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Pharmacist-led antimicrobial stewardship program in the treatment of *Staphylococcus aureus* bacteraemia in paediatric patients: a multivariate analysis

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SUMMARY

Background: Care bundles are a recognised strategy to improve treatment. When managed through an Antimicrobial Stewardship Program (ASP) based on the pharmacist-led program model, care bundles can be an effective tool to guide decision making in clinical practice and to improve patient outcomes. This study aimed to evaluate the results of a pharmacist-led ASP which included a care bundle based on clinical outcomes of *Staphylococcus aureus* bacteraemia (SAB) in a paediatric hospital.

Methods: A retrospective cohort study with multivariate analysis was conducted in a paediatric hospital in Brazil. The study comprised 120 paediatric patients with a positive blood culture for *S. aureus* with occurred between 2014 and 2021 and clinical and laboratory results consistent with infection. The study was classified into two periods: pre-intervention (n=44) and intervention (n=76). A pharmacist-led ASP program with a care bundle was established during the intervention period 2017–2021. The primary outcome assessed was the impact on clinical outcomes, including infection-related mortality and 90-day reinfection rate, both being considered therapeutic failure.

Results: The multivariate analysis demonstrated that the following variables had an impact on primary outcome: infant patients [Odds ratio (OR) 12.998, *P*=0.044]; use of more than three antimicrobial treatment regimens [OR 0.006, *P*=0.017]; intervention period [OR 0.060, *P*=0.034]; bundle item 1 – follow-up blood culture [OR 18.953, *P*=0.049]; bundle item 2 – early source control [OR 0.002, *P*=0.018]; bundle item 4 – de-escalation to oxacillin for methicillin-sensitive *S. aureus* [OR 0.041, *P*=0.046].

Conclusions: The pharmacist-led ASP model showed an increase in adherence to the care bundle between the two study periods, with reduced probability of a negative outcome. Furthermore, risk factors for *S. aureus* bacteraemia were identified that may inform management and contribute to better patient outcomes in the paediatric population.

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Introduction

Staphylococcus aureus is an epidemiologically important microorganism. According to the Global Antimicrobial Resistance Surveillance and Use System (GLASS) of the World Health Organization (WHO) [1], methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the eight most clinically significant bacteria in the world. As such, the management of *S. aureus* infections must be performed rigorously and follow well-established measures in clinical practice to avoid selective pressure, resistant strain development, and other complications, including reinfection and death [2,3].

It is necessary to monitor these patients through Antimicrobial Stewardship Programs (ASP), which are composed of multidisciplinary teams of infectious diseases (ID) physicians, clinical pharmacists, and microbiologists. The ASP supports the clinical team in decision making regarding infection to improve the quality of care, to achieve positive outcomes for the patient, to reduce healthcare system costs, and to promote the rational use of antimicrobials [4].

Within the multidisciplinary team, the clinical pharmacist plays a fundamental role, as they are knowledgeable about the clinical pharmacology of antimicrobials, and participate in and facilitate discussions between the medical team and the clinical microbiology team. As a result of their abilities, ASP models which centred on the pharmacist, or pharmacist-led programs, have demonstrated positive results in the management of *S. aureus* infections using care bundles [5—10].

A care bundle is a set of evidence-based practices that, when appropriately applied, are associated with better health outcomes. Furthermore, care bundles are tools that can optimise measurement of ASP effectiveness, enabling the analysis of service performance, with the aim of improving quality [10,11].

At the time of writing, no study in the literature has demonstrated the clinical impact of a pharmacist-led ASP combined with a care bundle strategy to manage *S. aureus* bacteraemia on the outcomes for paediatric patients. This study aimed to evaluate the impact of a pharmacist-led ASP during an eight-year period, in terms of adherence to the care bundle and the outcome of treatment for *S. aureus* bacteraemia (SAB) in a paediatric hospital.

Methods

Study setting

The study was conducted at a tertiary paediatric hospital in the city of Curitiba, Brazil. The hospital had 62 intensive care unit (ICU) beds, divided into four units, and 13 clinical wards, comprising a total of 372 beds. The hospital's antimicrobial stewardship program (ASP) began in mid-2009, with the appointment of a dedicated pharmacist in the Hospital Infection Control Service (HICS). In 2013, a multi-professional residency program began, in which three pharmacy residents enter the program annually and acquire specialised training in ASP. This is one of the mandatory components of the residency program, and it is an activity developed by clinical pharmacists in all clinical units.

The ASP model developed at the hospital is based on pharmacist-led programs, in which the management of antimicrobial use is mainly the responsibility of the clinical pharmacist, coordinated by the infectious diseases physician (program leader) and senior clinical pharmacist (co-leader). In this program model, the clinical pharmacist must have the technical competence to analyse, monitor, discuss with the specialist, and perform pharmaceutical interventions for antimicrobial use, as well as participate in the development and management of infection clinical protocols and clinical pathways.

Ethics statement

Ethical approval was obtained from the Ethics Committee at Pequeno Príncipe College and approved under number 4.769.334, CAAE: 47556621.0.0000.5580. The research was conducted in accordance with the Ethics Committee guidelines. All patients have been anonymised.

Study design

A retrospective cohort was defined according to the STROBE guidelines [12] and included patients between 0 and 18 years of age who presented positive blood cultures for *S. aureus* and signs and symptoms of infection. Two periods were defined for comparison based on the history of the service in the hospital:

- **Pre-intervention (2014—2016):** period in which the pharmacy residency program was being implemented; the number of clinical pharmacists was smaller and therapeutic drug monitoring (TDM) of vancomycin, an important aspect of pharmaceutical intervention, was being incorporated into the institution's protocols.
- **Intervention (2017—2021):** period during which pharmacy residents began to participate and were supervised by the senior clinical pharmacist, there was an increase in the number of clinical pharmacists, and vancomycin TDM was in place.

The pharmacist-led ASP was referred to as the 'intervention', recognising that the difference between the periods was the strengthening of the pharmacist-led ASP within the institution, where there was greater involvement of clinical pharmacy as part of the ASP, resulting in pharmacotherapeutic interventions.

Study population

Following other studies in the literature, we randomly selected 30% of the sample of patients with positive blood cultures for *S. aureus* between 2014 and 2021 to represent the population [13—18]. Inclusion criteria were patients who presented clinical and laboratory signs typical of infection. Exclusion criteria were patients with blood culture contamination where *S. aureus* was grown in the blood culture without clinical and laboratory signs of infection and who did not receive any treatment.

Care bundle

The care bundle proposed by López-Cortés *et al.* [7] (Table I) was used as a methodology for data collection and to validate the pharmacist-led ASP service by comparing adherence between the pre-intervention and intervention periods. This bundle

Table I
Quality-of-care indicators in the care bundle

Bundle item	Quality-of-care indicator	Definition
1	Follow-up blood cultures	Performance of control blood cultures 48—96 h after antimicrobial therapy;
2	Early source control	Removal of initial focus, such as non-permanent vascular catheter or drainage of an abscess in <72 h, if applicable;
3	Search for distant focus	Performance of echocardiography in patients with complicated bacteraemia;
4	De-escalation to oxacillin for MSSA	Definitive therapy with intravenous oxacillin in cases of methicillin-susceptible strains;
5	Vancomycin adjustment for MRSA	Adjustment of vancomycin dose based on trough levels, in cases of methicillin-resistant strains;
6	Treatment duration	Antimicrobial therapy for at least 14 days for uncomplicated bacteraemia and 28 days for complicated bacteraemia.

Adapted from López-Cortés *et al*. [7].

outlines the main items used in the treatment of *S. aureus* bacteraemia, which the authors refer to as "indicators of quality-of-care management." Due to their skills in monitoring and expertise in analysing the use of antimicrobials, the pharmacist is the qualified professional to implement the bundle.

Variables and definitions

Outcome

As the main outcome, the results of pharmacist-led ASP on clinical outcomes were evaluated, including infection-related mortality and re-infection within 90 days (both considered therapeutic failure).

Components of the care bundle (Table I)

Item 1 (follow-up blood cultures) established a 96-hour limit for follow-up blood culture collection.

The other items in the bundle had specific adherence characteristics. When the item was not applicable, it was classified as "NA".

- Item 2 (early source control): patients with a catheter that could not be removed (including severe haemodynamic instability, totally implanted venous catheter, or dialysis catheter) and who had catheter treatment with lock therapy were considered NA.
- Item 3 (search for distant focus): patients without suspicion of metastatic focus, who did not need an echocardiogram, were considered NA.
- Item 4 (de-escalation to oxacillin for MSSA): patients with methicillin-resistant *S. aureus* (MRSA) were considered NA.
- Item 5 (vancomycin adjustment for MRSA): patients with methicillin-sensitive *S. aureus* (MSSA) and patients hospitalised and treated between 2014 and 2015 were considered NA, as the institution did not perform therapeutic drug monitoring (TDM) of vancomycin at that time.
- Item 6 (treatment duration): patients who died before completing the proposed treatment period were considered NA.

Complexity of the infection

To identify whether the treatment duration was adequate (Item 6 of the bundle), the complexity of the infection was first analysed according to the following criteria:

- Uncomplicated cases: antimicrobial treatment should last at least 14 days and the case must adhere to the following criteria: negative control blood culture within 24—72 hours after the initial positive blood culture; absence of fever within 72 hours after the initial positive blood culture; absence of signs and symptoms of metastatic infection foci; echocardiogram without evidence of endocarditis; absence of intravascular prosthetic devices and, in cases of bacteraemia associated with intravascular catheters, the catheter should be removed within five days [9,19—23].
- Complicated cases: treatment should last between 28 and 42 days and must meet at least one of the following criteria: control blood culture with isolation of *S. aureus*; persistent fever; echocardiogram with evidence of endocarditis or signs and symptoms of distant infection [9,19—23].

Clinical cure

Clinical cure was defined as negative control blood culture associated with the absence of typical signs and symptoms of infection [7].

Reinfection

Reinfection was defined as the isolation of *S. aureus* in blood cultures and other typical clinical and laboratory signs of infection, during the same episode of hospitalisation or if not, within 90 days after clinical cure [7].

Age ranges

The age ranges were defined as follows: newborn: 0—28 days; infant: 28 days to 12 months; child: 1—12 years; adolescent: 12—18 years [45].

Statistical analyses

After data collation in the Excel® software (Microsoft Corporation), a descriptive analysis was performed to characterise the study population. For this, the variables were expressed in absolute (n) and relative (%) frequency, while numerical variables were expressed in median and interquartile range (IQR). The Mann-Whitney test was used for numerical variables and the Chi-square or Fisher test for categorical variables. In addition, univariate and multivariate analysis (logistic

Table II
Descriptive variables

Variable	All patients (n = 120)	Pre-intervention (2014–2016) (n = 44)	Intervention (2017–2021) (n = 76)	*P-value*
	n (%)	n (%)	n (%)	
Gender (male)	74 (62%)	26 (59%)	48 (63%)	0.659
Age group[a]				
newborn	16 (13%)	9 (21%)	7 (9%)	0.081
infant	34 (28%)	10 (23%)	24 (32%)	0.300
child	54 (45%)	18 (41%)	36 (47%)	0.493
teenager	16 (13%)	7 (16%)	9 (12%)	0.528
SUS[b]	75 (63%)	31 (70%)	44 (58%)	0.171
Unit (nursery)	71 (59%)	26 (59%)	45 (59%)	0.990
Total length of stay	31 DAYS (IQR 17–78)	39 DAYS (IQR 18–84)	29 DAYS (IQR 15–67)	0.214
ICU admission	70 (58%)	27 (61%)	43 (56%)	0.608
Time in ICU	33 DAYS (IQR 11–64)	39 DAYS (IQR 17–71)	26 DAYS (IQR 9–58)	0.322
Acquisition				
Hospital-acquired infection	84 (70%)	34 (77%)	50 (66%)	0.186
Community-acquired infection	36 (30%)	10 (23%)	26 (34%)	
Specialties that treated underlying diseases[c]				
Cardiology	30 (25%)	7 (16%)	23 (30%)	0.080
Neurology	24 (20%)	7 (16%)	17 (22%)	0.394
Orthopaedics	20 (17%)	7 (16%)	13 (17%)	0.865
Nephrology	17 (14%)	9 (21%)	8 (11%)	0.133
Gastroenterology	16 (13%)	9 (21%)	7 (9%)	0.081
Endocrinology	10 (8%)	6 (14%)	4 (5%)	0.168
Combined	25 (21%)	12 (27%)	13 (17%)	0.186
Others[d]	29 (24%)	13 (30%)	16 (21%)	0.295
Co-morbidities				
	93 (77%)	32 (73%)	61 (80%)	0.341
Source of bacteraemia				
BSI	56 (47%)	22 (50%)	34 (45%)	0.578
Bone and joint	24 (20%)	8 (18%)	16 (21%)	0.705
SSI	11 (9%)	3 (7%)	8 (10%)	0.498
Sepsis	8 (7%)	4 (9%)	4 (5%)	0.463
CAP	6 (5%)	1 (2%)	5 (7%)	0.413
Skin and/or soft tissue	5 (4%)	2 (5%)	3 (4%)	1.000
Clinical pneumonia	4 (3%)	3 (7%)	1 (1%)	0.139
Endocarditis	3 (3%)	1 (2%)	2 (3%)	1.000
VAP	2 (2%)	0	2 (3%)	0.532
UTI	1 (1%)	0	1 (1%)	1.000
Susceptibility (MRSA)				
	20 (17%)	6 (14%)	14 (18%)	0.498
Switch therapy				
	28 (23%)	9 (20%)	19 (25%)	0.322
Number of antimicrobial treatment regimens				
1	37 (31%)	13 (30%)	24 (32%)	0.938
2	30 (25%)	11 (25%)	19 (25%)	
3	28 (23%)	11 (25%)	17 (22%)	
4	12 (10%)	4 (9%)	8 (11%)	
5	5 (4%)	2 (5%)	3 (4%)	
6	5 (4%)	2 (5%)	3 (4%)	
8	1 (1%)	0	1 (1%)	
10	1 (1%)	0	1 (1%)	
12	1 (1%)	1 (2%)	0	

IQR - interquartile range; BSI - primary bloodstream infection; SSI - surgical site infection; CAP — community acquired pneumonia; VAP - ventilation-associated pneumonia; UTI - urinary tract infection (with haematogenous spread).

[a] Age range (newborn: 0–28 days; infant: 28 days to 12 months; child: 1–12 years; adolescent: 12–18 years) [45].

[b] SUS: Brazilian public health care system.

[c] Patients attended by more than one specialty were counted in all of them, resulting in an n greater than 120 for this variable.

[d] Pulmonology, oncology, immunology, general medicine, hepatology, haematology, dermatology, and bone marrow transplant.

Table III
Univariate analysis of care bundle adherence

Bundle item	Pre-intervention (2014–2016) (n = 44)	Intervention (2017–2021) (n = 76)	Odds ratio (CI 95%)	*P-value*
	n patients/n patients applicable (%) [a]			
1 - Follow-up blood cultures	17/44 (39%)	36/76 (47%)	1.429 (0.671–3.043)	0.354
2 - Early source control	18/20 (90%)	32/36 (89%)	0.889 (0.148–5.340)	0.898
3 - Search for distant focus	7/11 (64%)	15/15 (100%)	-	0.011[b]
4 - De-escalation to oxacillin for MSSA	14/23 (61%)	40/51 (78%)	2.338 (0.801–6.820)	0.120
5 - Vancomycin adjustment for MRSA[c]	2/2 (100%)	14/14 (100%)	1	-
6 - Treatment duration	23/42 (55%)	58/72 (81%)	3.422 (1.474–7.947)	0.004
Complete bundle adherence	5/44 (11%)	22/76 (29%)	3.178 (1.107–9.124)	0.032
Complete adherence without item 1 (follow-up blood cultures)	20/44 (45.5%)	53/76 (69.7%)	2.765 (1.281–5.967)	0.010

CI - confidence interval; MSSA - Methicillin-sensitive *Staphylococcus aureus*; MRSA - Methicillin-resistant *Staphylococcus aureus*.
[a] n patients=number of patients who met the item; n patients applicable (%) =number of applicable patients for the item, excluding NA.
[b] All patients fulfilled item 3 in the Intervention period, which makes it impossible to analyse OR due to the absence of patients who did not fulfil item 3.
[c] 2014 and 2015 were not evaluated for item 5 (n=26) due to the absence of vancomycin TDM in the institution.

regression) was performed to evaluate which factors affected the clinical outcome of interest (therapeutic failure). For this, the data were expressed in odds ratio (OR) and a 95% confidence interval (CI) was considered. Variables with $P < 0.05$ and OR greater than 1 indicated correlation with the outcome of interest. Variables with $P < 0.2$ in univariate analysis were considered eligible for multivariate analysis, in which the Bootstrap Backward Likelihood Ratio (LR) method was used. In this model, all variables are initially included, and after statistical considerations, non-significant variables were removed at each step, returning after all cycles to a final adjusted model. The IBM® software SPSS® Statistics version 2.0 was used for the analyses.

Results

Between 2014 and 2021, 378 patients had positive *S. aureus* blood cultures, with no distinction between contamination and infection. Of these, 120 infected patients were included in the analysis. The majority were male (62%) and within the age group of children (45%). The results of all other variables are presented in Table II.

The univariate analysis of bundle adherence (Table III) showed a statistically significant difference ($P < 0.05$) for bundle Items 3 (search for distant focus) [P=0.011] and Item 6 (treatment duration) [OR 3.422, P=0.004] and for adherence to the complete care bundle [OR 3.178, P=0.032] between study periods. Analysis of adherence to the complete bundle without item 1 (follow-up blood cultures) [OR 2.765, P=0.010] was conducted considering the relevance of Item 1 for paediatrics.

In the univariate analysis, the age group of infants stood out, as it had the greatest correlation with therapeutic failure [OR 2.582, P=0.038]; patients with hospital-acquired infection had a higher chance of presenting therapeutic failure [OR 4.400, P=0.023], as well as patients with comorbidities [OR 10.090, P=0.027] (Table IV). Regarding the source of the infection, patients with bloodstream infection (BSI) showed a greater chance of therapeutic failure [OR 2.895, P=0.021]. On the other hand, patients with bone and joint infections showed a better outcome [OR 0.117, P=0.040], indicating that these patients were less likely to present therapeutic failure outcomes.

The multivariate analysis (Table V) identified a model with variables defined by the Bootstrap Backward Likelihood Ratio method. The analysis indicted that the variables of applying up to three antimicrobial treatment regimens [OR 0.006, P=0.017], the intervention period [OR 0.060, P=0.034], and compliance with bundle Item 2 (early source control) [OR 0.002, P=0.018] and Item 4 (de-escalation to oxacillin for MSSA) [OR 0.041, P=0.046] were associated with a less chance of therapeutic failure. On the other hand, the variables of infant [OR 12.998, P=0.044] and bundle Item 1 (follow-up blood cultures) revealed a correlation with therapeutic failure [OR 18.953, P=0.049]. The model was able to predict 80.4% of the outcome of therapeutic failure, providing crucial information for pharmacist-led ASP in monitoring and managing the bundle. This enabled the identification of a patient profile that the team could potentially monitor to ensure strict adherence to the care bundle and to reduce the likelihood of negative outcomes.

Discussion

This was the first study conducted in an exclusively paediatric population with real-world data and retrospective analysis of eight years of pharmacist-led ASP service using the *S. aureus* care bundle as a management tool. The results suggest that pharmacist-led ASP achieved a significant impact on patient care over the years, achieving improved quality of follow-up and reducing negative outcomes for patients [4].

When comparing the study periods, pharmacist-led ASP proved to be a factor to reduce therapeutic failure. Patients monitored during the intervention period (2017–2021) were less susceptible to negative outcomes, indicating the impact of the team's performance on reducing death and/or reinfection.

In addition, the significant increase in bundle adherence during the intervention period (2017–2021) shows the implementation of actions that are recognised as quality indicators of care, according to López-Cortés *et al.* [7]. This result is consistent with other studies in the literature on care bundle

Table IV
Univariate analysis of therapeutic failure (death and reinfection)

Variables	Classification	n	OR	CI 95%	*P*-value
Sex	Male	74	————	————	————
	Female	46	1.388	0.582—3.309	0.459
Age range[a]	Newborn	16	0.200	0.025—1.589	0.128
	Infant	34	2.582	1.053—6.332	0.038
	Child	54	0.971	0.410—2.300	0.947
	Teenager	16	0.451	0.096—2.123	0.314
Attendance	Health insurance	45	————	————	————
	SUS[b]	75	1.455	0.609—3.471	0.399
Unit (ICU)	Nursery	71	————	————	————
	ICU	49	1.470	0.621—3.483	0.381
ICU admission	No	50	————	————	————
	Yes	70	1.577	0.642—3.874	0.321
Acquisition	Community-acquired infection	36	————	————	————
	Hospital-acquired infection	84	4.400	1.232—15.718	0.023
Comorbidity	No	27	————	————	————
	Yes	93	10.090	1.301—78.218	0.027
Source of bacteraemia	BSI	56	2.895	1.176—7.125	0.021
	Sepsis	8	0.473	0.056—4.019	0.492
	SSI	11	0.319	0.039—2.613	0.287
	Bone and joint	24	0.117	0.015—0.911	0.040
	Pneumonia	12	2.792	0.808—9.644	0.104
	Endocarditis	3	1.750	0.153—20.072	0.653
Susceptibility	MSSA	100	————	————	————
	MRSA	20	2.154	0.760—6.102	0.149
Number of antimicrobial treatment regimens	1 to 3 regimens	95	0.531	0.200—1.414	0.206
	More than 3 regimens	25	————	————	————
Periods	Pre-intervention	44	————	————	————
	Intervention	76	0.530	0.204—1.377	0.193
Adherence to complete bundle	No	93	————	————	————
	Yes	27	0.610	0.232—1.605	0.316
BUNDLE ITEM 1 (follow-up blood cultures)	No	67	————	————	————
	Yes	53	1.809	0.762—4.294	0.179
BUNDLE ITEM 2 (early source control)	No	70	————	————	————
	Yes	50	0.220	0.038—1.270	0.090
BUNDLE ITEM 3 (search for distant focus)	No	98	————	————	————
	Yes	22	0.882	0.074—10.464	0.921
BUNDLE ITEM 4 (de-escalation to oxacillin for MSSA)	No	40	————	————	————
	Yes	80	0.360	0.121—1.076	0.067
BUNDLE ITEM 5 (vancomycin adjustment for MRSA)	Yes	16	————	————	————
	No	0	————	————	————
BUNDLE ITEM 6 (treatment duration)	No	39	————	————	————
	Yes	81	0.597	0.221—1.612	0.309

n - sample number; OR - Odds Ratio; CI - confidence interval; ICU - intensive care unit; BSI - primary bloodstream infection; SSI - surgical site infection; MSSA - Methicillin-sensitive *Staphylococcus aureus*; MRSA - Methicillin-resistant *Staphylococcus aureus*.
[a] Age range (newborn: 0—28 days; infant: 28 days to 12 months; child: 1—12 years; adolescent: 12—18 years) [45].
[b] SUS: Brazilian public health care system.

adherence related to positive patient outcomes in the adult population [7,9,24—26].

Specifically, adherence to care bundle Items 2 and 4 (early source control and de-escalation to oxacillin for MSSA, respectively) indicates that these actions contribute to the proper management of *S. aureus* bacteraemia.

Early source control of *S. aureus* bacteraemia, such as removal of catheters or drainage of abscesses (Item 2), showed a correlation with positive patient outcome, with a lower chance of infection complication, reducing the risk of death and/or re-infection. This is consistent with the literature, which suggests that delayed source control is associated with persistent *S. aureus* bacteraemia [27,28].

De-escalation to oxacillin in patients with MSSA infection (Item 4) correlated with a lower chance of negative outcome. Although this finding has been reported previously in the literature [29—38], we believe that this is the first study to demonstrate this result in an exclusively paediatric population.

Table V
Multivariate analysis of therapeutic failure

Variable	OR	CI 95%	*P*-value
Infant[a]	12.998	1.074—157.363	0.044
Topography - BSI	8.615	0.613—121.129	0.110
Use of > 3 antimicrobial treatment regimens	0.006	0.000—0.395	0.017
Intervention (2017—2021)	0.060	0.005—0.806	0.034
Bundle item 1 - follow-up blood cultures	18.953	1.007—356.773	0.049
Bundle item 2 - early source control	0.002	0.000—0.341	0.018
Bundle item 4 - de-escalation to oxacillin for MSSA	0.041	0.002—0.941	0.046
Overall percentage: 80.4%			

OR - Odds Ratio; CI - confidence interval; BSI - primary bloodstream infection; MSSA - Methicillin-sensitive *Staphylococcus aureus*.
[a] Age range (newborn: 0—28 days; infant: 28 days to 12 months; child: 1—12 years; adolescent: 12—18 years) [45].

Another important finding was the correlation of better outcomes with the use of up to three antimicrobial treatment regimens, which is consistent with data from the literature [34]. The use of fewer regimens indicates the clinical service's ability to manage infection with the use of empirically established antibiotics. This may also be associated with shorter length of hospitalisation, as the results showed a reduction in the number of days per hospital stay between study periods. Similar to other studies, we can infer the impact of ASP on costs associated with hospitalisation [39].

Furthermore, with more targeted antimicrobial therapy, there is a lower chance of negative outcome for the patient, demonstrating the importance of the institution's knowledge and capability in epidemiology and understanding of the sensitivity profile of microorganisms. This in turn highlights the key role of clinical microbiology input in the ASP team.

The infant age group had a greater chance of negative outcome, indicating infant age as a risk factor in patients with *S. aureus* bacteraemia. This correlation is likely associated with the immaturity of the patients' immune system, in conjunction with greater social exposure of patients from 28 days to 12 months [40—42].

Collecting blood cultures to demonstrate source control 48—96 hours after the start of antimicrobial therapy (Item 1) correlated with negative outcomes and may be interpreted as a risk factor for patients with *S. aureus* bacteraemia. However, patients whose care did not follow this item did not necessarily have an unfavourable outcome. This is exemplified through

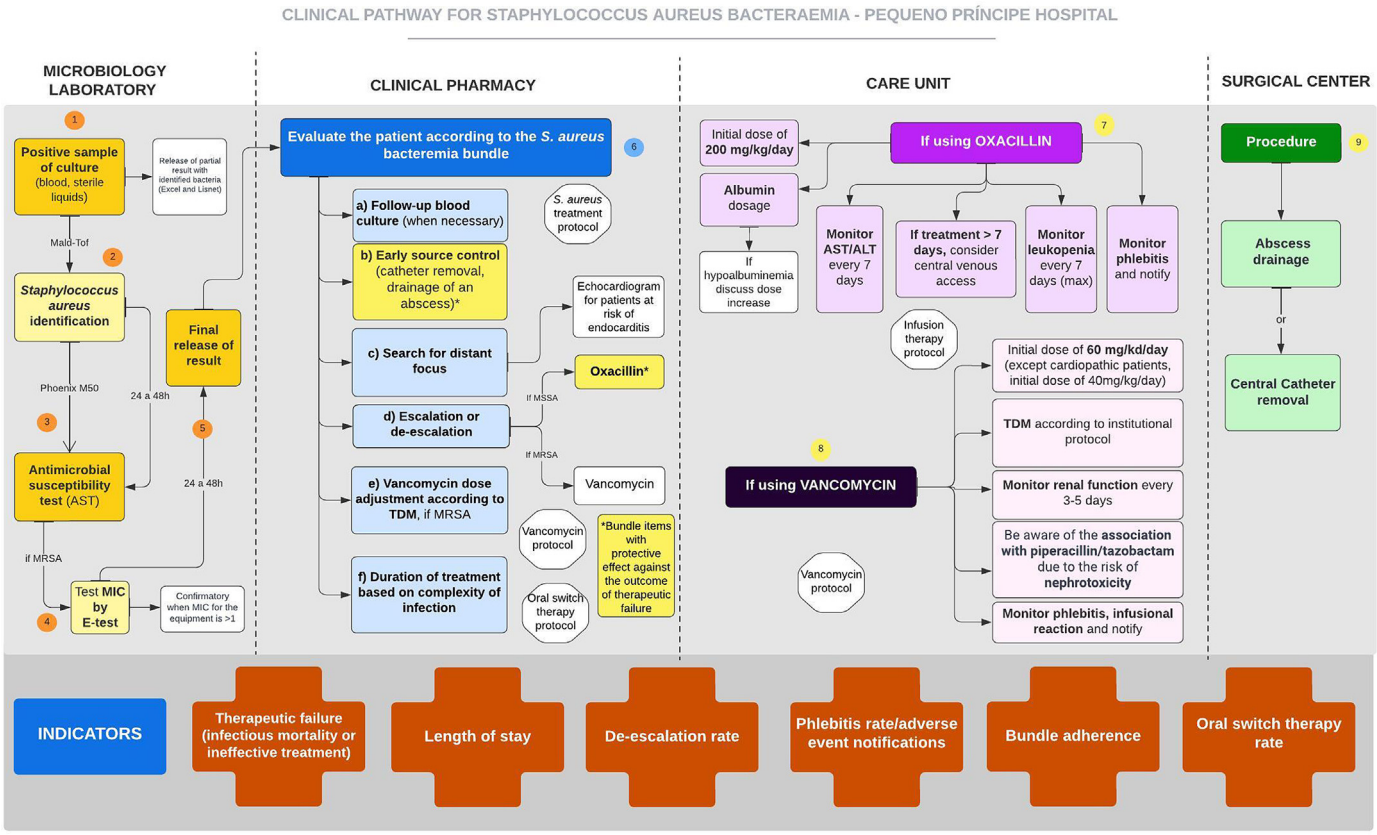

Figure 1. *Staphylococcus aureus* bacteraemia clinical pathway for paediatrics-Pequeno Príncipe Hospital.

patients with bone and joint infections who had better outcomes in terms of therapeutic failure, even though only four out of 24 patients with bone and joint infections complied with item 1 (follow-up blood cultures).

This finding suggests that the initial focus of infection and the patient's clinical presentation should be taken into consideration in the decision to collect blood culture for control, since there may be no need to collect a culture from a patient who is improving and who has a good prognosis. It should also be considered that for blood cultures, a relatively large volume of blood is necessary to improve the sensitivity of the test, which may be a limiting factor in paediatrics due to the difficulty in collecting blood cultures and the possibility of collecting only a small volume of blood [40,43,44]. Therefore, Item 1 (follow-up blood cultures) may be applied differently in paediatric patients compared with adult patients. In this case, follow up blood cultures to demonstrate source control should only be performed for more severely ill patients who do not show clinical signs of improvement after starting antimicrobial therapy.

There were several limitations to this study. It was a retrospective study, and as such some data may not be documented in the medical records. The analysis was focused on a single clinical institution and the results may not be applicable to other hospitals or healthcare institutions.

Following the results of this study, the pharmacist-led ASP aimed to implement a clinical pathway for *S. aureus* bacteraemia (Figure 1) with indicators of quality of care and with a focus on paediatrics.

Conclusions

During the eight years of implementation, the pharmacist-led ASP resulted in increased adherence to established standards of care for *S. aureus* bacteraemia, improving the quality of care for patients with *S. aureus* bacteraemia and contributing to a reduction of negative outcomes for the patient, such as death or reinfection. It was possible to identify risk factors for worse outcome for *S. aureus* bacteraemia, including the infant age group, the use of more than three antimicrobial treatment regimens, a delay in removal of the initial focus of infection such as a catheter or abscesses, and a delay in de-escalation to oxacillin when MSSA was identified. These results reinforce the effectiveness of the pharmacist-led ASP model in monitoring and managing the *S. aureus* bacteraemia care bundle in paediatrics.

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Author contributions

SCSBS: Conceptualisation, formal analysis, investigation, data curation, writing: original draft, writing: reviewing and editing, project administration.

MMF: Conceptualisation, methodology, formal analysis, data curation, writing: original draft, writing: reviewing and editing.

MCR: Conceptualization, methodology, writing: reviewing and editing, supervision.

FAM: Conceptualization, methodology, writing: reviewing and editing.

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Conflicts of interest statement

None.

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