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# Hemodialysis Catheter Device Protection: Damned if We Do; Patients Are Damned if We Don't

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EDITORIAL

# Hemodialysis Catheter Device Protection: Damned if We Do; Patients Are Damned if We Don't



In this issue of *Advances in Chronic Kidney Disease*, Guest Editor Mohanram Narayanan, MD, reinvigorates the prior theme of infections in kidney patients. Infections are frequent in nephrology patients and often deadly. Each of Dr. Narayanan's authors pointedly contributes his/her wisdom to the infection theme. So, before reading more, please read each article carefully to enhance your practical working knowledge on behalf of your patients.

As a member of the Michigan Chapter of the American College of Physicians, we recently had a robust discussion about pay for performance. Part of the discussion was about reimbursement for documentation of what the physician educated and intended the patient to do rather than what the patient outcomes are. We believe this to be fair because there must be some ownership of one's medical care and outcomes. Given the emphasis on patient centeredness and autonomy, health-care providers cannot go home with patients and "force" the issue.

As a corollary, should nephrologists be pilloried for their inability to achieve the laudable goals of the Fistula First Breakthrough Initiative? Better yet, can we achieve the more well-considered goal of the Catheter Last initiative? Probably not, if patients cannot successfully undergo arteriovenous (AV) fistula constructions or AV graft placements. Also, some patients, for personal, social, or environmental reasons, simply reject the idea of either AV fistula/graft surgery or peritoneal dialysis. The common denominator, for better or worse, is the hemodialysis (HD) catheter, the most frequently used in-hospital vascular access for acute kidney injury patients who require renal replacement therapy.

In the absence of renal recovery, the non-tunneled catheter is exchanged for a tunneled catheter, the consequence of which is the acquired disorder, "catheter perpetuation syndrome." This disorder is only cured after much cajoling by the nephrologist physician–care provider following episodic catheter-related bloodstream infections or central line-associated bloodstream infections (CLABSIs). Remarkably, catheter perpetuation usually involves the patient/decider who declares that catheters are not painful and also that the CLABSI is the fault of the provider. These arguments, although flawed, are clearly lucid to the patient (end-user). Thus, nephrology has a tautological problem of getting the world rid of CLABSIs that it has created. This is akin to the prosperity of industrialization with the penalty of climate change. As we should reduce carbon-based emissions to prevent global warming, we must decrease the frequency and prevalence of HD catheters and the complication of CLABSIs.

Nearly all the solutions have been imposed, and nephrology has implemented them at the provider level, ie, interdisciplinary chronic kidney disease clinics, patient education regarding AV fistula and graft surgery, inpatient rapid-start peritoneal dialysis for patients with acute kidney injury (AKI) requiring renal replacement therapy, and so forth. However, one solution with proven value has not been universally adopted. To apply the term "universally" is bloviation because this solution has hardly been adopted despite the fact that this answer is well researched, well published, well known, and consistently appears in nephrology examinations. Somehow, this sounds like promulgating handwashing to prevent infection. Admittedly, we have snatched victory from the jaws of defeat.

Most recent United States Renal Data Survey data published in 2017 indicate that the per-patient per-year cost to care for an in-center HD patient is $88,750.[1] A substantial proportion of this cost is related to dialysis access-related care and its associated complications.[2] Despite aggressive measures since the Fistula First Breakthrough Initiative began over a decade ago, 36% of AV fistulas still fail to


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ever mature, and 80% of patients with incident end-stage renal disease who are on HD still begin treatment with a tunneled HD catheter. At 1 year, catheter prevalence remains at approximately 20%.[1] When compared with patients on HD with AV access, patients receiving dialysis with a tunneled central venous catheter (CVC) have higher rates of access-related infection, sepsis, and mortality. The financial costs of CLABSI have been determined to approximate $45,000 per event.[3] The patient-centered costs are greater, and the long-term consequences are clearly more severe. Given the known concerns of life-threatening patient outcomes, long-term morbidity, and costs to the health-care system associated with CLABSIs (hospitalizations, repeated access procedures and patient fatigue, endocarditis and septic arthritis, hospital readmissions, and loss of reimbursement), can we do more for our patients?

The Centers for Disease Control published a group of "dialysis safety core interventions" in 2016 to help reduce CLABSIs. These standards have been applied throughout the country and have had a powerful impact on CVC complication rates in short-term studies.[4] These interventions include staff training, meticulous hand hygiene and surveillance, and use of best practices with vascular access care, chlorhexidine skin preparation, and "scrub the hub" catheter disinfection.[5] Application of antimicrobial ointment to the catheter exit site during dressing changes has also been shown to reduce CLABSI rates in patients with CVCs and is now part of the Centers for Disease Control's core interventions. Nevertheless, CLABSI rates continue to be reported anywhere between 1.1–5.5 episodes per 1000 catheter-days.[6]

Antimicrobial locks (AMLs) are solutions instilled into the catheter lumens of CVCs for the duration of time between dialysis treatments (48 to 72 hours) (Fig 1). Each contains a high concentration of an antimicrobial agent and has been used with the intention of eradicating bacteria that colonize the biofilm present in the internal lumens of all CVCs. The properties of an ideal AML solution should include adequate concentrations of antimicrobial agent to prevent CLABSIs without producing systemic toxicity, vascular thrombosis, or resistant bacteria.

Antimicrobial agents used in AML are generally categorized as either antibiotic or non-antibiotic and typically contain some form of anticoagulant (heparin, citrate, or tissue plasminogen activator). Differing antibiotics have been used in AML (eg, vancomycin, cefazolin, ceftazidime, ciprofloxacin), but gentamicin has been the most studied antibiotic, either with heparin or citrate. One of the first randomized, controlled trials (RCT) indicating the clinical benefit of AML was conducted by al Hweish and colleagues in 2007.[7] This group conducted an RCT of 63 subjects using either vancomycin plus gentamicin and heparin vs a standard heparin catheter lock solution. The intervention arm showed a significant reduction in CLABSIs of 0.65 events per 1000 dialysis sessions compared with 4.88 events per 1000 dialysis sessions in the control arm ($P < 0.001$).[7] Another RCT performed in 2009 by Zhang consisted of 140 subjects with over 34,000 catheter-days using a gentamicin-heparin AML vs standard heparin.[8] The intervention group showed statistically significant reductions in CLABSIs (0.06 per 1000 catheter-days) despite the fact that the control group had a very low rate of events as well (0.67 events per 1000 catheter-days).[8] As questions have been raised regarding the possible negative impact—rather than just neutral—of heparin as a catheter locking solution, Moran conducted an RCT using gentamicin with 4% sodium citrate vs standard heparin locking solution in 303 subjects totaling more than 72,000 catheter-days.[9] Again, core interventions led to a low incidence of CLABSIs in the control arm (0.91 events per 1000 catheter-days), whereas the gentamicin–4% citrate AML resulted in a significant reduction in CLABSIs (0.28 events per 1000 catheter-days).[9]

What about the risk of antibiotic resistance from long-term exposure to AML? A large, observational, retrospective study in 2010 (1410 patients with 142,000 catheter-days) was the first study to support such concerns. Although the intervention arm (gentamicin-heparin AML) lowered the CLABSI rate effectively (decrease from 17 to 0.83 events per 1000 catheter-days during the 4-year intervention), gentamicin resistance was noted within 6 months.[10] To further address this question, a prospective, multicenter, observational cohort study by Moore was published in 2014.[11] This has been the largest study of an AML to date (155,518 catheter-days). The gentamicin–4% citrate solution was compared with the standard heparin lock solution in 555 patients on HD over a 4-year period. The CLABSI rate in the antibiotic lock period (0.45 per 1000 catheter-days) was 73% lower than that in the heparin period (1.68 per 1000 catheter-days; $P = 0.001$). Equally important, AML therapy was associated with a survival advantage (hazard ratio, 0.32; 95% confidence interval, 0.14 to 0.75, after multivariate adjustment) and a reduction in the rate of gentamicin-resistant organisms (0.40 per 1000 person-years to 0.22 per 1000 person-years) in the AML period.[11]

Nonantibiotic AMLs such as solutions containing taurolidine, trisodium citrate, or ethanol have also been studied and show significant promise. Although helping to hopefully eliminate any potential risk for the emergence of antibiotic resistance, there are concerns regarding the potential for toxicity, as well as damage to catheter integrity.

The use of trisodium citrate at concentrations of 30% or higher to avoid catheter thrombosis has shown mixed results in several studies. These have primarily been used as an adjunct to antibiotic catheter locks.[12] The antimicrobial taurolidine has been reported in several studies, with citrate showing significant reductions in catheter-related bloodstream infections. However, there has been concern regarding the increased incidence of catheter thrombosis, leading to the use of heparin and urokinase in the most recent RCT.[13] Ethanol is another antimicrobial sterilant, with significant data reported in the pediatric literature for prophylaxis and catheter salvage of CLABSIs in children with long-term peripherally inserted central catheter lines due to severe malnutrition from short gut syndrome. Its prophylactic use in patients with end-stage renal disease with tunneled CVC has been studied over the last

several years and summarized with a recent meta-analysis of 7 RCTs consisting of 2575 patients with 3375 catheter-days, indicating significantly decreased risk of CLABSI (relative risk, 0.54; 95% confidence interval, 0.38 to 0.78; $P = 0.001$).[14] Of note, not all patients included in this study were using CVCs for dialysis. There has also been a concern regarding the use of ethanol and systemic toxicity (nausea and transient dizziness) and damage to catheter integrity despite more recent data from our group contradicting this concern.

In a recent Cochrane database meta-analysis of 39 studies and 4216 patients, the use of AMLs (antibiotic antimicrobial and combined antibiotic plus nonantibiotic lock solutions) decreased the incidence of CLABSIs compared with control lock solutions, usually heparin. The nonantibiotic lock solutions did not significantly reduce CLABSIs when compared with the standard heparin lock solutions.[15]

Finally, the Federal Drug Administration has more recently approved a nonantibiotic, antimicrobial CVC closure device consisting of CVC caps containing an internal rod coated with chlorhexidine that dissolves in a standard heparin lock solution upon contact. Chlorhexidine is a well-established nonantibiotic antimicrobial. It is currently used as part of the standard scrub the hub technique when accessing HD catheters and has shown superiority to povidone iodine solutions in terms of diminishing infection rates. Two prospective multicenter RCTs have evaluated these catheter caps (ClearGuard™). Collectively, there were dramatic and sustained reductions in CLABSI rates with no significant side effects. Cost has been the only deterrent to widespread use, ie, the cost is borne by the dialysis provider.[16,17]

Are AMLs cost-effective? Data regarding the cost-effectiveness of antibiotic catheter locks have been addressed and appear to support benefit. A recently published retrospective audit on CLABSI rates and associated financial implications from a single center in New Zealand supports this tenet. Goh and colleagues reported their experience during 3 phases of catheter locking solutions over a 5-year span from 2010 to 2015, during which time there was a 12.5-month absence of gentamicin-heparin AML (supplier had withdrawn the product from the market) that had been their standard of care for all HD tunneled CVCs for the previous 24 months from 2010 to 2012.[18] The authors used heparin locks (1000 units/mL) because of absence of AML only to resume AML practice with gentamicin-citrate in 2014. Over 144,000 catheter-days were reviewed with a total of 89 CLABSIs during this 5-year span. When compared to the heparin-only lock (1.42), both gentamicin-heparin and gentamicin-citrate AMLs had reduced CLABSI rates of 0.66 and 0.16 per 1000 catheter-days, respectively. Application of the same standard of care—including the scrub the hub technique—was the same throughout the entire period. Inpatient costs (in New Zealand dollars) as a result of CLABSI events were $27,792 per 1000 catheter-days for heparin-only locks, $10,608 per 1000 catheter-days for gentamicin-heparin AML, and $1898 per 1000 catheter-days for gentamicin-citrate AML.[18]

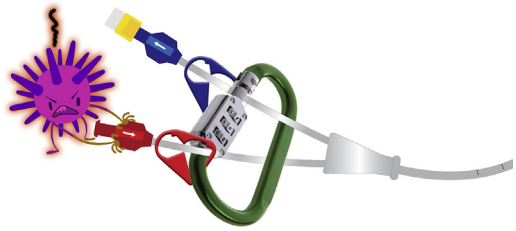

**Figure 1.** Antimicrobial lock solutions are proven prophylaxis for central line-associated bloodstream infections.

Who uses tunneled dialysis catheters? Typically, these are "crash starts" of patients with end-stage renal disease and those with acute kidney injury, those with failed and maturing vascular access, and those who have simply refused vascular access for a multiplicity of reasons. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that although patients with catheters and AV grafts have a higher number of access complications and higher mortality, the actual access complications may not explain this increased mortality rate, raising the question of patient baseline statistics (social economic status, medical comorbidities) as likely factors behind the ability to achieve not only successful AV access but also being the main driver behind mortality. Is the possession of a tunneled dialysis catheter simply an independent marker of health status? Most of our clinical experiences would indicate this being very likely true.[19]

Have our well-intentioned efforts to improve outcomes of patients on HD and societal costs led to an overestimation of the benefits of AV fistulas and ironically contributed to increased catheter prevalence? Does this represent the unintended consequence of confusing association (of catheters with mortality) with causality? Changing the perspective from a "Fistula First" initiative to a "Catheter Last" initiative did not remediate the problem at its core.

At the end of the day, we are tasked with making our patients safer with the most well-thought-out methods available. In the world of dialysis, this means decreasing infection rates while also fulfilling our responsibility of antibiotic stewardship to prevent the development of antibiotic resistance. Based on present-day data and over a decade of AML experience, a strong and logical argument can be made that it is actually costing health care more to not use and support the use of AMLs. Truly, regarding HD catheter protection devices, we are damned if we do, and patients are damned if we don't.

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## REFERENCES

1. United States Renal Data System. *2017 USRDS Annual Data Report: End-stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017:chapter 1.
2. Manns B, Tonelli M, Yilmaz S, et al. Establishment and maintenance of vascular access in incident hemodialysis patients: a prospective cost analysis. *J Am Soc Nephrol.* 2005;16(11):201-209.
3. Rupp M, Karnatak R. Intravascular catheter-related bloodstream infections. *Infect Dis Clin N Am.* 2018;32(4)765-787.
4. Patel PR, Yi SH, Booth S, et al. Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. *Am J Kidney Dis.* 2013;62(2):322-330.
5. Centers for Disease Control and Prevention. *Dialysis safety core interventions*. 2016 2016. Available at: https://www.CDC.gov/dialysis/prevention-tools/core-interventions.html. Accessed October 18, 2018.
6. Miller LM, Clark E, Dipchand C, et al. Hemodialysis tunneled catheter-related infections [published online September 27, 2016]. *Can J Kidney Health Dis*. 2016;3:1-11. https://doi.org/10.1177/2054358116669129.
7. Al-Hwiesh AK, Abdul-Rahman IS. Successful prevention of tunneled, central catheter infection by antibiotic lock therapy using vancomycin and gentamycin. *Saudi J Kidney Dis Transpl.* 2007;18(2):239-247.
8. Zhang P, Yuan J, Tan H, Lv R, Chen J. Successful prevention of cuffed hemodialysis catheter-related infection using an antibiotic lock technique by strictly catheter restricted antibiotic lock solution method. *Blood Purif.* 2009;27(2):206-211.
9. Moran J, Sun S, Khababa I, Pedan A, Doss S, Schiller B. A randomized trial comparing gentamicin/citrate and heparin locks for central venous catheters in maintenance hemodialysis patients. *Am J Kidney Dis.* 2012;59(1):102-107.
10. Landry D, Braden G, Gobeille S, Haessler S, Vaidya C, Sweet S. Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol.* 2010;5(10):1799-1804.
11. Moore CL, Besarab A, Ajluni M, et al. Comparative effectiveness of two catheter locking solutions to reduce catheter related bloodstream infection in hemodialysis patients. *Clin J Am Soc Nephrol.* 2014;9(7):1232-1239.
12. Zhao Y, Li Z, Zhang L, et al. Citrate versus heparin lock for hemodialysis catheters: a systematic review and meta-analysis of randomized controlled trials. *Am J Kidney Dis.* 2014;63(3):479-490.
13. Winnicki W, Herkner H, Lorenz M, et al. Taurolidine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled hemodialysis catheters. *Kidney Int.* 2018;93(3):753-760.
14. Zhao T, Liu H, Han J. Ethanol lock is effective on reducing the incidence of tunneled catheter-related bloodstream infections in hemodialysis patients: a systematic review and meta-analysis. *Int Urol Nephrol.* 2018;50(9):1643-1652.
15. Arechabala M, Catoni M, Claro JC, et al. Antimicrobial lock solutions for preventing catheter-related infections in haemodialysis. *Cochrane Database of.* 2018;(4):CD010597.
16. Hymes J, Mooney A, Van Zandt C, Lynch L, Ziebol R, Killion D. Dialysis catheter-related bloodstream infections: a cluster-randomized trial of the Clearguard HD antimicrobial barrier cap. *Am J Kidney Dis.* 2017 Feb;69(2):220-227.
17. Brunelli S, Van Wyck D, Njord L, Ziebol R, Lynch L, Killion D. Cluster-randomized trial of devices to prevent catheter-related bloodstream infection. *J Am Soc Nephrol.* 2018;29(4):1336-1343.
18. Goh t, Wei J, Semple D, Collins J. The incidence and costs of bacteremia due to lack of gentamicin lock solution for dialysis catheters. *Nephrology.* 2017;22(6):485.
19. Ravani P, Quinn R, Oliver M, et al. Examining the association between hemodialysis access type and mortality: the role of access complications. *Clin J Am Soc Nephrol.* 2017;12(6):955-964.