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# Comparison of Low-Dose Gentamicin With Minocycline as Catheter Lock Solutions in the Prevention of Catheter-Related Bacteremia

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• ***Background:*** **Catheter-restricted antibiotic lock solutions were found to be effective in the prevention of catheter-related bacteremia (CRB), but insufficient data are available about the ideal agent and dose. We hypothesized that a low concentration of gentamicin would be as effective as the high doses studied in the past.** ***Methods:*** **In this prospective, open-labeled, randomized, clinical trial of patients on long-term hemodialysis therapy, patients were randomly assigned to administration of an antibiotic lock solution of gentamicin/citrate (4 mg/mL), minocycline/EDTA, or the control solution of heparin. Patients were followed up until the study end point of CRB was reached or a censoring event occurred. Interim data analysis was performed after 6 months to assess data safety; efficacy was noted and the study was terminated early.** ***Results:*** **Sixty-two patients were enrolled into the study, evenly distributed in 3 arms, with data from 1 patient excluded from analysis. Seven of 20 patients in the heparin group (4.0 events/1,000 catheter days), 1 of 21 patients in the minocycline group (0.4 events/1,000 catheter days), and none of 20 patients in the gentamicin group developed bacteremia. Results were statistically significant by using 2-tailed Fisher exact test; heparin versus gentamicin, $P = 0.008$, and heparin versus minocycline, $P = 0.020$.** ***Conclusion:*** **Antibiotic lock solutions are superior to the standard heparin lock alone in the prevention of CRBs, and low-dose gentamicin solution has efficacy similar to that of greater concentrations used in previous studies.** ***Am J Kidney Dis*** **48:596-605.**



**INDEX WORDS: Hemodialysis; catheter; antibiotic lock; bacteremia; prevention; gentamicin.**

INFECTION IS A COMMON cause of morbidity and mortality in hemodialysis (HD) patients.[1,2] Despite clear recommendations for a native arteriovenous fistula as the preferred access for HD patients, international data from the Dialysis Outcomes and Practice Patterns Study[3] and US data from the End-Stage Renal Disease Clinical Performance Measures Project[4] and regional Network data[5] showed consistent and persistent use of catheters in more than 60% of incident and up to 30% of prevalent patients. Perhaps the use of some catheters as vascular access in the United States is unavoidable in a proportion of patients because of failed arteriovenous fistulae and grafts.[6] Twenty-eight percent of long-term dialysis patients use a catheter as permanent HD access.[7]

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HD catheters contribute significantly to bacteremia.[8] Septicemia rates in HD patients continue to increase, and hospital admissions for vascular access infection have doubled in the last decade.[9] The use of cuffed tunneled HD catheters instead of uncuffed catheters has not translated to a significant decrease in the incidence of catheter-related bacteremia (CRB) and resultant infective endocarditis in this population.[10] The most devastating complication is the development of endocarditis, to which patients with chronic kidney disease are particularly prone, with a 1-year survival rate of only 62%.[11] Increasingly, *Staphylococcus aureus* is the responsible microbe, typically acquired outside the hospital and increasingly resistant to methicillin.[12]

All indwelling vascular catheters are colonized by microorganisms within 24 hours after insertion.[13] The formation of "biofilm" on external and internal surfaces of vascular catheters is thought to have an important role in the colonization process. Although both external and internal surfaces develop biofilm, the absence of evidence of external site or tunnel infection in the majority of episodes of CRB suggests that the more important biofilm is endoluminal. Internal-surface biofilm also may be modifiable with endoluminal antibiotic locks. The biofilm produced by a combination of host factors and microbial products (eg, glycocalyx, or "slime") has a critical role in bacterial antimicrobial resistance and recalcitrant infections.[14] Such bacteria as

*S aureus* are able to communicate in groups to alter virulence and create biofilm.[15] Systemic antibiotics used to treat bacteremia do not penetrate the catheter lumen and therefore do not eradicate the biofilm,[16] leading to potential treatment failures and eventual sacrifice of the catheter.

A variety of techniques have been used to prevent CRB, summarized by the Centers for Disease Control and Prevention (CDC).[17] A protocol based on Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines focusing on "hub care"[18] was able to decrease the incidence of CRB from 6.8 to 1.6 episodes/1,000 catheter-days. Antibiotic lock solutions also were studied in vascular catheters in many clinical settings and successfully prevented CRB, including in HD catheters.[19] This effectiveness is commensurate with the elimination of biofilm from the catheter lumen.[20] However, debate continues on the appropriate antibacterial agent, as well as its optimal concentration, to eradicate a wide variety of organisms,[21-24] as well as concerns for ultimate bacterial resistance. When used after CRB has occurred, antibiotic lock solutions in conjunction with systemic antibiotics salvage catheters, but the success rate[22] is still less than that with catheter exchange.

Several studies examined primary prevention of CRB by means of intraluminal instillation of antibiotics: minocycline/EDTA (M/EDTA),[25] vancomycin/heparin,[26] and gentamicin.[27] Dogra et al[27] studied gentamicin at an intraluminal concentration of 40 mg/mL mixed with sodium citrate and successfully decreased the frequency of CRB. However, detectable blood levels of gentamicin evident before delivery of the following dose raised concerns for ototoxicity. Because the intraluminal concentrations used have concentrations orders of magnitude greater than those achieved systematically, we postulated that gentamicin at a lower concentration also might be effective. We also sought to determine whether duration of catheter implantation (vintage) before antibiotic lock solution was begun affected potential benefit.

## METHODS

### *Study Design*

The study design is a prospective, open-label, randomized, controlled trial conducted at a large tertiary-care urban medical center. The primary aim is to evaluate the efficacy of low-dose gentamicin compared with heparin as a locking solution at the end of treatments. The secondary goal is to determine whether prior duration of use affected the efficacy of the antibiotic lock. We used a 10-fold lower gentamicin concentration of 4 mg/mL mixed in a low concentration of citrate as the experimental antibiotic lock solution. Citrate was chosen as the anticoagulant because the stability of gentamicin in heparin for the required periods up to 1 week, either at room temperature or 4°C, could not be attained consistently. Physical stability for 1 week, along with biological efficacy against a spectrum of pathogens found with CRBs (shown in vitro in the microbiology laboratory), was crucial to the study to make it practical. To ensure efficacy, we also compared outcomes of the gentamicin lock with an M/EDTA antibiotic lock solution previously found effective in preventing bacteremia in HD patients.[28] The orange color of the minocycline solution precluded blinding of either patients or medical staff without masking the solutions. All antibiotic lock solutions were prepared at the central research pharmacy of Henry Ford Hospital (Detroit, MI) and shipped weekly, then stored at 4°C at regional dialysis centers. Solutions older than 1 week were discarded.

### *Evaluation of Antibiotic Lock Solution Bactericidal Efficacy*

Because it was observed that the orange color of the reconstituted M/EDTA solution discolored rapidly within 24 hours at room temperature, but not if refrigerated, we were concerned that inadvertent change during transfer from pharmacy to dialysis center or within dialysis units could lead to potential anxiety for patients and nursing staff, as well as alter bactericidal properties. We therefore evaluated in vitro bactericidal activity of the solution microbiologically. The M/EDTA mixture as used in the clinical trial was divided into 2 aliquots: 1 refrigerated and another stored at room temperature. Immediately after preparation and at 1, 2, and 7 days of storage, 100 $\mu$L from each of the refrigerated and room-temperature bottles was inoculated into separate 13-mm diameter blank filter paper disks (BBL Taxo; Becton Dickenson Microbiology Systems, Cockeysville, MD) and allowed to dry. Bactericidal activity was tested against a methicillin-resistant *S aureus* isolate from a patient. Culture plates were inoculated on blood agar in 5% carbon dioxide; after 18 to 24 hours, a direct colony suspension was prepared by transferring isolated colonies to a tube of sterile saline. Inoculum density was measured by using a spectrophotometer (Vitek DensiChek, St Louis, MO) to obtain turbidity optically similar to a 0.5 McFarland turbidity standard. The resulting suspension was inoculated onto the surface of a Mueller Hinton agar plate (BBL; Remel, Lenexa, KS) in the conventional manner and preprepared discs were placed onto the surface of inoculated plates. Plates were examined after a 16-hour incubation at 35°C, and the zone of inhibition around each disc was measured. The zone of inhibition was 43 mm initially, as well as after 1, 2, and 7 days of storage for both the refrigerated and room-temperature samples. Similar experiments were conducted with gentamicin/trisodium citrate (G/TC) with freshly prepared solutions stored for 7 days.

### Patients

Patients were enrolled from 3 HD centers within the Greenfield Health System (GHS) between October 4, 2003, and April 30, 2004. To adjust for individual center effect on the incidence of bacteremia (baseline CRB rates varied 2-fold among the 3 dialysis centers), permutated block randomization was performed at each center. All prevalent patients with either tunneled or nontunneled (only if placed in the internal jugular vein) catheters as their primary vascular access were eligible for the study. However, only tunneled catheters were studied because of a GHS policy prohibiting dialysis in their centers of patients with nontunneled catheters. Catheters of all vintages were included. Patients were excluded if they were younger than 18 years, required a surrogate decision maker, had antibiotic treatment within 2 weeks before the date of enrollment, had catheters with blood flow rates less than 300 mL/min, or required frequent thrombolytic solution dwells in the catheter lumen for malfunction. Patients also were excluded if they were admitted to an outside hospital for any illness or required thrombolytics for catheter thromboses on more than 3 occasions.

Enrolled patients were randomly assigned by using a block randomization protocol into 1 of 3 arms containing the following solutions: G/TC (4 mg/mL and 3.13%, respectively), M/EDTA (3 mg/mL and 30 mg/mL, respectively), and standard heparin solution alone (HS; 5,000 U/mL). Antibiotic solutions were prepared in the research pharmacy, transported to the individual centers on a weekly basis, and stored in the refrigerator. Nurses were trained to instill the solution into each of the 2 ports of the HD catheter at the end of each treatment, using the exact fill volume of each port. Similarly, this lock solution was withdrawn and discarded before the beginning of each subsequent treatment. In the event of hospitalization, the appropriate instillation of the 2 antibiotic lock solutions or HS was continued at the end of each dialysis treatment by the staff at Henry Ford Hospital. Tunneled HD catheters were inserted by experienced vascular access surgeons.

### Catheter-Related Bacteremia

Enrolled patients were routinely monitored clinically for symptoms and signs of bacteremia. Blood cultures were drawn if patients had fever, chills, rigors, sweats, change in mental status, or exit-site infection. The study protocol required peripheral and catheter blood cultures and an exit-site swab to be collected, if indicated. Empiric vancomycin and/or gentamicin also was administered based on clinical judgment. Catheters were removed based on CDC recommendations.[29] If the catheter was removed, the catheter tip was cultured. Patients with positive blood culture results were treated with systemic antibiotics driven by type of organism and antibiotic susceptibility. Blood stream infections were defined by CDC criteria.[29]

*Definite blood stream infection.* This is defined as the same organism from a semiquantitative culture of the catheter tip (>15 colony-forming units/catheter segment) and a peripheral or catheter blood sample in a symptomatic patient with no other apparent source of infection.

*Probable blood stream infection.* This is defined as defervescence of symptoms after antibiotic therapy with or without removal of the catheter in the setting in which blood cultures confirm infection, but catheter tip does not, or if catheter tip does, blood cultures do not, in a symptomatic patient with no other apparent source of infection.

We chose not to include "possible" blood stream infection, defined as the absence of laboratory confirmation of blood stream infection.

### Statistical Analysis

Primary end points of the study are the occurrence of bacteremia or a censoring event, such as removal of the catheter for any reason, need for thrombolytic instillation on more than 2 occasions, loss of follow-up of patients, or death or withdrawal from dialysis therapy of the patient. Infection-free survival of the catheter is defined as the number of days from instillation of the first catheter lock solution after randomization to the diagnosis of CRB, censure point, or end of study. Patient data were to be excluded from analysis if a patient in any group developed an interval acute medical illness within 2 weeks after enrollment because this would have precluded an effective period of therapy, particularly in a catheter of older vintage.

An audit of all HD patients at GHS HD centers with tunneled and nontunneled catheters showed a baseline risk for infection of 3.2 episodes/1,000 catheter-days for 2002, with the rate unchanged through the first 6 months of 2003. Using this rate of catheter infection, sample size for $\alpha$ of 0.05 and 80% power was calculated to be 280 catheters (3 groups) followed up for a total of 1,000 days, assuming an effect size of 50% and no difference between the 2 antibiotic lock solution groups, G/TC and M/EDTA. Conversely, if much larger effect sizes of 80% occurred, as reported for other interventions,[8,18,27] sample size could be decreased to 79 catheters followed up for 1,000 days. To avoid exposure of patients to unnecessary risk if antibiotic lock solution had large effects, interim analyses were planned after 5,000 and 10,000 total days at risk had accrued in enrolled patients.

Fisher exact test to determine differences in absolute events and Kaplan-Meier method and log-rank test were used to determine whether differences in cumulative infection-free catheter survival occurred. Infection-free catheter survival, adjusted for baseline covariates, was analyzed by using Cox proportional hazards test. All results are presented as mean ± SEM or 95% confidence intervals. Differences among groups in demographic characteristics were assessed by using chi-square or Fisher exact test. Differences in continuous variables were assessed by using analysis of variance followed by a protected *t*-test, if appropriate. Some variables were not normally distributed; therefore, Wilcoxon/Kruskal-Wallis rank-sum test also was used to compare the groups. *P* less than 0.05 is accepted as significant. *P* of 0.05 to 0.10 are given as absolute values in tables. All values greater than 0.10 are listed as not significant.

## RESULTS

At the start of the study, 116 of 523 patients (22%) from the 3 HD centers were being dia-

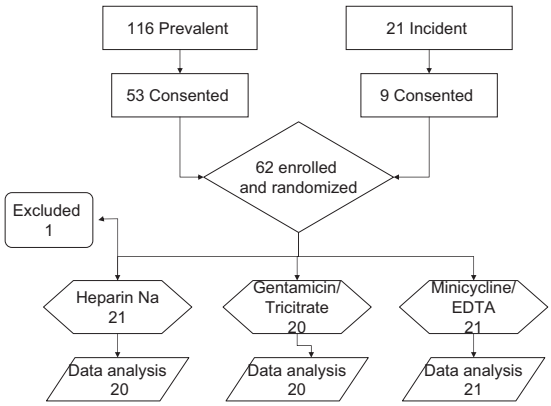


**Fig 1. Flow of patients into the study. See text.**

lyzed with tunneled catheters. Patient flow is shown in Fig 1. Of these, 53 patients were eligible and agreed to participate in the study, and an additional 9 incident patients were added during the following months. One prevalent patient (assigned to the control group) was excluded from analysis because of the development of bacteremia within 3 days of study enrollment, and the individual's demographic data also were removed from analyses. All data reported therefore are for the per-protocol population. All patients were seen on a weekly basis in the HD unit, and clinical events were examined closely. No patient was lost to follow-up. All catheters in use were tunneled because our institutional policy precluded use of acute catheters in GHS dialysis units.

Baseline demographic and clinical data were similar for all groups (Table 1). Average age was 58 to 60 years, and patients were predominantly Afro-American. Male-female ratio was nearly 1:1 in the HS and G/TC groups; the M/EDTA group had a slight excess of males (13:8), but there was no statistically significant difference between groups ($P > 0.5$ for all comparisons). Diabetes was underrepresented in the M/EDTA heparin group, 8 of 21 patients compared with the other 2 groups, in which diabetes was present in 60% or greater of subjects; however, the maximum difference did not reach significance ($P = 0.061$). The prerandomization vintage of catheters in days in use was not normally distributed, but was similar in all 3 groups: G/TC, 145 ± 33 days; M/EDTA, 198 ± 45 days; and HS, 111 ± 25 days. Median durations were 122, 98, and 63 days, respectively ($P = 0.45$ for differences among distributions). At the time of the first interim analysis, catheter-days at risk also did not differ: G/TC, 95 ± 11 days; M/EDTA, 97 ± 18 days; and HS, 85 ± 18 days. A total of 6,189 days at risk had accrued, distributed as 1,734 days in the HS group, 2,002 days in the G/TC group, and 2,453 days in the M/EDTA group. The higher total days at risk in the M/EDTA group accrued from a smaller number of censure events caused by death, withdrawal, or tissue-type plasminogen activator (tPA) use (Table 2). During the course of the study, 4 patients died: 1 each in the HS and M/EDTA

**Table 1. Demographic Characteristics of Study Groups**

| | HS (control) | G/TC | M/EDTA | *P* |
|---|---|---|---|---|
| No. of subjects | 20 | 20 | 21 | |
| Patient age (y) | 59 ± 4 | 58 ± 3 | 58 ± 3 | >0.5 |
| Catheter vintage (d) | 111 ± 25 | 145 ± 33 | 198 ± 45 | 0.28 |
| Median catheter vintage (d) | 63 | 122 | 98 | 0.27 |
| Catheter-days at risk | 85 ± 18 | 95 ± 11 | 97 ± 18 | >0.5 |
| Median catheter-days at risk | 71 | 96 | 80 | 0.45 |
| Race | | | | NS |
| Asian | 0 | 1 | 0 | |
| Afro-American | 12 | 10 | 15 | |
| Caucasian | 7 | 8 | 6 | |
| Hispanic | 1 | 1 | 0 | |
| Diabetes (yes/no) | 12:8 | 14:6 | 8:13 | 0.061* |
| Male-female ratio | 10:10 | 11:9 | 13:8 | NS |

NOTE. Data expressed as mean ± SEM unless noted otherwise. Analysis of variance used for comparison among means and Wilcoxon/Kruskal-Wallis rank sum used for comparison of medians.

Abbreviation: NS, not significant.

*Fisher exact *P* for largest difference, G/TC versus M/EDTA.

**Table 2. Mortality and Use of Thrombolytics for Access Patency**

| | HS | G/TC | M/EDTA | P* |
|---|---|---|---|---|
| Mortality | | | | |
| Deaths† | 1 | 2 | 1 | NS |
| Withdrawn from dialysis | 1 | 1 | 0 | NS |
| Use of tPA | | | | |
| No. of subjects | 3 | 2 | 1 | NS |
| No. of instillations | 10 | 4 | 1 | NS‡ |
| No. withdrawn (tPA > 2/wk) | 1 | 1 | 0 | NS |

Abbreviation: NS, not significant.
*For all $P > 0.1$, NS is used.
†No death was associated with CRB.
‡Calculated as number of tPA instillations/all dialysis treatments.

groups and 2 in the G/TC group. Overall rate was 26% per patient-year at risk. No death was caused by CRB.

Seven patients developed CRB in the HS (control) group at the time of the first interim analysis, whereas only 1 patient had CRB in the M/EDTA arm and no patient had CRB in the G/TC arm (2-tailed Fisher exact test for HS versus G/TC, $P = 0.008$, and for HS versus M/EDTA, $P = 0.02$). There was no difference between the M/EDTA and G/TC groups. Clinical examination and follow-up of patients with bacteremia did not show sources of infection in these patients other than the catheter. Some infected catheters were salvaged with use of intravenous antibiotic therapy; therefore, bacteriological identification of the catheter tip was not possible in all catheters. CRB rates were 4 episodes/1,000 catheter-days in the HS group and 0.4 episodes/1,000 catheter-days in the M/EDTA group. Because of these findings, the study was terminated. Kaplan-Meier analysis is shown in Fig 2. Log-rank test for difference was 0.0067. Infection-free survival rates at 120 days were 100% for the G/TC group, 95% for M/EDTA group, and 56% for the HS group. There was no difference in survival between the G/TC and M/EDTA groups.

Cox proportional hazard analysis of factors associated with risk for developing CRB showed that the CRB event rate occurred independent of patient age, catheter vintage, presence of diabetes, sex, center at which the patients received HD, and prerandomization blood flow attainable at its accompanying negative prepump pressure.

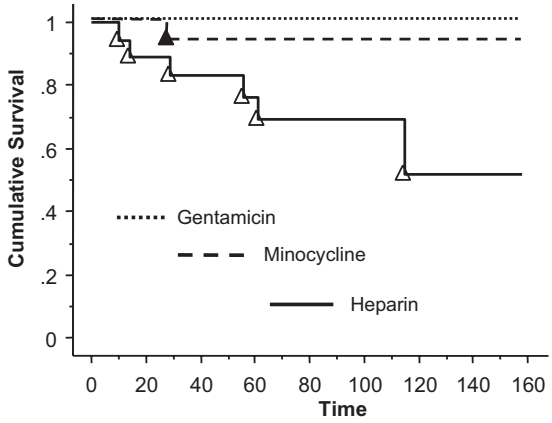


**Fig 2. Kaplan-Meier plot of cumulative survival of catheters in the 3 groups; HS control; gentamicin, 4 mg/mL in 3.13% tricitrate; and M/EDTA, 3 mg/mL and 30 mg/mL, respectively. Log-rank test, 0.0067. Both antibiotic lock solutions statistically prolonged the CRB-free period compared with heparin.**

$P$ for the entire model is 0.82, with likelihood ratio $P$ greater than 0.3 for all variables.

We collected data to determine whether catheter function changed before the diagnosis of CRB or at the end of the study. As listed in Table 3, pump blood flow rates measured as the average of 3 HD treatments in the week before study enrollment and the week before uncensored or censored events was similar in all arms. Similarly, prepump and postpump arterial pressures measured at the same times were similar in the 3 arms (Table 3).

Thrombolytic therapy was uncommon, but occurred more frequently in the HS group, in which

**Table 3. Blood Pump Flow and Negative Prepump Pressures Before Randomization and During the Study**

| | HS | G/TC | M/EDTA | P |
|---|---|---|---|---|
| Pre | | | | |
| QB (mL/min) | 307 ± 10 | 322 ± 11 | 310 ± 12 | NS |
| Pa (mm Hg) | 193 ± 9 | 202 ± 6 | 204 ± 7 | NS |
| Post | | | | |
| QB (mL/min) | 311 ± 15 | 310 ± 17 | 305 ± 10 | NS |
| Pa (mm Hg) | 199 ± 6 | 199 ± 6 | 194 ± 7 | NS |

NOTE. Absolute values for Pa given, actual values always negative. All values represent the average of 3 HD treatments in the week before study enrollment and the week before uncensored or censored events.

Abbreviations: NS, not significant; QB, blood pump flow; Pa, prepump pressures; pre, week before study enrollment; post, week before uncensored or censored events.

3 of 20 subjects were administered tPA. Two patients received 1 and 5 instillations during 10 and 12 weeks of follow-up, respectively. The other patient required 4 doses in less than 4 weeks and was withdrawn from the study per protocol. In the G/TC group, 2 patients required tPA: 1 patient received 1 dose during 14 weeks, and the other patient was withdrawn from the study after 3 doses of tPA during 5 dialysis treatments were administered. Only 1 patient required tPA in the M/EDTA group; 1 instillation in 12 weeks.

## DISCUSSION

Despite recommendations by the KDOQI and efforts to discourage the use of HD catheters, it is likely that a substantial number of patients will continue to require them.[30] In a study by End-Stage Renal Disease Network 11, a total of 63% of patients initiated HD therapy with a catheter as their sole form of vascular access in calendar year 2000.[5] At 6 months after initiation of HD therapy, 40% of these patients were still using a catheter. Three years later when we initiated our study, results had not improved. Nationally, use of catheters in incident patients had increased.[4]

HD patients represent a high-risk cohort for developing bacteremia because of many clinical and sociodemographic factors. Clinical factors include host factors that suppress the immune system, type of vascular access, reuse practices and membrane selection, and increased exposure to nosocomial organisms.[31] The US Renal Data System Wave 2 study, a prospective study of 2,358 incident HD patients, showed that dialysis access was the main antecedent of septicemia or bacteremia associated with greater risk for death, myocardial infarction, heart failure, and stroke.[32] In an analysis of US Renal Data System data, Nissenson et al[33] found that septicemia caused by *S aureus* in 11,572 patients was associated with mean length of stay of 13 days; 20.7% of all patients developed 1 or more complications, 11.8% of whom were readmitted within 12 weeks for care related to the infection. Thus, such infections result in lengthy hospitalizations and are costly.

Gentamicin in antibiotic lock solution was studied previously in HD patients. Some of these previous studies used much greater doses of gentamicin (10 to 40 mg/mL), with or without citrate as anticoagulant. In a randomized controlled trial of 112 catheters, Dogra et al[27] reported that 40 mg/mL of gentamicin with 3.13% citrate was highly effective (relative risk, 0.10 by means of Cox proportional hazard) in preventing CRB measured from the time of insertion. However, measurable gentamicin levels (range, 0.6 to 3.5 mg/L) in some patients raised concerns of potential ototoxicity. They suggested that lower gentamicin concentrations would still achieve significantly high minimal inhibitory concentrations inside the catheter lumen without the risk for ototoxicity.

Our study indicates that antibiotic lock solution with gentamicin at 4 mg/dL in combination with a low citrate concentration of 3.13% is very effective in preventing CRB. We did not measure gentamicin levels predialysis in our patients because we believed the total potential maximal dose per 44 to 72 hours was 8 to 11 mg, an amount within the excretory/metabolic capacity of anephric individuals without renal function.[34] McIntyre et al[35] also studied a lower concentration of gentamicin, 5 mg/mL in heparin, in 50 patients with new catheters. Use of antibiotic lock solutions was associated with greater mean hemoglobin levels (difference of 0.9 g/dL) despite use of a 16% lower epoetin dosage. No gentamicin levels were measured in this study.

Studies by Dogra et al[27] and McIntyre et al[35] evaluated antibiotic lock solution use immediately after insertion. Similarly, Kim et al[36] studied 120 new HD patients with noncuffed temporary catheters, but evaluated a combination of cefozolin (10 mg/mL) and gentamicin (5 mg/mL) in heparin. Although Kim et al[36] noted a marked decrease in CRB rate from 3.12 to 0.44 episodes/1,000 catheter-days in these new acute catheters, there was a minimal increase in CRB-free survival from 55 to 59 days, perhaps because most catheters were removed as arteriovenous fistulae matured.

Conversely, our study examined patients with catheters of various vintages, with median duration exceeding 2.5 months in all 3 groups. We hypothesized that gentamicin at 4 mg/mL would still be effective even when started relatively "late." Over the range of 4 to 706 days, there was no effect of catheter vintage on the likelihood of failure with antibiotic lock solution. However, we realize that our study sample is small. A similar study of a much larger at-risk population

might find that a critical pretreatment duration exists beyond which use of an antibiotic lock becomes relatively ineffective. Because of the uncertainty of starting low-concentration gentamicin late, the M/EDTA group with the use of full standard doses was included to provide a true control because this solution was efficacious in preventing and/or treating CRB in some studies[25,28] and in experimental models shown to penetrate biofilm.[37,38]

The effect we found with G/TC and M/EDTA was independent of duration of catheter implantation and amenable to routine outpatient use because the solutions were stable and retained their microbiological efficacy for up to a week, even when stored at room temperature. Of the 2 solutions, G/TC appears to be preferable because its components are less expensive than the comparator we studied (M/EDTA). Current per-patient-per-month cost (13 treatments) for the antibiotic and anticoagulant would be $32.07 for G/TC compared with $124.56, almost a 4-fold difference.

We also did not compare gentamicin with an agent like vancomycin,[39,40] which would be more specific to *S aureus*. In our centers, 33% of infections are caused by methicillin-sensitive *S aureus* or *Staphylococcus epidermidis*, 31% are caused by methicillin-resistant staphylococcal or enterococcal species, and the remaining 36% are caused by gram-negative organisms. An aminoglycoside would be effective against the latter.

The role of anticoagulant in antibiotic lock solutions currently is unknown. Sodium heparin is known to produce unintentional systemic anticoagulation[41]; the mechanism appears to result from the anticoagulant "dropping out" of the catheter because of its high specific gravity (~1.040), which is greater than that of blood.[42] High-concentration TC in dialysis catheters not only provides effective anticoagulation, but also broad-spectrum antimicrobial and antifungal effects.[43] The same is true for EDTA, but anti-staphylococcal[44] and anti-*Candida* fungal[45] activities are limited. Citrate used in high concentrations is an antimicrobial by chelating calcium and magnesium ions,[46] preventing microbial growth and biofilm. The inhibitory effect depends on concentration and microbial species. Although *Staphylococcal* species were inhibited by TC concentrations of 7.5%, *Pseudomonas* species required concentrations of 30%. The addition of gentamicin to the high concentration of TC provides the most potent antibacterial solution, but is associated, as also noted by Dogra et al,[27] with low systemic concentrations of the aminoglycoside.[47] A 30% TC solution was used in Europe[48] and decreased CRB in newly inserted catheters (tunneled or untunneled) by almost 75%. However, in the United States, there is a current Food and Drug Administration (FDA) ban on TC concentration greater than 4%.[49] The citrate concentration used in our study, 3.13%, is well within FDA limits. Whether it adds to the efficacy of the low-dose gentamicin is unknown. Our concentration is less than the 7% needed for antimicrobial effect.[46] TC solutions greater than 7% are denser than blood and would tend to drop out of catheters. However, even with the 30% solutions used by Weijmers et al,[48] there was no hint of excessive bleeding in almost 200 patients randomly assigned to TC use. Persistent bleeding after insertion or major bleeding events on follow-up were lower than in the HS control group locks with 5,000 UI/mL.

Our study shows that antibiotic lock solutions are very effective in preventing CRB in an HD population. Both antibiotic solutions studied were equally successful against an HS control. Additional analysis of the data shows that such factors as catheter vintage at enrollment and total treatment days on study were similar in the 3 arms. There was no center effect on CRB rate, although African Americans were more represented in center 1. This efficacy reached across all catheter vintages and was similar for the 3 centers. Our findings imply that antibiotic lock solutions could be initiated after a variable time in place. Prophylaxis can be applied to all patients, rather than just patients with new catheters. Lambie et al[50] reported that adoption of their antibiotic lock solution (gentamicin, 5 mg/mL) protocol can decrease CRB from 3.12 to 0.76 episodes/1,000 catheter-days. In addition, organisms from the 2 episodes of CRB were not resistant to gentamicin.

It is unlikely that catheter malfunctions contributed significantly to the development of bacteremia because prepump and postpump pressures, as well as arterial blood flows, did not change significantly from the time of enrollment to the end of the study. Similarly, the number of the

censoring events occurring in the 3 arms was similar. Duration of follow-up was independent of vintage age (data not shown, $r = 0.002$). However, it is of interest that in the Cox proportional hazard model, the only variables suggesting an effect were those related to the ability of the catheter to deliver adequate blood flow at a less negative prepump arterial pressure. Whether this reflects the presence of biofilm or other mechanical factors is unknown.

Presently, the ultimate role of antibiotic lock solutions is unclear. Certainly, one must start with excellent nursing care of dialysis catheters. The study by Beathard[18] showed a dramatic effect, decreasing CRB rate into the 1.5 to 1.7 episodes/1,000 days-at-risk range. Taurolidine was used successfully in Europe.[51] A small clinical trial comparing 20 patients with a taurolidine lock compared with 30 patients concurrently with a heparin lock performed in the United States led to an FDA request for a larger randomized clinical trial,[52] which has not been conducted. Thus, we currently are limited by the inability to use antimicrobials effectively. Thus, use of antibiotic lock solution is not likely to ever receive FDA approval for preventing CRB because of the possible development of antibiotic resistance. However, we continued to use antibiotic locks in our dialysis centers for the past 2 years in an attempt to minimize patient morbidity, and like Lambie et al,[50] have not seen toxicity or antibiotic resistance. However, the experience is still small.

All randomized studies evaluating antibiotic locks to date had short-term follow-ups (<6 months). This may preclude demonstration of potential problems with long-term use of this approach. These include the development of resistance to the antibiotics used and possible iatrogenic effects from the anticoagulants used. Unlike antibiotic locks, both taurolidine and citrate solutions appear to be freer of the risk of selecting for antibiotic-resistant infections during long-term use. To that end, a citrate-based solution containing 2 other antimicrobials is under development (S. Ash, personal communication, April 2006).

Until data for such newer locking solutions become available, we recommend that larger prospective double-blind randomized studies, perhaps using a lower, but still effective, concentration of gentamicin of 1 mg/mL, continue to be conducted (J. Moran, Satellite Health, CA, personal communication, April 2006) that enroll all catheters of all vintages to provide more conclusive data on this subject.

In conclusion, based on results of this study, we conclude that: (1) antibiotic lock solutions are effective in the prevention of CRB in prevalent tunneled cuffed catheters, and (2) low-dose gentamicin has similar efficacy compared with the high concentrations used in previous studies.

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