Reducing Catheter-Related Infections in Hemodialysis Patients

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Not all hemodialysis accesses are created equal: Compared with patients with ESRD who have an arteriovenous fistula, those with a tunneled central venous catheter have a 15-fold increased risk of catheter-related bloodstream infection (CRBSI) and an all-cause mortality rate ranging from 12% to 25% (1,2). Ten percent to 20% of CRBSIs are associated with metastatic complications, such as endocarditis, septic arthritis, and epidural abscess, and they cause considerable financial and physical burdens from catheter loss, repeated access procedures, and hospital admissions (2). A single-center study found that a CRBSI resulted in an average hospital stay of 11 days and cost approximately $23,000 (3); several other studies support these data (4,5). Despite the Fistula First Initiative, nearly 80% of patients initiate hemodialysis with a central venous catheter (6).

Efforts to reduce CRBSI have focused on comprehensive catheter management protocols and the use of antimicrobial catheter lock solutions. In 2011, the Centers for Disease Control and Prevention (CDC) published a list of core interventions aimed at decreasing the incidence of CRBSI (7). These measures include the use of chlorhexidine skin antiseptis at the catheter exit site, catheter hub disinfection, and the application of triple antibiotic (or povidone iodine) ointment to catheter exit sites during dressing changes. Similar “bundled” care efforts in intensive care units have shown dramatic decreases in nondialysis CRBSI rates (8,9). The CDC Dialysis Collaborative used a comprehensive dialysis catheter management protocol in 17 outpatient dialysis units and found a 54% reduction ($P<0.001$) in CRBSI during the 15-month intervention period (10).

More than 15 years of experience with antimicrobial lock solutions has still not led to a consensus regarding their use for CRBSI prevention. Boyce recently reviewed all antimicrobial lock studies (antibiotic- and non–antibiotic-based) performed from 1999 to 2012 and concluded that antimicrobial locks should be used for CRBSI prevention in all hemodialysis units (11). In addition, five meta-analyses or systematic reviews (12–16) published during this time period indicate significant reductions in CRBSI; in particular, two meta-analyses reported a number needed to treat to prevent one CRBSI of 3 to 4 (12,13). Most of the included studies compared an antimicrobial lock with heparin as the control and used different protocols for general catheter care, such that infection rates in the control groups were approximately 3 per 1000 catheter-days. Because more recent studies using bundled care without antimicrobial locks have achieved CRBSI rates of $\leq 1$ per 1000 catheter-days, can the use of antimicrobial locks further reduce CRBSI? Abbas et al. performed an observational study of gentamicin-heparin versus heparin catheter locks, while Maki and Moran and their colleagues performed randomized controlled trials with gentamicin-trisodium citrate (citrate) and citrate–methylene blue–methylparaben–propylparaben, respectively (17–19). All three studies achieved CRBSI rates of $<1$ per 1000 catheter-days in their control groups and yet still showed a significant decrease in infection rates with their interventions (Abbas, Moran, and Maki et al. reported rates of 0.62, 0.28, and 0.24 events per 1000 catheter-days, respectively).

However, two major unanswered questions remain: (1) Does the routine use of antimicrobial locks in dialysis patients with tunneled central venous catheters lead to a mortality benefit, and (2) is there risk of antibiotic resistance in patients using antibiotic-based lock solutions? In this issue of CJASN, Moore et al. try to answer these questions (20). The authors conducted a prospective, multicenter, observational cohort study in a metropolitan area to compare the effectiveness of a gentamicin-citrate lock versus heparin in 555 hemodialysis patients undergoing dialysis with a tunneled central venous catheter between 2008 and 2011. During the study period, three of the outpatient dialysis units crossed over from heparin to gentamicin-citrate lock at different times. Historical controls were compared with antimicrobial lock data. The comprehensive catheter management protocol used in both the historical and the antimicrobial lock time periods was similar to the 2011 CDC list of core interventions. This included the use of a triple antibiotic ointment (bacitracin, neomycin, and polymyxin B) on the exit site in all patients during the entire study period. The dose of gentamicin (0.32 mg/ml) used with 4% citrate was considered low compared with the dose used in many other trials (4 mg/ml). The authors report a reduced rate of CRBSI in the antibiotic lock period of 0.45 per 1000 catheter-days compared with 1.68 events during the heparin period ($P=0.001$), which was maintained after multivariate adjustment (adjusted relative
risk, 0.23; 95% confidence interval, 0.13 to 0.38). The use of gentamicin-citrate lock was also associated with a significant reduction in all-cause mortality (0.32; 95% confidence interval, 0.14 to 0.75 after multivariate adjustment).

Moore’s group also addressed the issue of antibiotic resistance by conducting in vitro gentamicin susceptibility testing on each blood bacterial isolate in one central microbiology laboratory. Gentamicin resistance rates decreased from 0.40 per 1000 person-years in the heparin period to 0.22 per 1000 person-years in the antimicrobial lock period ($P=0.01$). The authors do not report the outcomes of the patients with gentamicin-resistant CRBSI, but their comparison of gentamicin resistance to a nonantimicrobial lock period certainly is a strength of their study. Unfortunately, the duration of follow-up after the initiation of the gentamicin-citrate lock was only 7–8 months in two of their three centers. The authors suggest that either the low dose of gentamicin used in their study or the avoidance of heparin—which is known to increase the production of biofilm—may have played a role in the decrease in gentamicin resistance. Moreover, another prospective, randomized controlled study of low-dose gentamicin (0.32 mg/ml) and citrate lock likewise found no significant change in gentamicin resistance during a 5-year period or in the ensuing 3 years when the lock solution was universally implemented (19).

In contrast, our own published data were the first to raise the important question of antibiotic resistance with gentamicin lock. Our observational study of >1400 patients followed for >4 years used heparin with a high-dose gentamicin locking solution (4 mg/ml) but did not have comparison data from a historical control period (21). We used povidone-iodine rather than chlorhexidine as the skin antiseptic and covered the exit site with mupirocin, which has been associated with bacterial resistance (22). Another group found gentamicin resistance in their uncontrolled, observational study of 320 patients using 1 mg/ml gentamicin with heparin during a 3-year period (23), while Venditto et al. reported increased gentamicin resistance to Enterobacteriaceae (but none to Staphylococcus aureus) isolates during their study of 6-month sequential antimicrobial locks consisting of heparin, 47% citrate, and then gentamicin (2 mg/ml) with heparin (24).

Alternatives to antibiotic-based lock solutions have been studied for the purpose of eliminating the risk of antibiotic resistance. Several authors have evaluated citrate, but in some studies higher doses (47%) have failed to outperform heparin and have also raised concerns about the possibility of fatal arrhythmias induced by hypocalcemia or systemic emboli from catheter leakage (25,26). However, a recent meta-analysis by Zhao et al. indicated that low-to-moderate concentrations of citrate (1.04%–7%) appear to be of benefit in decreasing the risk for CRBSI (27). The combination of citrate with other novel antimicrobials, such as taurodand (28–31) and methylene blue–methylparaben–propylparaben, has shown efficacy in reducing CRBSI, but issues with catheter thrombosis have limited their use (18). Hemmelgarn et al. reported successful reduction in CRBSI with the use of once-weekly tissue plasminogen activator, but the long-term cost of this strategy is prohibitive (32). Ethanol locking solutions are effective sterilizing agents for CRBSI prophylaxis, as well as for salvage in silicone-based central venous catheters of oncology patients and pediatric patients receiving parenteral nutrition (33). However, safety of ethanol in polyurethane-based hemodialysis catheters has been an ongoing concern. We have shown that carbothane and silicone-based hemodialysis catheters can be exposed to 70% ethanol lock in vitro for at least 6 months without any evidence of damage to catheter integrity (data not shown).

This has been supported by the work of Crnich et al. (34), who studied the in vitro mechanical properties of silicone and polyurethane peripherally inserted central catheters exposed to 70% ethanol during a 10-week period. The HEALTHCATH trial was the first prospective, open-label, randomized, controlled trial in hemodialysis patients using once-weekly 70% ethanol lock (with two heparin locks between other dialysis sessions) versus thrice-per-week heparin lock for the control. This proof-of-concept study showed no significant difference in CRBSI (0.85 versus 0.28 events/1000 catheter-days in heparin versus ethanol groups; $P=0.12$), but the study was underpowered because of low recruitment. The authors did not report catheter integrity issues but also did not mention the type of dialysis catheters used (35).

Should antimicrobial locks be used to reduce CRBSI? Moore and colleagues have made a significant contribution showing evidence of a mortality benefit—without the development of gentamicin resistance—with use of gentamicin-citrate lock. The issue of developing gentamicin resistance may not be completely answered, but the preponderance of data would now suggest that low-dose gentamicin used with 4% citrate is safe. The CDC and the Infectious Diseases Society of America do not recommend the routine use of antimicrobial lock in hemodialysis patients dialyzed with a central venous catheter. They suggest reserving this treatment for patients with a history of multiple CRBSIs, citing concerns for the potential emergence of antibiotic resistance (36). In contrast, the European Best Practices Report has concluded that the effectiveness of antimicrobial lock to reduce CRBSI outweighs any potential risk and recommends prophylactic antimicrobial lock use in all patients with ESRD who have tunneled central venous catheters (37). If the “typical” CRBSI is associated with a 12%–25% risk of mortality and considerable cost to the health care system, the real question in 2014 is which locking solution we should use to prevent CRBSI, rather than whether to use a locking solution at all. Prospective, randomized controlled trials are needed comparing the newest antimicrobial locks in order to determine the one best suited to prevent CRBSI with the least propensity for the development of bacterial resistance. For now, we prefer to use low-dose gentamicin-citrate locks for CRBSI prevention in all patients with ESRD who have a tunneled central venous catheter.

Disclosures
None.

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