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ORIGINAL RESEARCH

Risk factors associated with length of hospital stay in children with Staphylococcus aureus bacteremia.

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Abstract

Introduction: Severe infections such as bacteremia have a high rate of morbidity and mortality, and high healthcare costs. These statistics could be modified by a better understanding of the risk factors that may influence the development of the disease and length of hospital stay.

Methods: We conducted a cross-sectional study that included patients older than 28 days of life up to 15 years who were hospitalized with Staphylococcus aureus bacteremia in a public hospital in Ecuador. The data were obtained from medical records, clinical characteristics, weight, comorbidities, antibiotic resistance and length of hospitalization due to this pathology. A univariate analysis was performed and descriptive statistics were used.

Results: 126 cases were included. 74/126 (59%) were male. Average age was 4.8 ± 5.1 years, average weight was 16.5 ± 2.3 Kg, and average hospitalization length was 10.47 days. Resistance to oxacillin was observed in 56/126 cases (44.4%) 95% CI 43.67-45.22%. There was prior use of antibiotics in 81/126 cases (64.29%) 95% CI 63.54-65.03%). The factors associated with a longer hospital stay were cardiac comorbidity OR 1.53 ((95% CI 1.33-1.75) *P* = 0.005; Admission to the PICU OR 5.3 (2.03 to 14.03) *P* <0.001, and peripheral access route OR 0.367 (95% CI 0.17-0.82) P = 0.015. Other variables were not significant.

Conclusions: Admission to intensive care is related to an increase in the length of hospital stay. The only comorbidity identified as a risk factor was heart disease, while the use of a peripheral intravenous device was found to be a protective factor.

Key words: Staphylococcus aureus, bacteremia, hospitalization, child.

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Introduction

Staphylococcus aureus is a facultative aerobic gram-positive coccus about 1µm in diameter. It is part of the bacterial flora of the skin and mucous membranes, which are areas that can be infected by Staphylococcus aureus causing disseminated infections [1].

Infections caused by Staphylococcus aureus have different incidences depending on the geographical area and are increasingly becoming antibiotic resistant. A review of 15 studies shows that between 13 and 74% of the worldwide Staphylococcus aureus infections are methicillin-resistant Staphylococcus aureus (MRSA) with 6% of cases reported in Central America and 80% in South America [2].

The indiscriminate use of antibiotics in both hospital and outpatient settings has generated serious problems. In the past, severe infections were acquired only in hospitals; today they are being transmitted in the community due to the development of resistance to multiple antibiotic treatments [3].

The development of a Staphylococcus aureus infection is mediated by the interaction of environmental factors, bacterial virulence, and clinical characteristics of the host, in which the role of environmental factors is established by contact with the health system, a factor that could be modified with hygienic measures, whereas bacterial or genetic factors are not modifiable [4].

The length of a hospital stay can vary according to various factors that the patient possesses. A well-identified factor is bacteremia caused by MRSA versus methicillin-susceptible Staphylococcus aureus (MSSA) with longer hospitalizations and consequently increased hospital costs associated with cases of methicillin resistance [5]. It has been observed that in patients with more than 120 hours of hospitalization, the risk of contracting a disease caused by multi-resistant bacteria is increased 5.3 times [6]. Age may be a risk factor that affects the development of bacteremia as it has been shown that patients <12 months of age have increased susceptibility to bloodstream infections by Staphylococcus aureus [7].

Bacteremia acquired in hospital settings have higher morbidity and mortality, admissions to the intensive care unit and longer hospital stay [8]. Consequently, treatment in the pediatric intensive care unit (PICU) entails a longer period of hospitalization for these patients, increasing the health risk and the hospital costs, which is why we considered the following questions:

What are the risk factors related to hospitalization for Staphylococcus aureus bacteremia in children at the Baca Ortiz Hospital from January 2016 - December 2018?

Are sociodemographic characteristics, such as age, weight, and sex related to the hospital stay in bacteremia?

Does the use of previous antibiotics, bacterial resistance, comorbidities, and intravenous devices increase the days of hospitalization?

Do bacteremias caused by nosocomial Staphylococcus aureus have a longer hospital stay than bacteremia caused by community-acquired Staphylococcus aureus?

The objective of the present investigation was to establish the risk factors associated with hospitalization in a group of patients diagnosed with Staphylococcus aureus.

Population and methods

Study design

The design was an observational, analytical, cross-sectional retrospective study.

Stage

The study was conducted at the Baca Ortiz Pediatric Hospital in Quito, Ecuador. The study period was between January 2016 and December 2018.

Participants

The reference population was patients hospitalized at the Baca Ortiz Pediatric Hospital with a diagnosis of Staphylococcus aureus bacteremia, for a total of 160 patients. The sample comprised the total number of patients with the diagnosis established in the corresponding period and who met the inclusion criteria, which were:

- Children over 28 days old and under 15 years of age who had a positive blood culture for Staphylococcus aureus hospitalized at the Baca Ortiz Hospital from January 2016 - December 2018.

- Patients who had a complete medical history to obtain the necessary data.

- Report of antibiogram for bacterial resistance that included the antibiotic oxacillin.

Variables

The descriptive demographic variables were age, weight, and sex. The clinical variables were the use of previous antibiotics, cardiac, renal or neurological comorbidities, length of hospital stay, admission to intensive care, use of central or peripheral intravenous devices, in-hospital or community contagion, and in-hospital mortality.

Data Sources / Measurement

The electronic medical record was consulted as the primary data source, additionally the physical record was consulted, and confirmed with the respective microbiological database. The data were compiled in an electronic sheet to be later transferred to the statistical software.

Control of sources of bias.

Medical records whose data were incomplete were excluded and the inclusion of lost or excluded data was avoided. The protocol of this study was pre-approved by the Institutional Teaching Committee.

Study size

The sample was non-probabilistic, in which all potentially eligible cases from the pediatric hospital were included.

Management of quantitative variables

The quantitative variables are presented in scale as means and standard deviations. Nominal quantitative variables are presented as frequency and percentage.

Statistical Methods

Descriptive statistics were used. The statistical package used was SPSS v.22 for Windows. A univariate analysis was performed. Measures of central tendency were used to analyze descriptive statistics. The statistical analysis used to establish an association was the adjusted Odds Ratio (OR), calculated using the logistic regression model and accompanied by its 95% confidence interval (CI). To establish statistical significance, the cut-off point was $P = 0.05$.

Results

Participants

The number of patients who could potentially participate in the study was 160 cases, of which only 126 were eligible by meeting the established inclusion criteria.

Participant characteristics

The resulting demographic characteristics of the patients included 74/126 (59%) males. The minimum age was 0.1 years and the maximum age was 15 years with a mean of 4.79 years and SD 5.123. Average weight 16.5 Kg, with a minimum of 2.3 Kg, maximum of 60 Kg and SD 14.1 Kg.

The patients presented with an average of 10.47 days of hospitalization (SD 4.514), with a minimum of 4 days, and a maximum of 24 days. Finally, in children at the Baca Ortiz Hospital from January 2016 - December 2018, bacterial resistance to oxacillin in bacteremia due to Staphylococcus aureus was present in 44.4% of the cases.

The use of previous antibiotics in Staphylococcus aureus bacteremia was evaluated in children at the Baca Ortiz Hospital from January 2016 - December 2018, and found that 64.3% of the patients had received previous antibiotic therapy (see Table 1).

Table 1 General descriptions of the group

	n=126 (100%)	(IC 95%)
Oxacillin resistance	56 (44.44%)	43.67-45.22%
Previous antibiotics	81 (64.29%)	63.54-65.03%
Deceased	2 (1.59%)	1.39-1.78%

Main results

From the examined factors, we found a statistically significant relationship for the peripheral access route as a protective factor. The presence of cardiac comorbidity, and admission to an Intensive Care Unit were identified as risk factors. Sex, prematurity, identification of nosocomial infection, previous use of antibiotics, neurological or nephrological pathology were not identified as risk factors. These data are reported in Table 2.

Secondary Analysis

With the statistically significant variables: cardiac comorbidity, ICU admission and access route, we performed a multivariate regression to predict the event

of a prolonged stay. The regression equation was not globally significant (*P*=0.998). The only factor that predicts the prolongation of hospital stay was admission to the PICU (see Table 3).

Table 2 Factors associated with prolonged hospital stay in patients with Staphylococcus aureus infection

	Prolonged hospital stay			
	Yes n=88	No n=38	OR (95% CI)	*P*
Low weight	38 (45%)	11 (29%)	1.8665 (0.823 a 4.228)	0.135
Sex Female vs. Male	38 (43%)	13 (34%)	1.462 (0.662 a 3.226)	0.346
Use of Antibiotics	61 (69%)	20 (53%)	2.033 (0.931 a 4.442)	0.075
Oxacillin resistance	44 (50%)	12 (32%)	2.167 (0.972 a 4.829)	0.560
Cardiac comorbidity	16 (18%)	0 (0%)	1.528 (1.334 a 1.750)	0.005*
Renal Pathology	8 (9%)	4 (11%)	0.850 (0.240 a 3.013)	0.801
Neurological Pathology	17 (19%)	3 (8%)	2.793 (0.767 a 10.172)	0.107
Prematurity	9 (10%)	3 (8%)	1.329 (0.339 a 5.209)	0.682
PICU admission	44 (50%)	6 (16%)	5.333 (2.028 a 14.026)	0.0007*
Peripheral vs central access route	39 (44%)	26 (68%)	0.367 (0.165 a 0.820)	0.0145*
Nosocomial vs community disease	71 (81%)	33 (87%)	0.633 (0.215 a 1.862)	0.403

Table 3. Logistic Regression to predict prolongation of the hospital stay

	B	Standard error	X^2	Sig. (*P*)	Exp ($_B$) (OR)	95% C.I. for EXP(B)	
						Lower	Upper
Cardiac (1)	20.4	9451.479	0.0001	0.998	NC	NC	NC
PICU admission (1)	1.409	.538	6.844	0.009*	4.091	1.424	11.753
Access route (1)	0.494	.467	1.123	0.289	1.640	0.657	4.092
Constant	22.33	9451.482	0.0001	0.998	.000		

NC: not computable (due to the presence of a zero value in one of the results of the contingency table).

Discussion

This study was conducted with patients diagnosed with Staphylococcus aureus bacteremia. During the study, a male predominance was identified with 59.5% (n = 75) and 40.5% female (n = 51). The mean age was 4.8 ± 5.1 years. Similar results are also reflected in various studies, in which males were predominant and the average age was 60 months [9].

In a retrospective study conducted between 2014 and 2017, a higher number of males was reported with a mean age of 56 months and an average weight of 15 kg [10].

Regarding the clinical characteristics, the patients in our study weighed an average of 16.5 kilograms, with a minimum of 2.3 kilograms, maximum of 60 kilograms and SD 14.1. Among the patients, 38.9% were underweight; however, this was not a cause for the increase in days in the hospital and there was no evidence of a statistically significant relationship between these variables (*P* greater than 0.05). In a study conducted in a rural hospital in Kenya, the researchers found no difference in a multivariate analysis of nutritional status and days of hospitalization. The only factor that led to higher mortality was the absence of a focus of infection consistent with staphylococcal infections [11].

In our study, the average hospitalization length of children with Staphylococcus aureus bacteremia was

10.47 days with a minimum of 4 days and a maximum of 24 days.

The duration of hospitalization due to bacteremia can vary. Bacteremia is considered persistent when it lasts longer than 7 days as indicated by positive blood cultures. Other studies recommend that if a blood culture remains positive on the third day, despite receiving antibiotic treatment, then a combination therapy should be considered [12].

In a multinational prospective study of 1030 patients of different Latin American nationalities, it was found that the average hospitalization length was 28 days [2].

In another retrospective study performed in a tertiary pediatric hospital in Australia, the infectious and therapeutic characteristics of Staphylococcus aureus bacteremia were investigated, and the researchers reported that the average duration of hospital stay was 6 to 24 days in cases of infections classified as simple and 16 to 50 days in cases classified as complex with a median of 42 days [10].

While bacterial resistance is a global problem, there are data differences according to geographical areas. The Pan American Health Organization (PAHO) reported a range of resistance to Staphylococcus aureus in Latin America from lower than 20% (low resistance), between 20% to 50% (moderate resistance), and greater than 51% (high resistance) in different Latin American countries [13].

In the Enrique Garcés Hospital in the Ecuadorian capital, 30 cases were isolated in 2013. Among these cases, 40% of the cultures were positive for S. aureus, of which 16.6% were MRSA [14]. In this retrospective study, 44.4% were resistant to oxacillin (moderate resistance) and a rapid increase in resistance is expected in the coming years.

With regard to whether bacterial resistance influences the duration of hospital stay, there is diverse literature indicating that infections associated with multi-resistant organisms cause prolonged hospitalization and therefore contribute to higher expenses for the health sector.

In a research study [2], when the researchers performed univariate analyzes, they found that there was a greater increase in the hospital stay with MRSA bacteremia; however, when performing a multivariate analysis, this association was not significant.

The results obtained in the present study show that there was not a significantly significant relationship between oxacillin resistance in Staphylococcus aureus bacteremia and hospitalization days (P= 0.56; OR 2.167, 95% CI 0.972 - 4.829). Of our analyzed patients, 64.3% received prior antibiotic therapy.

In this study, 82.5% of the blood cultures were nosocomial Staphylococcus aureus. Since the hospital where the study was conducted is a national reference hospital that receives patients from all regions of the country, all patients referred with positive blood cultures were considered nosocomial germs since the natural history of the infection was unknown and, in general, more than 48 hours of hospitalization had already elapsed in the different health centers of origin. Therefore, it is possible that the value reflected in this study of hospital etiology could be lower. However, no statistically significant association was established between nosocomial Staphylococcus aureus bacteremia versus community-acquired Staphylococcus aureus with respect to the duration of hospitalization.

The 17.5% community-acquired SA reflected in this report alerts us to the high incidence of this pathogen. In another study, it was established that the average number of days of hospitalization with community infections was 14 days with differences reported between patients who were admitted to intensive care, resulting in higher rates of admission in children with MRSA bacteremia [9].

Admission to pediatric intensive care led to a longer hospitalization time, establishing a statistically significant relationship between admission to intensive care and prolonged hospitalization in patients with Staphylococcus aureus bacteremia at Baca Ortiz Hospital from January 2016 - December 2018, with a risk that was 5.333 times higher.

In another study, 14.3% of all patients registered upon admission to the PICU remained in the hospital for an average of 7 days. All cases classified as complex had a median total hospitalization of 42 days compared with patients who did not require intensive therapy with a median 17 days hospitalization [10].

Londoño Restrepo, et al., reported that staying in a hospital and receiving treatment for more than 5 days increases the risk of infections 5.3 times. Additionally, if admission to intensive care is added, the risk will increase 2.37 times more. Therefore, being hospitalized

in intensive care is associated with a higher risk of re-infection and hospitalization [6].

Since the treatment for severe bacteremia infections involves intravenous and prolonged antibiotic therapy administered through central and/or peripheral venous access, this predisposes the patient to both local (phlebitis) and systemic (bacteremia) infections [15].

In the present study, bacteremia associated with the use of a catheter was not analyzed, but we did compare the access routes for treatment. We found that the use of both central and peripheral intravenous devices influenced the prolongation of hospitalization by Staphylococcus aureus bacteremia. The peripheral access route was identified as a protective factor, which is in accordance with findings that showed that about 30% of nosocomial infections are associated with the use of central venous catheters, as described in a prospective study where it was reported that the incidence of peripheral catheter infection is lower compared to central catheters, 0.5 and 1.6, respectively; arterial lines also had an incidence of 2.715. This could explain why using peripheral lines is related to a shorter duration of hospitalization. It should also be noted that patients who required central lines were generally in the intensive care unit.

In patients with Staphylococcus aureus bacteremia, the comorbidities of cardiac, kidney, and neurological disease were compared. We found a statistically significant relationship between cardiac comorbidity and prolonged hospital stay with a 1.528-fold probability of prolongation compared to the other comorbidities (renal, neurological), which were not shown to increase the risk of a prolonged hospital stay. However, there is a risk of bias since the patients who presented with these pathologies were scarce, resulting in a statistically insignificant sample.

In this investigation, as well as other studies, mortality was relatively low with this type of infection as evidenced by a high percentage (98.4%) of patients being discharged alive and only 1.6% deceased patients. Patients who died from this type of infection were not related to the presence of MRSA. A study by Seas, et al., indicates that there is no association between the increase in mortality at 30 days and the isolation of MRSA [2].

Conclusions

The prolongation of hospitalization in patients with Staphylococcus aureus infections was associated with receiving treatment in the Pediatric Intensive Care Unit, the use of a central venous catheter, and the presence of cardiovascular comorbidity. Resistance to oxacillin in positive blood cultures and prior antibiotic therapy did not influence prolonged hospitalization times.

Abbreviations

CA-MRSA: Community-acquired methicillin resistant Staphylococcus aureus
IDSA: Infectious Disease Societies of America
MSSA: Methicillin-susceptible Staphylococcus aureus
MRSA: Methicillin-resistant Staphylococcus aureus
PICU: Pediatric Intensive Care Unit
SA: Staphylococcus aureus
SAB: Staphylococcus aureus bacteremia
SCC: Staphylococcal chromosomal cassette
WHO: World Health Organization

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Authors' contributions

DAMC: Research idea, data collection, article writing, statistical analysis, editorial corrections.
AA: Research idea, study design, critical analysis, research direction.
HPO: Research idea, critical analysis, research direction.
All authors read and approved the final version of the manuscript.

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Availability of data and materials

Under a reasonable academic or investigative request the authors are willing to share their data.

Ethical statements

Protection of persons

The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of the data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

The authors have obtained the informed consent from the guardians of the patient referred to in the article. This document is in the possession of the corresponding author. The parents have signed the authorization for publication of this trial.

Competing interests

The authors have no competing interests to declare.

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