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Original article

Influence of vancomycin minimum inhibitory concentration on the outcome of methicillin-susceptible *Staphylococcus aureus* left-sided infective endocarditis treated with antistaphylococcal β -lactam antibiotics: a prospective cohort study by the International Collaboration on Endocarditis[☆]

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ABSTRACT

Objectives: Left-sided methicillin-susceptible *Staphylococcus aureus* (MSSA) endocarditis treated with cloxacillin has a poorer prognosis when the vancomycin minimum inhibitory concentration (MIC) is ≥ 1.5 mg/L. We aimed to validate this using the International Collaboration on Endocarditis cohort and to analyse whether specific genetic characteristics were associated with a high vancomycin MIC (≥ 1.5 mg/L) phenotype.

Methods: All patients with left-sided MSSA infective endocarditis treated with antistaphylococcal β -lactam antibiotics between 2000 and 2006 with available isolates were included. Vancomycin MIC was determined by Etest as either high (≥ 1.5 mg/L) or low (< 1.5 mg/L). Isolates underwent *spa* typing to infer clonal complexes and multiplex PCR for identifying virulence genes. Univariate analysis was performed to evaluate the association between in-hospital and 1-year mortality, and vancomycin MIC phenotype.

Results: Sixty-two cases met the inclusion criteria. Vancomycin MIC was low in 28 cases (45%) and high in 34 cases (55%). No significant differences in patient demographic data or characteristics of infection were observed between patients with infective endocarditis due to high and low vancomycin MIC isolates. Isolates with high and low vancomycin MIC had similar distributions of virulence genes and clonal lineages. In-hospital and 1-year mortality did not differ significantly between the two groups (32% (9/28) vs. 27% (9/34), p 0.780; and 43% (12/28) vs. 29% (10/34), p 0.298, for low and high vancomycin MIC respectively).

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Conclusions: In this international cohort of patients with left-sided MSSA endocarditis treated with antistaphylococcal β -lactams, vancomycin MIC phenotype was not associated with patient demographics, clinical outcome or virulence gene repertoire. **J.M. Pericàs, CMI 2017;•:1**

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Introduction

The impact of a high vancomycin minimum inhibitory concentration (MIC) phenotype (HVM; >1.5 mg/L) in methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia and infective endocarditis (IE) is poorly known. To date several studies have reported higher rates of complications and mortality in patients with MSSA bacteraemia caused by strains with HVM [1,2], as well as a correlation with *agr* dysfunction and *agr* type II polymorphism [3]. Nonetheless, a more recent study did not find significant differences on *agr* subgroup and function according to vancomycin MIC [4]. The association between HVM and significantly higher mortality was also demonstrated in a Spanish cohort of 93 patients with MSSA IE treated with cloxacillin [5].

We aimed to explore the association between high vancomycin MIC and clinical outcome among patients with left-sided MSSA IE in the International Collaboration Endocarditis (ICE) Cohort. We also aimed to study whether HVM was identifiable by a genetic signature of specific polymorphisms and virulence factors.

Methods

Database

The ICE prospective cohort study has been described previously [6]. All patients were included from sites that met performance criteria for participation, and the strains obtained from IE episodes were available in the ICE Microbiology Repository [7]. All participating sites had institutional review board or ethical committee approval or a waiver, and informed consent was obtained from all patients according to local standards as required by the coordinating centre (Duke University Medical Center).

Study sample

Patients and settings

IE isolates were obtained from the ICE Microbiology Repository [7]. Subjects in the ICE Microbiology Repository cohort with available frozen bloodstream isolates with definite MSSA IE treated with β -lactams were eligible for inclusion in this study. Seventeen of these strains were included in the Spanish cohort [5]. All patients who survived had at least 1 year's follow-up.

Definitions

IE was defined according to the modified Duke criteria [8] and was considered to be left-sided if no right-sided (tricuspid or pulmonary valve) vegetations were present on echocardiographic examination, surgery or autopsy. The rest of the definitions have been provided in detail elsewhere [9].

Geographic regions

Twenty-five sites from a variety of geographic regions participated in the study (Supplementary data).

Microbiologic methods

ICE methodology for microbiologic procedures has been defined elsewhere [6,10]. Detailed microbiologic methods can be found in the Supplementary data.

Statistical analysis

Categorical variables were expressed as percentages and compared by Fisher's exact test. Continuous variables were expressed as means or medians and compared by nonparametric tests. Survival analysis was performed by Kaplan-Meier analysis, and curves were compared by the log-rank test. A two-sided p value of <0.05 was considered statistically significant.

Results

The study flowchart is provided in Fig. 1.

The distribution of vancomycin MIC among the 62 cases included in the study is displayed in Fig. 2, along with the respective rates of mortality.

Demographics and clinical characteristics of patients with low vancomycin MIC (LVM) and HVM are shown in Table 1.

Complications, surgical rates and mortality according to vancomycin MIC groups are shown in Table 1. Differences between the two groups did not reach statistical significance for any of the variables. For LVM, in-hospital and 1-year mortality were 32% (9/28) and 43% (12/28) respectively, while in-hospital mortality was 27% (9/34) and 1-year mortality 29% (10/34) for HVM.

Differences in genotypic characteristics between the two groups according to MIC phenotypes are shown in the Supplementary data. No differences were detected regarding adhesins, toxins or other putative virulence factors.

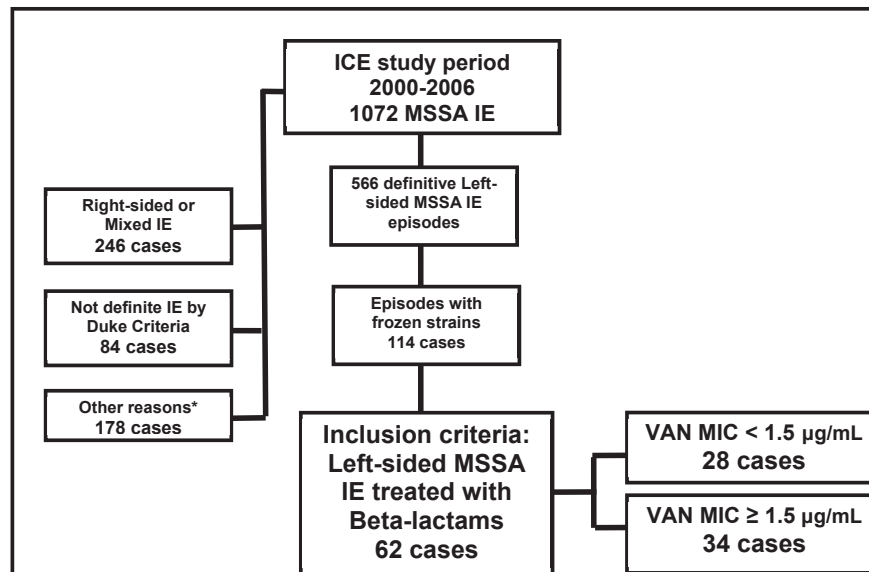
The univariate analysis of risk factors for 1-year mortality is shown in Table 2. HVM, type of *agr* and clonal complexes (CC) were not significantly associated with mortality. The analysis for in-hospital mortality using the same variables did not differ from that of 1-year mortality (data not shown).

The Kaplan-Meier survival plot at 1 year according to vancomycin MIC group is provided in the Supplementary data.

Discussion

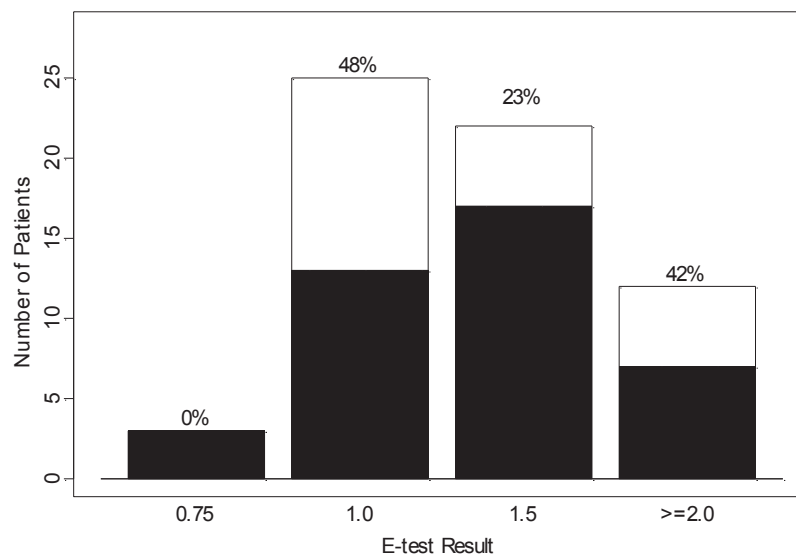
Vancomycin MIC was not associated with complications or mortality among patients with MSSA left-sided IE treated with β -lactams. Thus, this study was unable to validate findings from the study of Cervera *et al.* [5], from which two main hypotheses were raised: first, HVM in MSSA isolates was associated with higher mortality in patients with left-sided IE as a result of an increased rate of major embolic events; and second, a genomic signature identified MSSA isolates with HVM.

The main findings from studies investigating the relationship between vancomycin MIC and prognosis of MSSA and IE, as well as its relationship with *agr* dysfunction, are shown in Table 3.



*Other causes of exclusion were: lack of vegetations in the echocardiographic, surgical or post-mortem examination (123 patients), age below 18 years (7 patients) and relevant data missing in the CRD (48 patients).

Fig. 1. Flowchart of patients included in study. ICE, International Collaboration on Endocarditis; IE, infective endocarditis; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*; VAN, vancomycin.



VAN Group	0.75	1.0	1.5	≥ 2.0
N	3	25	22	12
Deaths	0	12	5	5

Percentages and white areas of every column indicate rates of one-year mortality per VAN MIC group. Black areas represent the percentage of patients alive at one-year.

Fig. 2. Distribution of vancomycin MIC within cohort of 62 left-sided MSSA infective endocarditis and overall 1-year mortality rates according to vancomycin MIC determination. MIC, minimum inhibitory concentration.

Higher mortality among patients with LVM than in patients with HVM was found in the present study, as well as higher rates of systemic embolic events (36% vs. 23%) and persistent bacteraemia (14% vs. 12%), neither of which reached statistical significance. Given that no significant differences were found in virulence factors between the two groups, we might speculate that in this data set, as a

result of the high proportion of patients with MSSA strains harbouring LVM and CC30, a high rate of detected and undetected haematogenous complications in the LVM may explain the higher mortality in this group.

With regard to genotypic features, the analysis of *agr* subgroup did not reveal a significant association between a specific *agr*

Table 1
Demographics, clinical characteristics and outcomes of 62 episodes of left-sided MSSA IE treated with β -lactams according to high or low vancomycin MIC

Characteristic	Vancomycin MIC <1.5 $\mu\text{g}/\text{mL}$ (n = 28)	Vancomycin MIC \geq 1.5 $\mu\text{g}/\text{mL}$ (n = 34)	p
Age, years, mean (SD)	61.1 (18.5)	60.1 (14.3)	0.396
Male gender, n (%)	19 (68%)	27 (79%)	0.386
Type of endocarditis			0.548
Native valve	23 (82%)	25 (74%)	
Prosthetic valve	5 (19%)	9 (27%)	
Origin of acquisition			0.916
Community acquired	17 (61%)	23 (68%)	
Nosocomial	8 (29%)	9 (26%)	
Healthcare related	2 (7%)	2 (6%)	
Unknown	1 (3%)	0	
Geographic area			0.333
North America	4 (14%)	10 (29%)	
Europe/Mideast	20 (71%)	22 (65%)	
South America	1 (4%)	0	
Australia/New Zealand	3 (11%)	2 (6%)	
Complications			
Heart failure	13 (46%)	10 (29%)	0.195
Systemic emboli	10 (36%)	8 (23%)	0.400
Stroke	7 (25%)	9 (27%)	1.000
Paravalvular complications	8 (29%)	11 (32%)	0.788
New conduction abnormality	0 (–)	3 (9%)	0.245
Persistent bacteraemia	4 (14%)	4 (12%)	1.000
Surgical treatment	9 (32%)	14 (41%)	0.599
Relapse ^a	0	0	1.000
Mortality			
In-hospital mortality	9 (32%)	9 (27%)	0.780
1-year mortality	12 (43%)	10 (29%)	0.298

IE, infective endocarditis; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*.

^a Defined as new episode of endocarditis due to the same microorganism that caused the first IE within next 12 months.

polymorphism and HVM or CC. We expected to find an association between a HVM and *agrII* polymorphism, relying on previous studies performed in MSSA bacteraemia [3,12]. In our study, *agrII* was two times more frequent in the HVM than in the LVM group (38% vs. 19%), but this did not reach statistical significance.

We did not identify a specific repertoire of virulence factors in the HVM group, as other previous studies did [6,7,10]. Although geographic regions are almost equally represented, changes in the genetic expression and phenotypic pattern in MSSA might be common over time, and geographic variations are also likely to occur as years pass. Another factor that could also have influenced the percentage of MSSA strains identified as HVM is the effect of freezer storage. Ludwig *et al.* [13] demonstrated a progressive decline of vancomycin MIC determination by Etest in methicillin-resistant *Staphylococcus aureus* bloodstream samples from the moment they were frozen.

This study has several limitations. First, the small sample size is a major shortcoming, greatly limiting the statistical power of the study and leading to the potential for a Type II error in the analysis. Second, the number of isolates tested and available is not representative of the overall ICE data set. However, we conducted a subanalysis comparing ICE left-sided MSSA frozen strains and those that were not frozen, and we did not detect significant differences regarding in-hospital and 1-year mortality and surgery rates (data not shown). Third, *agrII* dysfunction was not measured, so correlations with *agr* subgroup, vancomycin MIC and outcomes were not performed. Fourth, only cases occurring in the 2000–2006 period were included, which precluded observations regarding the temporal trends. Fifth, the potential variations of MSSA clones between geographic regions were not investigated. Finally, the specific type of β -lactam used was not available.

In conclusion, in this international cohort of left-sided MSSA IE treated with β -lactams, vancomycin MIC \geq 1.5 $\mu\text{g}/\text{mL}$ was not found to be an independent risk factor for complications of IE or for mortality. Stroke, paravalvular complications and some *S. aureus* genes were associated with a worse outcome. Differences in clonality and virulence factors were not found between strains with

Table 2
Bivariable analysis of risk factors for 1-year mortality^a

Variable	Alive (n = 39)	Dead (n = 22)	OR (95% CI)	p
Demographic data				
Age >65 years	16 (40%)	11 (50%)	1.5 (0.5–4.9)	0.593
Male sex	31 (78%)	15 (68%)	0.62 (0.2–2.4)	0.546
Prosthetic valve IE	11 (29%)	3 (14%)	0.41 (0.1–1.9)	0.338
Diabetes	8 (20%)	4 (18%)	0.89 (0.2–3.9)	1.000
Community acquisition	26 (65%)	14 (64%)	1.76 (0.0–141.9)	0.889
North America	8 (20%)	6 (27%)	1.77 (0.1–143.1)	0.444
Clinical features				
Paravalvular complications	8 (20%)	11 (50%)	4.0 (1.1–14.6)	0.021
Stroke	6 (15%)	10 (46%)	4.72 (1.2–19.1)	0.015
Heart failure	10 (46%)	10 (46%)	1.73 (0.5–5.7)	0.411
Persistent bacteraemia	5 (13%)	3 (14%)	1.11 (0.2–6.4)	1.000
Surgery	14 (35%)	9 (41%)	1.29 (0.4–4.2)	0.785
Microbiologic features				
Vancomycin MIC \geq 1.5 mg/L	24 (60%)	10 (45%)	0.56 (0.2–1.8)	0.298
CC30	7 (18%)	6 (27%)	1.77 (0.4–7.3)	0.516
CC8	1 (3%)	3 (14%)	6.16 (0.4–331.3)	0.546
CC15	6 (15%)	0	0.0 (0–1.1)	0.081
<i>agrI</i>	15 (38%)	7 (32%)	0.78 (0.2–2.6)	0.784
<i>agrII</i>	13 (33%)	6 (27%)	0.78 (0.2–2.7)	0.777
<i>agrIII</i>	11 (28%)	9 (41%)	1.83 (0.5–6.2)	0.394
<i>see</i>	8 (20%)	10 (46%)	3.33 (0.9–12.2)	0.044
<i>sei</i>	33 (83%)	22 (100%)	2.94 (1.1–13.7)	0.044
<i>chp</i>	39 (98)	16 (73%)	0.07 (0.0–0.7)	0.006
<i>eta</i>	8 (20%)	6 (27%)	1.5 (0.4–5.9)	0.539
<i>pvl</i>	4 (10%)	5 (23%)	2.65 (0.5–14.9)	0.259

CC, clonal complex; CI, confidence interval; IE, infective endocarditis; MIC, minimum inhibitory concentration; OR, odds ratio.

^a Analysis for in-hospital mortality using the same variables did not differ from that of 1-year mortality (data not shown).

Table 3

Summary of main findings from studies assessing the relationship between vancomycin MIC and prognosis in MSSA bacteraemia and left-sided IE

Study	Design	SAB/IE (n)	Overall mortality		Genetic factors	Main outcomes analysis
			Low VAN MIC (<1.5 µg/mL)	High VAN MIC (≥1.5 µg/mL)		
Kalil, 2014 [11]	Systematic review and metaanalysis	SAB (8291, both MRSA and MSSA)	25.8% (1430/5551)	26.8% (734/2740)	NA	RD 1.6% (95% CI –2.3 to 5.6); p 0.43 (for absolute risk of mortality, combining 30-day mortality and in-hospital mortality)
Holmes, 2011 [1]	Prospective multicentre cohort study	SAB (532; 266 of which MSSA treated with β-lactams only)	12.2% (24/193)	26.8% (18/68)	NA	p 0.011 (for 30-day mortality)
Holmes, 2014 [12]	Analysis of a subset of strains from [1]	SAB (252 MSSA isolates)	NA	NA	Associated to HVM: CC8, <i>agr</i> dysfunction, <i>agr</i> genotype II, <i>blaZ</i> , <i>sea</i> , <i>clfA</i> , <i>splA</i> and ACME locus Associated to LVM: CC22, CC88 and CC188	Associated to HVM: CC8 p <0.001, <i>agr</i> dysfunction (p 0.014), <i>agr</i> genotype II (p 0.043), <i>blaZ</i> (p 0.002), <i>sea</i> (p <0.001), <i>clfA</i> (p <0.001), <i>splA</i> (p <0.001) and ACME locus (p 0.02). Associated to LVM: CC22 (p <0.001), CC88 (p <0.001) and CC188 (p 0.002)
Aguado, 2011 [2]	Retrospective, single-centre cohort	Catheter-related SAB (99, all MSSA)	10.5% (8/76)	26.1% (6/23)	NA	p 0.13 (for 30-day mortality) OR = 22.9, (95% CI 6.7 to 78.1) for complicated SAB
López-Cortés, 2015 [4]	Prospective, single-centre cohort	SAB (135, all MSSA)	23.6% (25/106)	10.3% (3/29)	No differences in <i>agr</i> distribution or absence of δ-haemolysin between isolates with HVM and those with LVM. HVM was not more frequent in specific clones	RR = 0.44 (95% CI 0.14 to 1.35) for 14-day mortality
Viedma, 2014 [3]	Retrospective, single-centre cohort	SAB (84, all MSSA)	24.1% (7/29)	45.5% (25/55)	HVM: <i>agr II</i> polymorphism: 17.2% ; average levels of RNAIII gene expression: ΔC _t 1.5 ± 2.11 LVM: <i>agr II</i> polymorphism: 41.8% ; average levels of RNAIII gene expression: ΔC _t 4.05 ± 3.29	In-hospital mortality: p 0.057 <i>agr</i> dysfunction: p 0.023. RNAIII expression: p <0.01
Cervera, 2014 [5]	Prospective, single-centre cohort	MSSA IE (93)	31% (16/53)	53% (21/40)	NA	In-hospital mortality: p 0.035; Patients with HVM presented significantly more severe embolic events
Current study	Prospective, multicentre cohort	MSSA IE (62)	32% (9/28)	27% (9/34)	HVM: <i>agrII</i> polymorphism: 19% LVM: <i>agrII</i> polymorphism: 38%	In-hospital mortality: p 0.780. <i>agrII</i> polymorphism: p 0.157

CI, confidence interval; HVM, high vancomycin MIC; IE, infective endocarditis; LVM, low vancomycin MIC; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not addressed; OR, odds ratio; RD, relative difference; RR, relative risk; SAB, *S. aureus* bacteraemia; VAN, vancomycin.

LVM and HVM. Further studies in this field are warranted to expand on these findings and to elucidate whether the contradictory results obtained in this field [14] are due to methodologic limitations or rather to a difficult-to-interpret phenomenon.

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Transparency Declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2017.01.017>.

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