Predictors of Adverse Outcomes in Children With *Staphylococcus aureus* Bacteremia

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OBJECTIVES *Staphylococcus aureus* bacteremia is a common infection, associated with significant morbidity and mortality in children. Factors associated with adverse treatment outcomes are poorly understood in the pediatric population.

METHODS Our study compared clinical and microbiologic characteristics of children admitted during a 5-year period (2007–2012) to a large university-based hospital and found to have *S aureus* bacteremia with outcome measures, in order to identify risk factors associated with treatment failure (defined as 30-day mortality, delayed microbiologic resolution, or recurrence of *S aureus* bacteremia within 60 days of completing effective antibiotic therapy).

RESULTS In all, 71 patients were found to have *S aureus* bacteremia, and of these, 17 patients (24%) experienced treatment failure. Based on the logistic regression model, only high vancomycin minimum inhibitory concentration in combination with a high-risk source of infection (i.e., infected graft or device, intra-abdominal infection, or respiratory tract infection) was significantly associated with risk of treatment failure.

CONCLUSIONS Infection associated with a high-risk source may increase the chance of treatment failure in pediatric patients with *S aureus* bacteremia. Vancomycin minimum inhibitory concentration alone was not found to be a predictor of treatment outcomes.

ABBREVIATIONS AUC, area under the curve; ICU, intensive care unit; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NICU, neonatal intensive care unit; PVL, Pantan-Valentine leukocidin

KEYWORDS adverse outcome; bacteremia; children; MIC; *Staphylococcus aureus*; vancomycin

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Introduction

Staphylococcus aureus bacteremia remains a leading cause of bloodstream infections in children and is associated with both significant morbidity and mortality.¹⁻⁴ Risk factors related to the development of *S aureus* bacteremia in children are well described and frequently relate to underlying comorbidity and the presence of an intravascular device.⁵⁻⁸ Less is understood about predictors of adverse outcomes in this population. Pulmonary infection, endocarditis,^{9,10} underlying comorbidity, inadequate empiric therapy,¹¹ prematurity, and the presence of Pantan-Valentine leukocidin (PVL)-positive infection¹² have been observed as independent risk factors of mortality or treatment failure in children. The effect of several other variables is still unclear. There are conflicting data, for example, as to whether higher vancomycin minimal inhibitory concentrations (MICs), including values within the recommended upper ranges of susceptible (≤ 2 mg/L), may also increase mortality in patients with *S aureus* bacteremia.¹³⁻¹⁸ The primary aim

of the study was to describe the relationship between specific patient and pathogen characteristics, including vancomycin MIC, and clinical outcomes in pediatric patients with *S aureus* bloodstream infection in order to determine the risk factors most likely associated with treatment failure.

Materials and Methods

This study was a single-center, Institutional Review Board–approved, retrospective cohort study conducted at the University of Maryland Medical Children's Hospital, which is part of a large university teaching hospital and regional tertiary level referral center in Maryland, receiving approximately 4500 pediatric admissions annually. All patients admitted between July 1, 2007, and July 1, 2012, who were younger than 18 years and had at least one positive blood culture growing *S aureus* were included for analysis.

Clinical Data. Clinical data were extracted from the hospital central data repository. Variables of interest

included age, sex, ethnicity, recent hospitalization within 90 days of admission and antibiotic exposures within 60 days of admission, associated comorbid conditions, creatinine clearance (milliliters per minute) via the Schwartz method,¹⁹ mechanical ventilation, central venous catheter access, severity of illness as measured by intensive care unit (ICU) status, associated sites of infection (e.g., respiratory tract, urinary tract, endocarditis), antibiotic treatment data (timing to index blood culture, dosage regimen, and duration), vancomycin pharmacokinetic data (serum concentration levels and temporal relationship to vancomycin dose), and time to clearance of blood cultures. The presence of the following comorbid conditions was documented: prematurity (< 37 weeks' gestation), malignancy, prior transplantation, human immunodeficiency virus (HIV) or immune deficiency, neutropenia (absolute neutrophil count < 500), receipt of corticosteroid or immunomodulating agents (regimens equivalent to ≥ 2 mg/kg prednisone for ≥ 14 days), renal failure, hepatic failure, surgery (within 30 days of bacteremia), diabetes mellitus, congenital heart disease, parenteral nutrition, dialysis, and recent hospitalization (within 90 days of admission). Sources of infection were divided into 2 categories based on the risk of mortality associated with the origin of the bacteremia. Sources considered to be high risk (mortality risk of $\geq 10\%$) included grafts and devices, osteoarticular, lower respiratory, central nervous system, and intra-abdominal sites. Sources considered to be low risk (mortality risk <10%) included intravenous catheters, urinary tract and manipulation-related sources (e.g., arterial catheterization).^{20,21}

Microbiologic Data. Vancomycin MIC was measured on banked specimens by E-test (Biomeriux, Durham, NC) following the criteria of the Clinical and Laboratory Standards Institute²² and conducted by 2 trained personnel in a single laboratory. Prior to MIC testing, each isolate was subcultured to trypticase soy agar plates supplemented with 5% sheep blood. The plates were incubated overnight (18–24 hours) at 35°C in ambient air, and the subculturing process was repeated a second time. From these plates, portions of colonies were suspended in 0.45% saline to create a 0.5 McFarland turbidity standard. This standardized suspension was used to streak the inoculum onto the surface of a 150-mm Mueller-Hinton II agar plate to create a confluent lawn of microbial growth. The surface of the plate was allowed to dry for 15 minutes prior to vancomycin E-test strip application. In cases when more than one sample per patient had been stored, the first sample was used for analysis. Each MIC was read by 2 independent, trained personnel, and if there was any discordance between the two reads, a third read was completed by the director of the microbiology laboratory in order to decrease subjectivity.

Outcome Data. The primary outcome measure of treatment failure was a composite end point defined as

the presence of any of the following: 1) 30-day mortality, 2) delayed microbiologic resolution (positive blood culture for *S aureus* obtained at least 72 hours after the initiation of effective antibiotic therapy and before completion of treatment duration), or 3) recurrence of *S aureus* bacteremia within 60 days of completing effective antibiotic therapy. Secondary outcomes included length of stay after blood culture collection and adjustment of antibiotic therapy.

Statistical Analysis. Statistical analysis was performed using SPSS Version 21 (SPSS Inc, Chicago, IL). Patient variables were compared using a Pearson χ^2 or Fisher exact test for dichotomous variables and a 2-sample *t* test or Mann-Whitney *U* test for continuous variables. To identify risk factors that were independently associated with the primary outcome of interest, multivariate analysis was conducted using a logistic regression model, likelihood ratio test. A stepwise approach was used to derive a parsimonious model, and variables remained in the final model if the associated *p*-value was < 0.05. Automated forward/backward selection functions were used in preliminary analysis to assess the contribution of risk factors that did not meet statistical significance but had a *p*-value < 0.25. Risk factors had to be present in at least 10% in the overall population to be included in the model, regardless of their *p*-value. Multivariate logistic regression models were assessed by the Hosmer and Lemeshow goodness of fit statistic and the C-statistic representing the area under the receiver operating characteristic curve. Multicollinearity was assessed by examining the tolerance and variance inflation factor for each variable. This study was approved by the University of Maryland Institutional Review Board.

Results

Clinical and Demographic Characteristics. During the study period, 71 pediatric patients were identified with bloodstream infection caused by *S aureus*: 40 patients (56%) with methicillin-susceptible *S aureus* (MSSA) bacteremia, and 31 patients (44%) with methicillin-resistant *S aureus* (MRSA) bacteremia. All isolates were available for analysis. Most of the patients in the cohort were younger than 1 year (*n* = 44; 62%). Comorbidities in our population were high, with 51% having a preexisting central line, 49% requiring respiratory support by mechanical ventilation at the time of bacteremia, 31% receiving parenteral nutrition at the time of bacteremia, and 28% having a history of prematurity. Other comorbidities, such as immunosuppression, congenital heart disease, liver disease, and renal disease, were relatively low (Table 1). Overall, 53 patients (75%) received vancomycin within 48 hours of the index *S aureus* blood culture.

Microbiologic Characteristics. Most (75%) of the isolates had a vancomycin MIC of 1.5 mg/L, compared with the remainder (25%) of isolates having a vanco-

Table 1. Bivariate Comparison of Clinical and Microbiologic Features Between Low Vancomycin Minimum Inhibitory Concentration (MIC; MIC = 1) and High Vancomycin MIC (MIC = 1.5) and Between Treatment Failure and Successes Among 71* Children With *Staphylococcus aureus* Bacteremia, 2007–2012

Variable	n (%)	Low MIC (n = 18)	High MIC (n = 53)	Risk Estimate (95% CI)	p-Value	Failure (n = 17)	Success (n = 54)	Risk Estimate (95% CI)	p-Value
ICU patient	42 (60)	10 (55.6)	32 (60.4)	1.1 (0.7, 1.7)	0.72	11 (64.7)	31 (57.4)	1.1 (0.7, 1.7)	0.59
Female	21 (30)	4 (22.2)	17 (32.1)	1.4 (0.6, 3.7)	0.43	8 (47.1)	13 (24.1)	2.0 (1.0, 3.9)	0.07
Age ≥12 mo	44 (62)	13 (72.2)	31 (58.5)	0.8 (0.6, 1.2)	0.30	11 (64.7)	33 (61.1)	1.1 (0.7, 1.6)	0.79
Non-white	52 (73)	12 (66.7)	40 (75.5)	1.1 (0.8, 1.6)	0.47	11 (64.7)	41 (75.9)	0.9 (0.6, 1.2)	0.36
Comorbidities									
Malignancy	2 (3)	0	2 (3.8)		0.40	2 (11.8)	0		0.01
Transplant	1 (1)	0	1 (1.9)		0.56	0	1 (1.9)		0.57
HIV/ID	3 (4)	1 (5.6)	2 (3.8)	0.7 (0.1, 7.1)	0.75	0	3 (5.6)		0.32
Renal failure	5 (7)	0	5 (9.4)	N/A	0.18	2 (11.8)	3 (5.6)	2.1 (0.4, 11.6)	0.38
Surgery	9 (13)	0	9 (17)	N/A	0.06	3 (17.6)	6 (11.1)	1.6 (0.4, 6)	0.48
CHD	2 (3)	2 (11.1)	0	N/A	0.01	0	2 (3.7)		0.42
Neutropenia	2 (3)	0	2 (3.8)	N/A	0.40	1 (5.9)	1 (1.9)	3.2 (0.2, 48.1)	0.38
Steroids	6 (9)	1 (5.6)	5 (9.4)	1.7 (0.2, 13.6)	0.61	2 (11.8)	4 (7.4)	1.6 (0.3, 7.9)	0.57
TPN	22 (31)	4 (22.2)	18 (34)	1.5 (0.6, 3.9)	0.35	8 (47.1)	14 (25.9)	1.8 (0.9, 3.6)	0.1
Dialysis	1 (1)	0	1 (1.9)		0.56	0	1 (1.9)		0.57
Recent admit 90 days	19 (27)	5 (27.8)	14 (26.4)	1.0 (0.4, 2.3)	0.91	6 (35.3)	13 (24.1)	1.5 (0.7, 3.3)	0.36
Prematurity	20 (28)	3 (16.7)	17 (32.1)	1.9 (0.6, 5.8)	0.21	5 (29.4)	15 (27.8)	1.1 (0.5, 2.5)	0.9
Abx prior 60 days	19 (27)	3 (16.7)	16 (30.2)	1.8 (0.6, 5.5)	0.26	6 (35.3)	13 (24.1)	1.5 (0.7, 3.3)	0.36
Central line	36 (51)	6 (33.3)	30 (56.6)	1.7 (0.9, 3.4)	0.09	11 (64.7)	24 (44.4)	1.5 (0.9, 2.3)	0.15
Mechanical ventilation	35 (49)	8 (44.4)	27 (50.9)	1.1 (0.6, 2.0)	0.64	10 (58.8)	26 (48.1)	1.2 (0.8, 2.0)	0.44
Source					0.76				0.22
High-risk source*	20 (28)	6 (33.3)	14 (26.4)	0.8 (0.4, 1.8)	0.57	8 (47.1)	12 (22.2)	2.1 (1.0, 4.3)	0.05
Pathogen									
MRSA	31 (44)	7 (38.9)	33 (62.3)	1.6 (0.9, 3.0)	0.08	8 (47.1)	23 (42.6)	1.1 (0.6, 2.0)	0.75
MIC >1	53 (75)					14 (82.4)	39 (72.2)	1.1 (0.9, 1.5)	0.4
High-risk source* and high MIC	14 (20)					7 (41.2)	7 (13)	3.2 (1.3, 7.8)	0.01

Abx, antibiotics; CHD, congenital heart disease; CI, confidence interval; HIV, human immunodeficiency syndrome; ICU, intensive care unit (neonatal and pediatric units combined); ID, immune deficiency; MRSA, methicillin-resistant *S aureus*; N/A, not applicable; TPN, total parenteral nutrition

*No patients with hepatic failure, diabetes mellitus, or history of intravenous drug abuse were found in this cohort

†High-risk sources included graft/device, intraabdominal, and respiratory tract

Table 2. Univariate Analysis of Clinical Outcomes of 71* Children with *Staphylococcus aureus* Bacteremia by Low Vancomycin Minimum Inhibitory Concentration (MIC; MIC = 1) and High Vancomycin MIC (MIC = 1.5), 2007–2012

Outcome	Low MIC, n (%) [†]	High MIC, n (%) [†]	Risk Estimate (95% CI)	p-Value
Overall failure	3 (16.7)	14 (26.4)	1.6 (0.51, 4.9)	0.40
30-day mortality	0	3 (5.7)	N/A	0.30
Delayed microbiological resolution	2 (11.1)	11 (20.8)	1.9 (0.46, 7.6)	0.36
Recurrence within 60 days	1 (5.6)	1 (1.9)	0.34 (0.02, 5.2)	0.42
Switched to alternative therapy	13 (72.2)	13 (24.5)	0.86 (0.61, 1.2)	0.45

*No patients with hepatic failure, diabetes mellitus, or history of intravenous drug abuse were found in this cohort

[†]For each group: n = 18 (low MIC), and n = 53 (high MIC)

mycin MIC of 1.0 mg/L. No isolates had a vancomycin MIC of less than 1.0 mg/L or greater than 1.5 mg/L by E-test methodology. Regarding methicillin susceptibility, 33 of the MSSA isolates (82.5%) and 20 of the MRSA isolates (64.5%) had a vancomycin MIC of 1.5 ($p = 0.08$).

Treatment Failure. A total of 17 patients (24%) experienced treatment failure; 3 patients (4%) died within 30 days of the index *S aureus* blood culture (30-day mortality), 13 patients (18%) had delayed microbiologic resolution, and 2 patients (3%) had *S aureus* bacteremia recurrence within 60 days of the completion of effective antibiotic therapy (Table 2). One patient experienced both delayed microbiologic resolution and *S aureus* bacteremia recurrence within 60 days. All patients who met the definition of treatment failure were started on initially effective antibiotic therapy, with the exception of 2 patients. The first was a neonate who was empirically treated for sepsis with ampicillin and cefotaxime, and vancomycin was added on the day susceptibilities for the *S aureus* returned; clearance of bacteremia was demonstrated 72 hours after starting vancomycin. One patient with delayed microbiologic resolution had been started empirically on piperacillin/tazobactam, with vancomycin added 4 days into his hospital stay; however, blood cultures did not clear until 12 days after the start of the vancomycin therapy. All 13 patients with delayed microbiologic resolution were shown in post hoc analysis to have experienced persistent or worsening signs and symptoms of infection (data not shown). Of these 13 patients, the source of the *S aureus* bacteremia was presumed to be the respiratory tract in 4 patients (31%), central intravenous catheter in 3 patients (23%), skin and soft tissue in 2 patients (15%), and intra-abdominal in 2 patients (15%), and was unknown in only 2 patients (15%). The only variable found to be significantly related to treatment failure was infection from a high-risk source. Based on the logistic regression model, only high vancomycin MIC in combination with a high-risk source of infection (graft or device, intra-abdominal, or respiratory tract) was significantly associated with risk of poor outcome (Table 1). Vancomycin MIC >1.0 mg/L was not associated with treatment failure ($p = 0.40$; Table 1). The univariate analysis for MIC (Table 2) did not

identify a significant difference in any of the individual or composite outcomes for the high vancomycin MIC (1.5 mg/L) and low vancomycin MIC (1.0 mg/L) groups (Table 1). Infection with MRSA was not associated with treatment failure ($p = 0.75$ Table 1).

Duration of Hospital Stay. The median (interquartile range) hospital length of stay following the index culture was 14 days (7–28 days), compared with 19 days (8–53 days) for total length of stay. The 13 patients with delayed microbiologic resolution had a longer median length of stay following the index blood culture, compared with the 58 patients who did not have delayed microbiologic resolution (23 days vs. 12 days).

Alternative Antibiotic Therapy. Among the 31 patients with MRSA bacteremia, 22 patients (71%) received vancomycin within 48 hours of the index blood culture. Within this subgroup of 22 patients, 7 patients (32%) were switched to alternative therapy, and all 7 received linezolid. Use of linezolid was multifactorial and was often because of toxicity concerns with vancomycin or because of intravenous access issues. The median time before switching from vancomycin to linezolid was 4 days. For the remaining 9 patients with MRSA bacteremia, empiric initial antibiotic therapy included clindamycin ($n = 4$), ampicillin and gentamicin ($n = 2$), ampicillin and cefotaxime ($n = 1$), ceftriaxone ($n = 1$), and piperacillin-tazobactam ($n = 1$). Coverage for MRSA was added for all patients upon receipt of culture results. Among the 40 patients with MSSA bacteremia, 24 patients (60%) received vancomycin within 48 hours of the index blood culture. Within this subgroup of 24 patients, 19 patients (79%) were switched to alternative therapy; 16 patients (67%) were switched to nafcillin and 3 (13%) were switched to clindamycin. The median time before switching from vancomycin to either nafcillin or clindamycin was 3 days. The median trough concentration of vancomycin within 72 hours of therapy initiation was 10.1 mg/L (8–12.4 mg/L) for the high vancomycin MIC group and 10.9 mg/L (9.3–15.1 mg/L) for the low vancomycin MIC group. The median trough concentration of vancomycin >72 hours of therapy initiation was 11.15 mg/L (9.2–15.2 mg/L) for the high MIC group and 14.4 mg/L (10.5–17 mg/L) for the low MIC group.

Discussion

To our knowledge, the impact of host and pathogen factors on clinical outcomes in children with *S aureus* bacteremia is insufficiently described, and our study is one of only a few published studies to directly examine predictors of clinical outcomes in the pediatric population. Given the retrospective nature of our investigation, we opted to use an objective composite end point to represent treatment failure based on previously published criteria;¹² however, microbiologic failure was defined as a blood culture growing *S aureus* after 72 hours of effective therapy (a susceptible antibiotic dosed appropriately for the patient and site of infection), because persistent bacteremia beyond 4 or more days is associated with a higher rate of complications.²³ In our study, adverse outcomes were frequent, with nearly a quarter of all patients studied with *S aureus* bacteremia experiencing treatment failure. The all-cause case fatality rate was 4%; this rate is within the range of mortality rates reported in children with *S aureus* bacteremia who are in developing countries,^{9,10,12,24–28} and is considerably lower than the mortality rates seen with adult populations. In fact, age has consistently been noted to be the strongest predictor of all-cause and infection-related mortality, with fatality rates approaching 60% in adults older than 85 years.²⁹ In our study, 44 patients (62%) were younger than 1 year, representing a relatively young patient population and likely a reflection of our large neonatal ICU (NICU). High mortality and high treatment failure rates have also been reported in premature infants, particularly those born with a very low birth weight.³⁰ A recent retrospective study using a large administrative database of 600 US acute care hospitals to examine outcomes of children hospitalized with *S aureus* bacteremia found that hospital-onset infections were associated with longer postinfectious length of stay and higher mortality, but those with community-onset infection had a shorter median time to death from bacteremia onset (3 days vs. 6 days), supporting the need for early initiation of empiric therapy in children with *S aureus* bacteremia.²⁸ Similarly, another study found that among infants admitted to a NICU who developed *S aureus* bacteremia, inadequate empirical antibiotic therapy was associated with increased mortality at 30 days for those with MRSA infection.¹¹ Data from 30 years of surveillance of Danish children with *S aureus* bacteremia between 1971 and 2000 indicated that increased risk of mortality was associated with pulmonary infection and endocarditis, underlying comorbidities, and hospital-acquired infection, which was not replicated in our study.¹⁰ Of the 3 reported deaths in our study, one of the patients died of complications that appeared directly related to staphylococcal infection. The first patient was a NICU patient born prematurely at 23 weeks' gestation whose hospital course was complicated by severe bilateral intraventricular hemor-

rhage and posterior hemorrhagic hydrocephalus. On this 13th day of life he was found to have an intestinal perforation with MRSA sepsis, for which he was treated early with vancomycin and demonstrated clearance of bacteremia following 2 days of therapy. He had recurrent thrombus formation in his right atrium and died on the 45th day of life from respiratory failure related to acute pneumonia and pulmonary emboli. The second patient was also a NICU patient born prematurely at 24 weeks' gestation with extensive damage to the central nervous system secondary to prematurity and perinatal ischemia, who died of severe bilateral pneumonia secondary to coinfection with *Klebsiella pneumoniae* and MRSA. Two weeks prior to her death, she developed necrotizing enterocolitis with MRSA that was treated empirically with vancomycin and piperacillin/tazobactam and demonstrated clearance of bacteremia within 1 day. The third patient was a previously healthy 14-year-old female admitted to the pediatric intensive care unit who died of severe respiratory failure secondary to infection with H1N1 influenza. MSSA bacteremia was detected 2 days into her hospitalization. The patient received broad-spectrum antibiotic treatment with vancomycin, clindamycin, and meropenem while she was on extracorporeal membrane oxygenation, because of concern for pneumonia. Her blood cultures sterilized within 24 hours of antibiotic therapy initiation. She died 7 days into her hospitalization.

In our study, the median duration of bacteremia was 2 days (range, 1–12 days). Slightly more than 15% of patients had delayed microbiologic resolution, defined as positive blood culture for *S aureus* obtained at least 72 hours after the initiation of antibiotic therapy and before completion of treatment duration, accounting for most of our treatment failures. No patients had positive blood cultures beyond 12 days. Endocarditis was diagnosed in 5 patients (7%), and all 5 patients experienced delayed microbiologic resolution. Persistence of bacteremia, which often varies in definition between 3 and 7 days of bacteremia, is often used as a marker of complicated infection, because it is generally associated with worse outcomes.^{12,24} We opted to use a definition of persistent bacteremia after 3 days of effective antibiotic therapy based on this and expert opinion. In addition, a search for endocarditis with an echocardiogram is recommended in children with bacteremia more than 2 to 3 days in duration.³¹ Although there is no official guidance on the management of persistent bacteremia in children, this finding should prompt an aggressive search for removal or drainage of other foci of infection and an individualized approach to modification of antibiotic therapy.^{24,32}

In our analysis, only high-risk source of infection or the combination of high-risk source of infection and high MIC was significantly associated with treatment failure. The question of whether high but susceptible vancomycin MIC isolates (i.e., ≤ 2 mg/L) are associated

with increased risk of treatment failure and mortality has been a source of great controversy. Lodise et al¹⁴ found that vancomycin MIC of ≥ 1.5 mg/L was associated with a 2.4-fold increase in treatment failure compared with patients with MIC of ≤ 1.0 mg/L, in their retrospective analysis of patients ages 18 years and older with MRSA bacteremia treated with vancomycin. Several other reports have shown a high MIC of p-value ≥ 1.5 mg/L to be a predictor of mortality, regardless of MIC testing methodology used.^{15,16} Notably, Holmes et al¹³ also found that vancomycin MIC predicted mortality even in MSSA episodes appropriately treated with an antistaphylococcal penicillin, alluding to the possibility that elevated MIC may be a marker of an unidentified pathogenic-related factor, and not necessarily correlated with antibiotic treatment choice. Several meta-analyses have further attempted to address this question, also with conflicting results, likely reflecting the heterogeneity of the study populations included and outcomes measured. A meta-analysis of 22 studies conducted by van Hal et al¹⁷ compared overall 30-day mortality and treatment failure between high (≥ 1.5 mg/L) and low (< 1.5 mg/L) vancomycin MIC groups with MRSA bacteremia.³³ Patients in the high vancomycin MIC group had a higher mortality rate associated with MRSA infection, with a greater correlation in patients with an MIC of ≥ 2 mg/L. In contrast, a meta-analysis of 38 studies of patients with *S aureus* bacteremia conducted by Kalil et al concluded that overall mortality was 26%, and there was no statistically significant difference in the adjusted absolute risk of mortality demonstrated among patients with *S aureus* bacteremia isolates yielding high vancomycin MICs (≥ 1.5 mg/L) compared with those with low vancomycin MICs (< 1.5 mg/L). The risk difference between these groups was not statistically significant for 30-day mortality or hospital mortality when assessed separately, and there was no significant difference in risk of death observed in subgroups with high vancomycin MIC vs. low vancomycin MIC values across different study designs, microbiologic susceptibility assays (broth microdilution vs. E-test), MIC cutoffs (1.5, 2, 4, and 8 mg/L), clinical outcomes, duration of bacteremia, previous vancomycin exposure, and treatment with vancomycin.¹⁸

In our study, we did not find that vancomycin MIC was associated with treatment failure in children, consistent with other small, single-center experiences.^{12,34–37} It is worth noting our study contained no MIC > 1.5 mg/L, which varies from the distribution observed in our institution among adult patients conducted around the same time, in which *S aureus* isolates yielded vancomycin MICs of 1.5 mg/L (56%), ≤ 1 mg/L (31%), and ≥ 2 mg/L (13%) by E-test (unpublished data). Additionally, no difference was noted in vancomycin troughs achieved in either study group. The area under the curve during 24 hours (AUC)/MIC of ≥ 400 has been shown to best predict efficacy of vancomycin in adult patients.^{38,39} An

analysis of vancomycin AUC/MIC in pediatric patients at our institution found that an AUC of 400 correlated to a trough of 11 mg/L using a trapezoidal method to calculate AUC.⁴⁰ Based on the average troughs identified in our study, patients would have been at the goal AUC/MIC target of ≥ 400 in the low MIC group, but they would not have achieved this target in the high MIC group. Because vancomycin troughs are correlated with nephrotoxicity risk, prospective studies of AUC/MIC-based vancomycin dosage and outcomes related to vancomycin MIC are needed, particularly in the pediatric population, where these data are lacking.³⁷

Interestingly, in our study MRSA bacteremia did not increase the likelihood of treatment failure either. Following the rise in MRSA bacteremia during the past 2 decades, multiple publications have described an increase in mortality associated with methicillin-resistant strains. A meta-analysis of 31 studies performed by Cosgrove et al⁴¹ showed that the odds of mortality associated with MRSA bacteremia was nearly twice that associated with MSSA bacteremia, even after adjusting for potential confounders, such as age, sex, and severity of illness. Similarly, a meta-analysis of 7 neonatal and pediatric cohort studies found methicillin resistance was associated with higher mortality rate, but none of the cohort studies performed multivariable analysis to identify MRSA as an independent variable predictive of mortality, so it is unclear whether this was related to more severe infection or perhaps something like more complex underlying medical conditions.⁴² Conversely, Shane et al³⁰ found no difference in morbidity and mortality rates among very low-birth weight infants with MRSA vs. MSSA bacteremia or meningitis. Matched case controlled studies have also not shown a difference in mortality between MRSA and MSSA bacteremia.^{43,44} Molecular analysis of *S aureus* strains from both pediatric and adult populations seeking care for infections demonstrates substantial overlap between the genetic backgrounds of MSSA and MRSA isolates.^{45,46} One could speculate that differences in antibiotic prescribing patterns and inferiority of vancomycin for treatment of MRSA infections compared with the antistaphylococcal penicillins for the treatment of MSSA infections could also be contributing factors to differences in mortality noted in some studies.³¹

Although it was not evaluated in our study, PVL positivity has also been found to correlate with worse outcomes in children.^{12,47,48} Panton-Valentine leukocidin is a staphylococcal cytotoxin encoded by the gene set *lukSF-PV*, often found in community strains, such as the common USA300 strain, that also contain the methicillin resistance-encoding mobile genetic element *SCCmec*, but may also be found in methicillin-susceptible strains. Pantan-Valentine leukocidin-containing strains of MRSA are strongly associated with skin and soft-tissue infections. In contrast to children, a meta-analysis of adult populations with PVL-positive strains showed

PVL has not consistently been shown to cause more invasive disease or worse outcomes; the reason for these differences is unknown, and it is unclear whether PVL may serve as a virulence marker or be directly pathogenic.⁴⁹

There are several limitations to our study. The small sample size, retrospective nature of data collection, and use of a single center limit the generalizability of our findings. Most patients in our cohort were younger than 1 year, which could also limit the generalizability of our findings. Outcome measures were objective and did not require knowledge of clinical decision-making; however, we did not attempt to determine the cause of mortality in patients who died, we did not have complete data for source control, and we cannot exclude that patients may have presented to other facilities with *S aureus* bacteremia within 60 days of the index blood culture. We did not adjust for multiple comparisons made. Molecular characterization of the strains was not available. There may be other variables associated with treatment failure that were not captured in our study, particularly because vancomycin troughs were assessed, but AUC/MIC was not. As a retrospective study, we also analyzed frozen *S aureus* isolates, which may have affected MIC interpretation for a narrow range of values, such as 0.5 to 2.0 mg/L.⁵⁰ Additionally, reduced microbiologic failure rates may be attributed to differences in prescribing practices between pediatric and adult providers. Larger, observational multicenter studies will be needed to better understand the factors associated with treatment failure in pediatric patients with *S aureus* bacteremia.

In conclusion, our study suggests that infection associated with a high-risk source may increase the chance of treatment failure in pediatric patients with *S aureus* bacteremia. Vancomycin MIC (≤ 1 or 1.5) alone was not found to be a predictor of treatment outcomes. These findings encourage the continued practice of careful clinical assessments, source control of infection foci, and treatment choice based on available susceptibility data and individual patient response rather than vancomycin MIC.

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