Metastatic infections in pediatric patients with *Staphylococcus aureus* bacteremia assisted at a children's hospital in La Plata, Argentina

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ABSTRACT

Introduction. *Staphylococcus aureus* is one of the most prevalent infectious agents in children and may cause a wide variety of clinical presentations. *S. aureus* bacteremia is frequently associated with complications and metastatic infections. The epidemiological and clinical data about *S. aureus* bacteremia and its complications in pediatrics are scarce.

Objectives. To describe the epidemiology, frequency, distribution, and type of metastatic infections in a series of pediatric patients with *S. aureus* bacteremia and assess possible risk factors for its development.

Population and methods. Cross-sectional study of pediatric patients with *S. aureus* bacteremia admitted to a children's hospital of La Plata between January 2016 and June 2019.

Results. A total of 112 *S. aureus* bacteremia events were analyzed. The rate of metastatic infection was 34.8%; the lung was the most common infection site. The main risk factors for the development of metastatic infections were bacteremia due to methicillin-resistant *S. aureus* (odds ratio: 2.95; 95% confidence interval: 1.19-7.83; $p = 0.015$) and persistent positive control blood cultures at 48 hours (odds ratio: 3.17; 95% confidence interval: 1.22-8.46; $p = 0.012$).

Conclusion. The rate of metastatic infections among patients with *S. aureus* bacteremia was 34.8%. Associated risk factors were bacteremia due to methicillin-resistant *S. aureus* and persistent positive control blood cultures at 48 hours. The most common organs affected included the lungs, the osteoarticular system, and the skin and soft tissue.

Key words: *Staphylococcus aureus*, bacteremia, complications, pediatrics.

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INTRODUCTION

Staphylococcus aureus (SA) is one of the most prevalent infectious agents in children and may cause a wide variety of clinical presentations, some severe and life-threatening.¹⁻³ *S. aureus* bacteremia (SAB), a clinical entity associated with high morbidity and mortality levels, is defined as the isolation of SA in at least 1 blood culture with or without a related primary clinical site of infection. Its annual incidence is estimated at 8.4-28.4/100 000 individuals in the general population and across all age groups, and at 31-41 cases/10 000 hospitalized pediatric patients.³⁻⁵

In general, SAB is associated with potential secondary infectious complications (metastatic staphylococcal infections).⁴

A metastatic infection is the hematogenous dissemination of a specific infectious agent and its subsequent location in an organ other than the one where the infection started (primary site of infection). The terms *metastatic infections*, *deep sites of infection* or *secondary sites of infection* are used interchangeably.

The prevalence of such metastatic infections in SAB has been widely studied in adult patients and is approximately 50%.^{2,3,6} However, in pediatric patients, the evidence is scarce and based on studies conducted in adults, expert opinions, and few publications (most are retrospective, observational studies with a small population of patients). It has been pointed out that the prevalence of these complications may be lower (< 20%),^{6,7} and most commonly associated with predisposing underlying diseases, with a

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distribution and order that differ from those of adults.^{3,8,9}

At a local and regional level, there are not enough epidemiological data, guidelines or protocols for the diagnosis and/or management of SAB in pediatrics and its distant complications.^{2,9,10} The reported risk factors that have shown the greatest statistical significance for the development of distant metastasis in patients with SAB are persistent positive control blood cultures 48 hours after the first positive blood culture, presence of central venous catheters, and methicillin-resistant microorganisms.^{3,7,11}

The objective of this study was to describe the epidemiology, frequency, distribution, and type of metastatic infections in a series of pediatric patients with *S. aureus* bacteremia and assess possible risk factors for its development.

POPULATION AND METHODS

This was a descriptive, retrospective, cross-sectional study that identified, after reviewing the records of the Department of Microbiology, all patients aged between 1 month and 14 years, 11 months and 29 days hospitalized in Hospital de Niños Sor María Ludovica who had an event of SAB in the clinical setting of an acute infection. The study was carried out in the period between January 1st, 2016 and June 30th, 2019.

Medical records were identified by manual search; the epidemiological characteristics of the study population, the presence and location of metastatic infections, and risk factors for their development (underlying disease, empiric antibiotic therapy prior to initial blood cultures, prior central venous catheter, methicillin resistance, origin of infection, and primary site of infection) were collected.

Any patient whose medical record did not include the required data was excluded.

Definitions

Underlying condition: underlying chronic disease.

Therapy prior to initial blood cultures: antibiotic therapy administered before the initial collection of blood cultures for etiologic diagnosis.

Origin of the infection: a community-acquired infection is that with an initial SA positive blood culture done in the first 48 hours since patient hospitalization, whereas a nosocomial infection corresponds to a blood culture obtained after such period (> 48 hours).

Statistical analysis

The statistical analysis was performed with the R software, version 3.5.1. Qualitative variables were expressed as frequency (%). Age was described as median (interquartile range [IQR]). The association between the presence of metastatic infections and the other studied variables were analyzed with a χ^2 test. The odds ratios (OR) and 95% confidence intervals (CI) were adjusted based on logistic regression. A value of $p < 0.05$ was considered significant.

Ethical regulatory aspects

The protocol of this study was submitted before and approved by the Institutional Research Protocol Review Committee of Hospital de Niños Sor María Ludovica.

RESULTS

A total of 145 SAB events in 143 patients were detected; of these, 112 events occurred in 111 patients were analyzed (1 patient had 2 events of SAB during different hospitalizations); 33 events were excluded because medical records were incomplete.

Community-acquired SAB predominated over nosocomial cases (63.4% versus 36.6%, respectively).

The mean decimal age at onset was 4.54 years (range [r]: 0.06-14.68 years, median: 3.05 years). Males accounted for 56.7% of patients.

Associated comorbidities were observed in 53.6%; nutritional diseases were documented most frequently, followed by oncohematological diseases (Table 1).

In 91.1% of events, a primary site of infection was detected at onset. Skin and soft tissue infections (SSTI) were the most common ones (38.5% [n = 43]), followed by central venous catheter-associated infections (CAI) (25.9% [n = 29]), osteoarthritis (11.6% [n = 13]), respiratory disease (8.9% [n = 10]), and other (6.2% [n = 7]). Fever syndromes and/or sepsis without a source accounted for 8.9% (n = 10) of events.

In relation to antibiotic resistance, most isolated microorganisms corresponded to methicillin-resistant SA (MRSA). In relation to origin of the infection, community-acquired SAB was the most prevalent in general, as well as when events were differentiated by MRSA or methicillin-sensitive SA (MSSA). Figure 1 shows data for antibiotic resistance and origin of SA.

At least 1 supplementary test was requested to look for deep sites of infection in 84.8% of cases;

53 metastatic infections were detected in 39 SAB events (10 patients had more than 1 secondary site of infection) (Table 2).

A total of 401 supplementary tests were requested to look for deep sites of infection;

Table 1. Comorbidities associated with *S. aureus* bacteremia

Comorbidity	n (%)
Nutritional disease	25 (22.3)
[short bowel syndrome]	[17/25 (68)]
Oncohematological diseases	12 (10.7)
Neonatal disease	6 (5.3)
Immunosuppression	5 (4.5)
Heart disease	4 (23.6)
Kidney disease	2 (1.8)
Post-operative period	2 (1.8)
Other	4 (3.6)
Total comorbidities	60 (53.6)

82 were positive. An echocardiogram was the most common supplementary test to look for metastatic infections (in 76.8% of events), with 4 positive results. This was followed by abdominal imaging tests (66.7%), with 8 positive results; fundus (56.2%), with no positive finding; lung imaging tests (47.3%), with 32 results compatible with potential metastatic infections; and lastly, osteoarticular and skin and soft tissue imaging tests (26.8%), with 9 positive results. In relation to pulmonary supplementary tests, it should be noted that, out of all tests (n = 53), none was requested by the treating physician to specifically look for deep sites of infection, and none of the positive findings (60.4%) was deemed as a metastatic infection in the medical records. In relation to secondary pulmonary sites of infection, the following radiological diagnoses were described: pleuropulmonary suppuration, pulmonary condensation, and bilateral interstitial infiltrate (Table 3 and Table 4).

FIGURE 1. Analysis of antibiotic resistance and origin of infection

SA: *Staphylococcus aureus*, MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*.

TABLE 2. Distant metastasis by primary site of infection

Primary infection	Patients in whom a metastatic site was found	Total metastatic infections found
SSTI (n = 43)	19 (44.2%)	27
CAI (n = 29)	4 (13.8%)	4
Osteoarticular (n = 13)	8 (61.5%)	12
Respiratory disease (n = 10)	4 (40%)	5
Sepsis/FWS (n = 10)	2 (20%)	3
Other (n = 7)	2 (28.6%)	2
Total (n = 112)	39 (34.8%)	53

SSTI: skin and soft tissue infections, CAI: central venous catheter-associated infection, FWS: fever without a source.

Different variables have been described in the bibliography as risk factors for metastatic infection in SAB. Of these, the isolation of MRSA almost tripled the possibility for developing secondary sites of infection (OR: 2.95; 95% CI: 1.19-7.83; $p = 0.015$).

The persistence of positive control blood cultures beyond 48 hours after the first blood culture tripled the possibility for metastatic infections (OR: 3.17; 95% CI: 1.22-8.46; $p = 0.012$). However, the origin of infection (community-acquired or nosocomial), the presence of comorbidities, empiric antibiotic therapy prior to initial blood cultures, the presence of central venous catheter prior to SAB, and patient's sex did not show an association with the development of deep sites of infection in SAB.

When grouped by primary site of infection, only a reverse association was observed between CAI and the development of metastatic infections in general (OR: 0.22; 95% CI: 0.05-0.23), $p = 0.006$, compared to the rest of primary sources of infection, which did not show statistically significant differences among them.

The prevalence of bacteremia due to MRSA among patients with CAI was lower compared to the other sites of infection (CAI: 24.1% [$n = 7/29$] versus SSTI: 62.8% [$n = 27/43$], osteoarthritis: 84.6% [$n = 11/13$], fever or sepsis without a source: 60% [$n = 6/10$], respiratory disease: 80% [$n = 8/10$], and other: 57.1% [$n = 4/7$]).

When data were analyzed individually by type of metastatic infection, MRSA (OR: 3.63; 95% CI: 1.32-11.22; $p = 0.009$), persistence of positive control blood cultures at 48 hours (OR: 4.54; 95% CI: 1.67-12.74; $p = 0.001$), and osteoarticular origin of SAB (OR: 4.46; 95% CI: 1.16-19.11; $p = 0.019$) showed greater possibilities for the presence of pulmonary metastatic infections.

CAI showed a reverse association with the development of secondary sites of infection in the lungs (OR: 0.20; 95% CI: 0.04-0.75; $p = 0.008$) compared to the other primary sites of infection.

When a SSTI was the origin of SAB, the chances for the development of osteoarticular and skin and soft tissue metastatic infections increased in an independent manner (OR: 6.97; 95% CI: 1.21-73.56; $p = 0.02$).

Lastly, the persistence of positive control blood cultures 48 hours after the first positive blood culture was directly related to greater possibilities for metastatic infection due to MRSA (OR: 4.85; 95% CI: 1.61-17.87; $p = 0.002$). No other statistically relevant association was observed between the other variables and positive control blood cultures at 48 hours.

DISCUSSION

S. aureus is one of the most relevant microorganisms for humans, and the infections caused by it lead to a broad variety

TABLE 3. Metastatic infections found

Metastatic site of infection sought	Supplementary tests performed (n, %)	Metastatic infections found/ tests requested (n, %)
Ocular	63 (56.2)	0/63 (0)
Cardiac	86 (76.8)	4/86 (4.6)
Abdominal	75 (66.7)	8/75 (10.7)
Pulmonary	53 (47.3)	32/53 (60.4)
Osteoarticular and/or SST	30 (26.8)	9/30 (30)
Total	307	53/307

SST: skin and soft tissue.

TABLE 4. Description of pulmonary sites of infection found

Pulmonary sites of infection found	Site of infection found/pulmonary test requested (%)	Site of infection found/ total events (%)
PPS	8/53 (15.1)	8/112 (7.15)
Pulmonary condensation	16/53 (30.2)	16/112 (14.3)
Interstitial infiltrate	8/53 (15.1)	8/112 (7.15)
Total pulmonary sites of infection	32/53 (60.4)	32/112 (28.6)

PPS: pleuropulmonary suppuration.

of manifestations of diverse severity, both nosocomial and community-acquired.^{1,2,9}

SAB implies high levels of morbidity and mortality associated with complications and metastatic infections.^{1,2} This study established an overall rate of metastatic infections of 34.8% among pediatric patients with SAB, similar to what has been reported in a prospective, multicenter study conducted in Argentina with 647 patients and in a cross-sectional study with 424 patients in the United States.^{9,12}

According to regional epidemiological data, in this series, bacteremia due to MRSA and community-acquired SAB prevailed.^{9,11,12}

Currently, at Hospital de Niños Sor María Ludovica and in the field of pediatrics in general, screening for deep sites of infection in SAB is done based on data extrapolated from studies in adults, in whom metastatic infections are more commonly located in the cardiovascular, gastrointestinal, and ocular systems.^{13,14} Secondary infection sites in this series of patients were, in order of relevance: pulmonary, osteoarticular, skin and soft tissue, abdominal, and cardiovascular. The distribution was similar to that described in other series of pediatric patients with SAB.^{2,4,15,16}

Although the lungs were the main site of metastatic infection in this analysis, pulmonary imaging tests were not requested to screen for secondary sites of infection; the descriptions made here were a finding of the investigators. It is particularly striking that, in clinical practice, few supplementary tests are requested to look for pulmonary complications in SAB cases, which may result in an under-recording of such complications because, as detailed in the bibliography, they do not always present with respiratory compromise and may be oligosymptomatic or asymptomatic.^{2,17} However, a fundus was requested in 56.2% of events, although this is a very rare metastatic site in pediatrics, and no positive results were obtained.^{1,2}

The analysis of risk factors similar to those described in the bibliography for the development of metastatic infections due to SA in general, bacteremia due to MRSA and persistence of positive control blood cultures at 48 hours were the only independent statistically significant factors, and both tripled the probability for developing metastatic infections. In turn, the presence of MRSA showed a direct relation and was a risk factor for persistence of positive control blood cultures at 48 hours.^{7,12,17,18}

When grouped by primary source of SAB, there was a lower association between CAI and the development of metastatic infections; this is probably related to a lower prevalence of bacteremia due to MRSA in patients with CAI compared to the rest of infection sites in this series.

Subsequently, results were analyzed individually by type of metastatic infection in relation to the other variables. Bacteremia due to MRSA, persistence of positive control blood cultures at 48 hours, and osteoarticular origin showed a higher risk, in an independent manner, for the development of pulmonary metastatic infections. When the origin of SAB was a SSTI, it resulted in an increased risk for the presence of secondary infection at an osteoarticular and skin and soft tissue level. These results are similar to those reported in the few studies that established a relationship with the mentioned variables in pediatric patients.^{3,17}

Although there is certain consensus in the bibliography about requesting a control echocardiogram in the case of patients with SAB and persistence of positive control blood cultures 48 hours after the first positive blood culture, central venous catheter or children with congenital heart disease, no relationship has been established between these variables and the development of endocarditis in the studied patient series.^{3,7,15,17}

Based on this study and the analyzed bibliography, it is necessary to review everyday pediatric practice in the management of patients with SAB and to prioritize methicillin resistance and the persistence of positive control blood cultures as risk factors for the development of distant metastatic infections.¹⁴

As part of the approach to pediatric patients diagnosed with SAB, in addition to the protocol tests established by each institution, it is recommended to perform a blood culture 48 hours after the first positive blood culture and lung imaging tests (at least a chest X-ray), regardless of the patient's symptoms, as well as to delay the performance of a fundus, unless there is clinical evidence of ocular compromise. Further studies are required to accurately establish in which cases other supplementary tests should be requested to rule out secondary consequences in other parenchymas.

CONCLUSION

This analysis evidenced a rate of metastatic infections of 34.8% among pediatric patients

diagnosed with *S. aureus* bacteremia.

Risk factors associated with the presence of secondary sites of infection were bacteremia due to MRSA and the persistence of positive control blood cultures beyond 48 hours after the first positive blood culture. The most common organs affected included the lungs, the osteoarticular system, and the skin and soft tissue, although these were the least studied.

The development of pulmonary metastatic infections was directly related to the osteoarticular origin of SAB; whereas primary skin and soft tissue infections were related to osteoarticular and skin and soft tissue secondary sites of infection. ■

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