Use of Antimicrobial Catheter Lock Solutions to Prevent Catheter-Related Bacteremia

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Catheter-related bacteremia is an important source of morbidity and mortality in hemodialysis patients. A number of well-designed, controlled, prospective trials using antimicrobial catheter lock solutions to prevent catheter-related bacteremia have shown a dramatic, statistically significant decrease in not only infection but also mortality related to catheter-related bacteremia. Despite evidence of significant benefit, these locks are not routinely used in the United States. This review describes the epidemic problem of catheter-related bacteremia, reviews recent clinical trials with antimicrobial catheter lock solutions, and discusses current options and potential indications for catheter lock solutions in the hemodialysis population.

Epidemiology
Catheter-related bacteremia is an important source of morbidity and mortality in hemodialysis patients. A number of well-designed, controlled, prospective trials using antimicrobial catheter lock solutions to prevent catheter-related bacteremia have shown a dramatic, statistically significant decrease in not only infection but also mortality related to catheter-related bacteremia. Despite evidence of significant benefit, these locks are not routinely used in the United States. This review describes the epidemic problem of catheter-related bacteremia, reviews recent clinical trials with antimicrobial catheter lock solutions, and discusses current options and potential indications for catheter lock solutions in the hemodialysis population.

Citrate-Based Solutions

The best clinical trial of ACL solutions is a randomized trial from the Netherlands and Belgium showing a marked decrease in CRB with the use of a catheter lock that contains 30% citrate. At this concentration, citrate functions as both an antimicrobial agent and an anticoagulant. In this study, 291 patients were randomly assigned to heparin lock or citrate catheter lock. The citrate catheter lock was administered in prefilled syringes to avoid overdosage. CRB rates were 1.1/1000 patient-days for citrate and 4.1/1000 patient-days with heparin (P < 0.001). There were no infection-related deaths in the citrate group and five infection-related deaths in the heparin group (P = 0.028).

In general, when dialysis catheters are filled with locking solutions, there is overfill with spillage into the systemic circulation. Systemic leak occurs for two reasons. First, the catheter volume listed by the manufacturer is frequently 0.1 or 0.2 ml higher than the actual catheter volume, resulting in inadvertent instillation. Second, even when the appropriate fill volume is used, laminar flow results in the injected catheter lock’s streaming down the center of the lumen, with spillage of the ACL solution into the bloodstream. Systemic leak could result in transient hypocalcemia in the citrate group and an increased partial thromboplastin time in the heparin group. The latter would remain elevated until the heparin was metabolized. Nine patients in the citrate group and four patients in the
heparin group complained of a metallic taste or perioral paresthesias immediately after locking. These symptoms did not resolve with installation of smaller volumes of catheter lock. Bleeding after catheter placement occurred in 19 patients in the heparin group and six patients in the citrate group (P < 0.001). Sixteen patients had major bleeding episodes in the heparin group and five did in the citrate group (P = 0.01).

The citrate ACL seems to be ideal for prevention of catheter-related infection and mortality. Unfortunately, inadvertent administration of larger volumes of the citrate ACL than occurs with routine filling can lead to calcium complexation and hypocalcemia that could result in ventricular arrhythmias and sudden death. In April 2000, the Food and Drug Administration urged HD centers across the United States to stop using the product after a patient died of cardiac arrest after installation of 46.7% sodium citrate into an HD catheter that had just been placed (15). However, in the Netherlands, where prefilled syringes are used with a lower concentration of citrate, this has not occurred after the installation of >20,000 doses (M.C. Weijmer, personal communication, October 24, 2006). Citrate will not lead to resistance and seems to be the ideal agent for catheter locking at this time. Accurate instillation of solutions can be done safely, as evidenced in the Netherlands and by the frequent, careful administration of potassium and thrombolytics in hospitalized patients. Unfortunately, because of Food and Drug Administration warnings, it is unlikely that citrate will be used routinely in the near future.

Antibiotic-Based Solutions

Aminoglycoside catheter locks have also been shown to decrease catheter infection. Although gentamicin is inactive against Staphylococcus at levels reached in the serum, it is toxic to Staphylococcus at the high levels present in the catheter dwells. The most common solutions used are gentamicin and citrate or gentamicin and heparin. In a randomized, prospective trial of an ACL solution that contained 5 mg/ml gentamicin and 5000 IU heparin/ml in saline (2), there were 0.3 CRB events per 1000 patient-days with gentamicin/heparin and four CRB events per 1000 patient-days with heparin alone. All serum gentamicin levels were <0.2 mg/L during the study. In 1 yr follow-up data of this study, published in abstract form (16), CRB remained low throughout the study (0.12 infections per 1000 catheter-days), and there was no ototoxicity, solubility issues, or other adverse event reported; in addition, there was no evidence of development of resistant organisms. Two other groups reported no problems with solubility or adverse events in short-term (3 mo [17] and 6 mo [18]) studies with gentamicin and heparin.

Another randomized trial compared heparin (5000 U/ml) with a solution that contained 27 mg/ml gentamicin and 1.04% trisodium citrate (3). In this study, trisodium citrate was used at a concentration that provides anticoagulation but at a concentration that is unlikely to provide antimicrobial benefit and unlikely to result in significant hypocalcemia. CRB rates were 0.3/1000 d in the gentamicin group and 4.2/1000 d in the heparin group (P = 0.003). Spillage from this solution resulted in a median pre-HD gentamicin level of 2.8 mg/L (range 0.6 to 3.5 mg/L).

A recent, small, open-labeled, randomized clinical trial (19) compared a lower concentration of gentamicin/citrate (4 mg/ml and 3.13%, respectively) with minocycline and EDTA (3 and 30 mg/ml, respectively) and heparin. During a 6-mo period, seven of 20 patients in the heparin group, one of 21 patients in the minocycline EDTA group, and zero of the patients in the gentamicin group developed bacteremia (P = 0.008 for gentamicin versus heparin and P = 0.02 for heparin versus minocycline EDTA).

Major potential obstacles to the use of gentamicin heparin solutions are poor solubility, ototoxicity, and antimicrobial resistance. Gentamicin and heparin are considered to be incompatible because of solubility problems, even though this solution was used without difficulties in the three previously mentioned trials (2, 17, 18). There are no solubility issues reported with gentamicin citrate.

Another concern with aminoglycosides is ototoxicity. Spillage results in very low serum levels. For this reason, low levels of aminoglycosides and other antibiotics will be present in the serum, and there is a potential for ototoxicity with aminoglycosides. There has been one case report of ototoxicity with the use of an amikacin catheter lock solution (20). This occurred after the use of 10 mg/ml amikacin as a catheter lock and was associated with elevated serum amikacin levels. Given the potential for ototoxicity, lower gentamicin concentrations (5 mg/ml) used in the study of gentamicin heparin (2) might be more advisable than the 27 mg/ml gentamicin concentration used in the gentamicin/citrate study (3). There has been no evidence of clinically evident ototoxicity in all of these studies reported to date, although formal audiology testing was not done in these studies.

Another issue with gentamicin and other antibiotic ACL solutions is the development of bacterial resistance. Resistance may develop to high concentrations found in the catheter lock, or, as a result of environmental pressures, resistance may develop at the concentrations normally found in the serum or urine with treatment. After >1 yr of treatment, resistance resulting in inefficacy of the ACL solution has not developed with the gentamicin/heparin solution (16). One must weigh the development of resistance to antibiotics in ACL against the potential risk for development of antibiotic resistance to vancomycin, because without ACL solutions, more bacteremia episodes occur, and the use of vancomycin to treat infections is likely increased. Use of first-generation cephalosporins may now be replacing vancomycin in the treatment of sensitive organisms, and this may also decrease the likelihood of vancomycin resistance (21).

The use of antibiotic dwells could lead to bacteremia events in which the offending organism could be resistant to the antibiotic used in the dwell. A delay in achieving appropriate antibiotic treatment could lead to increased morbidity and mortality. For this reason, the use of vancomycin or cephalosporin antimicrobial dwells may be inadvisable. However, gentamicin and tetracycline derivatives are not a primary treatment for staphylococcal bacteremia. If aminoglycosides were being con-
sidered as initial therapy for a bacteremia, then the use of tobramycin or amikacin might be a better choice for empiric coverage in a patient who receives a gentamicin ACL.

One must also consider that CRB is frequent and life-threatening, and reserving these solutions to prevent the development of resistance may not be indicated. Refraining from the use of ACL solutions will prevent resistance but also result in excess mortality in patients for whom it is not prescribed.

A third solution that may be considered is minocycline EDTA (22). Two separate studies, one in HD patients, have shown a marked decline in CRB events in patients who have experienced recurrent CRB (18,23). Potential issues related to minocycline EDTA use include the higher cost of this solution and antibiotic resistance. Resistance to minocycline EDTA did not develop after >1 yr of use (18). In addition, intravenous minocycline is no longer available for use. Doxycycline or another antibiotic in the tetracycline group may be a suitable replacement for minocycline EDTA.

**Approach to CRB Prevention**

Why is there little emphasis on bacteremia prevention in general and the use of catheter lock solutions in particular? Potential reasons include lack of accountability, lack of nephrologist motivation, and lack of financial incentive. In terms of accountability, most networks direct attention toward a dialysis center’s proficiency in obtaining target Kt/V, parathyroid hormone, and hemoglobin levels, with little comparison with regard to infection. In addition, for improving outcomes in general, extensive physician education and motivation is required, and these services are frequently performed or funded by large pharmaceutical companies. These companies are also important in driving the guideline process (24). Large pharmaceutical manufacturers do not currently market products that prevent infection, and they therefore do not participate to a great degree in education in this area. The problem is further compounded with regard to catheter lock solutions. These solutions are not directly reimbursed to the dialysis centers; therefore, the dialysis center will lose money with their administration in patients without insurance coverage. Furthermore, whereas hospital admissions for bacteremia are extremely expensive, the dialysis center has only a small financial loss in terms of missed treatments.

What is the best approach for nephrologists who are interested in decreasing catheter infections? Undoubtedly, one should decrease the use of catheters as much as possible. This has been the subject of numerous investigations, although the truth of the matter is that catheters are unavoidable in some patients even under the best of circumstances. Given the necessity of a catheter, the nephrologists must take into account four important factors when deciding on the potential use of an ACL (Table 1): The underlying bacteremia rate of the dialysis center, whether a patient is at high risk for developing infection, whether a patient is at high risk if he or she develops bacteremia, and what the potential adverse effects for the particular patient are from an ACL.

The nephrologist should attempt to lower the bacteremia rate within his or her unit by ensuring the use of sterile procedure and adequate catheter care. Simply placing an emphasis and providing education on infection decreases infection rates (25). Multidisciplinary education of the patient, the nursing staff, and all dialysis unit personnel will be helpful in decreasing infection. A CDC survey of self-reporting US dialysis centers revealed a mean CRB rate of 1.5/1000 patient-days (9). Therefore, rates above 2/1000 patient-days suggest problems with CRB prevention. All dialysis personnel should be educated regularly in the use of sterile technique, and the rates of infection in individual bays should be monitored. The use of topical antimicrobials will also decrease infection (1). Unfortunately, the nephrologist may not be the medical director of the dialysis center and may not always be able to influence the infection rate. In centers with higher rates of infection, one may be more likely to consider the use of ACL solutions in patients who are at high risk.

Even with maximal use of sterile technique, infections will continue to occur, and the nephrologist must weigh the risks and benefits of ACL solutions for the individual patient. A subset of patients are at minimal risk for infection. This includes patients who have had catheters for long periods of time without infection. These patients may not wish to be exposed to the minimal risk associated with ACL solutions.

There is also a large group of patients for whom the risk of

<table>
<thead>
<tr>
<th>Table 1. Considerations for the use of ACL solutions&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Environment</strong></td>
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<tr>
<td>Catheter infection rate of patient’s dialysis center</td>
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<tr>
<td><strong>Individuals at high risk for infection</strong></td>
</tr>
<tr>
<td>Older</td>
</tr>
<tr>
<td>Diabetic&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunosuppressed</td>
</tr>
<tr>
<td>History of recurrent infection&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Femoral catheters&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Decreased serum albumin</td>
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<tr>
<td>Elevated serum ferritin</td>
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<tr>
<td>Nasal carriage of <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><strong>Individuals at high risk from infection</strong></td>
</tr>
<tr>
<td>Diabetic</td>
</tr>
<tr>
<td>Immunosuppressed</td>
</tr>
<tr>
<td>Individuals with artificial heart valves</td>
</tr>
<tr>
<td>Individuals with other cardiac valvular abnormalities</td>
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<tr>
<td>Individuals with transvenous pacemakers</td>
</tr>
<tr>
<td>Individuals with artificial joints</td>
</tr>
<tr>
<td>Individuals who developed sepsis from previous catheter infections</td>
</tr>
<tr>
<td>Individuals with vascular grafts</td>
</tr>
<tr>
<td>Individuals using last available hemodialysis access</td>
</tr>
</tbody>
</table>

<sup>a</sup>ACL, antimicrobial catheter lock.

<sup>b</sup>ACL solutions have been shown to decrease bacteremia rates in these groups.
infection is high or in whom the development of an infection will be catastrophic. Retrospective studies have identified risk factors for catheter infection: In an analysis of admissions for hospital-managed septicemia from a cohort of individuals in the case-mix study of the US Renal Data System (26), age >65 yr was associated with an adjusted relative risk of 1.75 (1.48 to 2.06) for being admitted for septicemia. In the same study, the relative risk for hospitalization for patients with diabetes was 1.26 (1.06 to 1.5) and for patients with a serum albumin <3.5 g/dl was 1.66 (1.38 to 1.99). These results have been confirmed in other studies (27). Other risk factors that have been identified include poor personal hygiene, nasal carriage of Staphylococcus aureus, and high serum ferritin levels (27).

Three factors are associated with very high rates of infection in which catheter lock solutions have been found to be beneficial: (1) Femoral vascular catheters. In one study of HD patients (28), the rate of CRB was 5.78/1000 patient-days for femoral catheters and 2.43/1000 and 3.25/1000 patient-days for subclavian and internal jugular catheters, respectively. There was a 63% reduction in risk to 2.16/1000 patient-days with the use of a cefotaxime/heparin catheter lock (P = 0.0001). Reduction in CRB rates for femoral catheters was also noted in an investigation that used a cefazolin/heparin ACL (29). (2) Patients with diabetes have also been found to be at increased risk for vascular catheter infections (26), and the use of a cefotaxime/heparin catheter lock (Table 2) (7) was found to decrease CRB incidence (1.56 versus 3.68 episodes per 1000 catheter-days; P < 0.0001) and to decrease CRB-related mortality (9.8 versus 23.4%; P = 0.015). (3) In a retrospective study of patients with a history of recurrent bacteremia (18), the use of minocycline EDTA or gentamicin/heparin ACL was found to decrease CRB incidence from 9.13/1000 catheter-days before ACL to 1.04 while the ACL was used (P < 0.001).

Patients in whom catheter infections would be catastrophic include patients with cardiac valvular disease or prosthetic heart valves. In a recent study of prosthetic valve endocarditis (30), mortality was 40% (10 of 25) in HD patients who had this condition. Patients with transvenous pacers are also at high risk from bacteremia, because the removal of an infected pacemaker is a procedure associated with significant morbidity (31). Pacemaker infection occurs in approximately 40% of patients who develop a bloodstream infection from Staphylococcus aureus (32). Patients with prosthetic joints are also at significant risk for hematogenous seeding and the development of septic arthritis. Other patients who are at significant risk from infection include patients who use one of their last potential dialysis access sites.

One must then consider the potential disadvantage of catheter lock solutions. As discussed, leakage of these solutions into the systemic circulation occurs, and there is a potential for the development of antibiotic resistance. Although few adverse events have been reported (2,5), one must consider the possibility of antibiotic allergy and the potential for ototoxicity in individuals with decreased auditory acuity if one is considering gentamicin as an ACL.

At present, K/DOQI guidelines do not discuss the use of ACL solutions for prophylaxis (33). The 2006 K/DOQI guidelines actually only reviewed literature on access until May 5, 2004. For this reason, the best randomized trials regarding catheter lock solutions were not evaluated. Similarly, CDC recommendations were published in 2002. These guidelines recommend the use of ACL in patients who have recurrent bacteremia and in whom maximum adherence to sterile technique has been determined (34).

Available ACL solutions include citrate, gentamicin-based solutions, cephalosporin-based solutions, and vancomycin heparin locks. Concerns regarding potential antimicrobial resistance would be most worrisome for vancomycin, and it would likely be preferable to consider other agents. Gentamicin-based solutions are inexpensive, and lower concentration gentamicin-based solutions may be the best alternative at present. Minocycline is no longer available; doxycycline EDTA may be a suitable alternative. Citrate seems to be the ideal solution, but

### Table 2. Randomized, controlled trials of ACL solutions

<table>
<thead>
<tr>
<th>Trial Solution</th>
<th>No. of Catheters (Intervention/Control)</th>
<th>Blinding</th>
<th>Infection Rate with Trial Solution (/1000 Patient-Days)</th>
<th>Infection Rate with Heparin (/1000 Patient-Days)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin citrate (3)</td>
<td>53/55</td>
<td>Double-blind, randomized</td>
<td>0.3</td>
<td>4.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cefazolin/heparin/gentamicin</td>
<td>60/60</td>
<td>Double-blind, randomized</td>
<td>0.44</td>
<td>3.12</td>
<td>0.031</td>
</tr>
<tr>
<td>Trisodium citrate (5)</td>
<td>148/143</td>
<td>Double-blind, randomized</td>
<td>1.1</td>
<td>4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Gentamicin heparin (2)</td>
<td>25/25</td>
<td>Open-label, randomized</td>
<td>0.3</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Cefotaxime heparin (7)</td>
<td>51/58</td>
<td>Double-blind, randomized</td>
<td>1.56</td>
<td>3.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taurolidine citrate (4)</td>
<td>39/39</td>
<td>Open-label, randomized</td>
<td>0</td>
<td>2.1</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Readers are directed to the appropriate reference for exact information on the preparation of the trial solutions.

a2 ml of 40 mg/ml gentamicin and 1 ml of 3.13% trisodium citrate in a 3-ml syringe.
bMixture of 10 mg/ml cefazolin, 5 mg/ml gentamicin, and 1000 U/ml heparin.
cTrisodium citrate, 30%.
dGentamicin 5 mg/ml, heparin 5000 IU/ml.
eCefotaxime dissolved directly in heparin sodium for a final concentration of 10 mg/ml cefotaxime and 5000 U/ml heparin.
f1.35% taurolidine and 4% sodium citrate.
obstacles to its use must be overcome in the United States. Taurolidine is also unavailable in the United States.

Once a solution is decided on, a pharmacy that can produce the solution must be identified, preferably in proximity to the dialysis center. Reimbursement then becomes an issue. The dialysis provider will frequently not desire to provide catheter lock solutions, because the unit will not be reimbursed. However, if the unit will not subsidize these solutions, then the nephrologists can contact a local pharmacy to mix the solution and provide it with a prescription. The solution can then be reimbursed through the patient’s insurance. If the patient does not have insurance for medications, then an inexpensive solution such as gentamicin citrate should be considered. If the dialysis center refuses to use the provided solution, then formal communication via correspondence regarding the need for the ACL solution in particular cases may be the best option.

Approximately 6000 patients die of CRB each year. These deaths are for the most part preventable with strict adherence to sterile technique and the use of ACL solutions when indicated. It is time for us as nephrologists to take the lead and prevent death in our patients who are at risk.

Disclosures
None.

References
flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infect Control Hosp Epidemiol* 26: 520–524, 2005


