

## Staphylococcus aureus bloodstream infections in Latin America: results of a multinational prospective cohort study

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**Background:** Substantial heterogeneity in the epidemiology and management of *Staphylococcus aureus* bacteraemia (SAB) occurs in Latin America. We conducted a prospective cohort study in 24 hospitals from nine Latin American countries.

**Objectives:** To assess the clinical impact of SAB in Latin America.

**Patients and methods:** We evaluated differences in the 30 day attributable mortality among patients with SAB due to MRSA compared with MSSA involving 84 days of follow-up. Adjusted relative risks were calculated using a generalized linear model.

**Results:** A total of 1030 patients were included. MRSA accounted for 44.7% of cases with a heterogeneous geographical distribution. MRSA infection was associated with higher 30 day attributable mortality [25% (78 of 312) versus 13.2% (48 of 363), adjusted RR: 1.94, 95% CI: 1.38–2.73,  $P < 0.001$ ] compared with MSSA in the multivariable analysis based on investigators' assessment, but not in a per-protocol analysis [13% (35 of 270) versus 8.1% (28 of 347), adjusted RR: 1.10, 95% CI: 0.75–1.60,  $P = 0.616$ ] or in a sensitivity analysis using 30 day all-cause mortality [36% (132 of 367) versus 27.8% (123 of 442), adjusted RR: 1.09, 95% CI: 0.96–1.23,  $P = 0.179$ ]. MRSA infection was not associated with increased length of hospital stay. Only 49% of MSSA bloodstream infections (BSI) received treatment with  $\beta$ -lactams, but appropriate definitive treatment was not associated with lower mortality (adjusted RR: 0.93, 95% CI: 0.70–1.23,  $P = 0.602$ ).

**Conclusions:** MRSA-BSIs in Latin America are not associated with higher 30 day mortality or longer length of stay compared with MSSA. Management of MSSA-BSIs was not optimal, but appropriate definitive therapy did not appear to influence mortality.

## Introduction

*Staphylococcus aureus* is one of the most common causes of bloodstream infections (BSI) worldwide.<sup>1</sup> An important challenge for the treatment of *S. aureus*-BSI is the presence of multidrug resistance. Indeed, MRSA isolates continue to pose important therapeutic challenges worldwide despite the availability of new antibiotics with anti-MRSA activity. The prevalence of MRSA in Latin America appears to be very heterogeneous, ranging from 6% in Central America to 80% in some South American countries.<sup>2</sup> Several studies have shown that mortality rates among patients with BSI caused by MRSA are almost twice as high compared with those patients infected with MSSA isolates.<sup>3–8</sup> For instance, a meta-analysis found that MRSA-BSI was associated with increased mortality compared with MSSA (pooled OR: 1.93, 95% CI: 1.54–2.42).<sup>3</sup> In addition, other studies have shown more healthcare utilization parameters in MRSA-BSI compared with MSSA-BSI.<sup>9–11</sup> MRSA-BSI was associated with a median increase in length of stay of 2 days and a mean excess hospital cost of US\$6916 compared with MSSA in one study.<sup>9</sup> All data available to date suggest that MRSA-BSI pose an important burden to healthcare services, particularly in developing countries where such systems lack robust resources.

Several studies have evaluated the burden of *S. aureus* infections in Latin America, but limited data are available on the clinical impact of MRSA infections in terms of outcomes, utilization of healthcare resources and evaluation of antibiotic management.<sup>2,12</sup> Additionally, studies focusing on the molecular epidemiology of MRSA suggest a high degree of genetic heterogeneity among Latin American MRSA isolates.<sup>12–14</sup> To assess comprehensively the clinical impact of MRSA-BSI and gain insights into the molecular epidemiology of these organisms in Latin America, we conducted a prospective cohort study to evaluate differences in 30 day attributable mortality among patients with clinically significant BSI due to MRSA compared with MSSA recruited from hospitals in nine Latin American countries. Secondary endpoints included the evaluation of parameters of healthcare utilization and appropriateness of treatment (MRSA versus MSSA).

## Patients and methods

### Study design

We conducted a prospective observational cohort study that included 24 hospitals in nine Latin American countries. Adult patients admitted to these hospitals with clinically significant bacteraemia caused by *S. aureus* (at least one positive blood culture was required) from January 2011 to July 2014 were included in the study. Each patient contributed only one episode, which was defined as the 14 day period after collection of the blood sample. Subsequent isolates obtained after the initial blood culture were collected and stored. Patients with polymicrobial bacteraemia or relapse of bacteraemia, those who were transferred from other institutions and those who withdrew from the hospital or died within the first 48 h after the diagnosis were excluded. All isolates were sent to a central laboratory in Bogota, Colombia, to confirm identification. Patients were prospectively followed up to determine outcomes up to 84 days after the initial blood culture.

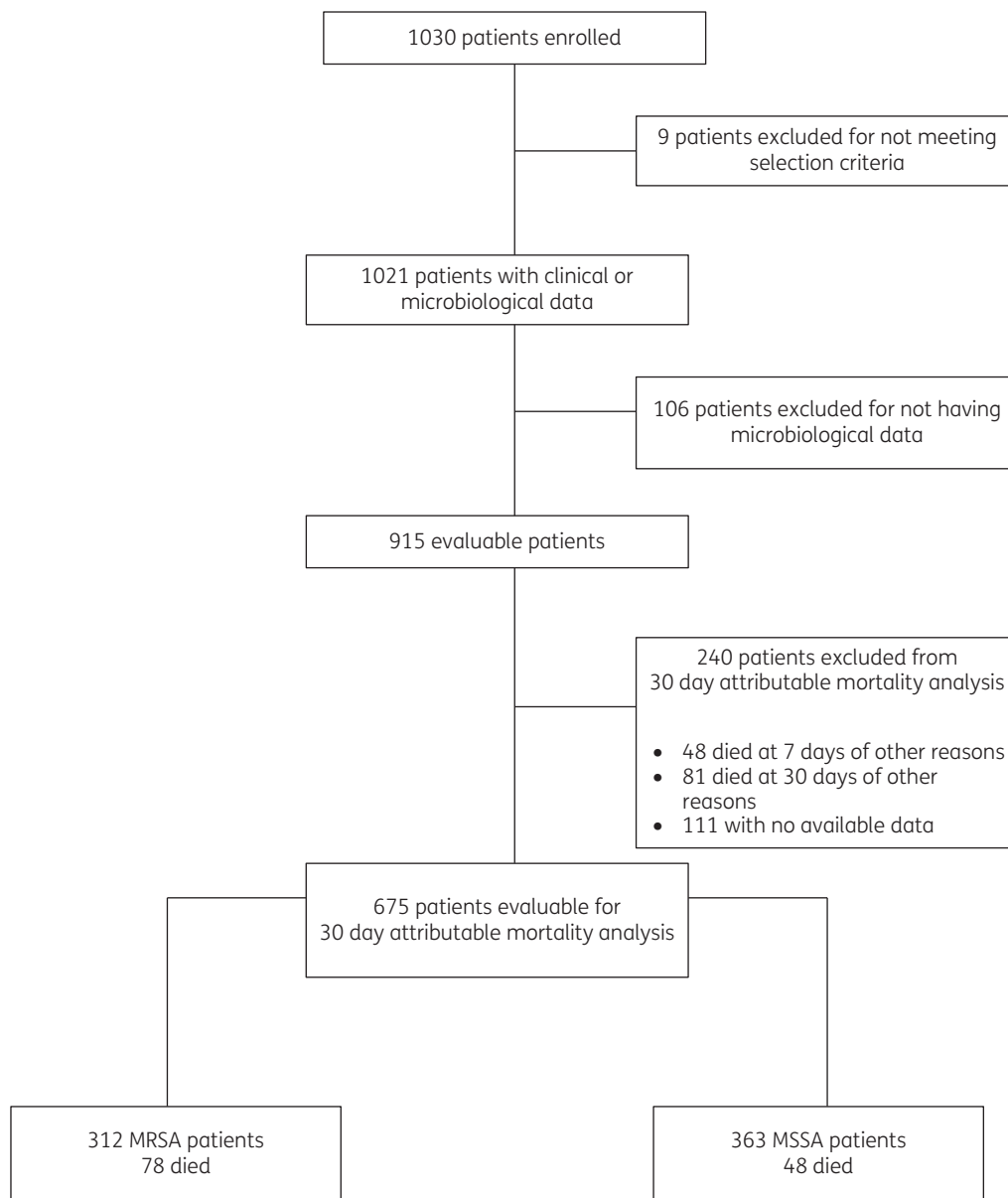
### Data collection

Data were obtained from patients' medical records and entered into a pre-designed electronic case report form. Data gathered included

demographics, comorbidities, microbiological information, antimicrobial therapy received during the 30 day period prior to the current episode, clinical information in the 48 h period before blood sampling, clinical and laboratory information on the current hospitalization, medical treatment provided and clinical outcomes. The place of acquisition was considered community-associated, healthcare-associated or hospital-associated (HA) based on standard definitions (see [Supplementary data](#) available at JAC Online). The Charlson weighted index of comorbidity and the McCabe–Jackson and APACHE II scores were used to evaluate comorbid conditions and severity of illness, respectively. The Pittsburgh bacteraemia score was used to predict mortality. A complicated BSI was defined as the presence of persistent positive blood cultures after 48–96 h, presence of endocarditis, deep tissue infection or metastatic infection. Clinical outcomes were measured at 7, 30 and 84 days after the initial blood culture. The primary outcome of the study was 30 day attributable mortality, but we also evaluated early mortality (7 days after positive blood culture) and late mortality (84 days after positive culture). Three categories of outcomes were considered: improved, unresolved and death. Death attributable to *S. aureus*-BSI was defined as the persistence of clinical signs and symptoms of sepsis without other identifiable cause of death or active infection at the time of death and positive blood cultures within 7 days of a patient's death. Clinical outcomes were obtained from the charts by the investigators at each centre while patients remained hospitalized; for those discharged, every investigator contacted the treating physician to perform a clinical evaluation at the designated times. The healthcare utilization parameters evaluated included length of hospital stay, admission to an ICU, duration of stay in the ICU, readmission rate in the 84 day period after diagnosis and readmission owing to *S. aureus* infection. Adequate management of *S. aureus*-BSI was evaluated by determining the performance of four recommended standards of care: (i) removal of infected foci; (ii) repeat blood cultures after initial sample; (iii) use of proper antibiotic therapy; and (iv) performance of echocardiography.<sup>15,16</sup> Antibiotic therapy was deemed appropriate if it was administered intravenously, and if it was given for at least 14 days for uncomplicated and for at least 28 days for complicated *S. aureus*-BSI. For MSSA-BSI, the appropriate empirical antibiotic therapy included use of  $\beta$ -lactam antibiotics with activity against MSSA with or without vancomycin, teicoplanin or daptomycin. For MRSA-BSI, the appropriate empirical antibiotic therapy included use of vancomycin, teicoplanin or daptomycin with or without a  $\beta$ -lactam. Appropriate definitive antibiotic therapy for MSSA-BSI included the use of  $\beta$ -lactams alone. Appropriate definitive therapy for MRSA-BSI included use of vancomycin, teicoplanin or daptomycin started within 4 days after blood sampling. We considered 4 days as the appropriate time for treating physicians to get susceptibility results from local laboratories.

### Statistical analysis

For sample size calculation, we estimated that two-thirds of the BSIs will be MRSA.<sup>2</sup> Mortality with MSSA was estimated at 25%.<sup>3–8</sup> Thus, we estimated that a sample of 1201 participants with a 95% CI and 80% power would allow us to detect a difference of  $\geq 8\%$  in the 30 day attributable mortality between MRSA and MSSA. The required sample size will decrease if the ratio of MRSA to MSSA is closer to 1, or if the mortality among MSSA is lower than expected. Data analysis was performed using Stata v8.2 (College Station, TX, USA). Frequencies and percentages are presented for categorical variables. For numeric variables, mean and SD or median and IQR were calculated. In bivariate comparisons, we used Fisher's exact test for categorical variable, and Student's *t*-test or Mann–Whitney test for numeric variables as required. For multivariate analysis on mortality, adjusted relative risks were calculated using the generalized linear model, using link log, all variables tested in the bivariate analysis were evaluated in the multivariate analysis. Variables with a  $P < 0.05$  were kept in the final model. A sensitivity analysis for 30 day mortality, evaluating all-cause mortality instead of



**Figure 1.** Flow diagram of patients included in the study.

attributable mortality was carried out. To model the length of hospital stay, we used multiple linear regression with log transformation of the outcome variable. All multivariate analyses were adjusted for clustering within hospital. The backward stepwise method based on *P* values was used to select variables for the final model.

### Ethics

The study was registered at the Institutional Review Board of Universidad Peruana Cayetano Heredia in Lima, Peru with the code number 56868 in March 2010; an approval was received in April 2010. Local approvals at each hospital were also obtained. Owing to the observational nature of the study no signed informed consent was needed.

## Results

### Patient characteristics

A total of 1030 patients were included in the study, nine patients were excluded for not meeting the selection criteria, and 106 were excluded for not having microbiological data. Of the remaining 915 evaluable patients (409 with MRSA, 44.7%), 240 patients were excluded from the primary analysis (Figure 1). The epidemiological and clinical characteristics of the 915 patients are presented in Table 1. Patients infected with MRSA-BSI were comparable to patients infected with MSSA-BSI in several parameters, including age, gender, source of bacteraemia, number of comorbidities, score values of Charlson, McCabe-Jackson, and

**Table 1.** Clinical characteristics of patients included in the study infected with MRSA or MSSA<sup>a</sup>

Characteristic	MRSA	MSSA	P value <sup>a</sup>
No. (%)	409 (44.7)	506 (55.6)	
Age, years, mean (SD)	59.2 (18.0)	58.9 (18.7)	0.815
Male gender	230 (56.2)	298 (59.2)	0.381
Source of bacteraemia			
primary	259 (63.3)	299 (59.4)	0.246
secondary	150 (36.7)	204 (40.6)	
Source of primary bacteraemia			
CVC related	181 (69.9)	197 (65.9)	0.320
not CVC related	78 (30.1)	102 (34.1)	
Source of secondary bacteraemia			
respiratory	34 (8.3)	43 (8.4)	1.000
skin	38 (9.3)	42 (8.2)	0.638
surgical	19 (4.6)	20 (3.9)	0.624
endovascular	16 (3.9)	32 (6.3)	0.135
bone/joint	26 (6.3)	34 (6.7)	0.894
urinary	6 (1.5)	10 (2.0)	0.621
abdominal	15 (3.7)	16 (3.1)	0.715
CNS	4 (1.0)	1 (0.2)	0.178
unknown	18 (4.4)	12 (2.4)	0.095
Place of acquisition			
community	35 (8.6)	115 (22.9)	<0.001
hospital acquired	296 (72.4)	257 (51.1)	
healthcare related	78 (19.1)	131 (26.0)	
Presence of any comorbidity in the 3 month period before diagnosis of BSI			
cancer	56 (13.6)	90 (17.7)	0.103
transplant	2 (0.5)	6 (1.2)	0.310
AIDS	3 (0.7)	9 (1.8)	0.244
myocardial infarction	26 (6.3)	25 (4.9)	0.386
heart failure	82 (20.0)	93 (18.2)	0.554
peripheral vascular disease	68 (16.6)	53 (10.4)	0.008
diabetes	122 (29.7)	130 (25.9)	0.159
lung disease	52 (12.7)	55 (10.8)	0.409
burn	5 (1.2)	8 (1.6)	0.782
liver disease	37 (9.0)	48 (9.4)	0.909
kidney disease	154 (37.5)	204 (40.0)	0.455
neurological disorder	95 (23.1)	53 (10.4)	<0.001
gastric/duodenal ulcer	14 (3.4)	25 (4.9)	0.324
connective tissue disease	16 (3.9)	22 (4.3)	0.868
previous surgery	123 (29.9)	104 (20.4)	0.001
immunosuppressive therapy	46 (11.2)	87 (17.1)	0.014
other comorbidities	157 (38.2)	213 (41.8)	0.280
Number of comorbidities, median (IQR)	2 (2–3)	2 (1–3)	0.138
Previous <i>S. aureus</i> infection	29 (7.1)	17 (3.3)	0.014
Previous MRSA infection	17 (4.1)	6 (1.2)	0.005
Previous hospitalization	164 (39.9)	164 (32.2)	0.044
Days since last hospitalization, median (IQR)	47 (22–83)	31 (16–63)	0.009
Use of antimicrobials 30 days before admission	233 (56.7)	123 (24.1)	<0.001
Ward of admission			
medical	256 (63.7)	372 (74.4)	0.003
surgical	76 (18.9)	60 (12.0)	
obstetrics/gynaecology	3 (0.8)	2 (0.4)	
emergency room	42 (10.5)	49 (9.8)	
other	25 (6.2)	17 (3.4)	

Continued

**Table 1.** Continued

Characteristic	MRSA	MSSA	P value <sup>a</sup>
Information 48 h before blood sampling			
mechanical ventilation	62 (15.1)	46 (9.0)	0.015
CVC in place	250 (60.8)	246 (48.2)	0.001
parenteral nutrition	27 (6.6)	17 (3.3)	0.062
surgical procedure	51 (12.4)	29 (5.7)	0.001
dialysis	111 (27.0)	139 (27.3)	0.827
severe sepsis	90 (22.2)	75 (15.0)	0.007
Charlson comorbidity scale, median (IQR)	2 (1–3)	2 (1–3)	0.485
Charlson score >2	157 (38.2)	195 (38.2)	1.0
McCabe–Jackson scale			0.957
rapidly fatal	60 (14.8)	72 (14.4)	
ultimately fatal	143 (35.3)	174 (34.8)	
non-fatal	202 (50.0)	254 (50.8)	
APACHE II score, median (IQR)	0 (0–14)	0 (0–12)	0.341
APACHE II score >0	67 (16.8)	58 (12.3)	0.066
Pittsburg score, median (IQR)	1 (0–3)	1 (0–2)	<0.001
Pittsburg score >1	187 (45.5)	190 (37.3)	0.013
Transthoracic echocardiography performed	162 (39.9)	243 (48.5)	0.015
Transthoracic echocardiography for CVC-related bacteraemia	70 (39.1)	91 (46.4)	0.246
Duration of fever, mean (SD), days	8.5 (22.5)	6.4 (8.2)	0.102
Total WBC×10 <sup>3</sup> , mean (SD)	12.0 (11.0)	10.1 (9.5)	0.006
Creatinine, mg/dL, median (IQR)	1.1 (0.6–3.3)	1.3 (0.7–4.3)	0.058
Glucose, mg/dL, mean (SD)	111.7 (93.3)	105.8 (94.6)	0.351
C-reactive protein, mg/dL, mean (SD)	20.5 (52.2)	24.4 (59.0)	0.309
Complicated bacteraemia	64 (15.6)	80 (15.7)	0.736
Focus of complicated bacteraemia			
infective endocarditis	22 (5.4)	31 (6.1)	0.672
others	46 (11.2)	52 (10.2)	0.668

Values are *n* (%) unless noted otherwise. WBC, white blood cells.

<sup>a</sup> $\chi^2$  or Fisher's exact test for categorical variables, Student's *t*-test when means are displayed and Kruskal–Wallis test when medians are displayed.

APACHE II scales, duration of fever and rates of complicated BSI. However, patients with an MRSA-BSI acquired the infection more frequently in the hospital, more commonly had a comorbid condition in the 3 months preceding the BSI (particularly a neurologic disorders or were receiving immunosuppressive therapy), more frequently had a previous *S. aureus* infection (including previous MRSA infection), were more frequently hospitalized before the current episode, were more prone to have received antibiotics in the 30 day period preceding the current BSI, needed more mechanical ventilation, insertion of central venous catheters (CVCs) and surgical procedures and had a higher risk of dying as determined by the Pittsburgh score compared with patients with MSSA-BSIs. The distribution of *S. aureus* isolates by country is presented in Figure 2. MRSA predominated in Brazil, Guatemala, Peru and Venezuela, while MSSA was more frequently isolated from BSIs in Argentina, Chile, Colombia and Ecuador. Figure 3 shows the predicted place of acquisition of the *S. aureus*-BSI. Interestingly, both MRSA- and MSSA-BSIs were mostly HA. No resistance or heteroresistance to vancomycin was found among the MRSA strains; MIC<sub>50</sub> and MIC<sub>90</sub> of vancomycin were 1 mg/L, respectively.<sup>17</sup>

### Primary and secondary outcomes

In the bivariate analysis, using investigators' assessment, patients with MRSA-BSI had higher 30 day attributable mortality compared with patients with MSSA-BSI; 25.0% (78 of 312) versus 13.2% (48 of 363), *P* < 0.001, Table 2. Using a generalized linear model, the difference in mortality remained significant after adjusting for covariates that included age, sex, presence of comorbidity, Charlson comorbidity score, source of bacteraemia, Pittsburgh bacteraemia score, complicated bacteraemia, place of acquisition, previous MRSA infection, previous hospitalization, previous antimicrobial therapy, severity of sepsis, clinical information 48 h before sampling and hospital (RR: 1.94, 95% CI 1.38–2.73, *P* = 0.019). The difference in attributable mortality was also observed at all time periods from 7–84 days.

Subsequently, a per-protocol analysis was performed in this analysis we used the pre-defined definitions for attributable mortality (Table 3). MRSA-BSI was associated with higher 30 day attributable mortality in the bivariate analysis: 13% (35 of 270) versus 8.1% (28 of 347), crude RR: 1.61 (1.01–2.54), but this difference disappeared in the multivariate analysis, adjusted RR: 1.10, 95% CI: 0.75–1.60, *P* = 0.616. Indeed, parameters of severity of illness prior

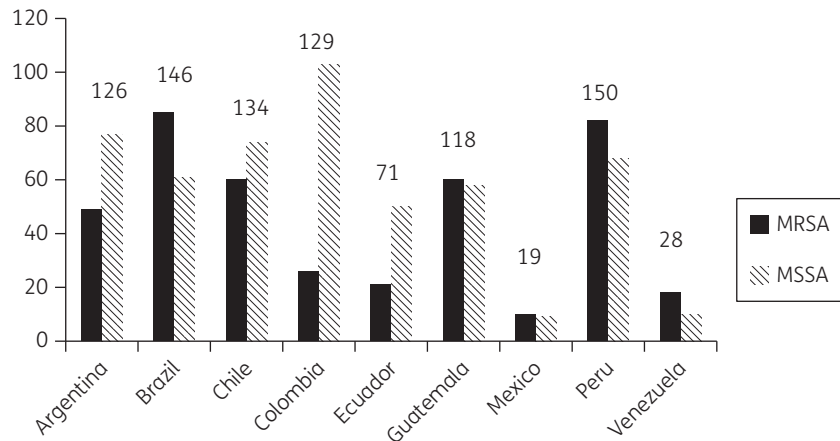


Figure 2. Distribution of *S. aureus*-BSIs by country. Total number of isolates is shown above each pair of bars.

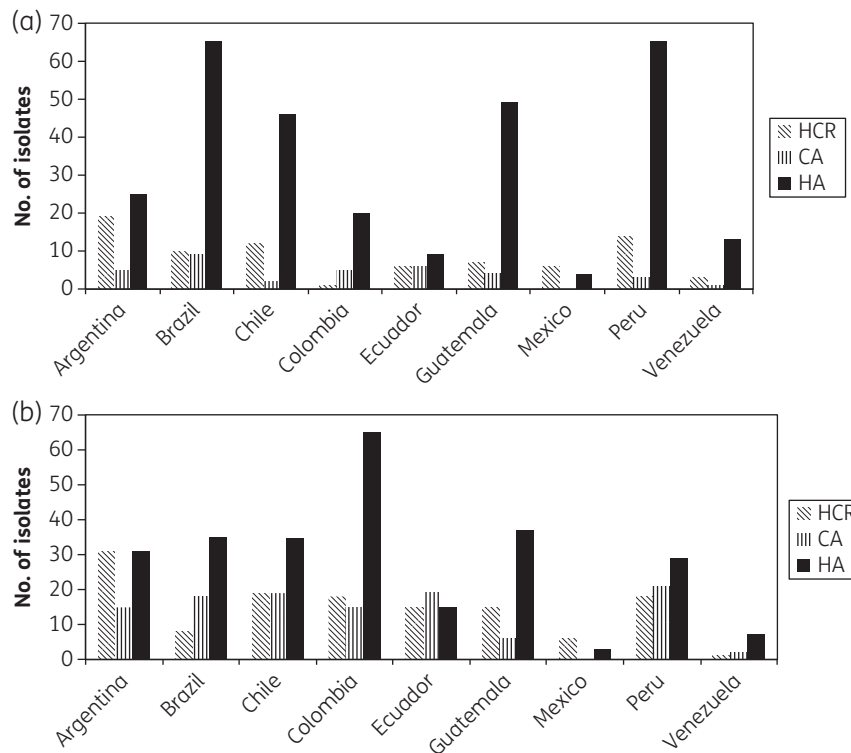


Figure 3. Place of acquisition of *S. aureus*-BSIs by country. (a) MRSA and (b) MSSA. HCR, healthcare associated; CA, community associated; HA, hospital associated.

to identification of the pathogen were associated with mortality, including Pittsburgh bacteraemia score and severity of sepsis. In addition, we performed a sensitivity analysis evaluating differences in 30 day all-cause mortality between MRSA- and MSSA-BSIs. MRSA was associated with higher mortality than MSSA in the bivariate analysis: 36% (132 of 367) versus 27.8% (123 of 442), crude RR: 1.28, 95% CI: 1.06–1.55,  $P = 0.010$ , but the difference was diluted in the multivariate analysis, adjusted RR: 1.09 (95% CI: 0.96–1.23,  $P = 0.182$ ). Moreover, the difference in mortality

disappeared when severity of sepsis and the Pittsburgh score were added into the model (Table S1 and S2, available as Supplementary information at JAC Online). A subset analysis excluding patients with a primary source of BSI did not also find a difference in 30 day mortality (Table S3).

MRSA-BSI were associated with increased parameters of healthcare utilization compared with MSSA-BSIs (Table 4). Indeed, patients with MRSA-BSI remained in the hospital and in the ICU longer with an excess of 10 and 4 days, respectively, compared

**Table 2.** Bivariate and multivariate analysis for the primary outcome of the 30 day attributable mortality based on investigators' assessment

Characteristic	Relative risk (95% CI)	
	bivariate analysis	multivariate analysis <sup>a</sup>
MRSA	1.89 (1.40–2.56)	1.94 (1.38–2.73)
Age, years	1.03 (1.01–1.04)	1.02 (1.01–1.03)
Male gender	0.87 (0.67–1.13)	
Charlson comorbidity score	1.14 (1.07–1.22)	1.10 (1.03–1.19)
Pittsburgh bacteraemia score	1.20 (1.16–1.25)	
Source of secondary bacteraemia	1.28 (0.78–2.04)	
Complicated bacteraemia	1.97 (1.18–3.28)	1.62 (1.13–2.32)
Place of acquisition		
community	(ref) <sup>b</sup>	(ref) <sup>b</sup>
healthcare associated	0.63 (0.38–1.04)	0.58 (0.40–0.83)
hospital acquired	0.69 (0.50–0.92)	0.64 (0.48–0.86)
Comorbidities		
peripheral vascular disease	1.11 (0.72–1.72)	
neurologic disease	1.64 (0.97–2.77)	
surgery	0.78 (0.56–1.09)	
immunosuppressive therapy	1.26 (0.83–1.91)	
Previous MRSA infection	1.29 (0.63–2.64)	
Previous hospitalization	1.20 (0.85–1.71)	
Previous antimicrobial therapy	1.52 (1.06–2.18)	
Clinical information within 48 h before blood sampling		
mechanical ventilation	1.55 (1.04–2.31)	
CVC in place	0.98 (0.70–1.38)	
surgical procedure	1.05 (0.50–2.22)	
Severity of sepsis		
sepsis	(ref) <sup>b</sup>	(ref) <sup>b</sup>
multi-organ failure	3.42 (1.57–7.45)	2.09 (0.88–4.94)
severe sepsis	2.26 (1.57–2.25)	1.6 (1.19–2.22)
septic shock	5.46 (3.67–8.14)	3.60 (2.77–4.69)

<sup>a</sup>Adjusted for clustering on hospital and other significant variables identified in the bivariate analysis.

<sup>b</sup>ref, indicates reference for comparison.

with patients with MSSA-BSI. However, MRSA was not associated with longer length of hospital stay than MSSA in a multivariate analysis that adjusted for significant covariates (difference in mean duration of hospital stay of 1.5 days,  $P = 0.248$ ; Table S4). No difference was observed in the rate of admission to ICU and hospital readmission rates, including early readmissions (within 30 days of discharge). However, early readmissions were more common in MRSA-infected patients: 51.9% (28 of 54) versus 23.8% (10 of 42),  $P = 0.006$ . We evaluated the management of MRSA- and MSSA-BSI by assessing rates of catheter removal; follow-up blood cultures; use of echocardiogram and targeted antimicrobial therapy using  $\beta$ -lactams and glycopeptides (or other anti-MRSA antibiotic) for MSSA and MRSA, respectively. No difference was observed in the rates of removal of CVCs, follow-up blood cultures during treatment and recommended duration of treatment for complicated and uncomplicated bacteraemia between MRSA- versus MSSA-BSI. Patients with MSSA-BSI underwent more transthoracic echocardiographic evaluations. Interestingly, a higher number of patients with MRSA-BSI received appropriate antimicrobial therapy (glycopeptides or other anti-MRSA antibiotics) compared with patients with MSSA-BSIs. However, a striking

finding was that a change in empirical regimen (usually vancomycin) when susceptibility results were available, occurred only in 49.2% of patients with MSSA-BSI. Vancomycin was continued (instead of a recommended antistaphylococcal  $\beta$ -lactam) as definitive therapy for MSSA in almost half of patients with MSSA-BSI. Thus, we evaluated the effect of appropriate definitive therapy for MSSA-BSI on 30 day all-cause mortality in a bivariate and multivariate analysis. A reduction of 30% in 30 day all-cause mortality was observed when appropriate definitive antimicrobial treatment was offered for patients with MSSA-BSI (crude RR: 0.70, 95% CI: 0.52–0.95,  $P = 0.024$ ), but the difference was not evident after adjusting for comorbidities (Charlson score) and Pittsburgh score, adjusted RR: 0.93, 95% CI: 0.70–1.23,  $P = 0.602$ .

## Discussion

Our results derived from this multinational comprehensive study of *S. aureus*-BSI in Latin America indicate that MRSA continues to cause a high burden of disease with almost half (44.7%) of episodes caused by MRSA, although important regional variations were observed. Importantly, MRSA-BSI were not associated with

**Table 3.** Bivariate and multivariate analysis for the primary outcome of the 30 day attributable mortality using per-protocol definitions

Characteristic	Relative risk (95% CI)	
	bivariate analysis	multivariate analysis <sup>a</sup>
MRSA	1.61 (1.01–2.54)	1.10 (0.75–1.60)
Age in years	1.00 (0.99–1.02)	
Male gender	1.03 (0.65–1.63)	
Charlson comorbidity score	1.11 (0.98–1.25)	
Pittsburgh bacteraemia score	1.31 (1.26–1.36)	1.21 (1.08–1.36)
Source of secondary bacteraemia	0.93 (0.61–1.42)	
Complicated bacteraemia	1.15 (0.78–1.70)	
Place of acquisition		
community	(ref) <sup>b</sup>	
healthcare associated	0.50 (0.25–0.99)	
hospital acquired	0.92 (0.58–1.46)	
Comorbidities		
peripheral vascular disease	1.18 (0.54–2.57)	
neurologic disease	1.94 (1.20–3.13)	
surgery	0.83 (0.43–1.59)	
immunosuppressive therapy	0.91 (0.52–1.59)	
Previous MRSA infection	0.50 (0.07–3.31)	
Previous hospitalization	0.85 (0.50–1.44)	
Previous antimicrobial therapy	1.72 (1.18–2.49)	
Clinical information within 48 h before blood sampling		
mechanical ventilation	3.50 (2.30–5.32)	
CVC in place	1.32 (0.88–1.99)	
surgical procedure	1.48 (0.69–3.19)	
Severity of sepsis		
sepsis	(ref) <sup>b</sup>	(ref) <sup>b</sup>
multi-organ failure	5.67 (2.37–13.59)	3.69 (1.98–6.87)
severe sepsis	3.01 (1.81–5.03)	2.11 (1.30–3.41)
septic shock	8.94 (5.45–14.66)	3.23 (1.47–7.08)

<sup>a</sup>Adjusted for clustering on hospital and other significant variables identified in the bivariate analysis.

<sup>b</sup>ref, reference for comparisons.

higher 30 day attributable mortality when a per-protocol analysis was performed. In addition, a sensitivity analysis evaluating 30 day all-cause mortality did not find that MRSA-BSIs were associated with higher mortality or longer hospital stay than those caused by MSSA.

Several studies have previously documented that MRSA-BSI was associated with higher mortality rates than MSSA-BSI.<sup>3–8</sup> More recent studies have provided additional support to this association. A study conducted in Taiwan in a single large hospital over a period of 15 years recruited 1148 patients with HA *S. aureus*-BSI; MRSA-BSI was associated with 1.78-fold higher mortality rates than MSSA-BSI, after adjusting for covariates in a multivariate analysis.<sup>18</sup> Another study conducted among 13 hospitals in Europe over a period of 2 years analysed 248 MRSA-BSI and 618 MSSA-BSI episodes in a matched case-control design.<sup>19</sup> MRSA-BSI was associated with excess 30 day mortality compared with MSSA-BSI (OR: 1.8, 95% CI: 1.04–3.20) in the multivariate analysis. An additional 3 year retrospective study conducted in Taiwan evaluated in-hospital mortality among 353 patients with *S. aureus*-BSI, and found higher crude mortality rates for MRSA-

BSI than for MSSA-BSI: 47.5% for HA-MRSA, 30.5% for community-associated MRSA and 23.3% for MSSA.<sup>20</sup> Older studies have been criticized for not adjusting properly for significant confounding variables, and this may be the case for the above-mentioned studies.<sup>21</sup> In contrast to these studies, an observational cohort study conducted in a single hospital in Australia, which included 185 episodes of MRSA-BSI and 397 episodes of MSSA-BSI, found no differences in long-term all-cause mortality and in infection-related mortality after adjusting for 13 covariates in the multivariate analysis.<sup>22</sup> Several caveats should be taken into consideration in interpreting the results of this study. The study followed a retrospective design; the number of MRSA infections was low and the setting had a low MRSA rate (18%); overadjustment cannot be ruled out, and causes of death were obtained from death certificates rather than from clinical charts.<sup>22–24</sup> Despite these drawbacks, the study demonstrated that MRSA itself may not be associated with higher mortality, which can be explained by comorbidities and proper management. Our results, using per-protocol and all-cause mortality analysis, are in agreement with these conclusions. In the per-protocol analysis, severity of sepsis



**Table 4.** Healthcare resource utilization parameters and management of *S. aureus*-BSIs

Patient characteristics	MRSA	MSSA	P value <sup>a</sup>
No. (%)	409 (44.7)	506 (55.3)	
Healthcare resource utilization parameters			
length of hospital stay, mean (SD), days	39.1 (37.6)	28.6 (31.2)	<0.001
admission to an ICU	149 (36.3)	159 (31.2)	0.107
length of stay in ICU, mean (SD), days	17.2 (16.6)	13.6 (14.8)	0.042
re-admission in the 84 day period	38 (14.6)	58 (15.6)	0.737
<i>S. aureus</i> episode in readmission	10 (27.0)	17 (32.1)	0.392
Management of <i>S. aureus</i> -BSI			
CVC removed in first 72 h in bacteraemia related to CVC	123 (68.0)	118 (60.0)	0.104
subsequent blood cultures taken after baseline	228 (57.6)	258 (52.0)	0.184
trans-thoracic echocardiography performed	162 (39.9)	243 (48.5)	0.015
duration of antibiotic treatment $\geq$ 14 days for uncomplicated bacteraemia	256 (79.0)	307 (75.8)	0.329
duration of antibiotic treatment $\geq$ 28 days for complicated bacteraemia	49 (79.0)	64 (81.0)	0.833
regimen modified based on susceptibility test results	103 (25.2)	249 (49.2)	<0.001
appropriate empiric antimicrobial therapy	284 (74.5)	202 (51.9)	<0.001
appropriate definitive antimicrobial therapy	304 (79.6)	290 (60.0)	<0.001

Values are *n* (%) unless noted otherwise.

<sup>a</sup> $\chi^2$  or Fisher's exact test for categorical variables, Student's *t*-test when means are displayed and Kruskal-Wallis test when medians are displayed.

and Pittsburgh bacteraemia score (indicative of risk of death) were independently associated with the 30 day attributable mortality but not MRSA by itself. For the 30 day all-cause mortality analysis, again, severity of sepsis, Pittsburgh bacteraemia and Charlson comorbidity score were independently associated with mortality, but MRSA was not. Taking all these results together, we can conclude that MRSA was not associated with 30 day mortality in the hospitals included in this study and mortality was more influenced by severity of illness and comorbidities.

MRSA-BSI was not associated with longer length of hospital stay, which correlated more with complications of BSI rather than with MRSA itself. Overall, the management of *S. aureus*-BSI in the region was comparable to that reported in developed countries for four parameters including removal of CVC, performance of echocardiography, repeated blood cultures taken during treatment and duration of treatment for complicated and uncomplicated BSI.<sup>15</sup> One of the most striking findings was the low modification rate of empirical regimens containing vancomycin or teicoplanin in MSSA-BSI when susceptibility test results were available (49%). Not surprisingly, appropriate definitive therapy for MSSA-BSI, which included a  $\beta$ -lactam antimicrobial, was associated with an almost 30% reduction in 30 day all-cause mortality in our study, and such findings have been reported previously.<sup>16</sup> However, our study had limited power to detect differences in 30 day all-cause mortality in the multivariate analysis (conducted among 433 subjects). A large study involving 5633 subjects who received definitive therapy for MSSA-BSI found 35% lower mortality among  $\beta$ -lactam recipients compared with those who received a glycopeptide.<sup>16</sup> Therefore, based on our findings we consider that infectious disease consultation should be mandatory in the region to guide properly the antimicrobial therapy and de-escalation. A recent study and a systematic review of the role of infectious disease consultation in the management of

*S. aureus*-BSI showed that the involvement of infectious diseases consultants improves management and survival.<sup>15,25</sup>

Our study has several limitations. First, the analysis of the primary outcome was restricted to 675 patients. However, the sample size was large enough to test the primary hypothesis of 8% difference in the 30 day attributable mortality between MRSA and MSSA. Second, participating hospitals were all major hospitals in capital cities of Latin America. These hospitals were selected based on good performance in laboratory identification of pathogens, as determined by a previous evaluation carried-out by the Pan-American Health Organization, and may not reflect the current situation in smaller hospitals of less developed regions in Latin America. Third, we could only get information on removal of CVC for primary bacteraemia related to CVC; no information was obtained on removal of other foci. Fourth, investigators overestimated 30 day attributable mortality in our study. This may be explained by the fact that they were not blinded to the susceptibility results. Two subsequent analyses, including both per-protocol 30 day attributable and 30 day all-cause mortality provided more accurate information on the actual association between MRSA-BSIs and the primary outcome. Finally, treating physicians used diverse dosing regimens; and we did not collect information on involvement of infectious disease consultation and of evaluation of pharmacokinetic parameters when vancomycin was used. The strengths of the study include the prospective design, multinational nature of participants from all over Latin America and large sample size. A large-scale study has not previously been attempted in the region. In conclusion, MRSA-BSIs are an important healthcare burden in Latin America but may not be associated with higher mortality or length of hospital stay compared with MSSA. Management of *S. aureus*-BSI should be improved in the region focusing on the involvement of infectious diseases consultants and strengthening antibiotic stewardship efforts.

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## Supplementary data

Definitions and Tables S1 to S4 appear as [Supplementary data](#) at JAC Online.

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