## Title

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# Vancomycin MIC Does Not Predict 90-Day Mortality, Readmission, or Recurrence in a Prospective Cohort of Adults with *Staphylococcus aureus* Bacteremia

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***Staphylococcus aureus*** **bacteremia (SAB) is a tremendous health burden. Previous studies examining the association of vancomycin MIC and outcomes in patients with SAB have been inconclusive. This study evaluated the association between vancomycin MICs and 30- or 90-day mortality in individuals with SAB. This was a prospective cohort study of adults presenting from 2008 to 2013 with a first episode of SAB. Subjects were identified by an infection surveillance system. The main predictor was vancomycin MIC by MicroScan. The primary outcomes were death at 30 and 90 days, and secondary outcomes included recurrence, readmission, or a composite of death, recurrence, and readmission at 30 and 90 days. Covariates included methicillin susceptibility, demographics, illness severity, comorbidities, infectious source, and antibiotic use. Cox proportional-hazards models with propensity score adjustment were used to estimate 30- and 90-day outcomes. Of 429 unique first episodes of SAB, 11 were excluded, leaving 418 individuals for analysis. Eighty-three (19.9%) participants had a vancomycin MIC of 2 μg/ml. In the propensity-adjusted Cox model, a vancomycin MIC of 2 μg/ml compared to <2 μg/ml was not associated with a greater hazard of mortality or composite outcome of mortality, readmission, and recurrence at either 30 days (hazard ratios [HRs] of 0.86 [95% confidence interval {CI}, 0.41, 1.80] [*P* = 0.70] and 0.94 [95% CI, 0.55, 1.58] [*P* = 0.80], respectively) or 90 days (HRs of 0.91 [95% CI, 0.49, 1.69] [*P* = 0.77] and 0.69 [95% CI, 0.46, 1.04] [*P* = 0.08], respectively) after SAB diagnosis. In a prospective cohort of patients with SAB, vancomycin MIC was not associated with 30- or 90-day mortality or a composite of mortality, disease recurrence, or hospital readmission.**

*Staphylococcus aureus* is a leading cause of bacteremia (1, 2). Even when an individual is appropriately treated, the risk of mortality from *S. aureus* bacteremia (SAB) is 20 to 40% per episode (3–8). Furthermore, the morbidity from SAB is striking, with 10 to 15% of episodes being complicated by endocarditis or a risk of metastatic disease elsewhere in the body (9, 10). The financial consequences of SAB are also significant, with health care costs ranging from $12,078 to $25,573 per episode of SAB (11–13). Typically, SAB is treated with narrow-spectrum beta-lactam antibiotics for methicillin-susceptible *S. aureus* (MSSA) isolates and the glycopeptide antibiotic vancomycin for methicillin-resistant *S. aureus* (MRSA) isolates (14–17). Isolates with vancomycin MICs of ≤2 μg/ml are considered susceptible, those with MICs of 4 to 8 μg/ml are considered intermediately resistant, and those with MICs of >8 μg/ml are designated resistant (18). The question of whether infection by *S. aureus* strains with vancomycin MICs of 2 μg/ml is associated with worse outcomes has been a topic of much research, although a consensus has not been reached. Compared with research methods such as Epsilometer testing (Etest) or broth microdilution (BMD), automated MIC measurements can be off by 1 dilution in either direction (e.g., a value of 2 μg/ml could mean 1 or 4 μg/ml if repeated) (19, 20), which adds to the deliberation over interpreting study results, although consistency between BMD and Etest results can also vary. In addition, most studies have focused on MRSA, but the role of vancomycin MIC in MSSA infection has not been fully evaluated. A number of studies, including systematic reviews and meta-analyses, have demonstrated increased mortality in the setting of SAB with vancomycin MICs of ≥2.0 μg/ml (21–28). Conversely, others have shown an increased risk of mortality in individuals with MICs of <2.0 μg/ml (29–32). In spite of these data, the majority of studies have failed to show any significant increase in the risk of mortality attributable to vancomycin MIC (5, 26, 33–55). A recent rigorous meta-analysis failed to demonstrate increased 30-day or in-hospital mortality attributable to vancomycin MIC, irrespective of the MIC cutoff that was chosen (1.5, 2.0, 4.0, or 8.0 μg/ml) (5). Although valuable, meta-analyses are lim-

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ited by the shortcomings of the studies that they include for analysis (56).

In general, studies have been limited by small sample sizes, few outcome events with a high probability of type II errors, failure to have uniform or systematically controlled infectious diseases (ID) consultation, and failure to consider differential antibiotic treatment. Such failures may result in confounding or mediation of the relationship between MIC and outcome, particularly when a higher MIC may lead to the differential use of antibiotics or ID consultation; the latter has been shown to improve outcomes, including mortality, in patients with SAB who receive such consultation (57–59, 76). Another limitation may be considering only inpatient mortality but not longer-term mortality. This is particularly important for individuals who have complicated disease associated with higher rates of mortality or recurrence but who also require longer courses of antibiotic therapy. Also, although potentially more scientifically accurate, several of these studies assessed vancomycin MICs with assays that are rarely used in routine clinical practice, which limits the generalizability of findings from such studies (15, 20, 57–64). Finally, understanding how treatment failure affects outcomes other than mortality, including readmission or SAB recurrence is of interest and should also be considered. In this prospective cohort study of adult patients with SAB, we sought to address previous methodological limitations while determining whether the vancomycin MIC affects clinical outcomes, including death, readmission, or recurrence of disease as well as a composite of all three outcomes at both 30 and 90 days.

(This work was presented in part at IDWeek 2014, Philadelphia, PA, 7 to 11 October 2014.)

## MATERIALS AND METHODS

**Population and study design.** This was a prospective cohort study of every patient ≥18 years of age with a blood culture drawn at San Francisco General Hospital (SFGH) from 1 January 2008 through 1 June 2013 that grew *S. aureus* in at least one bottle. Only participants with a first episode of SAB at SFGH were included. SFGH is a 270-bed academic urban safety net hospital and the only level 1 trauma center serving San Francisco County, with a racially, ethnically, and socioeconomically diverse patient population. Since 1 January 2008, the ID Division at SFGH has maintained a comprehensive SAB surveillance system that prospectively monitors all individuals with SAB. SFGH policy during this time mandated compulsory ID service consultation for all episodes of SAB. Comprehensive clinical information is available for each participant, including demographic, microbiological, treatment, and outcome data. All baseline data for the study were collected at the time of blood culture positivity; follow-up information regarding outcomes was collected subsequently over time. This study was approved by the University of California, San Francisco, Committee on Human Research (CHR) (approval number 13-11790) and was considered exempt from informed consent, as all data had been initially gathered as part of a hospital surveillance process, and minimal risk was presented to the participants at the actual time of the study. Prisoners could have been included, as data were initially collected as part of the hospital surveillance system, but study personnel were blind to any incarceration status of participants.

**Measurements. (i) Blood culturing.** Blood cultures were collected in aerobic and anaerobic blood culture bottles (containing tryptic soy broth with charcoal) and incubated with the BacT/Alert system (bioMérieux, Marcy-l'Étoile, France) for colorimetric identification of bacterial growth.

**(ii) MIC determination.** Vancomycin MICs were determined by using the MicroScan WalkAway system (Dade Behring, Deerfield, IL). Twenty-four MRSA isolates did not have MIC data available, but 17 of them had been stored for research purposes, and their MICs were determined by MicroScan. Of these 17 MIC values, 6 were randomly chosen and confirmed by Etest. The remaining seven MRSA isolates were excluded because MIC values were not known.

**(iii) Data recording.** A list of individuals with SAB is generated from microbiology databases each nonholiday weekday at SFGH. This list was conveyed to the inpatient ID team to collect specific clinical and demographical information for each patient with structured data collection forms. The data were entered into Microsoft Access (Microsoft Corp., Redmond, WA) by surveillance staff, and additional information regarding microbiological characteristics, clinical complications, treatment provided, and clinical outcome was added over time. Details regarding antibiotic treatment and duration were collected from pharmacy databases by an infectious diseases pharmacist (D.D.). Data was retrospectively confirmed for each participant by study personnel via manual chart review of the electronic health record (EHR).

**Explanatory variables. (i) Model covariates.** The primary explanatory variable of interest was vancomycin MIC (classified as <2 μg/ml or 2 μg/ml). For covariates, given the large number of variables that we evaluated, we considered only those variables in models that could be true confounders (that is, related to both exposure and outcome without being caused by exposure). Therefore, we did not consider mediators on the causal path between MIC and outcome, such as severity-of-illness scores, and we did not consider time until the first effective antibiotic given, which would affect the outcome but not clearly affect the MIC. The following covariates were included in all regression modeling given *a priori* interest: methicillin resistance, self-reported race, age in years, biological sex, Charlson comorbidity index as measured by comorbidities known to be present at the time of hospitalization (65), and hospital onset of infection (≥48 h after admission). Additional covariates were considered during forward stepwise model building in Cox regression models with and without propensity score adjustment, including immunosuppressed state, *S. aureus* infection or long-term-care facility admission in the prior 12 months, antistaphylococcal antibacterial exposure (vancomycin, daptomycin, linezolid, cefazolin, and nafcillin), hospital length of stay at diagnosis, and additional antibiotic treatment with agents active against *S. aureus* (aminoglycosides, carbapenems, cephalosporins, aminopenicillins, penicillin, and oral agents). Regarding source of infection, this was determined by the treating infectious diseases consultation team at the time of patient diagnosis.

**(ii) Antibiotic treatment.** Antibiotic treatment regimens were initially obtained by extraction of pharmacy data. Subsequently, the antibiotic course was confirmed and defined through individual manual review of inpatient medical records (including medication administration records), outpatient dialysis records, and discharge pharmacy data and review of records from hospitals to where patients were transferred when possible. SFGH has an in-hospital subacute nursing facility, an affiliated off-site long-term-care facility, and an outpatient infusion center. Records from these facilities, including antibiotic administration records, were reviewed. Controlling for antibiotic treatment was specific to MSSA and MRSA; that is, MSSA-active agents were considered for MSSA infections, and the same was true for MRSA (e.g., vancomycin could be considered for both settings if used, but the antibiotic courses also considered all other agents potentially used for a given isolate).

**Outcomes.** The primary outcome was 30- or 90-day mortality. To minimize loss to follow-up, mortality was determined as follows: manual chart review (including surrounding hospital systems where possible), extraction of SFGH EHR mortality data, query of publicly available internet death records, query of the Centers for Disease Control and Prevention National Death Index (through 2012), and query of the Social Security Administration Master Death File (through 2013). Readmission to SFGH or recurrence of SAB at SFGH was determined by chart review or electronic microbiology database review, respectively. Regarding recurrence of infection, this included both recurrence of disease (that is, clearance of bacteremia for some time, followed by recurrent infection attributed to an uncontrolled primary source) as well as repeat infection (that is, clearance of bacteremia and primary source control, followed by a second

infection due to reestablishment of a new primary source, in either the same location as before or a different location).

**Data analysis. (i) Univariate analysis.** Baseline variables were compared between individuals with *S. aureus* vancomycin MICs of <2 μg/ml and those with MICs of 2 μg/ml. Continuous variables were compared by using two-tailed *t* tests, and categorical variables were compared by using two-sided Fisher's exact test.

**(ii) Multivariate modeling.** We estimated the propensity to have an MIC of 2 μg/ml by using a logistic model including the following baseline covariates: age, 5-category race/ethnicity, Charlson comorbidity index, and hospital onset of infection. These covariates were not considered in models that included propensity adjustment. Survival analysis with Cox proportional-hazards models was used to estimate the effect of the MIC group on the hazard ratio (HR) of study outcomes of interest within 30 and 90 days. These models adjusted for quintiles of the propensity score as well as time-dependent covariates, including whether a patient was hospitalized and antibiotic treatment over time. To control for antibiotic exposures over time, we included all start and stop transitions as well as the simultaneous use of multiple antistaphylococcal agents. This accounted for appropriateness of treatment and duration of treatment on the individual level. The relatively low proportion of outcomes limited the number of covariates that could be safely included in models; accordingly, the time-dependent covariates were selected from an *a priori* list by using iterative forward selection with the inclusion criterion of a *P* value of <0.2. Because the time-dependent postbaseline covariates were potentially affected by MIC and in turn could affect the outcomes, the fully adjusted estimates are interpretable as the effect of MIC on the outcomes, independent of the duration of hospital stay and antibiotic treatment. The proportionality assumption of each Cox regression model was assessed by using the Therneau-Grambsch test for nonzero slope (66). For model covariates, an α value of 0.05 was considered statistically significant. Linearity assumptions were checked for all models. All data analyses were performed by using Stata (version 13; StataCorp LP, College Station, TX).

## RESULTS

There were 429 individuals with first episodes of SAB from January 2008 to June 2013. Of these 429 individuals, 7 did not have MIC data, and 4 did not have complete antibiotic data (1 was transferred to another hospital before antibiotics were given, and 3 did not have data recorded), and therefore, they were excluded, leaving 418 individuals for inclusion in the study. Table 1 summarizes the baseline characteristics of the 418 patients in the study, stratified by vancomycin MIC (MIC either less than or equal to 2 μg/ml). There were no patients with a first presentation of SAB caused by isolates with a vancomycin MIC of >2 μg/ml during the study period. In total, 335 of 418 (80.1%) individuals had a vancomycin MIC of <2 μg/ml, and 83 of 418 (19.9%) individuals had a vancomycin MIC of 2 μg/ml. Of the 335 individuals with a vancomycin MIC of <2 μg/ml, 36 (10.7%) isolates had vancomycin MICs of <0.5 μg/ml, and 299 (89.3%) isolates had vancomycin MICs of 1.0 μg/ml. Notably, the group with MICs of <2 μg/ml had fewer cirrhotics ($P = 0.04$) and fewer individuals with in-hospital case onset ($P = 0.004$) than the group with MICs of 2 μg/ml. No other differences between the two groups were noted. Table 2 provides the presumed source of bloodstream infection in patients with SAB stratified by vancomycin MIC status. Presumed sources of infection were similar between groups ($\chi^2 = 8.8$; $P = 0.79$).

Overall, the proportion of individuals who died at 30 days was 46/418 (11.0%), and the proportion of those who died at 90 days was 65/418 (15.6%). At 30 days, there was 1 (0.2%) case of recurrent SAB, and at 90 days, there were 10 (2.4%) recurrence events. At 30 days, there were 47/418 readmissions (11.2%), and at 90 days, there were 125/418 (30.0%) readmissions. Finally, after diagnosis of SAB, 93 individuals (22.2%) had at least one composite event in the first 30 days, and 182 individuals (43.5%) had at least one composite event in the first 90 days. Results from modeling for 30-day outcomes are shown in Table 3. There are no clear effects or statistically significant associations between vancomycin MIC and all-cause readmission, all-cause mortality, recurrence of SAB, or a composite of all three outcomes (all $P > 0.60$). The HRs for all of the Cox regression models, irrespective of adjustment, were not consistently in one direction or another to suggest an effect. For 90-day outcomes, the results are presented in Table 4. Although there are no statistically significant associations noted, the HRs for readmission and the composite outcome were far below 1, ranging from 0.60 to 0.75. No statistically significant reduction in mortality with MICs of 2 μg/ml compared to <2 μg/ml was noted, irrespective of adjustment for covariates, including propensity score ($P = 0.05$ to 0.15). No analyses were conducted for recurrent events due to there being too few outcomes at both 30 and 90 days. In the setting of the final multivariable Cox regression models, we explored the possibility of a statistical interaction between vancomycin MIC and duration of vancomycin use. For the 30-day and 90-day composite outcomes, there was no evidence of an interaction between vancomycin MIC and duration of vancomycin use ($P = 0.57$ and $P = 0.14$, respectively). The proportionality assumption of each adjusted Cox regression model was globally met by the Therneau-Grambsch test for a nonzero slope. In order to understand whether those individuals without any outcomes at 30 or 90 days were still alive and to some extent whether they did not have a recurrence or readmission at an outside facility, we performed a chart review for a random sample of 10% of those individuals who had none of the three possible outcomes at 90 days (418 − 182 with outcome = 236 individuals × 0.1 = random sample of 24 individuals). Of the 24 individuals who were randomly sampled, 23/24 (96%) of them at 30 days and 21/24 (87.5%) of them at 90 days were either still being monitored inpatient, had a follow-up appointment, or had some other documented contact with the SFGH system. None of these patients had outcomes that were not otherwise detected. This supports the fact that there was likely a limited selection bias due to differential loss to follow-up with respect to outcome.

Finally, we performed a subgroup analysis looking at all eight outcomes (all-cause readmission, recurrence of bacteremia, all-cause mortality, and composite of all three of these outcomes, for both 30 and 90 days from diagnosis) in the MRSA and MSSA subgroups separately. The results of these analyses are provided in Tables S1 (30-day results) and S2 (90-day results) in the supplemental material. These results were not substantially different from the results for the full cohort.

## DISCUSSION

*S. aureus* bacteremia continues to be associated with high mortality rates, and although a number of factors have been found to contribute to the risk of complicated infection and death (9), our data show that vancomycin MIC does not predict mortality or the composite outcome of mortality, recurrence of SAB, or hospital readmission at 30 or 90 days after initial diagnosis. For the 30-day outcomes, the lack of a vancomycin MIC effect was consistent across Cox regression models, with and without adjustment and also with and without the inclusion of propensity score adjustment, irrespective of the specific outcome of interest. For 90-day

**TABLE 1** Baseline characteristics of 418 patients with *Staphylococcus aureus* bacteremia stratified by the vancomycin MIC status (MIC of <2 μg/ml versus MIC of 2 μg/ml) of the isolate[a]

| Variable | Value for group | | *P* value |
|---|---|---|---|
| | MIC < 2 μg/ml (*n* = 335) | MIC = 2 μg/ml (*n* = 83) | |
| Mean age (yr) (SD) | 51.5 (14.7) | 54.2 (14.0) | 0.14 |
| No. (%) of patients of race/ethnicity | | | 0.73 |
| White | 134 (40.0) | 40 (48.2) | |
| African American | 81 (24.2) | 19 (22.9) | |
| Latino | 55 (16.4) | 9 (10.8) | |
| Asian/Pacific Islander | 49 (14.6) | 21 (25.3) | |
| Other[b] | 16 (4.8) | 3 (3.6) | |
| No. (%) of male patients | 242 (72.2) | 58 (69.9) | 0.68 |
| No. (%) of patients on hemodialysis | 210 (62.7) | 55 (66.3) | 0.61 |
| No. (%) of patients with alcoholism | 66 (19.7) | 20 (24.1) | 0.37 |
| No. (%) of immunosuppressed patients[c] | 16 (4.8) | 5 (6.0) | 0.58 |
| No. (%) of patients with cirrhosis | 29 (8.7) | 14 (16.9) | 0.04 |
| No. (%) of patients with diabetes mellitus | 87 (26.0) | 23 (27.7) | 0.78 |
| No. (%) of patients with active cancer | 18 (5.4) | 3 (3.6) | 0.78 |
| No. (%) of HIV-positive patients | 52 (15.5) | 13 (15.7) | 1.00 |
| Mean no. of CD4 cells/μl (SD) | 219 (264) | 202 (198) | 0.83 |
| No. (%) of homeless patients | 78 (23.3) | 17 (20.5) | 0.66 |
| No. (%) of patients with injection drug use | 88 (26.3) | 19 (21.7) | 0.58 |
| No. (%) of patients with prosthetic, including valvular | 17 (5.1) | 5 (6.0) | 0.49 |
| No. (%) of patients hospitalized in previous 12 mo | 127 (37.9) | 28 (33.7) | 0.53 |
| No. (%) of patients with *S. aureus* infection in previous 12 mo | 26 (7.8) | 4 (4.8) | 0.48 |
| No. (%) of patients with recent surgical procedure | 54 (16.1) | 15 (18.1) | 0.74 |
| No. (%) of patients with recent long-term-care facility or subacute nursing facility stay | 21 (6.3) | 8 (9.6) | 0.33 |
| Mean Charlson comorbidity index (SD) | 4.5 (3.4) | 4.7 (3.2) | 0.66 |
| No. (%) of patients with SIRS criteria at time of blood culture | 234 (69.9) | 57 (68.7) | 0.89 |
| No. (%) of patients with endocarditis | 52 (15.5) | 15 (18.1) | 0.62 |
| No. (%) of patients with epidural abscess or vertebral osteomyelitis | 33 (9.8) | 9 (10.8) | 0.84 |
| No. (%) of patients with MRSA isolated | 144 (43.0) | 44 (53.0) | 0.11 |
| No. (%) of patients with source risk[d] | | | 0.59 |
| Low | 56 (16.7) | 17 (20.5) | |
| Intermediate | 236 (70.4) | 58 (69.9) | |
| High | 43 (12.8) | 8 (9.6) | |
| No. (%) of patients admitted to ICU | 73 (21.8) | 21 (25.3) | 0.56 |
| No. (%) of patients with hospital onset | 53 (15.8) | 25 (30.1) | 0.004 |
| Mean bacteremia duration (days) (SD) | 1.9 (1.9) | 1.8 (1.9) | 0.69 |
| No. (%) of patients with bacteremia duration of >3 days | 38 (11.3) | 7 (8.4) | 0.56 |
| Mean length of stay (days) (SD) | 30.9 (133.1) | 37.8 (65.6) | 0.65 |

[a] SIRS, systemic inflammatory response syndrome; ICU, intensive care unit.
[b] Includes Native Americans, unknown, or self-described other.
[c] Includes those receiving chronic steroid therapy (>30 days), chemotherapy, or immunomodulatory medications such as biologics.
[d] Low-risk sources include intravascular catheter and urinary tract infection; intermediate-risk sources include abscess (skin/soft tissue), cellulitis (skin/soft tissue), bone, joint, surgical site infection, wound, soft tissue, and unknown; and high-risk sources include community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, implanted prosthetic material, endovascular infection, abdomen infection, and patients with >1 possible source (76).

outcomes, readmission and the composite outcome showed a large reduction in hazard, consistent with a "protective" effect of an MIC of 2 μg/ml in Cox modeling, but this was not statistically significant. If this effect were true, it would likely not be clinically meaningful, as it may not impact empirical or subsequent management of SAB, given that vancomycin is often recommended for empirical therapy for all SAB and for the duration of treatment of methicillin-resistant SAB. Duration of antibiotic treatment and other covariates were considered confounders in our model, but changes in behavior as a reflection of knowledge of MIC (which may explain this protective effect) would imply that such variables were actually mediators. By controlling for these covariates in the model as confounders, we isolated the specific effect of MIC on outcome independent of mediator pathways, which was our primary analytic goal. We analyzed the data in a number of different ways in order to first compare the results of our study to the results of other studies in the literature and then understand potential confounding attributable to differential antibiotic exposure or

**TABLE 2** Presumed source of infection in 418 patients with *Staphylococcus aureus* bacteremia by vancomycin MIC status (MIC of <2 μg/ml versus MIC of 2 μg/ml)

| Source | No. (%) of patients with source of infection | |
|---|---|---|
| | Vancomycin MIC < 2 μg/ml ($n$ = 335) | Vancomycin MIC = 2 μg/ml ($n$ = 83) |
| Community-acquired pneumonia | 12 (3.6) | 2 (2.4) |
| Hospital-acquired pneumonia | 3 (0.9) | 0 (0) |
| Ventilator-associated pneumonia | 3 (0.9) | 0 (0) |
| Implanted prosthetic material | 14 (4.2) | 3 (3.6) |
| Intravascular catheter | 48 (14.3) | 15 (18.1) |
| Abscess | 43 (12.8) | 8 (9.6) |
| Cellulitis | 21 (6.3) | 6 (7.2) |
| Musculoskeletal, bone | 20 (6.0) | 8 (9.6) |
| Musculoskeletal, joint | 10 (3.0) | 1 (1.2) |
| Surgical site infection | 5 (1.5) | 1 (1.2) |
| Urinary tract | 8 (2.4) | 2 (2.4) |
| Wound infection | 9 (2.7) | 0 (0) |
| Unknown | 128 (38.2) | 32 (38.6) |
| Other | 11 (3.3) | 5 (6.0) |

**TABLE 3** Comparison of regression modeling for outcomes 30 days after diagnosis of *Staphylococcus aureus* bacteremia, comparing participants with MICs of <2 μg/ml to those with MICs of 2 μg/ml

| Model | HR (95% confidence interval) | $P$ value |
|---|---|---|
| Mortality, all cause ($n$ = 46) | | |
| Cox regression, unadjusted | 1.19 (0.59, 2.41) | 0.63 |
| Cox regression, adjusted[a] | 1.19 (0.55, 2.59) | 0.66 |
| Cox regression with propensity score and covariate adjustment[b] | 0.86 (0.41, 1.80) | 0.70 |
| Readmission, all cause ($n$ = 47) | | |
| Cox regression, unadjusted | 0.94 (0.45, 1.95) | 0.87 |
| Cox regression, adjusted[c] | 1.03 (0.49, 2.16) | 0.94 |
| Cox regression with propensity score and covariate adjustment[d] | 0.97 (0.46, 2.04) | 0.94 |
| Recurrence of bacteremia ($n$ = 1) | | |
| Cox regression, unadjusted | —[g] | |
| Cox regression, adjusted | — | |
| Cox regression with propensity score and covariate adjustment | — | |
| Composite ($n$ = 93) | | |
| Cox regression, unadjusted | 1.05 (0.64, 1.75) | 0.84 |
| Cox regression, adjusted[e] | 0.98 (0.58, 1.66) | 0.95 |
| Cox regression with propensity score and covariate adjustment[f] | 0.94 (0.55, 1.58) | 0.80 |

[a] Adjustment covariates included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, recent long-term-care facility stay, immunosuppressive medication, cefazolin therapy, nafcillin therapy, and advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class).
[b] Adjustment covariates included advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class) and propensity score.
[c] Adjustment covariates included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, recent long-term-care facility stay, and cefazolin therapy.
[d] Adjustment covariates included only the propensity score.
[e] Adjustment covariates included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, recent long-term-care facility stay, and advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class).
[f] Adjustment covariates included advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class), recent long-term-care facility stay, and propensity score.
[g] —, the model was not undertaken given limited events.

failure of randomization. In time-to-event models, inclusion of precise estimates of antibiotic exposure addressed confounding attributable to variability in treatment, but adjustment in general did not dramatically affect the effect size of the HR. Overall, our findings are consistent with the plurality of data that have examined this question and support the use of vancomycin in the treatment of SAB caused by *S. aureus* isolates with an MIC of 2 μg/ml. We also performed subgroup analyses stratified by methicillin susceptibility, which did not differ from the full cohort with respect to outcomes, but we interpret these results with extreme caution. The number of outcome events was proportionally lower with smaller subgroup sample sizes, the overall sample size in each subgroup was lower and potentially underpowered, and the study was not initially designed to investigate the specific question. Irrespective of a concern for diminished power in this setting, the hazard ratio still demonstrated a protective effect of an MIC of 2 μg/ml, particularly with respect to the composite outcome at 90 days for MRSA. Therefore, if a type II error did occur, the data would still show that there was not an increased risk of the outcome with an MIC of 2 μg/ml compared to an MIC of <2 μg/ml, and there was possibly a lower risk.

Our study is consistent with the findings of several previous studies which failed to show any significant increase in the risk of mortality that could be attributable to vancomycin MIC (5, 26, 33–55, 67–71) while improving upon the limitations of many of those previous studies. We showed that there is no increase in readmission or recurrence of disease attributable to vancomycin MIC as well as no increase in the composite outcome of readmission, recurrence, and mortality at both 30 and 90 days. We had a large sample size and were able to monitor individuals serially over time. We comprehensively controlled for total antibiotic exposure over time in all included patients and were able to obtain inpatient, discharge, and outpatient antibiotic prescription data over the course of the study period, which allowed the isolation of the effect of MIC on outcome independent of treatment. We also controlled for the presence of chronic illness and admission to the intensive care unit and accounted for time within the hospital. These measures were taken in order to provide an estimate of the effect of vancomycin MIC for *S. aureus* isolates on outcomes of interest in this study while minimizing bias. Understanding the true nature of the relationship between vancomycin MIC and outcomes has a number of potential impacts. These results can reassure clinicians in the antibiotic treatment of persons presenting with SAB, particularly since vancomycin is often less expensive or more readily available than alternative treatment strategies in many health care settings.

There are limitations to the interpretation of these study results. The use of a MicroScan system to determine MIC potentially underestimates or overestimates values depending on the standard to which it is compared (19, 20, 32, 60–64, 72–74), which leads to nondifferential misclassification of the exposure. Some data have suggested that assessing the risk for mortality may be predicted more accurately by nonautomated systems for determining MIC than by automated systems such as MicroScan (32). We chose to use MicroScan in this study, as this is much more

**TABLE 4** Comparison of regression modeling for outcomes 90 days after diagnosis of *Staphylococcus aureus* bacteremia, comparing participants with MICs of <2 μg/ml to those with MICs of 2 μg/ml

| Model | HR (95% confidence interval) | *P* value |
|---|---|---|
| Mortality, all cause ($n = 65$) | | |
| Cox regression, unadjusted | 1.27 (0.71, 2.27) | 0.42 |
| Cox regression, adjusted[a] | 0.95 (0.52, 1.75) | 0.87 |
| Cox regression with propensity score and covariate adjustment[b] | 0.91 (0.49, 1.69) | 0.77 |
| Readmission, all cause ($n = 125$) | | |
| Cox regression, unadjusted | 0.60 (0.36, 1.00) | 0.05 |
| Cox regression, adjusted[c] | 0.61 (0.36, 1.04) | 0.07 |
| Cox regression with propensity score and covariate adjustment[d] | 0.63 (0.37, 1.06) | 0.08 |
| Recurrence of bacteremia ($n = 10$) | | |
| Cox regression, unadjusted | —[g] | |
| Cox regression, adjusted | — | |
| Cox regression with propensity score and covariate adjustment | — | |
| Composite ($n = 182$) | | |
| Cox regression, unadjusted | 0.75 (0.50, 1.11) | 0.15 |
| Cox regression, adjusted[e] | 0.69 (0.46, 1.04) | 0.08 |
| Cox regression with propensity score and covariate adjustment[f] | 0.69 (0.46, 1.04) | 0.08 |

[a] Adjustment covariates included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class), and immunosuppressive medication.
[b] Adjustment covariates included advanced beta-lactam use (ceftaroline, cefepime, or carbapenem class), immunosuppressive medication, and propensity score.
[c] Adjustment covariates included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, cefazolin use, vancomycin use, recent long-term-care facility stay, daptomycin use, and hospital length of stay.
[d] Adjustment covariates included recent long-term-care facility stay, hospital length of stay, and propensity score.
[e] Adjustment covariates (*a priori* interest) included methicillin resistance, age, race, gender, hospital onset, Charlson comorbidity index, immunosuppressive medication, vancomycin use, recent long-term-care facility stay, and linezolid use.
[f] Adjustment covariates (stepwise modeling) included hospital length of stay, immunosuppressive medication, and propensity score.
[g] —, the model was not undertaken given limited events.

reflective of clinical practice. Few centers primarily use Etest or BMD for routine monitoring of vancomycin MIC. The Etest has been compared directly to MicroScan, with variable results, including overestimation, underestimation, and no difference in determination of MICs between the two strategies (19, 32, 72–74). Irrespective of those previous studies, any bias in this setting would be nondifferential with respect to exposure and move the effect measure more toward no difference. Also, with respect to MIC, we analyzed the data as a dichotomy (≤2 μg/ml versus 2 μg/ml) because this has been the most controversial cutoff in the literature. We did not have any isolates during the study period with vancomycin MICs of >2 μg/ml, and therefore, we cannot draw conclusions on such isolates based on the data presented here. Although we used numerous methods to control for mortality as an outcome, we were less able to determine if individuals had a recurrence of disease or readmission outside the public hospital system in the 30 or 90 days after their initial event. This would represent nondifferential outcome misclassification; however, it is unlikely to represent a large proportion of persons given the nature of the SFGH population, except for individuals who became insured or who were initially treated at SFGH for trauma but received routine care elsewhere. We also sampled the study population and found it to be very unlikely that care was sought elsewhere. This study had a very large proportion of individuals with kidney disease on hemodialysis, and so the results of this study may not be easily generalizable to individuals in all clinical situations. Further limits to generalizability may be related to the unique environment at SFGH, given that the 30- and 90-day mortality proportions are relatively lower (11.0% at 30 days and 15.6% at 90 days) than those reported by other groups, typically 20 to 40% (3–7, 9, 75). The low mortality rate may be reflective of ID consultation for each patient in the study period, a service not offered by many hospital systems, or the unique ability of SFGH to accommodate marginalized patients to complete treatment courses (as outpatients or via in-hospital subacute nursing). These resources are rarely afforded to county hospitals, where patient volume and limited financial and logistical resources make the provision of this level of patient care challenging. Similarly, institutions with patient populations with different distributions of complicated disease or sources of infection may not be easily comparable (e.g., more pneumonia and less endocarditis). Finally, we did not calculate severity-of-illness scores, as it was felt to be a mediator of the relationship between vancomycin MIC and outcome and not a confounder. This was felt to be true because at initial presentation and in the absence of prior SAB (which is the patient population of this study), severity of illness could not lead to vancomycin MIC but presumably may or may not have been affected by it. Such mediators may not be required to be included in statistical modeling, as we are already measuring the total effect between exposure and outcome.

In spite of these limitations, there were several important strengths to this study that improve on previous work addressing this specific question. First, each patient received an ID service consultation, which reduces mortality from SAB and increases adherence to guidelines for treatment (57–59, 76). Other centers may preferentially consult ID teams for patients with higher MICs, which may differentially misclassify outcomes leading to bias. Second, in order to minimize selection bias due to differential loss to follow-up in this cohort, we rigorously confirmed mortality as an outcome. Third, we precisely controlled for antibiotic treatment by manually reconstructing the temporal antibiotic exposure for each participant. Finally, we used contemporary modeling to account for a lack of randomization.

In summary, in this prospective cohort study of 418 individuals presenting with SAB, where antibiotic treatment course and length of hospital stay were comprehensively measured and loss to follow-up was rigorously minimized, the vancomycin MIC, as determined by MicroScan, was not predictive of readmission, recurrence of disease, mortality, or a composite of all three outcomes at either 30 or 90 days. Given that randomized controlled trials are not cost-effective for this clinical question and unlikely to be conducted, the methods of comparative studies should focus on accounting for biases due to loss to follow-up and a lack of randomization, as we present here.

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