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Original

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Staphylococcus aureus bacteremia in a secondary level Spanish hospital: clinical implications of high vancomycin MIC

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ABSTRACT

Background. One of the most controversial issues in recent years has been the clinical significance of high vancomycin MIC in *Staphylococcus aureus* bacteremia. The aim of this study was to elucidate the clinical implication that this parameter has in the staphylococcal bacteremia of a second level hospital.

Material and methods. Retrospective descriptive study between January 2014 and September 2016 with 138 records from the blood culture Severo Ochoa University Hospital registry. A total of 98 cases were finally analized. Microbiological analysis of vancomycin MIC was performed using micro dilution technique.

Results. The mean age was 71.4 ± 12.45 and 63.26% of the patients had a Charlson index ≥6. A 30.61% were carriers of a venous central catheter. The most frequent source was venous central catheter (26.53%). There were 14.24% metastatic events. Global mortality rate at 30 days was 25.51%. The 43.87% of strains had a vancomycin MIC ≥ 2 mg/L. High vancomycin MIC was significantly associated with persistent bacteremia (OR 3.12 [1.13-8.93]), maintaining this statistical significance in methicillin-resistant *S. aureus* (MRSA) group (p =0.001) but no in methicillin-susceptible *S. aureus* (MSSA) group (p = 0.13). Persistent bacteremia was also significantly related with permanent catheter carriers (OR 4.18 [1.38-12.61]), peripheric catheter source (OR 5.18 [1.13-8.93]) and metastatic complications (OR 3.82 [1.03-12.81]). There was no significant association between high vancomycin MIC and mortality.

Conclusions. High vancomycin MIC may be useful in daily clinical practice as a marker of poor clearance of *S. aureus* bacteremia, specially when is due to MRSA strains.

Keywords: *Staphylococcus aureus* bacteremia, high vancomycin MIC, persistent bacteremia.

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Bacteriemia por *Staphylococcus aureus* en un hospital de segundo nivel en España: implicaciones de la CMI elevada a vancomicina

RESUMEN

Introducción. En los últimos años, el significado clínico de la CMI elevada a vancomicina en la bacteriemia por *Staphylococcus aureus* ha sido un tema de una enorme controversia científica. El objetivo de este estudio fue dilucidar la implicación clínica que este parámetro tiene en la bacteriemia estafilocócica de un hospital de segundo nivel.

Material y métodos. Estudio descriptivo retrospectivo entre enero 2014 y septiembre 2016 con 138 entradas del registro de hemocultivos del Hospital Universitario Severo Ochoa de Leganés. Se analizaron un total de 98 casos. El análisis microbiológico de la CMI a vancomicina se realizó mediante técnica de microdilución. El análisis estadísitico se realizó mediante SPSS 20.0: Shapiro Wilk, $\chi 2$, Mann Whitney, regresión logística y Kaplan Meier.

Resultados. La media de edad fue 71,4 ± 12,45. Un 63.26% de los pacientes tenían un índice de Charlson ≥6. El 30,61% eran portadores de vía venosa central (VVC). El foco más frecuente fue la VVC (26,53%). Hubo un 14,24% de embolismos a distancia. La mortalidad global a los 30 días fue de 25,51%. El 43,87% de las muestras tenían una CMI≥ 2mg/L a vancomicina. La CMI elevada a vancomicina se asoció de forma significativa con la bacteriemia persistente (OR 3,12 [1,13-8,93]), manteniendo esta significación estadística en el grupo de *S. aureus* resistente a meticilina (SARM) (p=0,001), pero no en el grupo

de *S. aureus* sensible a meticilina (SASM) (p=0,13). La bacteriemia persistente se relacionó también con portadores de VVC permanente (OR 4,18 [1,38-12,61]), con el foco asociado a vía venosa periférica (OR 5,18 [1,13-8,93]) y con las embolismos a distancia (OR 3,82 [1,03-12,81]). No se encontraron diferencias significativas entre la CMI a vancomicina y la mortalidad.

Conclusiones. La CMI elevada a vancomicina podría ser un parámetro útil como marcador de retraso en el aclaramiento de la bacteriemia por *S. aureus*, especialmente en el contexto de bacteriemia por SARM.

Palabras clave: bacteriemia por *Staphylococcus aureus*, CMI alta a vancomicina, bacteriemia persistente.

INTRODUCTION

Staphylococcus aureus is the most frequent pathogen in many situations such as nosocomial bacteremia, endocarditis and arthritis [1] and is also characterized by its high morbidity and mortality [2]. Since the first series of methicillin-resistant *S. aureus* (MRSA) were described in the 1960s, over the past 40 years the resistance to beta-lactams have been dispersed from nosocomial environment to the community. Furthermore, the already classic Cosgrove meta-analysis observed that MRSA bacteremia mortality rate is higher than associated with methicillin-susceptible *S. aureus* (MSSA) [3,4]. All of this has led to the fact that in recent years, vancomycin has become the drug of choice for the empirical treatment of *S. aureus* bacteremia (SAB) and practically, until 10 years ago, the only option for MRSA targeted treatment. In the last few years, several authors have described a progressive increase in *S. aureus* vancomycin minimal inhibitory concentration (MIC) [5-10]. This relies on the conformation of a thicker bacterial wall that makes vancomycin binding to peptidogly can D-Alanine residues in bacterial wall more difficult. Moreover, it has been observed that in apparently susceptible to vancomycin isolates it is possible to identify *S. aureus* sub populations with vancomycin-intermediate susceptibility (hVISA) [11]. The clinically distinct behavior of the strains with a vancomycin MIC in the upper limit of the sensitivity has also been reported [12-14]. However, the concrete role of this finding remains controversial [15]

The aim of this study was to identify possible factors associated with complicated SAB, its associated mortality and to establish a relationship between this outcomes and high vancomycin MIC.

MATERIAL AND METHODS

A retrospective descriptive study was performed between January 2014 and September 2016 from blood culture registry of Severo Ochoa University Hospital in Leganés, Madrid, Spain. It is a 382-bed hospital that serves to an estimated population of 250,000 habitants. It is also a reference hospital for 5 different socio-sanitary residence for elderly patients. A total of 138 records were retrospectively collected. Exclusion criteria were: recurrent bacteremia within 8 weeks, cases with definitive follow-up in another hospital, and cases in which no information was available about antibiotic therapy used. Clinical, microbiological, therapeutic and prognostic variables were analyzed for the 98 cases selected through paper and electronic medical records.

SAB was defined as at least one positive blood culture for *S. aureus*. Co-morbidity was measured by Charlson score index and it was later stratified in two groups (≥6 score vs. <6 score). Particular comorbid conditions were also collected, so as being central venous catheter (CVC) carrier and vascular device carrier (including pacemakers and endovascular grafts). Three acquisition categories were considered according to Friedman criteria [16]: 1) nosocomial SAB ifthe episode was diagnosed at least 48 hours after hospital admission; 2) healthcare related-SAB if the patient had had contact with healthcare system in the previous 3 months; 3) community acquired SAB source was defined as any event detected within 48 hours of hospital admission. Unknown source bacteremia was set out when its origin was uncertain after careful examination of clinical an microbiological data. Empirical antibiotic was defined as any treatment administered in the first 48 hours after bacteremia, despite of the lack ofmicrobiological information. Definitive antibiotic was considered as the treatment administered after appropriate microbiological isolation and susceptibility tests. Antibiotic treatment was considered appropriate if the strain was susceptible to at least one of the administered antibiotics, with the exception of aminoglycosides, which were considered inappropriate regardless of the sensitivity test. Guidelines concordant treatment was determined as any treatment that is contemplated in Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) guidelines (only vancomycin, daptomycin, linezolid, cloxacillin, fosfomycin) [17]. Persistent bacteremia was defined as positive blood cultures after more than 48 hours of appropriate antibiotic therapy. General complications were defined as every kind of complication during the hospitalization directly related or not with SAB. Metastatic complications were considered as the present of at least one secondary focus to bloodstream seeding. Focus control was considered if the catheter or foreign body was removed or if a surgical intervention was performed. Global mortality rate at 30 days was defined as death by any cause 30 days after the initial bacteremia. In-hospital mortality rate was defined as *exitus letalis* by any cause during the admission.

Blood cultures were processed by BACTEC 9240© (Becton Dickinson Diagnostic Instrument Systems, USA). Isolates were identified according to standard microbiological techniques. Minimum inhibitory concentration (MIC) was determined by microdilution method (ESTEN© 2009) in accordance with CLSI criteria in 2014 (S < 2 mg/L, I 4-8 mg/L, R ≥ 16 mg/L). All determinations were made under blind conditions without knowledge of any clinical outcome.

Shapiro-Wilk test for was performed to check normal distribution of the sample. Continuous variables were compared using Mann Whitney U-test. Qualitative and stratified continuous variables were compared using Pearson's chi-squared test. Multivariate analysis with logistic regression was performed for

Table 1 **Global series characteristics and outcomes. Univariate analysis between MRSA and MSSA subgroups.**

	SAB (98; 100%)	MRSA bacteremia (40; 40.81%)	MSSA bacteremia (58; 59.18%)	p (IC 95%)
Age	71.41 ± 12.45	75.65 ± 11.35	68.48 ±12.37	0.003
Sex				
Women	40 (40.80)	16 (40)	24 (41.37)	1.00
Men	58 (59.18)	24 (60)	34 (58.62)	
Charlson				
≥6	62 (63.26)	31 (77.5)	31 (53.44)	0.01
<6	36 (36.73)	9 (22.5)	27 (46.55)	
Morbidity				
Cardiovascular	51 (52.04)	25 (62.50)	26 (44.82)	0.10
Hepatic	15 (15.30)	5 (12.50)	10 (17.24)	0.58
Nephropaty	22 (22.44)	10 (25)	12 (20.68)	0.63
COPD	30 (30.61)	17 (42.5)	13 (22.41)	0.04
Arteriopathy	26 (26.55)	14 (35)	12 (20.68)	0.16
Immunosupression	14 (14.28)	8 (20)	6 (10.34)	0.24
Neoplasia	22 (22.44)	8 (36.36)	18 (24.13)	0.80
Diabetes	28 (28.57)	14 (35)	14 (24.13)	0.26
VCC	30 (30.61)	13 (32.5)	17 (29.3%)	0.82
Permanent	22 (22.44)	11 (27.5)	12 (20.7%)	0.47
Transient	8 (8.16)	3 (7.5)	5 (8.6)	1.00
Vascular device	9 (9.18)	6 (15)	3 (5.17)	0.15
Nosocomial	47 (47.95%)	21 (52.5)	26 (44.82)	0.53
Health-care related	24 (24.48%)	8 (20)	16 (27.58)	0.47
Community	27 (27.55%)	11 (27.5)	16 (27.58)	1.00
ICU admission	23 (23.46)	10 (25)	13 (22.80)	0.81
Source				
Endovascular	39 (39.79)	9 (22.5)	30 (51.72)	0.006
VCC	26 (26.53)	9 (22.5)	17 (29.31)	0.49
VPC	11 (11.22)	–	11 (18.96)	0.002
Vascular graft	2 (2.04)	–	2 (3.44)	0.51
Primary	23 (23.46)	11 (27.50)	12 (20.66)	0.47
Respiratory	9 (9.18)	5 (12.50)	4 (6.89)	0.48
Soft tissue	11 (11.22)	7 (17.5)	4 (6.89)	0.11
Osteoarthricular	2 (2.04)	–	2 (3.44)	0.51
Urinary	3 (3.06)	2 (5)	1 (1.70)	0.56
TTE done	54 (55.10)	22 (40)	32 (55.17)	1.00
TEE done	17 (17.34)	8 (20)	9 (15.51)	0.59
Empirical treatment				
Correct	71 (72.44)	23 (57.5)	48 (82.75)	0.11
Guidelines concordant	36 (36.73)	13 (32.5)	17 (29.31)	0.80
Vancomycin	27 (27.55)	2 (5)	14 (24.13)	0.37
Daptomycin	3 (3.06)	–	1 (1.72)	0.56
Linezolid	–	–	–	-
Cloxacillin	–		–	-
Definitive treatment				
Vancomycin	31 (31.62)	18 (45)	13 (22.41)	0.02
Daptomycin	10 (10.20)	7 (17.5)	3 (5.17)	0.08
Linezolid	15 (15.30)	11 (27.5)	4 (6.89)	0.009
Cloxacillin	23 (23.46)	–	23 (39.65)	0.000
Not concordant	19 (19.38)	4 (10)	15 (25.86)	0.06
Control blood cultures	51 (52.04)	21 (52.5)	30 (51.72)	1.00
Persistent bacteremia	24 (24.48)	8 (20)	16 (27.58)	0.47
Source control	38 (38.77)	11 (27.50)	27 (46.55)	0.26
General complications	41 (41.83)	17 (42.5)	24 (41.37)	1.00
Metastasic infection	14 (14.28)	5 (12.5)	9 (15.51)	0.74
Endocarditis	4 (4.08)	1 (2.5)	3 (5.17)	0.64
Thrombophlebitis	3 (3.06)	1 (2.5)	2 (3.44)	1.00
Osteomielitis	7 (7.14)	3 (7.5)	4 (6.89)	1.00
30 days mortality	25 (25.51)	10 (25)	15 (25.86)	1.00
In-hospital mortality	27 (27.55)	12 (30)	15 (25.86)	0.65

Data are no. (%) of patients. SAB (*S. aureus* bacteremia), COPD (Chronic Obstructive Pulmonary Disease), ICU (Intensive Care Unit), Venous Central Catheter (VCC), Venous Peripheral Catheter (VPP), TTE (Transthoracic Echocardiography), TEE (Transesophageal Echocardiography)

Table 2 **Comparative between MIC ≥ 2 mg/L and MIC <2 mg/L strains: characteristics and outcomes with univariate and multivariate analysis.**

	MIC ≥ 2 mg/L (n; %) (43/98; 43.87)	MIC < 2 mg/L (n; %) (55/98; 56.12)	p (IC 95%)	Multivariate analysis (p <0.20)
Age	71.49 ± 13.73	71.35 ±11.42	0.53	
Sex				
Women	20 (46.51)	20 (36.36)	0.40	
Men	23 (53.48)	35 (63.63)		
Charlson				
≥6	29 (67.44)	33 (60)	0.52	
<6	14 (32.55)	22 (40)		
Morbidity				
Cardiovascular	26 (60.46)	25 (45.45)	0.15	
Hepatic	4 (9.30)	11 (20)	0.16	
Nephropathy	12 (27.90)	10 (18.18)	0.30	
COPD	14 (32.55)	16 (29.09)	0.82	
Arteriopathy	15 (34.88)	11 (27.27)	0.11	
Immunodeficiency	4 (9.30)	7 (12.72)	0.75	
Neoplasia	9 (20.93)	13 (23.63)	0.81	
Diabetes	14 (32.55)	14 (25.45)	0.50	
Vascular device	6 (13.95)	3 (5.45)	0.17	
VCC	14 (32.55)	16 (29.09)	0.82	
Permanent	11 (25.6)	12 (21.8)	1.00	
Transient	4 (9.30)	4 (7.27)	0.72	
Nosocomial	19 (44.18)	28 (50.90)	0.54	
Health related	12 (27.90)	12 (21.81)	0.63	
Community	12 (27.90)	15 (27.27)	1.00	
ICU admission	10 (23,25)	13 (23.63)	1.00	
Source				
Endovascular	17 (39.53)	22 (40)	1.00	
VCC	11 (25.58)	15 (27,27)	1.00	
VPC	4 (9.30)	7 (12.72)	0.75	
Vascular graft	2 (4.65)	0 (0)	0.19	
Desconocido	11 (25.58)	12 (21.18)	0.81	
Respiratory	3 (6.97)	6 (10.90)	0.72	
Soft tissue	5 (11.62)	6 (10.90)	1.00	
Osteoarthricular	7 (16.27)	6 (10.90)	0.55	
Urinary	-	3 (10.90)	0.25	
TTE	26 (60.46)	28 (50.90)	0.41	
TEE	8 (18.60)	9 (16.36)	0.79	
Empirical treatment				
Correct	32 (74.41)	39 (70.09)	0.81	
Guidelines concordant	16 (37.20)	20 (36.36)	1.00	
Vancomycin	14 (32.55)	13 (23.63)	0.36	
Daptomycin	2 (4.65)	1 (1.81)	0.58	
Linezolid	–	–	-	
Cloxacillin	–	–	-	
Definitive treatment				
Vancomycin	10 (23.25)	21 (38.18)	0.13	
Daptomycin	9 (20.93)	1 (1.81)	0.04	P 0.01 OR 14.76 (1.75 – 124.09)
Linezolid	7 (16.27)	8 (13.54)	1.00	
Cloxacillin	10 (23.25)	13 (23.63)	1.00	
Not concordant	7 (16.27)	12 (21.81)	0.60	
MRSA	19 (47.5)	21 (52.2)	0.67	
MSSA	24 (41.4)	34 (58.6)	0.67	
Control blood cultures	22 (51.62)	30 (54.54)	0.68	
Persistent bacteremia	15 (34.88)	9 (16.36)	0.05	P 0.04 OR 2.83 (1.05 – 7.62)
Source control	16 (37.20)	22 (40)	1.00	
General complications	17 (39.53)	24 (43.63)	0.85	
Metastasic infection	6 (13.95)	8 (14.54)	1.00	
Endocarditis	3 (6.97)	1 (2.32)	0.31	
Thrombophlebitis	-	3 (5.45)	0.25	
Osteomyelitis	3 (6.97)	4 (7.27)	1.00	
30 days mortality	10 (23.25)	15 (27.27)	0.81	
In-hospital mortality	12 (27.90)	15 (27.27)	1.00	

Data are no. (%) of patients. COPD (Chronic Obstructive Pulmonary Disease), ICU (Intensive Care Unit), Venous Central Catheter (VCC), Venous Peripheral Catheter (VPP), TTE (Transthoracic Echocardiography), TEE (Transesophageal Echocardiography)

Table 3 **Univariate and multivariate analysis for factors associated with persistent *S. aureus* bacteremia.**

	Persistent bacteremia (24; 24.48%)	NO persistent bacteremia 74 (75.51%)	p (IC 95%)	Multivariate analysis (p<0.20)
Age	70.54 ± 14.33	71.69 ± 11.83	0.92	
Sex				
Women	11 (45.83)	29 (39.18)	0.63	
Men	13 (54.16)	45 (60.81)		
Charlson				
≥6	13 (54.16)	49 (66.21)	0.32	
<6	11 (45.83)	25 (33.78)		
Morbidity				
Cardiovascular	14 (58.33)	37 (50)	0.49	
Hepatic	2 (8.33)	13 (17.56)	0.34	
Nephropathy	5 (20.83)	17 (22.97)	1.00	
COPD	5 (20.83)	25 (33.78)	0.31	
Arteriopathy	6 (25)	20 (27.02)	1.00	
Immunodeficiency	2 (8.33)	9 (12.16)	1.00	
Neoplasia	4 (16.66)	18 (24.34)	0.57	
Diabetes	6 (25)	22 (29.79)	0.79	
Catheter	12 (50)	18 (24.3)	0.02	P 0.008, OR 4.08 (1.43 – 11.61)
Permanent	9 (37.5)	13 (17.6)	0.05	
Transient	3 (12.5)	5 (6.8)	0.40	
Vascular device	1 (4.16)	8 (10.81)	0.44	
Nosocomial	10 (41.66)	37 (50)	0.49	
Health-care related	7 (29.16)	17 (22.97)	0.58	
Community	7 (29.16)	20 (27.02)	1.00	
ICU admission	18 (75)	56 (75.67)	1.00	
Source				
Endovascular	12 (50)	27 (36.48)	0.30	
CVC	7 (29.16)	19 (25.67)	0.79	P 0.88, OR 3.50 (0.831 – 14.74)
PVC	5 (20.83)	6 (8.10)	0.13	
Vascular graft	–	2 (2.70)	1.00	
Unknown	7 (29.16)	16 (21.62)	0.58	
Respiratory	2 (8.33)	7 (9.45)	1.00	
Soft tissue	2 (8.33)	9 (12.16)	1.00	
Osteoarthricular	1 (4.16)	12 (16.21)	0.17	
Urinary	–	3 (4.05)	1.00	
TTE done	11 (14.78)	43 (58.10)	0.34	
TEE done	3 (12.5)	15 (20.27)	0.54	
Empirical treatment				
Correct	18 (75)	53 (71.62)	1.00	
Guidelines concordant	8 (33.33)	28 (37.83)	0.80	
Vancomycin	6 (25)	21 (28.37)	1.00	
Daptomycin	1 (4.16)	2 (2.7)	1.00	
Linezolid	–	–	-	
Cloxacillin	–	–	-	
Definitive treatment				
Vancomycin	5 (20.83)	26 (35.13)	0.21	
Daptomycin	2 (8.33)	8 (10.81)	1.00	
Linezolid	6 (25)	9 (12.16)	0.18	
Cloxacillin	5 (20.83)	18 (24.32)	1.00	
Not ideal	6 (25)	13 (17.56)	0.55	
Source control	11 (45.83)	27 (36.48)	0.47	
General complications	7 (29.16)	34 (45.94)	0.16	
Metastasic infection	6 (25)	8 (10.81)	0.10	P 0.04; OR 3.82 (1.03 – 12.81)
Endocarditis	3 (12.5)	1 (4.16)	0.44	
Thrombophlebitis	1 (4.16)	2 (2.70)	1.00	
Osteomyelitis	2 (8.33)	5 (6.75)	1.00	
MIC ≥ 2 mg/L	15 (62.5)	28 (37.83)	0.05	P 0.02; OR 3.12 (1.13– 8.93)
MRSA	8 (33.33)	32 (43.24)	0.47	
MSSA	16 (66.66)	42 (56.75)	0.47	
30 days mortality	6 (25)	20 (27.02)	1.00	

Data are no. (%) of patients. COPD (Chronic Obstructive Pulmonary Disease), ICU (Intensive Care Unit), Venous Central Catheter (VCC), Venous Peripheral Catheter (VPP), TTE (Transthoracic Echocardiography), TEE (Transesophageal Echocardiography)

Table 4 **Univariate and multivariate analysis for factors associated with persistent MRSA bacteremia and persistent MSSA bacteremia.**

	Persistent MRSA bacteremia YES (8/40; 20%)	Persistent MRSA bacteremia NO (32/40; 80%)	P	Persistent MSSA bacteremia YES (16/58; 27.58%)	Persistent MSSA bacteremia NO (42/58; 72.41%)	p
General complications	4 (50)	13 (40.62)	0.70	5 (31.25)	19 (45.23)	0.38
Metastasic infection	3 (37.5)	2 (6.25)	0.04	3 (18.75)	6 (14.28)	0.69
Endocarditis	1 (12.5)	–	0.20	2 (12.5)	1 (2.38)	0.18
Thrombophlebitis	1 (12.5)	–	0.20	–	2 (4.76)	1.00
Osteomyelitis	1 (12.5)	2 (6.25)	0.49	1 (6.25)	2 (4.76)	1.00
MIC ≥ 2 mg/L	6 (75)	2 (6.25)	0.001	9 (56.25)	14 (33.33)	0.13
30 days mortality	2 (25)	8 (25)	1.00	3 (18.75)	12 (28.57)	0.52

Data are no. (%) of patients. COPD (Chronic Obstructive Pulmonary Disease), ICU (Intensive Care Unit), Venous Central Catheter (VCC), Venous Peripheral Catheter (VPP), TTE (Transthoracic Echocardiography), TEE (Transesophageal Echocardiography)

all variables which achieved p<0.20 in univariate analysis. Odds ratio were calculated with 95% confidence interval. Kaplan Meier survival was determined up to week 135 from the start of the study date (January 1st, 2014). Associations that reached p value <0.05 (CI of 95%) were considered statistically significant. Analysis were performed using SPSS 20.0.0 (Microsoft, USA).

The regional ethical comitte aproved this work (EC 27/18), and because no direct patient contact was planned, the requirement for informed consent was waived.

RESULTS

Patients and episode characteristics. The mean age was 71.41±12.45 years with 59.2% of men and 63.3% of the patients had a Charlson comorbidity index ≥ 6. A 47.95% of patients had a SAB nosocomial episode and a 27.98% a health care related episode. There were 40 cases of MRSA bacteremia (40.81%) and 58 cases of MSSA bacteremia (59.18%). Other baseline characteristics are shown in table 1.

The most frequent bacteremia source was catheter (34.88%) followed by primary bacteremia (23.46%). Endovascular source was more common in MSSA than in MRSA group (51.72% vs. 22.50%, p=0.006) and this was at expense of peripheral venous catheter bacteremia (18.96% vs. 0, p=0.002). A 41.8% of patients had some type of complication during the episode and 14.24% had an episode attributable to blood spread: 7 cases of osteomyelitis, 4 cases of endocarditis and 3 cases of thrombophlebitis. A 63.26% of patients received an empirical antibiotic different than recommended by the SEIMC guidelines and vancomycin was also the drug of choice for definitive treatment (31.62%). Other clinical and episode characteristics are shown on table 1.

There were 43 cases (43.87%) with a vancomycin MIC³2 mg/L: 42 cases with MIC=2 mg/L and 1 case with MIC=4 mg/L. Distribution between MRSA and MSSA group was 47.5% and 41.1% respectively. Differences in patients characteristics according to vancomycin MIC were not found. There were no significant differences in age, comorbidity, source or complications according to vancomycin MIC. Daptomycin was the definitive treatment in vancomycin MIC ≥ 2 mg/L SAB (20.93% vs. 1.81%, p=0.01; OR 14.76 [1.75–124.09]). Other items are described in table 2.

Outcomes. Persistent bacteremia was present in a total of 24 patients (24.48%). Differences between MRSA and MSSA group were not found. However, persistent bacteremia was significantly more common in high vancomycin MIC SAB (34.88% vs. 16.36%, p 0.05). A multivariate analysis of risk factors for persistent SAB was performed (table 3). Having a CVC was the main risk factor (OR 4.18; 1.38-12.61; p=0.008) to have a persistent SAB, followed by metastatic infection in general (OR 3.82; 1.03–12.81; p=0.04) and vancomycin MIC=2 mg/L (OR 3.12; 1.13–8.93; p= 0.02). In the MRSA subgroup analysis this was more evident showing that vancomycin MIC ≥ 2 mg/L it is more frequently associated with persistent MRSA bacteremia (75% vs. 6.25%; p=0.001). Persistent MRSA bacteremia is also more associated with metastatic complications (37.5% vs. 6.25%, p=0.004). Other items are shown in table 4.

Overall mortality at 30 days was 25.5%. There were no differences between MRSA and MSSA group, although there were more general in-hospital mortality in the first group. Survival analysis confirms these findings, with a survival rate of 70% at 135 weeks of follow-up that occurs mainly in the first week after the episode. Differences according to vancomycin MIC were not found. Multivariate analysis (table 5) showed that mortality was independently associated with general complications (OR 4.03; 1.42–1.44; p=0.009), other definitive treatment different from the contemplated in national guidelines (OR 3.72; 1.12–12.63; p=0.03), respiratory source (OR 3.72; 1.12–12.63; p=0.09) and age (OR 1.04; 0.99–1.09; p=0.05).

Table 5 **Univariate and multivariate analysis for factors associated with global mortality at 30 days for *S. aureus* bacteremia between January 2014 and September 2016 in Severo Ochoa University Hospital.**

	Mortality 30 days YES (26; 26.53%)	Mortality 30 days NO (72; 73.46%)	P <0.05 (IC 95%)	Multivariate analysis (p <0.20)
Age	75.73 ± 10.47	69.85 ± 12.76	0.05	P 0.05 OR 1.04 (0.99 – 1.09)
Sex				
Women	10 (38.46)	30 (41.66)	0.82	
Men	16 (61.53)	42 (58.33)		
Charlson				
≥6	20 (76.92)	42 (58.33)	0.10	
<6	42 (58.33)	30 (41.66)		
Morbidity				
Cardiovascular	10 (38.46)	35 (48.61)	0.36	
Hepatic	6 (23.07)	9 (12.5)	0.21	
Nephropathy	8 (30.76)	14 (19.44)	0.27	
COPD	11 (42.30)	19 (26.38)	0.14	
Arteriopathy	9 (34.61)	17 (23.61)	0.30	
Immunodeficiency	3 (11.53)	8 (11.11)	1.00	
Neoplasia	5 (19.23)	17 (23.61)	0.78	
Diabetes	7 (26.92)	21 (29.16)	1.00	
Catheter	6 (23.10)	24 (33.33)	0.45	
Permanent	2 (7.69)	20 (27.8)	0.05	
Transient	4 (15.4)	4 (5.60)	0.20	
Vascular device	2 (7.69)	7 (9.72)	1.00	
Nosocomial	11 (42.30)	36 (50)	0.64	
Health-care related	6 (23.07)	18 (25)	1.00	
Community	9 (34.61)	18 (25)	0.44	
ICU admission	6 (23.07)	17 (23.61)	1.00	
Source				
Endovascular	6 (23.07)	33 (45.83)	0.61	
CVC	3 (11.58)	23 (31.94)	0.06	
PVC	2 (7.69)	9 (12.5)	0.72	
Vascular graft	1 (3.84)	1 (1.38)	0.46	
Unknown	8 (30.76)	15 (20.83)	0.41	
Respiratory	5 (19.23)	4 (5.55)	0.05	P 0.09 OR 3.72 (0.80 – 17.25)
Soft tissue	3 (11.53)	8 (11.11)	1.00	
Osteoarthricular	3 (11.53)	10 (13.88)	1.00	
Urinary	1 (3.84)	2 (2.77)	1.00	
TTE done	11 (42.30)	43 (59.72)	0.16	
TEE done	2 (7.69)	15 (20.83)	0.22	

Table 5 **Univariate and multivariate analysis for factors associated with global mortality at 30 days for *S. aureus* bacteremia between January 2014 and September 2016 in Severo Ochoa University Hospital (cont.).**

	Mortality 30 days YES (26; 26.53%)	Mortality 30 days NO (72; 73.46%)	P <0.05 (IC 95%)	Multivariate analysis (p <0.20)
Empirical treatment				
Correct	18 (69.23)	53 (73.61)	0.79	
Guidelines concordant	9 (34.61)	27 (37.5)	1.00	
Vancomycin	6 (23.07)	21 (29.16)	0.61	
Daptomycin	1 (3.84)	2 (2.77)	1.00	
Linezolid	–	–	-	
Cloxacillin	–	–	-	
Definitive treatment				
Vancomycin	7 (26.92)	24 (33.33)	0.62	
Daptomycin	4 (15.38)	6 (83.33)	0.44	
Linezolid	2 (7.69)	13 (18.05)	0.34	
Cloxacillin	5 (19.23)	18 (25)	0.78	
Not concordant	8 (30.76)	11 (15.27)	0.14	P 0.03 OR 3.72 (1.12 – 12.63)
Control blood cultures	13 (50)	34 (47.22)	0.82	
Persistent bacteremia	6 (23.07)	18 (25)	1.00	
Source control	5 (71.42)	33 (80.48)	0.62	
General complications	17 (65.38)	24 (33.33)	0.006	P 0.009 OR 4.03 (1.42 – 11.44)
Metastasic infection	2 (7.69)	12 (16.66)	0.34	
Endocarditis	-	4 (5.55)	0.57	
Thrombophlebitis	1 (3.84)	2 (2.77)	1.00	
Osteomyelitis	1 (3.84)	6 (8.33)	0.67	
MRSA	10 (38.46)	30 (41.66)	P 0.82	
MSSA	16 (61.53)	42 (58.33)	P 0.82	
MIC ≥ 2 mg/L	32 (41.66)	11 (42.30)	P 1.00	
MRSA MIC ≥ 2 mg/L	5/10 (50)	15/30(50)	P 1.00	
MSSA MIC ≥ 2 mg/L	6/16 (37.5)	17/42 (40.47)	P 1.00	

Data are no. (%) of patients. COPD (Chronic Obstructive Pulmonary Disease), ICU (Intensive Care Unit), Venous Central Catheter (VCC), Venous Peripheral Catheter (VPP), TTE (Transthoracic Echocardiography), TEE (Transesophageal Echocardiography)

DISCUSSION

A retrospective descriptive study of *S. aureus* bacteremia series with 98 episodes in a Spanish secondary hospital between January 2014 and September 2016 is presented. Firstly, SAB continues to be an entity related mainly to elderly and comorbid patients. This fact is particularly emphasized in MRSA subgroup in consonance with previous literature [18]. On the contrary on the literature reviewed [18-20], bacteremia of endovascular source is predominantly associated with MSSA group (p=0.006). This has to do with the association between MSSA bacteremia and peripheral venous catheter. Secondly, although empirical treatment is in most cases correct (72.44%), empirical treatment remains no concordant with guidelines (63.26%). What's more, follow-up cultures are only taken in half of the patients. Since there were no differences in follow-up time between patients who had follow-up cultures and those who did not, this may be related to the type of patient in our setting (elderly and with great comorbidity) and a tendency towards a more conservative attitude that limitates venipuncture. Furthermore, definitive treatment is not always adjusted to the clinical practice national guidelines (30.76%). As several jobs have shown in recent years [21-22], quality of care in SAB has an impact on prognosis. This is expressed in the study with the fact that no concordant definitive treatment is associated with mortality(OR 3.72; 1.12–12.63; p=0.003). The fact that our center does not have a multidisciplinary nosocomial infection management team in which the infectious diseases physician

advises other professionals on the adequate management of complex processes such as SAB, could explain this poor adherence to the guidelines.

Thirdly, the more important factors associated with persistent SAB are being a CVC carrier, having a metastatic complication and vancomycin MIC ≥ 2 mg/L. In the past few years, several authors have reported this vancomycin progressive high creep, with different results in clinical practice. There are several opinions on this point [23-25], but most of the research is in favor of high vancomycin MIC turns into a thickness of bacterial cell wall peptidoglycan and a delayed transition to the postexponential growth phase because of alterations in bacterial metabolism and possibly a blockage in the adhesive phase of *S. aureus* [26-28]. The *agr* system is a genetic regulon that encodes most of the proteins that have to do with these functions and it also has been observed that there is a correlation between reduced susceptibility to vancomycin and reduce *agr* regulon expression, particularly with *agr* genotype II [29]. All this could lead to a greater tendency to persistent bacteremia. As REIPI group has recently reported [30], in MRSA subgroup this is more evident and it seems that it could be related also with metastatic complications. In our series, any predisposing factor to having a high vancomycin MIC SAB was found. Although, high vancomycin MIC was related with persistent bacteremia, there were not any relationship between high vancomycin MIC and mortality or general complications. Contrary to many authors, no statistically significant association was found between persistent bacteremia and vancomycin MIC in the subgroup of MSSA, probably due to sample size. However, in MRSA subgroup analysis, this association was more evident showing that high vancomycin MIC it is more frequently associated with persistent MRSA bacteremia(75% vs. 6.25%, p=0.001) and also, that persistent MRSA bacteremia is more associated with metastatic complications (37.5% vs. 6.25%, p=0.004).

The strength of our study is the great proportion of high vancomycin MIC. *S. aureus* strains. We think that this may have to do with the fact that vancomycin is the most used antibiotic for gram positive bacteremia in our area, but we are aware of a genetic study of is maybe needed. Because this is a retrospective and descriptive study, it has many limitations. The reduced sample size make difficult to establish a statistically significant relationship between persistent MSSA bacteremia and high vancomycin. It also make difficult to establish risk factors for metastatic complications. Moreover, a multivariate analysis in persistent MRSA bacteremia subgroup could not be performed. There is also a lack of information related to days of persistent bacteremia and the lack of control blood cultures in 47.96% of patients. Furthermore, the fact that vancomycin MIC is measured with microdilution test, may compromise the external validity with other works that are mainly done with E-test.

In conclusion, high vancomycin MIC could be a marker of virulence that guides treatment optimization in SAB. The prevalence of this population in certain settings could also motivate greater compliance with national guidelines for the management of this entity. Although, the impact of this factor on mortality or metastatic complications in this study is low, it has a greater importance in MRSA bacteremia. Prospective and center individualized studies with bigger samples, could help to improve the care and prognosis of this entity in each center.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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