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Treatment Guidelines for Dialysis Catheter–Related Bacteremia: An Update

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Earlier this year, new guidelines for the management of intravascular catheter-related infections,[1] sponsored by the Infectious Diseases Society of America (IDSA), were published to update the previous 2001 guidelines.[2] Recognizing the unique aspects of the management of catheter-related infections in dialysis patients, the committee solicited participation of nephrologists for the first time. This document provides more comprehensive recommendations for the treatment of dialysis catheter–related bacteremia than those available in the 2006 update of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) vascular access guidelines.[3] Prevention of catheter-related bacteremia, although an important topic, was beyond the scope of the IDSA guidelines. The present commentary provides highlights of sections dealing with the management of dialysis catheter–related infections.

DIAGNOSIS OF CATHETER-RELATED BACTEREMIA

Dialysis catheter–related bacteremia frequently is diagnosed and treated in the outpatient setting. The definitive diagnosis of catheter-related bacteremia in hospitalized patients requires concurrent positive blood cultures from the catheter and a peripheral vein, with the colony count from the catheter at least 5-fold greater than that obtained from the peripheral vein if quantitative blood cultures are used. Alternatively, catheter cultures should become positive at least 2 hours earlier than the simultaneously drawn peripheral blood cultures (ie, differential time to positivity). Meeting these criteria is straightforward in nondialysis inpatients, but poses several challenges in the outpatient setting.

First, peripheral-blood cultures may not be feasible in dialysis patients, either because the peripheral veins have been exhausted or because of the need to avoid venipuncture in veins intended for future vascular access creation.[4] Second, if the fever manifests after starting the dialysis session, when systemic blood is circulating through the catheter, there may not be a meaningful difference between peripheral and catheter blood culture results. Thus, the majority of "peripheral-blood cultures" are actually drawn during hemodialysis from the blood tubing connected to the central venous catheter. Positive cultures obtained from the blood tubing are treated as "positive blood cultures" in practice, but their correlation with peripheral cultures obtained from a vein is unknown. Third, even when catheter and

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peripheral-blood cultures are obtained, handling of blood cultures is not standardized. Most outpatient dialysis units are geographically remote from a hospital laboratory and managed by a national dialysis provider. Blood-culture bottles obtained at these units usually are shipped by express mail to a central laboratory in another state, rather than processed at a local laboratory. Thus, there is a variable period before the culture bottles are placed in an incubator, and the temperature during transport may vary depending on the delay in shipping the samples and the season. These commercial laboratories do not provide quantitative colony counts and are less precise in reporting the time of bacterial growth. Moreover, the accuracy of differential time to positivity has been confirmed only when the blood-culture bottles are incubated within 6 hours of the blood draw.[5]

Because of these limitations, diagnosis of catheter-related bacteremia in a dialysis outpatient setting may require a lower standard of proof than in hospitalized patients. One practical definition used in some dialysis studies has been the requirement of positive blood cultures (drawn from blood tubing) in a symptomatic patient (fever or chills) in the absence of clinical evidence of an alternate source of infection.[6-8] There is no consensus about the extent of the workup required to exclude other potential sources of infection. Because the dialysis unit usually is at a remote site and a physician often is not present, the clinical evaluation is performed by a dialysis nurse. It consists of a focused history (eg, productive cough, dysuria, foot infection, diarrhea, or skin rash) and focused physical examination (eg, lung auscultation or inspection of the feet). Laboratory or radiological evaluation is rarely performed unless there is a clinical suspicion. Thus, it would be unusual for the patient to be sent to a hospital for a chest radiograph. Urine cultures are obtained infrequently because of either anuria or infrequent urine voids. Clearly, this practical definition of catheter-related bacteremia falls short of the rigorous IDSA criteria. Consequently, some dialysis patients with a diagnosis of catheter-related bacteremia actually have another source of bacteremia. However, insisting on the most rigorous diagnostic criteria would be a difficult standard to adhere to in this unique clinical setting and may even lead to underdiagnosis of catheter-related bacteremia.

CHOICE, DOSE, AND DURATION OF ANTIBIOTICS

Catheter-related bacteremia may be caused by a broad spectrum of Gram-positive and Gram-negative bacteria.[4] A substantial proportion of staphylococcal infections in dialysis patients are methicillin-resistant species.[7,9,10] Thus, empirical antibiotic therapy consists of vancomycin for Gram-positive bacterial coverage and an aminoglycoside or third-generation cephalosporin for Gram-negative bacterial coverage[4] (Table 1). However, in dialysis units with a low prevalence of methicillin-resistant *Staphylococcus aureus*, cefazolin is a reasonable empirical choice. When organism and sensitivity results are available, the antibiotic regimen should be modified accordingly. In particular, vancomycin should be substituted with cefazolin in patients with methicillin-sensitive *S aureus* bacteremia. Dialysis patients continued on vancomycin therapy have a 3-fold greater risk of treatment failure than those switched to cefazolin therapy for methicillin-susceptible staphylococci.[11] Moreover, unnecessary continuation of vancomycin therapy may promote the emergence of vancomycin-resistant infections.[12]

A concerted effort should be made to select antibiotics that have pharmacokinetics that permit administration after each dialysis session. This strategy is possible with vancomycin, aminoglycosides, ceftazidime, cefazolin, and daptomycin.[4] Vancomycin is the antibiotic of choice for methicillin-resistant *Staphylococcus* species if the isolate has a low vancomycin minimal inhibitory concentration. In patients with methicillin-sensitive *Staphylococcus* infection, either a penicillinase-resistant penicillin (eg, nafcillin) or a first-generation cephalosporin (eg, cefazolin) theoretically is acceptable. However, the pharmacokinetics of nafcillin in dialysis patients requires administering the drug every 6 hours.[13] Following such a regimen entails placement of a peripherally inserted central catheter, which should be avoided at all costs in dialysis patients. Peripherally inserted central catheters produce rapid thrombosis of veins, thereby jeopardizing future creation of a permanent access in the ipsilateral upper extremity.[14] For this reason, cefazolin is the preferred antibiotic in this situation because it can be administered after each dialysis session.[15] The majority (~95%) of Gram-negative bacteria in dialysis patients with catheter-related bacteremia are sensitive to both aminoglycosides and third-generation cephalosporins.[6,7] The pharmacokinetics of both drugs are compatible with administration after dialysis. However, a third-generation cephalosporin may be preferred because of the substantial risk of irreversible aminoglycoside ototoxicity and vestibulotoxicity in dialysis patients.[16] Vancomycin-resistant *Enterococcus* can be treated with daptomycin administered after each dialysis session. Candidemia in dialysis patients has been treated successfully with either amphotericin B or oral fluconazole in conjunction with catheter replacement.[6]

Dialysis patients with uncomplicated catheter-related bacteremia are treated with systemic antibiotics for 3 weeks. Those with metastatic infection (eg, endocarditis or osteomyelitis) should receive 6 weeks of antibiotic therapy. Monitoring serum antibiotic concentrations is challenging in dialysis outpatients. First, blood samples usually are sent to a central laboratory rather than to a local hospital, producing a 1- to 3-day delay in obtaining results. Second, there is uncertainty about the appropriate serum antibiotic levels in dialysis patients. In patients with normal kidney function, one tries to achieve high peaks and low troughs. In anephric patients, drugs that are dependent on renal excretion are removed only by dialysis. Thus, the antibiotic is removed during the dialysis session and readministered after the dialysis session. The peak concentration then is sustained for 2 to 3 days until the next dialysis session. Moreover, antibiotic clearance may vary between dialysis sessions, depending on the type of dialyzer used, dialysis blood flow, and duration of the dialysis session. For all these reasons, serum antibiotic levels are measured infrequently in dialysis outpatients. Antibiotic dosing guidelines in dialysis patients are based on results of limited publications. Published studies have validated appropriate dosing schedules for vancomycin and cefazolin to ensure therapeutic concentrations[15,17] (Table 1).

WHAT TO DO ABOUT THE TUNNELED CENTRAL VENOUS DIALYSIS CATHETER

This is a complex issue in long-term dialysis patients with tunneled catheters and bacteremia. Not only is the catheter the source of the infection, but it also is the vascular access for providing ongoing dialysis therapy. There are 4 potential management options:

(1) intravenous antibiotics alone, (2) prompt catheter removal with delayed placement of a new tunneled catheter, (3) exchange of the infected catheter with a new one over a guidewire, or (4) use of an antibiotic lock.[4] Administration of intravenous antibiotics alone is unsatisfactory because bacteremia recurs in approximately 75% of patients when the course of antibiotics has been completed.[8,9,18-20] Moreover, a recent prospective (nonrandomized) study observed a 5-fold greater risk of treatment failure in dialysis patients with catheter-related bacteremia that was treated with antibiotics alone compared with antibiotics and catheter removal.[21]

Prompt removal of the infected catheter takes care of the source of bacteremia, but creates hardships in providing subsequent dialysis treatments. A temporary nontunneled catheter is used for dialysis, and when the bacteremia is resolved, a new tunneled dialysis catheter is placed. Alternatively, the patient can be started on broad-spectrum intravenous antibiotic therapy without immediate catheter removal. If the fever resolves within 2 to 3 days (ie, by the next dialysis session), the infected catheter can be exchanged over a guidewire for a new catheter as an elective outpatient procedure. It is not necessary to routinely confirm negative culture results before catheter exchange as long as the patient is asymptomatic (ie, no fever or chills). Retrospective studies suggest that catheter exchange over a guidewire is associated with a cure rate similar to that observed with catheter removal and delayed replacement while reducing the number of access procedures required.[8,10,22-24]

An alternative approach is to use an antibiotic lock as adjunctive therapy to systemic antibiotics (Table 1). This lock consists of a very high concentration of antibiotic (~100-fold greater than therapeutic plasma concentrations). The antibiotic lock is instilled into each catheter lumen at the end of each dialysis session for the duration of the systemic antibiotic therapy (3 weeks). The goal is to sterilize the catheter lumens so that the catheter can be salvaged. If fever or bacteremia persists, the infected catheter is removed. This approach has been successful in treating bacteremia while salvaging the catheter in about two-thirds of episodes of catheter-related bacteremia.[6,7,25-27] The success rate varies considerably by organism, with an 87% to 100% cure rate for Gram-negative bacterial infections, 75% to 84% for *Staphylococcus epidermidis*, 61% for *Enterococcus* infections, and only 40% to 55% for *S aureus*.[7,26,27-29] Thus, the antibiotic lock approach should be pursued with *S aureus* bacteremia only in patients with major concerns about the availability of central veins for subsequent catheter placement because leaving the catheter in place increases morbidity and mortality with *S aureus* infections. The vast majority of outpatient dialysis units do not have a pharmacist. However, dialysis nurses can easily prepare the antibiotic-heparin lock solution from the antibiotic solutions used for systemic administration[6,7] (Table 1). Finally, the infected catheter should always be exchanged in patients with candidemia.[30]

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Table 1

Antibiotic Dosing in Hemodialysis Patients

Systemic Antibiotics

Antibiotic	Dosing Regimen
Vancomycin	20-mg/kg loading dose infused during the last hour of the dialysis session, then 500 mg during the last 30 min of each subsequent dialysis session
Gentamicin (or tobramycin)	1 mg/kg, not to exceed 100 mg, after each dialysis session
Ceftazidime	1 g IV after each dialysis session
Cefazolin	20 mg/kg IV after each dialysis session
Daptomycin	6 mg/kg after each dialysis session

Antibiotic Lock

	Volume of Solution (mL)			
Type of Lock Solution	Vancomycin*	Ceftazidime†	Cefazolin†	Heparin‡
Vancomycin/ceftazidime	1.0	0.5	—	0.5
Vancomycin	1.0	—	—	1.0
Ceftazidime	—	1.0	—	1.0
Cefazolin	—	—	1.0	1.0

Note: Empirical dosing, pending culture and sensitivity results, should include vancomycin with a third-generation cephalosporin or an aminoglycoside. Cefazolin may be used in place of vancomycin in units with a low prevalence of methicillin-resistant staphylococcus. Treatment duration is 3 weeks for uncomplicated bacteremia and 6 weeks for patients with metastatic infection. The antibiotic/heparin lock solution is prepared by the dialysis nurse immediately before instillation into the catheter lumen by mixing in a single syringe the appropriate solutions used for systemic administration of antibiotics, as indicated. If the volume of the catheter lumen is greater than 2 mL, the difference should be made up with an additional volume of heparin.

Abbreviation: IV, intravenously.

*Vancomycin, 5 mg/mL (in normal saline solution).

†Ceftazidime and cefazolin, 10 mg/mL (in normal saline solution).

‡Heparin, 1,000 U/mL.