Staphylococcus aureus Bacteremia Among Patients Receiving Maintenance Hemodialysis: Trends in Clinical Characteristics and Outcomes

Matthew R. Sinclair, Maria Souli, Felicia Ruffin, Lawrence P. Park, Michael Dagher, Emily M. Eichenberger, Stacey A. Maskarinec, Joshua T. Thaden, Michael Mohnasky, Christina M. Wyatt, and Vance G. Fowler Jr

Rationale & Objective: *Staphylococcus aureus (S aureus)* bacteremia (SAB) is associated with morbidity and mortality in patients receiving maintenance hemodialysis (HD). We evaluated changes in clinical and bacterial characteristics, and their associations with clinical outcomes with SAB in this population over a 21-year period.

Study Design: Prospective cohort study.

Setting & Participants: 453 hospitalized, non-neutropenic adults receiving maintenance HD who developed monomicrobial SAB between 1995 and 2015.

Exposure: Clinical characteristics and bacterial genotype.

Outcome: All-cause and SAB-attributable mortality, persistent bacteremia, and metastatic complications.

Analytical Approach: Proportions of participants experiencing each outcome were calculated overall and by calendar year. Secular trends were estimated using binomial risk regression, a generalized linear model with the log link function for a binomial outcome. Associations with outcomes were estimated using logistic regression.

Results: Over the 21-year study period, patients receiving maintenance HD experienced significant increases in age- and diabetes-adjusted SAB-attributable mortality (0.45% [95% CI, 0.36%-0.46%] per year), persistent bacteremia (0.86% [95% CI, 0.14%-1.55%] per year), metastatic complications (0.84% [95% CI, 0.11%-1.56%] per year), and infection with the virulent *S aureus* clone USA300 (1.47% [95% CI, 0.33%-2.52%] per year). Over time, the suspected source of SAB was less likely to be a central venous catheter (−1.32% [95% CI, −2.05 to −0.56%] per year) or arteriovenous graft (−1.08% [95% CI, −1.54 to −0.56] per year), and more likely to be a nonvascular access source (1.89% [95% CI, 1.29%-2.43%] per year). Patients with a nonvascular access suspected source of infection were more likely to die as a result of their *S aureus* infection (OR, 3.20 [95% CI, 1.36-7.55]). The increase in USA300 infections may have contributed to the observed increase in persistent bacteremia (OR, 2.96 [95% CI, 1.12-7.83]) but did not explain the observed increases in SAB-attributable mortality (OR, 0.83 [95% CI, 0.19-3.61]) or metastatic complications (OR, 1.34 [95% CI, 0.53-3.41]).

Limitations: Single-center, inpatient cohort.

Conclusions: The clinical and molecular epidemiology of SAB in patients receiving maintenance HD has changed over time, with an increase in SAB-attributable mortality and morbidity despite a decline in catheter-related infections.

Visual Abstract online

Complete author and article information provided before references.

Correspondence to V.G. Fowler (vance.fowler@duke.edu)

Am J Kidney Dis. XX(XX):1-11. Published online month xx, xxxx.

doi: 10.1053/j.ajkd.2021.06.018

Infection is the second leading cause of mortality in patients with kidney failure on hemodialysis (HD), with bacteremia accounting for the majority of infections.[1-3] Compared with the general population, infection-related mortality is up to 100 times greater in patients who receive dialysis.[4,5] *Staphylococcus aureus* (*S aureus*) is the most common cause of bacteremia in patients receiving maintenance HD, accounting for >30% of all bloodstream infections.[6,7] *S aureus* bacteremia (SAB) can lead to severe complications, including endocarditis, osteomyelitis, septic arthritis, and abscesses.[1,8-10] Importantly, bacterial genotype plays a critical role in pathogenesis, as methicillin-resistant *S aureus* (MRSA) infections are associated with significantly higher mortality than methicillin-susceptible *S aureus* (MSSA) infections.[11,12] MRSA was first isolated in the 1960s,[13] and over the past 50 years nosocomial and community-acquired MRSA infection rates among maintenance HD patients have increased,[14] accounting for >40% of all *S aureus* samples isolated from outpatient HD centers in 2014.[7]

The primary objective of this study is to describe the clinical and molecular epidemiology of SAB among patients receiving maintenance HD over a 2-decade period at our institution. To accomplish this objective, we evaluated the maintenance HD subgroup of our recently published work involving over 2,300 prospectively enrolled patients with SAB.[15] A secondary objective of this study was to describe differences in characteristics and outcomes between patients in the cohort receiving maintenance HD versus those who did not.

Methods

Database and Study Population

The *S aureus* Bacteremia Group Prospective Cohort Study (SABG-PCS) is an ongoing, prospective cohort at Duke

PLAIN-LANGUAGE SUMMARY

Staphylococcus aureus (*S aureus*) bacteremia (SAB) is a leading cause of morbidity and mortality in patients with kidney failure on hemodialysis. The clinical characteristics and the characteristics of the *S aureus* isolates have changed over time, but it is unknown how these changes have affected patient outcomes. In this study, we examined these changing characteristics and their associations with clinical outcomes among 453 patients receiving maintenance hemodialysis who were hospitalized with SAB over a period of 21 years. The most common suspected sources of infection changed over time. Additionally, virulent strains of *S aureus* became more prevalent. These changes were associated with worse outcomes, including SAB-attributable mortality, persistent bacteremia, and tissue infections, all of which increased over time.

University Medical Center (DUMC). The overall cohort, study design, and ascertainment strategies have been described elsewhere.[15] SABG-PCS and the present study were approved by the Duke institutional review board. Patients or their legal representatives provided written informed consent. If patients died before notification of their blood culture results, they were included in the SABG using a Notification of Decedent Research.

Inclusion and Exclusion Criteria

Adults hospitalized with monomicrobial SAB at DUMC were eligible for enrollment in the SABG-PCS if they did not meet any of the following exclusion criteria: were <18 years of age, were neutropenic (absolute neutrophil count $\leq 1 \times 10^9$/L), had no signs or symptoms of infection, had a second clinically significant bacterial pathogen other than *S aureus* isolated from their blood culture, did not speak English, or declined to participate.

Only patients whose initial bloodstream *S aureus* isolate was available for further testing were included in the current analysis, and only the index hospitalization was considered. In our analyses comparing patients who were receiving maintenance HD with those who were not, all eligible SABG-PCS patients were included, and defining patients as receiving maintenance HD was based on their status before confirmation of bacteremia. For the remaining analyses, only patients receiving maintenance HD were included.

Definitions

SAB was determined to be either hospital-acquired (HA) or community-acquired (CA), according to previously defined criteria.[16] Community-acquired SAB was then further categorized as either community acquired, non–health care associated (CA-NHCA) or community acquired, health care associated (CA-HCA).[16] Patients on maintenance HD with kidney transplants were confirmed to be receiving HD and have non-functioning kidney transplants at the time of enrollment. Additional types of organ transplants included lung, heart, pancreas, liver, and bone marrow.

Suspected sources of infection included central venous catheter (CVC), arteriovenous graft (AVG), arteriovenous fistula (AVF), or non–vascular access, with the latter defined as an infection that was determined not to originate in a CVC, AVG, or AVF. (The footnote to Table 1 has more information on non–vascular access sources.) Suspected sources of infection were determined based on the best judgment of the individuals who collected the data in the case report form, in addition to 2 independent reviewers who adjudicated the data before it was imported into the database. One of the independent reviewers was an infectious disease physician. These judgments were informed based on clinical progress notes from the providers who took care of the patients (including nephrologists and infectious disease physicians), and was often supported by imaging findings. At our center, only patients undergoing home HD were cannulated via the buttonhole technique, and patients undergoing in-center HD were always cannulated via the rope-ladder technique. Among patients who had a suspected AVF source of infection, only one was on home HD and had an AVF cannulation performed via the buttonhole technique.

Designated clinical outcomes were all-cause mortality, SAB-attributable mortality, persistent bacteremia, and metastatic complications. SAB-attributable mortality was defined as death due to SAB and included all patients who died with persistent signs or symptoms of systemic infection, positive blood culture results, or a persistent focus of infection in the absence of another explanation for death. Outcomes were tracked for 90 days after enrollment into the SABG-PCS.

A metastatic complication was defined as a *S aureus* infection resulting from the spread from an initial site, either via direct extension or bloodstream seeding, and included any of the following conditions: a metastatic abscess or another deep tissue abscess (eg, psoas or epidural abscess), infective endocarditis,[17] vertebral osteomyelitis, septic arthritis, septic emboli, or septic thrombophlebitis. Persistent bacteremia was defined as ≥5 days of positive blood cultures after the initiation of an appropriate treatment regimen.[15] Antibiotic therapy was considered to be appropriate if it included at least one antibiotic with in vitro activity against the patient's bloodstream *S aureus* isolate.

Susceptibility Testing and Molecular Typing

All *S aureus* isolates underwent methicillin susceptibility testing and *spa* typing, as previously described elsewhere.[15] MRSA isolates were identified as USA300 if they exhibited a *spa*-CC08 (multilocus sequence type [MLST] CC008)

genotype and were positive by polymerase chain reaction (PCR) for arginine catabolic mobile element (ACME) and Panton-Valentine leukocidin (PVL)-encoding genes.[14,18-21]

Statistical Analysis

Patient and bacterial characteristics and clinical outcomes are summarized using medians with interquartile range or counts and percentages. For comparisons between groups, statistical significance was evaluated with Mann-Whitney U or Fisher exact test. For the primary objective, the proportion of participants receiving maintenance HD with each clinical or bacterial characteristic or experiencing each outcome was calculated overall and by calendar year. Secular trends in proportions were estimated with binomial outcome risk regression,[22] fit with an independent variable calendar year as a linear term, which estimates average percentage change in proportion over the entire study period. An assumption was made that the denominator for all outcome proportions was equal, disregarding the competing risk of death and early discharge not attributable to SAB. Lowess curves for each of the characteristics and outcomes examined have been constructed. For 2 characteristics, AVF as the suspected source of infection and USA300 infection, secular trends were summarized only for the period 2004-2015 because there were no occurrences before 2004.

In sensitivity analyses, we examined secular trends in suspected source of infection, bacterial characteristics, and outcomes over this same truncated time period. Univariable and multivariable logistic regression models were used to assess adjusted associations of clinical characteristics and *S aureus* genotypes with mortality (both all-cause and SAB attributable), persistent bacteremia, and metastatic complications. Analyses were performed with SAS 9.4 (SAS Institute).

Results

Study Population

Between January 1, 1995, and December 31, 2015, a total of 2,423 unique patients were enrolled in the SABG-PCS. A total of 53 patients were excluded because their initial bloodstream isolates could not be retrieved, another 22 were excluded due to inconsistent data regarding clinical outcomes, and 7 were excluded due to inconsistent data entry for key covariates. For analyses focused on patients receiving maintenance HD, we excluded an additional 26 participants who required kidney replacement therapy during the index hospitalization but who were not on maintenance HD before confirmation of bacteremia. Of the 2,315 patients included in the current analysis, 453 (19.6%) were found to be receiving maintenance HD.

The baseline characteristics of the included SABG-PCS participants are summarized in Table 1. Among maintenance HD patients, the suspected source of bacteremia was the vascular access in 78.3% (CVC in 54.9%, AVG in 18.8%, and AVF in 4.6%). Over the truncated 2004-2015 time period, the suspected source of bacteremia in patients receiving maintenance HD was the vascular access in 68.6% (Table S1).

Clinical Outcomes

Patients who were receiving maintenance HD were more likely than those who were not to have persistent bacteremia (30.9% vs 20.0%, $P < 0.001$) (Table 2). This finding was consistent when comparing patients with MRSA bacteremia who did and did not receive maintenance HD and when examining the truncated 2004-2015 time period (Table 3; Tables S2 and S3).

Changes in Maintenance HD Population over Time

Over the period from 1995 to 2015, the suspected source of SAB changed, with significant reductions in suspected CVC (annual reduction, −1.32% [95% CI, −2.05 to −0.56]) or AVG infection (annual reduction, −1.08% [95% CI, −1.54 to −0.56]) and significant increases in nonvascular access sources (annual increase, 1.89% [95% CI, 1.29%-2.43%) (Fig 1). Lowess curves for other clinical characteristics are presented in Figure S1. In a sensitivity analysis examining the suspected source of SAB, considering only the period from 2004 to 2015 when suspected AVF infections and USA300 infections were first observed, these trends were qualitatively similar to the overall time period, although no longer statistically significant (Fig S2). Although all-cause mortality did not change significantly during the study period, the prevalence of SAB-attributable mortality increased significantly (age- and diabetes-adjusted annual increase, 0.45% [95% CI, 0.36%-0.46%). The adjusted frequency of persistent bacteremia (adjusted annual change, 0.86% [95% CI, 0.14% to 1.55%]) and metastatic complications (adjusted annual change, 0.84% [95% CI, 0.11% to 1.56%]) also increased during the study period (Fig 2). When outcomes were examined among only patients with MRSA, all-cause mortality decreased over time (adjusted annual change, −1.22% [95% CI, −1.35% to −0.22%]) while SAB-attributable mortality increased (adjusted annual change, 0.04% [95% CI, 0.01% to 1.21%]) (Fig 3). Sensitivity analyses examining these outcomes for the 2004-2015 period are shown in Figures S3 and S4. Frequencies and proportions of outcomes by year are shown in Table S4.

Molecular Genotyping in Maintenance HD Patients

Previously, we found that a specific bacterial genotype, the epidemic community-associated MRSA clone termed USA300, was significantly associated with increasing rates of persistent bacteremia and metastatic complications.[15] Thus, in the current study we tested the hypothesis that increasing rates of complications among patients receiving maintenance HD might be due to the emergence and establishment of the virulent USA300 clone of MRSA in

Table 1. Demographics and Clinical Characteristics in Patients, by Maintenance HD Status

	Receiving Maintenance HD		
	Yes (n = 453)	No (n = 1,862)	*P*
Age, y	57 [47-67]	60 [47-71]	0.01[a]
Female sex	212 (46.8%)	784 (42.1%)	0.08
Race			<0.001[a]
Black	347 (76.9%)	484 (26.2%)	
White	94 (20.8%)	1,311 (70.9%)	
Other	10 (2.2%)	54 (2.9%)	
Route			<0.001[a]
HA	41 (9.1%)	672 (36.1%)	
CA-HCA	412 (90.9%)	964 (51.8%)	
CA-NHCA	0 (0)	225 (12.1%)	
DM	258 (57.0%)	631 (33.9%)	<0.001[a]
Neoplasm	26 (5.8%)	434 (23.3%)	<0.001[a]
Corticosteroid use	45 (9.9%)	400 (21.5%)	<0.001[a]
Transplant[b]	34 (7.5%)	124 (6.7%)	0.5
HIV	11 (2.4%)	55 (3.0%)	0.6
Surgery within 30 d[c]	73 (16.2%)	563 (30.4%)	<0.001[a]
Previous endocarditis	22 (4.9%)	49 (2.6%)	0.02[a]
MRSA	206 (45.5%)	898 (48.2%)	0.3
USA300	24 (5.3%)	143 (7.7%)	0.09
Foreign body cardiac device	44 (9.7%)	260 (14.0%)	0.02[a]
Foreign body central venous catheter	280 (61.8%)	265 (14.2%)	<0.001[a]
Source of infection[d]			
Central venous catheter	248 (54.9%)	331 (17.9%)	<0.001[a]
Arteriovenous graft	85 (18.8%)	7 (0.4%)	<0.001[a]
Arteriovenous fistula	21 (4.6%)	1 (0.1%)	<0.001[a]
Non–vascular access[e]	98 (21.7%)	1,515 (81.7%)	<0.001[a]

Values given as count (%) except for age, which is given as median [interquartile range]. Abbreviations: CA-HCA, community-acquired, health care associated; CA-NHCA, community-acquired, non–health care associated; DM, diabetes mellitus; HA, hospital-acquired; HD, hemodialysis; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]*P* values are statistically significant.
[b]Twenty-seven nonfunctioning kidney transplants in maintenance HD cohort and 25 functioning kidney transplants in non–maintenance HD cohort.
[c]Within 30 days of index positive blood culture.
[d]Suspected source of infection.
[e]Includes abscess, septic arthritis, biliary tract, burn, arterial catheter, intra-aortic balloon pump, peripheral catheter, other non-central venous catheter, cellulitis, decubitus ulcer, dermatitis, empyema, foot/leg ulcer, furuncle, gangrene, intravenous drug use, mediastinitis, percutaneous nephrostomy, peritoneal dialysis catheter, pneumonia, sinusitis, wound, and unknown/unspecified source of infection.

Table 2. Clinical Outcomes in Patients, by Maintenance HD Status

	Receiving Maintenance HD		
	Yes (n = 453)	No (n = 1,862)	*P*
All-cause mortality	106 (23.4%)	505 (27.1%)	0.1
SAB-attributable mortality	60 (13.2%)	253 (13.6%)	0.9
Persistent bacteremia	140 (30.9%)	373 (20.0%)	<0.001[a]
Metastatic complications (overall)	160 (35.4%)	692 (37.2%)	0.5
Metastatic abscess	31 (6.8%)	164 (8.8%)	0.2
Psoas abscess	5 (1.1%)	41 (2.2%)	0.2
Epidural abscess	5 (1.1%)	64 (3.5%)	0.01[a]
Endocarditis	78 (17.2%)	237 (12.8%)	0.02[a]
Vertebral osteomyelitis	16 (3.5%)	89 (4.8%)	0.3
Septic arthritis	25 (5.5%)	137 (7.4%)	0.2
Septic emboli	32 (7.1%)	105 (5.7%)	0.3
Septic thrombophlebitis	28 (6.2%)	67 (3.6%)	0.02[a]

Abbreviations: HD, hemodialysis; SAB, *Staphylococcus aureus* bacteremia.
[a]*P* values are statistically significant.

Table 3. Clinical Outcomes in Patients With MRSA Bacteremia, by Maintenance HD Status

	Receiving Maintenance HD		
	Yes (n = 206)	No (n = 898)	*P*
All-cause mortality	65 (31.6%)	288 (32.1%)	0.9
SAB-attributable mortality	35 (17.0%)	163 (18.2%)	0.8
Persistent bacteremia	91 (44.2%)	235 (26.2%)	<0.001[a]
Metastatic complications (overall)	84 (40.8%)	327 (36.5%)	0.3
Metastatic abscess	16 (7.8%)	86 (9.6%)	0.5
Psoas abscess	4 (1.9%)	19 (2.1%)	0.9
Epidural abscess	4 (1.9%)	25 (2.8%)	0.6
Endocarditis	41 (19.9%)	114 (12.7%)	0.01[a]
Vertebral osteomyelitis	9 (4.4%)	36 (4.0%)	0.9
Septic arthritis	9 (4.4%)	55 (6.1%)	0.4
Septic emboli	15 (7.3%)	56 (6.3%)	0.6
Septic thrombophlebitis	18 (8.7%)	34 (3.8%)	0.01[a]

Abbreviations: HD, hemodialysis; MRSA, methicillin-resistant *Staphylococcus aureus;* SAB, *Staphylococcus aureus* bacteremia.
[a]*P* values are statistically significant.

that population. From 1995-2015, the genotypes of *S aureus* changed significantly among patients receiving maintenance HD in the cohort. The prevalence of MRSA increased significantly in the maintenance HD population over the 21-year study period (annual increase, 1.44% [95% CI, 0.67% to 2.17%]) (Fig 4A), although it remained

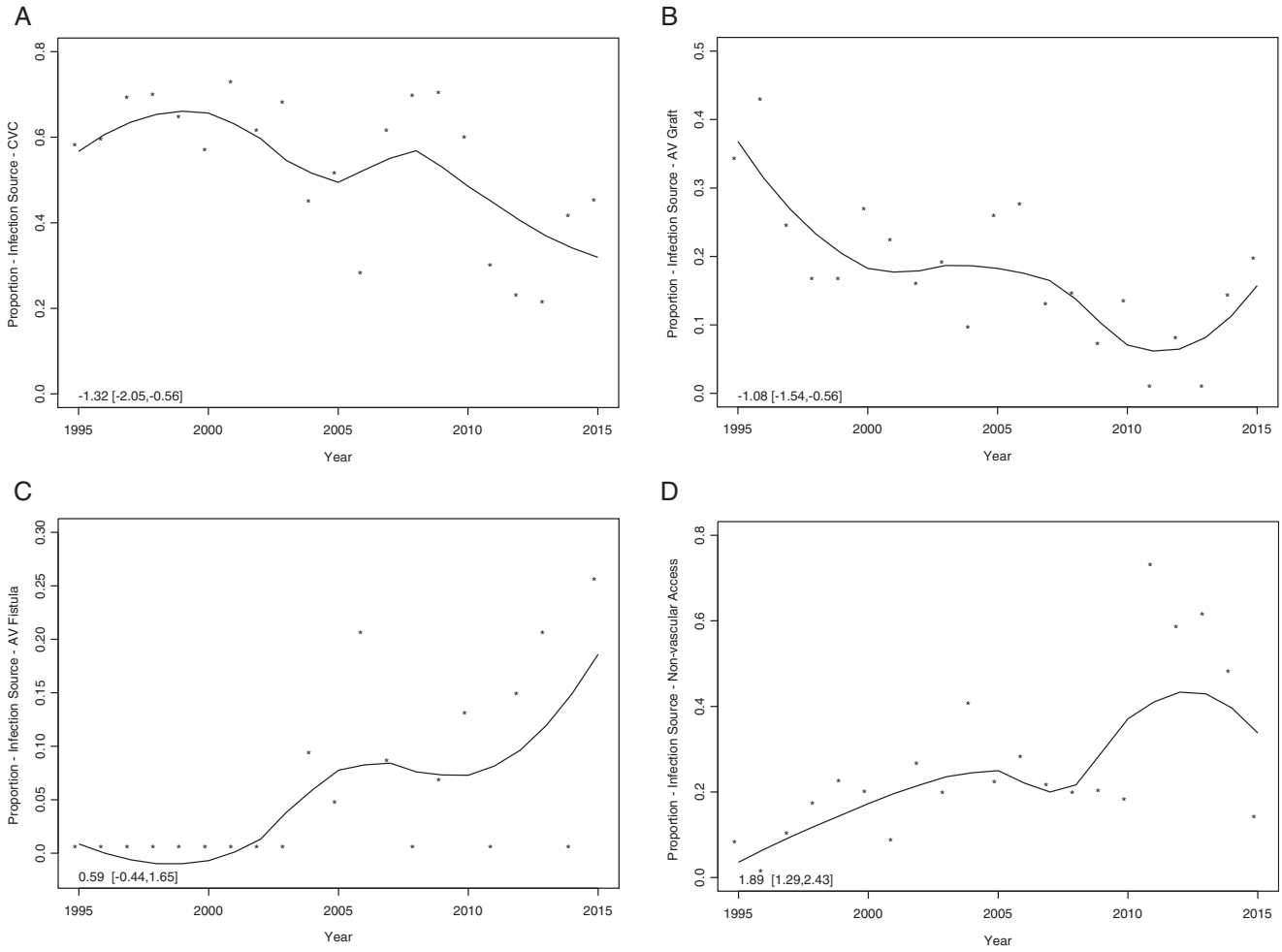

Figure 1. Secular trends in suspected source of infection in maintenance hemodialysis patients. (A) Central venous catheter (CVC). (B) Arteriovenous (AV) graft. (C) AV fistula. (D) Non–vascular access.

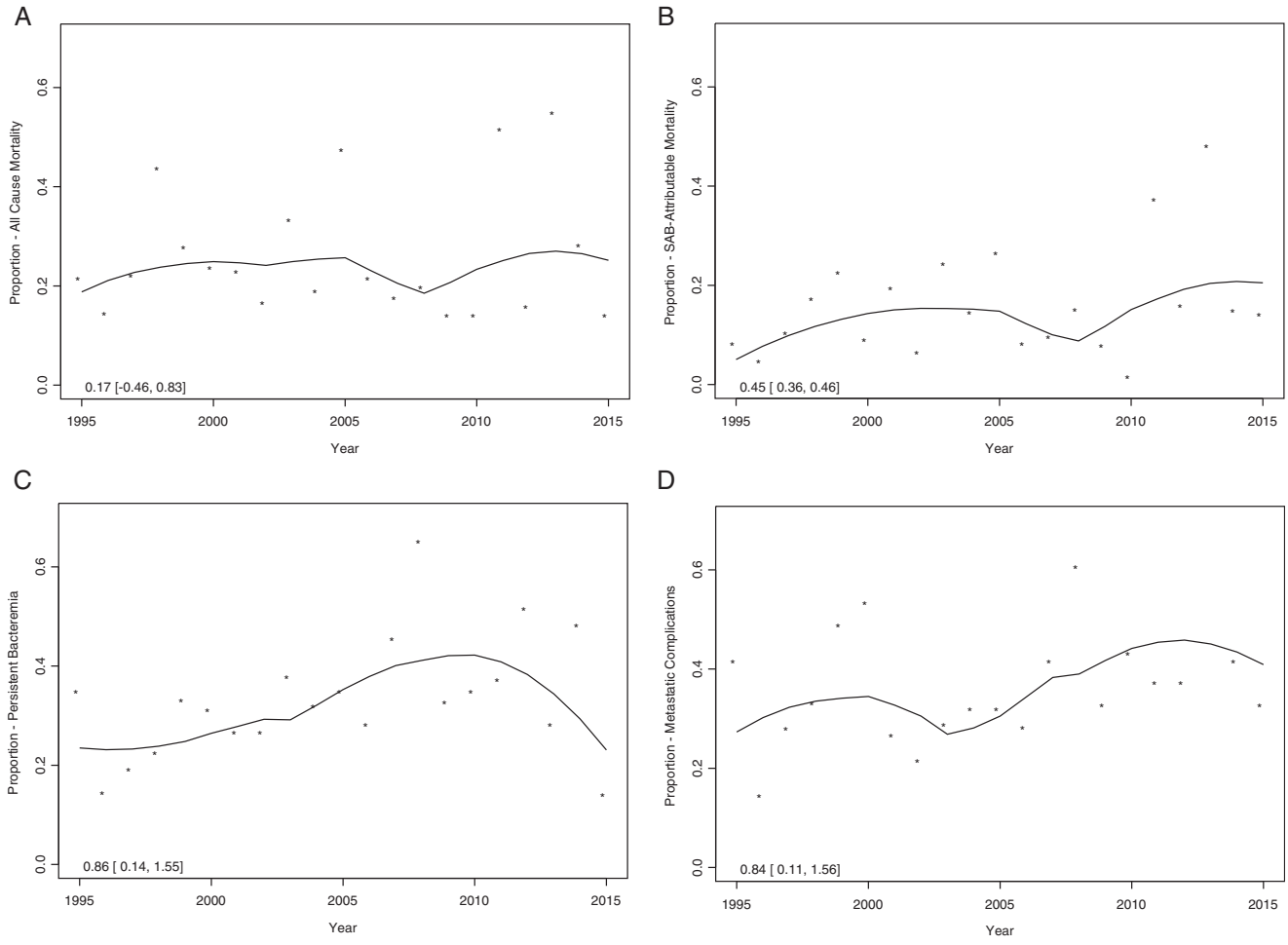

Figure 2. Secular trends in (A) all-cause mortality, (B) *Staphylococcus aureus* bacteremia (SAB)-attributable mortality, (C) persistent bacteremia, and (D) metastatic complications in maintenance hemodialysis patients.

consistent from 2004-2015 (Fig S5A). The USA300 genotype only emerged as a cause of SAB in the maintenance HD cohort in 2004, but the prevalence of USA300 increased significantly in the maintenance HD patient population from 2004-2015 (annual increase, 1.47% [95% CI, 0.33% to 2.52%]) (Fig 4B; Fig S5B). Despite the increase in prevalence, only 24 (5.3%) of the 453 maintenance HD patients had SAB due to USA300 infection during the study period (Table 1).

In the univariable analysis comparing outcomes in patients receiving maintenance HD with USA300 versus non-USA300 bacteremia, USA300 infection was not found to be significantly associated with any of the outcomes (Table 4). In the multivariable analysis, USA300 infection was found to be associated with persistent bacteremia when compared with MSSA infection (odds ratio [OR], 2.96 [95% CI, 1.12-7.83]). No significant associations between USA300 infection and mortality or metastatic complications were identified in the multivariable analysis. Non-USA300 MRSA was found to be associated with all-cause mortality (OR, 2.27 [95% CI, 1.36-3.80]), persistent bacteremia (OR, 3.55 [95% CI, 2.21-5.69]), and metastatic complications (OR, 1.56 [95% CI, 1.01-2.43]) (Table 5).

Patient Characteristics and Clinical Outcomes Among Maintenance HD Patients

Next, we considered potential associations between patient characteristics and clinical outcomes. Age > 65 years was strongly associated with both all-cause (OR, 2.65 [95% CI, 1.18-5.95]) and SAB-attributable (OR, 3.42 [95% CI, 1.17-10.03]) mortality. Black patients were less likely to experience SAB-attributable mortality compared with non-Hispanic White patients (OR, 0.49 [95% CI, 0.25-0.94]). Corticosteroid use was associated with persistent bacteremia (OR, 2.39 [95% CI, 1.11-5.18]) and metastatic complications (OR, 3.66 [95% CI, 1.72-7.80]). The presence of a foreign body CVC was not found to be significantly associated with any of the outcomes. As compared with patients receiving maintenance HD with a CVC as the suspected source of infection, patients receiving maintenance HD with a suspected non–vascular access source were significantly

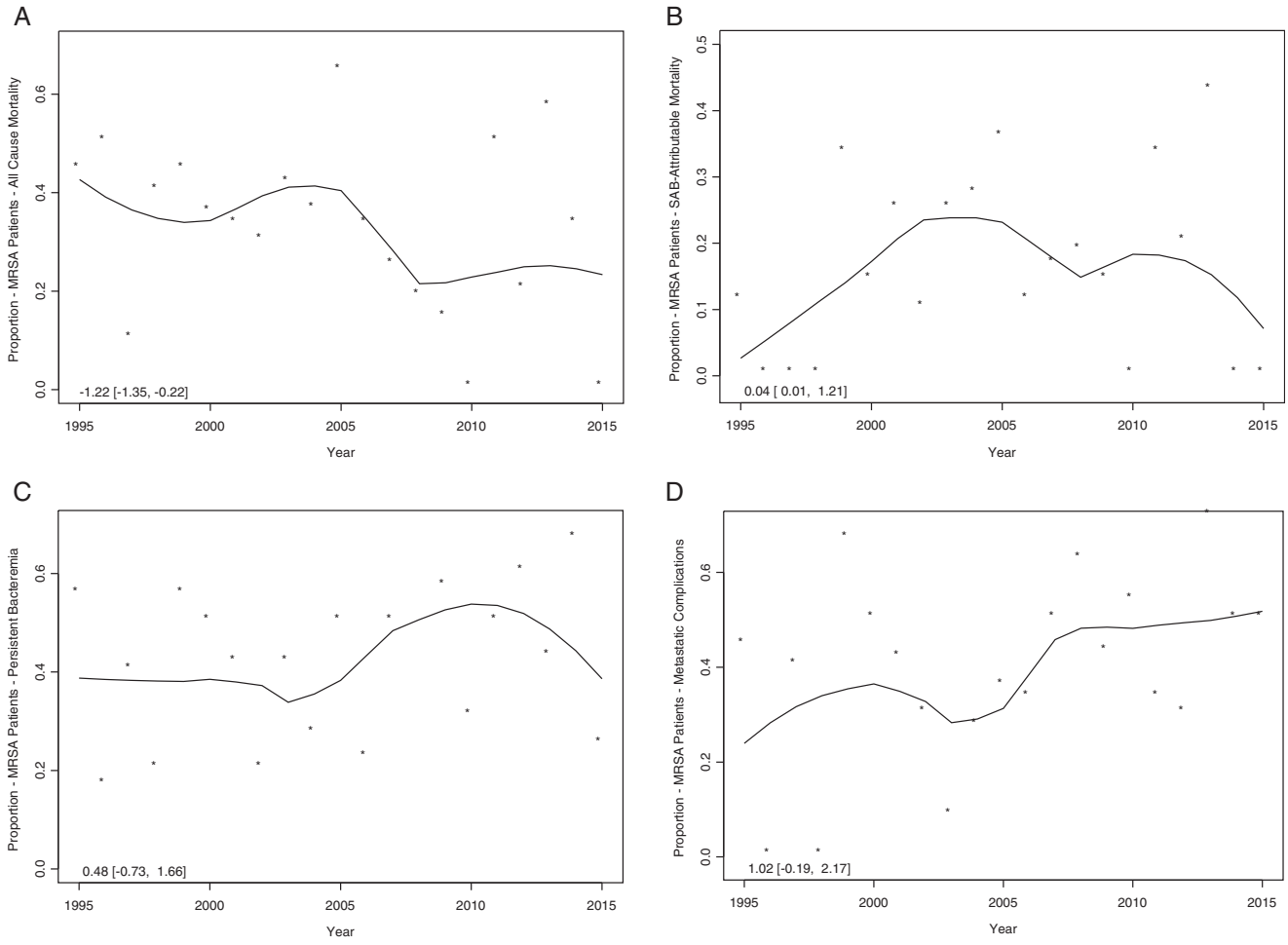

Figure 3. Secular trends in (A) all-cause mortality, (B) *Staphylococcus aureus* bacteremia (SAB)-attributable mortality, (C) persistent bacteremia, and (D) metastatic complications in maintenance hemodialysis patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

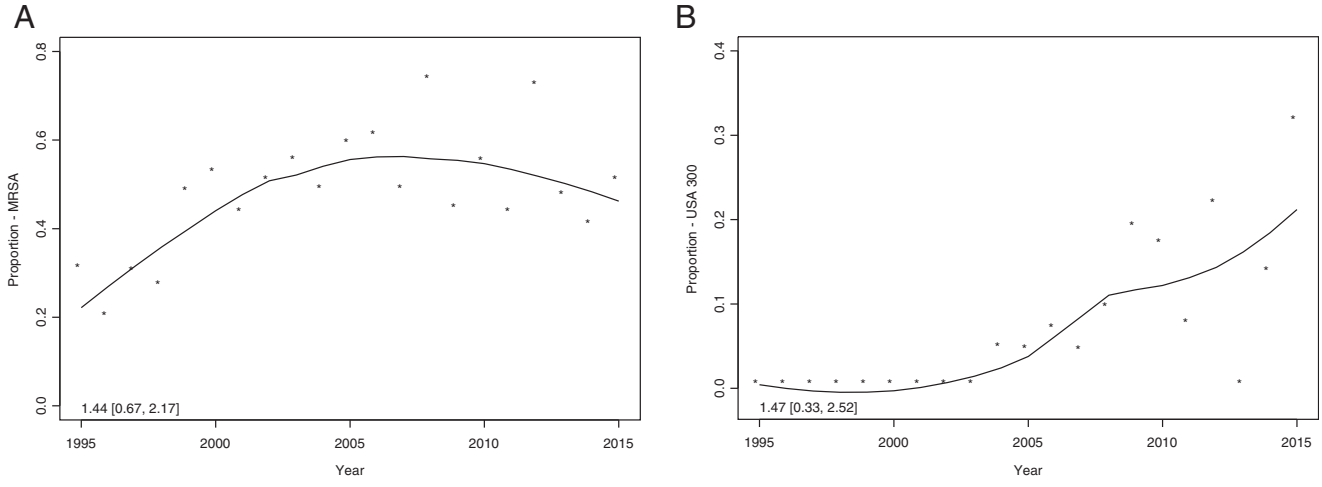

Figure 4. Secular trends in bacterial characteristics in maintenance hemodialysis patients. (A) Methicillin-resistant *Staphylococcus aureus* (MRSA). (B) USA300.

Table 4. Univariable Analysis of Associations Between Genotypes (USA300 vs Non-USA300) and Outcomes in Maintenance HD Patients With *Staphylococcus aureus* Bacteremia

	Genotype		
	USA300	Non-USA300	*P*
All-cause mortality	3 (12.5%)	103 (24.0%)	0.3
SAB-attributable mortality	3 (12.5%)	57 (13.3%)	0.9
Persistent bacteremia	10 (41.7%)	130 (30.3%)	0.3
Metastatic complications (overall)	11 (45.8%)	149 (34.8%)	0.3

Values given as n (%) with outcome. *P* values were calculated based on Fisher exact test. Abbreviations: HD, hemodialysis; SAB, *Staphylococcus aureus* bacteremia.

more likely to suffer overall mortality (OR, 3.34 [95% CI, 1.60-6.97]), to die as a result of their *S aureus* infection (OR, 3.20 [95% CI, 1.36-7.55]), and to have persistent bacteremia (OR, 2.11 [95% CI, 1.05-4.22]) (Table 5).

Discussion

This study demonstrates that the clinical and molecular epidemiology of SAB in patients receiving maintenance HD has changed significantly over the past 2 decades. These findings have several key implications.

The suspected source of infection changed during the study period. Fewer patients had a CVC or AVG as the suspected source of infection, while the frequency of a non–vascular access suspected source of infection increased. The decrease in suspected CVC-associated infections may reflect the impact of the Fistula First Breakthrough Initiative (FFBI), which sought to increase the prevalence of AVFs in patients receiving maintenance HD

Table 5. Multivariable Analysis of Characteristics Associated with Mortality, Persistent Bacteremia, and Metastatic Complications in Maintenance HD Patients

	All-Cause Mortality[a]	SAB-Attributable Mortality[a]	Persistent Bacteremia[a]	Metastatic Complications[a]
No. of events	106 (23.4%)	60 (13.2%)	140 (30.9%)	160 (35.3%)
Genotype				
MSSA	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-USA300 MRSA	2.27 (1.36-3.80)[b]	1.78 (0.95-3.36)	3.55 (2.21-5.69)[b]	1.56 (1.01-2.43)[b]
USA300	0.44 (0.10-1.88)	0.83 (0.19-3.61)	2.96 (1.12-7.83)[b]	1.34 (0.53-3.41)
Age				
<45 y	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
45-54 y	1.46 (0.59-3.63)	1.49 (0.44-5.14)	1.23 (0.60-2.54)	1.10 (0.57-2.11)
55-64 y	2.30 (0.99-5.22)	2.41 (0.80-7.23)	1.34 (0.66-2.70)	0.95 (0.50-1.82)
65+ y	2.65 (1.18-5.95)[b]	3.42 (1.17-10.03)[b]	1.74 (0.88-3.43)	1.12 (0.60-2.08)
Female sex	1.04 (0.63-1.72)	0.94 (0.51-1.74)	1.01 (0.65-1.58)	0.77 (0.50-1.16)
Race				
Non-Hispanic White	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	0.71 (0.40-1.28)	0.49 (0.25-0.94)[b]	1.58 (0.90-2.80)	0.82 (0.49-1.37)
Other	2.04 (0.43-9.76)	2.33 (0.43-12.49)	6.62 (1.52-28.91)[b]	2.53 (0.64-9.96)
Comorbidities				
Diabetes mellitus	0.99 (0.59-1.68)	0.86 (0.46-1.61)	1.08 (0.68-1.73)	1.44 (0.92-2.26)
Neoplasm	1.91 (0.77-4.78)	0.64 (0.17-2.45)	0.44 (0.15-1.27)	0.22 (0.07-0.73)[b]
Transplantation	0.67 (0.20-2.17)	0.54 (0.11-2.76)	0.91 (0.35-2.35)	0.46 (0.18-1.16)
Corticosteroid use	0.72 (0.27-1.95)	0.61 (0.16-2.37)	2.39 (1.11-5.18)[b]	3.66 (1.72-7.80)[b]
Foreign body CVC	1.65 (0.75-3.60)	1.27 (0.52-3.12)	0.93 (0.45-1.92)	0.84 (0.42-1.66)
Site of acquisition				
HA	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
CA-HCA	0.25 (0.12-0.53)[b]	0.39 (0.17-0.88)[b]	0.89 (0.42-1.87)	1.82 (0.85-3.93)
Source of infection[c]				
CVC	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Arteriovenous graft	1.03 (0.38-2.80)	1.69 (0.54-5.30)	1.20 (0.50-2.87)	0.70 (0.31-1.62)
Arteriovenous fistula	1.36 (0.28-6.66)	2.65 (0.50-13.90)	0.30 (0.07-1.35)	1.51 (0.48-4.73)
Non–vascular access[d]	3.34 (1.60-6.97)[b]	3.20 (1.36-7.55)[b]	2.11 (1.05-4.22)[b]	1.51 (0.79-2.91)

Values given as odds ratio (95% confidence interval) unless otherwise indicated.
Abbreviations: CA-HCA, community-acquired, health care associated; CVC, central venous catheter; HA, hospital-acquired; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.
[a]Results for each variable are adjusted for all other variables shown.
[b]Odds ratios and confidence intervals are statistically significant.
[c]Suspected source of infection.
[d]Includes abscess, septic arthritis, biliary tract, burn, arterial catheter, intra-aortic balloon pump, peripheral catheter, other non-central venous catheter, cellulitis, decubitus ulcer, dermatitis, empyema, foot/leg ulcer, furuncle, gangrene, intravenous drug use, mediastinitis, percutaneous nephrostomy, peritoneal dialysis catheter, pneumonia, sinusitis, wound, and unknown/unspecified source of infection.

while reducing CVC and AVG use.[23] This initiative came about in part because of the greatly increased risk of infection in patients who undergo dialysis using a CVC.[24] Interestingly, suspected AVF sources of infection only emerged in our cohort in the year 2004, after the implementation of the FFBI in 2003. It is possible that this could be related to process-of-care issues that occurred due to increasing AVF use after the FFBI was implemented, but more research is needed to fully elucidate this relationship.

Although previous reports have noted the presence of foreign body CVC as being associated with all-cause mortality,[25] this trend was not seen in our study. Importantly, however, there are underlying patient factors that may predispose patients to getting a CVC placed as opposed to an AVF for primary HD access, some of which have been shown to contribute to mortality.[26] We found a higher likelihood of all-cause and SAB-attributable mortality among patients whose suspected source of infection was not their HD access. This finding may be due in part to delays in source control for non–vascular access sources of infection. The increase in suspected non–vascular access sources of infection may explain in part the increased prevalence of SAB-attributable mortality over time. The cause of the increased prevalence of persistent bacteremia and metastatic complications is likely to be multifactorial and related to changes in both patient characteristics and molecular epidemiology of SAB.

Nearly three-quarters of the patients receiving maintenance HD with SAB in our study were Black. Interestingly, among Black patients with SAB there was a significant association with decreased SAB-attributable mortality. This finding is consistent with the well-described "survival paradox," with older Black patients on HD having lower mortality than older White patients on HD,[27,28] and with some[29] but not all[30] previous reports of outcomes among patients with SAB. However, more research is needed to better clarify potential interactions between race and clinical outcome among patients receiving maintenance HD with SAB and other bloodstream infections.[31]

Consistent with previous studies, we noticed a significant association between MRSA and adverse outcomes.[11,12,32] The prevalence of bloodstream infections caused by the USA300 strain of MRSA increased in the maintenance HD cohort during the study period. Although a few studies have evaluated shifts in molecular epidemiology of *S aureus* among maintenance HD patients,[33-35] they were limited by a retrospective study design, small patient population, and/or short study period. Consistent with what was seen in the overall cohort,[15] our study demonstrated that USA300 was strongly associated with the development of persistent bacteremia in maintenance HD patients. However, among the maintenance HD patients, no significant independent associations were found between bacteremia with USA300 and metastatic complications. It is possible that our study was underpowered to account for this difference, as only 24 patients receiving maintenance HD were infected with USA300 over the study period. It is also possible that patients receiving maintenance HD with SAB are diagnosed sooner and receive earlier treatment and source control than patients not receiving HD, given their thrice weekly HD regimen and frequent use of empirical antibiotics for suspected bacteremia. Further study is needed with adequately sized cohorts to better establish the relationship between bacterial genotype and clinical outcomes among patients receiving maintenance HD with SAB.

Our study has limitations. The number of patients receiving maintenance HD who experienced SAB due to USA300 was small, limiting the power to detect statistically significant differences. Our data came from patients hospitalized at a single academic referral center, so they may not fully generalize to other regions of the country or to patients receiving maintenance HD with SAB who are treated in the outpatient setting or in community hospitals. With an increase in the outpatient management of bacteremia in patients receiving maintenance HD in recent years, it is possible that only patients receiving maintenance HD with more severe SAB infections required hospitalization in later years of the study, which may have contributed to the worsening clinical outcomes we observed over time.

Although the suspected source of infection was determined based on clinical notes and imaging findings reviewed by the data collector and verified by 2 independent clinical adjudicators, strict Infectious Diseases Society of America[36] and Kidney Health Initiative[37] guidelines on catheter-related bloodstream infections (CRBSI) and arteriovenous graft- or fistula-associated bloodstream infections were not met. These updated guidelines were published in 2009 and 2018, respectively, and data collection for our cohort began in 1995. Due to missing time-to-event data for events other than death, we were unable to censor patients in our analyses who may have died from causes other than SAB before experiencing SAB-attributable mortality, persistent bacteremia, or metastatic complications, or who were lost to follow-up evaluation within the 90 days after enrollment. Therefore, in performing analyses for SAB-attributable mortality, persistent bacteremia, and metastatic complications, our denominator was likely higher than the true number of patients eligible to experience these outcomes. However, we know that the number of patients who died for reasons other than SAB remained constant over time (Fig S6), and the result of an inflated denominator would be a conservative estimate.

Finally, although the point estimates and 95% confidence intervals in our binomial risk regression models are intended to represent trends (eg, annual increase or decrease) in patient and bacterial characteristics and outcomes over the study period, there may be individual years when the direction is opposite that of the overall point estimate. For this reason, we have included figures with all

reported point estimates and have not reported point estimates for trends that were clearly nonlinear.

Despite these limitations, our study showed that the clinical presentation, clinical outcomes, and molecular epidemiology of SAB in patients receiving maintenance HD have changed significantly over the past 2 decades. The suspected source of infection shifted over the study period: non–vascular access infections became more prevalent; SAB-attributable mortality, persistent bacteremia, and metastatic complications increased; and the patients who had a non–vascular access source of infection were more likely to die from *S aureus* than those whose source was a CVC. USA300 emerged as an increasingly prevalent cause of SAB and was found to be strongly associated with persistent bacteremia.

More research is needed to better clarify the clinical impact of the emergence of USA300 among patients receiving maintenance HD. We plan to address this in future studies by genotyping bacterial isolates in patients receiving maintenance HD with SAB beyond the year 2015. Determining this will help to decide whether there is future clinical and therapeutic utility in genotyping *S aureus* isolates among patients receiving maintenance HD with SAB, or if we should focus exclusively on patient-specific factors to improve outcomes in this patient population.

Supplementary Material

Supplementary File (PDF)

Figure S1: Lowess curves of clinical characteristics in maintenance HD patients.

Figure S2: Secular trends in suspected source of infection in maintenance HD patients, 2004-2015.

Figure S3: Secular trends in all-cause mortality, SAB-attributable mortality, persistent bacteremia, and metastatic complications in maintenance HD patients, 2004-2015.

Figure S4: Secular trends in all-cause mortality, SAB-attributable mortality, persistent bacteremia, and metastatic complications in maintenance HD patients with MRSA bacteremia, 2004-2015.

Figure S5: Secular trends in bacterial characteristics in maintenance HD patients, 2004-2015.

Figure S6: Secular trend in non–SAB-attributable mortality.

Table S1: Demographics and clinical characteristics in patients who did versus did not receive maintenance HD, 2004-2015.

Table S2: Clinical outcomes in patients who did versus did not receive maintenance HD, 2004-2015.

Table S3: Clinical outcomes in patients who did versus did not receive maintenance HD who had MRSA bacteremia, 2004-2015.

Table S4: Frequencies and proportions of patients experiencing clinical outcome by year.

Article Information

Authors' Full Names and Academic Degrees: Matthew R. Sinclair, MD, Maria Souli, MD, PhD, Felicia Ruffin, PhD, MSN, RN, Lawrence P. Park, PhD, Michael Dagher, MD, Emily M. Eichenberger, MD, Stacey A. Maskarinec, MD, PhD, Joshua T. Thaden, MD, PhD, Michael Mohnasky, MBS, Christina M. Wyatt, MD, MS, and Vance G. Fowler Jr, MD, MHS.

Authors' Affiliations: Division of Nephrology (MRS, CMW) and Division of Infectious Diseases (FR, LPP, MD, EME, SAM, JTT, MM, VGF), Department of Medicine, Duke University School of Medicine, Duke University Medical Center, Durham, North Carolina; Duke Global Health Institute, Durham, North Carolina (LPP); Duke Clinical Research Institute, Durham, North Carolina (MRS, MS, CMW, VGF).

Address for Correspondence: Vance. G. Fowler Jr, MD, MHS. Rm 185 Hanes Bldg, 315 Trent Dr, Division of Infectious Diseases, Department of Medicine, Box 102359, Duke University Medical Center, Durham, NC 27710. Email: vance.fowler@duke.edu

Authors' Contributions: Research idea and study design: MRS, MS, FR, LPP, MD, EME, SAM, JTT, MM, CMW, VGF; data acquisition: MRS, MS, FR, VGF; data analysis/interpretation: MRS, MS, FR, LPP, VGF; statistical analysis: MRS, LPP; supervision or mentorship: CMW, VGF. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was supported in part by grants R01-AI068804 and T32-DK007731, and grant K24-AI093969 (to VGF). The funders had no role in the study design, analysis, reporting, or decision to submit the manuscript for publication.

Financial Disclosure: Dr Fowler has received grants/research support from MedImmune, Cerexa, Forest, Actavis, Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist, Merck, Medical Biosurfaces, Locus, Affinergy, Contrafect, Karius, Genentech, Regeneron, and Basilea; is a paid consultant for Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co, Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, and Destiny; has membership as Merck Co-Chair V710 Vaccine; has received educational fees from Green Cross, Cubist, Cerexa, Durata, Theravance; and Debiopharm; has received royalties from UpToDate; and has a patent pending for sepsis diagnostics. The remaining authors declare that they have no relevant financial interests.

Peer Review: Received September 10, 2020. Evaluated by 3 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form June 6, 2021.

References

1. Inrig JK, Reed SD, Szczech LA, et al. Relationship between clinical outcomes and vascular access type among hemodialysis patients with *Staphylococcus aureus* bacteremia. *Clin J Am Soc Nephrol*. 2006;1(3):518-524.
2. Jaber BL. Bacterial infections in hemodialysis patients: pathogenesis and prevention. *Kidney Int*. 2005;67(6):2508-2519.
3. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2019;73(3)(suppl 1):A7-A8.
4. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*. 2000;58(4):1758-1764.
5. Vogelzang JL, van Stralen KJ, Noordzij M, et al. Mortality from infections and malignancies in patients treated with renal

replacement therapy: data from the ERA-EDTA registry. *Nephrol Dial Transplant*. 2015;30(6):1028-1037.
6. Tokars JI, Miller ER, Stein G. New national surveillance system for hemodialysis-associated infections: initial results. *Am J Infect Control*. 2002;30(5):288-295.
7. Nguyen DB, Shugart A, Lines C, et al. National Healthcare Safety Network (NHSN) dialysis event surveillance report for 2014. *Clin J Am Soc Nephrol*. 2017;12(7):1139-1146.
8. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med*. 1997;127(4):275-280.
9. Marr KA, Kong L, Fowler VG, et al. Incidence and outcome of *Staphylococcus aureus* bacteremia in hemodialysis patients. *Kidney Int*. 1998;54(5):1684-1689.
10. Kovalik EC, Raymond JR, Albers FJ, et al. A clustering of epidural abscesses in chronic hemodialysis patients: risks of salvaging access catheters in cases of infection. *J Am Soc Nephrol*. 1996;7(10):2264-2267.
11. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*. 2003;36(1):53-59.
12. Del Rio A, Cervera C, Moreno A, Moreillon P, Miró JM. Patients at risk of complications of *Staphylococcus aureus* bloodstream infection. *Clin Infect Dis*. 2009;48(suppl 4):S246-S253.
13. Barber M. Methicillin-resistant staphylococci. *J Clin Pathol*. 1961;14:385-393.
14. Carrel M, Perencevich EN, David MZ. USA300 methicillin-resistant *Staphylococcus aureus*, United States, 2000-2013. *Emerg Infect Dis*. 2015;21(11):1973-1980.
15. Souli M, Ruffin F, Choi SH, et al. Changing characteristics of *Staphylococcus aureus* bacteremia: results from a 21-year, prospective, longitudinal study. *Clin Infect Dis*. 2019;69(11):188-1877.
16. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137(10):791-797.
17. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633-638.
18. Berlon NR, Qi R, Sharma-Kuinkel BK, et al. Clinical MRSA isolates from skin and soft tissue infections show increased in vitro production of phenol soluble modulins. *J Infect*. 2015;71(4):447-457.
19. David MZ, Daum RS, Bayer AS, et al. *Staphylococcus aureus* bacteremia at 5 US academic medical centers, 2008-2011: significant geographic variation in community-onset infections. *Clin Infect Dis*. 2014;59(6):798-807.
20. O'Hara FP, Suaya JA, Ray GT, et al. spa Typing and multilocus sequence typing show comparable performance in a macro-epidemiologic study of *Staphylococcus aureus* in the United States. *Microb Drug Resist*. 2016;22(1):88-96.
21. Diep BA, Gill SR, Chang RF, et al. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2006;367(9512):731-739.
22. Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am J Epidemiol*. 1986;123(1):174-184.
23. Lee T. Fistula first initiative: historical impact on vascular access practice patterns and influence on future vascular access care. *Cardiovasc Eng Technol*. 2017;8(3):244-254.
24. Lok CE, Foley R. Vascular access morbidity and mortality: trends of the last decade. *Clin J Am Soc Nephrol*. 2013;8(7):1213-1219.
25. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol*. 2013;24(3):465-473.
26. Brown RS, Patibandla BK, Goldfarb-Rumyantzev AS. The survival benefit of "fistula first, catheter last" in hemodialysis is primarily due to patient factors. *J Am Soc Nephrol*. 2017;28(2):645-652.
27. Kalantar-Zadeh K, Kovesdy CP, Norris KC. Racial survival paradox of dialysis patients: robust and resilient. *Am J Kidney Dis*. 2012;60(2):182-185.
28. Kucirka LM, Grams ME, Lessler J, et al. Association of race and age with survival among patients undergoing dialysis. *JAMA*. 2011;306(6):620-626.
29. Roghmann MC. Predicting methicillin resistance and the effect of inadequate empiric therapy on survival in patients with Staphylococcus aureus bacteremia. *Arch Intern Med*. 2000;160(7):1001-1004.
30. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA*. 2007;298(15):1763-1771.
31. Van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev*. 2012;25(2):362-386.
32. Chong YP, Park S-J, Kim HS, et al. Persistent *Staphylococcus aureus* bacteremia: a prospective analysis of risk factors, outcomes, and microbiologic and genotypic characteristics of isolates. *Medicine*. 2013;92(2):98-108.
33. Hidalgo M, Carvajal LP, Rincon S, et al. Methicillin-resistant *Staphylococcus aureus* USA300 Latin American variant in patients undergoing hemodialysis and HIV infected in a hospital in Bogota, Colombia. *PLoS One*. 2015;10(10):e0140748.
34. Patel G, Jenkins SG, Mediavilla JR, et al. Clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* among patients in an ambulatory hemodialysis center. *Infect Control Hosp Epidemiol*. 2011;32(9):881-888.
35. Johnson LB, Venugopal AA, Pawlak J, Saravolatz LD. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* infection among patients with end-stage renal disease. *Infect Control Hosp Epidemiol*. 2006;27(10):1057-1062.
36. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1-45.
37. Allon M, Brouwer-Maier DJ, Abreo K, et al. Recommended clinical trial end points for dialysis catheters. *Clin J Am Soc Nephrol*. 2018;13(3):495-500.

Staphylococcus aureus Bacteremia Among HD-Dependent Patients

Design & Participants

Retrospective cohort study

- 453 patients
- Academic medical center
- HD-dependent
- Hospitalized with *Staphylococcus aureus* bacteremia (SAB)

Changing Characteristics

1995 → 2015

↓ CVC	-1.32% (-2.05, -0.56)
↓ AVG	-1.08% (-1.54, -0.56)
↔ AVF	0.59% (-0.44, 1.65)
↑ Non-Vascular	1.89% (1.29, 2.43)
↑ MRSA USA300	1.47% (0.33, 2.52)

Worsening Outcomes

1995 → 2015

↑ SAB Attributable Mortality	0.45% (0.36, 0.46)
↑ Persistent Bacteremia	0.86% (0.14, 1.55)
↑ Metastatic Complications	0.84% (0.11, 1.56)

CONCLUSION: Over the study duration, CVCs and AVGs were less likely sources of *S. aureus* bacteremia, with more virulent bacterial strains, and worse clinical outcomes.

Matthew R. Sinclair, Maria Souli, Felicia Ruffin, et al (2021)

@AJKDonline | DOI: 10.1053/j.ajkd.2021.06.018