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Effect of Reduced Vancomycin Susceptibility on Clinical and Economic Outcomes in *Staphylococcus aureus* Bacteremia

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Reduced vancomycin susceptibility (RVS) may lead to poor clinical outcomes in *Staphylococcus aureus* bacteremia. The objective of this study was to evaluate the clinical and economic impact of RVS in patients with bacteremia due to *S. aureus*. A cohort study of patients who were hospitalized from December 2007 to May 2009 with *S. aureus* bacteremia was conducted within a university health system. Multivariable logistic regression and zero-truncated negative binomial regression models were developed to evaluate the association of RVS with 30-day in-hospital mortality, length of stay, and hospital charges. One hundred thirty-four (34.2%) of a total of 392 patients had bacteremia due to *S. aureus* with RVS as defined by a vancomycin Etest MIC of >1.0 μg/ml. Adjusted risk factors for 30-day in-hospital mortality included the all patient refined-diagnosis related group (APRDRG) risk-of-mortality score (odds ratio [OR], 7.11; 95% confidence interval [CI], 3.04 to 16.6), neutropenia (OR, 13.4; 95% CI, 2.46 to 73.1), white blood cell count (OR, 1.05; 95% CI, 1.01 to 1.09), immunosuppression (OR, 6.31; 95% CI, 1.74 to 22.9), and intensive care unit location (OR, 3.51; 95% CI, 1.65 to 7.49). In multivariable analyses, RVS was significantly associated with increased mortality in patients with *S. aureus* bacteremia as a result of methicillin-susceptible (OR, 3.90; 95% CI, 1.07 to 14.2) but not methicillin-resistant (OR, 0.53; 95% CI, 0.19 to 1.46) isolates. RVS was associated with greater 30-day in-hospital mortality in patients with bacteremia due to methicillin-susceptible *S. aureus* but not methicillin-resistant *S. aureus*. Further research is needed to identify optimal treatment strategies to reduce mortality associated with RVS in *S. aureus* bacteremia.

Staphylococcus aureus is a leading cause of nosocomial and community-acquired infections worldwide (15, 20) and is associated with increased mortality, length of hospital stay, and total health care expenditures (7). Vancomycin has long been considered the mainstay of therapy for infections due to methicillin-resistant *S. aureus* (MRSA) as well as infections due to methicillin-susceptible *S. aureus* (MSSA) in patients with intolerance to beta-lactam antibiotics. However, a recently recognized phenomenon of increasing vancomycin MICs over time has been described among vancomycin-susceptible *S. aureus* isolates, referred to as vancomycin "MIC creep" (13, 37, 40).

Several studies suggest that reduced vancomycin susceptibility (RVS), even with vancomycin MICs in the susceptible range, is associated with higher rates of treatment failure and mortality, particularly in bloodstream infections due to MRSA (2, 14, 17, 21, 26, 28, 29, 31, 33, 36, 42, 44). However, these studies have been limited by small sample sizes (2, 14, 26, 28, 29, 31, 33, 42, 44), methodological issues with the selection of patients and study endpoints (2, 14, 28, 29, 33, 36), and evaluation of potential confounders (29, 36, 42). Furthermore, there are very few reports evaluating the association between RVS and clinical outcomes in infections due to MSSA instead of MRSA (2, 17, 31). These studies have similarly been limited by small sample sizes (2, 31) and incomplete ascertainment of potential confounders (17, 31).

Given these issues, it is critical to elucidate the clinical impact of RVS in both MRSA and MSSA infections in order to identify optimal treatment strategies and reduce associated mortality. We conducted this cohort study to determine the association between RVS and mortality in *S. aureus* bacteremia. Furthermore, to our knowledge, our study is the first to investigate the relationship between RVS and length of stay (LOS) and total hospital charges in patients with *S. aureus* bacteremia.

MATERIALS AND METHODS

Study design and setting. This retrospective cohort study was conducted at two hospitals in the University of Pennsylvania Health System (UPHS) in Philadelphia, PA: the Hospital of the University of Pennsylvania (HUP), a 725-bed academic tertiary care medical center, and Penn Presbyterian Medical Center (PPMC), a 344-bed urban community hospital. The study was approved by the institutional review board of the University of Pennsylvania.

Study population. All adult inpatients with an episode of *S. aureus* bacteremia occurring between 1 December 2007 and 31 May 2009 were identified through the HUP Clinical Microbiology Laboratory, which processes all specimens obtained from patients at HUP and PPMC. For patients with multiple episodes of *S. aureus* bacteremia, only the first episode of bacteremia was included for analysis.

Microbiological identification and susceptibility testing of *S. aureus* isolates. Identification and susceptibility testing of *S. aureus* were performed and interpreted according to standard methods (3–5). Standard susceptibility testing was performed using the Vitek2 instrument method. The vancomycin MIC of the isolates was determined by the Etest using Mueller-Hinton agar (BBL; BD Diagnostic Systems, Franklin Lakes, NJ) (1), with RVS *a priori* defined as an Etest vancomycin MIC of >1.0 μg/ml (21, 25, 26, 38). In addition, for the purposes of secondary analyses, vancomycin MICs were determined for all *S. aureus* isolates by the broth microdilution method (5), utilizing a susceptibility panel containing half-dilution vancomycin concentrations (Trek Diagnostic Systems,

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Cleveland, OH). Vancomycin heteroresistance was screened for by the macro-Etest method using Etest GRD vancomycin/teicoplanin strips with brain heart infusion agar (1) and by growth on vancomycin-containing brain heart infusion agar (34); a positive result for either screening test was confirmed by population analysis using a Spiral Plater (Advanced Instruments, Norwood, MA) and inoculation onto vancomycin brain heart infusion agar (BBL) (9, 43). Detection of genes encoding Panton-Valentine leucocidin (PVL) was performed using real-time PCR (24). All isolates were evaluated for accessory gene regulator (*agr*) dysfunction via delta-hemolysin production using a beta-hemolytic disk, as previously described (35).

Data collection. Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD), which includes demographic, laboratory, pharmacy, and billing information and has been used in prior studies of antibiotic use and resistance (11, 23). The following clinical data were collected for all patients: baseline demographics, origin at the time of hospital admission (i.e., physician referral, transfer from another facility, or admission through the emergency department), hospital location at the time of infection (i.e., intensive care unit [ICU] or medical floor), prior admission to UPHS in the 30 days prior to the culture date, nosocomial infection (date of the first positive culture ≥48 h from the date of admission), health care-associated infection (date of the first positive culture ≥48 h from the date of admission or admitted as a transfer from another institution), community-acquired infection (date of the first positive culture <48 h from the date of admission and not admitted as a transfer from another institution), and the all patient refined-diagnosis related group (APRDRG) risk-of-mortality and severity-of-illness scores (19). The presence of the following concurrent conditions was documented in relation to the date of the positive blood culture: diabetes mellitus, malignancy, solid organ or hematopoietic stem cell transplantation, renal insufficiency (creatinine level of ≥2.0 mg/dl or the requirement of dialysis), HIV infection, neutropenia (absolute neutrophil count < 500/mm^3), and receipt of an immunosuppressive agent, including corticosteroids, in the prior 30 days. Furthermore, chart review was performed to collect data on the presence of complicated infection (i.e., endocarditis, osteomyelitis, septic arthritis, epidural, and/or spinal abscess) and the presence and subsequent removal of intravascular devices (i.e., intravascular catheter, pacemaker or defibrillator, or arteriovenous fistula or graft) prior to the episode of bacteremia. In addition, the Charlson comorbidity index was calculated for each subject (32). The primary outcome was crude in-hospital 30-day mortality, defined as death in the hospital from any cause occurring in the 30 days after the date of the first positive blood culture. Secondary outcomes were (i) length of stay (LOS), defined as the total number of days in the hospital from the first positive blood culture to discharge or death, and (ii) hospital charges, defined as total hospital charges generated after the date of the first positive culture.

Information on all inpatient antimicrobial therapy administered during the same hospitalization was obtained. Antibiotics were considered to be appropriate in relation to treatment of the episode of *S. aureus* bacteremia if they were determined to be active *in vitro* against the isolate via standard susceptibility testing and generally would be considered a clinically appropriate treatment regimen (e.g., oral trimethoprim-sulfamethoxazole would generally not be considered clinically appropriate treatment for bacteremia). Using this definition, treatment was classified for each patient as the first appropriate antibiotic received, if any. However, given that in most cases the first appropriate antimicrobial agent administered would be empirical therapy (i.e., selected before availability of methicillin susceptibility information), subsequent switches in antimicrobial therapy were also documented (e.g., empirical vancomycin switched to nafcillin for a patient with a methicillin-susceptible isolate).

Statistical analysis. Continuous variables were compared using the Student *t* test or Wilcoxon rank sum test, and categorical variables were compared using the χ^2 or Fisher exact test. Bivariable analyses were conducted to determine the association between RVS and each of the study outcomes. Analyses were further stratified as planned *a priori* by methicillin susceptibility, location in the ICU, and health care-associated status. Multivariable analyses were performed to evaluate the impact of RVS on 30-day in-hospital mortality, LOS, and total hospital charges. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using multiple logistic regression for the primary outcome of 30-day in-hospital mortality. Due to overdispersion and the absence of zero values for hospital LOS and charges, a zero-truncated negative binomial regression model was used to estimate the association between RVS and these secondary outcomes (12). An indicator for death in the hospital was included in each model to account for the impact of censoring. A stepwise selection procedure was used for all multivariable analyses, with variables with *P* values of <0.20 on bivariable analyses considered candidate variables and maintained in the final model if their inclusion resulted in a ≥15% change in the effect measure for the primary association of interest or if they were statistically significant in likelihood ratio testing (27).

In a secondary analysis, the above-described analyses were repeated using vancomycin cutoffs determined by broth microdilution MICs, with RVS *a priori* defined as a vancomycin MIC of >0.5 μg/ml. For all calculations, a 2-tailed *P* value of <0.05 was considered significant. All statistical calculations were performed using commercially available software (STATA version 11.0; StataCorp LP, College Station, TX).

RESULTS

Study population. A total of 392 patients with discrete episodes of *S. aureus* bacteremia were identified during the study period. The distribution of vancomycin MICs among isolates, as determined by Etest, was as follows: 17 (4.3%) with a MIC of ≤0.5 μg/ml, 83 (21.2%) with a MIC of 0.75 μg/ml, 158 (40.3%) with a MIC of 1.0 μg/ml, 123 (31.4%) with a MIC of 1.5 μg/ml, and 11 (2.8%) with a MIC of 2.0 μg/ml. Accordingly, 34.2% of the *S. aureus* bloodstream isolates demonstrated RVS as defined by a vancomycin MIC of >1.0 μg/ml by Etest. Baseline clinical and demographic characteristics of patients with and without *S. aureus* isolates characterized by RVS are shown in Table 1.

Risk factors for 30-day in-hospital mortality. A total of 60 patients died while hospitalized for *S. aureus* bacteremia, resulting in a crude mortality rate of 15.3%. Results of bivariable analyses of risk factors associated with in-hospital mortality are given in Table 2. The majority of patients, specifically 99.7% of patients who survived and 96.6% of patients who died during hospitalization, received appropriate antibiotics, with vancomycin the most commonly administered initial antibiotic (74.2% and 77.6%, respectively; $P = 0.87$). Only 4 patients experienced recurrent bacteremia during hospitalization, defined as a new positive blood culture for *S. aureus* at least 5 days after the first negative blood culture on therapy, and all of these patients survived.

In multivariable analyses of risk factors for 30-day in-hospital mortality (Table 3), there was significant effect modification by methicillin susceptibility ($P = 0.03$). The unadjusted ORs between RVS and mortality were 1.47 (95% CI, 0.61 to 3.54; $P = 0.39$) and 0.74 (95% CI, 0.34 to 1.60; $P = 0.45$) for infections due to MSSA and MRSA, respectively. In multivariable analyses, independent risk factors for in-hospital mortality included a higher APRDRG risk-of-mortality score (OR, 7.11; 95% CI, 3.04 to 16.6; $P < 0.001$), neutropenia (OR, 13.4; 95% CI, 2.46 to 73.1; $P = 0.003$), a higher white blood cell (WBC) count on the culture date (OR, 1.05; 95% CI, 1.01 to 1.09; $P = 0.02$), receipt of immunosuppression in the preceding 30 days (OR, 6.31; 95% CI, 1.74 to 22.9; $P = 0.005$), and ICU location on the culture date (OR, 3.51; 95% CI, 1.65 to 7.49; $P < 0.001$). After controlling for confounders, RVS was significantly associated with greater 30-day in-hospital mor-

TABLE 1 Characteristics of patients with *Staphylococcus aureus* bacteremia

Characteristic	No. (%)[a] of patients with each characteristic: With RVS ($n = 134$)	Without RVS ($n = 258$)	*P* value
Mean age (yr) (SD)	58 (16.5)	57 (17.3)	0.67
Female	55 (41.0)	96 (37.2)	0.46
White	73 (56.6)	120 (48.2)	0.12
HUP patient	86 (64.2)	188 (72.9)	0.08
Physician referral on admission	27 (20.2)	46 (17.8)	0.58
Health care-associated infection	60 (44.8)	113 (43.8)	0.85
Prior admission to UPHS within the preceding 30 days	28 (20.9)	58 (22.5)	0.72
Mean APRDRG risk-of-mortality score (SD)[b]	2.0 (1.0)	2.1 (1.0)	0.73
Mean APRDRG severity-of-illness score (SD)[b]	2.5 (0.7)	2.5 (0.7)	0.63
Mean Charlson comorbidity score (SD)	4.5 (4.2)	4.5 (4.2)	0.88
Complicated infection	38 (28.4)	69 (26.7)	0.73
Diabetes mellitus	36 (26.9)	84 (32.6)	0.25
HIV	5 (3.7)	8 (3.1)	0.77
Malignant neoplasm	29 (21.6)	71 (27.5)	0.21
Renal insufficiency	50 (37.3)	89 (34.6)	0.60
Neutropenia	9 (6.7)	11 (4.3)	0.34
Transplant (solid organ or hematopoietic stem cell)	11 (8.2)	28 (10.9)	0.48
Receipt of any immunosuppression ≤30 days prior to the culture date	20 (14.9)	30 (11.6)	0.35
ICU location on culture date	35 (26.1)	60 (23.3)	0.53
Methicillin-resistant isolate	76 (56.7)	114 (44.2)	0.02
Receipt of any antibiotic ≤30 days prior to the culture date	46 (34.3)	45 (17.4)	<0.001
Receipt of vancomycin ≤30 days prior to the culture date	19 (14.2)	19 (7.4)	0.05
Mean in-hospital length of stay prior to culture date (days) (SD)	4.5 (10.4)	5.3 (34.7)	0.02
30-day in-hospital mortality	21 (15.7)	39 (15.1)	0.89

[a] Values are the numbers of patients (percentages of the total number of patients) unless otherwise indicated.
[b] Risk of patient death and severity of illness as based on DRG. The four subclasses are numbered sequentially from 1 to 4, indicating, respectively, minor, moderate, major, or extreme risk of mortality or severity of illness.

tality but only in patients with MSSA bacteremia (OR, 3.90; 95% CI, 1.07 to 14.2; $P = 0.04$). This increased risk of death was not significant in patients with MRSA bacteremia (OR, 0.53; 95% CI, 0.19 to 1.46; $P = 0.22$). Notably, when comparing patients with MRSA and MSSA bacteremia, there were no significant differences in regard to the Charlson comorbidity index ($P = 0.16$), the APRDRG severity-of-illness score ($P = 0.42$), or the APRDRG risk-of-mortality score ($P = 0.52$).

RVS and secondary outcomes. The mean hospital LOS after the first positive blood culture were 16.2 (standard deviation [SD], 18.0) and 17.8 (SD, 31.3) days in patients with *S. aureus* isolates with and without RVS, respectively. In multivariable analyses, there was significant effect modification by whether the infection was health care associated or community acquired ($P = 0.01$). Variables associated with hospital LOS in multivariable analyses are shown in Table 4. After adjustment for confounders in the final model for health care-associated infections, bacteremia due to *S. aureus* with RVS was associated with a 24% relative decrease in total mean LOS compared to the LOS for bacteremia due to *S. aureus* without RVS ($P = 0.049$). There was no significant difference in adjusted LOS for patients with *S. aureus* bacteremia with and without RVS for community-acquired infections ($P = 0.54$).

The mean total hospital charges after the first positive blood culture were $211,444 (SD, $361,563) and $263,776 (SD, $746,041) in patients with *S. aureus* isolates with and without RVS, respectively. In multivariable analyses, there was significant effect modification by whether the infection was health care associated or community acquired ($P = 0.01$). Variables associated with total hospital charges in multivariable analyses are shown in Table 5. After adjustment for confounders, there was no significant difference in total adjusted charges for patients hospitalized with *S. aureus* bacteremia with and without RVS for either health care-associated ($P = 0.71$) or community-acquired ($P = 0.52$) infections.

Etest versus broth microdilution. Analyses were repeated with RVS defined using broth microdilution cutoffs. The distribution of vancomycin MICs among the 392 subjects was as follows: 1 (0.3%) with a MIC of 0.25 μg/ml, 78 (19.9%) with a MIC of 0.5 μg/ml, 240 (61.2%) with a MIC of 0.75 μg/ml, 62 (15.8%) with a MIC of 1.0 μg/ml, and 11 (2.8%) with a MIC of 1.5 μg/ml. Accordingly, 313 (79.8%) isolates had RVS as defined by a broth microdilution MIC of >0.5 μg/ml. There was a significant, although weak, correlation between vancomycin Etest MICs and vancomycin broth microdilution MICs (Spearman's correlation = 0.50; $P < 0.001$). Of note, as half-dilution vancomycin concentrations were used to determine MICs, isolates with a vancomycin MIC of >0.5 μg/ml in the present study would be classified by clinical microbiology laboratories not performing half-dilutions as ≥1.0 μg/ml. In multivariable analyses, there was no significant difference in 30-day in-hospital mortality between patients with isolates characterized by the presence of RVS and those with isolates characterized by the absence of RVS for either MSSA bacteremia (OR, 3.79; 95% CI, 0.65 to 22.0; $P = 0.14$) or MRSA bacteremia (OR, 0.21; 95% CI, 0.04 to 1.11; $P = 0.07$). Given the

TABLE 2 Unadjusted risk factors associated with in-hospital mortality in *Staphylococcus aureus* bacteremia

Variable	No. (%)[a] of patients with each characteristic who:		*P* value	OR (95% CI)
	Survived ($n = 332$)	Died ($n = 60$)		
Mean age (yr) (SD)	56.8 (17.1)	61.9 (16.1)	0.04	NA[e]
Female	121 (36.5)	30 (50.0)	0.05	1.74 (0.96–3.15)
White	164 (49.4)	29 (48.3)	0.88	0.96 (0.53–1.72)
HUP patient	227 (68.4)	47 (78.3)	0.12	1.67 (0.84–3.51)
Physician referral on admission	68 (20.5)	5 (8.3)	0.03	0.35 (0.11–0.93)
Nosocomial infection	84 (25.3)	16 (26.7)	0.82	1.07 (0.54–2.06)
Prior admission to UPHS within the preceding 30 days	74 (22.3)	12 (20.0)	0.69	0.87 (0.40–1.77)
Mean total duration of bacteremia from culture date (days) (SD)[b]	3.0 (3.9)	3.2 (4.1)	0.65	NA
Receipt of appropriate antibiotic(s)	328 (99.7)	56 (96.6)	0.06	0.085 (0.00–1.68)
Mean no. of days to receipt of appropriate antibiotics (SD)	0.6 (1.0)	0.4 (0.6)	0.13	NA
Mean APRDRG risk-of-mortality score (SD)[c]	1.9 (1.0)	2.9 (0.4)	<0.001	NA
Mean APRDRG severity-of-illness score (SD)[c]	2.4 (0.7)	2.9 (0.3)	<0.001	NA
Mean Charlson comorbidity score (SD)	4.4 (4.1)	5.3 (4.6)	0.14	NA
Intravascular device	155 (46.8)	28 (46.7)	0.98	0.99 (0.55–1.79)
Removal of intravascular device	119 (76.8)	20 (71.4)	0.63	0.76 (0.29–2.16)
Complicated infection	92 (27.7)	15 (25.0)	0.75	0.87 (0.43–1.68)
Diabetes mellitus	101 (30.4)	19 (31.7)	0.85	1.06 (0.55–1.98)
Malignant neoplasm	80 (24.1)	20 (33.3)	0.15	1.56 (0.82–2.94)
Renal insufficiency	113 (34.1)	26 (43.3)	0.18	1.47 (0.81–2.67)
Transplant (solid organ or hematopoietic stem cell)	34 (10.2)	5 (8.3)	0.82	0.80 (0.23–2.18)
Receipt of any immunosuppression ≤30 days prior to the culture date	36 (10.8)	14 (23.3)	0.01	2.50 (1.15–5.19)
ICU location on culture date	63 (19.0)	32 (53.3)	<0.001	4.88 (2.63–9.04)
Mean WBC count ($\times 10^9$/liter) (SD)	12.9 (7.8)	15.8 (11.6)	0.15	NA
Methicillin-resistant isolate	155 (46.7)	35 (58.3)	0.10	1.60 (0.88–2.92)
Reduced vancomycin susceptibility	113 (34.0)	21 (35.0)	0.89	1.04 (0.56–1.92)
hGISA[d]	17 (5.1)	3 (5.0)	1.00	1.06 (0.07–64.7)
PVL	52 (15.7)	6 (10.0)	0.33	0.60 (0.20–1.49)
agr dysfunction	54 (16.3)	12 (20.0)	0.46	1.29 (0.58–2.66)
Receipt of vancomycin ≤30 days prior to the culture date	30 (9.0)	8 (13.3)	0.31	1.55 (0.58–3.70)

[a] Values are the numbers of patients (percentages of the total number of patients) unless otherwise indicated.
[b] For patients who demonstrated clearance of the episode of bacteremia (i.e., had at least one negative blood culture following the first positive blood culture date).
[c] Risk of patient death and severity of illness as based on DRG. The four subclasses are numbered sequentially from 1 to 4, indicating, respectively, minor, moderate, major, or extreme risk of mortality or severity of illness.
[d] hGISA, glycopeptide-heterointermediate *Staphylococcus aureus*.
[e] NA, not applicable.

high proportion of isolates designated to have RVS by broth microdilution, analyses were repeated using a cutoff vancomycin MIC of ≥1.0 μg/ml to determine RVS (i.e., with 18.6% of isolates having RVS). In multivariable analyses, there remained no significant association between RVS and mortality ($P = 0.59$).

TABLE 3 Adjusted risk factors associated with in-hospital mortality in *Staphylococcus aureus* bacteremia

Variable	OR (95% CI)	*P* value
APRDRG risk-of-mortality score[a]	7.11 (3.04–16.6)	<0.001
Neutropenia	13.4 (2.46–73.1)	0.003
Receipt of immunosuppression ≤30 days prior to the culture date	6.31 (1.74–22.9)	0.005
ICU location on culture date	3.51 (1.65–7.49)	<0.001
WBC count on culture date	1.05 (1.01–1.09)	0.02
Reduced vancomycin susceptibility		
MSSA isolates	3.90 (1.07–14.2)	0.04
MRSA isolates	0.53 (0.19–1.46)	0.22

[a] Risk of patient death based on DRG. The four subclasses are numbered sequentially from 1 to 4, indicating, respectively, minor, moderate, major, or extreme risk of mortality.

TABLE 4 Adjusted variables associated with total length of stay in *Staphylococcus aureus* bacteremia

Variable	Effect on expected LOS (95% CI)[a]	*P* value
Duration of bacteremia[b]	1.06 (1.03–1.08)	<0.001
APRDRG risk-of-mortality score[c]	1.48 (1.36–1.61)	<0.001
Diabetes mellitus	0.76 (0.63–0.88)	0.001
Receipt of any antibiotic ≤30 days prior to the culture date	1.44 (1.15–1.72)	<0.001
Reduced vancomycin susceptibility		
Health care-associated infections	0.76 (0.55–0.97)	0.049
Community-acquired infections	1.06 (0.86–1.27)	0.54

[a] Exponentiated coefficient of the multivariable model; for example, each additional day of bacteremia multiplies the expected LOS by 1.06 (i.e., adds 6% to the expected mean LOS).
[b] For patients who demonstrated clearance of the episode of bacteremia (i.e., had at least one negative blood culture following the first positive blood culture date).
[c] Risk of patient death based on DRG. The four subclasses are numbered sequentially from 1 to 4, indicating, respectively, minor, moderate, major, or extreme risk of mortality.

TABLE 5 Adjusted variables associated with total hospital charges in *Staphylococcus aureus* bacteremia

Variable	Effect on expected charges (95% CI)[a]	*P* value
Age	0.99 (0.98–0.99)	<0.001
Hospital of admission[b]	0.72 (0.59–0.84)	<0.001
ICU location on the culture date	1.39 (1.09–1.70)	0.003
APRDRG risk-of-mortality score[c]	1.74 (1.60–1.88)	<0.001
Diabetes mellitus	0.77 (0.63–0.90)	0.002
Reduced vancomycin susceptibility		
Health care-associated infections	0.95 (0.70–1.20)	0.71
Community-acquired infections	1.07 (0.85–1.29)	0.52

[a] Exponentiated coefficient of the multivariable model.
[b] Penn Presbyterian Medical Center or the Hospital of the University of Pennsylvania.
[c] Risk of patient death based on DRG. The four subclasses are numbered sequentially from 1 to 4, indicating, respectively, minor, moderate, major, or extreme risk of mortality.

DISCUSSION

In this large cohort study, we found that RVS was associated with increased mortality in bacteremia due to MSSA but not MRSA. Furthermore, RVS was associated with decreased LOS in health care-associated but not community-acquired *S. aureus* bacteremia. However, RVS had no impact on total hospital charges accrued after the first positive blood culture date.

Previous studies have suggested increased mortality in patients treated with vancomycin for infections due to *S. aureus* with RVS. However, these studies have been limited by issues such as small sample size (2, 14, 26, 28, 29, 31, 33, 42, 44), limited use of multivariable regression analysis and/or ascertainment of potential confounders (17, 29, 31, 36, 42), enrollment of patients over a prolonged period of time during which antibiotic use, risk factors, and clinical practice could have changed (36), evaluation of a patient population that was highly enriched for vancomycin treatment failure (28, 29, 33), and lack of objective clinical or microbiological endpoints (14, 36). To our knowledge, the present study is the second in the literature to evaluate RVS as a risk factor for mortality in patients with *S. aureus* bacteremia associated with both methicillin-susceptible and methicillin-resistant strains, and the results are further strengthened by the large size of our cohort, the capture of comprehensive clinical data, the consideration of important potential confounders, including *agr* function and intravascular device removal, and the evaluation of secondary endpoints of considerable public health significance, specifically LOS and total hospital charges.

The overall 30-day in-hospital mortality rate in our study was 15.3% for *S. aureus* bacteremia, a rate which is on the lower end of those found in previously reported studies (6, 36, 41) though similar to those reported by two larger cohort studies of *S. aureus* bacteremia (17, 21). It is notable that the majority of patients in our study received appropriate empirical antibiotic therapy without significant delay, underwent removal of intravascular devices, and had low rates of persistent bacteremia (>3 days), all of which might have contributed to the observed lower mortality rate.

A novel finding of our study is that RVS was associated with increased in-hospital mortality in bacteremia as a result of MSSA but not MRSA. While 60.9% of patients with MSSA bacteremia in our study received vancomycin as the initial appropriate therapy (i.e., before methicillin susceptibility was known), 65.9% were subsequently switched to a beta-lactam (with the majority receiving nafcillin) at a mean of 2.8 (SD, 1.3) days from the culture date. As such, the majority of patients (79.2%) with bacteremia due to MSSA received definitive therapy with a beta-lactam. Furthermore, among patients with MSSA bacteremia who received beta-lactams initially instead of vancomycin, there were no significant differences in either mortality rates (15.2% and 10.6%, respectively; $P = 0.38$) or time to receipt of the appropriate antibiotic (mean of 0.47 [SD, 0.84] days from the culture date versus a mean of 0.58 [SD, 0.84] days, respectively; $P = 0.19$). Therefore, the receipt of vancomycin instead of a beta-lactam for initial empirical therapy among a proportion of patients in our study was thought to be a less likely explanation for the observed association between RVS and increased mortality.

Along these lines, the association between RVS and poor clinical outcomes in patients receiving vancomycin has been attributed in part to difficulty achieving an optimal vancomycin area under curve (AUC)/MIC ratio (21). However, a recently published study demonstrating increased mortality in bacteremia due to *S. aureus* with RVS challenges this notion (17). In this large cohort study, the association between RVS and increased mortality was still observed in patients with MSSA bacteremia who were treated exclusively with flucloxacillin instead of vancomycin. Similarly, the results of our study demonstrated increased mortality with RVS in patients with MSSA bacteremia, the majority of whom also received definitive treatment with beta-lactam therapy. The authors of the aforementioned study and others (16) have postulated that the association between RVS and mortality in patients receiving vancomycin may not be causal but, rather, that an elevated vancomycin MIC may be a marker of an as-yet-unidentified organism or host factor associated with virulence.

Of note, approximately 75% of our cohort was *agr* functional, and rates of *agr* dysfunction were not significantly different between MSSA and MRSA isolates. While *agr* dysfunction has been associated with vancomycin treatment failure, persistent bacteremia, and increased mortality in severely ill patients (10, 35), *agr* dysfunction was not associated with increased mortality in bivariable and multivariable analyses. In general, MRSA strains responsible for hospital-acquired infections may have reduced microbial fitness compared to that of MSSA strains (8). Interestingly, some studies suggest that MRSA strains with elevated vancomycin MICs may be less virulent than strains with lower MICs, with a lower degree of systemic inflammatory response and a nonsignificant trend toward lower risk of septic shock in a retrospective cohort study (22), a highly significant reduction in septic shock in patients with bacteremia (36), and impaired early growth during the first hours of incubation in an invertebrate model (30). To our knowledge, the association between elevated vancomycin MICs and lower virulence and fitness has not been demonstrated in MSSA strains, and it is possible that this may, in part, explain the findings of our present study. Nevertheless, further research is warranted in terms of elucidating the contribution of RVS to poor clinical outcomes in infections due to methicillin-susceptible and methicillin-resistant *S. aureus*, including host and pathogen factors that may be specific to particular strains.

There was no significant association between RVS defined by broth microdilution and mortality in our study, although the directions of the associations (i.e., ORs) were equivalent to those obtained with RVS defined by Etest when stratified by MRSA status. Previous studies have demonstrated poor correlation between the Etest and broth microdilution MIC methods, with the Etest

providing consistently higher MIC results (18, 39). There is still uncertainty regarding the optimal approach to defining RVS in terms of both method and cutoff, particularly for purposes of comparison across studies. Nevertheless, these studies suggest that the Etest method is more reliable for predicting treatment response as well as detecting glycopeptide-intermediate strains of *S. aureus*, and this was the method used for primary analyses in our study.

Despite accounting for censoring by death, RVS was associated with a shorter mean length of hospital stay in health care-associated infections. It is unclear why this may have been the case, but it is possible that patients with *S. aureus* bacteremia with RVS were discharged to lower levels of care (e.g., skilled nursing facilities) to complete treatment on an earlier basis. Furthermore, there was no difference in total hospital charges in patients with *S. aureus* bacteremia with and without RVS. Patients with *S. aureus* bacteremia overall are critically ill and require substantial hospital resources for care. It is likely that after adjustment for clinically important confounders, including a standardized risk-of-mortality score as well as ICU location (and, therefore, overall use of ICU resources), there is no difference in total hospital charges between these two patient groups. Nevertheless, further research, including evaluation of rates of hospital readmission, is needed to clarify these associations.

There are several potential limitations of the present study. We were unable to ascertain pharmacologic data on therapeutic drug monitoring in patients receiving vancomycin, although this will be analyzed in future investigations. Furthermore, there was no standard approach to the frequency of obtaining blood cultures in patients with bacteremia and we did not have information on rehospitalization rates, both of which may have affected our estimate of duration and recurrence rates of bacteremia. Selection bias is often a potential concern in studies of antimicrobial resistance and clinical outcomes; however, subjects were identified through the Clinical Microbiology Laboratory, which processed and cultured all specimens obtained at HUP and PPMC during the study period, thereby minimizing the likelihood of excluding potential study subjects. Finally, the present study was conducted in a single health care system, and these results may not be generalizable to other institutions.

In conclusion, the results of our study demonstrate that RVS is associated with increased mortality in bacteremia due to MSSA but not MRSA, and this may be in part due to potentially lower virulence and fitness of methicillin-resistant strains. Future studies will be needed to identify host and organism factors that are associated with RVS and increased mortality in bacteremia due to MSSA and MRSA strains with elevated but still susceptible vancomycin MICs and to elucidate optimal strategies for the treatment of these serious and increasingly common infections.

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