CONCISE COMMUNICATION

Impact of Vancomycin Minimum Inhibitory Concentration on Mortality among Critically Ill Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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We retrospectively evaluated 99 intensive care unit patients with methicillin-resistant *Staphylococcus aureus* bacteremia to determine whether having a vancomycin minimum inhibitory concentration (MIC) of 2 mg/L affected mortality. This MIC was found in 5.1% of patients and was associated with the probability of death (adjusted odds ratio, 13.9 [95% confidence interval, 1.1–171.2]) independent of other factors.

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Multiple investigators have noted a shift in the susceptibility of MRSA to vancomycin.[1,2] The minimum inhibitory concentrations (MICs) for methicillin-resistant *Staphylococcus aureus* (MRSA) relative to vancomycin appear to have evolved, with some strains now having vancomycin MICs of 2 mg/L. The clinical significance of this "MIC creep" remains unclear, particularly for critically ill patients. Most analyses indicate that bacteremia with a MRSA strain with a vancomycin MIC of 2 mg/L correlates with worse outcome.[3-5] Other researchers have either failed to note a relationship between vancomycin MIC and survival or have paradoxically noted lower mortality among those with infections caused by strains with higher MICs.[6,7]

Many earlier studies of MIC creep and outcome have been limited. First, most have pooled data for critically ill and noncritically ill patients.[3-5] Second, severity of illness is often not sufficiently assessed. Third, multiple analyses have focused on a pooled end point of clinical failure that conflates mortality with persistent bacteremia and/or infection recurrence rather than addressing mortality alone.

Because of these concerns, we sought (1) to describe the prevalence of a vancomycin MIC of 2 mg/L among intensive care unit (ICU) patients with MRSA bacteremia and (2) to assess the association between the MIC and in-hospital mortality.

METHODS

Study Overview and Subjects

We retrospectively identified all patients admitted to any ICU (eg, cardiac, medical, surgical, and burn) at our hospital with MRSA bacteremia over a 2-year period (January 2009 through December 2010). MRSA bacteremia was considered present if at least 1 blood culture revealed growth of MRSA. We included only adult patients (age 18 years or older) admitted to the ICU for the management of their infectious syndrome or who developed MRSA bacteremia while in the ICU (eg, in the ICU either when the blood culture was obtained or within 48 hours after the blood culture was obtained). We excluded persons with a planned admission to the ICU after surgery for known MRSA endocarditis. For patients with multiple episodes of bacteremia, we only addressed the first occurrence. Our hospital institutional review board approved this study.

End Points and Susceptibility Testing

Death while hospitalized after the index MRSA bacteremia served as our primary end point. The prevalence of an MIC of 2 mg/L represented a secondary end point. Susceptibility testing was performed by an automated system (BD Phoenix Automated Microbiology System; Becton Dickinson).

Covariates and Definitions

We collected information regarding demographic characteristics, comorbid illnesses, severity of illness, and infection-related characteristics. Comorbidities included the presence of diabetes mellitus, congestive heart failure (CHF), chronic obstructive pulmonary disease, peripheral vascular disease, end-stage renal disease requiring hemodialysis, malignancy, and infection with HIV. We classified as immunosuppressed those individuals who had AIDS, who had active malignancy and were undergoing chemotherapy, and/or were treated with immunosuppressants (ie, 10 mg of prednisone or equivalent daily for at least 30 days or other immunomodulatory pharmacotherapy). For severity of illness, we calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the basis of the day on which the positive blood culture sample was drawn, and we assessed whether the patient required mechanical ventilation or was in shock. We defined shock as the need for vasopressor therapy for greater than 2 hours and further determined whether the subject met the criteria for acute lung injury/acute respiratory distress syndrome (ALI/ARDS). We categorized the bacteremia according to source (primary, other, or device related) and according to whether it was nosocomial in onset. Bacteremias identified by a blood culture obtained after the patient had

been hospitalized for more than 48 hours were classified as nosocomial. The presence of endocarditis was also noted. Endocarditis was diagnosed on the basis of the modified Duke criteria along with the presence of a valvular vegetation. The use of both transthoracic and transesophageal echocardiograpy was not protocolized. Finally, we determined whether the patient had received therapy with vancomycin within 12 hours of obtaining the initially positive blood culture. At our institution, vancomycin is the only agent readily available to clinicians for treatment of presumptive MRSA bacteremia. Thus, we classified receipt of vancomycin as indicating administration of an appropriate antibiotic.

Statistics

We conducted univariate analyses with either Fisher exact test or Student *t* test, as appropriate. All comparisons were unpaired and two tailed. We assumed that a *P* value of less than .05 represented statistical significance. To determine independent factors associated with mortality, we employed logistic regression. Variables significant at a *P* value of less than .10 in univariate analyses were entered into the model, and we used a stepwise backward elimination approach to develop the most parsimonious model. Variables were removed from the model when the probability of the likelihood ratio statistic was less than .10. For this model, all MIC values were dichotomized as either 2 mg/L or less than 2 mg/L. The 95% confidence intervals (CIs) are reported where appropriate. The model's goodness-of-fit was assessed via calculation of the R^2 value and the Hosmer-Lemeshow *c* statistic. All analyses were performed with SPSS software, version 17.0 (SPSS).

RESULTS

The final cohort included 99 patients (mean age ± standard deviation [SD], 59.7 ± 1.9 years; female sex, 45.5%), and this represented 46.0% of all MRSA bacteremias in the hospital during the study time period. The mean APACHE II score (± SD) in the population was 18.9 ± 8.3, with approximately 60% of persons meeting criteria for shock and requiring vasopressors. The crude in-hospital mortality rate equaled 35.3%. An MIC of 2 mg/L was noted in only 5 patients (5.1%).

As Table 1 shows, patients who died while hospitalized were older than those who did not. CHF was the only comorbid illness that was more prevalent in decedents than in survivors (60.0% vs 31.2%; $P = .010$). Table 1 also documents that ALI/ARDS was infrequent in the cohort and that both shock and the need for mechanical ventilation were associated with mortality. The APACHE II score was lower in those who survived, but this discordance was not statistically significant. The overall distribution of bacteremia sources was similar between the groups. Those who died were approximately 4.5 times more likely than those who survived to have received a diagnosis of endocarditis (odds ratio [95% CI], 4.52 [1.60–12.78]).

TABLE 1. Patient Characteristics

Variable	Decedents ($n = 36$)	Survivors ($n = 63$)	*P*
Demographic characteristic			
Male sex	52.8	56.2	.835
Race			
White	13.9	15.6	.984
Black	83.3	79.7	
Other	2.8	4.7	
Age >65 years	55.6	21.9	.001
Comorbidity			
DM	55.6	39.1	.144
CHF	58.3	31.2	.011
COPD	16.7	32.8	.102
ESRD	38.9	23.4	.114
PVD	22.2	18.8	.795
Malignancy	22.2	17.2	.599
HIV infection	2.8	4.7	.999
Immunosupression	16.7	28.1	.231
Severity of illness			
Shock	72.2	53.1	.088
Mechanical ventilation	75.0	53.1	.035
ALI/ARDS	2.9	3.1	.999
APACHE II, mean score ± SD	20.6 ± 7.7	18.0 ± 8.6	.126
Infection characteristic			
Source			
Primary	8.3	12.5	.227
Device related	41.7	50.0	
Other	50.0	37.5	
Nosocomial	30.6	37.5	.520
Vancomycin initiated within 24 hours of infection presentation	83.3	90.6	.342
Endocarditis	37.1	12.7	.009

NOTE. Data are percentage of patients, unless otherwise indicated. ALI, acute lung injury; APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; PVD, peripheral vascular disease; SD, standard deviation.

Mortality rates escalated as the MIC increased. Among patients with an MIC of 0.5 mg/L, there were no deaths, whereas 80.0% of persons infected with a pathogen with an MIC of 2 mg/L died. We noted a dose response relationship between increasing MIC and unadjusted mortality ($P < .001$). When examined as a binary variable (MIC either 2 mg/L or <2 mg/L), an MIC of 2 mg/L conferred a substantial increase in the risk for death (odds ratio [95% CI], 10.21 [1.11–90.74]).

The complete results of the logistic regression are displayed in Table 2. Four variables were independently associated with in-hospital mortality. Advanced age, presence of shock, and

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TABLE 2. Factors Independently Associated with Mortality

Variable	Adjusted odds ratio	95% confidence interval	*P*
Age ≥65 years	5.81	2.04–16.55	.001
Endocarditis	4.53	1.35–15.22	.014
Shock	2.98	1.01–8.84	.049
Receipt of mechanical ventilation	2.89	0.98–8.52	.055
Vancomycin MIC of 2 mg/L	13.87	1.12–171.23	.014

NOTE. MIC, minimum inhibitory concentration.

development of endocarditis represented independent factors related to death. Although the need for mechanical ventilation nearly tripled the probability of mortality, this distinction only approached statistical significance. In addition, a vancomycin MIC of 2 mg/L continued to remain associated with mortality. The adjusted odds ratio for in-hospital death was 13.87 (95% CI, 1.12–171.23). Overall, the model had good fit with an R^2 of 0.40 and a Hosmer-Lemeshow *c* statistic of $P = .70$.

DISCUSSION

Our retrospective analysis of MRSA bacteremia in critically ill patients documents that such cases are associated with high short-term mortality rates. A vancomycin MIC that equals 2 mg/L occurs infrequently. Despite the fact that an MIC of 2 mg/L, although elevated, is considered to indicate susceptibility, isolates with MICs at this level appear to be associated with a greater chance for death due to MRSA bacteremia.

Earlier reports have described a range in the prevalence of MRSA isolates with MICs of 2 mg/L. Rybak and colleagues[8] noted a substantial shift in the vancomycin MICs among MRSA isolates, and few strains had values of less than 1 mg/L.[2] Multicenter microbiology surveillance initiatives, however, have failed to detect such a shift. This inconsistency, along with our finding of a low prevalence of organisms with MICs of 2 mg/L, suggests that MIC creep may be sporadic. In addition, earlier studies have not expressly examined ICU populations, and this may also explain the discord between our results and those of others.

The relationship between an elevated MIC and mortality due to MRSA bacteremia is controversial. Our finding that an elevated MIC is linked with mortality confirms, in part, the observations of some researchers. Lodise and colleagues[3] noted that infection with an isolate with an MIC of greater than 1.5 mg/L conferred a 2.4-fold elevation in the risk for clinical failure. Soriano et al[9] examined 414 cases of MRSA bacteremia and concluded that an MIC of 2 mg/L increased the patient's risk for death substantially. On the other hand, Mutsa et al[6] reviewed nearly 500 patients with MRSA bacteremia, and despite a vancomycin MIC of 2 mg/L correlating with worse survival in univariate analysis, this relationship did not hold in multivariate analysis.

In an effort to better summarize the complicated literature, van Hal et al[10] conducted a meta-analysis that explored the relationship between the vancomycin MIC and outcome in MRSA infection. They determined that an elevated MIC remained significantly associated with mortality, irrespective of either MIC methodology or infection source. Their meta-analysis, however, pooled studies that looked at a range of infections and was not restricted to bacteremia. They also combined data from ICU patients with data from less ill subjects. More importantly, they identified confusion in the literature as to the definition of an elevated MIC, with some categorizing only MICs of 2 mg/L as elevated, whereas others placed the threshold at 1.5 mg/L.[10]

Our endeavor helps to clarify the connection between the MIC and mortality. First, by including only critically ill patients, we addressed a population at sufficiently high risk for death. Hence, the outcome measure was not prone to assessment bias. A more precise accounting of severity of illness further represents a strength of our analysis. Other studies have generally used crude markers of disease severity (eg, hospitalization in the ICU). Second, we specifically examined variables that may be important in determining outcomes and that have not been included consistently in earlier studies (eg, initial therapy).

The retrospective nature of the study exposes it to various forms of bias. We attempted to minimize these by identifying patients through a review of actual blood culture results and by having mortality serving as the primary end point. The focus on the ICU and use of data from a single center limit the generalizability of our findings. Broth microdilution represents the gold standard for determining MICs, whereas our institution relies on an automated susceptibility system. Furthermore, the search for one determinant of outcome, the presence of endocarditis, was not protocolized. We may have missed cases of endocarditis. Finally, the number of isolates with an MIC of 2 mg/L was small. As a result, the 95% CI around our estimate for the adjusted odds ratio for death is wide and may overstate the true extent, although not direction, of the relationship.

In conclusion, MRSA bacteremia leads to considerable in-hospital mortality. An elevated vancomycin MIC of MRSA independently elevates the chance for death. Although an MIC of 2 mg/L occurs infrequently, its adverse impact on mortality persists after controlling for measures of disease severity, chronic illness, and infection site.

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