MAJOR ARTICLE

Use of Vancomycin or First-Generation Cephalosporins for the Treatment of Hemodialysis-Dependent Patients with Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

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Background. Because of its ease of dosing, vancomycin is commonly used to treat methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia in patients undergoing long-term hemodialysis. Clinical outcomes resulting from such a therapeutic strategy have not been well defined.

Methods. We prospectively identified patients undergoing long-term hemodialysis who received a diagnosis of MSSA bacteremia. Clinical outcomes were grouped according to the predominant antibiotic received during their therapy (vancomycin or a first-generation cephalosporin [cefazolin]). Treatment failure (defined as death or recurrent infection) was determined at 12 weeks after the initial positive blood culture results. A multivariable analysis was used to adjust for confounders.

Results. During an 84-month period, 123 hemodialysis-dependent patients with MSSA bacteremia were identified. Patients receiving vancomycin ($n = 77$) tended to be younger (51 vs. 57 years; $P = .06$) and had a lower rates of metastatic complications at presentation (11.7% vs. 36.7%; $P = .001$) than did those receiving cefazolin ($n = 46$). The 2 groups were similar with regard to Acute Physiology and Chronic Health Evaluation II scores, comorbidities, source of infection, type of hemodialysis access, and access removal rates. Treatment failure was more common among patients receiving vancomycin (31.2% vs. 13%; $P = .02$). In the multivariable analysis, factors independently associated with treatment failure included vancomycin use (odds ratio, 3.53; 95% confidence interval, 1.15–13.45) and retention of the hemodialysis access (odds ratio, 4.99; 95% confidence interval, 1.89–13.76).

Conclusions. Hemodialysis-dependent patients with MSSA bacteremia treated with vancomycin are at a higher risk of experiencing treatment failure than are those receiving cefazolin. In the absence of patient specific circumstances (e.g., allergy to β-lactams), vancomycin should not be continued beyond empirical therapy for hemodialysis-dependent patients with MSSA bacteremia.

Patients undergoing long-term hemodialysis are at high risk of developing *Staphylococcus aureus* bacteremia [1–5]. As a result of increasing rates of methicillin-resistant *S. aureus* (MRSA) infection [6], vancomycin has become a widely accepted empirical treatment for proven or suspected bloodstream infections in hemodialysis-dependent patients. Although vancomycin remains a standard treatment for infections caused by MRSA, β-lactam antibiotics, including first-generation cephalosporins (e.g., cefazolin), are generally preferred for infections caused by methicillin-susceptible *S. aureus* (MSSA) [7–9]. In vitro data [10–12] and limited clinical data [12–17] suggest that vancomycin may be less satisfactory than β-lactam antibiotics for the treatment of MSSA. However, the ease of dosing for vancomycin for patients undergoing hemodialysis [18] has led to the common practice of using vancomycin to treat MSSA

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infection in these patients. Although this practice is not consistent with recent guidelines from the Centers for Disease Control and Prevention [19] and may contribute to the development of vancomycin resistance, its clinical implications have not been well characterized.

In this study, we prospectively evaluated a cohort of hemodialysis-dependent patients with MSSA bacteremia treated primarily with vancomycin or first-generation cephalosporins (i.e., cefazolin). We focused our study on the evaluation of clinical outcomes associated with such therapeutic strategies.

METHODS

Patients and setting. We prospectively identified all hemodialysis-dependent patients with end-stage renal disease who were admitted to Duke University Medical Center (Durham, NC) during the period from 1 September 1994 through 31 August 2001 and who had blood cultures positive for MSSA. Clinical and economic outcomes for the overall cohort of these long-term hemodialysis patients with *S. aureus* bacteremia have been reported elsewhere [20–22].

Daily reports were received from the microbiology laboratory regarding all patients with ⩾1 blood culture positive for *S. aureus.* All patients were evaluated within 36 h after identification of *S. aureus.* We excluded patients if they were aged <18 years, had polymicrobial bacteremia, had neutrophil counts <1000 cells/mm^3, died before final blood culture reports were available, or did not receive either vancomcyin or cefazolin as their definitive therapy. Among hemodialysis patients at our institution, cefazolin is generally used preferentially over nafcillin. Only the index hospitalization for *S. aureus* bacteremia was included in the analysis cohort. This study was approved by the institutional review board of Duke University Medical Center.

Data collection. Prospectively collected data included the patient's demographic characteristics, comorbid conditions, details of the infection (e.g., suspected source), type and duration of antibiotic therapy, complications of infection, and clinical outcomes at discharge from the hospital and 12 weeks after the date of the initial positive blood culture result. APACHE II scores were calculated on the date of initial positive blood culture result [23].

Definitions. An intravascular catheter was considered to be the portal of entry if inflammation was present around the insertion site and/or a catheter tip culture was positive for MSSA and no other source of infection was evident [24]. Infections were classified as nosocomial if the initial positive blood culture result was obtained >48 h after admission to the hospital and the patient did not have symptoms of infection at the time of admission. Infective endocarditis was defined according to Duke University Medical Center criteria [25]. Metastatic infections were defined by presence of an infection site remote from the primary focus caused by hematogenous seeding (e.g., abscess or vertebral osteomyelitis) [26]. Recurrent infection was defined by the isolation of *S. aureus* from any sterile body site during the follow-up period. The predominant antibiotic regimen was defined as the antibiotic used for the majority of the patient's treatment course. Methicillin susceptibility was determined by the oxacillin test using criteria of the CLSI [27].

Antibiotic therapy. All treatment decisions, including antibiotic dosing schedules and monitoring of serum vancomycin levels, were made by the patient's treating team. Because standard practice at our institution is to empirically treat all hemodialysis-dependent patients with suspected *S. aureus* bacteremia with vancomycin, pending the availability of antimicrobial susceptibility data for the infecting pathogen, all patients in the study were given an initial dose of vancomycin at the time of their initial recognition by the health care system. Antibiotic lock therapy was not used at our institution.

Hemodialysis settings. Inpatient dialysis treatments were offered at Duke University Medical Center using a limited supply of 3 membranes, with the vast majority of patients receiving the same membrane and a very limited number of patients receiving 1 of 2 other membranes on the basis of body size (e.g., for pediatric patients) and allergies to membranes or sterilants. Hemodialysis was performed using standard techniques to achieve benchmarks in dialysis adequacy. The standard practice at Duke University Medical Center at the time that data were collected was as follows: (1) to administer a loading dose of vancomycin of 15 mg/kg, (2) to administer a 500-mg dose of vancomycin after each dialysis treatment because of the use of high-flux dialysis membranes, and (3) to administer a 2-g dose of cefazolin when dialysis was anticipated to occur again in 2 days and a 3-g dose when dialysis was anticipated to occur in 3 days. In patients who finally received cefazolin as their principal therapy, administration of the drug was started when susceptibility data became available, usually within 72 h after the blood culture results. For patients in whom vancomycin therapy was monitored, the goal at our institution was usually to achieve a serum concentration of 10–15 μg/mL. For the purpose of this study, the length of therapy was determined as the period of time in days in which the drug was administered.

Determining the MIC of vancomycin. Isolates of *S. aureus* were stored frozen at −70°C before testing. Each isolate was thawed and subcultured twice on sheep blood agar to ensure purity and viability. Identification of *S. aureus* was made by Gram stain appearance, colonial morphology, positive catalase results, and positive Staphaurex (Remel) and/or tube coagulase test results. The MIC of vancomycin was tested for each isolate by the broth microdilution method with cation-adjusted Mueller-Hinton broth. Frozen single inoculum broth microdilution reference panels (Sensititre [Trek Diagnostics Systems] and Microscan [Dade Behring]) were used. Inocula were pre-

Table 1. Demographic characteristics, comorbidities, and types of hemodialysis access for 123 patients with methicillin-susceptible *Staphylococcus aureus* bacteremia.

Variable	Principal antibiotic regimen		P[a]
	Vancomycin (n = 77)	Cefazolin (n = 46)	
Demographic characteristic			
Age, mean years ± SD	51.3 ± 14.8	56.5 ± 14.8	.06
African American race[b]	65 (84.4)	38 (82.6)	.99
Female sex	43 (55.8)	26 (56.5)	.94
Comorbidity			
Diabetes mellitus	33 (42.9)	25 (54.3)	.22
Injection drug use	6 (7.8)	5 (10.9)	.75
Long-term steroid use	5 (6.5)	2 (4.4)	.71
Malignancy	5 (6.5)	0 (0)	.16
HIV infection	2 (2.6)	0 (0)	.53
Allergy to penicillin	7 (9.1)	1 (2.2)	.26
History of kidney transplantation	12 (15.6)	4 (8.7)	.27
Duration of hemodialysis, median years (IQR)[c]	2.57 (0.47–5.06)	1.59 (0.53–4.24)	.46
Hemodialysis access data, including nonfunctional grafts			
Tunneled catheter[d]	42 (54.6)	25 (54.4)	.98
Polytetrafluoroethylene graft	44 (57.1)	27 (58.7)	.87
Primary arteriovenous fistula	16 (20.8)	9 (19.6)	.87
Nosocomial acquisition of infection	4 (5.2)	0 (0)	.30

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] The t test was used for continuous variables, and Fisher's exact test or the χ^2 test was used for categorical variables, as appropriate.

[b] Data were available for 45 patients in the cefazolin group.

[c] Data were available for 75 patients in the vancomycin group.

[d] Two patients in the vancomycin group and 1 patient in the cefazolin group had nontunneled catheters in place.

pared by the colony suspension method, with a turbidity equivalent to that of a 0.5 McFarland standard. This process provided a final inoculum density of ~5×10^5 CFU/mL. The reference microdilution panels were incubated at 35°C in ambient air for 24 h before visual determination of the MIC value.

Statistical analysis. The primary end point of the analysis, treatment failure, was defined as either death or recurrent infection during the 12-week follow-up period. Comparisons between categorical variables were calculated using the χ^2 or Fisher's exact test, as appropriate. Comparisons between continuous variables were conducted using Student's t test or the Wilcoxon rank sum test, as indicated. All tests were 2-sided, and P values <.05 were considered to be statistically significant. To adjust for potential confounders, forward stepwise logistic regression was used. Variables with P values <.1 in the bivariable analysis were including in the final model, as permitted by the effective sample size. Interactions between variables in the final model were also explored.

RESULTS

One hundred forty patients undergoing long-term hemodialysis who had MSSA bacteremia were identified during the study period. Seventeen patients were excluded from the study because they did not receive vancomycin or cefazolin (12 received antistaphylococcal penicillins, and 5 received other antibiotics). Thus, 123 patients were included in the study. Most were African American (84%), more than one-half were female (56%), and the mean age (±SD) was 53.3 ± 15.0 years old. Seventy-seven patients (63%) received vancomycin and 46 (37%) received cefazolin as the predominant treatment for MSSA bacteremia. Only 9% of the patients who received vancomycin had documented histories of allergies to penicillin or cephalosporins.

The 2 groups were similar with regard to distribution of hemodialysis intravascular access types (table 1), presumed infection source, APACHE II scores, and total number of surgical infection–related procedures (table 2). Patients treated with vancomycin had fewer metastatic complications at the initial evaluation (11.7% vs. 36.7%; P = .001) and received a shorter mean duration of therapy (24.5 vs. 28.8 days; P = .04), compared with patients who were treated predominantly with cefazolin. Cure rates at discharge were 83.1% and 91.3% in the vancomycin and cefazolin groups, respectively (P = .70).

Among patients who received vancomycin as their principal treatment, serum levels at the beginning of therapy were available for 38 subjects (table 2). For the 30 patients who were cured and the 8 patients whose therapy failed, the median

Table 2. Clinical characteristics at presentation, infection-related procedures, duration of treatment, and clinical outcomes among patients with methicillin-susceptible *Staphylococcus aureus* bacteremia.

Characteristic	Principal antibiotic regimen		*P*
	Vancomycin (*n* = 77)	Cefazolin (*n* = 46)	
Clinical characteristic at presentation			
Mean APACHE II score ± SD	18.0 ± 4.6	18.8 ± 5.0	.30
Presence of fever[a]	73 (94.8)	43 (93.5)	.99
Blood pressure <90 mm Hg	7 (9.1)	8 (17.4)	.17
Heart failure	1 (1.3)	3 (6.5)	.14
CNS involvement	6 (7.8)	4 (8.7)	.99
Metastatic infection	9 (11.7)	17 (36.7)	.001
Endocarditis	4 (5.2)	8 (17.4)	.06
Metastatic abscess	3 (3.9)	1 (2.17)	.99
Hemodialysis access as the source of bacteremia[b]	71 (94.7)	40 (88.9)	.29
Procedures, length of stay, duration of treatment, and cure at discharge			
Hemodialysis access removed[c]	48 (67.7)	31 (75.6)	.37
Tunneled catheter removed[d]	38 (90.5)	23 (92)	.99
Polytetrafluoroethylene graft removed[d]	14 (32.8)	11 (19.3)	.46
Arteriovenous fistula removed[d]	0 (0)	1 (11.1)	.36
Source of infection removed[e]	49 (70)	31 (75.6)	.52
Median no. of infection-related procedures (IQR)	3 (0–8)	2 (0–5)	.70
Length of hospitalization after diagnosis of bacteremia, median days (IQR)[f]	13 (9–24)	6.5 (4–10)	.18
Duration of antibiotic treatment, mean days ± SD	24.5 ± 11.0	28.8 ± 11.0	.04
Serum levels of vancomycin, median μg/mL (IQR)[g]	14.0 (11.6–18.5)	…	
Cure at discharge[h]	64 (83.1)	42 (91.3)	.70
Clinical outcome at 12 weeks			
Treatment failure	24 (31.2)	6 (13.0)	.02
Death	8 (10.4)	2 (4.4)	.32
Recurrent infection	16 (20.8)	4 (8.7)	.08

NOTE. Data are no. (%) of patients, unless otherwise indicated. AV, arteriovenous; IQR, interquartile range.

[a] Defined as a temperature >38°C.

[b] Data were available for 75 patients in the vancomycin group and 45 patients in the cefazolin group.

[c] Data were available for 71 patients in the vancomycin group and 41 patients in the cefazolin group; a single patient may have had >1 access removed; access removal rates are regardless of source of infection status.

[d] From the total of patients with tunneled catheters, polytetrafluoroethylene grafts, and AV fistulas, respectively.

[e] Data were available for 70 patients in the vancomycin group and 41 patients in the cefazolin group.

[f] Data were available for 76 patients in the vancomycin group.

[g] Data were available for 38 patients in the vancomycin group.

[h] Status at discharge was not available for 8 patients in the vancomycin group and 2 patients in the first-generation cephalosporin group; missing values were included in the calculations.

serum levels of vancomycin were 13.7 μg/mL (interquartile range, 9.3–18 μg/mL) and 16.8 μg/mL (interquartile range, 13.6–21.8 μg/mL), respectively. The lowest serum level documented among patients for whom therapy with vancomycin failed was 12.4 μg/mL. There was no significant difference in serum levels of vancomycin between patients whose treatment failed or those who were cured at 12 weeks ($P = .19$, by Wilcoxon test). Among patients mainly treated with vancomycin, all strains tested (76 of 77) had an MIC of vancomycin ≤2 μg/mL, and most of them had an MIC of 1 μg/mL (table 3). No significant difference was found in the proportions of MICs (≥1 and <1 μg/mL) by clinical outcomes (cure or failure; $P = .61$, by Fisher's exact test). Among the 8 patients who died and who had received vancomycin as their principal therapy, hemodialysis access was removed in 4 patients and retained in 2 patients (removal status was unknown for 2 patients). Persistence of clinical signs or symptoms of systemic infection, positive blood culture results, and/or focus of infection were documented in 3 of these patients. Among 2 patients who died and who had received cefazolin, dialysis access was removed in 1 patient (removal status was unknown for 1 patient).

More patients treated with vancomycin experienced treatment failure at 12 weeks (31.2% vs. 13%; $P = .02$), compared with cefazolin recipients. Individual rates of death or of recurrent infection were higher at 12 weeks among patients receiving vancomycin, though the increases did not reach statis-

Table 3. Clinical outcomes and MICs for methicillin-susceptible *Staphylococcus aureus* strains recovered from patients who had been mainly treated with vancomycin.

MIC of vancomycin, μg/mL	No. (%) of patients	
	Cure	Treatment failure[a]
0.5	20 (37.7)	7 (30.4)
1	31 (58.5)	15 (65.2)
2	2 (3.8)	1 (4.4)

[a] Data were available for 23 of 24 strains.

tical significance (table 2). Variables associated with treatment failure in the bivariable analysis were retention of hemodialysis access (OR, 5.08; 95% CI, 1.95–13.24) and use of vancomycin as the predominant antibiotic regimen (OR, 3.02; 95% CI, 1.13–8.08). In the multivariable analysis, both retention of hemodialysis access (OR, 4.99; 95% CI, 1.89–13.76) and the use of vancomycin as the predominant antibiotic (OR, 3.53; 95% CI, 1.15–13.45) were associated with treatment failure (table 4). No significant interactions between variables in the final model were detected. To adjust for patient comorbidity, an APACHE II score >20 was incorporated into the model with the use of vancomycin as the predominant antibiotic and retention of hemodialysis access. Inclusion of the APACHE II score did not affect the model or the predictive variables.

DISCUSSION

Vancomcyin is widely used for empirical treatment of hemodialysis-dependent patients with suspected gram-positive bacteremia. Many physicians continue to administer vancomycin as the principal antibacterial treatment for confirmed MSSA bacteremia. Clinical data suggesting that vancomycin is inferior to β-lactams to treat MSSA infection come from studies involving populations with different comorbidities [12–14, 16, 17]. Therefore, clinical outcomes associated with vancomycin use for the treatment of MSSA bacteremia in well-defined patient groups remain unclear. This study, which included a prospective and homogeneous cohort of hemodialysis-dependent patients with MSSA bacteremia, provides important observations.

First, the use of vancomycin as the predominant antibacterial therapy was associated with higher rates of treatment failure at 12 weeks. In our cohort, almost one-third of patients receiving vancomycin experienced treatment failure. Importantly, vancomycin was identified as an independent risk factor for treatment failure even after adjustment for confounders, such as access removal. This finding is consistent with prior reports suggesting that vancomycin is a suboptimal agent for treatment of severe MSSA infection [13, 14, 16, 17]. Other investigations have found vancomycin therapy to be associated with inferior clinical outcomes in the treatment of patients with MSSA bacteremia. For example, Chang et al. [13] showed that vancomycin therapy was independently associated with relapse in a subgroup of patients with *S. aureus* bacteremia. Similarly, Gonzalez et al. [14] found that vancomycin was associated with higher mortality in patients with bacteremic *S. aureus* pneumonia, although only 10 cloxacillin recipients were included in the comparison. However, unlike these previous studies, our investigation involved a large, homogeneous cohort of hemodialysis-dependent patients with MSSA bacteremia. Importantly, inadequate empirical therapy was eliminated as a potential confounder in our study, because all strains of *S. aureus* were susceptible to the initially administered antibiotics.

In agreement with other investigations [7–9], our study suggests that cefazolin therapy is safe and effective for the treatment of MSSA infection in patients undergoing hemodialysis. Importantly, patients who received cefazolin as their principal antibacterial therapy had superior outcomes, despite the fact that these patients tended to be older and had more metastatic infections at presentation than did patients who were treated with vancomycin. Interestingly, these results also suggest that physicians administered cefazolin to patients whom they believed to be at high risk of having adverse outcomes.

Hemodialysis access retention was independently associated with treatment failure, regardless of the antibiotic therapy. This finding is in agreement with several clinical studies, indicating that removal of the vascular access is a key treatment factor for most patients with *S. aureus* bacteremia [1, 13, 28–30]. In the vast majority of our patients (~90%), hemodialysis access

Table 4. Bivariable and multivariable analysis for clinical variables associated with treatment failure at 12 weeks.

Variable	Bivariable analysis		Multivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age >50 years	0.79 (0.35–1.81)	.58	…	
Male sex	1.98 (0.86–4.55)	.11	…	
APACHE II score >20	1.43 (0.59–3.50)	.42	…	
Vancomycin as principal therapy	3.02 (1.13–8.08)	.02	3.53 (1.15–13.45)	.04
Retention of hemodialysis access[a]	5.08 (1.95–13.24)	<.01	4.99 (1.89–13.76)	.001

[a] Data were available for 112 patients, regardless of the source of infection status.

was considered to be the source of infection. Thus, is not surprising that most patients in our cohort underwent hemodialysis access removal. Importantly, ~90% of patients in both groups with tunneled catheters underwent for access removal.

Finally, we did not find a relationship between clinical outcomes and MICs for MSSA strains in patients who received vancomycin, regardless of whether therapy succeeded or failed. Most MSSA strains from patients mainly treated with vancomycin had an MIC of 1 μg/mL regardless of the clinical outcome. This observation contrasts what was described for clinical strains of MRSA [31], where one-half of the strains from patients who failed therapy with vancomcyin had MICs of 2 μg/mL. However, further research in this area including bactericidal activity by sensitivity of the MSSA isolates to vancomycin is needed.

This study has several limitations. First, it had an observational design in which antibacterial type, dose, and schedule were decided by treating physicians. Second, serum levels of vancomycin were not available for all patients. However, when we analyzed serum levels for almost one-half of the patients who received vancomycin as their principal therapy, no differences were found between patients who were cured and those whose therapy failed. Interestingly, all patients whose vancomycin therapy failed had serum levels >10 μg/mL. Therefore, at least in these patients, failure can not be attributed to suboptimal dosing. Data correlating serum levels of vancomycin with clinical outcomes are limited, and routine monitoring of vancomycin levels remains controversial [32–34]. Third, we did not make a distinction between relapse and reinfection. In this regard, it has been shown that most recurrences that occur within 90 days in patients with *S. aureus* bacteremia are relapses [29, 30]. Finally, the current investigation was conducted at a single institution, and these results may not be generalizable to other centers.

In summary, vancomycin appears to be inferior to cefazolin for the treatment of MSSA bacteremia in patients who are undergoing long-term hemodialysis. In addition to the use of β-lactams in patients with MSSA infection, early removal of central catheters is associated with significantly fewer treatment failures. Thus, in absence of patient-specific circumstances (e.g., an allergy to β-lactams), vancomycin treatment should not be continued beyond empirical therapy for hemodialysis-dependent patients with MSSA bacteremia.

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