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Management of hemodialysis catheter-related bacteremia with an adjunctive antibiotic lock solution

Zipporah Krishnasami, Donna Carlton, Lisa Bimbo, Maria E. Taylor, Daniel F. Balkovetz, Jill Barker, and Michael Allon

Division of Nephrology, Department of Pharmacy, and Biostatistics Unit, Comprehensive Cancer Center, University of Alabama at Birmingham, and Birmingham Veterans Administration Hospital, Birmingham, Alabama, USA

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Background. Tunneled dialysis catheters are complicated by frequent systemic infections. Standard therapy of catheter-associated bacteremia involves both systemic antibiotics and catheter replacement. Recent data suggest that biofilms in the catheter lumen are responsible for the bacteremia, and that instillation of an antibiotic lock (highly concentrated antibiotic solution) into the catheter lumen after dialysis sessions can eradicate the biofilm.

Methods: We analyzed prospectively the efficacy of an antibiotic lock protocol, in conjunction with systemic antibiotics, for treatment of patients with dialysis catheter-associated bacteremia without catheter removal. Protocol success was defined as resolution of fever and negative surveillance cultures one week following completion of the protocol. Protocol failure was defined as persistence of fever or surveillance cultures positive for any pathogen. In addition, infection-free catheter survival was compared to that observed in institutional historical control patients treated with catheter replacement.

Results: Blood cultures were positive in 98 of 129 of episodes (76%) in which patients dialyzing with a catheter had fever or chills. Protocol success occurred in 40 of 79 infected patients (51%) treated with the antibiotic lock. Protocol failure occurred in 39 cases (49%): 7 had persistent fever, 15 had positive surveillance cultures (9 for *Candida* and 6 for bacteria), and 17 required catheter removal due to malfunction. Each of the pathogens in the surveillance cultures was different from the original pathogen in that patient. Eight of the 9 secondary *Candida* infections and all 6 secondary bacterial infections resolved after catheter exchange and specific antimicrobial treatment. Overall catheter survival with the antibiotic lock protocol was similar to that observed among patients managed with catheter replacement (median survival, 64 vs. 54 days, $P = 0.24$).

Conclusions: Use of an antibiotic lock, in conjunction with systemic antibiotic therapy, can eradicate catheter-associated bacteremia while salvaging the catheter in about one half of cases. Moreover, this management approach offers clinical advantages over routine catheter exchange.

Key words: hemodialysis, dialysis catheter, infection, antibiotic, Candida, vascular access.

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About 20% of the prevalent hemodialysis patients in the United States use a tunneled central vein catheter for vascular access [1, 2]. Infections are the most serious complication of tunneled dialysis catheters. Catheter-associated bacteremia occurs at a frequency of 2 to 5.5 per 1000 patient-days [3–7], may be caused by both Gram-positive and Gram-negative pathogens [5, 8], and often results in serious systemic infections, including endocarditis, osteomyelitis, epidural abscess, septic arthritis, and even death [5, 8]. Treatment of catheter-associated bacteremia with systemic antibiotics alone without catheter removal is regarded as ineffective; only 22 to 37% of tunneled catheters can be salvaged without catheter removal [3–5, 7, 9]. Moreover, attempting to salvage the infected catheter with systemic antibiotics alone, incurs the risk of serious systemic complications, including endocarditis and epidural abscess [10]. For this reason, current guidelines recommend that dialysis-catheter associated bacteremia be managed by a combination of systemic antibiotics, as well as removal of the catheter [11]. The new catheter can be placed a few days after removal of the infected catheter, or it can be exchanged immediately over a guidewire [6, 12, 13]. Tanriover et al reported similar infection-free survival rates with both catheter replacement strategies [8]. However, either approach requires an additional radiologic procedure, is costly, and is burdensome to the patient and the dialysis unit.

Management of dialysis catheter-associated bacteremia would be simplified if it were possible to eradicate the source of the infection without having to replace the catheter. Scanning electron microscopy demonstrates the presence of a biofilm coating the inner lumen in 80% of indwelling central vein catheters within days of their placement [14, 15]. Instillation of concentrated antibiotic solutions into the lumen of silicone vascular catheters (antibiotic lock) in vitro eliminates the biofilm [16], suggesting a useful clinical application. Finally, preliminary studies in tunneled central vein catheters used for total parenteral nutrition [17], chemotherapy catheters [18], and subcutaneously implanted hemodialysis vascular access devices [19] have suggested that the biofilm can be eradicated by an antibiotic lock solution instilled into the catheter lumen, permitting bacteriologic cure without replacing the catheter. These type of studies have prompted a recent consensus panel to recommend use of antibiotic locks for clinical management of uncomplicated bacteremia related to tunneled central vein catheters [20]. However, there are no large, prospective studies assessing the efficacy of this approach in treating hemodialysis patients. The goal of the present study was to evaluate prospectively the efficacy of a defined antibiotic lock protocol for management of dialysis catheter-associated bacteremia without catheter replacement.

METHODS

Patient population

The University of Alabama at Birmingham (UAB) provides chronic dialysis to approximately 500 in-center hemodialysis patients. About 20% of the prevalent patients dialyze with tunneled dialysis catheters. The demographics of the patients dialyzing with catheters are as follows: 26% of the patients are age 65 or older; 51% of the patients are female; 84% of the patients are black and 16% are white; and 41% of the patients have diabetes. All patient hospitalizations, surgical procedures, and radiologic procedures are done at UAB Hospital.

Management of dialysis catheter-associated bacteremia

Infection was suspected clinically by the dialysis nurse whenever patients with a dialysis catheter developed fevers or chills, in the absence of another obvious source of infection. Treatment with empiric broad-spectrum antibiotics (vancomycin and gentamicin) was initiated immediately after obtaining blood cultures from a peripheral vein, as both Gram-positive and Gram-negative organisms grow frequently from these cultures [5, 7, 8]. Patients with clinical sepsis (some combination of high fever, persistent shaking chills or hypotension) were hospitalized for further management, whereas those with milder symptoms (low grade fever and stable blood pressure) were managed as outpatients. The dialysis catheter was removed promptly if there was a persistent fever or hemodynamic instability 48 hours after initiation of antibiotic therapy.

Patients with suspected dialysis catheter-associated bacteremia received loading doses of vancomycin (20 mg/kg) and gentamicin (1.5 mg/kg), followed by maintenance doses of antibiotics during each of the next 8 consecutive dialysis sessions. The maintenance dose of vancomycin was 500 mg [21], and the maintenance dose of gentamicin was 1 mg/kg, but not exceeding 100 mg. Vancomycin was infused during the last hour of dialysis, and gentamicin was given immediately after completion of the dialysis session. Due to the logistic hurdles in obtaining pharmacokinetic data in dialysis outpatients, the drug doses were not adjusted. The bacteriologic reports were reviewed daily by the Dialysis Access Coordinators (D.C. and L.B.). If the initial blood cultures had no growth for five days, the antibiotics were discontinued. All patients with positive blood cultures were treated with intravenous antibiotics for three weeks. Once the pathogen was identified and antibiotic sensitivities available, the antibiotic regimen was modified accordingly. Surveillance blood cultures were obtained routinely from the patients one week after completing the antibiotic lock protocol.

Antibiotic lock

Both vancomycin-heparin and cefazolin-heparin locks maintain their stability when incubated in vitro for up to ten days in implantable venous devices [22]. In contrast, gentamicin is believed to be incompatible with heparin, due to its precipitation in solution [23]. For this reason, other investigators have prepared gentamicin antibiotic locks (40 mg/mL) by using sodium citrate as a vehicle (abstract; Sodemann et al, *J Am Soc Nephrol* 8:173A, 1997). Since heparin is widely used in the United States to fill the dialysis catheters between dialysis sessions, and citrate is no longer commercially available for this purpose, we re-evaluated the compatibility of gentamicin with heparin. Gentamicin at concentrations ≥10 mg/mL precipitated immediately when mixed with heparin; however, at lower concentrations (≤4 mg/mL), the solution remained clear for up to 72 hours of incubation at 37°C. We also confirmed the compatibility in heparin (2500 units/mL) of vancomycin (2.5 mg/mL), cefazolin (5 mg/mL), vancomycin + gentamicin (1 mg/mL), and cefazolin + gentamicin at 37 degrees. At these drug concentrations, which are approximately 100-fold higher than the respective therapeutic plasma concentrations, the antibiotics remained in solution for up to 72 hours. Previous studies had suggested that heparin inhibits the bactericidal effect of gentamicin [24]. In vitro incubation with *Escherichia coli* revealed that heparin partially inhibited the bactericidal action of gentamicin, but this effect was overcome at a gentamicin concentration of 1 mg/mL (Table 1). All the antibiotic-heparin locks were prepared from the antibiotic solutions used for systemic administration (Table 2). The locks were instilled into both lumens of the dialysis catheter upon completion of each dialysis session, and withdrawn immediately prior to the next dialysis session. Once the course of antibiotics was completed, standard heparin locks were resumed.

Data analysis

Consent for review of the patients' medical records for research purposes was obtained from the UAB Institutional Review Board. The Access Coordinators tracked all blood culture results, changes in antibiotics, and patient outcomes. A protocol success was defined prospec-

Table 1. In vitro compatibility and antimicrobial activity of gentamicin with heparin

	Gentamicin concentration $\mu g/mL$					
	0	1	4	32	128	1000
No heparin	0.57 ± 0.04	0.28 ± 0.02	0.14 ± 0.01	-0.06 ± 0	-0.06 ± 0	-0.06 ± 0
Heparin	0.16 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.11 ± 0	0.06 ± 0.02	-0.06 ± 0

The values in the Table are absorbance (± SD) at OD 600 nm. Using the broth macrodilution technique, sodium heparin was added to vials containing various concentrations of gentamicin. A standardized suspension of *E. coli* was added to each tube to obtain a final concentration of 4.5×10^5 CFU/mL. The final heparin concentration was 2500 U/mL in all vials. After a 48 hour incubation at 37°C, the visible turbidity was determined as the absorbance measured at OD 600 nm. The MIC was defined as the lowest concentration at which no bacterial growth occurred, as evidenced by the absence of turbidity (absorbance = 0). In the absence of gentamicin, heparin partially inhibited bacterial growth. Heparin partially inhibited the antimicrobial effect of gentamicin, but this inhibition was overcome at a gentamicin concentration of 1 mg/mL.

Table 2. Preparation of the antibiotic lock solution

	Volume of solution mL				
Type of lock solution	Vanc[a]	Gent[b]	Cefaz[c]	Heparin[d]	NS
Vancomycin/gentamicin	1.0	0.5	—	0.5	—
Vancomycin	1.0	—	—	0.5	0.5
Gentamicin	—	0.5	—	0.5	1.0
Cefazolin	—	—	1.0	0.5	0.5
Cefazolin/gentamicin	—	0.5	1.0	0.5	—

The antibiotic/heparin lock solutions were prepared from the following solutions used for systemic administration of antibiotics: [a] vancomycin, 5 mg/mL (in NS, normal (0.9%) saline); [b] gentamicin, 4 mg/mL (in NS); [c] cefazolin, 10 mg/mL (in NS); [d] heparin, 10,000 units/mL. The final drug concentrations in the antibiotic lock solutions was: vancomycin, 2.5 mg/mL, gentamicin, 1 mg/mL, cefazolin, 5 mg/mL, and heparin, 2500 units/mL.

tively as catheter salvage with resolution of symptoms within 48 hours of initiation of the antibiotic lock protocol and negative surveillance cultures one week after completing the antibiotic regimen. A protocol failure was defined as (*1*) persistent fever or hemodynamic instability >48 hours after initiation of the antibiotic lock protocol or (*2*) post-treatment surveillance cultures positive for *any* organism. Catheters that were removed for noninfectious reasons before completion of the antibiotic lock protocol were excluded from this analysis.

Survival analysis techniques were used to model infection-free catheter survival from the time of initiation of the antibiotic lock protocol. Patients whose catheter malfunctioned, was electively removed (permanent vascular access ready to use), or who died with a functioning catheter were considered censored. Survival distributions were plotted using the Kaplan Meier curve. We compared catheter survival with this protocol to that previously reported from our institution for 69 non-concurrent, historical patients whose catheter-related bacteremia was managed with catheter replacement (either exchange over a guidewire or removal with delayed placement of a new catheter) [8]. Because of the possibility that some catheter malfunctions could be related to infection, we repeated the catheter survival analysis with both infection and malfunction being considered as catheter failures. The log rank test was used to compare catheter survival between the two treatment groups.

RESULTS

During the six-month period from June 1, 2000 to November 30, 2000, a total of 129 episodes of catheter-related bacteremia were suspected on clinical grounds (Fig. 1). In 31 cases the blood cultures were negative at five days, the antibiotics discontinued, and the catheter continued to be used. Blood cultures from the remaining 98 episodes yielded a total of 124 pathogens, resulting in an overall dialysis catheter-associated infection rate of 5.4 per 1000 patient-days. A single Gram-positive coccus grew in 50% of the cases, a single Gram-negative organism grew in 30% of the cases, and 20% of positive cultures yielded two or more organisms. Of the 124 pathogens grown from blood cultures, 61% were Gram-positive cocci, and 39% were Gram-negative rods. The Gram positive organisms consisted largely of *Staphylococcal* species (63%) and *Enterococcus* (30%), with the remaining comprised of *Streptococcal* species (7%). About 63% of the *Staphylococcal* species were methicillin resistant. The Gram negative organisms included *Klebsiella* (29%), *Enterobacter* (25%), *Serratia* (13%), *E. coli* (11%), *Proteus* (8%), *Acinetobacter* (6%), *Stenotrophomonas* (4%), *Citrobacter* (2%), and *Morganella* (2%).

Thirty-six episodes of positive blood cultures were excluded from analysis because (*1*) the catheter was removed for noninfectious reasons prior to completing the antibiotic lock protocol, (*2*) the catheter was removed without attempting the antibiotic lock protocol, (*3*) there was an incomplete patient follow-up, or (*4*) the culture grew *Candida* (Fig. 1). Of the remaining 62 episodes, 40 cases (64.5%) were protocol successes (the patient remained asymptomatic with negative surveillance cultures and the catheter was salvaged). The remaining 22 cases (35.5%) were considered protocol failures. The success rate of the protocol, sorted by pathogen (Table 3), was similar for Gram-positive and Gram-negative infections [odds ratio (OR) 1.22; 95% confidence interval (CI) 0.49 to 3.08, $P = 0.66$]. If catheter dysfunction was included as a catheter failure, the success rate of the protocol was 51% (40 of 79 catheters).

The protocol failures included seven patients whose fever persisted longer than 48 hours after initiation of

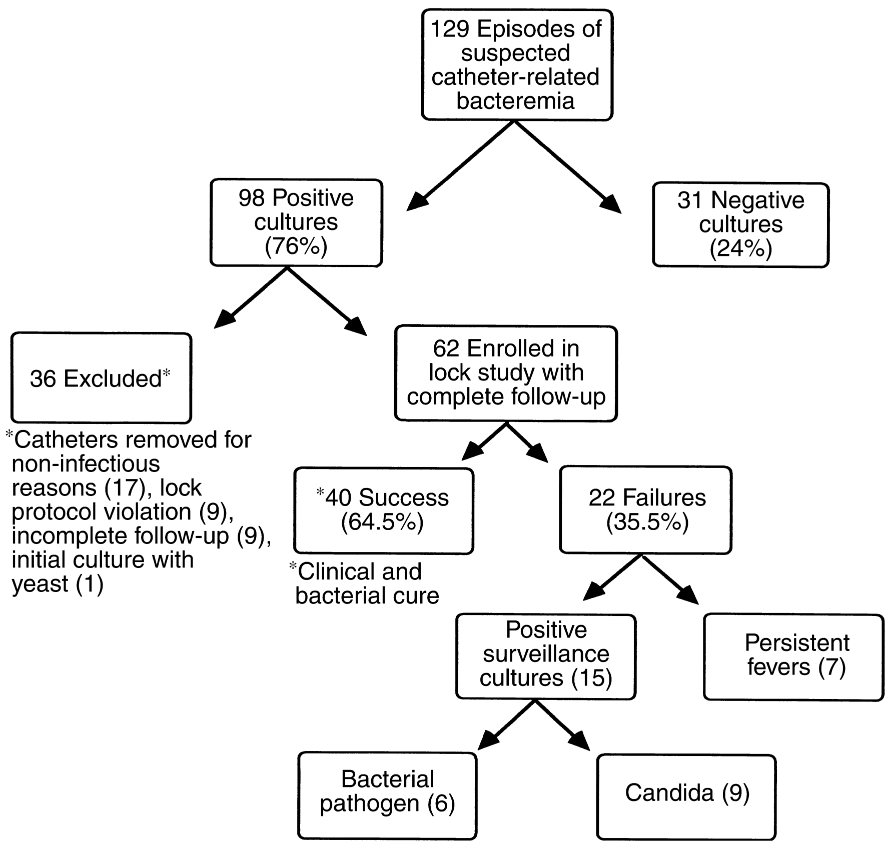

Fig. 1. Clinical outcomes of all episodes of dialysis catheter-related bacteremia during a six-month period.

Table 3. Outcomes of episodes of catheter-associated bacteremia treated with the antibiotic lock protocol

Pathogen[a]	*N* catheters	Success *N*	Success %
Gram positive cocci	44	28	64
Staphylococcus	29	20	69
MRSE	19	15	79
MSSE	6	4	67
MRSA	1	0	0
MSSA	1	0	0
Other	2	1	50
Enterococcus	12	5	42
Strep species	3	3	100
Gram-negative rods	34	20	59
Klebsiella	12	8	66
Enterobacter	8	6	75
Serratia	5	1	20
Stenotrophomonas	2	1	50
Acenitobacter	2	1	50
E. coli	2	1	50
Proteus	2	1	50
Citrobacter	1	1	100

Bacteriologic success was defined as absence of recurrent fever and negative surveillance cultures after completion of the protocol. Abbreviations are: MRSE, methicillin-resistant *Staph epidermidis*; MSSE, methicillin-sensitive *Staph epidermidis*; MRSA, methicillin-resistant *Staph aureus*; MSSA, methicillin-sensitive *Staph aureus*.

[a] Some episodes of bacteremia were associated with >1 pathogen

the antibiotic lock protocol, and 15 who had positive surveillance cultures one week after completing the antibiotic course (Fig. 1). The latter included 6 patients whose surveillance cultures grew a new bacterial pathogen, and 9 who grew *Candida*. Thus, all 15 positive surveillance cultures obtained one week after completing the three-week protocol grew a new pathogen, different from that present in the initial blood culture. Of the 15 patients with positive surveillance cultures, 14 were asymptomatic and one had septic *Candida* arthritis. Eight of the 9 *Candida* infections were treated by catheter exchange, as well as anti-fungal therapy (fluconazole or amphotericin for 2 weeks); in all cases the subsequent surveillance cultures obtained one week after completing the anti-fungal medication were negative. The ninth patient with secondary *Candida* infection died of bacterial endocarditis before completing the course of anti-fungal therapy. All 6 patients whose surveillance cultures were positive for a bacterial pathogen were treated with a catheter exchange as well as systemic antibiotics, and had negative blood cultures subsequently.

Five of the 9 patients whose surveillance cultures grew *Candida* had been treated with broad spectrum antibiotics (vancomycin and gentamicin) for three weeks due to an initial *enterococcal* bacteremia. The likelihood of a sec-

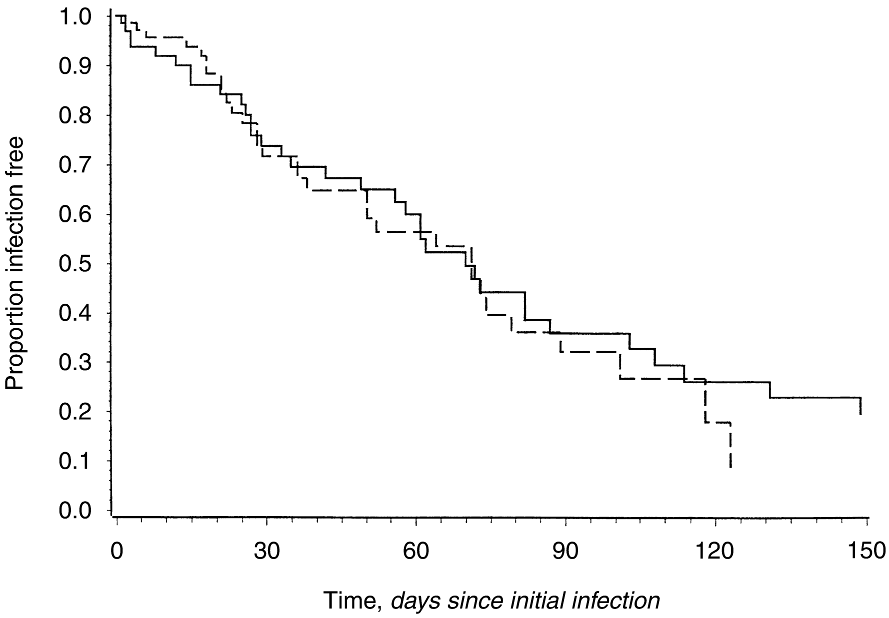

Fig. 2. Life-table analysis (Kaplan Meier survival curves) for *infection-free catheter survival* among patients whose initial episode of catheter-related bacteremia was treated with one of two strategies: antibiotic lock protocol without catheter replacement (solid line) or replacement of the infected catheter (dashed line) (P = 0.57).

ondary *Candida* infection was 42% when the original pathogen was *Enterococcus*, as compared with 8% for all other pathogens (OR 8.21, 95% CI 1.77 to 38.18, P = 0.003). In addition, two patients with Candidemia had been on chronic immunosuppressive medications (one for myasthenia gravis, and one for polyneuropathy).

Among the 62 patients with documented catheter-associated bacteremia enrolled in the antibiotic lock protocol, serious systemic complications occurred in 11 cases, or 18% of the total. These complications included septic shock in 5 patients, septic arthritis in 2 patients (one of whom also had septic shock), endocarditis in 3 cases, and spinal osteomyelitis in one patient. In addition, one patient required mechanical ventilation due to respiratory failure. Six of the infections resulting in serious systemic complications were caused by Gram-negative organisms (3 *Serratia*, 2 *Enterobacter*, and 1 *Klebsiella*), and five were due to Gram-positive infections (3 *Staphylococcus* and 2 *Enterococcus*). The frequency of serious systemic complications with catheter-related bacteremia was not significantly different with Gram-negative versus Gram-positive infections (18 vs. 11%, P = 0.43).

Infection-free catheter survival after initiation of the antibiotic lock protocol was compared to that previously observed in non-concurrent control patients treated with catheter replacement. The patients in the two treatment groups were similar in terms of their mean age (55 ± 14 vs. 52 ± 16 years), proportion of females (48% vs. 51%), proportion of blacks (80% vs. 84%), and proportion of diabetics (45% vs. 41%). The survival curves for the two treatment groups were very similar (Fig. 2). The median infection-free catheter survival was 70 days for patients treated with the antibiotic lock protocol and 71 days for patients treated with catheter replacement (P = 0.57). Re-analysis of the data with catheter failure being defined as infection or malfunction also showed similar overall catheter survival for the two treatment groups (Fig. 3). In this analysis, catheter survival was 64 days for patients treated with the antibiotic lock protocol and 54 days for patients treated with catheter replacement (P = 0.24).

DISCUSSION

The antibiotic lock protocol was successful in achieving a clinical and bacteriologic cure of dialysis catheter-associated bacteremia in 64.5% of the patients enrolled in this study, without requiring catheter replacement. Treatment with systemic antibiotics alone (without catheter replacement) is rarely successful in salvaging an infected catheter [3–5, 9], most likely because it does not eradicate the biofilm responsible for the bacteremia [14, 15]. For this reason, the current standard of care is to replace the infected catheter [11]. In the absence of an antibiotic lock, the antibiotic levels within the catheter are negligible during systemic administration of the drug, and are inadequate to treat this source of the infection [25]. The antibiotic lock solutions used in the current study are about 100-fold higher than therapeutic plasma concentrations, and thereby adequate to eradicate the biofilm, without requiring removal of the catheter. Serious systemic complications occurred in 18% of the cases treated with the antibiotic lock protocol. This frequency is comparable to the 19% rate of serious complications observed at our institution when prompt catheter replacement was employed [8], suggesting that the anti-

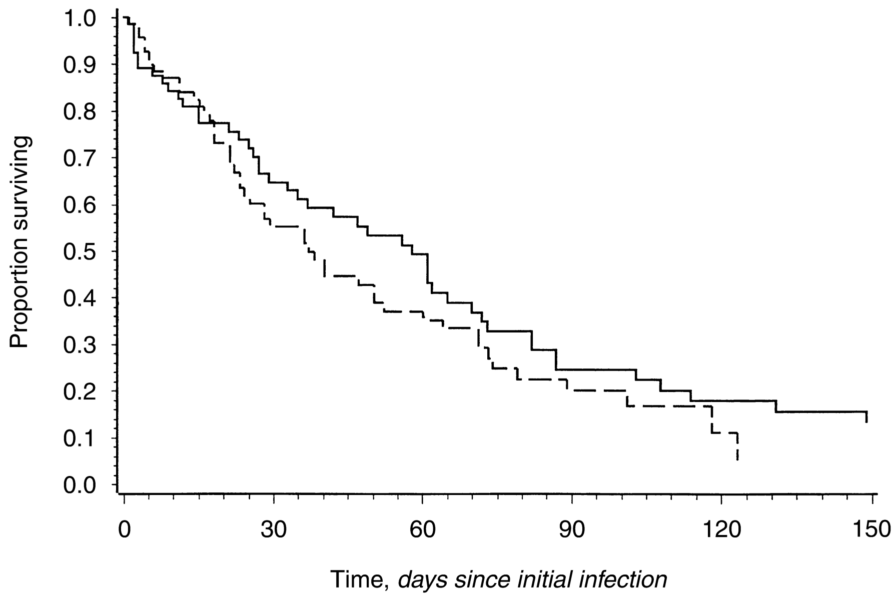

Fig. 3. Life-table analysis (Kaplan-Meier survival curves) for *overall catheter survival* among patients whose initial episode of catheter-related bacteremia was treated with one of two strategies: antibiotic lock protocol without catheter replacement (solid line) versus replacement of the infected catheter (dashed line). Catheter failures included infection or dysfunction (P = 0.24).

biotic lock protocol does not increase the risk of serious complications.

Few studies have examined the use of antibiotic locks for treatment of tunneled central venous catheter infections. Messing et al achieved a bacteriologic cure in 10 of 11 (91%) catheters used for total parenteral nutrition [17]. Panagea and Galloway successfully used an antibiotic lock to treat bacteremia associated with chemotherapy catheters in 17 of 22 cases (77%) [18]. Finally, Boorgu et al reported successful eradication of bacteremia with the antibiotic lock in 14 of 14 (100%) hemodialysis patients dialyzing with a subcutaneous vascular access device [19]. The current study observed a bacteriologic cure in 40 of 62 (64.5%) of patients with dialysis catheter-associated bacteremia treated with an antibiotic lock protocol. Among the 15 patients with positive surveillance cultures, each grew a different organism than that present in the initial blood cultures, suggesting that the original infection had been eradicated, and the patient had a new infection.

The results observed in the current study are in agreement with the recent recommendations by the consensus panel on the management of uncomplicated infections related to tunneled central vein catheters [20]. The consensus panel also recommended that when the infection is due to *Staphylococcus aureus*, catheter salvage with the antibiotic lock should only be attempted if a transesophageal echocardiogram does not show vegetations. Only two infections in the present study were due to *Staphylococcus aureus* (Table 3), and neither responded to the antibiotic lock protocol. Finally, the three-week course of antibiotics used in the current study is longer than the two-week course recommended by the consensus panel.

During this six-month period of prospective data collection, we observed an overall catheter-associated infection rate of 5.4 per 1000 patient-days, comparable to the range of 2 to 5.5 per 1000 patient days described in previous published series [3–7]. The presence of fever or chills among patients with a dialysis catheter who did not have another obvious source of infection was associated with positive blood cultures in 76% of cases. The high likelihood of bacteremia and the wide variety of potential pathogens supports empiric initiation of broad-spectrum antibiotic therapy in these patients. Follow-up of the blood culture results permitted early discontinuation of antibiotics at day 5 in culture negative patients (about one quarter of the cases). Moreover, in the majority of patients with positive blood cultures, it was possible to switch to narrower spectrum antibiotic regimen within a few days, once the antibiotic sensitivities of the pathogens has been elucidated. Successful achievement of these goals was expedited by centralized monitoring of the protocol by Dialysis Access Coordinators, under the supervision of a nephrologist [26].

The surveillance cultures were positive for *Candida* species in 9 of 62 (14%) of the patients enrolled in the antibiotic lock protocol. Similarly, Messing et al reported a 9% frequency of secondary *Candida* infections among a group of home parenteral nutrition patients whose catheter-associated bacteremia was treated with an antibiotic lock [17]. Only one of the 9 patients with secondary Candidemia in the present study was symptomatic or exhibited evidence of metastatic infection. Furthermore, catheter exchange in conjunction with anti-fungal therapy (fluconazole or amphotericin) was uniformly successful in eradicating the fungemia. Most patients with candidemia following their antibiotic lock protocol could be predicted, because they had received broad-spectrum antibiotic therapy (vancomycin + gentamicin) for three weeks due to an *enterococcal* infection or had been on concomitant immunosuppressive therapy. In dialysis patients with these risk factors, it might be preferable to proceed with prompt catheter exchange, rather than attempt to salvage the catheter with an antibiotic lock protocol. Of interest, after we adopted this revised protocol, only 1 of 61 patients (1.7%) of patients with catheter-related bacteremia who were treated with the antibiotic lock developed subsequent fungemia.

In summary, prospective evaluation of our antibiotic lock protocol suggests that dialysis catheter-associated bacteremia can be eradicated in about two-thirds of cases, without requiring removal of the infected catheter. If the culture-negative cases are included in the analysis, 71 of 93 (76%) of catheters with suspected bacteremia were salvaged by this treatment protocol. Moreover, the delay in removal of catheters among patients who fail to respond to the protocol did not increase the risk of serious infectious complications. Successful treatment of an episode of catheter-associated bacteremia with the antibiotic lock protocol did not preclude a subsequent episode (Fig. 2). However, the likelihood of a subsequent infection was no different than that observed among patients whose initial infection was treated with catheter replacement. The ability to resolve most cases of dialysis catheter-related bacteremia without removal of the infected catheter may result in a substantial economic benefit.

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Reprint requests to Michael Allon, M.D., Division of Nephrology, 1900 University Blvd, S. THT 647 Birmingham, Alabama 35294, USA. E-mail: mallon@nrtc.uab.edu

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