Effect of Vancomycin Minimal Inhibitory Concentration on the Outcome of Methicillin-Susceptible *Staphylococcus aureus* Endocarditis

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Background. *Staphylococcus aureus* endocarditis has a high mortality rate. Vancomycin minimum inhibitory concentration (MIC) has been shown to affect the outcome of methicillin-resistant *S. aureus* bacteremia, and recent data point to a similar effect on methicillin-susceptible *S. aureus* bacteremia. We aimed to evaluate the effect of vancomycin MIC on left-sided *S. aureus* infective endocarditis (IE) treated with cloxacillin.

Methods. We analyzed a prospectively collected cohort of patients with IE in a single tertiary-care hospital. Vancomycin, daptomycin, and cloxacillin MIC was determined by E-test. *S. aureus* strains were categorized as low vancomycin MIC (<1.5 µg/mL) and high vancomycin MIC (≥1.5 µg/mL). The primary endpoint was in-hospital mortality.

Results. We analyzed 93 patients with left-sided IE treated with cloxacillin, of whom 53 (57%) had a vancomycin MIC < 1.5 µg/mL and 40 (43%) a vancomycin MIC ≥ 1.5 µg/mL. In-hospital mortality was 30% (n = 16/53) in patients with a low vancomycin MIC and 53% (n = 21/40) in those with a high vancomycin MIC ($P = .03$). No correlation was found between oxacillin MIC and vancomycin or daptomycin MIC. Logistic regression analysis showed that higher vancomycin MIC increased in-hospital mortality 3-fold (odds ratio, 3.1; 95% confidence interval, 1.2–8.2) after adjustment for age, year of diagnosis, septic complications, and nonseptic complicated endocarditis.

Conclusions. Our results indicate that vancomycin MIC could be used to identify a subgroup of patients with methicillin-susceptible *S. aureus* IE at risk of higher mortality. The worse outcome of staphylococcal infections with a higher vancomycin MIC cannot be explained solely by suboptimal pharmacokinetics of antibiotics.

Keywords. methicillin-susceptible *Staphylococcus aureus*; left-sided endocarditis; cloxacillin; vancomycin minimal inhibitory concentration; mortality.

Staphylococcus aureus is the leading cause of infective endocarditis (IE) worldwide [1]. Native-valve *S. aureus* endocarditis is more frequently caused by methicillin-susceptible *S. aureus* (MSSA) (85% of cases vs 15% in endocarditis caused by methicillin-resistant *S. aureus* [MRSA]), leading to a higher incidence of embolic events, reduced need for surgery, and higher mortality than non–*S. aureus* native valve endocarditis [2]. Despite considerable advances in diagnosis and surgical and medical management, the in-hospital mortality of MSSA endocarditis has remained unchanged at around 25% in recent decades [2, 3].

In the last few years, several investigations have addressed the issue of the high mortality associated with MRSA bacteremia. A higher vancomycin minimum inhibitory concentration (MIC) has been shown to confer a worse prognosis for MRSA bacteremia [4–6].

The results of the only study to analyze the effect of vancomycin MIC on the outcome of MRSA endocarditis [7] revealed more frequent persistent bacteremia and a higher incidence of heart failure and mortality when the vancomycin MIC was >1.5 mg/L; however, the sample size was too small to draw firm conclusions.

A strong association between vancomycin MIC and the outcome of MSSA bacteremia was recently reported, regardless of the antibiotic treatment administered (antistaphylococcal penicillin or vancomycin) [8, 9]. The study by Holmes et al [8] revealed that mortality increased 2.4-fold in patients with a vancomycin MIC > 1.5 mg/L. In addition, the choice of antibiotic (vancomycin or betalactam) for the treatment of S. aureus bacteremia had no statistically significant effect on 30-day mortality in the multivariable model [8]. Moreover, in another article by the same authors, vancomycin MIC was an independent risk factor for 30-day mortality of MSSA bacteremia after adjustment for comorbidities and disease severity [10]. This finding is very relevant, as it demonstrates that higher vancomycin MIC is a prognostic factor for mortality in S. aureus bacteremia, regardless of resistance to methicillin or the treatment administered. However, the pathophysiologic mechanisms underlying this finding remain unknown, and data for patients with MSSA endocarditis are lacking.

The aim of this study was to analyze whether the MIC of vancomycin could be a prognostic marker in cloxacillin-treated, left-sided MSSA endocarditis.

METHODS

We designed a retrospective analysis of a prospectively collected cohort in Hospital Clínic of Barcelona, an 800-bed tertiary-care teaching center in Spain.

All consecutive case patients with IE diagnosed from 1995 to 2011 at our center were collected in a case report form and a prospective database. The variables recorded included demographics, characteristics of the IE episode, complications, treatment, and outcome. All patients who survived were followed for at least 1 year. All case patients with MSSA endocarditis were treated with intravenous cloxacillin (2 g/4 hours) according to American Heart Association guidelines [11]. We included only patients with confirmed endocarditis. Throughout the study period, the senior team in charge of patients with endocarditis remained unchanged (A. M., M. A., S. N., J. C. P., C. A. M., J. M. G., F. M., and J. M. M.). We included only patients with confirmed endocarditis.

Definitions

The diagnosis of confirmed endocarditis was based on the modified Duke criteria [12]. Septic complicated endocarditis was defined as endocarditis with severe sepsis or septic shock at

diagnosis, both defined following the International Sepsis Definitions Conference [13]. We defined nonseptic complicated endocarditis as endocarditis with >1 of the following complications: systemic emboli, periannular abscess, and heart or renal failure at baseline or during the first 2 weeks of follow-up.

Vancomycin MIC Determinations

S. aureus strains were collected and stored at −80°C. The selected isolates were thawed and used to determine the MICs of oxacillin, vancomycin, and daptomycin (E-test).

Primary Endpoint

The primary endpoint was in-hospital survival. One-year survival was analyzed as a secondary endpoint.

Statistical Analysis

Categorical variables are expressed as a percentage and were compared using the χ^2 or Fisher exact test. Continuous variables are expressed as means or medians (depending on homogeneity) and were compared using the t test or Mann–Whitney test. Survival was analyzed using the Kaplan–Meier method. Plots were compared using the log-rank test. Correlations were calculated using Spearman's rho test. We used backward stepwise logistic regression analysis to identify independent variables associated with 1-year mortality and included those variables with $P < .30$ in the univariable analysis. A 2-tailed P value < .05 was considered statistically significant.

RESULTS

Figure 1 shows the flow diagram of the patients included in the study following the CONSORT recommendations (http://www.consort-statement.org/consort-statement/flow-diagram0/; accessed 3 January 2014). From January 1995 to December 2011, we prospectively included 762 episodes of IE, of which 228 (30%) were caused by S. aureus. The isolate was available for determination of MIC in 163 patients (71%). Of these 163 patients, 70 were excluded because of right-sided or intracardiac device IE (46), left-sided MRSA IE (20), or left-sided MSSA IE not treated with cloxacillin (4) (Figure 1). Of the 93 episodes of left-sided MSSA endocarditis treated with cloxacillin, the vancomycin MIC was < 1.5 μg/mL in 53 cases and ≥1.5 μg/mL in 40 cases.

In these 93 strains, no correlation was found between the E-test oxacillin MIC and the vancomycin MIC (Spearman's rho = 0.028; P = .79; Figure 2A) or daptomycin MIC (Spearman's rho = −0.118; P = .26; Figure 2B).

Table 1 shows the differences in left-sided MSSA endocarditis according to vancomycin MIC. MSSA strains with a higher vancomycin MIC were more frequent in the earlier period of the study (1994–1998). MSSA endocarditis with a higher
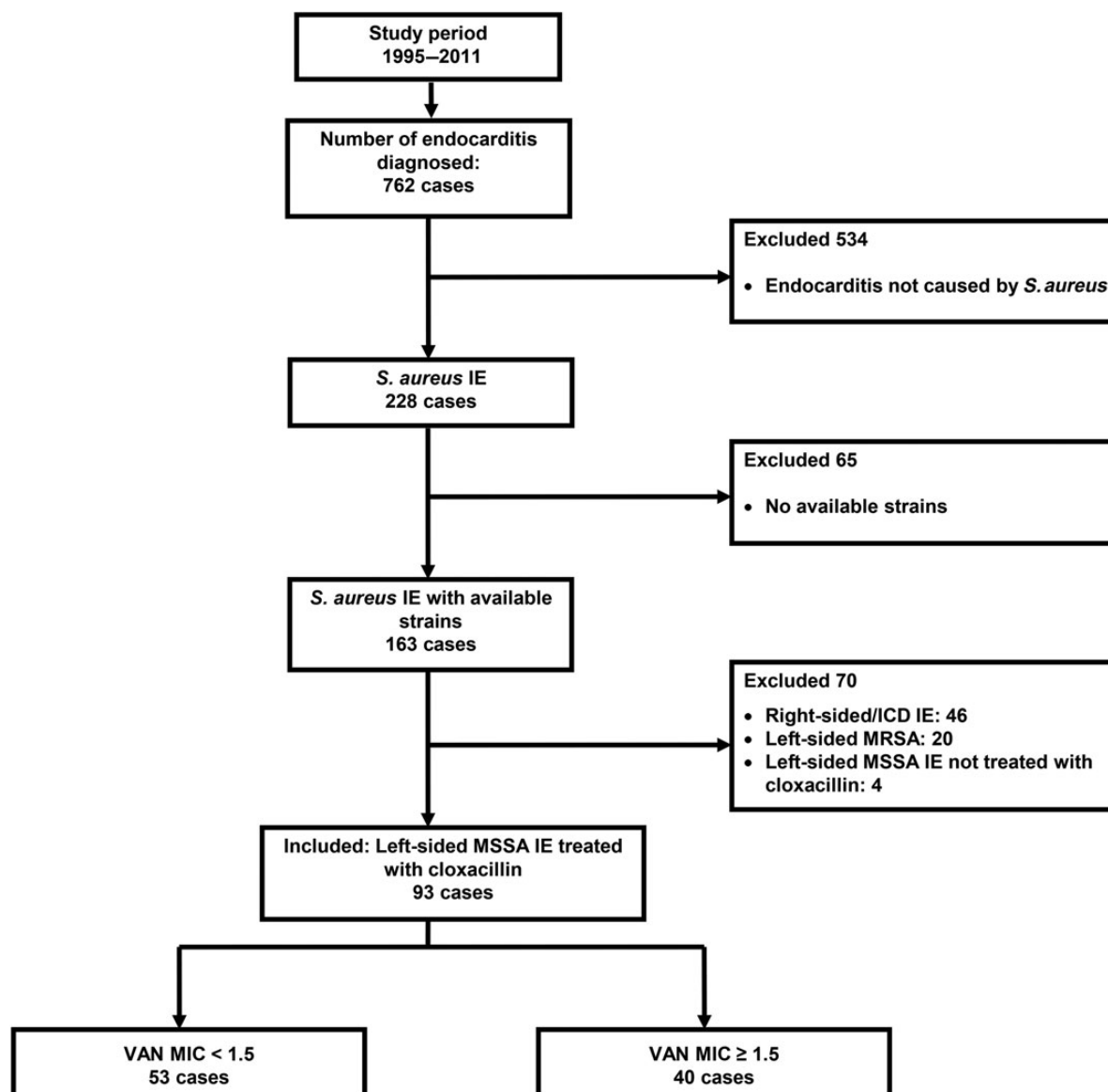
Figure 1. Flowchart of the patients included in the study. Abbreviations: ICD, intracardiac device; IE, infective endocarditis; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; VAN, vancomycin.

vancomycin MIC was more frequently associated with systemic emboli ($P = .01$) and higher in-hospital and 1-year mortality ($P = .03$ and $P = .04$, respectively). No additional differences were found between patients according to vancomycin MIC. Figure 3 shows the Kaplan–Meier survival analysis according to vancomycin MIC at 90 days of follow-up (survival at 1 year follow-up, 50% vs 71.5% for vancomycin MIC ≥ 1.5 μg/mL and <1.5 μg/mL, respectively). The effect of vancomycin MIC on in-hospital mortality was also maintained when the analysis was restricted to patients with native valve endocarditis

(73 patients; mortality 10/39 [26%] and 17/34 [50%] in patients with low and high vancomycin MIC, respectively; $P = .03$).

In-hospital mortality was 40% (37 patients); mortality at 1 year of follow-up was 43% (40 patients). The cause of in-hospital death included surgical complications (n = 10), multiorgan failure (n = 8), septic shock (n = 4), stroke (n = 5), other embolic events (n = 2), heart failure (n = 5), arrhythmias (n = 2), and nosocomial infection (n = 1). Three additional patients died after hospital discharge, 1 because of heart failure, 1 because of an arrhythmic event, and 1 of unknown cause. No differences
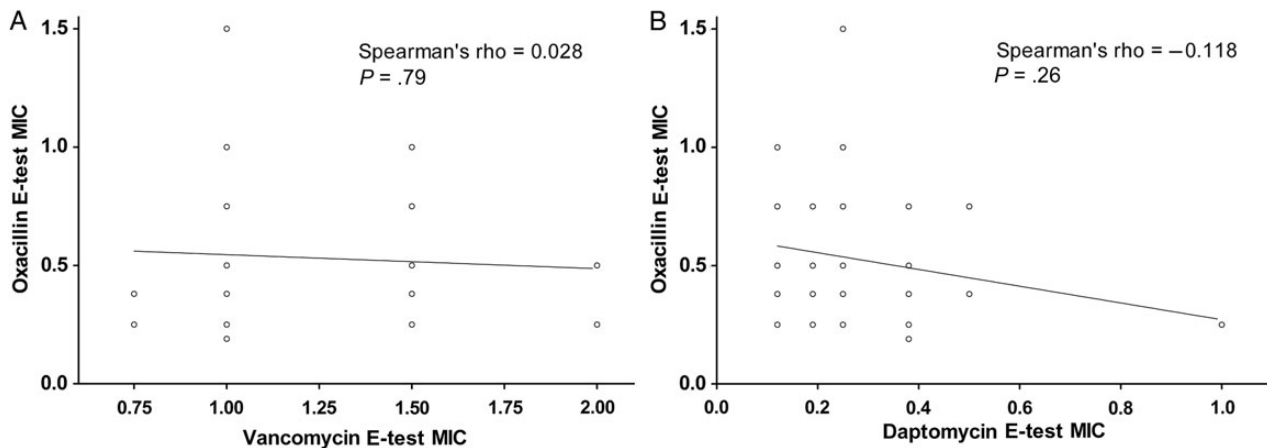
Figure 2. Cloud graph analyzing the correlation between oxacillin minimum inhibitory concentration (MIC) by E-test with vancomycin MIC by E-test (*A*) and daptomycin MIC by E-test (*B*). No significant correlation was found in any case. Abbreviation: MIC, minimum inhibitory concentration.

in the cause of death according to vancomycin MIC were detected ($P = .82$).

Table 2 shows the analysis of the risk factors associated with in-hospital mortality. The year of diagnosis of endocarditis was not associated with changes in mortality risk. Nonseptic complicated endocarditis was associated with 5-fold higher mortality, and septic complicated endocarditis increased in-hospital mortality 5.5-fold. Patients with endocarditis by an MSSA strain with a vancomycin MIC ≥ 1.5 µg/mL had 3-fold higher mortality (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.2–8.2). Finally, age was forced into the final logistic model, although it did not modify the mortality risk (OR, 1.8; 95% CI, .7–4.7).

DISCUSSION

Ours is the first study to show that vancomycin MIC (as determined by the E-test) is an independent risk factor for in-hospital mortality in patients with left-sided MSSA IE. After adjustment for covariables, MSSA endocarditis caused by strains with a vancomycin MIC ≥ 1.5 mg/L had a 3-fold higher in-hospital mortality rate. The E-test is fast and inexpensive and can easily stratify the risk of mortality in patients with *S. aureus* left-sided endocarditis.

Progressively increasing rates of *S. aureus* endocarditis have been documented during the last decade in the United States [14], although no improvement in the mortality rates of this devastating disease—around 23% for MSSA endocarditis and 30%–37% for MRSA endocarditis—has been achieved in the last 25 years [2, 3]. Prognostic factors for *S. aureus* endocarditis include environmental factors (country and place of acquisition), variables related to the patient's health (eg, age, comorbidities, and prosthetic valve endocarditis), and complicated course of infection (eg, persistent bacteremia, periannular

abscess, stroke, and heart failure). Our data revealed a prognostic factor based on specific microbiological characteristics of the strain.

We did not find any epidemiological differences between *S. aureus* isolates with high and low vancomycin MICs. However, a statistically significant trend toward a higher percentage of MSSA strains with a high vancomycin MIC was observed during the early part of the study. The same trend was observed by Miller et al [15] in the United Kingdom in 821 consecutive episodes of MRSA bacteremia diagnosed between 1999 and 2009. Nonetheless, we do not believe that the year of diagnosis affected prognosis because the senior team in charge of these patients remained unchanged throughout the study period, antibiotic treatment and surgical management were the same in all the periods analyzed, and no trend in different mortality rates was identified within the different periods analyzed after adjusting for confounders.

With regard to clinical outcomes, patients with left-sided endocarditis caused by strains of *S. aureus* with a higher vancomycin MIC had a higher probability of in-hospital and 1-year mortality. This study tried to confirm the previous results of Holmes et al [8] in patients with *S. aureus* bacteremia, for whom vancomycin MIC was an independent risk factor for mortality regardless of the antibiotic regimen administered. To prove this hypothesis, we selected those patients with MSSA endocarditis treated with cloxacillin, as several studies and 1 meta-analysis have confirmed this association with MRSA bacteremia treated with vancomycin [4–6].

Logistic regression analysis showed that vancomycin MIC was an independent variable associated with in-hospital mortality. Many previous studies showed that complicated endocarditis (eg, periannular abscess, heart failure) is associated with higher mortality of *S. aureus* endocarditis [2, 3]. In our cohort,

Table 1. Differences in Episodes of Methicillin-Susceptible *Staphylococcus aureus* Endocarditis According to Vancomycin Minimum Inhibitory Concentration

Variable	Vancomycin MIC < 1.5 µg/ mL n = 53	Vancomycin MIC ≥ 1.5 µg/ mL n = 40	P Value
Mean age (SD)	61.0 (16.1)	59.1 (17.3)	.60
Male sex	38 (72)	29 (73)	.93
Comorbidities			
Diabetes	4 (8)	5 (13)	.49
Liver cirrhosis	10 (19)	4 (10)	.24
Chronic renal failure	5 (9)	7 (18)	.25
HIV infection	7 (13)	5 (12)	.83
Other immunosuppression[a]	3 (6)	2 (5)	1.00
Intravenous drug use	6 (11)	5 (13)	1.00
Underlying cardiovascular disease[b]	29 (57)	22 (43)	.92
Median Charlson score (IQR)	1.0 (1.0–3.0)	2.0 (1.0–3.0)	.34
Type of endocarditis			.19
Native valve	39 (74)	34 (85)	
Prosthetic valve	14 (26)	6 (15)	
Acquisition			.36
Community acquired	33 (62)	29 (72)	
Nosocomial	16 (31)	7 (18)	
Healthcare related	4 (8)	4 (10)	
Valve involvement			.87
Aortic	18 (34)	17 (43)	
Mitral	24 (45)	15 (38)	
Mitral + tricuspid	3 (6)	1 (2)	
Aortic + tricuspid	1 (2)	1 (2)	
Mitral + aortic	4 (7)	2 (5)	
Unknown	3 (6)	4 (10)	
Presence of vegetations[c]	39 (74)	26 (65)	.49
Year of diagnosis			<.001
1995–1999	12 (23)	19 (47)	
2000–2003	15 (28)	7 (18)	
2004–2007	8 (15)	13 (32)	
2008–2011	18 (34)	1 (3)	
Complications			
Heart failure	25 (47)	22 (55)	.46
Kidney failure	33 (62)	22 (55)	.48
Systemic emboli	6 (11)	13 (33)	.01
CNS emboli	3 (6)	7 (18)	.09
Osteoarticular metastases[d]	4 (8)	7 (18)	.20
Periannular abscess	9 (17)	6 (15)	.80
Surgical treatment	22 (42)	13 (25)	.38
Emergency surgery	13 (33)	11 (28)	.75
Median days of fever (IQR)	3.0 (2.0–5.0)	4.0 (2.0–8.0)	.38
Prolonged bacteremia[e]	5 (10)	4 (10)	1.00
Initial treatment with gentamicin	30 (57%)	27 (68%)	.29
Relapses	2 (4%)	2 (5%)	1.00

Table 1   continued.

Variable	Vancomycin MIC < 1.5 µg/ mL n = 53	Vancomycin MIC ≥ 1.5 µg/ mL n = 40	P Value
Mortality			
In-hospital mortality	16 (30%)	21 (53%)	.03
One-year mortality	18 (34%)	22 (55%)	.04

Data are No. (%) unless otherwise noted.

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; IQR, interquartile range; MIC, minimum inhibitory concentration; SD, standard deviation.

[a] Immunosuppression included transplantation (n = 4) and active neoplasm (n = 1).

[b] Underlying cardiovascular disease included the following (patients can have >1): mechanical prosthetic valve (n = 12), aortic valve sclerosis (n = 11), biological prosthetic valve (n = 8), intracardiac device (n = 8), rheumatic valvular disease (n = 6), previous episode of infective endocarditis (n = 4), mitral valve disease (n = 2), hypertrophic myocardiopathy (n = 2), and bicuspid aortic valve (n = 2).

[c] As far as vegetations detected using echocardiography were concerned, no differences in size were found according to vancomycin MIC (median size, 10 mm [IQR, 5–15 mm] vs 10 mm [IQR, 5–12 mm] in patients with low and high vancomycin MIC, respectively; P = .46).

[d] Osteoarticular metastases included the following: septic arthritis (n = 6), vertebral osteomyelitis (n = 3), and nonvertebral osteomyelitis (n = 2).

[e] Positive blood cultures ≥7 days after antimicrobial treatment.

complicated endocarditis increased in-hospital mortality 5.5-fold. In addition, patients who were more critically ill at diagnosis had a poorer prognosis. However, of greater relevance is the fact that patients with MSSA endocarditis caused by a strain with a higher vancomycin MIC had 3-fold higher mortality after correction for other covariables.

The poorer prognosis of MRSA bacteremia has been explained mainly because of the pharmacokinetic/pharmacodynamic properties of vancomycin. The area under the curve (AUC)/MIC ≥400 is the best predictor of the efficacy of vancomycin to treat MRSA infections. As when treating cases of MRSA bacteremia with a vancomycin MIC of 2 µg/mL using a dose of vancomycin of 15 mg/kg/12 hours we would have trough concentrations and AUC/MIC ratio around 10 mg/L and 200, respectively [16], which is clearly under the ideal threshold of clinical efficacy, it is recommended to increase the vancomycin dose to achieve trough concentrations of 15–20 mg/L [17]. However, in experimental models of MRSA endocarditis caused by strains with a vancomycin MIC of 2 µg/mL, no statistically significant differences were found in the percentage of sterile vegetations or the number of colony-forming units of MRSA in vegetations between animals treated with the recommended doses of vancomycin and those treated with higher doses [18]. In addition, when we adjusted the doses of vancomycin to reach an AUC/MIC ≥400 or higher in another experimental model of MRSA endocarditis, the sterilization rate and reduction in bacterial density in the vegetations did not improve
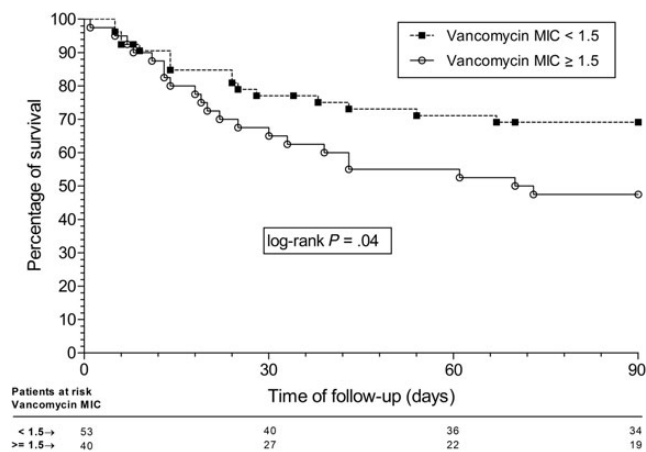
Figure 3. Kaplan–Meier survival graph of mortality at 90 days of follow-up (in-hospital mortality) according to vancomycin minimum inhibitory concentration. Abbreviation: MIC, minimum inhibitory concentration.

after comparison of strains with a vancomycin MIC of 0.5, 1, and 2 µg/mL [19]. Thus, doubts arise if we try to explain the lack of efficacy of vancomycin to treat MRSA bacteremia or endocarditis caused by strains with a high vancomycin MIC only by means of the vancomycin pharmacokinetic/pharmacodynamic model.

In the relationship between vancomycin MIC and the prognosis of cloxacillin-treated *S. aureus* bacteremia and left-sided endocarditis, pathogen-dependent factors could influence the final outcome. One hypothesis is that strains with a high vancomycin MIC could be associated with specific MSSA clonal complexes (CCs). However, most MSSA CCs involved in the development of endocarditis in a local study [20] and an international study [21] were CC30 and, to a lesser extent, CC5. In addition, endocarditis-associated genes only predominated in CC30 [22]. However, because this association between *S. aureus* CC30 and endocarditis was found in 2 studies from 1994–2003 and 2000–2006, there are no data to support that CC30 is now associated with a higher risk of endocarditis. Another hypothesis is that a higher vancomycin MIC phenotype could be associated with strains carrying more virulence factors. However CC30 implies an increased risk of endocarditis in humans, although in animal models virulence is attenuated [23]. This is because of single nucleotide polymorphisms in *S. aureus* CC30 *agrC* and *hla* that restrict this microorganism to the hospital setting, where it can cause endocarditis in more-compromised hosts [23]. Finally, vancomycin MIC could be associated with mutations in the accessory gene regulator (*agr*), which, together with the staphylococcal accessory regulator (*sarA*), regulates the formation of *S. aureus* biofilm. Beenken et al [24] showed that mutations in *agr* lead to increased biofilm formation (and a subsequent increased risk of embolism) and decreased antibiotic susceptibility. A recently published study found that MSSA strains with reduced susceptibility to vancomycin (MIC ≥ 1.5 µg/mL) had a significantly higher prevalence of polymorphisms in *agr*II, regardless of the clonal complex, although a trend toward a higher vancomycin MIC was identified for CC5 [25]. This hypothesis could explain why patients with a high vancomycin MIC phenotype had a higher risk of emboli in our study. In any case, additional studies to clarify the clinical significance of a high vancomycin MIC phenotype are urgently needed.

If an association between vancomycin MIC and outcome of MSSA endocarditis is confirmed, we must determine whether it can explain the differences in mortality observed for left-sided *S. aureus* IE around the world and whether the episodes of IE

Table 2. Logistic Regression Model of Variables Evaluated as Predictors of Hospital Mortality in Patients With *Staphylococcus aureus* Endocarditis

Variable	Category	No.	In-Hospital Mortality No. (%)	Univariable Analysis		Multivariable Analysis	
				OR (95% CI)	P Value	OR (95% CI)	P Value
Age	Age ≥ 60	55	24 (44)	1.5 (.6–3.5)	.36	1.8 (.7–4.7)[a]	.26[a]
	Age < 60	38	13 (34)				
Year of diagnosis	1995–2003	53	24 (45)	0.6 (.25–1.4)	.21	. . .	. . .
	2004–2011	40	13 (33)				
Septic complicated endocarditis	Yes	19	14 (74)	6.2 (2.0–19.3)	.002	5.5 (1.6–18.7)	.007
	No	74	23 (31)				
Nonseptic complicated endocarditis	Yes	74	35 (47)	7.6 (1.6–35.4)	.009	5.2 (1.1–25.9)	.04
	No	19	2 (11)				
Vancomycin MIC	≥1.5 µg/mL	40	21 (53)	2.6 (1.1–6.0)	.03	3.1 (1.2–8.2)	.02
	<1.5 µg/mL	53	16 (30)				

Abbreviations: CI, confidence interval; MIC, minimum inhibitory concentration; OR, odds ratio.

[a] The variable age was forced into the final regression model for theoretical reasons.

caused by a strain with a high vancomycin MIC should receive more aggressive treatment (eg, early cardiac surgery or more potent antibiotic regimens). Worldwide differences in the mortality of *S. aureus* endocarditis could result from different clustering of *S. aureus* with a high vancomycin MIC phenotype rather than from different national management strategies.

Our study is subject to a series of limitations. It is an observational study in a single, tertiary, referral center for patients with IE. Because the number of cases analyzed is low, we were unable to investigate subpopulations of interest (eg, native valve vs prosthetic valve endocarditis). In addition, clonality and virulence of the MSSA strains were not analyzed according to the vancomycin MIC phenotype.

In conclusion, a higher vancomycin MIC conferred a worse prognosis for left-sided *S. aureus* endocarditis treated with cloxacillin. Although these results require confirmation in further studies, this simple approach can be used to stratify the risk of mortality of patients with *S. aureus* endocarditis. Our results also suggest that the worse outcome of staphylococcal infections with a higher vancomycin MIC cannot be explained solely by suboptimal pharmacokinetics of antibiotics.

Notes

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Appendix

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