Relationship between Clinical Outcomes and Vascular Access Type among Hemodialysis Patients with *Staphylococcus aureus* Bacteremia

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The association between hemodialysis vascular access type, costs, and outcome of *Staphylococcus aureus* bacteremia (SAB) among patients with ESRD remains incompletely characterized. This study was undertaken to compare resource utilization, costs, and clinical outcomes among SAB-infected patients with ESRD by hemodialysis access type. Adjusted comparisons of costs and outcomes were based on multivariable linear regression and multivariable logistic regression models, respectively. A total of 143 hospitalized hemodialysis-dependent patients had SAB at Duke University Medical Center between July 1996 and August 2001. A total of 111 (77.6%) patients were hospitalized as a result of suspected bacteremia; 32 (22.4%) were hospitalized for other reasons. Of the 111 patients, 59.5% (n = 66) had catheters as their primary access type, 36% (n = 40) had arteriovenous (AV) grafts, and 4.5% (n = 5) had AV fistulas. Patients with fistulas were excluded from analyses because of small numbers. Patients with catheters were more likely to be white, had shorter dialysis vintage, and had higher Acute Physiology and Chronic Health Evaluation II scores compared with patients with grafts. Unadjusted 12-wk mortality did not significantly differ between patients with catheters compared with patients with grafts (22.7 *versus* 10.0%; P = 0.098); neither did 12-wk costs differ by access type ($22,944 ± 18,278 *versus* $23,969 ± 13,731, catheter *versus* graft; P > 0.05). In adjusted analyses, there was no difference in 12-wk mortality (odds ratio 1.63; 95% confidence interval 0.29 to 9.02; catheter *versus* graft) or 12-wk costs (means ratio 0.84; 95% confidence interval 0.60 to 1.17; catheter *versus* graft) among SAB-infected patients with ESRD on the basis of hemodialysis access type. Twelve-week mortality and costs that are associated with an episode of SAB are high in hemodialysis patients, regardless of vascular access type. Efforts should focus on the prevention of SAB in this high-risk group.

Clin J Am Soc Nephrol 1: 518–524, 2006. doi: 10.2215/CJN.01301005

Infections are the second leading cause of mortality in dialysis patients, accounting for nearly one fourth of all deaths in patients with ESRD (1). *Staphylococcus aureus* is a leading cause of bacteremia among hemodialysis-dependent patients (1–11), and rates may be increasing (1). Complications of *S. aureus* bacteremia (SAB) include sepsis, endocarditis, osteomyelitis, septic arthritis, and metastatic abscesses (12–14).

Vascular access is a major risk factor for bacteremia (15,16) and infection-related hospitalization and mortality (17,18) among hemodialysis patients. Evidence suggests that tunneled-cuffed catheters might be associated with a higher frequency of infectious complications than other forms of dialysis vascular access. For example, the frequency of hospitalizations for infectious complications among patients with ESRD has increased (1) at the same time that the proportion of patients who have ESRD and have catheters as their primary vascular access has climbed (19–21). However, the association between vascular access type and clinical outcomes among patients with ESRD and SAB still is unclear.

Despite its clinical significance, the economic impact of SAB among patients with ESRD remains incompletely characterized. Previous studies provided insight into the economic burden of *S. aureus* (22,23). Engemann *et al.* (24) found that the mean cost of an episode of SAB among a cohort of patients with ESRD was $24,034 per episode, and patients with complicated SAB episodes incurred even higher costs. Similarly, Reed *et al.* (25) found community-dwelling patients who had ESRD and methicillin-resistant *S. aureus* (MRSA) bacteremia incurred higher costs compared with patients with methicillin-sensitive *S. aureus* (MSSA) bacteremia. Despite these observations, however, the potential relationship between intravascular access type, costs, and clinical outcomes among patients with SAB is undefined. Herein, we sought to analyze differences in resource utilization, costs, and clinical outcomes by access type among patients who have ESRD and are admitted to the hospital for suspected SAB.

Received October 12, 2005. Accepted February 22, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/103-0518

Materials and Methods

Study Design

A prospective cohort of hemodialysis patients with SAB was used to describe and compare resource utilization, costs, and clinical outcomes among patients with various types of hemodialysis access. Characteristics of these patients have been reported previously (24,25).

Patients and Study Setting

All adult patients who had ESRD, were undergoing hemodialysis, and were admitted to Duke University Medical Center with SAB between July 1, 1996, and August 31, 2001, were identified prospectively and included in this study. Daily reports were received from the microbiology laboratory regarding all patients with at least one positive blood culture for *S. aureus*, and all patients subsequently were evaluated and consented for enrollment within 36 h of identification of *S. aureus*. Exclusion criteria were SAB in nonhospitalized patients, age <18 yr, polymicrobial infection, neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L), or death before evaluation. For maintaining independence of observations, the analysis was limited to the first episode of SAB for each patient but was inclusive of recurrent infections that occurred during the 12 wk after the date of the first positive blood culture. The institutional review board of Duke University Medical Center approved this study.

Data Collection

Clinical data were collected at the time of a patient's hospitalization and entered into an electronic database (Access; Microsoft Corp., Redmond, WA). The data that were collected included patient demographic characteristics, comorbid conditions, antibiotic therapy, complications of infection, duration of ESRD and hemodialysis, type of vascular access, history of kidney transplant, and suspected cause of the patient's kidney disease. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated on the date of initial positive blood culture (26). Outcomes (including death or metastatic complications) were assessed during the initial hospitalization and 12 wk after the date of the initial positive blood culture. Data regarding resource utilization (*e.g.*, medical tests, procedures, length of hospitalization) were obtained by medical record abstraction. Cost data information for all patients was retrieved from the Duke University Medical Center hospital accounting system (Transition Systems, Inc., Boca Raton, FL).

Definitions

Patients were categorized into groups on the basis of type of intravascular access used for hemodialysis at the time of admission: (*1*) Tunneled, cuffed, long-term catheter access; (*2*) synthetic arteriovenous (AV) graft; or (*3*) native AV fistula. Patients with catheter access were categorized further into two subgroups for sensitivity analyses: (*1*) Patients with catheters as their sole active access type and (*2*) patients with alternative active access types (maturing or active AV grafts or AV fistulas). Corticosteroid use was defined as either chronic low-dose or acute high-dose therapy used within the previous 30 d. Prevalent congestive heart failure at baseline was ascertained through self-report with medical record verification. Self-report was used to classify injection drug use. Sepsis was defined by standard criteria (27). Central nervous system involvement was defined by a positive culture for *S. aureus* obtained from cerebrospinal fluid. Infective endocarditis was defined according to Duke criteria (28). Metastatic infections were defined by the presence of an infection remote from the determined primary focus of infection (*e.g.*, vertebral osteomyelitis, distant abscess). Methicillin susceptibility was determined from the oxacillin test using criteria of the National Committee for Clinical Laboratory Standards (29).

Cost Data

The cost analysis was performed from the perspective of the health system and includes all direct medical costs that are associated with treatment of SAB and its sequelae during a 12-wk period. Because patients were included in the analysis only when their hospitalization was due to SAB, the entire cost of the admission was attributed to the infection. Cost data were available for all patients who were admitted after July 1, 1998. Hospital costs were obtained from the hospital cost accounting system and were adjusted to 2001 US dollars using the Consumer Price Index for Medical Care (30). Physician fees for inpatient and outpatient services were assigned using the 2001 reimbursement rates from the Centers for Medicare and Medicaid Services for providers in North Carolina. Total inpatient costs for the initial hospitalization included inpatient costs and physician fees. Outpatient costs and rehospitalization costs that occurred within 12 wk after the date of the initial positive blood culture were included only for procedures and admissions related to *S. aureus* infection. To be consistent with preferred methods (31), costs results were reported as means.

Statistical Analyses

Because of small numbers, patients with native AV fistulas as their sole access were excluded from further analyses. Descriptive statistics are presented as counts and percentages for discrete variables. Continuous variables are reported as means unless noted otherwise. In unadjusted analyses, continuous variables were compared using *t* tests when the data approximated a normal distribution and Wilcoxon rank sum tests when the data were non-normally distributed. Categorical variables were compared using Pearson χ^2 tests. Unadjusted comparisons of costs were based on nonparametric bootstrapping because the data did not approximate either a normal or log-normal distribution and because of nonequal variances (32,33). A bias-corrected method was applied to obtain the 95% confidence interval (CI) of the difference between cost estimates. An unadjusted comparison of clinical outcomes (mortality at discharge and at 12 wk) by access type was performed using Pearson χ^2 tests.

Adjusted comparisons of costs were based on a multivariable generalized linear model (GLM) specified with a γ distribution and a log link to account for heteroscedasticity and skewness associated with the cost data (34–36). Previous investigators have shown through a series of simulated data sets that GLM are less biased than ordinary least squares (OLS) regression on log-transformed cost data (34). GLM are more resilient to various data structures that are often represented with cost data, and the GLM approach typically is more conservative than OLS because the standard errors tend to be greater than those estimated by OLS (34). Cost analyses were performed using SAS PROC GLM.

Adjusted comparisons of clinical outcomes were performed using a multivariable logistic regression model. Variables that were entered into the regression model included demographic characteristics, comorbidities, APACHE II scores, infection-related factors (admitted from home, nursing home, or other hospital), and infection with methicillin-sensitive *S. aureus* or MRSA. All analyses were performed using SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

From July 1996 to August 2001, 143 hemodialysis patients who were admitted to Duke University Medical Center had positive blood cultures for *S. aureus*. Of these, 111 (77.6%) patients were admitted for suspected bacteremia and 32 (22.4%) were admitted for other reasons and therefore were excluded from further analyses. Of the 111 patients, 59.5% (n = 66) had a catheter as their sole access type for hemodialysis upon admission, 36.0% (n = 40) had a synthetic AV graft, and 4.5% (n = 5) had a native AV fistula.

Patient Characteristics According to Intravascular Access Type

Patients with catheters as their sole access type were more likely to be white and have a shorter dialysis vintage compared with patients with AV grafts (Table 1). Patients with catheters also had higher total APACHE II scores on diagnosis with SAB compared with patients with AV grafts. There were no significant differences between groups with regard to gender, age, admission from a nursing home, underlying cause of renal disease, other comorbidities, or infection with MRSA.

Resource Utilization and Outcomes

In unadjusted analyses, resource utilization during the initial hospitalization was similar between patients with catheters and patients with AV grafts, with the exception of the number of procedures that were performed related to a foreign device (4.1 *versus* 2.3 for catheter *versus* graft; P = 0.001; Table 2). During the 3-mo follow-up period, 13.8% of patients with catheters were re-hospitalized compared with 23.7% of patients with grafts (P = 0.21) with a similar number of mean inpatient days during the 12-wk period (12.6 *versus* 12.4 d for catheter *versus* graft; P = 0.33).

Metastatic infections occurred in 22 (33.3%) patients with catheters and in 12 (30.0%) patients with AV grafts (P = 0.72). Metastatic complications included endocarditis (n = 17), septic emboli (n = 8), abscess (n = 6), septic arthritis (n = 5), meningitis (n = 3), nonvertebral osteomyelitis (n = 3), vertebral osteomyelitis (n = 3), septic thrombophlebitis (n = 2), cerebro-

Table 1. Baseline patient characteristics by access type among ESRD patients hospitalized with SAB[a]

Characteristic	Tunneled, Cuffed Catheter (n = 66)	AV Graft (n = 40)	P[b]
Male	32 (48.5%)	17 (42.5%)	0.55
Race			
white	18 (27.3%)	2 (5.0%)	0.02
black	46 (69.7%)	38 (95.0%)	
other	2 (3.0%)	0 (0%)	
Age (mean ± SD)	55.3 ± 15.0	57.7 ± 15.5	0.42
Duration of hemodialysis (mean ± SD)	1.87 ± 2.24[c]	4.26 ± 4.01[c]	<0.001
Admitted from			
home	54 (81.2%)	35 (87.2%)	0.46
nursing facility	10 (15.2%)	3 (7.5%)	
another hospital	1 (3.6%)	2 (5.0%)	
Cause of renal failure			
hypertension	34 (51.5%)	25 (62.5%)	0.27
diabetes	35 (53.0%)	16 (40.0%)	0.19
glomerulonephritis	3 (4.6%)	4 (10.0%)	0.27
cystic kidney disease	1 (1.5%)	0 (0%)	0.43
other	8 (12.1%)	3 (7.5%)	0.45
unknown	0 (0%)	2 (5.1%)	0.29
Comorbidities			
cancer	3 (4.6%)	1 (2.5%)	0.59
HIV	1 (1.5%)	0 (0%)	0.43
corticosteroids within 30 d	6 (9.1%)	2 (5.0%)	0.44
diabetes	39 (59.1%)	19 (47.5%)	0.24
injection drug use	5 (7.6%)	4 (10.0%)	0.66
previous infective endocarditis	3 (4.5%)	0 (0%)	0.17
none	14 (21.2%)	13 (32.5%)	0.20
Total APACHE II score (mean ± SD)	19.8 ± 5.4	17.5 ± 4.4	0.043
Infection with MRSA	24 (36.4%)	11 (37.5%)	0.35

[a]APACHE II, Acute Physiology and Chronic Health Evaluation II; AV, arteriovenous; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *S. aureus* bacteremia.
[b]P values for continuous variables are based on t tests or Wilcoxon rank sum tests; P values for categorical variables are based on χ^2 tests.
[c]Missing data for three patients in the catheter group and three patients in the graft group.

Table 2. Unadjusted resource utilization, outcomes, and costs among patients with ESRD and SAB during their initial hospitalization and at 3-months[a]

	Tunneled, Cuffed Catheter (n = 66)	AV Graft (n = 40)	Difference with 95% CI or P
Resource utilization			
initial hospitalization			
inpatient days (mean ± SD)	10.6 ± 10.1	10.3 ± 6.4	0.79
procedures related to (mean ± SD)			
foreign device	4.1 ± 3.1	2.3 ± 2.5	0.001
nonforeign device	0.3 ± 1.1	0.1 ± 0.3	0.75
12-wk period			
rehospitalization[b]	8 (13.8%)	9 (23.7%)	0.21
inpatient days (mean ± SD)	12.6 ± 11.1	12.4 ± 6.8	0.33
Outcomes			
initial hospitalization			
metastatic infection	22 (33.3%)	12 (30.0%)	0.72
died	8 (12.1%)	2 (5.0%)	0.22
12-wk period			
died	15 (22.7%)	4 (10.0%)	0.098
Costs	(n = 39)	(n = 23)	
initial hospitalization			
mean ± SD	$16,679 ± 12,063	$17,509 ± 11,267	−$830 (−$7,161 to $5,117)
median (±IQR)	$13,776 (±82961 to 18,698)	$13,663 (±10,868 to 23,607)	
12-wk period			
mean ± SD	$22,944 ± 18,278	$23,969 ± 13,731	−$1,024 (−$8,459 to $6,792)
median (±IQR)	$17,392 (±11,945 to 29,425)	$18,318 (±13,663 to 31,660)	

[a]CI, confidence interval; IQR, interquartile range.
[b]Patients who died during initial hospitalization were excluded.

vascular event (n = 2), epidural abscess (n = 1), and other (n = 5). More than one metastatic complication could be present in the same patient.

Inpatient mortality during the initial hospitalization was 12.1% for patients with catheters and 5.0% for patients with AV grafts (P = 0.22). Unadjusted 3-mo mortality did not differ significantly on the basis of hemodialysis access type (22.7 *versus* 10.0% for catheter *versus* graft; P = 0.098). In the 15 patients who had catheters and died, cause of death was related to SAB in eight and unrelated in seven. All four deaths in patients with AV grafts were due to SAB or its complications.

Cost Analysis

Patients with catheters had similar mean costs during the initial hospitalization for SAB ($16,679 ± $12,063) compared with patients with AV grafts ($17,509 ± $11,267; difference −$830; 95% CI −$7,161 to $5,117). Mean total 3-mo costs that were associated with SAB also were similar between patients with catheters ($22,944 ± $18,278) and patients with AV grafts ($23,969 ± $13,731; difference −$1,024; 95% CI −$8,459 to $6,792).

Multivariable Analysis

After adjustment for patient characteristics, the odds of death at 3 mo did not differ significantly by access type (Table 3). In contrast, an increasing APACHE II score (odds ratio [OR] 1.19; 95% CI 1.02 to 1.39) and bacteremia caused by MRSA (OR 10.33; 95% CI 2.15 to 49.66) were associated with increased mortality at 12 wk. Twelve-week costs did not differ significantly between patients with catheters and patients with AV grafts (means ratio 0.84; 95% CI 0.60 to 1.17) after adjustment for patient characteristics.

Subgroup Analyses of Patients with Catheters

Among the 66 patients with catheters, 20 had alternative active access (maturing or active AV grafts or fistulas), 18 had failed AV grafts or fistulas, and the remaining 28 had no alternative active or inactive access type. Inpatient and 12-wk mortality did not differ between patients without alternative active access (n = 46) compared with patients with maturing AV fistulas or grafts (n = 20; inpatient mortality 13 *versus* 10% [P = 0.73]; 12-wk mortality 26 *versus* 15% [P = 0.32]; catheter only *versus* alternative active access, respectively). Among patients who had a catheter but no alternative active access, the mean costs for the initial hospitalization were $18,162 (±$11,687) compared with $12,903 (±$12,740) among patients with maturing AV grafts or fistulas (difference $5259; 95% CI −$5056 to $12,627). At 12 wk, mean costs for patients who had a catheter but no alternative access were $25,738 (±$19,415) compared with $15,831 (±$13,198) for patients who had a catheter and a maturing AV graft or fistula (difference $9907; 95% CI −$944 to $20,183).

After adjustment for patient characteristics, there was no difference in 12-wk mortality between patients who had a catheter but no alternative access and those with a maturing AV

Table 3. Associations between clinical and demographic variables and mortality and costs among patients with ESRD and SAB[a]

Variable	12-Wk Mortality		12-Wk Costs	
	Odds Ratio	95% CI	Means Ratio	95% CI
Catheter only[b]	1.63	0.29 to 9.02	0.84	0.60 to 1.17
Female gender	0.24	0.05 to 1.12	0.89	0.65 to 1.23
White race	0.90	0.12 to 6.90	1.19	0.77 to 1.86
Diabetes	1.72	0.34 to 8.80	1.12	0.81 to 1.54
Hypertension	3.02	0.53 to 17.36	0.86	0.61 to 1.21
History of kidney transplant	0.29	0.01 to 6.32	1.05	0.61 to 1.21
CNS involvement	3.32	0.48 to 22.89	1.39	0.79 to 2.46
Heart failure	2.11	0.16 to 27.85	1.54	0.80 to 2.98
Sepsis	3.93	0.47 to 32.76	1.14	0.67 to 1.93
APACHE II	1.19	1.02 to 1.39	0.97	0.94 to 1.01
MRSA	10.33	2.15 to 49.66	1.09	0.77 to 1.55
Admit from nursing facility/other hospital	0.69	0.10 to 4.65	1.45	0.87 to 2.44

[a]CNS, central nervous system.
[b]Graft only served as the reference group.

graft or fistula (OR 1.71; 95% CI 0.25 to 11.75). In adjusted analyses, 12-wk costs also did not differ significantly on the basis of the absence or presence of alternative active access (means ratio 1.52; 95% CI 0.98 to 2.35).

Discussion

SAB is a serious, common complication of intravascular access in hemodialysis-dependent patients (1). Our investigation shows that morbidity, mortality, and costs that are associated with an episode of SAB among hemodialysis-dependent patients are pronounced but do not vary significantly by different forms of intravascular access.

The clinical impact of an episode of SAB in hemodialysis patients is considerable and is highlighted by our cohort. Metastatic complications occurred in 34% of patients, including infective endocarditis, osteomyelitis, and abscesses. The high rate of metastatic complications among our patients is consistent with previous reports (10,12) and highlights the virulence of *S. aureus*, particularly in an immunocompromised host with an intravascular foreign device. It is interesting that the rate of metastatic infections did not differ among patients on the basis of their intravascular access type. This observation suggests that the risk for metastatic complications that are associated with SAB in hemodialysis patients is high regardless of the potential source of infection. Overall mortality also was high in this investigation but did not vary significantly among patients with different vascular access types, even after adjustment for differences in acute and chronic comorbidities.

Although vascular access type did not affect length of hospitalization, the number of procedures that were performed during the initial hospitalization was highest among patients with catheters. This reflects the standard practice at our institution of prompt removal of a hemodialysis catheter in any patient with documented SAB whenever clinically possible. Patients who had AV grafts and developed SAB also required extensive medical therapy, because half of these patients required surgical removal or revision of their vascular access, and approximately one quarter required re-hospitalization during the follow-up period (37).

The findings from our cost analysis of hemodialysis-dependent patients with SAB are unique and show that overall costs are pronounced (approximately $23,000 during 12 wk). Surprisingly, costs did not differ statistically between patients with catheters and patients with AV grafts, despite the high surgical costs associated with an AV graft revision/removal and replacement (38). As the total costs for treating the 111 hemodialysis patients who had SAB and were reported in this study was $2,440,987, access-related SAB represents a significant economic burden to the health care system. It should be highlighted that these costs are in addition to the already substantial health care costs associated with maintenance hemodialysis and initial dialysis access placement (38–40).

There are a number of potential reasons that no significant associations were noted between a patient's hemodialysis access type and his or her ultimate clinical outcome. First, among patients with AV grafts, complications and costs that are associated with an AV graft revision/resection can be significant (37,38,41). In contrast, patients with catheters required a large number of procedures (*e.g.*, catheter removal and replacement, prosthetic device removal, surgery for infective endocarditis), which likely escalated the mortality rate and cost in this cohort. The lack of our ability to detect a difference in costs among patients who had a catheter and who did and did not have alternative active access types may be due to the lack of power within this subgroup analysis. Alternatively, the other active access type may not have been readily usable at the time of admission and therefore was unable to confer a cost savings; in addition, if the maturing AV graft or fistula had been placed recently, then management of postsurgical infectious complications may have increased costs in this subgroup.

Our study has a number of limitations. First, our data were derived from an observational design with a modest sample size, thereby limiting our ability to detect statistically significant differences between groups. Second, groups that were based on access type had distinct differences in comorbidities; however, we tried to identify and adjust for all potential confounders between groups in our statistical analysis. Third, although we did not capture costs for patients who were admitted to outside hospitals, follow-up was complete on all patients at 12 wk, thus making the risk for missing an outside hospital admission small. Fourth, we did not include in our cost analysis outpatients who were treated for bacteremia, although this is less relevant as it is standard practice for patients with documented SAB to be treated as inpatients and therefore this should not have affected our results. Finally, referral bias may overestimate the cost and outcome of SAB if only sicker patients were admitted to our institution. This risk is minimized by the fact that the majority of patients in this study are cared for by university-affiliated hemodialysis units that use our institution for all hospital admissions.

Despite these limitations, our cohort highlights the significant morbidity, mortality, and costs that are associated with an episode of SAB among hemodialysis patients. Furthermore, our investigation suggests that a patient's hemodialysis access type is not significantly associated with differential costs or clinical outcomes during an episode of SAB, even if the vascular access is readily removable. Given the significant patient, physician, and cost burden associated with an episode of SAB in patients with ESRD, effective interventions to try to prevent *S. aureus* infections in this high-risk group are warranted.

Acknowledgments

This research was supported in part by a research agreement between Duke University and Nabi Biopharmaceuticals. J.K.I. was supported by a clinical research fellowship endowment from Earl Dalbey and by National Institutes of Health grant K12 RR-017630. V.G.F. was supported by National Institutes of Health grant R01-AI059111.

This study was presented in abstract form at the European Renal Association-European Dialysis and Transplant Association Annual Congress, Lisbon, Portugal, May 15 to 18, 2004.

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