Relationship between Vancomycin MIC and Failure among Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia Treated with Vancomycin

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There is growing concern that vancomycin has diminished activity for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, with vancomycin MICs at the high end of the CLSI susceptibility range. Despite this growing concern, there are limited clinical data to support this notion. To better elucidate this, a retrospective cohort study was conducted among patients with MRSA bloodstream infections who were treated with vancomycin between January 2005 and May 2007. The inclusion criteria were as follows: at least 18 years old, nonneutropenic, with an MRSA culture that met the CDC criteria for bloodstream infection, had received vancomycin therapy within 48 h of the index blood culture, and survived >24 h after vancomycin administration. Failure was defined as 30-day mortality, bacteremia ≥10 days on vancomycin therapy, or a recurrence of MRSA bacteremia within 60 days of vancomycin discontinuation. Classification and regression tree (CART) analysis identified the vancomycin MIC breakpoint associated with an increased probability of failure. During the study period, 92 patients met the inclusion criteria. The vancomycin MIC breakpoint derived by CART analysis was ≥1.5 mg/liter. The 66 patients with vancomycin MICs of ≥1.5 mg/liter had a 2.4-fold increase in failure compared to patients with MICs of ≤1.0 mg/liter (36.4% and 15.4%, respectively; P = 0.049). In the Poisson regression, a vancomycin MIC of ≥1.5 mg/liter was independently associated with failure (adjusted risk ratio, 2.6; 95% confidence interval, 1.3 to 5.4; P = 0.01). These data strongly suggest that patients with MRSA bloodstream infections with vancomycin MICs of ≥1.5 mg/liter respond poorly to vancomycin. Alternative anti-MRSA therapies should be considered for these patients.

Despite its sustained in vitro microbiologic inhibitory activity, clinicians now question the continued utility of vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) infections (18, 23). Within the past 5 years, multiple reports have described MRSA strains with vancomycin MICs at the high end of the CLSI susceptibility range (MICs of 2 mg/liter) (6, 18, 22). Data suggest that vancomycin has reduced activity against MRSA infections, with vancomycin MICs at the high end of the CLSI susceptibility range (6, 11, 16, 19, 20).

At the Albany Medical Center Hospital (AMCH), a large proportion of the MRSA bloodstream isolates have vancomycin MICs at the high end of the CLSI susceptibility range. The MIC50 and MIC90 for the 76 MRSA bloodstream isolates (59 patients) obtained by using the Etest method and recovered between January 2005 and June 2006 were 1.5 and 2.0 mg/liter, respectively. To date, the relationship between vancomycin MICs and outcomes has not been explored at our institution. The primary goal of this study was to examine the relationship between vancomycin MICs and outcomes among patients with MRSA bloodstream infections treated with vancomycin. Specifically, this study sought to identify the vancomycin MIC threshold value within the CLSI susceptibility range that is associated with an increased probability of failure.

(This study was presented in part as a poster presentation at the 45th Annual Meeting of the Infectious Diseases Society of America (IDSA), San Diego, CA, October 2007.)

MATERIALS AND METHODS

Study design and population. A retrospective cohort study was conducted at the AMCH, a 631-bed, tertiary care, academic hospital located in upstate New York. All patients with MRSA bloodstream infections (4) between January 2005 and May 2007 were eligible. Patients were included in the study if they were (i) at least 18 years old, (ii) nonneutropenic (an absolute neutrophil count of ≥1,000 cells/mm3), (iii) with an MRSA culture that met the CDC criteria for bloodstream infection (4), (iv) had received vancomycin therapy within 48 h of the index blood culture collection (10), and (v) had survived ≥24 h after vancomycin administration. If a patient had more than one episode during a study period, only the first episode was considered. For patients with multiple MRSA blood cultures, the vancomycin MIC of the index bloodstream isolate was considered in the analysis.

Classification and regression tree (CART) analysis was used to identify the vancomycin MIC breakpoint among MRSA patients associated with an increased probability of treatment failure (24). With this method, the MIC that maximized the difference in treatment failure was identified, and MRSA patients were divided into the following two groups: those who had high likelihood of treatment failure and those who had low risk of experiencing treatment failure. These two groups were considered the high and low vancomycin MIC groups, respectively, for the outcome analyses.

Data. Data were extracted from patients’ medical records by a trained reviewer using a structured data instrument. Data elements included the following con-
ditions: age, sex, weight, height, medical history and comorbidity, healthcare institution exposure for greater than 72 h within 180 days of hospital admission, receipt of antibiotics in the 30 days prior to the index blood culture collection, length of hospitalization prior to collection of index blood culture, hospital unit residence at the time of index blood culture collection, creatinine clearance (CrCl) estimated by the Cockcroft-Gault formula (2) at the time of index blood culture collection, illness severity, antibiotic treatment data (date, time, dosing regimen, and duration), vancomycin concentrations (date, time, and temporal relationship to vancomycin dose), source of MRSA bloodstream infection, presence of infective endocarditis, microbiologic data, and outcome.

The presence of the following comorbid conditions was documented: diabetes mellitus, heart failure (New York Heart Association classes I to IV), chronic obstructive pulmonary disease, hepatic dysfunction, renal failure (as indicated by the necessity for dialysis), history of cerebrovascular accident, human immunodeficiency virus infection, and major surgeries (e.g., hip and knee replacement). The source of the MRSA bloodstream infection was determined from an assessment of other positive S. aureus cultures at the time of the index culture collection, and the physician’s clinical decision in the medical record. When clinical and microbiological criteria precluded determination of the source, it was considered unknown (5). The presence of infective endocarditis was also recorded (9).

Microbiologic data. All clinical MRSA isolates from blood cultures were collected at AMCH during the study period. The date and time of the MRSA cultures were recorded, as well as the time of the last MRSA blood culture and first negative blood culture. All isolates were identified as S. aureus according to standard methods (1). Initial susceptibility testing for oxacillin resistance was performed according to CLSI guidelines, using a 30-μg cefoxitin disc and Mueller-Hinton agar (1). Individual isolates were then stored in trypticase soy broth with 20% glycerol at −70°C until MIC testing was performed. No thawing or subculturing of isolates was performed between the initial storage and the MIC testing.

For patients that met the study criteria, Etest methodology was used to determine the vancomycin MIC for the index bloodstream isolate. Prior to MIC testing, each isolate was subcultured to trypticase soy agar plates supplemented with 5% sheep blood. The plates were incubated overnight (18 to 24 h) 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 min prior to vancomycin Etest strip application.

The vancomycin MIC was determined by using Etest (0.016 to 256 mg/liter) (AB Biodisk, Solna, Sweden) according to the manufacturer’s instructions. Reference strain ATCC 29213 was used for quality control. MIC testing of the index MRSA blood culture specimen, the index MRSA blood culture date was considered the first day in calculating days of bacteremia.

We did not attempt to determine if 30-day mortality was attributable to the MRSA bloodstream infection. Rather than basing microbiological failure on persistent signs and symptoms of infection, treatment was considered a microbiological failure only if the duration of bacteremia was ≥10 days and before therapy was completed, as proposed by Jenkins and colleagues (7). We believed these aforementioned definitions allowed for an objective assessment of these end points and minimized any subjective biases that may result from assessing and interpreting retrospective clinical data. We recorded the length of hospital stay after the index blood culture was collected. Lastly, the proportion of patients who were switched to an alternative anti-MRSA antibiotic (e.g., daptomycin, linezolid, or tigecycline) was calculated.

Statistical analyses. Categorical variables were compared by the Pearson χ² test or Fisher’s exact test, and continuous variables were compared by Student’s t test or the Mann-Whitney U test. Breakpoints in the distribution of continuous variables were determined by CART analysis. This analytical tool identifies breakpoints within an ordinal or continuous variable where the outcome of interest is distinctly different between the resulting groups (24). The CART technique was used to identify significant breakpoints in ordinal and continuous features (vancomycin MIC, age, weight, length of stay prior to index culture collection, baseline CrCl, and APACHE II and CDS-ID score) that were associated with an increased proportion of treatment failure. For the CART analysis, node splitting was based on the goodness of split statistic, and optimal tree selection was performed on the basis of pruning and 10-fold cross-validation. (24).

Due to the large proportion of treatment failures, Poisson regression was used to determine the independent association of the high vancomycin MIC group with failure while adjusting for potential confounding variables (14, 21). Poisson regression was used as a substitute for log-binomial regression because the log-binomial models did not converge to provide parameter estimates (14, 21). All covariates that differed between high and low vancomycin MIC groups (P < 0.2) or were associated with failure (P < 0.2) in the bivariate analysis were included at model entry in the Poisson regression model, and a stepwise approach was used to identify independent predictors of treatment failure. In all analyses, P < 0.05 was considered significant for two-tailed tests. All calculations were performed with SYSTAT for Windows (version 11.0) and SPSS version 11.5 (Chicago, IL).

RESULTS

During the study period, 105 nonneutropenic patients at least 18 years of age had MRSA bloodstream infections. Of these, 92 patients received vancomycin within 48 h of the first positive MRSA blood culture and survived >24 h after administration of vancomycin. The distribution of vancomycin MICs is displayed in Fig. 1. The majority of MICs were ≥1.5 mg/liter (n = 66). The median (interquartile range [IQR]) hospital length of stay following the index culture was 15.5 (9.0 to 32.5) days. The vancomycin MIC distribution is displayed in Fig. 1. The majority of MICs were ≥1.5 mg/liter (n = 66). The median (interquartile range [IQR]) hospital length of stay following the index culture was 15.5 (9.0 to 32.5) days.
days. A total of 28 unique patients (30.4%) suffered treatment failure; 15 patients (16.3%) died within 30 days of an index MRSA blood culture (30-day mortality), 6 patients (6.5%) had documented MRSA blood cultures for ≥10 days while on vancomycin therapy (microbiological failure), and 12 patients (13.0%) had an MRSA bloodstream recurrence within 60 days of the completion of vancomycin therapy. Of the 28 failures, 21 patients met one failure criterion, 4 met two criteria, and 1 met all three criteria. A post hoc analysis of patients with microbiological failure (n = 6) was performed, and all had persistent or worsening signs and symptoms of infection. Of the six patients with microbiologic failure, the source of the MRSA bloodstream infection was an intravenous catheter for five patients, and the intravenous catheter was removed within 4 days of the index MRSA blood culture in all cases (7, 15). Furthermore, patients with microbiological failure had a significantly longer median (IQR) hospital length of stay post-index culture collection than patients that did not experience microbiological failure (34 [30 to 72] days versus 14 [8 to 30] days, respectively; P = 0.007). Thirty-day mortality was also significantly higher among patients that had a microbiological failure than among those that did not (50% versus 14.0%; P = 0.02).

Among these 92 patients, 15 were switched to an alternative anti-MRSA agent; 10 were switched to linezolid, 4 were switched to daptomycin, and 1 was switched to tigecycline. These 15 patients received vancomycin for a median (IQR) of 9 (6 to 22) days before switching to the alternative agent. Six of the 15 patients (40.0%) that had therapy switched were treatment failures; 3 patients died within 30 days of index blood culture collection, 2 patients had had documented MRSA blood cultures for ≥10 days while on vancomycin therapy, and 4 patients had a MRSA bloodstream recurrence within 60 days of the completion of vancomycin therapy. Of these six, three patients met one failure criterion and three met two criteria.

The vancomycin MIC breakpoint derived by CART analysis to delineate the risk of overall failure was 1.5 mg/liter; 66 patients (71.7%) had vancomycin MICs of ≥1.5 mg/liter (high vancomycin MIC group) and 26 patients (28.3%) had vancomycin MICs of <1.5 mg/liter (low vancomycin MIC group). A comparison of outcomes between the high and low vancomycin MIC groups is presented in Table 1. Patients with vancomycin MICs of ≥1.5 mg/liter had over a twofold increase in failure compared to patients who had MICs of <1.5 mg/liter (36.4% and 15.4%, respectively; P = 0.049). The median hospital length of stay was longer for the high vancomycin MIC group than for the low vancomycin MIC group (21 days versus 10.5 days, respectively; P = 0.02). Although not significantly different, a greater proportion of the high vancomycin MIC group versus the low vancomycin MIC group was switched to an alternative MRSA agent (13 patients [19.7%] versus 2 patients [7.7%], respectively; P = 0.21). Of the 13 patients with vancomycin values of ≥1.5 mg/liter who switched therapies, 6 (61.5%) were failures, while the 2 patients with vancomycin MICs of <1.5 mg/liter who switched therapies were successes. A bivariate comparison of clinical characteristics between failures and successes and between the high and low vancomycin MIC groups is shown in Table 2. Using CART analysis, significant breakpoints were identified for weight, baseline CrCl, and APACHE II score; CART analysis was unable to identify significant breakpoints for the other variables. Variables that were significantly different between failure and success in the bivariate analysis were a weight of ≥112 kg, presence of infective endocarditis, hepatic dysfunction, baseline CrCl, a CrCl of ≤33 ml/min, APACHE II score, and an APACHE II score of ≥20. In the high vancomycin MIC versus low vancomycin MIC bivariate analysis, intensive care unit (ICU) residence at the time of index blood culture collection and concomitant administration of gentamicin were the only variables that were significantly different between the groups. Neither variable, however, was associated with failure. Given the overrepresentation of ICU residence for patients with vancomycin MICs of ≥1.5 mg/liter, a stratified analysis was performed to examine the relationship between vancomycin MIC and treatment failure among non-ICU patients; a stratified analysis that included only patients in the ICU could not be performed since only two patients with vancomycin MICs of ≥1.0 mg/liter were in the ICU at the time of index culture collection. Among non-ICU patients, failure was significantly higher among patients with vancomycin MICs of ≥1.5 mg/liter than among those with vancomycin MICs of ≤1.0 mg/liter (37.8% versus 12.5%; P = 0.03). These observed failure percentages are consistent with the overall failure rates for the groups, indicating that confounding or effect modification are not likely.

Vancomycin trough levels were available for 53 patients. Among these 53 patients, the median initial and primary vancomycin trough values were not significantly different between the vancomycin MIC groups and the failure and success groups. In addition, the ability to achieve a primary trough of 15 mg/liter was not associated with a higher probability of success compared to not achieving a primary trough of 15 mg/liter (76.9% versus 77.8%, respectively; P = 0.9), and this was irrespective of the vancomycin MIC group.

The Poisson regression analysis included all disparate co-variates (P < 0.2) and those associated with treatment failure (P < 0.2) in the bivariate analysis. Of these, the following were independently associated with treatment failure: a vancomycin MIC of ≥1.5 mg/liter (adjusted risk ratio [ARR], 2.6; 95% confidence interval [CI], 1.3 to 5.4; P = 0.01), APACHE II

### TABLE 1. Comparison of outcomes between high (≥1.5 mg/liter) and low (<1.5 mg/liter) vancomycin MICs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High MIC (n = 66)</th>
<th>Low MIC (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall failure</td>
<td>24 (36.4)</td>
<td>4 (15.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>12 (18.2)</td>
<td>3 (11.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Microbiologic failure</td>
<td>6 (9.1)</td>
<td>0 (0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Recurrence within 60 days</td>
<td>11 (16.7)</td>
<td>1 (3.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospital length of stay after</td>
<td>21 (9.0–43.0)</td>
<td>10.5 (9.0–16.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>culture collection, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switched to alternative antibiotic</td>
<td>13 (19.7)</td>
<td>2 (7.7)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*All data presented are no. (percent) of patients.*
TABLE 2. Bivariate comparison of baseline demographic features between the high and low vancomycin MIC groups and between treatment failures and successes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High MIC (n = 66)</th>
<th>Low MIC (n = 26)</th>
<th>P value</th>
<th>Failure (n = 28)</th>
<th>Success (n = 64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr, mean (SD)</td>
<td>59.3 (16.6)</td>
<td>60.9 (16.0)</td>
<td>0.7</td>
<td>60.5 (14.5)</td>
<td>59.4 (17.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male gender†</td>
<td>48 (72.7)</td>
<td>17 (65.4)</td>
<td>0.5</td>
<td>21 (75.0)</td>
<td>44 (68.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Wt in kg, mean (SD)</td>
<td>80.7 (23.9)</td>
<td>85.4 (26.0)</td>
<td>0.4</td>
<td>87.8 (30.1)</td>
<td>79.5 (21.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Wt of ≥112 kg†</td>
<td>7 (10.6)</td>
<td>5 (19.2)</td>
<td>0.3</td>
<td>8 (28.6)</td>
<td>6 (9.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ht in inches, mean (SD)</td>
<td>66.3 (4.3)</td>
<td>66.7 (3.3)</td>
<td>0.6</td>
<td>66.1 (4.7)</td>
<td>66.6 (3.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Healthcare institution exposure</td>
<td>45 (68.2)</td>
<td>17 (65.4)</td>
<td>0.9</td>
<td>22 (78.6)</td>
<td>40 (62.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>History of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (45.5)</td>
<td>10 (38.5)</td>
<td>0.5</td>
<td>13 (46.4)</td>
<td>27 (42.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21 (31.8)</td>
<td>6 (23.1)</td>
<td>0.4</td>
<td>9 (32.1)</td>
<td>18 (28.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (25.8)</td>
<td>6 (23.1)</td>
<td>0.8</td>
<td>7 (25.0)</td>
<td>16 (25.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dialysis</td>
<td>15 (22.7)</td>
<td>8 (30.8)</td>
<td>0.4</td>
<td>12 (42.9)</td>
<td>11 (17.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>3 (4.5)</td>
<td>2 (7.7)</td>
<td>0.5</td>
<td>4 (14.3)</td>
<td>1 (1.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Decubitus ulcers</td>
<td>15 (22.7)</td>
<td>2 (7.7)</td>
<td>0.14</td>
<td>6 (21.4)</td>
<td>11 (17.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>14 (21.2)</td>
<td>6 (23.1)</td>
<td>0.8</td>
<td>7 (25.0)</td>
<td>13 (20.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>HIV</td>
<td>2 (3.0)</td>
<td>3 (11.5)</td>
<td>0.14</td>
<td>1 (3.6)</td>
<td>4 (6.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>6 (9.1)</td>
<td>3 (11.5)</td>
<td>0.7</td>
<td>2 (7.1)</td>
<td>7 (10.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Surgery in previous 30 days†</td>
<td>16 (24.2)</td>
<td>9 (34.6)</td>
<td>0.3</td>
<td>9 (32.1)</td>
<td>16 (25.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Antibiotics in previous 30 days†</td>
<td>34 (51.5)</td>
<td>18 (69.2)</td>
<td>0.12</td>
<td>19 (67.9)</td>
<td>35 (54.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Length of stay in days prior to index culture collection, median (IQR)</td>
<td>2.5 (0–15)</td>
<td>0 (0–6)</td>
<td>0.08</td>
<td>1 (0–21.5)</td>
<td>0 (0–12.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>ICU at onset†</td>
<td>21 (31.8)</td>
<td>2 (7.7)</td>
<td>0.02</td>
<td>8 (28.6)</td>
<td>15 (23.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline CrCl in ml/min, median (IQR)</td>
<td>56.3 (28.8–78.3)</td>
<td>39.6 (16.3–67.8)</td>
<td>0.15</td>
<td>31.9 (11.4–67.1)</td>
<td>55.5 (30.5–81.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>CrCl of ≤33 ml/min†</td>
<td>19 (28.8)</td>
<td>12 (46.2)</td>
<td>0.1</td>
<td>15 (53.6)</td>
<td>16 (25.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>14.2 (6.6)</td>
<td>13.8 (6.0)</td>
<td>0.8</td>
<td>18.3 (6.5)</td>
<td>12.2 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II score of ≥20†</td>
<td>11 (16.7)</td>
<td>4 (15.4)</td>
<td>0.9</td>
<td>11 (39.3)</td>
<td>4 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDS-ID score at admission, mean (SD)</td>
<td>3.5 (2.1)</td>
<td>3.7 (2.7)</td>
<td>0.7</td>
<td>3.8 (2.0)</td>
<td>3.4 (2.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Source of bacteremia†</td>
<td></td>
<td></td>
<td>0.6</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>36 (54.5)</td>
<td>12 (46.2)</td>
<td>15 (53.6)</td>
<td>33 (51.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and soft tissue/bone</td>
<td>10 (15.2)</td>
<td>5 (19.2)</td>
<td>3 (10.7)</td>
<td>12 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>3 (4.5)</td>
<td>3 (11.5)</td>
<td>2 (7.1)</td>
<td>4 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>6 (9.1)</td>
<td>2 (7.7)</td>
<td>4 (14.3)</td>
<td>4 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>4 (6.1)</td>
<td>1 (3.8)</td>
<td>0 (0)</td>
<td>5 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected graft/device</td>
<td>5 (7.6)</td>
<td>0 (0)</td>
<td>1 (3.6)</td>
<td>4 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3.0)</td>
<td>3 (11.5)</td>
<td>3 (10.7)</td>
<td>2 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>7 (10.6)</td>
<td>2 (7.7)</td>
<td>1.0</td>
<td>6 (21.4)</td>
<td>3 (4.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vancomycin trough within 72 h of therapy initiation, median (IQR) (mg/liter)</td>
<td>10.5 (8.9–15.6)</td>
<td>9.2 (6.2–13.4)</td>
<td>0.1</td>
<td>11.9 (9.8–17.2)</td>
<td>10.0 (6.3–13.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Vancomycin trough concn &gt;72 h of therapy initiation, median (IQR) (mg/liter)</td>
<td>14.1 (11.0–19.5)</td>
<td>16.75 (12.1–23.2)</td>
<td>0.4</td>
<td>15.1 (10.0–20.2)</td>
<td>14.3 (11.4–19.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Concomitant antibiotics administered &gt;48 h†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>9 (13.6)</td>
<td>0 (0)</td>
<td>0.06</td>
<td>2 (7.1)</td>
<td>7 (10.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Linezolid</td>
<td>4 (6.1)</td>
<td>0 (0)</td>
<td>0.6</td>
<td>3 (10.7)</td>
<td>4 (6.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Macrolide</td>
<td>2 (3.0)</td>
<td>1 (3.8)</td>
<td>0.8</td>
<td>1 (3.6)</td>
<td>2 (3.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Rifampin</td>
<td>11 (16.7)</td>
<td>3 (11.5)</td>
<td>0.6</td>
<td>4 (14.3)</td>
<td>10 (15.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>4 (6.1)</td>
<td>3 (11.5)</td>
<td>0.4</td>
<td>0 (0)</td>
<td>7 (10.9)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

† All data are no. (percent) of patients. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; TMP-SMX, trimethoprim-sulfamethoxazole.
score (ARR, 1.1; 95% CI, 1.05 to 1.1; P < 0.001), presence of infective endocarditis (ARR, 2.5; 95% CI, 1.6 to 4.1; P < 0.001), and a weight of ≥112 kg (ARR, 2.5; 95% CI, 1.4 to 4.3; P = 0.001). In a second Poisson regression analysis in which the APACHE II score of ≥20 was substituted for the APACHE II score at model entry, the following were independently associated with treatment failure: a vancomycin MIC of ≥1.5 mg/liter (ARR, 2.5; 95% CI, 1.2 to 5.2; P = 0.01), an APACHE II score of ≥20 (ARR, 2.8; 95% CI, 1.6 to 5.0; P = 0.001), presence of infective endocarditis (ARR, 3.0; 95% CI, 1.7 to 5.5; P < 0.001), and a weight of ≥112 kg (ARR, 2.6; 95% CI, 1.4 to 4.6; P = 0.001).

**DISCUSSION**

To date, published data that have examined the relationship between vancomycin MICs and the outcomes of MRSA infections have been limited to the following studies: two post hoc examinations of MRSA infections from participants in a larger multicenter, phase III and IV prospective studies (16, 19), a retrospective examination of dialysis patients with MRSA bloodstream infections (11), a retrospective cohort study of patients with a mixed group of MRSA infections (6), and an observational cohort study of patients with MRSA bloodstream infections (20). We are aware of only one published study that specifically examined the relationship between vancomycin MICs and treatment outcomes among MRSA bactremic patients treated appropriately with vancomycin, and the only outcome evaluated in this study was mortality (20).

CART analysis determined that patients with vancomycin MICs of ≥1.5 mg/liter had significantly higher failure rates than those with vancomycin MICs of <1.5 mg/liter. It is unlikely that this observed relationship is due simply to a confounded effect. The vancomycin MIC groups were highly comparable at the baseline. The only variable that differed between vancomycin MIC groups at a P value of ≤0.2 and that was predictive of failure was a baseline CrCl of ≤33 ml/min, which was more pronounced in the low vancomycin MIC group. Our results persisted despite this potential bias toward the null hypothesis. The Poisson regression analysis that controlled for potential confounding variables confirmed that a high vancomycin MIC was a robust predictor of failure. A twofold increase in median hospital length of stay postcollection of index blood culture was observed among high vancomycin MIC patients. Patients in the high vancomycin MIC group were also more likely to be switched to an alternative agent. In addition, there was a higher use of concomitant therapies (e.g., gentamicin, linezolid, etc.) for the group with vancomycin MICs of ≥1.5 mg/liter than for the group with vancomycin MICs of ≤1.0 mg/liter. While causality cannot be established because of the nature of the study design, switching therapy or adding therapies is typically indicative of treatment failure. Collectively, these data strongly suggest that MRSA bloodstream infections with higher vancomycin MICs (≥1.5 mg/liter) do not respond as well to vancomycin as MRSA bloodstream infections with low vancomycin MICs (<1.5 mg/liter).

Our results are generally consistent with three recent studies that evaluated the relationship between vancomycin MICs and outcomes among patients with MRSA infections. The 27% difference in success rates between the vancomycin MIC groups observed in our study is comparable to the 23% difference observed in the study by Hidayat et al. (6), the 25% difference in the study by Moise-Broder et al. (16), and the 45% difference in the study by Sakoulas et al. (19). The more-dramatic difference in success rates in the last study is most likely a function of differences between study populations. We examined all patients treated with vancomycin for MRSA bloodstream infections at our institution, while Sakoulas and colleagues examined MRSA bactremic patients from vancomycin refractory compassionate use studies (19). The majority of these patients had unsatisfactory responses to vancomycin. Another interesting similarity noted between our study and that of Hidayat et al. (6) was the observed relationship between the vancomycin trough and the outcome. In both studies, achieving a vancomycin trough in excess of 15 mg/liter did not improve success rates. Similar to the observations in a study of MRSA bactremic dialysis patients by Maclayton et al. (11), our observations revealed a 1.6-fold increase in mortality and a doubling of morbidity. For morbidity, we observed a twofold increase in length of stay in the hospital postcollection of index blood culture, while Maclayton et al. noted a 1.8-fold increase in mean hospitalization cost (11). Lastly, mortality associated with MRSA bactremia was significantly higher when vancomycin was used empirically for the treatment of infection with strains with a high vancomycin MIC (>1 mg/liter) in the study by Soriano and colleagues, and this is consistent with our findings (20).

The first limitation of our study is that MRSA blood culture data were collected from a single site; institutional differences in prescribing patterns, antibiotic formularies, and patient populations may affect the applicability of these results to other institutions. Second, our study excluded neutropenic patients; therefore, the results may not be generalizable to this patient group. Third, caution should be exercised in interpreting the P values shown in Table 2, given the large number of bivariate tests performed and hence the high likelihood that one or more of the “significant” results are false positive. Finally, since most strains in our institution had an MIC of 1.5 mg/liter, additional molecular studies are needed to determine if one clone or several clones are driving the observed results between vancomycin MIC and treatment failure at our institution.

In conclusion, our analyses strongly suggest that MRSA bloodstream infections with higher vancomycin MICs (≥1.5 mg/liter) have a higher likelihood of treatment failure. These patients had a longer duration of bacteremia, a higher likelihood of recurrence, and a longer hospital length of stay. Higher vancomycin troughs of ≥15 mg/liter were not found to improve success rates. Based on our findings, we believe that nonvancomycin anti-MRSA therapies should be considered for patients with MRSA bloodstream infections with vancomycin MICs of ≥1.5 mg/liter and that the CLSI and FDA vancomycin susceptibility breakpoint for MRSA bloodstream infections should be lowered from ≥2.0 mg/liter to ≤1.0 mg/liter. Currently, daptomycin is the only drug approved by the FDA for MRSA bloodstream infections. However, it was found to be noninferior to vancomycin for *S. aureus* bacteremia and infective endocarditis in its phase III clinical study (3). Data are needed solely to determine if daptomycin or any other alternative antibiotic can remedy the outcomes observed with
vancomycin for MRSA bloodstream infections with vancomycin MICs of ≥1.5 mg/liter. In addition, further studies are needed to determine if optimization of vancomycin therapy can improve outcomes without subjecting patients to an increased risk of vancomycin-related toxicities.

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