Prevention and management of catheter-related infection in hemodialysis patients

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Central venous catheter-related infections have been associated with high morbidity, mortality, and costs. Catheter use in chronic hemodialysis patients has been recognized as distinct from other patient populations who require central venous access, leading to recent adaptations in guidelines-recommended diagnosis for catheter-related bacteremia (CRB). This review will discuss the epidemiology and pathogenesis of hemodialysis CRB, in addition to a focus on interventions that have favorably affected CRB outcomes. These include: (1) the use of prophylactic topical antimicrobial ointments at the catheter exit site, (2) the use of prophylactic catheter locking solutions for the prevention of CRB, (3) strategies for management of the catheter in CRB, and (4) the use of vascular access managers and quality initiative programs.

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BACKGROUND

Vascular access is not only known as the obvious 'Achilles heel' of hemodialysis (HD) but it is also the quiet undercurrent of trends in patient outcomes. This is apparent when one follows the growth and impact of the central venous catheter (CVC) over two decades since its introduction as a 'permanent' access in the mid-1980s.[1–3] At present, the prevalent CVC use has increased to ~25% while >80% of patients initiate HD with a catheter.[4] When such large numbers are affected, trends in patient outcomes serve to highlight the catheter's associations with high morbidity and mortality. For example, the most recent USRDS (US Renal Data System) report observed high first- and second-month death rates after HD initiation, coincident with the increase in CVC placement rates.[5] A significant cause of CVC-related morbidity and mortality is infection. For example, rates of mortality from infection in the first year of HD are now 2.4 times greater than in 1981 and is largely attributed to CVC use.[5] Hospitalizations due to vascular access infections more than doubled between 1993 and 2005 in the United States[6] and mirror the marked increase in CVC use during the same period, suggesting that increased hospitalization may not be solely attributable to poor CVC care but due to increased CVC use itself. Catheter-related infections encompass exit site infections, tunnel infections, and bacteremias; however, bacteremias are the most clinically important because of their common occurrence and potential to transform into sepsis. The risk of sepsis with a CVC is twofold to fivefold higher than that with arteriovenous grafts and arteriovenous fistulae.[7] After an episode of sepsis, the rate of adverse cardiovascular events increases by up to twofold. These include myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebral vascular accident events.[8] Unquestionably, CVC-related infections and sepsis are associated with high morbidity and hospitalization rates, high treatment costs, and poor survival.[5,8–14] However, welcome relief has been observed in the USRDS 2009 data with a recent decline (2006–2007) in overall vascular access-related hospitalizations due to infection, but they are still approximately two times higher than a decade before.[5] The hopeful speculation for this improved trend is of a heightened awareness of the high risks associated with catheter-related

bacteremia (CRB) and the implementation of evidence-based preventative and management strategies along with other quality improvement measures. This paper will review the epidemiology and pathophysiology of CRB and emphasize evidence-based strategies to prevent and manage CRB.

EPIDEMIOLOGY

Diagnosis

Given the gravity of CRB in HD patients dialyzing with a catheter access, a precise diagnosis and definition of CRB would seem crucial. However, this seemingly basic requirement has been challenging because of the unique circumstances of HD patients, whereby the rigorous standard of requiring quantitative blood cultures and/or determining differential time to positivity from a peripheral vein and catheter blood culture cannot be obtained because of logistic or other reasons.[15] For example, the priority of preserving arm veins for future fistula creation, fragile and damaged vessels, and patient refusal render venipuncture impractical. The IDSA (Infectious Disease Society of America) has recently acknowledged these significant challenges, and provision has been made 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. Drainage at the CVC exit site should be cultured as the diagnosis of CRB is strengthened by a positive culture of the same organism at the exit site and in the blood. However, there is often no drainage at the exit site. Therefore, when there is an absence of drainage at the exit site and alternate sources of infection cannot be found, positive blood cultures obtained from an HD catheter should be considered a possible CRB in a symptomatic patient and treated as such, with initiation of antimicrobial therapy.[15] Although this is only considered a 'possible' CRB by precise IDSA standards, it is an appropriate definition of HD CRB. The CDC has recently provided definitions and tools for dialysis units for the reporting of dialysis vascular access infections as 'dialysis event/100 patient-months' for surveillance purposes.[16] However, reporting of CRB as event/1000 catheter days has been recognized as the most informative measure, and can be used for benchmarking, clinical monitoring, surveillance, and investigational studies, but requires appropriate resources for accuracy.[17] Tracking of CRB has been recognized as an important aspect of dialysis patient care[18–23] and has been recently recommended as a clinical performance measure by a CMS clinical technical expert panel as part of monitoring dialysis access-related infections (http://www.cms.gov/CPMProject/Downloads/ESRD2010TechnicalExpertPanelReport.pdf).

Rates, risk factors, and pathogens

The incidence of CRB ranges between 0.6 and 6.5 episodes per 1000 catheter days.[14,24–36] The majority of CRB-associated isolates are Gram-positive organisms (52–84%), with *Staphylococcus aureus* accounting for between 21 and 43% in most series, and methicillin-resistant *S. aureus* (MRSA) reported in approximately 12–38%.[14,24,25,27,37] Risk factors for CRB that have been identified include poor patient hygiene, previous CRB, recent hospitalization, longer duration of catheter use, inadequate dialysis, hypoalbuminemia, *S. aureus* nasal carriage, diabetes mellitus, immunocompromised status, atherosclerosis, and hypertension.[37–41]

Serious metastatic infectious complications occur in 3–44% of episodes, and include endocarditis, osteomyelitis, thrombophlebitis, septic arthritis, spinal epidural abscess, and large atrial thrombi[13,14,25,34,37,42–44] (Table 1). The incidence of infectious complications is higher when catheter salvage is attempted.[13,44] Epidural abscess and large atrial thrombi occur uncommonly, and are usually associated with *Staphylococcus* isolates and with

Table 1 | Metastatic complications of catheter-related bacteremia (CRB)

Complication	Frequency (%)	References
Endocarditis	3–17	Engemann *et al.*[9]; Mokrzycki *et al.*[13]; Tanriover *et al.*[14]; Saad[24]; Marr *et al.*[37]
Large atrial thrombi	Rare	Negulescu *et al.*[42]; Ghani *et al.*[45]; Kingdon *et al.*[138]; Shah *et al.*[139]
Spinal epidural abscess	Rare	Kovalik *et al.*[44]; Obrador and Levenson[46]; Philipneri *et al.*[47]
Septic pulmonary emboli	0.4	Mokrzycki *et al.*[13]
Septic emboli other organs (for example, the brain)	1–2	Engemann *et al.*[9]; Tanriover *et al.*[14]
Other abscess	1.5	Mokrzycki *et al.*[13]
Septic arthritis	2–5	Tanriover *et al.*[14]; Marr *et al.*[37]
Osteomyelitis	1.5–15	Engemann *et al.*[9]; Mokrzycki *et al.*[13]; Marr *et al.*[37]
Death	6–34	Marr *et al.*[10]; Mokrzycki *et al.*[13]; Lok *et al.*[27]; Lentino *et al.*[57]; Inrig *et al.*[58]; Lowy[140]

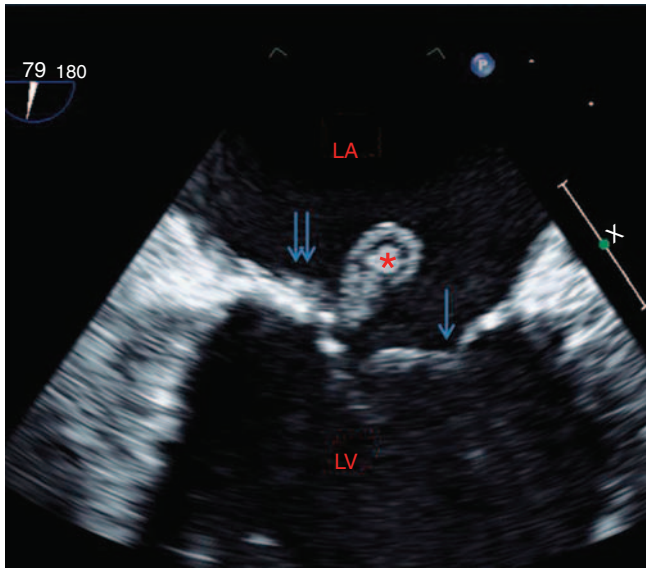

Figure 1 | Two-dimensional transesophageal echocardiogram image of the mitral valve (MV), anterior MV leaflet (↑), and posterior MV leaflet (↑↑) with a vegetation (*) attached by a stalk to the left atrial (LA) side of the posterior MV leaflet, near its tip. LV, left ventricle.

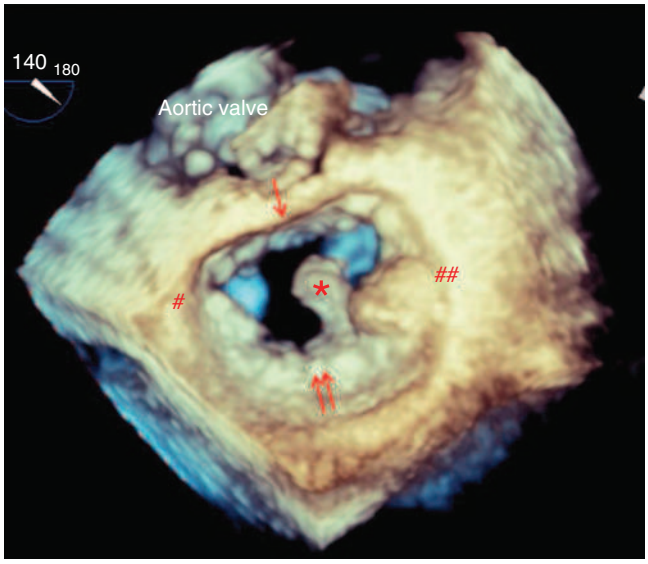

Figure 2 | Three-dimensional transesophageal echocardiogram image of the open mitral valve seen *en face* from the LA with the aortic valve at 12 o'clock ('surgeon's view'). A large vegetation (*) is seen attached to the (↑↑) posterior MV leaflet, (↑) anterior MV leaflet, (#) lateral, and (##) medial MV annulus after LA cropped. LA, left atrial; MV, mitral valve.

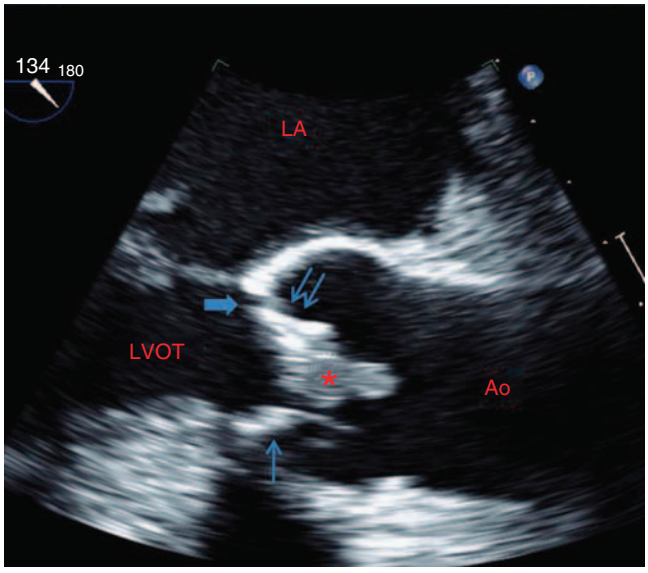

Figure 3 | Two-dimensional transesophageal echocardiogram image of the aortic valve in mid-systole with opening of the non-coronary cusp (↑↑) and the right coronary cusp (↑). A large vegetation (*) is attached to the aortic (Ao) side of the non-coronary cusp, with an associated perforation (thick arrow) of the cusp. LA, left atrial; LVOT, left ventricular outflow tract.

poor outcomes. These include severe neurological deficits, such as paresis and paralysis (50–72%) with epidural abscess, septic pulmonary emboli with large atrial thrombus (Figures 1–4), and high mortality rates (17–60%).[42,44–47]

The rate of *S. aureus* nasal carriage due to *S. aureus* in the HD population ranges between 11 and 57%, and is associated

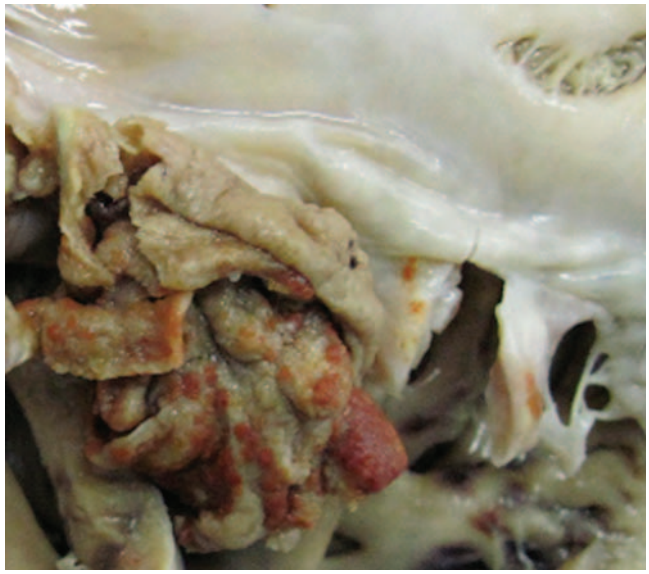

Figure 4 | Autopsy image of a large cardiac valvular vegetation.

with a threefold higher relative risk of developing *S. aureus*-related CRB.[27,28,48–55] *S. aureus* is a particularly lethal microbiologic isolate, and the annual incidence of *S. aureus* bacteremia in HD patients is between 6 and 27%.[54,56] *S. aureus* CRB is associated with a more than threefold higher rate of infectious complications, and a fourfold greater risk of recurrent bacteremia or septic death in 3 months, relative to other microbiologic isolates.[13] The mortality rate associated with *S. aureus* access infections has been reported to be as high as 30%.[9,57,58] In some HD units, up to one-third of CRBs are caused by MRSA, which has been demonstrated to be associated with greater costs and three to five times higher mortality compared with methicillin-sensitive strains.[59]

Gram-negative species are isolated in 27–36% of episodes and fungal isolates are less common ($\leqslant$10%).[13,25,34,37] *Pseudomonas/Stenotrophemonas* species account for 4–16% of CRB isolates in HD patients.[24,27,60] In contrast to the high mortality rates reported in *Pseudomonas* sepsis associated with visceral nosocomial infections (non-CRB), Golestaneh *et al.*[60] reported favorable outcomes and no deaths in 18 episodes of *Pseudomonas* HD CRB, likely due to catheter removal in 89% of cases. Multiple organisms may be present in 7–21% of CRB cases[27,34,43] and are particularly challenging to treat.[61]

PATHOGENESIS

There are two main routes by which organisms gain entry into the bloodstream to cause CRB: an extraluminal pathway and an intraluminal pathway.[62] The extraluminal pathway involves initial contact between skin surface organisms and the external surface of the catheter at the time of insertion or thereafter, before complete exit site healing and endothelialization of the subcutaneous tunnel (Figure 5). Consequently, organisms can colonize or migrate down the intercutaneous

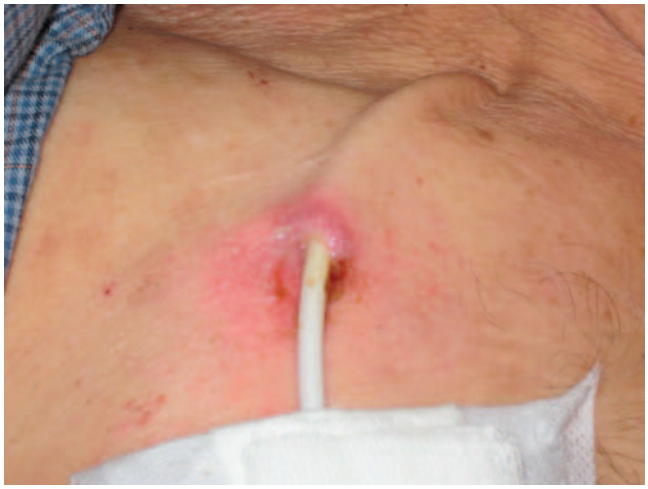

Figure 5 | Exit site infection. Erythema and purulent discharge is evident at the catheter exit site.

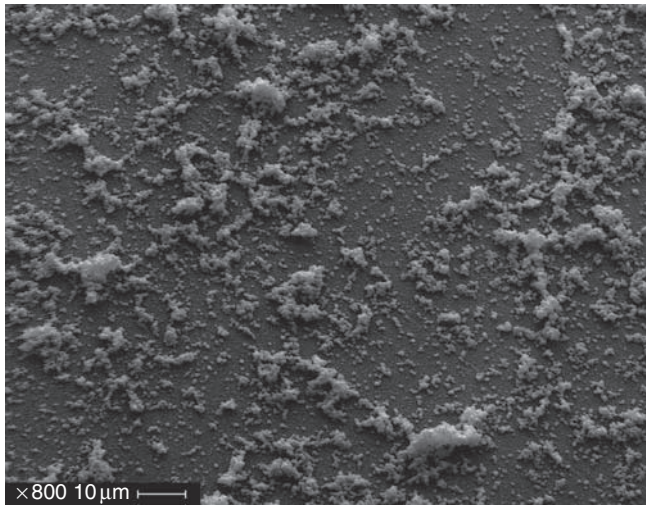

Figure 6 | *S. aureus* biofilm detected by scanning electron microscopy. Picture courtesy of Lavern M. Vercaigne, Faculty of Pharmacy, University of Manitoba. *S. aureus*, *Staphylococcus aureus*.

exterior tract of the catheter to the tip where hematogenous spread occurs with blood flow perturbation, exacerbated by dialysis, and leads to CRB. The intraluminal pathway involves transfer of organisms by contact from the hands of individuals (usually health-care workers) accessing the CVC or the patient's skin/surrounding clothing to catheter hubs or caps, resulting in the contamination of internal catheter surfaces. The extraluminal pathway tends to predominate early on after CVC insertion, whereas the potential for organism entry through the intraluminal route persists for the entire catheter lifespan. Regardless of the route, once entry is gained, the organism may adhere directly to the CVC surface or may become incorporated within a fibrin sheath; this sheath envelopes the CVC to variable extents and often develops within 24 h of CVC insertion.[63] The critical adherence of the organism to the catheter surface initiates the common pathway of biofilm production. A mature biofilm is a unique self-sustaining community of microorganisms protected by an exopolysaccharide matrix that is stimulated and secreted by the microorganisms.[64,65] It is noteworthy that close examination of catheters by scanning electron microscopy has demonstrated universal endoluminal coverage of material consistent with biofilm but without universal colonization by bacteria.[66] This is in contradiction to previous findings and teachings of universal CVC microbial colonization;[67] such a discrepancy is likely due to the ability of advanced technology to distinguish minute biological material from bacteria. This non-colonized biofilm-like material is distinctly different by the absence of microorganisms and should be termed simply as 'fibrin sheath' or 'adherent biological material'. Common microorganisms found in biofilms include *Staphylococcus*, *Candida*, *Pseudomonas*, and others[64,65] (Figure 6). The mature multilayered biofilm's exopolysaccharide shell may be 100-fold larger than the microorganisms that it protects,[68] and acts as a superresistant barrier to antibiotic penetration and action. Some mechanisms for antibiotic resistance include the ability of the glycomatrix to react with and neutralize the antimicrobial agent, in addition to providing an effective diffusion barrier to the antimicrobial agent and other multicellular strategies.[69,70] The dynamic characteristics of the biofilm facilitate sustained infection and subsequent hematogenous dissemination of the infecting organism. Clearly, the critical step in the management of CRB is the prevention of microorganism adherence to the catheter and biofilm development.

PREVENTION

Core prophylactic CRB measures begin with the routine CVC care performed by the HD staff at each dialysis session. Both the patient and the HD staff should follow universal precautions and hygienic measures. KDOQI (Kidney Disease Outcomes Quality Initiative) recommends that staff manipulating catheters should wear a mask and clean or sterile disposable gloves;[20] the data supporting masks are extrapolated from studies of their use during CVC insertion.[71,72] Acceptable exit site cleaning solutions are chlorhexidine 2% and alcohol 70% or povidone-iodine 10% solution;[20,73,74] comparative studies of these two antiseptics have been performed in various populations requiring CVC use. Randomized studies and meta-analysis demonstrate superior antisepsis with chlorhexidine,[75–80] whereas povidone-iodine and alcohol remain effective alternatives if chlorhexidine cannot be used. Recent data indicate that there is no significant difference between transparent, semi-permeable dressings, and standard gauze dressings with respect to catheter exit site colonization or CRB.[81–84]

The routine application of topical antibiotic ointments at the CVC exit site has been shown to be associated with a 75–93% reduction in the risk of CRB.[27,49–51] Topical ointments that have been studied include mupirocin, povidone-iodine, and polysporin triple antibiotic ointment.[85]

Medical-grade honey has antimicrobial effects against both resistant bacteria, protozoa, viruses, and fungi.[86] This is mediated by its high osmolarity, low water content, acidic pH(3.2–4.5), the generation of hydrogen peroxide upon its dilution, as well as its flavonoid and phenolic acid contents.[87] It has been shown to have equivalent efficacy as mupirocin for CRB prophylaxis.[28,29] Table 2 summarizes the details of six clinical trials using prophylactic topical agents in HD catheters.

Mupirocin nasal decolonization in HD patients has also been shown to reduce the rate of *S. aureus* bacteremia by 78%, and is cost effective, but may require repeat applications.[52,53,88,89] The reported risk of developing mupirocin resistance with short-term use is low; this includes a study treating HD patients with *S. aureus* nasal carriage.[52] High-level mupirocin resistance has been reported in 8–25% *S. aureus* isolates in peritoneal dialysis patients when used for long-term prophylaxis at the exit site. Mupirocin-resistant strains were isolated in 3–16% of the peritoneal dialysis population in these studies.[90–92] Despite its efficacy, mupirocin is not routinely used in the HD population because of concerns of emergence of resistance. In contrast, there are currently no reports in the literature of microbial resistance to other prophylactic agents applied to the exit site, such as povidone-iodine in dialysis patients. A 6-year prospective follow-up study using a polysporin triple ointment application at the exit site of HD catheters has not demonstrated microbial resistance or loss of efficacy for infection prophylaxis, with bacteremia rates consistently <1.0/1000 catheter days.[85] Microbial resistance to honey has never been reported, also rendering it a promising future topical agent for CRB prophylaxis.

There are 25 clinical trials evaluating prophylactic antimicrobial locking solutions (ALSs) for the reduction of CRB in HD patients and the results are summarized in Table 3. Detailed comparisons of prophylactic ALSs have

Table 2 | Summary of clinical trials using topical medicinal barriers at the exit site for prophylaxis of catheter-related bacteremia in hemodialysis patients

First author, year	Prophylactic agent	Comparator	*n*	Outcome	Bacteremia/1000 catheter days	Rate ratio (95% CI)	*P*-value
Levin, 1999[49]	Povidone-iodine (PI)	No ointment (N)	129	CRB	0.4 (PI) vs 4.6 (N)	0.07 (0.06–0.24)	<0.01
Sesso, 1998[50]	Mupirocin (M)	No ointment (N)	136	*S. aureus* CRB	0.71 (M) vs 8.92 (PI)	0.14 (0.03–0.63)	<0.001
Johnson, 2002[28]	Mupirocin (M)	No ointment (N)	50	CRB	1.6 (M) vs 10.5 (N)	0.15 (0.03–0.8)	<0.01
Lok, 2003[27]	Polysporin triple (PO)	Placebo (P)	169	CRB, death	0.63 (PO) vs 2.48 (P)	0.25 (0.19–0.34)	0.0004
					4% (PO) vs 16% (P)		0.0004
Johnson, 2005[29]	Medihoney (H)[a]	Mupirocin (M)[a]	101	CRB	0.97 (H) vs 0.85 (M)	0.94 (0.27–3.24)	0.92

Abbreviations: CI, confidence interval; CRB, catheter-related bacteremia; H, medihoney; HD, hemodialysis; M, mupirocin; N, no ointment; P, placebo; PI, povidone-iodine; PO, polysporin triple antibiotic; *S. aureus*, *Staphylococcus aureus*.
[a]Equivalent efficacy.

Table 3 | Summary of clinical trials using prophylactic antimicrobial lock (AML) for catheter-related bacteremia (CRB) associated with hemodialysis catheters (CVC)

First author, year	Subject number	Antimicrobial lock (AML)	Controls (C) (U/ml)	CRB rate AML vs C/1000 CVC days	*P*-value
Pervez, 2002[97]	36	Gentamicin 20 mg/ml+citrate 4.67%	Heparin 1000	0.62 vs 2.11	NA
Dogra, 2002[142]	83	Gentamicin 27 mg/ml+citrate 1%	Heparin 5000	0.3 vs 4.2	0.0003
McIntyre, 2004[143]	50	Gentamicin 5 mg/ml+heparin 5000 U/ml	Heparin 5000	0.3 vs 4	0.02
Nori, 2006[144]	30	Gentamicin 4 mg/ml+citrate 3.13%; or	Heparin 5000	0 vs 4	0.008
Venditto, 2010[109]	265	Gentamicin 2 mg/ml+heparin 5000 U/ml	Heparin 5000	0.4 vs 2.9	0.06
Onder, 2009[145]	43	Tobramycin 5 mg/dl+TPA 1 mg/ml	Heparin 5000	6.2 vs 16.8	0.2
Bleyer, 2005[146]	60	Minocycline 3 mg/ml+EDTA 30 mg/ml	Heparin (dose NA)	0 vs 0.47	0.35
	30	Minocycline 3 mg/ml+EDTA 30 mg/ml	Heparin 5000	0.4 vs 4	0.02
Saxena, 2005[147]	96	Cefotaxime 10 mg/ml+heparin 5000 U/ml	Heparin 5000	1.65 vs 3.13	NA
Saxena, 2006[148]	113	Cefotaxime 10 mg/ml+heparin 5000 U/ml	Heparin 5000	1.44 vs 3.15	<0.001
Al-Hwiesh, 2007[149]	63	Vancomycin 25 mg/ml+gentamicin 40 mg/ml+heparin 5000 U/ml	Heparin 5000	4.54 vs 13.11	0.05
Kim, 2006[150]	120	Cefazolin 10 mg/ml+gentamicin 5 mg/ml+heparin 1000 U/ml	Heparin 1000	0.44 vs 3.12	0.031
Allon, 2003[35]	50	Taurolidine 1.35%+citrate 4%	Heparin 5000	0.6 vs 5.9	<0.001
Betjes, 2004[108]	58	Taurolidine 1.35%+citrate 4%	Heparin 5000	0 vs 2.1	0.047
Solomon, 2010[33]	110	Taurolidine 1.35%+citrate 4%	Heparin 5000	1.4 vs 2.4	0.1
Weijmer, 2005[30]	291	Trisodium citrate 30%	Heparin 5000	1.1 vs 4.1	<0.001
Winnett, 2008[110]	413	Trisodium citrate 46.7%	Heparin 5000	0.81 vs 2.13	<0.001
Power, 2009[31]	232	Trisodium citrate 46.7%	Heparin 5000	0.7 vs 0.7	0.9
Venditto, 2010[109]	265	Trisodium citrate 46%	Heparin 5000	3.4 vs 2.9	NS

Abbreviations: CRB, catheter-related bacteremia; CVC, central venous catheter; EDTA, ethylenediaminetetraacetic acid; NA, not available; NS, non-significant; TPA, tissue plasminogen activator.

been published in several recent meta-analyses and reviews.[93–96] A marked reduction in CRB is associated with the use of ALS (range: 51–99%). In a recent systematic review of 9 randomized controlled trials, the CRB baseline risk was 3.0/1000 CVC days; the benefit of ALS corresponded to a number needed to treat of 3 patients to prevent 1 CRB with an average CVC insertion time of 146 days (range: 37–365).[96] However, analysis of studies does reveal the potential presence of publication bias, whereby studies with less beneficial effect and larger sample sizes are less likely to be published. Furthermore, caution is required because of the potential threat of antibiotic resistance with prolonged ALS prophylaxis. Although in previous trials of ALS, only one case of gentamicin resistance has been reported, there has been a recent report of emergence of gentamicin-resistant Gram-positive organisms with long-term prophylactic use of gentamicin locks in HD catheters.[97,98] In a study by Landry *et al.*,[98] gentamicin–heparin ALS was associated with 29 cases of gentamicin-resistant Gram-positive bacteremia, required a relatively long period of time (mean 25 days) before blood cultures cleared, and were associated with a 21% mortality rate in 2 months.

The use of non-antibiotic locks would be a desirable solution to address the problem of antibiotic resistance. Solutions demonstrated to effectively eradicate biofilm include EDTA (ethylenediaminetetraacetic acid), trisodium citrate at concentrations $>0.5\%$, taurolidine, and ethanol. They have been demonstrated to effectively reduce biofilm by a number of mechanisms, including the chelation of metallic cations (namely Ca^{2+}, Mg^{2+}, and Fe^{3+}) required for biofilm development.[99–107] However, not all solutions have undergone clinical trials. Initial studies using a non-antibiotic ALS (taurolidine 1.35%-citrate 4%) reported 90–99% reduction in the incidence of CRB, although a recently published trial found no difference in time to first CRB.[33,35,108] Furthermore, an increase in the utilization of thrombolytic therapy has been reported with taurolidine-citrate.[33,35] The data on CRB reduction with higher concentrations of trisodium citrate (between 30 and 46.7%) are conflicting. Initial studies reported a 62–75% risk reduction in CRB incidence using 30% citrate ALS; however, 2 recently published clinical trials report no benefit of using 46.7% citrate ALS.[30,31,109,110] In 2000, the US FDA (Food and Drug Administration) issued a warning against the use of high-dose citrate lock because of a reported death associated with 46.7% citrate with excessive overfill,[111] which led to a manufacturer's recall of this product. Recently, hypertonic citrate (43%) solutions have been associated with symptomatic pulmonary and cerebral embolisms, likely due to seepage from multiple side holes and exacerbated by the solution's hyperosmolarity.[112] Clearly, caution must be exercised when using high-concentration citrate lock. However, other novel antimicrobial locks have demonstrated the ability to reduce biofilm;[101,103,113] preliminary clinical trial safety and efficacy data seem promising and final results are expected in the near future.

Intraluminal surface modification is another strategy to limit or eradicate biofilm and prevent CRB. Inherent intraluminal irregularities can promote lodgment of organisms into the catheter surface and also promote biofilm formation.[114,115] A recent randomized cross-over study has demonstrated that a surface-modifying additive limited catheter surface breakdown, improved surface irregularity, and reduced bacterial growth compared with catheters without surface modification.[116] Alternatively, impregnating catheters with antiseptic or antimicrobial agents such as chlorhexidine, silver sulfadiazine, and minocycline/rifampin has demonstrated reductions in microbial colonization and CRB in non-dialysis patients,[117–120] but their short activity may not be generalizable to the chronic CVC use required in HD patients. No benefit was observed in a randomized study of 91 HD patients who received dialysis through silver-treated catheters.[121] Other agents, not typically known for their antimicrobial properties, may hold promise. Bismuth has been demonstrated to have antibiofilm and antibiotic properties;[122,123] a single randomized clinical trial of bismuth-coated temporary non-tunneled HD catheters in 77 patients showed a reduction in catheter colonization compared with non-coated catheters.[124] Further studies with clinical outcomes using long-term tunneled catheters coated with bismuth will be elucidating. Finally, although heparin is traditionally used as an anticoagulant, two clinical studies of heparin-coated catheters have been associated with low rates of CRB but did not improve overall CVC patency.[125,126] This is somewhat surprising as heparin has been demonstrated to enhance *S. aureus* biofilm formation on CVC surfaces.[99] However, the overriding anticoagulant properties of heparin might inhibit thrombus and fibrin sheath formation, limiting the nidus upon which a biofilm forms. This highlights the importance of the microorganism's potential contact surface and catheter surface modification as a promising area of future research.

TREATMENT OF CRB

Antibiotic therapy

Initial empiric antibiotic therapy usually includes a broad-spectrum coverage for both Gram-positive and Gram-negative organisms. Owing to the high prevalence of MRSA in the HD setting, empiric therapy should include coverage for MRSA. Vancomycin or teicoplanin may be used. Published vancomycin protocols[127–129] may be adopted to encourage safe and effective administration. However, when the minimum inhibitory concentration for vancomycin exceeds 2 μm/ml, alternative antibiotics, such as daptomycin, should be used.[15,130] Patients found to have methicillin-sensitive *S. aureus* should be changed to cefazolin if there is no allergic contraindication.[15,131] Empiric Gram-negative coverage should be based on local antibiotic sensitivities.[15] Subsequent antibiotics are prescribed according to the identification and sensitivities of the isolate. When the organism is susceptible to more than one antibiotic, preference should be given to antibiotics with a pharmaco-

kinetic profile that allows for administration at the end of dialysis to improve patient compliance and treatment efficacy. Examples of such antibiotics include vancomycin, cefazolin, ceftazidime, and daptomycin. Furthermore, the presence of residual renal function should be considered when determining the choice, dose, and frequency of antibiotics. For example, aminoglycosides should be avoided in Gram-negative bacteremia if a patient has residual renal function and is sensitive to third-generation cephalosporins. The newly published IDSA guidelines for long-term catheter-related infections recommend 4–6 weeks of antimicrobial therapy for uncomplicated *S. aureus* CRB, 7–14 days for CRB with Gram-negative bacilli or enterococcus, and a minimum of 14 days for CRB with *Candida* species. Complicated CRB characterized by the presence of septic thrombophlebitis and/or endocarditis should be treated for 4–6 weeks, whereas osteomyelitis should be treated for a minimum of 6–8 weeks.[15]

Catheter management

Catheter removal with delayed CVC replacement is required in (1) clinically unstable patients, (2) when a persistent fever is present after 48 h, (3) when a tunnel infection is present, (4) or if a metastatic infectious complication is present. In clinically stable patients, in addition to systemic antibiotic therapy, the strategies for CVC management that have been studied include catheter salvage without antibiotic lock (SVG), catheter removal with delayed replacement (DR), catheter exchange over wire (CEX), or catheter salvage with antibiotic lock (ABL). The latter three strategies address the removal or eradication of microorganisms embedded in the catheter biofilm. When ABL is used for the treatment of CRB, concentrated antibiotic–anticoagulant solutions are instilled into the catheter lumen during the interdialytic period at concentrations 100-fold higher than the respective therapeutic plasma concentrations. In general, although CVC salvage has been attempted with some success, it is more often associated with high failure rates ($>65\%$) and should be avoided.[37,44,132,133] Catheter salvage is the most costly way of managing CRB, predicted to be associated with approximately twofold higher expected total costs.[134]

Studies reporting the outcomes of catheter management strategies are summarized in Tables 4 and 5. A comparison of outcomes reported by individual studies is difficult because of the fact that most are prospective, uncontrolled studies in which catheter management decisions were not based on the same clinical criteria, and because of differences in both study methodology and the definitions of treatment failure. Blood cultures should be obtained even after completion of an antibiotic course in those patients in whom there is suspected persistent infection. If these blood cultures are positive, the catheter should be removed and a new tunneled catheter be placed only after additional negative blood cultures are obtained.

Vascular access teams

The use of a designated vascular access nurse (VAN) manager in conjunction with evidence-based guidelines to assist

Table 4 | Studies evaluating catheter management for the treatment of catheter-related bacteremia in hemodialysis patients

First author, year	Study design	*n*	Catheter management	Treatment	Definition of success	% Success	Comment
Capdevila, 1993[133]	R	13	Salvage	Salvage	Afebrile in 48 h, infection-free catheter survival	100% (Salvage)	Only 15% of isolates were *S. aureus*
Marr, 1997[37]	P	62	Salvage	Salvage	Catheter still present after 90 days or removed for non-infectious etiology	32% (Salvage)	
Beathard, 1999[34]	P	77	Exchange vs removal with delayed replacement (DR)	CEX/existing tunnel (ET) (no tunnel or exit site infection) CEX/new tunnel (NT) (tunnel or exit site infection) DR	No recurrence of bacteremia in 45 days	87.8% (CEX/ET) 75% (CEX/NT) 86.5% (DR)	*P*=NS
Saad, 1999[24]	P	73	Salvage vs exchange	Salvage CEX	No recurrence of bacteremia, fever, or symptoms in 30 days	36.7% (Salvage) 81.4% (CEX)	*P*=0.0005
Tanriover, 2008[14]	R	69	Exchange vs delayed removal	CEX DR	Infection-free catheter survival in 30 days	~78% (CEX) ~80% (DR)	*P*=NS
Mokrzycki, 2006[135]	P	219	Salvage vs exchange vs delayed removal	Salvage CEX DR	No recurrence of bacteremia or death from sepsis in 90 days	74% (Salvage) 97% (CEX) 89% (DR)	*P*=0.002
Ashby, 2009[132]	P	208	Salvage vs delayed removal	Salvage DR	No recurrence of bacteremia or complication in 180 days	66.1% (Salvage) 91% (DR)	*P*<0.001

Abbreviations: CEX, catheter exchange over wire; DR, delayed reinsertion of catheter; NS, non-significant; *S. aureus*, *Staphylococcus aureus*.

Table 5 | Studies evaluating antibiotic lock for the treatment of CRB in hemodialysis patients

First author, year	Study design	*n* analyzed	Catheter management	Treatment	Definition of success	% Success	Comments
Krishnasami, 2002[25]	P	62	ABL/heparin	ABL (gentamicin 1 g/ml or vancomycin 2.5 mg/ml or cefazolin 5 mg/ml)+ heparin (2500 U/ml)	Clinical cure: absence of fever/chills and hemodynamic stability by 48 h or posttreatment surveillance blood cultures negative	64.5%	Catheter survival similar to historical controls whose CVC was replaced, 64 vs 54 days; *P*=NS; candidemia excluded from study protocol
Poole, 2004[43]	P	47	ABL/heparin	ABL (vancomycin 2.5 mg/ml or cefazolin 5 mg/ml or ceftazidime 5 mg/ml)+ heparin (2500 U/ml)	Clinical cure: absence of fever and hemodynamic stability by 48 h or posttreatment surveillance blood cultures negative	All patients: 70% GN: 87% *S. epi*: 75% *S. aureus*: 40%	Infection-free catheter survival better than historical controls whose CVC was replaced, 154 vs 71 days; *P*=0.02 (enterococcus and *Candida* excluded from the protocol)
Onder, 2008[61]	R	76	ABL/TPA	TPA (2 mg/2 ml)+ABL (vancomycin 5 mg/ml or tobramycin 5 mg/ml)	Successful CRB clearance at 2 weeks	83% Short-term success	Worse outcomes with polymicrobial CRBs
					Infection-free survival at 6 weeks	75% Long-term success	
Onder, 2008[26]	RCT	24	ABL/TPA vs ABL/heparin	TPA (2 mg/2 ml) vs heparin (5000 U/ml)+ ABL (vancomycin 5 mg/ml or tobramycin 5 mg/ml)	Successful CRB clearance at 2 weeks (short-term success)	100% Short-term success	Fungal infections excluded
					Days infection-free catheter survival (long-term success)	ABL/TPA: 126 days vs ABL/heparin: 154 days (*P*=NS)	Equivalent outcomes; 6/24 (25%) had recurrence of symptoms within 6 weeks
Beigi 2010[151]	P	67	ABL	ABL (vancomycin 5 mg/ml)	Catheter removal (failure)	96%	Heparin was not used as the anticoagulant; whether citrate or other used was unspecified

Abbreviations: ABL, antibiotic lock; CRB, catheter-related bacteremia; CVC, central venous catheter; GN, Gram-negative organism; NS, non-significant; *S. epi*, *Staphylococcus epidermidis*; *S. aureus*, *Staphylococcus aureus*; TPA, tissue plasminogen activator.

physicians in the management of CRB in the outpatient HD unit has been shown to reduce treatment failure rates and septic death, largely due to a reduction in CVC salvage. In an interventional controlled trial prospectively following 233 episodes of CRB, the addition of a designated VAN was associated with a significantly lower treatment failure rate (recurrent bacteremia with the same isolate in 3 months) compared with controls (VAN: 6% vs control 18%, $P = 0.015$).[135] The intervention was also associated with a significantly lower rate of death due to sepsis (VAN: 0 vs control 6%, $P < 0.02$). Similar results were reported by Shiell *et al.*[136] in a prospective cohort study of 158 patients with catheters, in which introduction of a multidisciplinary CVC care team was associated with a significant reduction in non-elective CVC removal (odds ratio = 0.59, confidence interval: 0.36–0.96, $P = 0.035$), largely attributable to reductions in CVC loss due to infection (65% decline).[12,58] The most effective intervention for reducing catheter-related infections is the complete avoidance of a CVC vascular access. Implementation of a VAN and an algorithm in the predialysis setting has been shown to be efficacious in increasing the use of arteriovenous fistulae as first vascular access upon HD initiation (34% increase, $P = 0.007$) and in reducing the total number of CVC days by 40%.[137]

COSTS

The economic impact of CRB is considerable. In contrast to arteriovenous fistulae, catheters are associated with 25% higher total costs, much of which are excess expenditures for the treatment of CRB.[5] Two centers reported data from the mid-1990 to 2001 and demonstrated that the mean cost of treating CRB in hospitalized HD patients was approximately $23,000–$24,000, including readmissions and outpatient costs over 12 weeks.[9,58] Although a recent retrospective study performed in 2005 reported similar costs,[12] it is important to note that in general, costs for vascular access infection have been on the rise since the late 1990s and are currently 35% greater than in 1998.[5] Furthermore, *S. aureus* is associated with higher health-care costs, particularly when associated with a complication requiring hospital

admission ($\sim$\$32, 500),[12,58] or if due to MRSA.[59] The estimated expenditures for CRB treated in the outpatient setting would be expected to be considerably lower ($<$66% for hospital costs), between \$7000 and \$15,000 per episode.[9,134] Prevention of CRB and reduction in catheter use overall are paramount to cost containment of the health-care budget for HD.

CONCLUSIONS

Catheter-related bacteremia is a significant cause of poor health outcomes in infected HD patients; however, recent declines in catheter-related infectious morbidity suggest efficacy in evidence-based prophylactic and management strategies. Topical ointments act as a barrier to limit the extraluminal route of organism entry and have been proven to prevent CRB. Intraluminal strategies to prevent CRB include interdialytic ALSs that also have clinical trial-based proven efficacy. However, justified concerns regarding the emergence of antibiotic-resistant organisms have led to the development of novel antimicrobial lock solutions that are promising. The diagnosis of CRB is challenging and unique in the HD population. CRB surveillance and management can be effectively facilitated by multidisciplinary vascular access teams to further reduce CRB rates and complications, and use of catheters in HD patients.

DISCLOSURE

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