International Journal of Infectious Diseases 96 (2020) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Adherence to standards of care and mortality in the management of *Staphylococcus aureus* bacteraemia in Peru: A prospective cohort study

Alvaro Schwalb[a,b,*], Rodrigo Cachay[a,b], Adriana de la Flor[b], Coralith García[a,b,c], Carlos Seas[a,b,c]

[a] Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru
[b] School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru
[c] Hospital Cayetano Heredia, Lima, Peru

ARTICLE INFO

Article history:
Received 8 April 2020
Received in revised form 31 May 2020
Accepted 1 June 2020

Keywords:
Staphylococcus aureus
MRSA
MSSA
Standards of care
Mortality

ABSTRACT

Background: Despite high mortality rates, physicians can alter the course of the *Staphylococcus aureus* bacteraemia (SAB) by following recommended standards of care. We aim to assess the adherence of these guidelines and their impact on mortality.
Methods: Substudy from a prospective cohort of hospitalized patients with SAB from three hospitals from Peru. Hazard ratios were calculated using Cox proportional regression to evaluate the association between 30-day mortality and the performance of standards of care: removal of central venous catheters (CVC), follow-up blood cultures, echocardiography, correct duration, and appropriate definitive antibiotic therapy.
Results: 150 cases of SAB were evaluated; 61.33% were MRSA. 30-day attributable mortality was 22.39%. CVC removal was done in 42.86% of patients. Follow-up blood cultures and echocardiograms were performed in 8% and 29.33% of cases, respectively. 81.33% of cases had appropriate empirical treatment, however, only 22.41% of MSSA cases were given appropriate definitive treatment, compared to 93.47% of MRSA. The adjusted regression for all-cause mortality found a substantial decrease in hazards when removing CVC (aHR 0.28, 95% CI: 0.10 - 0.74) and instituting appropriate definitive treatment (aHR 0.27, 95% CI: 0.08 - 0.86), while adjusting for standards of care, qPitt bacteraemia score, comorbidities, and methicillin susceptibility; similar results were found in the attributable mortality model (aHR 0.24, 95% CI: 0.08 - 0.70 and aHR 0.21, 95% CI: 0.06 - 0.71, respectively).
Conclusions: Deficient adherence to standards of care was observed, especially definitive treatment for MSSA. CVC removal and the use of appropriate definitive antibiotic therapy reduced the hazard mortality of SAB.
© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

The Gram-positive bacteria *Staphylococcus aureus* is a leading cause of mild to life-threatening clinical infections of the skin, soft tissue, lungs, bone, and bloodstream (Tong et al., 2015). The incidence rates of *Staphylococcus aureus* bacteraemia (SAB) range from 15 - 40 per 100,000 population per year, associated with mortality rates of 15 - 25% (Laupland et al., 2013). Clinical outcomes differ according to antimicrobial susceptibility. Several studies show that methicillin-resistant *Staphylococcus aureus* (MRSA) infections are associated with higher mortality rates compared to methicillin-susceptible (MSSA) infections (van Hal et al., 2012; Yaw et al., 2014; Seas et al., 2018).

First-line antibiotic therapy of SAB is tailored to the pathogen's susceptibility: β-lactams are used for MSSA and daptomycin or glycopeptides, such as vancomycin, for MRSA (Liu et al., 2011; Tong et al., 2015). Given the higher mortality associated with MRSA infections, regimens containing antistaphylococcal β-lactams combined with vancomycin have also been used, resulting in *in vitro* synergistic bactericidal activity (Davis et al., 2015), albeit no clear superiority in clinical trials (Davis et al., 2016).

* Corresponding author at: Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430, Urb. Ingeniería, 15012, San Martín de Porres, Lima, Perú.
E-mail address: alvaro.schwalb@upch.pe (A. Schwalb).

https://doi.org/10.1016/j.ijid.2020.06.002
1201-9712/© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Many factors contribute to patient outcomes. Most are non-modifiable factors such as methicillin-resistance and comorbidities; however, physicians can alter the course of the disease by following the recommended standards of care for SAB (Ten Oever et al., 2019). The Infectious Diseases Society of America (IDSA) published evidence-based guidelines for the management of MRSA infections. Recommendations for SAB include the use of vancomycin for MRSA bacteraemia, treatment duration of at least 14 days, assessment of source and removal of infectious foci, additional blood cultures after initial positive culture, and echocardiography (Liu et al., 2011).

Although these standards of care are available in clinical guidelines, their quality and adherence vary between hospitals. These factors could play a significant role in the clinical course of SAB (Nambiar et al., 2018). According to reports over the last few years, Peru is one of the Latin American countries with high MRSA prevalence (Reyes et al., 2009). To our knowledge, no data exists on standards of care adherence in the Peruvian healthcare system. In an effort to address this gap in the literature, we assess adherence to standards of care in the management of SAB and its effect on mortality.

2. Methods

This is a substudy from the prospective cohort by the *Latin American Working Group on Antimicrobial Resistance*, which included 24 hospitals in nine countries from February 2011 to July 2014 (Seas et al., 2018). Data was obtained from three hospitals in Peru: Hospital Nacional Guillermo Almenara Irigoyen, Hospital Cayetano Heredia, and Hospital Nacional Alberto Sabogal Sologuren; three tertiary referral hospitals with 818, 452, and 408 beds, respectively. Hospitalized adult patients with SAB were included in the study. Diagnosis of bacteraemia required at least one positive blood culture; susceptibility results from local laboratories were available to treating physicians. Exclusion criteria included polymicrobial bacteraemia, relapse of bacteraemia, patients transferred from other institutions, and patients who withdrew from the hospital or died within the first 48 hours after the diagnosis was made.

Data were obtained from patients' medical records without any interference between the study team and the clinicians during patient stay. Data retrieved included demographics, comorbidities, susceptibility results, risk factors, clinical information of current hospitalization, antimicrobial therapy and medical management provided. Patients were followed to determine clinical outcomes at 7, 30 and 84 days after the initial blood culture.

Bacteraemia source was based on the presence of an identified portal of entry; bacteraemia was classified as primary if no portal of entry or associated infected site could be determined. This was further categorized according to the presence of central venous catheters (CVC). The quick Pittsburgh bacteraemia (qPitt) score and Charlson Comorbidity Index (CCI) were used to predict mortality and assess comorbidities, respectively (Charlson et al., 1987; Battle et al., 2019). Mortality attributed to SAB was defined as the persistence of clinical signs and symptoms of sepsis without other identifiable causes or active infection at the time of death and positive blood cultures within 7 days of a patient's death. Standards of care for SAB included: 1) removal of infectious foci such as CVC, 2) follow-up blood cultures 2-4 days after initial culture, 3) echocardiography, 4) correct duration of therapy and, 5) appropriate definitive antibiotic therapy. Definitive antibiotic therapy was deemed appropriate for MSSA if β-lactams were used and for MRSA if vancomycin was used. Empirical antibiotic therapy was deemed appropriate if β-lactams, with or without vancomycin, were used when suspecting MSSA infection; likewise, it was deemed appropriate if vancomycin, with or without β-lactams, were used when suspecting MRSA infection. Duration was considered correct if treatment was given for at least 14 days for uncomplicated bacteraemia and 28 days for complicated bacteraemia; patients were censored if they died or were lost to follow-up before treatment completion (Table 1).

Anonymized patient data in an electronic database was analyzed in Stata SE 16.1 (StataCorp., US). Categorical variables were presented as frequencies and numeric variables were presented as means with standard deviation (SD) or medians

Table 1
Standards of care and operational definition of variables.

Operational definition of variables (Seas et al., 2018)	
Polymicrobial bacteraemia	Blood culture positive for more than one pathogen.
Relapse of bacteraemia	Recurrence of a previous bacteraemia episode with a phenotypically similar isolate during current hospitalization.
Primary bacteraemia	Bacteraemia for which no portal of entry or associated infected site can be determined.
CVC-related bacteraemia	Growth of more than 15 colonies in catheter tip or inflammation present at insertion site, and no alternate source of infection.
Secondary bacteraemia	Bacteraemia with identified portal of entry or documented infection with the same pathogen at another body site.
Complicated bacteraemia	Any of the following: positive blood culture 48-96 hours after first blood sampling; infective endocarditis; metastatic infection or further spread of the infection to any organ.
Attributable mortality to bacteraemia	Persistence of clinical signs and symptoms of sepsis without other identifiable causes or active infection at the time of death or positive blood cultures within 7 days of a patient's death.
Standards of care for management of *Staphylococcus aureus* bacteraemia (IDSA) (Liu et al., 2011)	
Removal of infectious foci	Clinical assessment to identify the source and extent of the infection with elimination and/or debridement of other sites of infection.
Follow-up blood cultures	Additional blood cultures 2-4 days after initial positive cultures and as needed thereafter to document clearance of bacteraemia.
Echocardiography	Recommended for all adult patients. Transesophageal echocardiography is preferred over transthoracic echocardiography.
Duration of therapy	Administration of antibiotic therapy for at least 14 days for uncomplicated bacteraemia and at least 28 days for complicated bacteraemia.
Appropriate empirical therapy	Suspected MSSA infection: β-lactams with or without vancomycin. Suspected MRSA infection: vancomycin with or without β-lactams.
Appropriate definitive therapy	MSSA infection: vancomycin. MRSA infection: β-lactams.

CVC: Central venous catheter. MSSA: Methicillin-susceptible Staphylococcus aureus. MRSA: Methicillin-resistant Staphylococcus aureus.

with interquartile ranges (IQR). Chi-square test was used for comparison of categorical values; Student's t-test and Kruskal-Wallis test were used when means or medians were displayed, respectively. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression to examine the association between the performance of the standards of care and all-cause and attributable mortality at 30 days, adjusted for qPitt, CCI and methicillin susceptibility. Patients were censored if death occurred after 30 days or if they were lost to follow-up prior to 30 days. Authorization for this substudy was granted by the Institutional Ethics Committee of Universidad Peruana Cayetano Heredia (SIDISI: 64939).

3. Results

A total of 150 cases of SAB were analyzed. MRSA was isolated in 61.33% of cases. Most patients (84%) acquired the strain in a hospital or in a health-care associated setting; the remainder acquired it in the community. The total median duration of hospitalization was 23 days (IQR: 31); the median duration of hospitalization for patients with MRSA bacteremia (29 days) was significantly greater than the median duration of hospitalization for patients with MSSA bacteremia (18 days) ($p = 0.002$). Intensive care unit (ICU) admission and hospital readmissions were reported for 33/150 and 14/94 patients, respectively (Table 2).

Antibiotic use within the last 30 days and surgery 3 months prior to admission were risk factors for MRSA infection in the bivariate analysis. Likewise, MRSA infections were associated with high qPitt scores compared to MSSA. SAB attributable mortality at 30 days was 30/134 (22.39%); 24 of these cases were MRSA. At the 30-day period, 16 (10.66%) patients were lost to follow-up and therefore censored in the Cox regression. Early (7 days) and late (84 days) mortality also occurred predominantly in cases of MRSA bacteraemia.

Removal of CVC was only performed in 39/91 (42.86%) patients with CVC-related SAB. Follow-up blood cultures and echocardiograms were performed in 8% and 29.33% of cases, respectively. The correct duration of antibiotic therapy was observed in 80% of cases of complicated SAB compared to 56.43% of uncomplicated cases. Due to broad initial coverage of SAB with β-lactams and vancomycin, most patients (81.33%) had appropriate empirical treatment; however, only 22.41% received appropriate definitive treatment for MSSA bacteraemia. The latter rate was much lower than the rate of appropriate definitive treatment for MRSA bacteraemia (93.48%) (Table 3). Standards of care were generally comparable between the three hospitals in the study; however, significant differences arose in definitive antibiotic treatment choice where Hospital A registered better rates of management for MSSA bacteraemia.

Through unadjusted Cox regression (Table 4), the removal of CVC reduced the hazard of 30-day all-cause and attributable mortality by 72% (HR 0.28, 95% CI: 0.12-0.71) and 71% (HR 0.29, 95% CI: 0.11 - 0.79), respectively. The performance of echocardiogram and adequate treatment duration also reduced hazards of all-cause and attributable mortality, though not significantly. MRSA and a high qPitt score were associated with increased all-cause and attributable mortality. Adequate treatment duration reduced the number of observations and failures in the multivariate analyses, which did not allow adjusted HRs to be calculated and, ultimately, was not included in the final Cox regression model. The adjusted regression for all-cause mortality found a substantial decrease in hazards when removing CVC (aHR 0.28, 95% CI: 0.10 - 0.74) and instituting appropriate definitive treatment (aHR 0.27, 95% CI: 0.08 - 0.86), while adjusting for the standards of care, qPitt, CCI, and methicillin susceptibility; likewise, similar decrease in hazards were found in the attributable mortality model (aHR 0.24, 95% CI: 0.08 - 0.70 and aHR 0.21, 95% CI: 0.06 - 0.71, respectively). For both mortality outcomes, MRSA and high qPitt scores were associated with greater hazards after adjusting for the model's variables.

Table 2
Clinical and demographic characteristics of patients included in the study.

Characteristic (n = 150)	Total	MRSA 92 (61.33)	MSSA 58 (38.67)	P value[a]
Age, years, mean (SD)	59.39 (18.39)	60.79 (19.03)	57.17 (17.23)	0.24
Male gender	81 (54.00)	50 (54.35)	31 (53.45)	0.94
Source of bacteraemia				
Primary	105 (70.00)	66 (71.74)	39 (67.24)	0.56
Secondary	45 (30.00)	26 (28.26)	19 (32.76)	
Source of primary bacteraemia, CVC-related (n = 105)	80 (76.19)	49 (74.24)	31 (79.49)	0.54
Place of acquisition				
Community	24 (16.00)	10 (10.87)	14 (24.14)	0.09
Healthcare-related	32 (21.33)	20 (21.74)	12 (20.69)	
Hospital	94 (62.67)	62 (67.39)	32 (55.17)	
Previous hospitalization, last 3 months prior to admission	56 (37.33)	38 (41.30)	18 (31.03)	0.21
Previous surgery, last 3 months prior to admission	28 (18.67)	24 (26.09)	4 (6.90)	0.003
Antibiotic use, last 30 days prior to admission	77 (51.33)	55 (59.78)	22 (37.93)	0.009
Quick Pittsburgh bacteraemia score (≥2)	59 (39.33)	44 (47.83)	15 (25.86)	0.007
Charlson Comorbidity Index (≥3)	68 (45.33)	42 (45.65)	26 (44.83)	0.921
Complicated bacteremia	27 (18.00)	18 (19.57)	9 (15.52)	0.53
Duration of hospitalization, days, median (IQR)	23 (31)	29 (32)	18 (23)	0.002
ICU admission	33 (12.00)	24 (26.09)	9 (15.52)	0.13
Readmission to hospital (n = 94)	14 (14.89)	10 (20.41)	4 (8.90)	0.12
7-day all-cause mortality	14 (9.33)	13 (14.13)	1(1.72)	0.011
30-day all-cause mortality	35 (25.18)	29 (32.95)	6 (11.76)	0.006
84-day all-cause mortality	42 (34.43)	33 (44.00)	9 (19.15)	0.005
7-day attributable mortality (n = 148)	12 (8.11)	11 (12.22)	1 (1.72)	0.022
30-day attributable mortality (n = 134)	30 (22.39)	24 (28.92)	6 (11.76)	0.021
84-day attributable mortality (n = 113)	33 (29.20)	26 (38.24)	7 (15.56)	0.009

Values are n (%) unless noted otherwise. SD: Standard deviation. IQR: Interquartile range. MRSA: Methicillin-resistant Staphylococcus aureus. MSSA: Methicillin-susceptible Staphylococcus aureus. CVC: Central venous catheter. ICU: Intensive care unit.

[a] Chi-square test for categorical values, Student's t-test when means are displayed and Kruskal-Wallis test when medians are displayed.

Table 3
Standards of care of *Staphylococcus aureus* bacteraemia.

Standard of care (n = 150)	Total	Hospital A 43 (28.67)	Hospital B 48 (32.00)	Hospital C 59 (39.33)	P valuea
Removal of CVC (n = 91)	39 (42.86)	8 (32.00)	17 (54.84)	14 (40.00)	0.208
Follow-up blood cultures	12 (8.00)	3 (6.98)	3 (6.25)	6 (10.17)	0.727
Echocardiogram	44 (29.33)	12 (27.91)	16 (33.33)	16 (27.12)	0.759
Adequate treatment durationb (n = 116)	69 (59.48)	18 (56.25)	27 (67.50)	24 (54.55)	0.438
Uncomplicated bacteraemia (n = 101)	57 (56.43)	13 (46.43)	17 (54.84)	27 (64.28)	0.329
Complicated bacteraemia (n = 15)	12 (80.00)	3 (75.00)	7 (77.78)	2 (100)	0.744
Appropriate empirical treatmentc	122 (81.33)	33 (76.74)	40 (83.33)	49 (83.05)	0.658
MSSA (n = 58)	45 (77.59)	11 (61.11)	12 (66.67)	22 (100)	0.006
MRSA (n = 92)	77 (83.69)	24 (96.00)	20 (66.67)	33 (89.19)	0.007
Appropriate definitive treatmentd	99 (66.00)	26 (60.47)	31 (64.58)	42 (71.19)	0.512
MSSA (n = 58)	13 (22.41)	10 (55.55)	2 (11.11)	1 (4.54)	<0.001
MRSA (n = 92)	86 (93.48)	24 (96.00)	27 (90.00)	35 (94.59)	0.628

Values are n (%). CVC: Central venous catheter. MSSA: Methicillin-susceptible Staphylococcus aureus. MRSA: Methicillin-resistant Staphylococcus aureus.
[a]Chi-square test.
[b]Adequate treatment duration is considered 14 days for uncomplicated bacteraemia and 28 days for complicated bacteraemia
[c]Appropriate empirical treatment is considered if β-lactams, with or without vancomycin, were used when suspecting MSSA infection and if vancomycin, with or without β-lactams, were used when suspecting MSSA infection.
[d]Appropriate definitive treatment is considered if β-lactams were used for MSSA and vancomycin for MRSA.

Table 4
Impact of adherence to standards of care on S. aureus bacteraemia 30-day all-cause and attributable mortality.

Characteristic	All-cause mortality HR (95%CI)	aHR (95%CI)	Attributable mortality HR (95%CI)	aHR (95%CI)
Removal of CVC	0.28 (0.12-0.71)	0.28 (0.10-0.74)	0.29 (0.11-0.79)	0.24 (0.08-0.70)
Follow-up blood cultures	2.07 (0.80-5.34)	1.43 (0.47-4.34)	2.45 (0.94-6.41)	1.69 (0.54-5.28)
Echocardiogram	0.45 (0.19-1.08)	0.59 (0.22-1.60)	0.55 (0.22-1.33)	0.76 (0.27-2.14)
Adequate treatment durationa	0.50 (0.11-2.24)	-	0.45 (0.07-2.68)	-
Appropriate definitive treatmentb	1.35 (0.65-2.81)	0.27 (0.08-0.86)	1.08 (0.51-2.31)	0.21 (0.06-0.71)
MRSA	3.49 (1.45-8.42)	4.43 (1.17-16.83)	2.87 (1.17-7.04)	3.96 (1.01-15.53)
High qPitt (≥2)	3.57 (1.77-7.19)	2.84 (1.25-6.44)	3.69 (1.72-7.89)	2.99 (1.20-7.46)
High CCI (≥3)	1.69 (0.86-3.31)	1.05 (0.48-2.29)	1.65 (0.80-3.39)	1.01 (0.42-2.42)

CVC: Central venous catheter. MRSA: Methicillin-resistant Staphylococcus aureus. qPitt: Quick Pittsburgh bacteraemia score. CCI: Charlson comorbidity index.
a Adequate treatment duration is considered 14 days for uncomplicated bacteraemia and 28 days for complicated bacteraemia
b Appropriate definitive treatment is considered if β-lactams were used for MSSA and vancomycin for MRSA.

4. Discussion

Our study finds deficient rates of adherence to standards of care of SAB management from three referral hospitals in Peru; these results provide insight on the quality of SAB management nationwide, which is a key starting point towards improvement to, consequently, safeguard patients. The quality of management was seen proportional among all three included hospitals, with few exceptions on antibiotic choice according to isolate susceptibility; although over 60% of isolates were methicillin-resistant, there was an overwhelming poor rate of definitive MSSA antibiotic treatment. Assessment of the impact of the performance of standards of care on mortality found reduced hazards by adhering to the timely removal of CVC and prescribing appropriate definitive antibiotic treatment, while adjusting for other standards of care and patient characteristics. Standards of care are key modifiable factors that can alter a patient's clinical outcome and have been thoroughly explored before.

Regarding the definitive treatment of MSSA bacteraemias, we found that only 22.41% of patients were treated appropriately with β-lactams while the remaining patients continued with the use of vancomycin despite culture results. Such treatment with vancomycin has been found to present greater risk of treatment failure in patients with MSSA bacteremia compared to patients who received β-lactams (31.2% vs. 13%, p = 0.02)(Stryjewski et al., 2007). Similarly, a study found 35% lower mortality in patients who had received β-lactams as definitive treatment for MSSA bacteremia in comparison to those who received vancomycin (McDanel et al., 2015). Other studies have found nafcillin and cefazolin to be superior to vancomycin in preventing relapses and persistent bacteremia (Chang et al., 2003; Schweizer et al., 2011). Additionally, inappropriate use of vancomycin has been associated with the emergence of vancomycin-resistance in Enterococci and MRSA (Tiwari and Sen 2006; Wang et al., 2019). The possible negative outcomes during the treatment of MSSA bacteremia highlight the importance of adequate targeted therapy. In terms of MRSA bacteremia, appropriate definitive treatment was well implemented (93.47%); this positive outcome is related to the extensive use of vancomycin for SAB which we found that contributes to patient survival in the first 30 days from diagnosis.

Empirically, adequate coverage for SAB bacteraemia was initiated in 81.33% of our patients as most used a combined regimen of β-lactams and vancomycin. For MSSA and MRSA bacteraemias, there were no significant differences in mortality between patients receiving inappropriate or appropriate empirical antibiotics (McDanel et al., 2015; Yoon et al., 2016). These findings seem to contradict the previously reported suggestion that mortality is associated with inappropriate antibiotic choice (Khatib et al., 2006; Bassetti et al., 2017). In spite of this incongruence, a timely start to antibiotic treatment is beneficial for patient survival, with delays of 24 to 72 hours contributing to increased infection-related mortality (van Hal et al., 2012). Clinical practice should mandate a broad and rapid start of antibiotic treatment, followed by appropriate de-escalation when susceptibility results are available.

Treatment duration was also substandard in our study. One study found no difference between treatment failure or death between a short course (<14 days) and an intermediate course

(≥14 days) of treatment; however, short courses have been associated with relapse (Chong et al., 2013). For complicated SAB, higher survival is observed when treatment lasts more than 14 days (Abbas et al., 2019). Adequate treatment duration was difficult to judge as most deaths occurred in the first 30-day period, during the time many patients were still receiving antibiotic treatment; many of these deaths were considered censored data as there was no assurance that treatment duration was going to meet the minimum number of days recommended. We believe that this reduction in observations prevented us from including it into an overfitted multivariate analysis.

The removal of foci of infection is a common practice for other medical conditions, and, in the case of bacteraemias, it is of paramount importance for management. Failure to manage the bacteraemia source, which for primary bacteraemia is almost exclusively associated with CVC, resulted in recurrence in 74% of cases (Szubert et al., 2019); additionally, higher survival rates have been reported with CVC removal at 7 (82.2% vs. 47.3%, p = 0.002) and 30 days (85.6% vs. 61.5%, p = 0.002) (Bassetti et al., 2017). Our study shows a significant reduction in mortality associated with the removal of CVC, emphasizing the importance of adherence to this standard of care for SAB.

Similarly, performing an echocardiogram was also a protective factor, albeit not statistically significantly in our study. In cases of SAB at low risk for infective endocarditis (IE), echocardiography is not associated with survival (Heriot et al., 2018); nonetheless, up to 22% of SAB have IE and differences in mortality are evident at 180 days when IE is present (Rasmussen et al., 2011). A systematic screening of SAB patients with echocardiography revealed that 25% of patients were diagnosed with IE although clinical suspicion was only present in 7% (Fowler et al., 1997); these findings suggest that echocardiography should be performed in all SAB patients. Though transesophageal echocardiography is generally preferred over transthoracic, if low-risk factors for IE are present, the invasive transesophageal approach should be avoided (Holland et al., 2014).

Alarmingly, the standard of care performed least frequently (8%) was the follow-up blood culture, which should be obtained 2 to 4 days after the initial result. Our results indicate that performing follow-up blood cultures is associated with higher mortality (HR: 2.45, 95%CI 0.94 - 6.41, p = 0.067), which could be explained by the fact that repeat blood cultures were taken primarily in patients with dire clinical status, as opposed to those who experienced symptom remission soon after starting antibiotic treatment. However, one study on quality indicators for SAB management suggests that follow-up blood cultures should be taken regardless of clinical evolution (Ten Oever et al., 2019). Alternatively, the skip phenomenon, a fluctuating positivity of blood cultures that has been reported in 4% of cases and has been associated with a longer duration of bacteraemia, may have been at play (Fiala et al., 2019). Future studies are necessary to investigate this phenomenon, its possible threat to patients, and any appropriate guideline adjustments.

Though worldwide mortality of SAB ranges from 20 - 40% (López-Cortés et al., 2013), the effect of methicillin-resistance on mortality is controversial and must be carefully interpreted. One systematic review documented a pooled OR of 2.2 (95% CI, 1.2–3.8; P=.007) when mortality was specifically related to MRSA compared to MSSA bacteremia (Cosgrove et al., 2003). Whilst the Latin American study concluded that all-cause mortality was not associated with MRSA bacteremia but was influenced by illness severity and patient comorbidities (Seas et al., 2018); we found that MRSA increased mortality outcome hazards when adjusting for the standards of care in management. This implies that, while guided management must be implemented for all SAB patients, high quality care should be ensured in the case of MRSA bacteraemia.

Since the adherence to standards of care improves patient outcomes, infectious disease (ID) consultation has been recommended to help guide physicians in the management of SAB. ID consultation has improved compliance in follow up blood cultures, performance of echocardiography, removal of CVC, and appropriate treatment duration (Lahey et al., 2009; Bai et al., 2015; Narsana et al., 2015; Chesdachai et al., 2020). Furthermore, ID consults are also associated with reduced in-hospital mortality and earlier discharge among patients with SAB (Bai et al., 2015). Early ID consult could prevent the overall poor adherence to SAB standards of care that was observed in the three reference hospitals from our study. Unfortunately, information on involvement of ID physicians was not collected; we suggest that future studies investigate the role of ID consultations in Peru and their impact on mortality.

Several limitations must be addressed. First, although the hospitals included in this study are important referral hospitals, a larger sample size from more than three hospitals would be necessary to generalize our results. In regards to treatment, data on dosage and administration routes were missing. Similarly, removal of infectious foci was limited to CVC; information on the removal of other infectious foci was not available. Furthermore, due to the observational nature of the original study design, data on the performance of follow-up cultures might be missing as these hospitals still rely on paper-based charts. The incomplete nature of the dataset might indicate other shortcomings in the management of SAB patients. Finally, the difficulty in judging adequate treatment duration (as discussed above) limited the presence of this standard of care in the multivariate Cox regression model.

5. Conclusions

Our study found that an overall lack of adherence to the standards of care recommended by the IDSA led to deficient management of SAB. SAB patients who had their CVC removed during their management had decreased mortality. Definitive therapy for SAB was found to be a protective factor and the high percentage of inadequate antibiotic treatments given to patients with MSSA bacteraemia must be addressed in Peruvian hospitals to alter the presence of negative patient outcomes. Continued misuse of vancomycin for MSSA might increase risk of poor outcomes and the development of resistant strains. Periodic evaluations of adherence to standards of care should be considered to improve management of SAB and overall patient care in Peru.

Funding

None.

Conflicts of interest

All authors: None to declare.

Summary

Deficient adherence to standards of care of *Staphylococcus aureus* bacteraemia (SAB) was observed, especially in the definitive treatment for MSSA. The removal of CVC and the use of appropriate definitive antibiotic therapy reduced the hazard mortality of SAB.

Acknowledgments

The authors would like to thank the *Latin America Working Group on Antimicrobial Resistance*, especially our collaborators from Hospital Nacional Guillermo Almenara Irigoyen and Hospital Nacional Alberto Sabogal Sologuren, for their procurement of SAB data in Peru. We would also like to thank Nicola Young for her help in reviewing this manuscript and Dr. Cesar Ugarte-Gil for his support in the statistical analyses.

References

Abbas M, Rossel A, de Kraker ME, von Dach E, Marti C, Emonet S, et al., Association between treatment duration and mortality or relapse in adult patients with Staphylococcus aureus bacteraemia: a retrospective cohort study. Clin Microbiol Infect [Internet]. 2019 Jul 26; Available from: https://doi.org/10.1016/j.cmi.2019.07.019.

Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, et al. Impact of Infectious Disease Consultation on Quality of Care. Mortality, and Length of Stay in Staphylococcus aureus Bacteremia: Results From a Large Multicenter Cohort Study. Clin Infect Dis. 2015;60(10):1451–61.

Bassetti M, Peghin M, Trecarichi EM, Carnelutti A, Righi E, Del Giacomo P, et al. Characteristics of Staphylococcus aureus Bacteraemia and Predictors of Early and Late Mortality. PLoS One. 2017;12(2):e0170236.

Battle SE, Augustine MR, Watson CM, Bookstaver PB, Kohn J, Owens WB, et al. Derivation of a quick Pitt bacteremia score to predict mortality in patients with Gram-negative bloodstream infection. Infection. 2019;47(4):571–8.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

Chesdachai S, Kline S, Helmin D, Rajasingham R. The Effect of Infectious Diseases Consultation on Mortality in Hospitalized Patients With MRSA, Candida, and Pseudomonas Bloodstream Infections. Open Forum Infect Dis [Internet]. 2020 Jan 11 [cited 2020 Jan 12]; Available from: https://academic.oup.com/ofid/advance-article-abstract/doi/10.1093/ofid/ofaa010/5700621.

Chong YP, Moon SM, Bang K-M, Park HJ, Park S-Y, Kim M-N, et al. Treatment duration for uncomplicated Staphylococcus aureus bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother. 2013;57(3):1150–6.

Davis JS, Sud A, O'Sullivan MVN, Robinson JO, Ferguson PE, Foo H, et al. Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial. Clin Infect Dis. 2016;62(2):173–80.

Davis JS, Van Hal S, Tong SYC. Combination antibiotic treatment of serious methicillin-resistant Staphylococcus aureus infections. Semin Respir Crit Care Med. 2015;36(1):3–16.

Fiala J, Palraj BR, Sohail MR, Lahr B, Baddour LM. Is a single set of negative blood cultures sufficient to ensure clearance of bloodstream infection in patients with Staphylococcus aureus bacteremia?. The skip phenomenon. Infection. 2019;47(6):1047–53.

Fowler Jr. VG, Li J, Corey GR, Boley J, Marr KA, Gopal AK, et al. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: experience in 103 patients. J Am Coll Cardiol. 1997;30(4):1072–8.

van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012;25(2):362–86.

Heriot GS, Tong SYC, Cheng AC, Liew D. Benefit of Echocardiography in Patients With Staphylococcus aureus Bacteremia at Low Risk of Endocarditis. Open Forum Infect Dis. 2018;5(12):ofy303.

Holland TL, Arnold C, Fowler Jr. VG. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014;312(13):1330–41.

Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2006;25(3):181–5.

Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from Staphylococcus aureus bacteremia. Medicine. 2009;88(5):263–7.

Laupland KB, Lyytikäinen O, Søgaard M, Kennedy KJ, Knudsen JD, Ostergaard C, et al. The changing epidemiology of Staphylococcus aureus bloodstream infection: a multinational population-based surveillance study. Clin Microbiol Infect. 2013;19(5):465–71.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18–55.

McDanel JS, Perencevich EN, Diekema DJ, Herwaldt LA, Smith TC, Chrischilles EA, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals. Clin Infect Dis. 2015;61(3):361–7.

Nambiar K, Seifert H, Rieg S, Kern WV, Scarborough M, Gordon NC, et al. Survival following Staphylococcus aureus bloodstream infection: A prospective multinational cohort study assessing the impact of place of care. J Infect. 2018;77(6):516–25.

Narsana N, Mills K, Wortmann G. Compliance With Staphylococcus aureus Bacteremia Quality-of-Care Guidelines. Open Forum Infect Dis [Internet]. 2015 Dec 1 [cited 2020 Jan 9];2(suppl_1). Available from: https://academic.oup.com/ofid/article/2/suppl_1/846/2635067.

Rasmussen RV, Høst U, Arpi M, Hassager C, Johansen HK, Korup E, et al. Prevalence of infective endocarditis in patients with Staphylococcus aureus bacteraemia: the value of screening with echocardiography. Eur J Echocardiogr. 2011;12(6):414–20.

Reyes J, Rincón S, Díaz L, Panesso D, Contreras GA, Zurita J, et al. Dissemination of methicillin-resistant Staphylococcus aureus USA300 sequence type 8 lineage in Latin America. Clin Infect Dis. 2009;49(12):1861–7.

Seas C, Garcia C, Salles MJ, Labarca J, Luna C, Alvarez-Moreno C, et al. Staphylococcus aureus bloodstream infections in Latin America: results of a multinational prospective cohort study. J Antimicrob Chemother. 2018;73(1):212–22.

Szubert A, Bailey SL, Cooke GS, Peto T, Llewelyn MJ, Edgeworth JD, et al., Predictors of recurrence, early treatment failure and death from Staphylococcus aureus bacteraemia: Observational analyses within the ARREST trial. J Infect [Internet]. 2019 Aug 6; Available from: https://doi.org/10.1016/j.jinf.2019.08.001.

Ten Oever J, Jansen JL, van der Vaart TW, Schouten JA, Hulscher MEJL, Verbon A. Development of quality indicators for the management of Staphylococcus aureus bacteraemia. J Antimicrob Chemother [Internet]. 2019 Aug 8; Available from: https://doi.org/10.1093/jac/dkz342.

Tong SYC, Davis JS, Eichenberger E, Holland TL, Fowler Jr. VG. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603–61.

Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive Staphylococcus aureus bacteraemia: an observational cohort study. Lancet Infect Dis. 2014;14(10):967–75.

Yoon YK, Park DW, Sohn JW, Kim HY, Kim Y-S, Lee C-S, et al. Effects of inappropriate empirical antibiotic therapy on mortality in patients with healthcare-associated methicillin-resistant Staphylococcus aureus bacteremia: a propensity-matched analysis. BMC Infect Dis. 2016;16:331.