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# Central venous catheter-related bacteremia in chronic hemodialysis patients: epidemiology and evidence-based management

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## SUMMARY

**Central venous catheter-related blood stream infection (CRBSI) is a major cause of morbidity and mortality in patients with end-stage renal disease treated with chronic hemodialysis. Risk factors include *Staphylococcus aureus* nasal colonization, longer duration of catheter use, previous bacteremia, older age, higher total intravenous iron dose, lower hemoglobin and serum albumin levels, diabetes mellitus and recent hospitalization. Symptoms that raise clinical suspicion of bacteremia in chronic hemodialysis patients are fevers and chills. When CRBSI is suspected, blood cultures should be obtained and empirical therapy with broad spectrum intravenous antibiotics initiated. The diagnosis of CRBSI is confirmed by isolation of the same microorganism from quantitative cultures of both the catheter and the peripheral blood of a patient that has clinical features of infection without any other apparent source. Gram-positive cocci, predominantly *S. epidermidis* and *S. aureus*, cause bacteremia in two-thirds of cases. Among the various approaches to management of CRBSI, removal and delayed replacement of the catheter, catheter exchange over a guidewire in selected patients, and the use of antimicrobial/citrate lock solutions have all been found to be promising for treatment and/or prevention; however, resolution of issues regarding selection, dose, duration and emergence of antibiotic-resistant organisms with chronic use of antibiotic lock solutions, as well as the safety of long-term use of trisodium citrate lock solutions, await further randomized, multicenter trials involving larger samples of hemodialysis patients.**


**KEYWORDS antibiotic lock solution, catheter-related bacteremia, central venous catheter, hemodialysis**

### REVIEW CRITERIA

The main source of literature reviewed for this article was PubMed. The following search terms were used: "catheter-related bacteremia", "catheter-related septicemia", "central venous catheter", "vascular access", "chronic hemodialysis", and "antibiotic lock solutions".

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## INTRODUCTION

Central venous catheter-related blood stream infection (CRBSI) is a leading cause of hospitalization and death in patients treated with chronic hemodialysis.[1] Despite this, central venous catheters (CVCs) are quite frequently used for vascular access. The predominant reasons for use of CVCs include temporary loss of permanent hemodialysis access, late referral for initiation of dialysis, the need to await maturation of arteriovenous fistulas (AVFs), and limited access options in patients with severe peripheral vascular disease. Types of CVC used for chronic hemodialysis include tunneled cuffed catheters, nontunneled catheters and implantable devices. The risk of developing bacteremia varies with site of CVC insertion, type of device and duration of CVC use.[1] *Staphylococcus aureus* and *S. epidermidis* are the most common bacteria isolated from patients with CRBSI.

Several modalities for management of CRBSI have been explored, ranging from salvage of the catheter to antibiotic catheter-lock solutions. CRBSI can lead to further infectious complications, such as infective endocarditis, septic pulmonary emboli, osteomyelitis and abscesses (Box 1), as a result of hematogenous seeding and, therefore, is an important cause of morbidity and mortality, and places a financial burden on health care systems. This issue warrants exploration with research focused on improving patient outcomes. We present the epidemiology of CRBSI, concentrating on that associated with tunneled cuffed catheters, and offer a detailed review of the literature on evidence-based management and prevention of this condition.

## EPIDEMIOLOGY OF CRBSIs

### Incidence of CRBSIs

The incidence of dialysis-related CRBSI is reported to be 2.5–5.5 cases per 1,000 catheter-days, or 0.9–2.0 episodes per patient-year.[2,3] The risk of bacteremia is highest in hemodialysis patients using a CVC for vascular access, and

increases in a linear fashion with the duration of catheter use.[2,4–8] A prospective study on the incidence of bacteremia in ten hospital-based hemodialysis centers found that 15.2% of episodes occurred in patients with an AVF or graft access, and 84.8% in patients with a CVC ($P<0.001$).[5] The Canadian Nosocomial Infection Surveillance Program found an increased relative risk of bacteremia in patients with cuffed or uncuffed CVCs, compared with patients with an AVF (relative risk [RR] 8.49, 95% CI 3.03–23.78 for cuffed CVCs; RR 9.87, 95% CI 3.46–28.20 for uncuffed CVCs).[6] In the HEMO study (a multicenter randomized clinical trial designed to evaluate the effects of hemodialysis dose and flux on morbidity and mortality) CVCs were present in 32% of study patients with access-related infections despite CVCs being used for only 7.2% of vascular accesses.[8]

Rates of complication and readmission are high among hemodialysis patients with bacteremia, resulting in increased demands on resources. Serious complications, including infective endocarditis, septic arthritis, septic emboli, osteomyelitis, epidural abscess and severe sepsis, have been reported in 20% of cases.[9–11] *S. aureus* has been predominantly isolated from those patients with the most-devastating infectious metastatic complications as a result of the predilection of *S. aureus* for heart valves and bone. Infective endocarditis, which is one of the most life-threatening complications of CRBSI, is observed primarily in access systems composed of exogenous artificial materials, such as polytetrafluoroethylene grafts or CVCs. Marr *et al.* found that 9 of 41 (22%) bacteremic patients developed osteomyelitis, septic arthritis, infective endocarditis or death.[12] In another study, Marr and co-workers reported 65 episodes of *S. aureus* bacteremia (1.2 episodes per 100 patient-months) with complications occurring in 44% of the patients, including infective endocarditis in 12%.[13]

High rates of CRBSI-related complications result in a high incidence of hospitalization and increased costs to the healthcare system. A retrospective analysis of the US Renal Data System revealed that 20.7% of 11,572 patients admitted for *S. aureus* bacteremia developed complications, and that 11.8% were readmitted within 12 weeks for care related to *S. aureus* infection.[14] In this study, the average cost to Medicare for index admission was US$17,307. Average episodic cost for patients with one complication was $25,804. Average duration of hospital stay was 13.0 days, increasing by 4–7 days if complications developed.[14]

**Box 1** Complications associated with hemodialysis central venous catheter-related blood stream infections.

Sepsis
Infective endocarditis
Osteomyelitis
Septic arthritis
Septic pulmonary emboli
Spinal epidural abscess
Death

Infection is second only to cardiovascular disease as a cause of death in end-stage renal disease. Septicemia accounts for more than 75% of infection-related deaths.[1] In the HEMO study, there was a significantly increased likelihood of infection-related death among patients being dialyzed with catheters compared with AVFs (RR 2.30, 95% CI 1.45–3.64).[8] Furthermore, occurrence of first infection-related hospitalization or death was significantly more common in patients with catheters than in those with AVFs (RR 1.85, 95% CI 1.47–2.33). A nationwide US prospective cohort study of 1,041 patients found that the use of CVCs for hemodialysis was associated with a 50% higher adjusted risk of mortality, and a 41% higher risk of infection-related death, compared with use of AVFs.[15]

## Pathogenesis of, and risk factors for, CRBSIs

Several interrelated factors have been proposed to participate in the pathogenesis of CRBSI (Figure 1). Impaired host immunity in end-stage renal disease, caused by neutrophil dysfunction in the setting of iron overload, hyperparathyroidism and retention of uremic solutes, has been implicated.[1] The hemodialysis procedure might have a role in increasing the risk of bacteremia via contamination of dialysate or equipment, inadequate water treatment, or dialyzer reuse.[1,4] The catheter itself can be involved in four different pathogenic pathways: colonization of the catheter tip and cutaneous tract with skin flora; colonization of the catheter lumen caused by contamination; hematogenous seeding of the catheter from another infected site; and contamination of the lumen of the catheter with infusate.[1] Resistance to antibiotic therapy, resulting from adhesion of bacteria to the surface

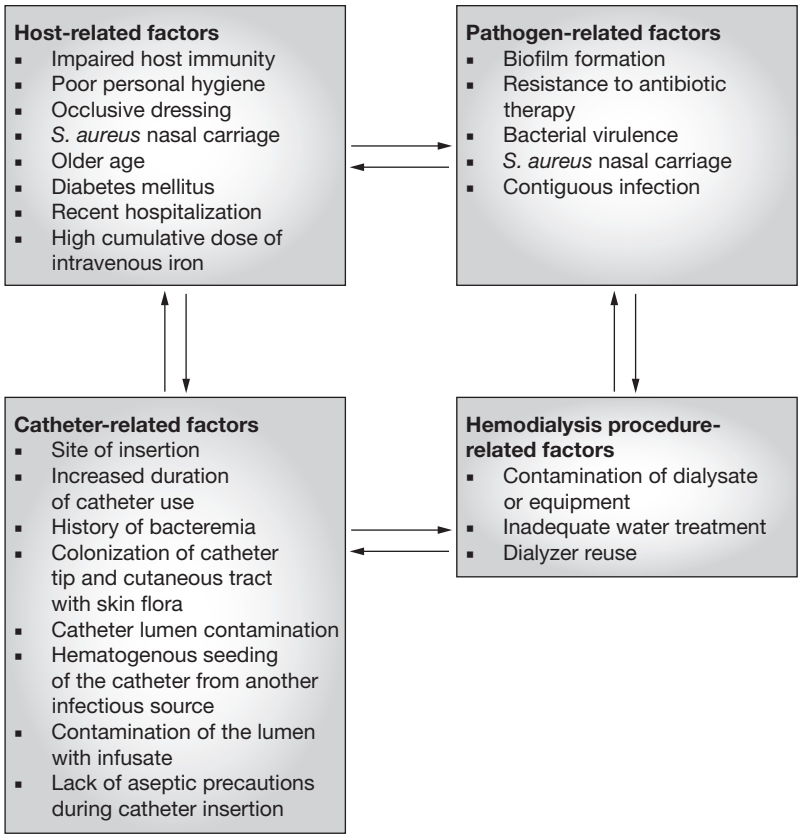


**Figure 1** Relationships between factors associated with hemodialysis central venous catheter-related blood stream infections.

of the catheter and biofilm formation, could also have a role in development of bacteremia.[16] Passerini *et al.* detected biofilms in 100% of CVCs removed from 26 intensive care unit patients; bacteria were present in the biofilms of 88% of CVCs.[17] Reports of local risk factors, such as poor personal hygiene, occlusive transparent dressing, moisture around the exit site, *S. aureus* nasal colonization and contiguous infection, support the role of bacterial colonization in the pathogenesis of CRBSI.[6,18–21]

The site of catheter insertion, duration of catheter use and previous bacteremia all affect the likelihood of dialysis CRBSI.[6,18,22–25] In a prospective observational study of 129 tunneled, dual-lumen hemodialysis catheters, bacteremic catheters were more frequently observed in patients with *S. aureus* nasal carriage, previous bacteremia, and longer catheter survival time.[23] The incidence of CRBSI and exit-site infection associated with tunneled cuffed catheters was significantly lower at 2 weeks compared with nontunneled catheters (2.9 vs 12.8 episodes per 1,000 catheter-days; $P<0.001$).[25] The incidence of CRBSI associated with nontunneled catheters was highest for femoral catheters, followed by internal jugular catheters then subclavian catheters (7.6, 5.6, and 0.7 episodes per 1,000 catheter-days, respectively).[25] It should be noted that the lower risk of infection with subclavian catheters might not apply to tunneled catheters, and that the subclavian location is associated with the highest rate of future catheter-associated central venous stenosis.[18,20] Furthermore, although the duration of primary catheter patency was substantially shorter for tunneled femoral catheters compared with tunneled internal jugular catheters, infection-free survival was similar in both groups.[26]

Other risk factors for dialysis CRBSI include older age,[4] higher total intravenous iron dose,[23,27] increased recombinant human erythropoietin dose,[25] lower hemoglobin level,[22,27] lower serum albumin level[4,28] diabetes mellitus,[3,18] peripheral atherosclerosis,[23] and recent hospitalization or surgery.[28] Although increased risk of CRBSI in immunosuppressed patients has been reported,[8,10] higher rates of CRBSI were not found among HIV-infected patients.[29]

Neither the association of urea reduction ratio with infection[28] nor the 9% lower relative risk of infection-related death for each 0.1-unit increase in single pool *Kt/V* reported by Bloembergen *et al.*[30] was confirmed by the HEMO study[8]—nor was an association found between infection-related death and dialysis membrane flux.[8]

## Microbiological organisms responsible for CRBSIs

The organisms responsible for dialysis-related CRBSI are Gram-positive in two-thirds of cases, predominantly *S. epidermidis* and *S. aureus* (Table 1).[11,16,18,22,31] Other causative bacterial agents are enterococci and Gram-negative rods.[16,18] An observational study of 114 episodes of hemodialysis CRBSI revealed that 70.7% were associated with a Gram-positive organism only, 17.9% with a Gram-negative organism only, 9.8% with both Gram-positive and Gram-negative organisms, and 1.6% with an acid-fast organism.[16] Bolan *et al.* reported an outbreak of CRBSI during which 27 of 140 hemodialysis patients from a single center in Louisiana were infected with rapidly growing mycobacteria; of 26 identified isolates, 25 were *Mycobacterium chelonei* ssp. abscesses and one was an *M. chelonei*-like organism. The water

treatment system used to process dialyzers was contaminated with nontuberculous mycobacteria.[32] Summers *et al.* reported one case of *Mycobacterium tuberculosis* causing an exit-site infection.[33] Although cases of mycobacteria and fungal isolates causing CRBSI are rare, these should be considered as possible etiologic agents in patients with risk factors that might predispose them to such infections.

The majority of the Gram-positive organisms responsible for CRBSI are cocci, including *S. epidermidis*, *S. aureus* and *Enterococcus faecalis*; there have been a few cases of infection with *Corynebacterium* species. Causative Gram-negative organisms have included *Enterobacter cloacae*, *Pseudomonas*, *Acinetobacter baumanii*, *Citrobacter* and *Serratia* species, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Escherichia coli*. Observational data indicate that HIV-infected patients treated with hemodialysis might be at increased risk of CRBSI caused by Gram-negative rods and fungi.[29]

The prevalence of *S. aureus* nasal carriage in patients on hemodialysis is 35–62%,[15] a factor that might predispose these patients to *S. aureus* bacteremia.[21,23] Zimakoff *et al.* found that CRBSI with *S. aureus* occurred most often in patients who had nasal colonization; in more than 50% of infected patients, the same strain of *S. aureus* was detected in nose (or skin) and catheter.[20,21] In hemodialysis patients with CRBSI, *S. aureus* is an independent risk factor for both infectious complications and failure of bacteremia treatment.[34] A single-center, retrospective study performed in Denmark found that, compared with patients not on dialysis, those on dialysis (379 hemodialysis and 31 peritoneal dialysis patients) were four times more likely to die from *S. aureus* CRBSI (5.3% vs 1.3%; $P<0.001$).[35]

**Table 1** Organisms responsible for hemodialysis central venous catheter-related bloodstream infections.

| Organism | Percentage reported* |
|---|---|
| Gram-positive cocci | 52–85% |
| *Staphylococcus aureus* | 22–60% |
| *Staphylococcus epidermidis* | 9–13% |
| Meticillin-resistant *Staphylococcus aureus* | 6–29% |
| *Enterococcus faecalis* | 2–18% |
| Gram-negative bacilli | 20–28% |
| *Pseudomonas aeruginosa* | 2–15% |
| *Enterobacter cloacae* | 9% |
| *Escherichia coli* | 10% |
| *Acinetobacter* species | 13% |
| *Serratia marcesens* | 1–2% |
| *Klebsiella pneumoniae* | 6% |
| Polymicrobial | 16–20% |
| Acid-fast organisms | Rare |
| Fungi | Rarely reported |

*Percentages do not add up to 100% because data are drawn from different sources.

## CLINICAL PRESENTATION AND DIAGNOSIS OF CRBSIs

The diagnosis of CRBSI is often suspected clinically in a hemodialysis patient using a CVC who presents with fever or chills, unexplained hypotension and no other localizing signs.[3,18] Mild symptoms include malaise and nausea, in the setting of a normal catheter exit site or tunnel, on physical exam. More-severe symptoms include high fever with rigors, hypotension, vomiting and changes in mental status.[16] Older and more-immunocompromised patients might present with low-grade fever, hypothermia, lethargy, hypoglycemia, or diabetic ketoacidosis.[18] Although positive blood cultures can confirm a diagnosis of CRBSI, the source of bacteremia might not be the CVC in all patients. For example, potential sources of bacteremia in hospitalized patients can include pneumonia or a CVC other than the one used for hemodialysis.

A definitive diagnosis can be made when blood cultures drawn through both the CVC and a peripheral vein grow the same organism[3] (refer to Box 2 for Centers for Disease Control definitions of CRBSI). Positive cultures from the CVC alone might be indicative of colonization and, therefore, should be interpreted with caution and perhaps confirmed with supportive evidence of active infection such as clinical symptoms of fever and chills, or isolation of the same organism from blood cultures drawn from the periphery. In a retrospective cohort of hospitalized patients with cancer who had paired cultures drawn through both a peripheral vein and the CVC, the positive predictive value for determination of true fungemia or bacteremia was 63% (95% CI 50–75%) for CVC cultures versus 73% (95% CI 60–86%) for peripheral vein cultures.[36] Negative predictive values were, however, high for both routes (99% and 98%, respectively), which led the authors

**Box 2** Centers for Disease Control definitions for central venous catheter-related blood stream infections.[68]

**Catheter exit-site infection**
A positive semi-quantitative culture of the drainage material in the presence of redness, crusting, and exudates at the catheter exit site.

**Catheter colonization**
In the absence of clinical signs of infection at the catheter exit site, <10 CFU (colony forming units) on quantitative cultures (vortex method) or <15 CFU on semi-quantitative cultures (roll-plate technique).

**Catheter-related blood stream infection**
The isolation of the same organism from a quantitative culture of the distal segment of the catheter and from the blood of a patient with clinical symptoms of sepsis in the absence of any other noticeable source of infection.

to conclude that negative cultures from blood drawn through a CVC might be an acceptable criterion for ruling out CRBSI.[36]

Collignon *et al.* analyzed the predictive values of semi-quantitative culturing of catheter tips as an index for CRBSI in critically ill patients, and found that, when the presence of five or more colonies per plate was taken as a positive result, the sensitivity of the method was 92% and the specificity 83%.[37] Although the negative predictive value was very high at 99.8%, the positive predictive value was low (8.8%) in the sample studied, in which there was a low incidence of bacteremia (2%).[37] Differential quantitative blood cultures have been reported to be valuable in the diagnosis of CRBSI. A colony count fourfold higher in blood drawn through the catheter than in blood drawn from a peripheral vein yielded a sensitivity of 94%, a specificity of 100%, and a positive predictive value of 100%.[38] Of course, in the clinical setting of the outpatient hemodialysis unit, obtaining peripheral cultures might be challenging in patients with severe peripheral vascular disease and a history of multiple failed vascular accesses. In such a setting, a clinical diagnosis can be made after exclusion of alternative sources of infection.[3]

CRBSI can be complicated by catheter exit-site or tunnel infection. Exit-site infection is indicated by the presence of erythema, swelling, tenderness and purulent drainage around the catheter exit and the part of the tunnel external to the cuff[16] (Box 2). Symptoms of tunnel infection are swelling, erythema, fluctuance and tenderness over the catheter tunnel central to the cuff.[16]

Severe sepsis and metastatic infectious complications, such as infective endocarditis, septic arthritis, osteomyelitis, spinal epidural abscess and septic emboli, can prolong the course of CRBSI,[9–12] and should be considered in patients who do not respond appropriately to treatment. Infective endocarditis should be suspected in those patients with onset of new cardiac murmur, repeatedly positive blood cultures, and other features of the modified Duke criteria. These patients should be evaluated with transthoracic and/or transesophageal echocardiography.[39]

## EVIDENCE-BASED MANAGEMENT OF CRBSIs

The selection of appropriate antibiotics and the decision as to whether or not it is appropriate to remove the catheter are the two main issues in management of CRBSI (Figure 2). The latter decision is not easy in patients who have limited or no alternative sites for vascular access, especially in the setting of severe peripheral vascular disease. In such cases, catheter salvage has been attempted, in an effort to minimize the number of separate procedures, avoid insertion of temporary femoral catheters[11] and preserve future central venous access sites, as repeated catheter replacement can potentially lead to central venous stenosis.[40] Three major treatment modalities explored are administration of antibiotics while leaving the catheter in place (catheter salvage); administration of antibiotics plus catheter exchange over a guidewire; and prompt removal of the catheter followed by replacement after an interval. Administration of antibiotics via catheter-lock solutions has also been studied.

### Management of central venous catheters

No randomized controlled trials have compared the three strategies for catheter management in hemodialysis patients with CRBSI; available evidence is derived from retrospective analyses, case series, and prospective observational studies. Although catheter salvage with administration of intravenous antibiotics has been attempted with some success in a few studies, attempts at salvage are associated with significant risks of complications and high failure rates.[9,12] In a prospective observational study of 36 double-lumen CVCs, 11 patients experienced 13 episodes of CRBSI

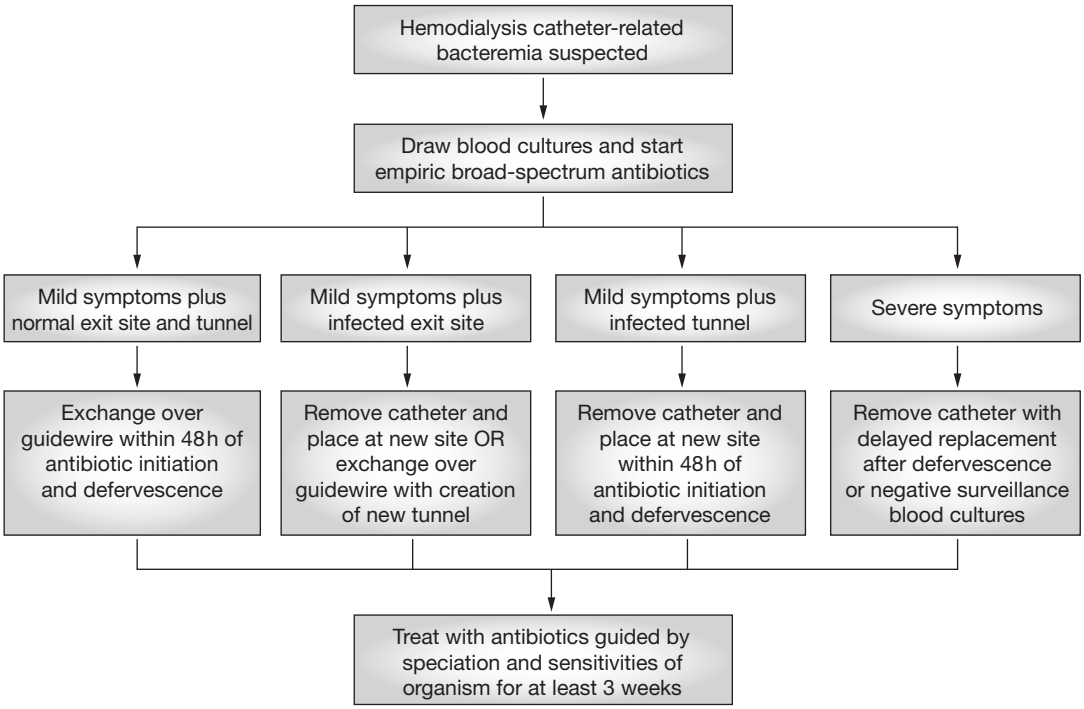


**Figure 2** Management of central venous hemodialysis catheter-related bacteremia.

and were successfully treated with antibiotics without catheter removal.[41] By contrast, in a larger prospective study of 102 hemodialysis patients, 40% of whom developed bacteremia, Marr *et al.* observed a 68% failure rate following attempted catheter salvage.[12] Salvage was less likely to succeed when the pathogen was a Gram-positive organism (as opposed to Gram-negative), but this difference was not statistically significant.[12] Although almost one-quarter of bacteremic patients had complications (all in patients infected with Gram-positive organisms), no complications were associated with attempted catheter salvage. The authors concluded that antibiotic therapy without catheter removal is unlikely to eradicate CRBSI, but attempted salvage might not increase the risk of complications.[12] Limitations of this study include the lack of a randomized control group and, perhaps, a lack of power to detect a statistically significant difference.

Instilling antibiotic lock solutions into both lumens of tunneled catheters, in order to eliminate biofilm without necessitating catheter removal, has had little success as a treatment option for CRBSI. Dialysis catheter locks of heparin plus vancomycin or cefazolin, and heparin plus gentamicin plus vancomycin or cefazolin in addition to systemic antibiotics, were studied prospectively in patients with clinically diagnosed CRBSI without persistent fever or hemodynamic instability.[10] Protocol success, defined as catheter salvage plus resolution of symptoms within 48 h of initiation of therapy and negative cultures 1 week after completion of the regimen, was reported in 64.5% of patients. If, however, catheter dysfunction was categorized as catheter failure, the treatment success rate was only 51%.[10] A subsequent study by the same group using a similar protocol reported a 70% catheter salvage success rate, but one-third of cases were excluded from analysis for reasons that included catheter malfunction and patient death.[42]

There is a larger body of evidence for successful management of CRBSI with catheter exchange over a guidewire in clinically stable patients in whom the tunnel is not infected; however, these data come primarily from observational studies. The reliability of these studies might be compromised by the lack of randomized control groups, indication biases, small patient numbers and inadequate durations of follow-up. A retrospective study compared two groups of patients with dialysis CRBSI treated with intravenous antibiotics for 3 weeks; one group

was treated with guidewire exchange, the other with removal of the infected catheter followed by replacement after 3–10 days.[11] The infection-free survival time associated with the subsequent catheter was similar in the two groups. It should be noted that patients who were more seriously ill—such as those with exit-site infection, those still febrile after 48 h of antibiotic administration, and those with severe sepsis—and patients in whom the catheter was not replaced within 10 days were excluded from analysis.[11] In addition, assignment to treatment groups occurred at the discretion of individual nephrologists and was largely directed by subjective impressions of symptom severity. This might have resulted in bias by indication.[11]

Shaffer reported initially successful management of dialysis CRBSI in 10 patients subjected to guidewire exchange, while preserving the same venous insertion site.[43] Three patients needed a second exchange in order to eliminate the infection.[43,44] Robinson *et al.* reported a series of 23 cases treated with catheter guidewire exchange plus 3 weeks of parenteral antibiotics.[40] Although no patient showed signs of tunnel tract infection and all defervesced within 48 h of initiation of antibiotic therapy, bacteremia had developed again in 18% of patients after 90 days of follow-up.[40]

Beathard reported a prospective observational series in which catheter management was based upon the clinical presentation.[16] Patients with minimal symptoms and a normal-appearing tunnel and exit site underwent catheter exchange over a guidewire within 48 h of antibiotic initiation ($n=49$); patients with minimal symptoms plus tunnel or exit-site infection underwent exchange over a guidewire with creation of a new tunnel ($n=28$). Catheters were removed from those with severe symptoms, and replaced after defervescence ($n=37$).[16] All patients were treated with a 3-week antibiotic regimen tailored on the basis of culture sensitivities. Cure rates, defined as a 45-day symptom-free interval after completion of antibiotics, were 87.8%, 75.0% and 86.5% in the exchange, new-tunnel, and delayed-replacement groups, respectively. A statistically significant difference was detected between the exchange and new-tunnel groups only ($P=0.025$). It should be noted that results were classified as indeterminate in 10 cases (9%).[16]

A decision-analysis model to assess the cost-effectiveness of strategies for management of tunneled cuffed catheters in clinically mild or asymptomatic bacteremia revealed that guidewire exchange (as compared with catheter salvage or immediate removal with delayed reinsertion) was the most cost-effective strategy when the probability of treatment failure (defined as recurrent bacteremia within 3 months) was less than 25%.[45]

### Choice of antibiotics

If CRBSI is suspected, blood cultures should be obtained and treatment with empirical antibiotics initiated promptly.[3,16,18] Pending the identification and speciation of cultures, initiation of intravenous vancomycin—which provides broad-spectrum coverage of Gram-positive organisms, including meticillin-resistant *S. aureus*—and an aminoglycoside or third-generation cephalosporin with broad-spectrum Gram-negative coverage is recommended.[46,47] The emergence of vancomycin-resistant enterococci has, however, led several authorities to question the liberal use of vancomycin. It has been recommended that use should be limited to patients with beta-lactam allergy or with serious infections with beta-lactam-resistant Gram-positive bacteria such as meticillin-resistant *S. aureus* or *S. epidermidis*.[46] Cefazolin, either alone or in combination with gentamicin, might be a suitable alternative to vancomycin.[46] As soon as culture sensitivity reports are available, the antibiotic regimen can be adjusted to limit unnecessary antibiotic exposure and the potential for development of resistant organisms.[3,18] As previously mentioned, most clinical trials have involved treating patients with 3 weeks of intravenous antibiotics.[11,16,40]

### Treatment failure

In a 2-year, prospective, multicenter observational study of 226 patients who were undergoing hemodialysis via tunneled cuffed catheters, treatment failure—defined as recurrent CRBSI with the same organism or death from sepsis—had occurred in 12% of patients at 3 months.[34] Infectious complications such as endocarditis, septic pulmonary emboli, osteomyelitis, infection of an arteriovenous graft, and abscess occurred in 7% of bacteremic episodes. In a multivariate analysis, both *S. aureus* infection (odds ratio 4.2, 95% CI 1.7–10.6) and catheter salvage (odds ratio 5.4, 95% CI 2.2–13.4) were significant predictors of treatment failure after adjustment for potential confounders including diabetes

mellitus, abnormal catheter exit site, hospitalization, hepatitis C infection and intravenous iron administration.[34] In addition, presence of an abnormal catheter exit site was associated with a significantly higher rate of death from sepsis.[34] Those patients with treatment failure resulting from CRBSI-related complications should have their CVCs removed.

### Prevention of CRBSIs

Many regimens for prevention of CRBSI have been studied. These range from the application of topical antibiotics to the use of different catheter-lock solutions. Topical agents applied to catheter exit sites have included povidone iodine, mupirocin, Polysporin® (Burroughs Wellcome & Co. [USA] Inc., Tuckahoe, NY) and antibacterial honey.[48–52] When compared with gauze dressing alone, application of 10% topical povidone iodine ointment reduced colonization of subclavian dialysis catheter tips and the number of episodes of bacteremia.[48] In a randomized controlled trial, application of 2% mupirocin after povidone iodine to the hemodialysis catheter exit site (vs povidone iodine alone) reduced the rates of *S. aureus* exit-site infection and catheter colonization, as well as the incidence of *S. aureus* bacteremia (0.35 vs 5.95 episodes of bacteremia per 1,000 patient-days; $P<0.001$).[49] In another open-label, randomized controlled trial, there were significantly fewer episodes of dialysis CRBSI in the mupirocin group (7 vs 35; $P<0.01$) and longer infection-free survival (108 vs 55 days; $P<0.01$) than in the group that received no ointment.[50] Studies of oral rifampin or nasal mupirocin ointment for eradication of nasal carriage of *S. aureus* in chronic hemodialysis patients have also reported a reduction in the incidence of *S. aureus* bacteremia.[53–55] Long-term follow-up is needed to establish whether prolonged use of such treatments selects for antibiotic-resistant strains. For example, emergence of high-level mupirocin-resistant *S. aureus* occurred after 4 years of prophylactic mupirocin application to the catheter exit site in 4 of 149 chronic peritoneal dialysis patients.[56]

In a multicenter, double-blinded, placebo-controlled, randomized trial, use of Polysporin® Triple Ointment resulted in fewer episodes of bacteremia per 1,000 catheter-days (0.63 in the treatment group vs 2.48 in the placebo group; $P<0.0004$) and a significantly longer time to first bacteremia episode occurring within the 6-month study period.[51] At baseline, the prevalences of nasal carriage of *S. aureus* and colonization of the exit site were similar in the treatment and placebo groups.[51] There was no statistically significant difference between the groups in the incidence of yeast-related infections, but the authors did acknowledge the potential risk of increased rates of yeast infection with chronic use of broad-spectrum antibiotics.[51]

Given the risk of selecting for resistant strains with chronic use of antibiotic ointments, an open-label, randomized controlled trial compared the use of topical exit-site Medihoney® (antibacterial honey; Medihoney Pty Ltd, Richlands, Queensland, Australia) with mupirocin in patients with tunneled cuffed hemodialysis catheters.[52] The incidences of CRBSI were comparable in the two groups, but the study was not adequately powered to assess therapeutic equivalence of these drugs.[52]

As *in vitro* studies using citrate lock and antibiotic lock solutions have demonstrated inhibition of staphylococcal biofilm formation,[57,58] several *in vivo* studies have evaluated antibiotic lock solutions for CRBSI prevention. A prospective case-control study that compared the efficacy of cefotaxime/heparin lock solutions (10 mg/ml cefotaxime, 5,000 U/ml heparin) with that of standard heparin lock solution (5,000 U/ml) in nontunneled catheters found a lower incidence of CRBSI in the group treated with the combination lock (1.65 vs 3.13 episodes per 1,000 catheter-days; $P=0.021$).[59] A randomized study of the combination of cefazolin 10 mg/ml, gentamicin 5 mg/ml and heparin lock versus heparin lock alone found a reduction in CRBSI rate per 1,000 catheter-days in the combination lock group (0.44 vs 3.22; $P=0.031$), as well as an increase in CRBSI-free catheter survival.[60] In a double-blind, randomized controlled study of 112 tunneled catheters, gentamicin/citrate lock solution (40 mg/ml gentamicin and 3.13% citrate; ratio 2:1) significantly decreased catheter-related infection rates (0.03 vs 0.42 per 100 catheter-days; $P=0.003$) relative to heparin-only lock.[61] Furthermore, the mean duration of infection-free catheter survival was increased in the gentamicin/citrate lock group (282 vs 181 days; $P=0.002$).[61] The median predialysis gentamicin level of 2.8 mg/l (range 0.6–3.5 mg/l) in this study, however, raises concerns regarding the risk of ototoxicity, loss of residual renal function, and bacterial resistance with prolonged use.[48] A lower infection rate

was also reported in a second, nonblinded, randomized study using lower concentrations of gentamicin (5 mg/ml).[47] Although all random gentamicin levels were less than 0.2 mg/l in this second study, the risk of adverse effects associated with chronic aminoglycoside exposure remains uncertain.

Given the potential for adverse effects and emergence of bacterial resistance following long-term antibiotic lock use, the efficacy of trisodium citrate 30% versus heparin lock for prevention of CRBSI was studied in a multicenter, double-blind study of 98 tunneled and 193 nontunneled dialysis catheters.[62] CRBSI rates were 1.1 per 1,000 catheter-days in the citrate group and 4.1 per 1,000 catheter-days in the heparin group ($P<0.001$).[62] There were significantly fewer major bleeding episodes in the citrate group; there was no difference in catheter thrombosis rate between groups. The mechanisms proposed by the authors by which citrate might reduce infection rate include an antimicrobial effect, and prevention of biofilm formation and colonization via chelation of calcium and magnesium by citrate.[62] No serious adverse events were reported, but nine patients in the citrate group and four in the control group experienced paresthesias or metallic taste, which could be attributable to temporary decreases in serum levels of ionized calcium and magnesium.[62] Although the antimicrobial efficacy of trisodium citrate as a catheter-locking solution has been demonstrated, in the absence of serious adverse reactions, there have been no long-term follow-up studies to confirm the safety of chronic use in patients with end-stage renal disease.

Efforts have been made to design novel catheters that have lower infection rates. A randomized controlled trial of intensive care patients showed that noncuffed CVCs impregnated with chlorhexidine gluconate and silver sulfadiazine had lower rates of colonization when removed and were less likely to be associated with CRBSI than control catheters (1.6 vs 7.6 episodes per 1,000 catheter-days; RR 0.21, 95% CI 0.03–0.95).[63] Use of silver-coated tunneled catheters, however, did not significantly affect colonization or catheter-related infection rates (compared with control tunneled catheters without silver coating) in a study of 91 randomly assigned patients on hemodialysis.[64] Ponikvar *et al.* studied 30 temporary, precurved jugular catheters with 4% citrate as locking solution and mupirocin ointment at the exit site as vascular access in hemodialysis patients; they observed two exit-site infections (0.2/1,000 catheter-days) and two cases of bacteremia (0.2/1,000 catheter-days).[65] Larger clinical trials are warranted to compare the efficacy and infection rate of temporary precurved jugular catheters with tunneled catheters.

Subcutaneous access devices designed to minimize CRBSI were studied in a multicenter, open-label, prospective phase I trial of patients randomized to either the LifeSite® Hemodialysis Access System (VascA Inc., Tewksbury, MA) for subcutaneous venous access or to the transcutaneous Tesio®-Cath (Medical Components Inc., Harleysville, PA) tunneled cuffed catheter.[66,67] In the initial phase I trial, 0.2% sodium oxychlorosene was used as the antimicrobial agent for the LifeSite® device.[66] This initial phase was followed by a nonrandomized phase II trial during which 70% isopropyl alcohol was used as the antimicrobial agent for the LifeSite® device.[66] There were no statistically significant differences in device-related infection rates between the Tesio®-Cath and oxychlorosene-impregnated LifeSite® groups. There were, by contrast, significant differences in infection rates per 1,000 device-use-days between the alcohol-treated LifeSite® group and the other two groups (1.3 for LifeSite® plus alcohol vs 3.3 for Tesio®-Cath and 3.4 for LifeSite® plus oxychlorosene; $P<0.05$ for both comparisons).[66] Device survival was also significantly better in the LifeSite® plus alcohol group. Further studies are required to establish the cost-effectiveness of the LifeSite® system given that it is more time-consuming to insert and remove, and also to access in the outpatient dialysis setting.[66]

## CONCLUSION

CRBSI is an important problem in patients undergoing hemodialysis, which puts them at increased risk of morbidity and mortality. Problems of clinical management are the salvage of vascular access for hemodialysis, and the treatment of bacterial infection to prevent further complications such as endocarditis. There have been no randomized controlled trials on which to base catheter management in the setting of bacteremia; evidence in the literature comes from retrospective analyses and prospective observational studies. On the basis of current evidence, for patients presenting with mild symptoms and no evidence of tunnel infection, exchange of the catheter over a guidewire can be considered. Most

studies of this technique report a failure rate of about 20%. More-frequent recurrence of infection and treatment failure has been reported with attempted salvage of the catheter. Strategies that aim to prevent CRBSI, ranging from the application of topical antibiotics to the use of different catheter-lock solutions, have been studied, but their long-term use might be associated with adverse events and the development of resistant infectious organisms. Local factors, such as the use of aseptic technique during catheter placement and the use of local antibiotics such as Polysporin®, are also important aspects of the management of these patients, although there are no conclusive evidence-based studies supporting these practices.

## KEY POINTS

- Central venous catheter-related blood stream infection (CRBSI)—most often with *Staphylococcus aureus* or *S. epidermis*—is a common complication and cause of death among maintenance hemodialysis patients
- Diagnosis of CRBSI is confirmed by isolation of the same microorganism from quantitative cultures of both the catheter and the peripheral blood of a patient that has clinical features of infection without any other apparent source
- Choice of antibiotics for initial empirical treatment of CRBSIs is a major management decision, as is determining whether catheter removal is appropriate
- Topical antibiotics and catheter-lock solutions are the primary means of preventing CRBSIs, but risk of antibiotic-resistant organism emergence should be considered

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