THE IMPACT OF METHICILLIN RESISTANCE IN *STAPHYLOCOCCUS AUREUS* BACTEREMIA ON PATIENT OUTCOMES: MORTALITY, LENGTH OF STAY, AND HOSPITAL CHARGES

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ABSTRACT

OBJECTIVE: To evaluate the impact of methicillin resistance in *Staphylococcus aureus* on mortality, length of hospitalization, and hospital charges.

DESIGN: A cohort study of patients admitted to the hospital between July 1, 1997, and June 1, 2000, who had clinically significant *S. aureus* bloodstream infections.

SETTING: A 630-bed, urban, tertiary-care teaching hospital in Boston, Massachusetts.

PATIENTS: Three hundred forty-eight patients with *S. aureus* bacteremia were studied; 96 patients had methicillin-resistant *S. aureus* (MRSA). Patients with methicillin-susceptible *S. aureus* (MSSA) and MRSA were similar regarding gender, percentage of nosocomial acquisition, length of hospitalization, ICU admission, and surgery before *S. aureus* bacteremia. They differed regarding age, comorbidities, and illness severity score.

RESULTS: Similar numbers of MRSA and MSSA patients died (22.9% vs 19.8%; $P = .53$). Both the median length of hospitalization after *S. aureus* bacteremia for patients who survived and the median hospital charges after *S. aureus* bacteremia were significantly increased in MRSA patients (7 vs 9 days, $P = .045$; $19,212 vs $26,424, $P = .008$). After multivariable analysis, compared with MSSA bacteremia, MRSA bacteremia remained associated with increased length of hospitalization (1.29 fold; $P = .016$) and hospital charges (1.36 fold; $P = .017$). MRSA bacteremia had a median attributable length of stay of 2 days and a median attributable hospital charge of $6,916.

CONCLUSION: Methicillin resistance in *S. aureus* bacteremia is associated with significant increases in length of hospitalization and hospital charges (*Infect Control Hosp Epidemiol* 2005;26:166-174).

Resistance to antimicrobial drugs is an important health, as well as economic, problem. Infections caused by resistant organisms are thought to cause increased morbidity, longer hospitalizations, and higher costs when compared with infections caused by susceptible strains; however, the magnitude of effect may vary based on pathogen, resistance to specific antimicrobials, and even mechanisms of resistance. Only a few studies have examined quantitatively both the health impact and the economic impact of antimicrobial resistance.[1-4]

Staphylococcus aureus is an important pathogen in both community and nosocomial infections, and the numbers of infections resulting from *S. aureus* have risen during the past two decades.[5] Bacteremia with *S. aureus* has been reported to be associated with mortality rates between 15% and 60%.[6,7] Resistance to methicillin in *S. aureus* isolates is a growing problem; 55% of nosocomial infections in U.S. intensive care unit (ICU) patients are due to methicillin-resistant *S. aureus* (MRSA), representing a 29% increase in the incidence of MRSA infections during the past 4 years.[5] Community-acquired MRSA infections are increasingly recognized as an emerging problem.[8]

Several studies have investigated the difference in mortality between patients with infections caused by methicillin-susceptible *S. aureus* (MSSA) and those with infections caused by MRSA. A recent meta-analysis by our group showed that patients with MRSA bacteremia have an increased risk of mortality compared with patients with MSSA bacteremia, with an odds ratio (OR) of death of 1.93.[9] Less is known about the impact of methicillin resistance on other patient outcomes, specifically length of hospitalization and hospital charges. Small studies have suggested that methicillin resistance confers increased hospital stays and charges; however, because MRSA affects a patient population different from that affected by MSSA, larger-scale investigations are needed to allow adjustment for the many variables that may confound hospital outcomes.[10,11] The objective of this study was to quantify the impact of methicillin resistance on patients

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Presented in part at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16-19, 2001; Chicago, IL.

with *S. aureus* bacteremia by examining the outcomes of in-hospital mortality, length of hospital stay, and hospital charges for patients with MRSA bacteremia compared with MSSA bacteremia.

METHODS

Setting

Beth Israel Deaconess Medical Center is a 630-bed, urban, tertiary-care teaching hospital in Boston, Massachusetts. It has 50 ICU beds and approximately 40,000 adult patient admissions per year.

Study Design and Data Collection

We conducted a cohort study of patients admitted to the hospital between July 1, 1997, and June 1, 2000, who had clinically significant *S. aureus* bloodstream infections. A patient was considered to have clinically significant *S. aureus* bacteremia if cultures of two or more blood specimens were positive for *S. aureus* within 24 hours or if one blood specimen was positive and the patient had signs and symptoms of infection and did not have a concurrent infection with another organism that would explain the signs and symptoms.

Patient characteristics and microbiology data were prospectively collected in the hospital data repository. Variables relating to demographics (age and gender), comorbidities (underlying cancer, cardiovascular disease, chronic lung disease, diabetes, liver disease, renal disease, solid organ transplant, and dialysis dependence), hospital events (nosocomial acquisition of bacteremia, ICU admission, transfer from another institution, and major surgical procedure), microbiology, and charges were extracted from administrative, accounting, and laboratory databases and medical records. All cases of bacteremia were confirmed, prospectively investigated by the infection control team, and collected in a designated database. All recorded hospital events occurred prior to the detection of *S. aureus* bacteremia. Data were then compiled into a single data set using a relational database management system (Access, Microsoft Corp., Redmond, WA).

Microbiology

S. aureus was identified using standard laboratory procedures. Methicillin resistance was determined according to National Committee for Clinical Laboratory Standards guidelines[12] using automated microdilution testing or disk-diffusion testing and an oxacillin agar screen plate.

Definitions

Nosocomial bloodstream infection was defined as occurring after 48 hours of hospitalization. A bacteremia was considered central venous catheter–associated if a catheter was in use during the 48-hour period before development of the bacteremia and no other source was evident.[13]

In-hospital mortality was defined as any death of a patient during the study period. Mortality was considered directly attributable to *S. aureus* bacteremia if (1) the patient had positive blood cultures within 7 days of death with persistent clinical signs and symptoms of sepsis and no other clear cause of death, or (2) the patient had active infection with *S. aureus* at other sites at the time of death and no other clear cause of death. Mortality was considered possibly attributable to *S. aureus* bacteremia if patients had positive blood cultures during their admission and no other clear cause of death.

Severity of illness was classified using the criteria of McCabe and Jackson and was assessed 48 hours prior to the detection of *S. aureus* bacteremia by one of the investigators (SEC).[14] The investigator was not aware of the methicillin-resistance status or outcome of the patient under review. A specific date for review was assigned for each patient and data were evaluated only until this date. For patients who were admitted with the diagnosis of *S. aureus* bacteremia, we assigned the McCabe–Jackson score based on preadmission functional status and illnesses obtained from clinic notes and the admission past medical history. Patients were categorized into three groups: those with rapidly fatal illnesses expected to die within 2 weeks (score = 1), those with ultimately fatal diseases expected to live for less than 5 years (score = 2), and those with non-fatal illnesses (score = 3).

Cost Estimates

Total hospital charges were collected from the hospital's billing system. Charges after the development of *S. aureus* bacteremia were determined by subtracting charges starting on the day of the bacteremia until the end of hospitalization from total hospital charges. Hospital costs were estimated by adjusting charges using the overall Medicare cost-to-charge ratio for our institution. Charges and costs attributable to MRSA bacteremia compared with MSSA bacteremia were determined by multiplying the median charge or cost for MSSA bacteremia by the multiplicative effect for increased charges or costs due to MRSA bacteremia.

Statistical Analysis

Statistical analyses were performed with SAS software (version 8; SAS Institute, Inc., Cary, NC). Comparisons between patients with MSSA bacteremia and those with MRSA bacteremia were performed using the two-sided Wilcoxon rank sum test for continuous variables, the Cochran–Mantel–Haenszel estimate for binary variables, and the chi-square trend test for ordinal variables.

Univariate analysis of the association between individual variables and the three outcomes studied was performed using regression models that examined the individual variable of interest. Mortality was analyzed with logistic regression. Length of hospital stay after *S. aureus* bacteremia for patients who did not die was analyzed using a semi-parametric survival analysis model (Weibull

distribution). Hospital charges after *S. aureus* bacteremia were log transformed to achieve a normal distribution and analyzed with linear regression models. The coefficients were converted to the measures of effect using an exponential transformation; the measures of effect are referred to as the multiplicative effect.

Three separate multivariable analyses were performed for the three outcomes using the same regression methods described above. Variables with a *P* value of less than .2 on the univariate analysis were included in the corresponding multivariable analysis. All predictors were checked for confounding and colinearity. Possible confounding variables were added one by one into the model, and if this resulted in a change in the coefficient estimate of a covariate of 10% or more, the variable was left in the model. Variables reflecting comorbid disease and severity of underlying disease were added to the final models to ensure that their effect was reflected in the models. Effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. The final regression models were analyzed for overfitting by the bootstrap method (1,000 bootstrap samples of all of the data were used).

All statistical tests were two-tailed; a *P* value of .05 or less was considered significant.

RESULTS

Three hundred forty-eight patients were identified with clinically relevant *S. aureus* bacteremia and were included in the study. Two hundred fifty-two of the patients had MSSA and 96 (28%) had MRSA.

Patient characteristics are listed in Table 1. Patients with MRSA bacteremia were older than those with MSSA bacteremia (mean age, 69 vs 60 years; $P < .001$). The mean age of the cohort was 62 years and 48.3% of the patients were older than 65 years. The two groups were similar regarding gender, with a slight male predominance. Patients with MRSA bacteremia had a median of three comorbidities, whereas patients with MSSA bacteremia had a median of two comorbidities ($P < .001$). Specific comorbidities, with the exception of chronic lung disease and renal disease, occurred with similar frequencies between the two groups. Chronic lung disease and renal disease were more likely to exist in patients with MRSA bacteremia: 48% of patients with MRSA bacteremia, compared with 29% of patients with MSSA bacteremia, had chronic lung disease ($P < .001$) and 44% of patients with MRSA bacteremia, compared with 31% of patients with MSSA bacteremia, had renal disease ($P = .03$). However, the numbers of patients requiring dialysis in each group were similar ($P = .17$). McCabe severity of illness scores assessed prior to the development of *S. aureus* bacteremia revealed that patients with MRSA bacteremia were more likely to have ultimately fatal illness than were patients with MSSA bacteremia ($P = .004$); however, there were equal percentages of patients with rapidly fatal illnesses in each group.

One hundred fifty-five (45%) of the cases of *S. aureus* bacteremia occurred after 48 hours of hospitalization. The most common source of *S. aureus* bacteremia was central venous catheters (38.2%), and the percentages of catheter-related bacteremias due to MSSA and MRSA were equal. Equal percentages of patients with MSSA and MRSA bacteremia had skin and soft tissue, surgical wound, endovascular, bone and joint, and peritoneal sources. However, having a respiratory source of infection compared with another source was more common in patients with MRSA bacteremia than in patients with MSSA bacteremia (13.5% vs 5.2%; OR, 2.88; $P = .008$). Urinary sources of bacteremia were also more common in patients with MRSA (7.3% vs 2.4%; OR, 3.22; $P = .03$).

Patients in the two groups had similar hospital exposures before the development of *S. aureus* bacteremia: 21% (72) of the cohort was admitted to the ICU and 16% (57) had a major surgical procedure before *S. aureus* bacteremia occurred. More patients with MRSA bacteremia than with MSSA bacteremia were transferred from another institution (36.5% vs 24.2%; $P = .02$) and had been admitted to the hospital in the preceding 12 months (81.3% vs 45.2%; $P < .001$). The median length of stay prior to the development of *S. aureus* bacteremia for patients with MRSA and MSSA bacteremia was 0 days because similar numbers in the two groups were admitted on the same day that the bacteremia was detected (53%). The mean length of hospitalization prior to the development of *S. aureus* bacteremia was 4 days for patients with MRSA bacteremia and 3 days for patients with MSSA bacteremia ($P = .17$). Median hospital charges prior to isolation of *S. aureus* bacteremia were higher for patients who subsequently developed MRSA bacteremia compared with MSSA bacteremia: $2,085 (interquartile range [IQR], $0 to $27,118) versus $1,005 (IQR, $0 to $17,022) ($P = .04$).

Mortality

Seventy-two of the 348 patients in the cohort died in the hospital (case fatality rate, 20.7%). Mortality rates were similar for the two groups of patients: 22 (22.9%) of the patients with MRSA bacteremia died, compared with 50 (19.8%) of the patients with MSSA bacteremia ($P = .53$). There were no differences in mortality rates in either group when stratified by severity of illness using the McCabe score. Among patients older than 65 years, more with MSSA bacteremia than with MRSA bacteremia died (34.6% vs 26.2%; P = not significant). Older patients were more likely to have MRSA bacteremia than were younger patients (OR, 2.36; $P < .001$). The median time to death after developing bacteremia was 4 days (IQR, 3 to 10 days) for patients with MRSA bacteremia and 4.5 days (IQR, 2 to 12 days) for patients with MSSA bacteremia. This difference was not statistically significant ($P = .74$).

Results of the crude analysis for the association of the cohort characteristics with mortality are given in Table 2. Significant univariate predictors of mortality included age older than 65 years (OR, 3.91; $P < .001$),

TABLE 1
DESCRIPTIVE CHARACTERISTICS OF THE COHORT

Characteristic	MRSA*	MSSA†	P
Demographics			
Mean age, y	69.1	59.6	< .001
Male	54 (56.3%)	158 (62.7%)	.27
Comorbidities			
Cancer	17 (17.7%)	40 (16%)	.68
Cardiovascular disease	73 (76%)	182 (72.2%)	.47
Chronic lung disease	46 (47.9%)	72 (28.6%)	< .001
Diabetes	38 (39.6%)	83 (32.9%)	.25
Liver disease	10 (10.4%)	26 (10.3%)	.98
Renal disease	42 (43.8%)	78 (31%)	.03
Transplant	4 (4.2%)	10 (4.0%)	.93
Dialysis	19 (19.8%)	35 (13.9%)	.17
No. of comorbidities			
0 to 1	11 (11.5%)	70 (27.8%)	< .001
2	24 (25%)	75 (29.8%)	
3	42 (43.8%)	73 (29%)	
4 to 5	19 (19.8%)	34 (13.5%)	
McCabe score			
Rapidly fatal	17 (17.7%)	43 (17.1%)	.004
Ultimately fatal	61 (63.5%)	102 (40.5%)	
Non-fatal	18 (18.8%)	107 (42.5%)	
Source			
Catheter	37 (38.5%)	96 (38.1%)	.94
Respiratory	13 (13.5%)	13 (5.2%)	.008
Skin and soft tissue	10 (10.4%)	33 (13.1%)	.5
Surgical wound	10 (10.4%)	28 (11.1%)	.85
Endovascular	7 (7.3%)	29 (11.5%)	.25
Bone and joint	6 (6.3%)	20 (7.9%)	.59
Urinary	7 (7.3%)	6 (2.4%)	.03
Peritonitis	1 (1.0%)	2 (0.8%)	.82
Unknown	5 (5.2%)	25 (9.9%)	.16
Hospital event			
Median LOS before isolation (IQR)	0 (0–5.5)	0 (0–4)	.17
Median charge before isolation (IQR)	$2,085 ($0–$27,118)	$1,005 ($0–$17,022)	.04
Acquisition after 48 hours	48 (50%)	107 (42.5%)	.21
Transfer from another hospital	35 (36.5%)	61 (24.2%)	.02
ICU stay	24 (25%)	48 (19.1%)	.22
Surgical procedure	21 (21.9%)	36 (14.3%)	.09
Involvement of prosthetic material	21 (21.9%)	44 (17.5%)	.35
Last hospital admission			
None	18 (18.8%)	138 (54.8%)	< .001
< 1 mo	35 (36.5%)	51 (20.2%)	
1 to 3 mo	32 (33.3%)	32 (12.7%)	
4 to 12 mo	11 (11.5%)	31 (12.3%)	
Outcome			
Death	22 (22.9%)	50 (19.8%)	.53
Median LOS after *Staphylococcus aureus* bacteremia (IQR)	9 (5–16)	7 (5–12)	.045
Median hospital charge after *S. aureus* bacteremia (IQR)	$26,424 ($14,006–$50,484)	$19,212 ($9,999–$36,548)	.008
Median hospital cost after *S. aureus* bacteremia (IQR)	$14,655 ($7,768–$27,998)	$10,655 ($5,545–$20,270)	.008

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; LOS = length of stay; ICU = intensive care unit; IQR = interquartile range.
*Ninety-six patients (27.6% of the cohort).
†Two hundred fifty-two patients (72.4% of the cohort).

TABLE 2
UNIVARIATE ANALYSIS OF THE IMPACT OF COHORT CHARACTERISTICS ON MORTALITY, LENGTH OF HOSPITAL STAY, AND HOSPITAL CHARGES

	Mortality		Length of Stay		Hospital Charges	
Characteristic	**OR (CI_{95})**	***P***	**HR (CI_{95})**	***P***	**ME (CI_{95})**	***P***
Demographics						
Age > 65 y	3.91 (2.20–6.95)	< .001	0.91 (0.74–1.11)	.34	0.88 (0.7–1.1)	.27
Male	1.32 (0.78–2.24)	.3	0.89 (0.72–1.09)	.26	0.85 (0.67–1.07)	.17
Comorbidities						
Cancer	1.47 (0.76–2.83)	.25	0.83 (0.63–1.09)	.18	0.94 (0.69–1.29)	.72
Cardiovascular disease	4.20 (1.85–9.55)	< .001	1.18 (0.95–1.46)	.14	1.1 (0.85–1.43)	.47
Chronic lung disease	3.17 (1.86–5.41)	< .001	1.53 (1.24–1.90)	< .001	1.26 (0.99–1.6)	.06
Diabetes	1.35 (0.79–2.30)	.27	1.33 (1.08–1.64)	.008	1.31 (1.03–1.66)	.03
Liver disease	1.11 (0.48–2.55)	.81	1.15 (0.62–1.21)	.41	1.22 (0.84–1.78)	.3
Renal disease	1.48 (0.87–2.51)	.15	1.17 (0.94–1.44)	.16	1.15 (0.9–1.46)	.27
Solid organ transplant	*	*	1.46 (0.92–2.29)	.1	1.52 (0.85–2.73)	.16
McCabe score	36.03 (16.6–78.2)	< .001	1.24 (1.05–1.46)	.03	1.11 (0.97–1.34)	.11
Dialysis	0.63 (0.28–1.39)	.25	0.71 (0.54–0.92)	.01	0.67 (0.5–0.94)	.02
No. of comorbidities	2.01 (1.54–2.62)	< .001	1.16 (1.07–1.26)	< .001	1.14 (1.03–1.25)	.013
Source						
Catheter	1.6 (0.95–2.7)	.079	0.89 (0.72–1.1)	.29	0.86 (0.68–1.09)	.21
Respiratory	6.34 (2.77–14.5)	< .001	1.03 (0.62–1.72)	.9	0.85 (0.55–1.32)	.47
Skin and soft tissue	0.08 (0.01–0.58)	.013	0.61 (0.47–0.81)	< .001	0.59 (0.42–0.84)	.003
Surgical wound	0.3 (0.09–1.0)	.051	1.28 (0.95–1.73)	.11	1.61 (1.11–2.32)	.012
Endovascular	0.77 (0.31–1.94)	.59	1.65 (1.2–2.28)	.002	1.88 (1.29–2.74)	.001
Bone and joint	0.3 (0.07–1.3)	.11	1.14 (0.8–1.62)	.48	1.4 (0.9–2.17)	.13
Urinary	0.31 (0.04–2.42)	.26	1.05 (0.64–1.72)	.85	0.99 (0.14–6.87)	.99
Peritonitis	*	*	0.82 (0.31–2.15)	.69	1.0 (0.29–3.46)	.99
Unknown	2.07 (0.92–4.63)	.079	0.64 (0.44–0.94)	.025	0.78 (0.52–1.17)	.23
Hospital event						
MRSA bacteremia	1.20 (0.68–2.12)	.53	1.29 (1.03–1.61)	.03	1.44 (1.12–1.86)	.005
Acquisition after 48 hours	1.42 (0.84–2.38)	.19	1.28 (1.05–1.56)	.02	1.27 (1.01–1.59)	.045
Transfer from another hospital	2.65 (1.54–4.56)	< .001	1.13 (0.89–1.43)	.32	1.08 (0.84–1.4)	.55
ICU stay before *Staphylococcus aureus* bacteremia	2.59 (1.45–4.62)	.001	1.58 (1.23–2.04)	< .001	1.11 (0.84–1.48)	.46
Surgical procedure before *S. aureus* bacteremia	0.90 (0.44–1.85)	.78	1.17 (0.9–1.53)	.24	1.27 (0.93–1.73)	.13
Involvement of prosthetic material	0.68 (0.31–1.35)	.24	1.32 (1.03–1.69)	.03	1.36 (1.01–1.82)	.04

OR = odds ratio; HR = hazard ratio; ME = multiplicative effect; CI_{95} = 95% confidence interval; MRSA = methicillin-resistant *S. aureus*; ICU = intensive care unit.
*Numbers too small to calculate.

underlying cardiovascular disease (OR, 4.2; $P < .001$), chronic lung disease (OR, 3.17; $P < .001$), respiratory source of bacteremia (OR, 6.34; $P < .001$), greater number of comorbidities (OR, 2.01; $P < .001$), transfer from another institution (OR, 2.65; $P < .001$), ICU admission before *S. aureus* bacteremia (OR, 2.59; $P = .001$), and lower McCabe score (OR, 36.03 for each incremental decrease; $P < .001$). MRSA bacteremia was not a significant risk factor for mortality on the univariate analysis (OR, 1.2; $P = .53$).

The results of a multivariable analysis are provided in Table 3. After adjustment for potential confounders, only underlying cardiovascular disease (OR, 4.49; $P = .01$), respiratory source of bacteremia (OR, 4.09; $P = .02$), and lower McCabe score (OR, 38.5 for each incremental decrease; $P < .001$) remained significant predictors of death in our cohort of patients with *S. aureus* bacteremia. The presence of methicillin resistance did not confer increased in-hospital mortality on multivariable analysis (OR, 0.72; $P = .45$).

An analysis of patients whose deaths were directly or probably attributable to *S. aureus* bacteremia also showed no statistically significant association between the presence of methicillin resistance and increased mortality (OR, 1.1; $P = .75$).

Length of Hospital Stay

The median length of stay after the development of *S. aureus* bacteremia for patients in the cohort who did not die was 7.5 days (IQR, 5 to 13 days). Patients with MRSA bacteremia had a longer stay than did patients with MSSA bacteremia: 9 days (IQR, 5 to 16 days) versus 7 days (IQR, 5 to 12 days) ($P = .045$).

Results of the crude analysis for the association of

patient variables with length of stay are given in Table 2. MRSA bacteremia was associated with an increased length of stay after the development of *S. aureus* bacteremia (hazard ratio [HR], 1.29; $P = .03$). Other significant univariate predictors of increased length of stay included chronic lung disease (HR, 1.53; $P < .001$), diabetes (HR, 1.33; $P = .008$), endovascular source of bacteremia (HR, 1.65; $P = .002$), increased number of comorbidities (HR, 1.16; $P < .001$), the presence of prosthetic material (HR, 1.32; $P = .03$), nosocomial acquisition of bacteremia (HR, 1.28; $P = .02$), ICU admission before *S. aureus* bacteremia (HR, 1.58; $P < .001$), and rapidly fatal underlying illness (HR, 1.24; $P = .03$). Requiring dialysis (HR, 0.71; $P = .01$) and having a skin and soft tissue (HR, 0.61; $P < .001$) or unknown (HR, 0.64; $P = .025$) source of bacteremia were predictive of shorter hospitalizations after *S. aureus* bacteremia.

The results of the multivariable analysis of hospital stay are provided in Table 3. After adjustment for confounding, methicillin resistance in *S. aureus* bacteremia remained a significant predictor of increased length of hospitalization after *S. aureus* bacteremia. A 1.29-fold increase in hospital stay occurred for patients with MRSA bacteremia compared with MSSA bacteremia ($P = .016$). MRSA bacteremia had an average attributable hospital stay of 2.2 days in our cohort. An increased number of comorbidities (HR, 1.18; $P < .001$) and the presence of prosthetic material (HR, 1.45; $P = .002$) were also independent predictors of increased length of hospital stay. Requiring dialysis (HR, 0.51; $P < .001$) and having a skin and soft tissue source of bacteremia (HR, 0.63; $P < .001$) were predictive of a shorter hospital stay after *S. aureus* bacteremia.

Charges

The median hospital charge after the development of *S. aureus* bacteremia for patients in the cohort was $20,549 (IQR, $10,652 to $40,118) and the median hospital cost was $11,396 (IQR, $5,908 to $22,249). The median hospital charge after bacteremia was significantly higher for patients with MRSA bacteremia ($26,424; IQR, $14,006 to $50,484) than for patients with MSSA bacteremia ($19,212; IQR, $9,999 to $36,548; $P = .008$), as was the median hospital cost ($14,655 [IQR, $7,768 to $27,998] vs $10,655 [IQR, $5,545 to $20,270]).

Results of a crude analysis for the association of the cohort characteristics with hospital charges are provided in Table 2. MRSA bacteremia was associated with a 1.44-fold increase in hospital charges after the development of bacteremia ($P = .005$). Other significant univariate predictors of increased hospital charges included diabetes ($P = .03$), surgical wound ($P = .012$) or endovascular ($P = .001$) source of bacteremia, increased number of comorbidities ($P = .013$), the presence of prosthetic material ($P = .04$), and nosocomial acquisition of bacteremia ($P = .045$). Requiring dialysis ($P = .02$) and having a skin and soft tissue source of bacteremia ($P = .003$) were predictive of lower hospital charges after *S. aureus* bacteremia.

TABLE 3
MULTIVARIATE ANALYSIS OF THE IMPACT OF COHORT CHARACTERISTICS ON MORTALITY, LENGTH OF HOSPITAL STAY, AND HOSPITAL CHARGES

	Methicillin Resistance	
Outcome	**Measure of Effect (CI_{95})**	***P***
Mortality*	OR = 0.72 (0.39–1.96)	.45
Length of hospital stay after *Staphylococcus aureus* bacteremia†	HR = 1.29 (1.05–1.59)	.016
Hospital charges after *S. aureus* bacteremia‡	ME = 1.36 (1.06–1.75)	.017

OR = odds ratio; HR = hazard ratio; ME = multiplicative effect; CI_{95} = 95% confidence interval.
*Variables included in the model: lower McCabe score (OR = 38.5 for each incremental decrease; $P < .001$), cardiovascular disease (OR = 4.49; $P = .01$), and respiratory source (OR = 4.09; $P = .02$).
†Variables included in the model: dialysis (HR = 0.51; $P < .001$), involvement of prosthetic material (HR = 1.45; $P = .002$), increased number of comorbidities (HR = 1.18; $P < .001$), skin and soft tissue source (HR = 0.63; $P < .001$), and lower McCabe score (HR = 1.03 for each incremental decrease; $P = .74$).
‡Variables included in the model: dialysis (ME = 0.6; $P = .006$), involvement of prosthetic material (ME = 1.37; $P = .03$), increased number of comorbidities (ME = 1.13; $P = .04$), surgical wound source (ME = 1.17; $P = .005$), bone and joint source (ME = 1.17; $P = .046$), and lower McCabe score (ME = 1.07 for each incremental decrease; $P = .49$).

The results of the multivariable analysis of hospital charges are provided in Table 3. After adjustment for confounding, methicillin resistance in *S. aureus* bacteremia remained a significant predictor of increased hospital charges after *S. aureus* bacteremia. A 1.36-fold increase in hospital charges occurred for patients with MRSA bacteremia compared with MSSA bacteremia ($P = .017$). MRSA bacteremia had an average attributable hospital charge of $6,916 and hospital cost of $3,836 per patient in our cohort. Increased number of comorbidities ($P = .04$), surgical wound ($P = .005$) or bone and joint ($P = .046$) source of bacteremia, and the presence of prosthetic material ($P = .03$) were also independent predictors of increased hospital charges. Dialysis use was predictive of lower hospital charges after *S. aureus* bacteremia ($P = .006$). An analysis of hospital charges for patients who did not die during hospitalization revealed a similar result: a 1.32-fold increase in hospital charges occurred for patients with MRSA bacteremia compared with MSSA bacteremia ($P = .03$).

DISCUSSION

S. aureus is the most common cause of nosocomial infections reported to the National Nosocomial Infections Surveillance System.[5] It is the leading cause of nosocomial pneumonia and surgical-site infections and the second leading cause of bloodstream infections in the United States. Methicillin resistance in *S. aureus* isolates continues to increase. Given the high incidence of infections caused by MRSA, quantifying the health impact and the economic impact of methicillin resistance in *S. aureus* is important for clinicians and hospital administrators and policy makers. This information is essential to justify

resource allocation for the development of strategies to combat antibiotic resistance and to prevent the spread of resistant organisms within the healthcare environment.

In this study, we investigated a cohort of 348 patients with *S. aureus* bacteremia, 96 of whom had methicillin-resistant isolates, to further clarify the health and economic ramifications of methicillin resistance. We showed that methicillin resistance in *S. aureus* was associated with increased length of hospitalization for patients who survived and hospital charges despite not being associated with increased mortality in our cohort. On univariate and multivariable analyses, methicillin resistance was associated with an increase in length of hospital stay (increased 1.29 fold) and hospital charges (increased 1.36 fold) after the bacteremia.

Our study showed increases in length of stay and hospital charges due to MRSA similar to those from a study that examined *S. aureus* surgical-site infections.[4] That study noted a 1.2-fold increase in length of hospitalization and in hospital charges among patients with surgical-site infections due to MRSA compared with MSSA. The additional length of stay attributable to MRSA infection was 2.6 days (vs 2.2 days in our cohort), and the additional hospital charge was $13,901 (vs $6,916 in our cohort). The higher charges associated with surgical-site infection likely reflect the need for repeat operating room visits and associated testing required for management of these infections.

Several studies have demonstrated an increase in mortality among patients with MRSA bacteremia versus MSSA bacteremia, and we recently summarized this in a meta-analysis.[9] We hypothesize that delay in the initiation of appropriate therapy for patients with MRSA bacteremia may lead to higher mortality rates in some studies. The data collected in this study did not allow the specific examination of the effect of timing of appropriate antibiotic therapy; however, knowing our institution's prescribing patterns, we believe that the similar mortality rates for MSSA and MRSA bacteremia in our cohort may be related to the fact that during the study period most empiric antibiotic therapy was effective against MRSA. The standard practice at our institution is to treat patients with two or more blood specimens positive for gram-positive cocci within 24 hours or one blood specimen positive with signs and symptoms of infection (our case definition for *S. aureus* bacteremia) with vancomycin empirically.

Previous studies examining the impact of delayed appropriate antibiotic therapy have shown conflicting results. Roghmann examined a cohort of 128 patients with *S. aureus* bacteremia, of whom 38 had MRSA bacteremia.[15] Although 55% of patients with MRSA bacteremia received ineffective antibiotics in the first 48 hours, the relative risk of death for patients with MRSA bacteremia given ineffective therapy was not higher than that for those given effective therapy. Because there were only 12 deaths in the MRSA bacteremia group, the sample size of the study limits its power to detect a statistically significant difference.

Lodise et al. examined 167 cases of *S. aureus* bacteremia, of which 103 were due to MRSA.[16] In this cohort, MRSA infection was the most significant predictor of delayed treatment beyond 45 hours (OR, 8.3; $P < .001$); 42 of the 48 episodes of delayed treatment were in patients with MRSA bacteremia. Delayed treatment was an independent predictor of both infection-related mortality (33.3% in the delayed treatment group vs 19.3% in the early treatment group; OR, 3.8; $P = .01$) and length of stay after bacteremia (20.2 vs 14 days; $P = .05$). Differing results between studies may be related to study definitions, methodology, and small sample size rather than to the true effect. Additional studies clearly are essential to elucidate the importance of appropriate empiric therapy in the treatment of *S. aureus* bacteremia, as such data will potentially alter physicians' prescribing practices.

An additional explanation for the lack of a difference in mortality rates between patients with MSSA bacteremia and patients with MRSA bacteremia in our cohort was the relatively small proportion of patients with pneumonia and endovascular infection. Infections due to MRSA involving these sites have been associated with increased mortality relative to MSSA infections involving the same sites.[17,18] The relatively small proportions of these patients combined with the large proportion of patients with catheter-associated infections in which the focus of infection was removable may account for similar mortality rates in the two groups.

Our analysis of length of hospital stay after the development of *S. aureus* bacteremia included only patients who ultimately survived. Length of hospitalization is a measure of morbidity; however, patients who died were prematurely censored from the analysis despite having the highest morbidity. We believed that excluding these patients would give a more accurate assessment of the attributable length of hospital stay due to MRSA bacteremia. In contrast, we did not exclude patients who died from our primary hospital charge analysis because patients who die have high resource utilization despite having abbreviated lengths of stay and we wanted to describe the full economic burden of MRSA bacteremia. An analysis of hospital charges among survivors also showed a 1.32-fold increase in charges for patients with MRSA versus MSSA bacteremia; thus, the attributable charge is slightly lower in this subgroup of survivors.

Of interest, requiring dialysis was negatively associated with both length of hospitalization and hospital charges in our cohort. Initiation of dialysis is usually associated with increased morbidity in a hospitalized patient; however, most of our dialysis patients were receiving long-term dialysis as outpatients. Thirty (60%) of the 50 patients receiving hemodialysis had central catheters as the source of infection, and such patients are usually quickly discharged after the catheter is replaced to complete antibiotics as outpatients during hemodialysis.

A challenge in quantifying the difference in outcomes between patients with infections caused by susceptible versus resistant organisms is adequately adjusting for the severity of underlying illness, which may independently drive mortality as well as length and cost of hospitalization. Inadequate adjustment has been cited by investigators as a reason why infection with MRSA may appear to have more adverse outcomes than infection with MSSA.[19] We used the McCabe–Jackson score to adjust for underlying disease severity. The McCabe–Jackson score has been used in multiple studies as a means to assess severity of illness in patients with infection. To the best of our knowledge, there are no other validated or generally used measures to adjust for severity of illness when non-ICU patients are studied for in-hospital events. Acute Physiology and Chronic Health Evaluation scores have been used for ICU patients and adjustment for Acute Physiology and Chronic Health Evaluation score may have improved our ability to assess the impact of underlying disease severity in this study; however, the data required to calculate an Acute Physiology and Chronic Health Evaluation score are not routinely available for non-ICU patients. In addition to the McCabe–Jackson score, we used other measures to assess our patients' severity of illness, including ICU stay prior to bacteremia and number and type of underlying comorbidities.

Interestingly, the patients in our cohort with MRSA bacteremia had both a larger number of underlying comorbidities and more ultimately fatal disease (McCabe score = 2); we adjusted for these differences using multivariable models. Given the use of these statistical techniques and the fact that equal numbers of patients with MRSA bacteremia and MSSA bacteremia had rapidly fatal disease (McCabe score = 1) and died, we believe that the groups were similar enough to produce valid estimates of the increased length of stay and hospital charges attributable to MRSA bacteremia compared with MSSA bacteremia.

Nevertheless, hidden bias that exists but was not adjusted for in our cohort may overestimate the true relationship between methicillin resistance and length of hospital stay and hospital charges; therefore, additional studies examining the health impact and the economic impact of methicillin resistance in *S. aureus* bacteremia would be helpful. Clearly, the development of more comprehensive validated methods for adjustment of underlying severity of illness and for prediction of costlier patients would improve studies that examine outcomes of patients with infectious diseases.

We reported hospital charges as our main economic outcome in this study. Hospital charges are relatively easy to retrieve from administrative databases, are consistent from patient to patient, and have been used in other economic analyses; however, they are an overestimate of actual cost.[1,4,20] To estimate hospital costs, which more accurately reflect the economic burden of a particular hospital, we used the overall Medicare cost-to-charge ratio for our institution during the study period to convert charges to costs. Department-level cost-to-charge ratios, which would have provided a more accurate estimate of hospital costs, were not available. The costs that we calculated reflected only our hospital's perspective of the costs of resistance; costs could be higher or lower in other institutions or settings. In addition, our cost estimates did not include physicians' professional fees, medical costs accrued beyond hospitalization, or non-direct medical costs. Thus, the costs to patients, third-party payers, and society were underestimated by our analysis.

Based on the results of this study, the estimated average marginal additional cost of MRSA was $3,836 per patient in our cohort; this translates into an additional yearly cost due to methicillin resistance in *S. aureus* bacteremia at our hospital of $122,752. The additional costs accrued for patients with MRSA bacteremia compared with MSSA bacteremia are likely due to a combination of increased length of stay, caused by delay in diagnosis and possibly suboptimal therapeutic options; costs of isolation; and cost of ICU stay (more MRSA patients were in the ICU prior to bacteremia and thus remained in the ICU after bacteremia). Given the health and economic costs associated with methicillin resistance in *S. aureus*, measures to minimize the spread of MRSA within the hospital are essential.

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