBI based on blood cultures

##### Methicillin-resistant staphylococci infection

In cases of bacteremia caused by MRSA or methicillin-resistant CoNS, the minimum inhibitory concentration (MIC) of vancomycin should be determined. If the MIC is above 2 µg/mL, the microorganism is resistant to vancomycin, which should be replaced by an alternative antibiotic, such as daptomycin or linezolid. The presence of species of heterogeneous vancomycin intermediary *S. aureus* (hVISA) should be considered in cases of delayed response to vancomycin. The hVISA is a strain of slow growing and thicker cell walls, which makes it less permeable to vancomycin. In such situations, susceptibility test should be considered and the daptomycin could be a therapeutic alternative. Table I describes the duration of treatment (59).

##### Methicillin-sensitive staphylococci bacteremia

Patients receiving empiric therapy with vancomycin when blood cultures show methicillin-sensitive staphylococcus should have the antibiotic replaced by cefazolin. The advantages of cefazolin include its broad-spectrum, favorable pharmacokinetics which allows intravenous administration only after dialysis, in addition to its bactericidal activity which contrasts to the bacteriostatic activity of vancomycin. The use of vancomycin to treat infections by methicillin-sensitive bacteria increases significantly the risk of treatment failure (8, 56, 57).

##### *E. faecalis* bacteremia

Ampicillin is used mostly to treat *E. faecalis* bacteremia in HD patients. Although vancomycin has obvious ease of dosing, it has a higher clinical failure rate in the treatment of *E. faecalis* infection and can lead to the emergence of vancomycin-resistant *Enterococcus* (60). Ampicillin is preferable to ampicillin/sulbactam, which may underdose the ampicillin component in HD patients (61, 62). Normal dosing would require 8-12 g of ampicillin daily in 4-6 divided doses. In HD patients, the dosage ranges from 1 to 2 g every 12-24 hours. If dosed every 24 hours, the dose should be given daily, but after dialysis on dialysis days (62).

**TABLE I - Catheter-related bloodstream infection management**

*Nontunneled catheter with bloodstream infection, uncomplicated* (fever with resolution up to 72 hours in patients who do not have a vascular prosthesis and without evidence of endocarditis or thrombophlebitis).

1. Coagulase-negative staphylococci  
Catheter removal and treatment with systemic antibiotics for 5 to 7 days. If catheter salvage is attempted, systemic plus lock antibiotic therapy for 10 to 14 days
2. *Staphylococcus aureus*  
Catheter removal and systemic antibiotic therapy for 14 days or more
3. Gram-negative germ or enterococci spp.  
Catheter removal and systemic antibiotic therapy for 7 to 14 days
4. *Candida* spp.  
Catheter removal and antifungal treatment for 14 days after negative blood cultures

*Tunneled central vein catheter with bloodstream infection, uncomplicated*

1. Coagulase-negative staphylococci  
Catheter salvage attempt with systemic plus lock antibiotic therapy for 10 to 14 days  
Catheter removal if clinical deterioration, maintenance or recurrence of bacteremia
2. *Staphylococcus aureus*  
Catheter removal and systemic antibiotic therapy for 4 to 6 weeks
3. Enterococci spp.  
Catheter salvage attempt with systemic plus lock antibiotic therapy for 7 to 14 days  
Catheter removal if clinical deterioration, maintenance or recurrence of bacteremia
4. Gram-negative germ  
Catheter removal and systemic antibiotic therapy for 7 to 14 days  
If catheter salvage is attempted, systemic and lock antibiotic therapy for 10 to 14 days; catheter removal if clinical deterioration, maintenance or recurrence of bacteremia
5. *Candida* spp.  
Catheter removal and antifungal treatment for 14 days after first negative blood cultures

*Tunneled or nontunneled central vein catheter with bloodstream infection, complicated (suppurative thrombophlebitis, endocarditis or osteomyelitis)*

Catheter removal and treatment with systemic antibiotics for 4 to 6 weeks; 6 to 8 weeks if osteomyelitis in adult patients

Adapted with permission from (56): Weber DJ, Rutala WA. Central line-associated bloodstream infections: prevention and management. *Infect Dis Clin North Am.* 2011;25(1):77-102.

### **Candidemia**

In these cases, echinocandin should be the first choice; fluconazole should be reserved to selected cases (e.g., patients without azole exposure in the previous 3 months and in health care settings with low risk of *Candida krusei* or *Candida glabrata*) (47). The CVC-related infection by *Candida* is associated with increased risk of treatment failure or early recurrence, so catheter removal is the first therapeutic choice.

### **Catheter management in CRBI**

In addition to systemic antibiotic therapy, the different strategies for CVC management include catheter removal, salvage with lock therapy or exchange over guidewire. Studies comparing the outcomes of different catheter management strategies are mostly uncontrolled, with different methodologies, criteria and outcome definitions, which preclude their comparison (63-74).

### **Catheter salvage**

The CVC could be preserved in cases of uncomplicated and short-time bacteremia caused by CoNS or gram-negative bacilli other than *Pseudomonas* species, with no signs of tunnel infection. In these cases, intravenous antibiotic therapy should be initiated and, if there were symptom resolution and no evidence of metastatic infection after 72 hours, the catheter can be retained, using an antibiotic lock as adjunctive therapy (3, 47). Antibiotic lock therapy should not be used alone, but always associated with systemic antibiotic. The antibiotic lock should be replaced every 48 hours, after each HD session (75). The aim is to achieve antibiotic concentration above the therapeutic ones within the catheter lumen, which allows biofilm eradication and elimination of bacteria attached to the catheter. The usual concentrations of antibiotics used in the lock therapy are described in Table II (57, 75). The antibiotic lock therapy associated with systemic antibiotic could make possible the preservation of the catheter

**TABLE II** - Antibiotic concentration in lock therapy

Antibiotic	Concentration (mg/dL)
Vancomycin	2.5-5.0
Cefazolin	10.0
Ceftazidime	10.0
Gentamycin	4.0
Tobramycin	5.0

Adapted with permission from (57): Vanholder R, Canaud B, Fluck R, et al. Catheter-related blood stream infections (CRBSI): a European view. *Nephrol Dial Transplant*. 2010;25(6):1753-1756.

in clinically stable patients with bacteremia caused by low virulence pathogens. However, the success rates in *S. aureus* infections are low, around 40% (75), as with *Pseudomonas* infections. In enterococci infection antibiotic lock therapy may not be indicated, because although the rate of success is around 60%, the need for longer treatment increases the risk of subsequent fungemia (76). Blood cultures should be obtained 1 week after completion of an antibiotic treatment if the catheter has been retained, and if results are positive, the catheter should be removed. In a study of catheter salvage, bacteremia recurrence was more frequent than with catheter removal (33.0% vs. 8.1%) but at the expense of lower risk of mechanical complications (0.9% vs. 14.3%). In this study, the salvage approach included only systemic antibiotics, without antibiotic lock therapy (77).

### Catheter removal

Guidelines of the IDSA recommend that the catheter should always be removed in cases of CRBIs due to *S. aureus*, *Pseudomonas* or fungi species (47). Other indications for catheter removal include severe sepsis, hemodynamic instability, endocarditis, other metastatic infections, concomitant tunnel infection or persistent bacteremia after 72 hours or more of adequate antibiotic treatment. In cases of catheter salvage attempt, blood cultures should be collected after 72 hours of adequate antibiotic therapy and 1 week after conclusion of treatment, and the catheter should be removed if any of these blood culture results remain positive (57) (Tab. I). After catheter removal, the best approach is the insertion of a nontunneled catheter temporarily in another anatomic site. A long-term tunneled catheter can be placed only after blood cultures with negative results are obtained (47).

### Catheter exchange over wire

In cases of catheter salvage attempt, if there is no evidence of metastatic infection or associated exit site or tunnel infection, and there is symptom resolution after 72 hours of antibiotic therapy, the catheter exchange over a guidewire is an alternative to antibiotic lock therapy, with insertion of a new, tunneled HD CVC (3, 47).

In situations with indications for immediate catheter removal, a new nontunneled temporary CVC can be placed over

guidewire only if absolutely no alternative sites are available for catheter insertion. After that, clinical follow-up should be maintained and blood cultures obtained. In cases of persistent clinical signs of infection and bacteremia after 48 hours, the CVC should be removed. A long-term tunneled catheter can be placed only after blood cultures with negative results are obtained (47).

### Treatment of catheter-related bacteremia complications

Severe sepsis or metastatic infections, such as endocarditis, osteomyelitis, epidural abscess or septic arthritis, are indications for hospital admission. In cases of endocarditis, the antibiotic treatment should be according to the sensitivity pattern of the pathogen and should be maintained for 6 weeks. In osteomyelitis cases, the antibiotic treatment should last for 8 weeks (Tab. I).

### Conclusions

Despite the great number of potential complications, CVCs are frequently used in HD patients. In such situations, adherence to strict aseptic protocols and infection surveillance programs can reduce complications. All patients using catheter should be closely monitored for evidence of infection, and if it is suspected, blood and/or exudate cultures should be promptly obtained. In cases of CRBI, early empirical broad-spectrum antibiotic therapy should be instituted and adjusted after culture results. Because HD patients depend on the vascular access to stay alive, and there is a limited number of options to provide such access, attempts to salvage catheter or insertion site are usual. Excluding some situations such as CRBI with *S. aureus*, *Pseudomonas* or fungi, associated tunnel infection, severe sepsis or metastatic infections, we can try to maintain the catheter while using systemic and lock antibiotic therapy, or preserve at least the insertion site by catheter exchange over wire.

Adherence to guidelines of catheter-related infections – prophylaxis, diagnosis and treatment – can save lives. But above all, avoiding the use of CVC is the best way to prevent infectious complications. It can be reached through early nephrologist referral and effort to preserve the veins of chronic kidney disease patients, enabling proper timing of AVF creation, with its associated impact on morbidity and mortality in HD patients.

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