Eckardstein A, Mild and Moderate Kidney Disease (MMKD) Study Group: Serum creatinine, cystatin C, and beta-trace protein in diagnostic staging and predicting progression of primary nondiabetic chronic kidney disease. *Clin Chem* 56: 740–749, 2010

11. Astor BC, Muntner PM, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 162: 1401–1408, 2002
12. Lewis J, Greene T, Appel L, Contreras G, Douglas J, Lash J, Toto R, Van Lente F, Wang X, Wright JT: A comparison of iothalamate-GFR and serum creatinine-based outcomes: Acceleration in the rate of GFR decline in the African American Study of Kidney Disease and Hypertension. *J Am Soc Nephrol* 15: 3175–3183, 2004
13. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, Safford MM, Zhang X, Muntner P, Warnock D: Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 305: 1545–1552, 2011
14. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51: 395–406, 2008
15. Astor BC, Levey AS, Stevens LA, Van LF, Selvin E, Coresh J: Method of glomerular filtration rate estimation affects prediction of mortality risk. *J Am Soc Nephrol* 20: 2214–2222, 2009

See related article, "Measured GFR Does Not Outperform Estimated GFR in Predicting CKD-Related Complications," on pages 1931–1937.

Antimicrobial Catheter Locks: Searching for the Ideal Solution

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In this issue of *JASN*, Campos *et al.* report a well performed, prospective, randomized clinical trial demonstrating the benefit of an antimicrobial catheter lock solution (ACL) containing minocycline and EDTA (M-EDTA) in the prevention of hemodialysis catheter-related bacteremia.[1] It is unclear why most nephrologists do not use ACLs in this setting; a number of clinical trials consistently demonstrate their superiority to conventional solutions.[2–7] Oddly enough, we have no trouble pursuing other kinds of treatments for which robust clinical benefit is lacking, such as moderately increasing dialysis dosage in peritoneal and hemodialysis, using statins in dialysis patients, low protein diets in chronic kidney disease, or early asymptomatic initiation of dialysis.

ACLs are instilled into dialysis catheters at the end of a hemodialysis treatment. Small amounts of the ACL will enter the systemic circulation when instilled initially and through diffusion during the interdialysis interval. The ideal ACL should have the following properties: it should be nontoxic when administered systemically; it should prevent catheter thrombosis; it should be effective against a wide variety of microorganisms; it should be biocompatible with the catheter; it should not lead to antibiotic resistance; and it should be readily available and inexpensive.

A variety of solutions have been tried over the last decade, but there is no consensus on the ideal solution. Hypertonic sodium citrate is an effective and inexpensive catheter lock,[3] but inadvertent systematic administration results in severe hypocalcemia and cardiac arrest.[8] Ethanol may be an effective agent, but there are concerns about thrombosis and compatibility with catheter materials.[9] ACLs containing gentamicin[4,6,7] are extremely effective in preventing infection; the high concentrations achievable within the catheter are toxic to staphylococci. ACLs containing gentamicin are inexpensive and highly effective. Unfortunately, the use of these solutions has been discouraged because of the potential risk for antimicrobial resistance. The Interpretative Guidance for Conditions of Coverage state: "The CDC advises that prophylactic antibiotic lock solutions be reserved for use only in special circumstances, for example, in units where the rate of catheter-related bloodstream infection has not decreased despite optimal maximal adherence to aseptic technique."[10]

Avoidance of antimicrobials in catheters seems at odds with the effective use of antimicrobials in the prevention of other infections. Antimicrobial prophylaxis is given routinely for many surgeries, dental procedures in individuals with cardiac valvular abnormalities, prevention of urinary tract infections, and prevention of infection in immunosuppressed transplant patients. In the dialysis center, gentamicin ointment is routinely applied to reduce peritoneal catheter exit site infection,[11] and a polyantibiotic ointment is often placed at the exit site of hemodialysis catheters.[12] The use of gentamicin as an antimicrobial catheter lock may lead to gentamicin resistance, an antibiotic for which alternative choices exist. However, the use of vancomycin in dialysis units is increased markedly without prophylactic antimicrobial catheter lock solutions, and this clearly has the potential to lead to *Staphylococcus aureus* that are resistant to vancomycin. Notably, some of the first vancomycin-resistant *Enterococci*[13] and coagulase-negative *Staphylococcus epidermidis* species were found in dialysis patients.[14] Vancomycin-intermediate *S. aureus* species have also been identified in dialysis patients.[15]

In the study by Campos *et al.*,[1] M-EDTA was very effective and well tolerated. The rate of catheter-related bacteremia was 4.3 per 1000 catheter-days in the control group receiving heparin dwells and 1.1 per 1000 catheter days in the M-EDTA group ($P = 0.005$). The rate of catheter removal due to dysfunc-

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tion was 4.6 per 1000 catheter-days for the M-EDTA group and 3.2 per 1000 catheter-days for heparin-filled catheters ($P = 0.31$). Thus, there were fewer infections and the rate of catheter thrombosis appeared similar. One concern in prior ACL trials has been high infection rates in the control group. Ideally, dialysis centers should have a catheter-related bacteremia rate less than 1 per 1000 catheter-days, and the rate in the control group in this study was much higher. However, in other studies of ACLs with control groups having lower rates of infection, a significant treatment effect has still been observed.[2,16] In another prospective randomized trial using M-EDTA,[17] catheter colonization was found to be far lower in the M-EDTA group.

Minocycline has fewer important clinical applications, and the authors postulate that resistance to minocycline would be less of a clinical problem compared with other antibiotics that have been used in ACLs, including gentamicin. This might be a distinct clinical advantage. However, two areas of concern remain: the cost of the solution and its pharmaceutical preparation. Although these compounds are easily synthesized and produced, market factors may make the cost of the mixture higher than the standard catheter locks used in dialysis centers. Compounding this solution is also a potential problem for dialysis centers.

Although none of the ACLs that have been tested to date are ideal, many vastly out-perform our current catheter-locking solutions. While we await the perfect solution, the mortality of patients on hemodialysis relating to catheter bacteremia remains high. What should nephrologists do? First, it is incumbent that we each be aware of the catheter-related bacteremia rate in our dialysis centers. This number is easily calculated by dividing the number of bacteremic events by the number of patient-days during the period under study. Optimal hygiene should be pursued in using access catheters. If bacteremic rates are elevated, one should consider the use of ACLs. In addition, in our opinion, patients at extremely high risk from infection—such as patients with dialysis catheters who have artificial heart valves, transvenous pacers, or defibrillators—should receive these solutions or at a minimum be informed of their availability and the reason they are not being used.

Catheter-related bacteremia is responsible for the deaths of approximately 2000 to 5000 hemodialysis patients each year.[8] The time is right to translate the results of clinically robust trials into action, thereby preventing a large proportion of catheter-related bacteremia with associated morbidity, mortality, and higher healthcare costs.

DISCLOSURES

None.

REFERENCES

1. Campos RP, Mazza do Nascimento M, Chula DC, Riella MC. Minocycline-EDTA lock solution prevents catheter-related bacteremia in hemodialysis. *J Am Soc Nephrol* 22: 1939–1945, 2011
2. Maki DG, Ash SR, Winger RK, Lavin P: A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: A multicenter, controlled, randomized trial. *Crit Care Med* 39: 613–620, 2011
3. Weijmer MC, van den Dorpel MA, Van de Ven PJ, ter Wee PM, van Geelen JA, Groeneveld JO, van Jaarsveld BC, Koopmans MG, le Poole CY, Schrander-Van der Meer AM, Siegert CE, Stas KJ; CITRATE Study Group: Randomized, clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients. *J Am Soc Nephrol* 16: 2769–2777, 2005
4. Dogra GK, Herson H, Hutchison B, Irish AB, Heath CH, Golledge C, Luxton G, Moody H: Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: A randomized controlled study. *J Am Soc Nephrol* 13: 2133–2139, 2002
5. Betjes MG, van Agteren M: Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. *Nephrol Dial Transplant* 19: 1546–1551, 2004
6. Kim SH, Song KI, Chang JW, Kim SB, Sung SA, Jo SK, Cho WY, Kim HK: Prevention of uncuffed hemodialysis catheter-related bacteremia using an antibiotic lock technique: A prospective, randomized clinical trial. *Kidney Int* 69: 161–164, 2006
7. McIntyre CW, Hulme LJ, Taal M, Fluck RJ: Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney Int* 66: 801–805, 2004
8. Bleyer AJ: Use of antimicrobial catheter lock solutions to prevent catheter-related bacteremia. *Clin J Am Soc Nephrol* 2: 1073–1078, 2007
9. Heng AE, Abdlkader MH, Diaconita M, Nony A, Guerraoui A, Caillot N, Rince M, Deteix P, Souweine B: Impact of short term use of interdialytic 60% ethanol lock solution on tunneled silicone catheter dysfunction. *Clin Nephrol* 75: 534–541, 2011
10. Tag Number V147: CDC Recommendations for Placement of Intravascular Catheters in Adults and Children, page 36. http://www.esrdnetwork6.org/utils/pdf/Interpretive%20Guidance%202008.pdf. 2011
11. Chu KH, Choy WY, Cheung CC, Fung KS, Tang HL, Lee W, Cheuk A, Yim KF, Chan WH, Tong KL: A prospective study of the efficacy of local application of gentamicin versus mupirocin in the prevention of peritoneal dialysis catheter-related infections. *Perit Dial Int* 28: 505–508, 2008
12. Battistella M, Bhola C, Lok CE: Long-term follow-up of the Hemodialysis Infection Prevention with Polysporin Ointment (HIPPO) Study: A quality improvement report. *Am J Kidney Dis* 57: 432–441, 2011
13. Kaplan AH, Gilligan PH, Facklam RR: Recovery of resistant enterococci during vancomycin prophylaxis. *J Clin Micro* 26: 1216–1218, 1988
14. Schwalbe RS, Stapleton JI, Gilligan PH: Emergence of vancomycin resistance in coagulase-negative staphylococci. *N Engl J Med* 316: 927–931, 1987
15. Weinstein RA, Fridkin SK: Vancomycin-intermediate and -resistant Staphylococcus aureus: What the infectious disease specialist needs to know. *Clin Infect Dis* 32: 108–115, 2001
16. 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* 27: 206–211, 2011
17. Bleyer AJ, Mason L, Russell G, Raad II, Sherertz RJ: A randomized, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infect Control Hosp Epidemiol* 26: 520–524, 2005

See related article, "Minocycline-EDTA Lock Solution Prevents Catheter-Related Bacteremia in Hemodialysis," on pages 1939–1945.