MAJOR ARTICLE

Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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Background. Vancomycin treatment failure in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is not uncommon, even when MRSA is susceptible to vancomycin. The aim of our study was to evaluate whether vancomycin minimum inhibitory concentration has any influence on the mortality associated with MRSA bacteremia.

Methods. A total of 414 episodes of MRSA bacteremia were prospectively followed-up from 1991 through 2005. MIC of vancomycin for the first isolate was determined by E-test. Clinical variables recorded were age, comorbidity, prior administration of vancomycin, use of corticosteroids, prognosis of underlying disease, source of bacteremia, the need for mechanical ventilation, shock, and mortality. A "treatment group" variable was created and defined as follows: (1) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL (38 episodes), (2) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL (90 episodes), (3) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL (40 episodes), and (4) receipt of inappropriate empirical therapy (246 episodes). Univariate and multivariate analyses were performed.

Results. Episodes caused by strains with a vancomycin MIC of 2 μg/mL were independently associated with a lower risk of shock (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.15–0.75). Multivariate analysis selected receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL (OR, 6.39; 95% CI, 1.68–24.3), receipt of inappropriate empirical therapy (OR, 3.62; 95% CI, 1.20–10.9), increasing age (OR, 1.02; 95% CI, 1.00–1.04), use of corticosteroids (OR, 1.85; 95% CI, 1.04–3.29), an ultimately (OR, 10.2; 95% CI, 2.85–36.8) or rapidly (OR, 1.81; 95% CI, 1.06–3.10) fatal underlying disease, high-risk (OR, 3.60; 95% CI, 1.89–6.88) and intermediate-risk (OR, 2.18; 95% CI, 1.17–4.04) sources of bacteremia, and shock (OR, 7.38; 95% CI, 4.11–13.3) as the best predictors of mortality.

Conclusions. Mortality associated with MRSA bacteremia was significantly higher when the empirical antibiotic was inappropriate and when vancomycin was empirically used for treatment of infection with strains with a high vancomycin MIC (>1 μg/mL).

Staphylococcus aureus is a major cause of serious hospital- and community-acquired bacteremia worldwide and is associated with a high morbidity and mortality [1]. The emergence of methicillin-resistant *S. aureus* (MRSA) strains since 1961 has complicated the treatment of *S. aureus* infections, and glycopeptides (vancomycin or teicoplanin) are, in many cases, the only therapeutic alternative. In recent years, new antistaphylococcal antibiotics, such as linezolid or daptomycin, have been developed, but their cost and the absence of large clinical trials demonstrating a clear superiority over vancomycin maintains glycopeptides as a first-line option when infection due to MRSA is suspected or diagnosed [2, 3]. However, vancomycin treatment failure is not uncommon, even when MRSA strains are fully susceptible to vancomycin (MIC $\leq$2 μg/mL) [4, 5]. A reduction in the efficacy of vancomycin against MRSA strains with a high vancomycin MIC (1–2 μg/mL) has been described in observational studies with

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low number of patients [6–8], suggesting that subtle changes in the MIC may explain clinical failures. Another possible explanation for vancomycin failure when the MIC is at the limit of the susceptibility range could be the presence of heteroresistance; however, the prevalence of heteroresistance in different articles varied from 0% to >50% [9–11], making it difficult to establish the importance of heteroresistance in clinical settings.

Recent data have shown a high rate of vancomycin treatment failure when the vancomycin MIC was 4–8 μg/mL [12]; as a result, the Clinical Laboratory Standards Institute modified the breakpoint, and currently, vancomycin susceptibility is considered when the MIC is ⩽2 μg/mL [13]. However, in Spain, as in other European countries, a vancomycin MIC of 1–2 μg/mL is not uncommon [14, 15]. Therefore, it is necessary to confirm the impact of minimal changes in the vancomycin MIC on the efficacy of vancomycin to establish the most appropriate breakpoint.

Appropriate empirical antimicrobial therapy has proved to be a major prognostic factor in patients with sepsis, including those with *S. aureus* bacteremia (due to both methicillin-susceptible and methicillin–resistant strains) [1,16]. Therefore, we hypothesized that, if there would be any detrimental effect of higher vancomycin MIC values on the efficacy of this antibiotic in patients with MRSA bacteremia, then a progressive increase in the risk of mortality associated with the empirical use of vancomycin as the vancomycin susceptibility of the involved strain diminishes was likely to occur. The present study was intended to test this hypothesis in 414 episodes of MRSA bacteremia diagnosed during a 15-year period at a university hospital.

PATIENTS AND METHODS

Setting. The Hospital Clinic in Barcelona, Spain, is a 700-bed university center that provides specialized medical and surgical care and is equipped with an intensive care unit.

Microbiological methods. During the 15-year study period, blood cultures were processed by BACTEC 9240 (Becton Dickinson). Isolates were identified according to standard techniques. Methicillin and vancomycin susceptibility were determined by microdilution using Clinical Laboratory Standards Institute methods. During the study period, 478 episodes of MRSA bacteremia were recorded, and the first isolated strains from 414 episodes were stored at −80°C. In 64 cases, which were distributed across the study period, it was not possible to store the strain. During 2006, vancomycin E-test MICs were determined using a 0.5 McFarland inoculum streaked evenly with a swab onto brain heart infusion agar plates [17]. Vancomycin MICs were determined under blinded conditions without the knowledge of any clinical outcome.

Patients. The present study focuses on episodes of bacteremia due to MRSA that were diagnosed from January 1991 through December 2005 at a single center. Patients were consecutively enrolled in the study and were prospectively followed up. The following data were obtained for all patients: age, sex, preexisting comorbidities, prognosis of the underlying disease, receipt of prior vancomycin therapy, current administration of >20 mg of prednisone per day (or equivalent corticosteroid) for >30 days, origin of the infection (community-acquired, hospital-acquired, or health care–related infection), source of bacteremia, need for mechanical ventilation, presence of shock when the blood samples were obtained for culture (early shock), and mortality. A "treatment group" variable was defined that combined the empirical antibiotic treatment and the vancomycin MIC value and that included 4 categories, as follows: (1) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL (38 episodes), (2) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL (90 episodes), (3) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL (40 episodes), and (4) receipt of inappropriate empirical therapy (246 episodes).

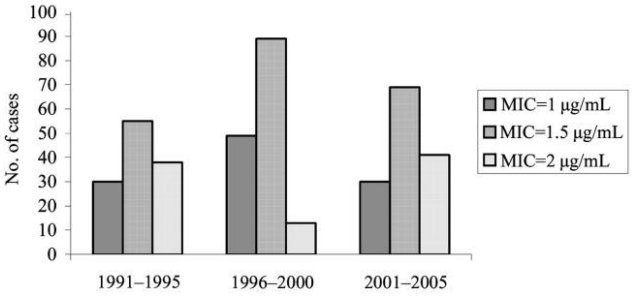

Figure 1. Number of cases of bacteremia stratified by the vancomycin MIC of the infecting strain and the study period.

Term definitions. Staphylococcal bacteremia was defined as occurring in a patient with at least 1 blood culture positive for *S. aureus* and clinical signs and symptoms of sepsis based on a previous definition [18]. Comorbidity was defined as a disease or therapy that could predispose patients to infection, alter defense mechanisms, or cause functional impairment, such as the following: diabetes, liver cirrhosis, renal failure, alcoholism (consumption of >100 g of alcohol per day), active neoplastic disease, receipt of a solid-organ or bone marrow transplant, neutropenia, severe chronic obstructive pulmonary disease, severe cardiac disease with symptomatic heart failure, HIV infection, severe dementia, and administration of immunosuppressive drugs (>20 mg of prednisone on a regular basis or antineoplastic chemotherapy). Prognosis of the underlying disease was classified, according to modification of the criteria of McCabe and Jackson [19], as rapidly fatal (when death was expected within 3 months), ultimately fatal (when death was expected within a period of >3 months but <5 years), and nonfatal (when life expectancy was >5 years). Prior van-

Table 1. Clinical and demographic characteristics of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia, by vancomycin MIC for the infecting strain.

Characteristic	MIC			*P*
	1 μg/mL (n = 109)	1.5 μg/mL (n = 213)	2 μg/mL (n = 92)	
Age, mean years ± SD	65.27 ± 16.41	63.54 ± 16.36	66.24 ± 16.96	.37
Male sex	71 (65.1)	138 (64.7)	62 (67.4)	.85
Comorbidity				
HIV infection	6 (5.5)	9 (4.2)	3 (3.3)	.72
Alcoholism	3 (2.8)	12 (5.6)	1 (1.1)	.13
Dementia	3 (2.8)	5 (2.3)	2 (2.2)	.96
Liver cirrhosis	17 (15.6)	35 (16.4)	4 (4.3)	.01
Heart failure	4 (3.7)	3 (1.4)	7 (7.6)	.02
Renal failure	23 (21.1)	38 (17.8)	17 (18.5)	.81
COPD	20 (18.3)	25 (11.7)	12 (13)	.25
BMT	0 (0)	5 (2.3)	3 (3.3)	.20
SOT	5 (4.6)	9 (4.2)	1 (1.1)	.33
Solid neoplasm	14 (12.8)	29 (13.6)	12 (13)	.98
Hematologic neoplasm	12 (11)	25 (11.7)	11 (11.9)	.98
Diabetes	22 (20.2)	47 (22)	20 (21.7)	.93
Neutropenia	4 (3.7)	6 (2.8)	5 (5.4)	.53
Prognosis of underlying disease				
Nonfatal	49 (44.9)	98 (46)	40 (43.5)	
Ultimately fatal	56 (51.3)	108 (50.7)	45 (48.9)	.51
Rapidly fatal	4 (3.7)	7 (3.3)	7 (7.6)	
Prior vancomycin therapy	10 (9.5)	17 (8)	8 (8.7)	.92
Receipt of corticosteroids	20 (18.3)	46 (21.6)	25 (27.2)	.30
Origin of the infection				
Hospital acquired	74 (67.9)	163 (76.5)	70 (76)	
Community acquired	28 (25.7)	32 (15)	13 (14.1)	.16
Health care related	7 (6.4)	18 (8.4)	9 (9.8)	
Source of bacteremia				
Low risk	39 (35.8)	93 (43.7)	44 (47.8)	
Intermediate risk	34 (31.2)	70 (32.9)	27 (29.3)	.27
High risk	36 (33)	50 (23.5)	21 (22.8)	
Receipt of mechanical ventilation	6 (5.5)	26 (12.2)	7 (7.6)	.15
Receipt of empirical vancomycin	38 (34.9)	90 (42.2)	40 (43.5)	.26
Shock	31 (28.4)	43 (20.2)	10 (10.9)	.007
Infection-related mortality	26 (23.8)	44 (20.6)	18 (19.6)	.72
Mortality	30 (27.6)	60 (27.2)	26 (28.3)	.99

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease; SOT, solid-organ transplantation.

comycin therapy was defined as the use of any vancomycin for >7 days during the month prior to the occurrence of the bacteremic episode. The source of bacteremia was divided into 3 categories: low-risk sources (related mortality rate, <10%), which included intravenous catheter, urinary tract, ear-nose-larynx, gynecologic sources, and several manipulation-related sources (including digestive endoscopy, arterial catheterization, and sclerosis of esophageal varices); intermediate-risk sources (associated mortality rate, 10%–20%), which included osteoarticular sources, soft-tissue sources, and unknown sources; and high-risk sources (mortality rate, >20%), which included endovascular sources, lower respiratory tract, abdominal sources, and CNS foci.

Bloodstream infections were considered to be nosocomial when cultures of blood specimens obtained >48 h after hospital admission had positive results [20], community acquired when culture samples were obtained prior to admission or during the first 48 h of hospitalization from patients without hospitalization or health care contact during the month before bacteremia, and health care–related when there was hospitalization

Table 2. Factors associated with shock in univariate analysis of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Variable	Shock		*P*
	No (n = 330)	Yes (n = 84)	
Vancomycin MIC group			
1 μg/mL	78 (23.6)	31 (36.9)	
1.5 μg/mL	170 (51.6)	43 (51.2)	.008
2 μg/mL	82 (24.8)	10 (11.9)	
Age, mean years ± SD	63.95 ± 17.26	67.05 ± 13.01	.07
Male sex	224 (67.8)	47 (55.9)	.04
Comorbidity			
HIV infection	18 (5.4)	0 (0)	.02
Alcoholism	10 (3)	6 (7.1)	.08
Dementia	7 (2.1)	3 (3.6)	.43
Liver cirrhosis	39 (11.8)	17 (20.2)	.04
Heart failure	9 (2.7)	5 (5.9)	.14
Renal failure	61 (18.5)	17 (20.2)	.71
COPD	43 (13)	14 (16.7)	.38
BMT	7 (2.1)	1 (1.2)	.58
SOT	12 (3.6)	3 (3.6)	.97
Solid neoplasm	40 (12.1)	15 (17.8)	.16
Hematologic neoplasm	41 (12.4)	7 (8.3)	.29
Diabetes	71 (21.5)	18 (21.4)	.98
Neutropenia	12 (3.6)	3 (3.5)	.97
Prognosis of underlying disease			
Nonfatal	154 (46.7)	33 (39.3)	
Ultimately fatal	165 (50)	44 (52.4)	.09
Rapidly fatal	11 (3.3)	7 (8.3)	
Receipt of corticosteroids	68 (20.6)	23 (27.3)	.18
Origin of bacteremia			
Community acquired	58 (15.5)	15 (17.8)	
Hospital acquired	241 (73)	66 (78.6)	.21
Health care related	31 (9.4)	3 (3.6)	
Source of bacteremia			
Low risk	151 (45.7)	25 (29.7)	
Intermediate risk	106 (32.1)	25 (29.7)	.001
High risk	73 (22.12)	34 (31.5)	
Receipt of mechanical ventilation	22 (6.6)	17 (20.2)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease; SOT, solid-organ transplantation.

or health care contact during the month before bacteremia (e.g., for patients receiving dialysis). Empirical treatment was defined as the antibiotic administered before the definitive microbiological testing result was obtained, and it was considered to be inappropriate when the isolated MRSA strain was resistant. Shock was defined as a systolic pressure of <90 mm Hg that did not respond to fluid treatment and required vasoactive drug therapy [21]. Mortality was defined as death that occurred within 30 days after onset of bacteremia [22].

Vancomycin was the empirical treatment of choice that was recommended in our hospital when infection due to MRSA was suspected, and the dosage was adjusted to obtain a trough serum concentration of ⩾10 μg/mL by determining the peak and trough serum concentrations after 3 doses. Bayesian forecasting techniques, implemented in appropriate software, were used to interpret vancomycin concentrations by balancing the information of the measured concentrations against the prior knowledge provided by population pharmacokinetic parame-

Table 3. Factors independently associated with shock in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
MIC		
1 μg/mL	1	
1.5 μg/mL	0.59 (0.33–1.05)	.07
2 μg/mL	0.33 (0.15–0.75)	.012
Female sex	1.81 (1.07–3.05)	.025
Liver cirrhosis	2.09 (1.06–4.11)	.03
Source of bacteremia		
Low risk	1	
Intermediate risk	1.25 (0.66–2.36)	.48
High risk	2.40 (1.28–4.49)	.008
Receipt of mechanical ventilation	3.19 (1.53–6.66)	.002

ters. Individual pharmacokinetic parameters were obtained and further used to individually readjust vancomycin dosage to achieve trough concentrations >10 μg/mL.

Follow-up period. Patients were followed up from the time of diagnosis of bacteremia until in-hospital death or discharge from the hospital.

Statistical analysis. Categorical variables were compared by the χ^2 test with Yates' correction or Fisher's exact test when necessary, and continuous variables were compared using the Student's *t* test. All of the variables considered in the univariate analysis were subjected to further selection by using a stepwise forward nonconditional logistic procedure.

RESULTS

The MIC of vancomycin was 1.5 μg/mL for 213 strains (51.4%), 1 μg/mL for 109 (26.4%), and 2 μg/mL for 92 (22.2%). The evolution of vancomycin MIC throughout the study period is shown in figure 1. The main clinical characteristics of the MRSA bacteremia episodes according to the vancomycin MIC are shown in table 1. There were no differences among the 3 groups in terms of age, sex, comorbidity (except with respect to liver cirrhosis and heart failure), prognosis of underlying disease, prior receipt of vancomycin therapy, use of corticosteroids, origin of the infection, source of bacteremia, the need for mechanical ventilation, appropriate empirical antibiotic therapy, or mortality (related or not related to the bacteremic episode). However, shock was documented in 28.4%, 19.9%, and 10.8% of the episodes due to strains with vancomycin MICs of 1 μg/mL, 1.5 μg/mL, and 2 μg/mL, respectively ($P = .007$). To elucidate the role of vancomycin MIC in the development of shock, univariate and multivariate analyses using shock as a dependent variable were performed. In the univariate analysis, sex, HIV infection, liver cirrhosis, source of bacteremia, receipt of mechanical ventilation, and vancomycin MIC were associated with shock (table 2). In the multivariate analysis, female sex (OR, 1.81; 95% CI, 1.07–3.05), liver cirrhosis (OR, 2.09; 95% CI, 1.06–4.11), a high-risk source of bacteremia (OR, 2.40; 95% CI, 1.28–4.49), and receipt of mechanical ventilation (OR, 3.19; 95% CI, 1.53–6.66) were factors independently associated with shock, whereas a vancomycin MIC of 2 μg/mL was independently associated with a lower risk of shock (OR, 0.33; 95% CI, 0.15–0.75) (table 3). Because vancomycin MIC was associated with shock, we considered that, in the multivariate analysis, it was necessary to adjust the risk of mortality for the presence or absence of this factor.

Factors associated with mortality in the univariate analysis included age, prognosis of underlying diseases, use of corticosteroids, source of bacteremia, receipt of mechanical ventilation, and shock (table 4). After adjusting for confounding, receipt of mechanical ventilation dropped out of the model, whereas receipt of empirical vancomycin and having an isolate with a vancomycin MIC of 2 μg/mL (OR, 6.39; 95% CI, 1.68–24.3) and receipt of inappropriate empirical therapy (OR, 3.62; 95% CI, 1.20–10.9) were included as independent predictors (table 5). This was entirely because of the fact that both shock and having a high-risk source of bacteremia were more prevalent among individuals who received empirical vancomycin and had isolates with a vancomycin MIC of 1 μg/mL (10 [26%] of 38 episodes and 14 [37%] of 38 episodes, respectively) than among those who had isolates with a vancomycin MIC of 1 μg/mL (4 [10%] of 40 episodes and 9 [23%] of 40 episodes, respectively) and those with receipt of inappropriate empirical therapy (49 [26%] of 246 episodes and 59 [24%] of 246 episodes, respectively); thus, they acted as negative confounders of the association of treatment group with death. The results were similar when infection-related mortality was used as a dependent variable (data not shown).

DISCUSSION

The results of the present study suggest that vancomycin MIC may have important consequences on the efficacy of this antibiotic and on mortality in patients with bacteremia due to MRSA. According to the present data, the impact on outcome of the empirical use of vancomycin or other antibiotic without anti-MRSA activity for strains with a MIC of 2 μg/mL is similar. The fact that the univariate analysis did not show a significant association between the empirical use of vancomycin in patients with strains with low vancomycin MICs (≤1 μg/mL) and better survival was a case of negative confounding caused by shock and the source of bacteremia. Our findings suggest that vancomycin cannot be considered to be an optimal option for treatment of infection due to strains with vancomycin MICs >1 μg/mL when using a vancomycin trough serum concentration >10 μg/mL as a target. The influence of MIC on vanco-

Table 4. Factors associated with mortality in a univariate analysis of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Variable	Survival (n = 298)	Death (n = 116)	OR (95% CI)
MIC			
1 μg/mL	79 (26.51)	30 (25.86)	1
1.5 μg/mL	153 (51.34)	60 (51.72)	1.03 (0.6–1.7)
2 μg/mL	66 (22.14)	26 (22.41)	1.04 (0.6–1.9)
Age, mean years ± SD	63.08 ± 16.98	68.75 ± 14.05	…
Male sex	199 (66.77)	72 (62.06)	0.8 (0.5–1.3)
Comorbidity			
HIV infection	16 (5.36)	2 (1.72)	0.3 (0.1–1.4)
Alcoholism	9 (3.02)	7 (6.03)	2 (0.7–6)
Dementia	5 (1.67)	5 (4.31)	2.6 (0.7–9)
Liver cirrhosis	38 (12.75)	18 (15.51)	1.3 (0.7–2)
Heart failure	8 (2.68)	6 (5.17)	2 (0.7–5.9)
Renal failure	60 (20.13)	18 (15.51)	0.7 (0.4–1.3)
COPD	35 (11.74)	22 (18.96)	1.8 (0.9–3.6)
BMT	6 (2.01)	2 (1.72)	0.9 (0.2–4)
SOT	11 (3.69)	4 (3.44)	0.9 (0.3–3)
Solid neoplasm	38 (12.75)	17 (14.65)	1.2 (0.6–2)
Hematologic neoplasm	34 (11.40)	14 (12.06)	1.1 (0.5–2)
Diabetes	60 (20.13)	29 (25)	1.2 (0.8–2)
Neutropenia	10 (3.35)	5 (4.31)	1.3 (0.4–4)
Prognosis of underlying disease			
Nonfatal	146 (48.99)	41 (35.34)	1
Ultimately fatal	147 (49.32)	62 (53.44)	1.5 (0.9–2.4)
Rapidly fatal	5 (1.67)	13 (11.20)	9.3 (3–28)
Receipt of prior vancomycin therapy	26 (8.72)	9 (7.75)	1 (0.5–2)
Receipt of corticosteroids	53 (17.78)	38 (32.75)	2.3 (1.4–4)
Origin of bacteremia			
Community acquired	53 (17.78)	20 (17.24)	1
Hospital acquired	216 (72.48)	91 (78.44)	1.1 (0.6–2)
Health care related	29 (9.73)	5 (4.31)	0.5 (0.2–1.4)
Source of bacteremia			
Low risk	148 (49.66)	28 (24.13)	1
Intermediate risk	91 (30.53)	40 (34.48)	2.3 (1.3–4)
High risk	59 (19.79)	48 (41.37)	4.3 (2.5–7.5)
Shock	31 (10.40)	53 (45.68)	7.3 (4–12)
Receipt of mechanical ventilation	19 (6.37)	20 (17.24)	3 (1.6–6)
Receipt of empirical vancomycin	125 (41.94)	43 (37.06)	0.8 (0.5–1.3)
Treatment group			
VMIC1	32 (10.73)	6 (5.17)	1
VMIC1.5	66 (22.14)	24 (20.68)	1.9 (0.8–5)
VMIC2	27 (9.06)	13 (11.20)	2.6 (0.9–8)
NA	173 (58.05)	73 (62.93)	2.3 (0.9–6)

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease; NA, receipt of inappropriate empirical therapy; SOT, solid-organ transplantation; VMIC1, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL; VMIC1.5, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL; VMIC2, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL.

mycin efficacy could be explained in terms of pharmacokinetic and pharmacodynamic parameters. In vitro and neutropenic mouse thigh infection models have demonstrated that the area under the concentration curve divided by the MIC (AUC/MIC) is the best predictor of vancomycin activity against *S. aureus*. Therefore, a change in the MIC from 1 μg/mL to 2 μg/mL reduces the AUC/MIC by one-half. Moise et al. [23] examined the relationship between the vancomycin AUC/MIC and outcome for 63 patients with lower respiratory tract infection due to *S. aureus* treated with vancomycin. An AUC/MIC value of

Table 5. Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
Age, per year	1.02 (1.00–1.04)	.013
Receipt of corticosteroids	1.85 (1.04–3.29)	.034
Prognosis of underlying disease		
Nonfatal	1	
Rapidly fatal	1.81 (1.06–3.10)	.029
Ultimately fatal	10.2 (2.85–36.8)	<.001
Source of bacteremia		
Low risk	1	
Intermediate risk	2.18 (1.17–4.04)	.014
High risk	3.60 (1.89–6.88)	<.001
Treatment group		
VMIC1	1	
VMIC1.5	2.86 (0.87–9.35)	.08
VMIC2	6.39 (1.68–24.3)	<.001
NA	3.62 (1.20–10.9)	<.001
Shock	7.38 (4.11–13.3)	<.001

NOTE. NA, receipt of inappropriate empirical therapy; VMIC1, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL; VMIC1.5, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL; VMIC2, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL.

⩾350 was an independent factor associated with clinical success (OR, 7.19; 95% CI, 1.91–27.3). The probability of achieving this AUC/MIC target when the MIC is 1 μg/mL using a vancomycin trough serum concentration of 10 or 15 μg/mL is 40% and 60%, respectively. However, when the MIC is 2 μg/mL, the probability is 0% at both concentrations [24, 25]. This fact may explain the findings of Hidayat et al. [26], who studied the efficacy of high vancomycin trough serum concentration (⩾15 μg/mL) in a cohort of 95 patients with MRSA infection according to the MIC (<2 μg/mL vs. ⩾2 μg/mL). Despite achieving a high trough concentration (⩾15 μg/mL), the high-MIC group (⩾2 μg/mL) had a lower success rate (62%) than did the low-MIC group (85%; $P = .02$). Other possible explanations for their results could be that vancomycin has slow bactericidal activity against strains with a high MIC [27, 28].

For the present study, we decided to analyze the impact of empirical antibiotic treatment on mortality, because there is a large amount of evidence to support the importance of early antibiotic administration [1, 29, 30]. Other authors did not find that a 2-day delay in the use of appropriate antibiotics had a negative effect on mortality [31, 32]; however, they did not include vancomycin MIC in their studies. Our results suggest that, in addition to the selection of an antibiotic that is active in vitro, reaching the pharmacokinetic and pharmacodynamic target (based on the serum concentration of the antibiotic and the MIC value) within the first 24 h after therapy is initiated is essential to achieve a high rate of clinical success.

In the light of our results, it is important to identify those factors that are associated with a vancomycin MIC >1 μg/mL. Although the prior administration of vancomycin has been correlated with the development of vancomycin resistance [12], there were no differences in our cohort between the 3 MIC groups with respect to prior administration of vancomycin. However, in our database, prior administration of antibiotics refers only to administration of antibiotics during the month before the onset of bacteremia. Therefore, we cannot exclude the possibility that differences might have been observed if the administration of prior antibiotics 6–12 months before the onset of bacteremia would have been recorded.

The low ability of MRSA strains with a vancomycin MIC of 2 μg/mL to trigger shock could be associated with alterations in the structure of the cell wall. MRSA strains with intermediate resistance to vancomycin have reduced levels of peptidoglycan cross-linking, which is compensated for by increasing the thickness of the cell wall [33, 34]. Teichoic and lipoteichoic acids extend the peptidoglycan and have the ability to stimulate the release of proinflammatory cytokines that trigger shock. We hypothesize that the thickness of the cell wall in strains with high vancomycin MICs covers the teichoic and lipoteichoic acids, preventing the immune activation and, consequently, the development of shock. Furthermore, MRSA strains with a high MIC have been associated with a slow growth rate [35] and a loss of function of the accessory gene regulator operon *(agr)* that controls many virulence factors [36]. Thus, there seems to be a link between pathogenicity and resistance to vancomycin. Although the majority of these changes have been described in vancomycin-resistant strains (MIC ⩾4 μg/mL), our findings suggest that these or other alterations could be present in those strains with a vancomycin MIC >1 μg/mL, diminishing their capacity to induce shock.

The main drawback of the present study was the lack of information about serum vancomycin concentrations. As stated in the Patients and Methods section, the dosage of vancomycin was adjusted to obtain a trough serum concentration of >10 μg/mL, but the precise values of pharmacokinetic and pharmacodynamic parameters were not available in the database. Nonetheless, this is a large study and provides robust information about the influence of minor changes in vancomycin MIC on the clinical presentation and outcome of MRSA bacteremia treated with vancomycin.

In conclusion, mortality associated with MRSA bacteremia was significantly higher when the empirical antibiotic was vancomycin and the strain had a vancomycin MIC of 2 μg/mL or when the empirical antibiotic was inappropriate. These findings suggest that (1) empirical vancomycin treatment when MRSA infection is suspected should be administered using a trough serum concentration of ⩾20 μg/mL as a target until a precise MIC is obtained, and (2) it would be necessary to clarify

whether new antistaphylococcal agents, such as linezolid, daptomycin, tygecicline or dalvavancin, could be superior to vancomycin when the strain has a vancomycin MIC >1 μg/mL.

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