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Review Article

Prevention of hemodialysis catheter infections: Ointments, dressings, locks, and catheter hub devices

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Abstract

Tunneled central venous catheters used for the provision of hemodialysis are associated with excess morbidity and mortality. Catheter related exit site and blood stream infections are major risks of their use. Although catheter-avoidance is the best strategy to reduce infections and mortality in the hemodialysis population, the use of catheters remains unacceptably high.

In this review, the existing clinical practice guidelines for the prevention of hemodialysis catheter associated infections are outlined, and a comprehensive evidenced-based summary of interventions is provided. This includes details about the use of topical antimicrobial ointments and dressings, intranasal ointment application, prophylactic use of antibiotic and non-antibiotic catheter lock solutions, and catheter hub devices for the prevention of catheter blood stream infections.

Keywords: Bacteremia, catheter, hemodialysis, infection, vascular access

CATHETER ACCESS RATES FOR PATIENTS ON HEMODIALYSIS AND THE RISKS ASSOCIATED WITH CATHETER USE

Tunneled hemodialysis catheters (TCs) have made it possible for efficient access placement in patients who need dialysis on an urgent/emergent basis and as a bridge until a functioning arteriovenous access is available. In 2004, the fistula-first breakthrough initiative (FFBI) set for an ambitious mandate to reduce the rate of TCs and to increase arteriovenous fistula (AVF) placement to 65% by 2009, and, currently, the prevalent AVF use has surpassed this goal (66%).[1,2] The challenge of this mandate was the creation of functional AVFs that were mature and could be successfully cannulated at the start of dialysis.[3] However, in 2016, the USRDS reported that 33.8% of AVFs were unable to be used at initiation of dialysis due to either surgical or maturation failure.[2] The major unintended outcome of the FFBI has been that approximately 80% of patients still initiate hemodialysis with a TC, and TC use remains unacceptably high at 90 days (68.5%) and 1 year (18%) after HD initiation.[2]

Unfortunately, TCs are associated with significant morbidity and mortality in hemodialysis patients.[4] Hospitalization rates for patients with TCs are more than twofold higher than those in patients with AVFs, (15.7 vs. 7.7 per 100 patient months), and vascular access associated blood stream infections (BSI) rates are eightfold higher, (4.2 vs. 0.5 per 100 patient months).[5–7] Furthermore, compared to patients using AVFs, patients using TCs have higher risks of all-cause mortality (RR = 1.53), fatal infections (RR 2.12), and cardiovascular events (RR 1.38).[6] These mortality rates are even greater in the first 120 days for patients who initiate hemodialysis with a TC compared to those with an AVF: Crude all-cause mortality rate (deaths/100 patient-years; OR = 2.97, 95% CI:2.17-4.06), cardiovascular causes (OR 1.84, 95% CI:1.17-2.89), and for infection-related causes 4.58 (95% CI: 2.00-10.52).[7,8]

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PREVENTION OF CATHETER-RELATED INFECTIONS

CDC clinical practice guidelines

Strategies to prevent CRBSI have targeted the pathophysiologic routes of entry of microorganism, the extraluminal (TC exit site) and intraluminal routes (TC hub). In 2011, the Centers for Disease Control (CDC) published guidelines on the prevention of infection in the dialysis setting.[9] Strategies to prevent CRBSI begin with staff and patient education and training on acceptable standard aseptic technique when accessing TCs, which includes hand hygiene, clean gloves, and masks. Prior to accessing the TC hub, it should be disinfected with an appropriate antiseptic agent, which may be either chlorhexidine >0.5% with alcohol, 70% alcohol, or 10% povidone-iodine solution.

Topical antimicrobial ointments and dressings

Figure 1 outlines various topical antimicrobial agents and devices which target the extraluminal route of entry, and have been studied for the prevention of CRBSI.

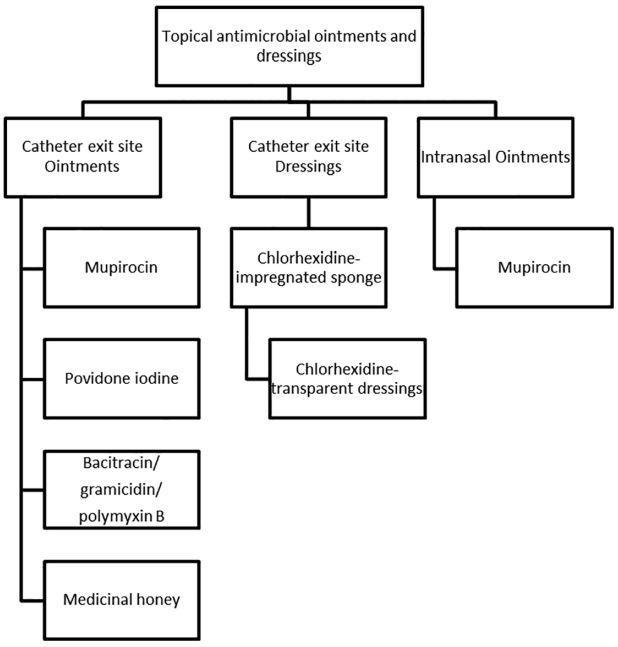

Figure 1 Topical antimicrobial ointments and dressings use for the prevention of infection in hemodialysis catheters.

Catheter exit site application

Application of a topical antibiotic ointment at the TC exit site is recommended at time of TC insertion and at each HD session. The CDC recommends using bacitracin/gramicidin/polymyxin B ointment or povidone iodine ointment.[9] These evidence-based recommendations are based on clinical trials which report a 75-93% reduction in CRBSI, however only bacitracin/gramicidin/polymyxin B ointment was associated with a significant reduction in mortality (4% vs. 16% placebo), and long-term follow up over 6 years was not associated with a change in microbiologic isolates over time.[10–12] Unfortunately, Bacitracin/gramicidin/polymyxin B ointment is not available in the United States, however triple antibiotic ointment (bacitracin/neomycin/polymyxin B) is, and may have similar benefit, but has not been adequately studied. Mupirocin has also been associated with an 85% reduction in CRBSI, however there is concern about emergence of resistant organisms with its routine use.[13,14] Medicinal honey has been shown to have similar rate of CRBSI to mupirocin in a single study, however it was underpowered to show equivalence.[15] The advantage of medicinal honey is that it has a low likelihood for selecting resistant strains and is effective against antibiotic-resistant microorganisms, however well designed and adequately powered studies are needed before it can be recommended for routine use.[15] It is important to be check catheter compatibility with ointments, as there are reports of polyurethane catheter materials being degraded with mupirocin and other agents. Stepwise instructions for the "scrub-the-hub" protocol, a catheter-ointment compatibility chart, and other invaluable educational resources are available on the CDC website.[9]

In the 2017 update to the 2011 CDC guidelines for the prevention of intravascular catheter related infections, chlorhexidine impregnated sponge dressings have been newly added as an alternative to ointments at the exit site for prophylactic use in short term, nontunneled catheters.[9] These data are derived from studies performed in hospitalized adult patients with short term, nontunneled catheters in an ICU setting in which there was a marked reduction in the CRBSI rate using chlorhexidine-impregnated dressings, (HR: 0.30, 95% CI: 0.10-0.92, P = 0.04).[16,17] There are two published studies in which chlorhexidine-based exit site applications were performed in patients using TCs for hemodialysis, however their the outcomes are conflicting.[18,19] The first study compared a chlorhexidine-impregnated sponge dressing vs. a transparent dressing (dressings were changed weekly in both groups), and found no difference in CRBSI in a small cross-over study.[18] In contrast, a significant reduction in

CRBSI was reported in a recent quality improvement project using chlorhexidine transparent dressings (changed weekly) vs. dry gauze dressings and antibiotic ointment (changed thrice weekly).[19] A well-powered, and well-designed study is needed to evaluate chlorhexidine-based exit site applications for use in hemodialysis TCs.

Intranasal Mupirocin application

Staphylococcus nasal carriage has been reported in 26% of hemodialysis patients.[20] Intranasal mupirocin decolonization significantly reduces the risk of *Staphylococcus aureus* bacteremia (78% reduction) in the hemodialysis setting. [21,22] Protocols of either weekly mupirocin for all hemodialysis patients or mupirocin therapy given every 3 months (only in hemodialysis patients with documented *S. aureus* nasal colonization) are cost effective and are estimated to potentially save up to 1 million dollars per 1000 hemodialysis patients annually.[23] Although intranasal mupirocin has been proven to be both efficacious and cost effective, it has not been widely utilized in the hemodialysis setting due to concerns about the emergence of mupirocin resistance, which have been largely reported in hospitalized patients and associated with prolonged use.[24] The limited use of intranasal mupirocin in hemodialysis patients using TCs for vascular access, particularly those with previous Staphylococcus TC associated infections, should be reevaluated.

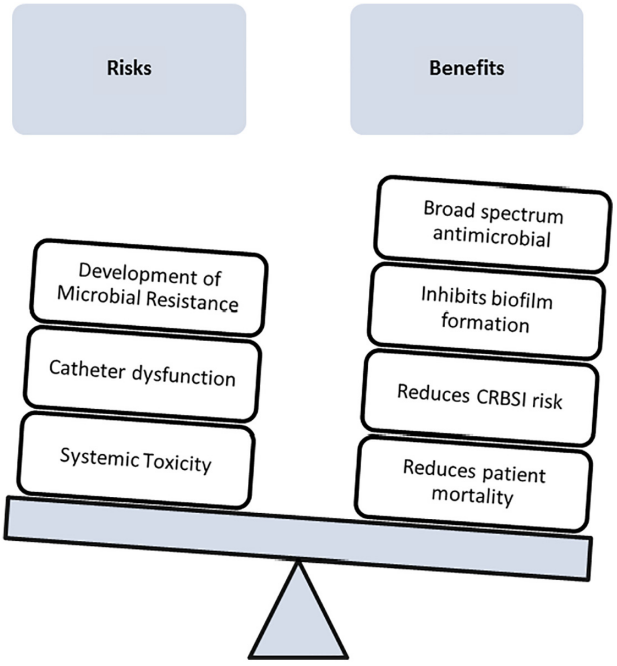

Figure 2 Characteristics of an ideal antimicrobial locking agent. [Color figure can be viewed at wileyonlinelibrary.com]

CATHETER LOCK SOLUTIONS USED FOR CRBSI PROPHYLAXIS

Antibiotic locks

Antimicrobial lock (AML) solutions are highly concentrated antiseptic/antibiotic or anticoagulant agents, which are used alone or in combination, and are instilled in the TC while the catheter is not in use. The goal is to prevent colonization and biofilm formation, for which an antimicrobial agent is needed. An anticoagulant is needed to prevent catheter dysfunction. Heparin promotes biofilm formation, whereas citrate in concentrations of >0.2% prevents biofilm formation.[25,26] The ideal AML would prevent CRBSI and reduce mortality, prevent biofilm formation, have a broad spectrum of activity, without increasing risk of TC dysfunction or causing selection for resistant organisms (Figure 2).

Figure 3 outlines the various antimicrobial catheter locking agents which target the intraluminal route of entry and have been studied for the prevention of CRBSI. The prophylactic use of combination antibiotic-anticoagulant AMLs is associated with a significant reduction in CRBSI 50% to 100%.[4,27,28] The antibiotics used in these trials were gentamicin, tobramycin, minocycline, cefotaxime, vancomycin, and cefazolin, with gentamicin most commonly studied. These early trials used high dose gentamicin (4-27 mg/mL), and reported that gentamicin alone was as effective as other antibiotic combinations, and had a broad spectrum of activity against both gram positive, including *S. aureus*, and gram negative bacteria in drug levels achieved in the catheter lumen.[27] The emergence of gentamicin resistant strains of Enterococcus, Staphylococcus (non-aureus and aureus) associated with serious CRBSI and one death has been reported has been reported using gentamicin AML (1-4 mg/mL).[29,30] In two more recent studies, both using a lower concentration of gentamicin AML (0.32 mg/mL) with 4% citrate, no gentamicin resistance was observed.[31,32] The first was a randomized controlled trial in 303 patients with a 7 year follow-up period.[31] The second was a prospective observational cohort study comparing different time periods (heparin lock vs. gentamicin/citrate lock) in 555 patients, which observed a decline in gentamicin resistance (0.40-0.22/1000 person-years, P = 0.01) in the antibiotic lock period over a 2 year period.[32] In this study, low dose gentamicin-citrate AML was associated with significant reduction in CRBSI (risk ratio 0.23; 95% CI, 0.13-0.38),

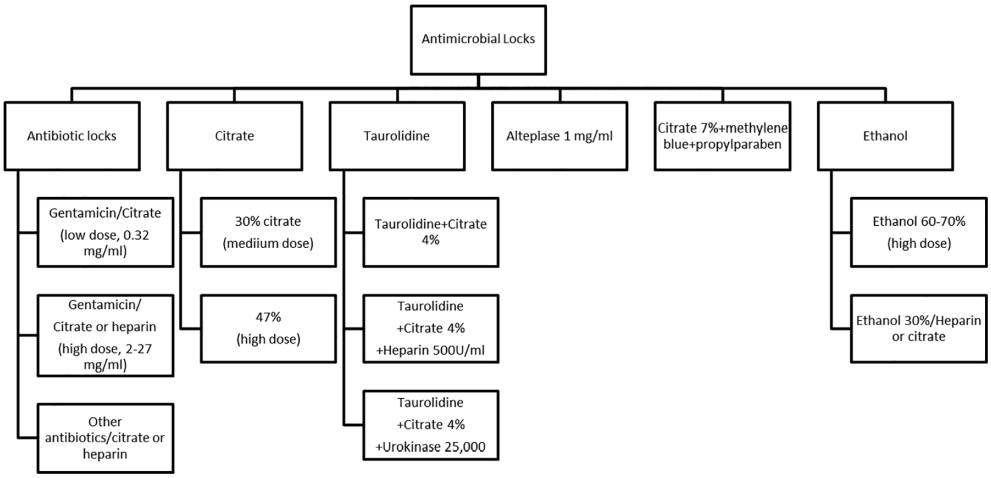

Figure 3 Antimicrobial locks used for the prevention of catheter associated blood stream infection in the hemodialysis catheters.

infection related hospitalization (1.36 vs. 0.96 per person-year, P = 0.001), and mortality (hazard ratio, 0.32; 95% confidence interval, 0.14-0.75). In addition, there was a substantial reduction in CRBSI-attributable inpatient costs reported with gentamicin AML use compared to heparin lock.

Nonantibiotic antimicrobial locks

In an attempt to avoid the development of antimicrobial resistance the search for a potentially "safer" nonantibiotic AML began. Trisodium Citrate (4%) lock, when used alone, is not associated with reduction in CRBSI rates compared to heparin catheter lock.[33,34] The data associated with medium and high dose trisodium citrate (TSC 30%-47%) AML are conflicting; two studies reported a reduction in CRBSI, and three studies reported no advantage of TSC over heparin.[35–39] TSC at these concentrations (30%-47%) is not FDA approved due to one patient death caused by inadvertent overfill of the TC.[40] There are additional reports of cardiac and embolic complications due to precipitation of TSC (30%-47%) in the TC, and an increase in thrombolytic requirements for TC dysfunction.[41,42] In summary, citrate alone cannot be recommended.

Taurolidine is a broad-spectrum, antimicrobial agent used in AMLs (with an anticoagulant agent) that reduces biofilm formation. The advantage of taurolidine in an AML is that it does not cause bacterial resistance. While taurolidine+citrate4% AML was associated with a reduction in CRBSI when compared to heparin lock, there was also an increased need for thrombolytic therapy in one study, indicating the need for a more efficacious anticoagulant.[43–45] Subsequent studies using taurolidine+ citrate4% +heparin 500 units/mL, with or without or taurolidine+ citrate4% +urokinase 25,000 units once weekly, reported an improvement in TC dysfunction and reduction in CRBSI.[46–48] A cost analysis was performed in a small study using the following taurolidine AML protocol: taurolidine+ citrate4% +heparin 500 unit/mL twice weekly, and taurolidine+ citrate4% +urokinase 25,000 units once weekly (N = 52 patients) compared to citrate4% AML (N = 54 patients). Although upfront baseline costs were higher in the taurolidine AML protocol, the total costs (treatment of complications due to CRBSI and dysfunction) were 43% lower compared to the citrate4% AML group.[48] Although taurolidine AML is available for use in Europe, it is not yet approved for use in the United States.

In the Pre-CLOT trial, recombinant tissue plasminogen activator (rt-PA) AML was shown to be associated with a significant reduction in catheter dysfunction (~50%) and CRBSI (~67%), using a protocol of rt-PA 1 mg once weekly and heparin 5000 units twice weekly, compared to a control group using heparin 5000 units thrice weekly.[49] Although the immediate cost of the rt-PA protocol was higher (Canadian dollars $323), a decision analysis model calculate that there would be no significant difference in the mean overall cost of an rt-PA/heparin strategy as a locking solution for catheters compared with thrice-weekly heparin.[50] The immediate costs of a rt-PA were counterbalance by anticipated reduced cost of CRBSI associated hospitalizations.

The AZEPTIC trial investigators reported that a novel non-antibiotic AML containing citrate 7%-methylene blue, methylparabens/propylparaben (C-MB-P) was

associated with a significant reduction (~70%) in CRBSI and in TC removal for dysfunction.[51] The C-MB-P AML was not approved by the FDA because the study definition of CRBSI did not meet stringent Infectious Disease Society of America criteria for "definite CRBSI."

Ethanol (30%-70%) AML have been studied for CRBSI prevention in the HD setting studies.[52–55] The potential advantage of ethanol is it is inexpensive, reduces biofilm, no risk of resistance, and has broad antimicrobial and antifungal properties. Two studies used high concentration ethanol 70% lock.[52,53] In a small proof of concept study in 49 patients, ethanol 70% used once weekly and heparin 1000 units twice weekly was associated with a reduction in CRBSI compared to heparin thrice weekly, (0.28 vs. 0.85 per 1000 days, P = 0.12).[52] A larger prospective randomized study in 103 patients comparing and AML with ethanol 70% + heparin 2000 units/mL thrice weekly vs. heparin alone. There was a significant reduction in CRBSI rates in the ethanol/heparin group (2.53 vs. 6.7 per 1000 catheter days (P = 0.04).[53] In a large (N = 1460 patients), multicenter, randomized controlled trial in nontunneled catheters, 60% ethanol AML was instilled for 2 minutes and removed after each HD session vs. saline lock.[54] There was no reduction in CRBSI. The concern about using ethanol locks at high concentrations (70%-100%) is that they have been associated with catheter dysfunction, reports of headaches, nausea, dizziness, fatigue, hepatotoxicity, and structural changes in the catheter integrity, including elution of molecules from the catheter polymers. The efficacy and safety of lower concentrations of ethanol AML has been evaluated, and, in concentrations of 30%, ethanol AML was not associated with changes in carbothane catheter integrity.[56] In a small clinical study (40 HD patients), ethanol 30%+citrate 4% AML was instilled after each HD session and was compared to heparin (1000 units) lock.[57] The ethanol 30%+citrate 4% lock was associated with a reduction in TCs removed for dysfunction and there were no reported CRBSI episodes. During this study period only one CRBSI episode occurred, and this was in the heparin lock group. One silicone catheter was found to have a crack, and this occured in the ethanol 30% group. Larger, well-powered clinical trials using low concentration 30% ethanol lock are needed. Ethanol locks should be only be used in alcohol compatible catheters composed of carbothane or silicone, require aspiration prior to initiation of hemodialysis, and used at low concentrations (30%).[58] The current CDC recommendations advise the use prophylactic AML only in TCs in hemodialysis patients who have a history of multiple CRBSI.

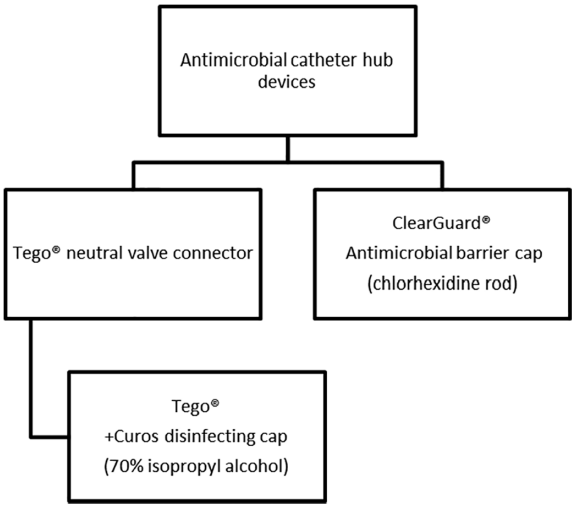

Figure 4 Catheter hub devices used for the prevention of catheter associated blood stream infections.

Catheter hub devices

The two available catheter hub devices are shown in Figure 4. The use of a neutral-valve connector (Tego® ICU Medical, Inc.) at the catheter hub, which is changed weekly and locked with either saline or heparin was reported to be associated with a small (10%-12%) reduction in CRBSI in a large (17,000 patients) retrospective study among patients with TCs receiving in-center hemodialysis at a large dialysis organization.[59] In this study, the definition of CRBSI was defined as the administration of intravenous antibiotic initiation. There was no difference between the Tego® vs. control groups in the rate of positive blood cultures.

Another catheter hub device developed for CRBSI prevention is the ClearGuard HD Antimicrobial Barrier Cap (Pursuit Vascular, Inc.) which contains a rod coated with chlorhexidine, which extends into the TC hub, and is changed three times a week, using heparin lock.[60,61] Chlorhexidine is a nonantibiotic antimicrobial agent, therefore the risk of selection for resistance organisms is minimal. In a prospective cluster-randomized trial in 40 hemodialysis units, pairing control and treatment facilities with similar CRBSI rates, the use of the ClearGuard cap was associated with a significant (56%) reduction in the rate of positive blood cultures compared to standard CVC caps, (P = 0.01).[60] A recently published prospective cluster-randomized trial compared CRBSI rates between HD facilities using the ClearGuard cap with HD facilities using the Tego® connectors with Curos (3 M Healthcare) disinfecting caps, which kills microbes on the outside surface of the Tego® using 70% isopropyl alcohol.[61] The use of the ClearGuard cap was associated with a

significant (63%) reduction in CRBSI compared to the Tego® connectors + Curos cap (P = 0.003). The ClearGuard HD cap is FDA approved for use in TC used for HD, is efficacious and has a low-risk of resistance.

CONCLUSION

In conclusion, the frequent use of TCs in hemodialysis patients increases the risk of infectious complications, hospitalizations, and mortality. Catheter avoidance and reduction are the obvious strategies for avoiding these complications, however in those instances where the use of dialysis catheters is unavoidable, implementation of the CDC clinical practice recommendations for preventing hemodialysis infections is imperative, and has been proven to reduce CRBSI rates and hospitalization rates.[62] The nephrologists transforming dialysis safety (NTDS) is a nationwide project to engage nephrologists, in concert with state/federal health care-associated infection programs, to "target zero infections" in the hemodialysis setting. The NTDS vascular access workgroup's major focus is to review recent clinical trials, consider novel ways of preventing CRBSI, and build upon the current CDC clinical practice recommendations.[63]

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