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The clinical spectrum of Staphylococcus aureus infections in children admitted to Chris Hani Baragwanath Academic Hospital, South Africa: A retrospective, descriptive study

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Background. *Staphylococcus aureus* infection is associated with considerable morbidity and mortality. There are relatively few studies describing invasive *S. aureus* infections in children, particularly in low- and middle-income countries.
Objectives. To describe the clinical spectrum and outcomes associated with *S. aureus* infection in children <14 years of age hospitalised at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa, and to identify risk factors of invasive disease.
Methods. A retrospective, descriptive study was conducted at CHBAH to define the spectrum of clinical presentation, risk factors, duration of treatment and outcomes of paediatric *S. aureus* infections for the period January through December 2013. Data were sought for all children <14 years of age.
Results. Four hundred and twenty-two episodes of *S. aureus* infection were identified. Three hundred and forty-two (81%) infections were caused by methicillin-susceptible *S. aureus* (MSSA) and 80 (19%) by methicillin-resistant *S. aureus* (MRSA). Clinical data were obtained for 286 (67.8%) cases, on which all further analyses were based. Clinical presentations for MSSA bacteraemia included skin and soft tissue infection (45%), pneumonia (10%), meningitis (6%), bone/joint infections (5%) and urinary tract infections (3%). Five (8.3%) cases of MRSA were community-acquired. Admission to intensive care unit (ICU) was the only risk factor associated with MRSA infection (adjusted odds ratio (aOR) 125.55; 95% confidence interval (CI) 11.67 - 1 350.68). Hospital-acquired *S. aureus* infection was the only factor associated with mortality on multivariate analysis (aOR 8.70; 95% CI 1.55 - 48.77).
Conclusion. *S. aureus* is frequently isolated in paediatric bacterial infections. Closer attention to infection control would impact on MRSA and *S. aureus* mortality rates in our setting.

S Afr J Child Health 2023;17(2):e1937. https://doi.org/10.7196/SAJCH.2023.v17i2.1937

Staphylococcus aureus is a virulent pathogen, which is associated with considerable morbidity and mortality.[1] Among Gram-positive bacteraemias, *S. aureus* bacteraemia (SAB) is one of the infections most prevalent and difficult to treat.[2] Most studies have been performed on adults and little is known about bloodstream and other infections due to *S. aureus* in children, particularly in low- and middle-income countries (LMICs).[3]

Infections caused by *S. aureus* are often classified in terms of the clinical isolate's antibiotic susceptibility to methicillin, as being either methicillin-susceptible (MSSA) or methicillin-resistant (MRSA). MRSA infection may be community-acquired (CA-MRSA) or hospital-acquired (HA-MRSA).[4] CA-MRSA is diagnosed within 48 hours of hospitalisation, in the absence of any medical devices or indwelling catheter, and no recent hospitalisation.[4]

Paediatric *S. aureus* bacteraemia usually presents as bone and joint infection, followed by skin and soft tissue infections (SSTI),[5] although a study from New Zealand reported SSTI in two-thirds of children presenting with *S. aureus* infection.[6] Malnutrition and HIV infection have been identified as risk factors for SAB, and infection with MRSA.[3,7,8] Other comorbid conditions predisposing to MRSA infection include congenital heart disease and concurrent tuberculosis.[7]

There is a wide spectrum of disease severity in paediatric SAB, with C-reactive protein (CRP), duration of therapy, and length of stay greater in those with complex disease.[9] Most invasive *S. aureus* infections in paediatric patients are caused by methicillin-susceptible strains as reported in recent studies.[10,11] The epidemiology of MRSA and MSSA has changed in recent years, with an increased risk of paediatric intensive care unit admission, mechanical ventilation and inotropic support associated with MRSA in paediatric patients.[12] A recent study in Iran showed a high prevalence of MRSA of 42% among culture-positive cases of *S. aureus*.[13] The high prevalence of MRSA in Iranian children may be due to insufficient infection control measures in hospitals, inappropriate use of methicillin, inadequate staff training, and over-prescription of antibiotics.[13] There is wide variation in antibiotic prescription practices among clinicians, corresponding

with escalating case complexity and persisting MRSA bacteraemia.[14] Hospital-acquired *S. aureus* bacteraemia has an increased long-term risk for mortality, particularly in children with chronic diseases.[15]

The aim of the present study was to describe the clinical spectrum and outcomes associated with *S. aureus* infection in children <14 years of age hospitalised at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa, and to identify risk factors of invasive disease.

Method

Study design

We conducted a retrospective, descriptive analysis of clinical records of children <14 years hospitalised at CHBAH during the 12-month period from January to the end of December 2013 from whom *S. aureus* was cultured on clinical specimens. The National Health Laboratory Service (NHLS) Central Data Warehouse was used to identify eligible patients, and case clinical data and demographics were obtained from the electronic patient registry of the Department of Paediatrics and Child Health at CHBAH. A review of clinical records was also undertaken, where possible.

Definitions

***Staphylococcus aureus* infection** was defined as the isolation of *S. aureus* from clinical specimens, including blood, cerebrospinal fluid, pleural fluid, pericardial fluid, pus, tissue, synovial fluid and urine. In patients with multiple specimens positive for S. aureus, a single episode of S. aureus infection was defined if the organism was isolated within 21 days of a previous positive specimen.

MRSA was defined as *S. aureus* resistant to methicillin on laboratory testing.

Community-acquired MRSA was defined as MRSA isolated from a patient in the outpatient environment, or within 48 hours of hospitalisation, with no history of prior HA-MRSA infection, hospitalisation, indwelling device, or residence in a long-term care facility.

Hospital-acquired MRSA was defined as MRSA isolated from a patient beyond 48 hours into a hospitalisation episode; or MRSA isolated from admission blood cultures in children with a history of prior hospitalisation, indwelling devices, a prior history of HA-MRSA infection, or who were resident in long-term care facilities.

Malnutrition was classified according to the World Health Organization (WHO) growth standards. Moderate malnutrition was defined as weight-for-height between -2 and -3 standard deviations (SD) below the mean. Severe malnutrition was defined as weight-for-height less than -3 SD below the mean, or the presence of oedema.

HIV infection was confirmed by the presence of a positive HIV PCR in children <18 months of age, or a positive HIV ELISA in children ≥18 months of age.

Statistical analysis

Descriptive statistics presented continuous variables as means and standard deviations (SDs) for normally distributed data, and as medians with interquartile ranges (IQRs) for skewed data. Student's *t*-test was used to compare means, and the Mann-Whitney U test was used to compare medians. Risk factors for *S. aureus* infection were deduced by univariate and multivariate logistic regression analysis. Odds ratios and 95% confidence intervals (95% CIs) were used to describe risk factors. Two-sided *p*-values <0.05 were considered significant. Data were analysed using Stata version 12.0 (StataCorp, College Station, Texas).

Ethical considerations

Approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Ethics Clearance Certificate: M140729) and from the hospital.

Results

Between January and end-December 2013, 422 episodes of *S. aureus* infection were identified in children <14 years of age. Three hundred and forty-two (81%) infections were caused by MSSA and 80 (19%) by MRSA isolates. Demographic and clinical data were obtained for 286 (67.8%) patients. Subsequent analyses were done on the subset of children (*n*=286) in whom a record review was conducted, except for the descriptive analysis of antibiotic susceptibility profiles of the isolates (which were available for all 422 *S. aureus* infection episodes).

Characteristics of patients with S. aureus infection

The median age of patients from whom *S. aureus* was cultured, was 11.3 months (IQR 0.6 - 60.3 months). One hundred and sixty-five (57.7%) patients were HIV uninfected, and 36 (12.6%) were HIV infected (Table 1). HIV status was not documented for 85 (29.7%) children.

Nutritional status was determined for 147 (51.3%) patients and, of these, 84 (57.1%) had normal nutritional status, 18 (12.2%) were moderately malnourished and 45 (30.6%) were severely malnourished (Table 1).

Two hundred and fourteen (74.8%) of the 286 patients had community-acquired infections and72 (25.2%) had hospital-acquired infections. Of the 214 patients who had community-acquired infections, 209 (97.7%) cultured MSSA and 5 (2.3%) cultured MRSA. Clinical data were available for 3 of the 5 children with CA-MRSA. In the group with hospital-acquired infection (*n*=72 patients), 56 (77.8%) cultured MRSA and 16 (22.5%) cultured MSSA.

Spectrum of clinical presentation

MSSA was significantly associated with SSTI, whereas MRSA was associated with septic wounds.

Duration of hospital stay

The median duration of hospitalisation for all patients was 11 days (IQR, 5 - 24 days). The median duration of hospitalisation was significantly longer in children with MRSA (35 days; IQR 24 - 65 days) compared with those with MSSA infection (8 days; IQR 4 - 18 days), $p<0.001$.

Risk factors for MRSA infection

Factors associated with MRSA infection on univariate analysis included severe malnutrition, residence in a long-term facility, presence of an indwelling device, prematurity, burns, prolonged hospitalisation, intensive care unit (ICU) admission and acquisition of infection in the hospital setting (Table 2). On multivariate analysis, only acquisition of infection during hospitalisation, specifically during an admission to ICU, retained significance as a risk factor for MRSA infection (Table 2).

Antibiotic susceptibility and management

Antimicrobial susceptibility patterns were available for all of the clinical isolates (*N*=422). MSSA episodes were susceptible to most antimicrobials against which they were tested, although 98.9% were

Table 1. Characteristics of patients with S. aureus infection

Characteristics	All (*N*=286)	MRSA (*n*=60)	MSSA (*n*=226)	*p*-value*
Age in months (median, IQR)	11.3 (0.6 - 60.3)	19.8 (0 - 56.1)	9.5 (0.73 - 60.9)	0.47
Nutritional status (*n*=147)				
Severe malnutrition	45 (30.6%)	16 (33.3%)	29 (22.8%)	<0.001
Moderate malnutrition	18 (12.2%)	2 (4.2%)	16 (12.6%)	0.38
Normal	84 (57.1%)	19 (51.3%)	65 (59%)	0.75
HIV infection				
HIV infected	36 (12.6%)	13 (21.7%)	23 (10.2%)	<0.001
HIV uninfected	165 (57.7%)	22 (36.7%)	143 (63.3%)	<0.001
Unknown HIV status	85 (29.7%)	25 (41.7%)	60 (26.5%)	

HIV = human immunodeficiency virus type 1; IQR = interquartile range; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.
**p*-values were derived by using the Mann Whitney test (comparing medians) and Pearson 's chi-square test (comparing proportions), comparing the MRSA and MSSA groups.

resistant to penicillin. All of the MRSA isolates were susceptible to vancomycin.

Among the 286 children with clinical folders available for review, empiric antibiotics commonly used for community-acquired infections included cloxacillin (54.3%), amoxicillin-clavulanate (28.5%) and cefotaxime or ceftriaxone (14.5%). Vancomycin was used empirically for most hospital-acquired infections (53.1%). The median duration of treatment for all groups of *S. aureus* infections was 12 days (IQR 5 - 21 days). Twenty-seven (10.8%) patients, all of whom had *S. aureus* infection of septic wounds, did not receive any antibiotics. These patients were treated with antiseptic dressings only.

Duration of antibiotic therapy according to *S. aureus* syndrome

The duration of antibiotic treatment varied according to the clinical diagnosis. Patients with bone and joint infections (*n*=13) and infective endocarditis (*n*=1) were treated for a median of 6 weeks (IQR 3 - 8 weeks) of antibiotic therapy. Children with meningitis (*n*=17) were treated for a median of 3 weeks (IQR 2 - 6 weeks). All other groups of *S. aureus* infection were treated for a median duration of 12 days (IQR 5 - 21 days). Five patients with persistent SAB were treated with a combination of cloxacillin and fusidic acid, for a median of 14 days (IQR 13 - 20 days). In addition to antibiotic therapy, 2 patients who presented with empyema had intercostal drain insertion and subsequently underwent video-assisted thoracoscopic surgery.

Outcome

There were 22 (7.7%) deaths in total among the 286 children with available clinical records, of which 17 were due to HA-MRSA infections and 5 were community acquired. Four (18.2%) of the patients who died (3 with MRSA and 1with MSSA infection) were not initiated on appropriate antimicrobial therapy before time of death. The remaining 18 (18/22, 81.8%) patients who died were on appropriate antimicrobial therapy for a median duration of 6 days (IQR 5 - 14 days) before time of death. Children with community-acquired infections had a better outcome.

Of the 17 patients with HA-MRSA who died, 10 (58.8%) had septic burn wounds, 4 (23.5%) had bacteraemic pneumonia, 2 (11.8%) had bacteraemia without a focus and 1 (5.9%) had infective endocarditis.

Risk factors for mortality

On univariate analysis, hospital-acquired infection, severe malnutrition, MRSA infection, children with haematology/oncology conditions and critically ill newborns were factors associated with mortality. However, on multivariate analysis, only acquisition of infection from the hospital setting were independently associated with mortality (Table 3).

Discussion

S. aureus is an important pathogen contributing to prolonged hospital stay and morbidity in paediatric patients. In this series of paediatric patients with *S. aureus* infection, hospitalised over a 12-month period, there was on average over one *S. aureus* episode diagnosed each day across neonatal, general paediatric and surgical disciplines. Most (81%) invasive *S. aureus* infections in our retrospective study were caused by methicillin-susceptible strains, although MRSA should be considered, particularly in the context of hospitalised patients. CA-MRSA infections appear to have been uncommon in our setting during the study period; however, more recent studies are required as MRSA epidemiology appears to be changing.

Two published South African studies have described the epidemiology of SAB in children in the 21st century to date. A retrospective study from Soweto identified 161 episodes of community-onset SAB over a 2-year period (January 2005 to December 2006), with an incidence of 26/100 000.[16] Sixty-three (39%) of the 161 isolates were identified as MRSA, with an incidence if 10/100 000.[16] A study from Cape Town reported 365 episodes of SAB over a 5-year period (January 2007 to December 2011).[7]

Rates of MRSA have been trending upwards in paediatric studies, ranging between 10% and 24%,[7,16-18] with an increasing incidence in nosocomial SAB described in Cape Town accounting for ~half of all cases of MRSA SAB in that study.[7] In both South Africa and the United Kingdom, MRSA was found to be the most significant risk factor associated with a high mortality rate among children with SAB.[7,19]

Paediatric *S. aureus* infections appear to affect different age groups, depending on the populations studied. South African studies show a predilection of *S. aureus* infections in the younger age groups.[7] whereas studies from Canada and New Zealand show that older children are more prone to *S. aureus* infections requiring hospitalisation.[5,6] The reason for these age differences may be related to the social determinants of health, including malnutrition, overcrowding, poverty and lack of sanitation, which are prevalent in LMICs.

Table 2. Risk factors for MRSA infection

Risk factors	Univariate analysis OR* (95% CI)	Multivariate model aOR (95% CI)
Moderate malnutrition	2.50 (0.42 - 14.83)	
Severe malnutrition	11.03 (3.41 - 35.74)*	
HIV-positive	1.54 (0.46 - 5.13)	
Long-term facility resident	12.46 (3.81 - 40.77)*	
Indwelling device	12.08 (5.86 - 24.90)*	
Prematurity	14.42 (5.72 - 36.34)*	
Burns	38.01 (15.33 - 94.21)*	
Duration of hospital stay	1.02 (1.01 - 1.03)*	
ICU admission	11.22 (5.60 - 22.45)*	125.55 (11.67 - 1 350.68)*
Place of infection (hospital)	99.62 (37.68 - 263.36)*	

OR = odds ratio; aOR = adjusted odds ratio; HIV = human immunodeficiency virus type 1; ICU = intensive care unit; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.
*p-value <0.05.
The multivariate model adjusted for nutritional status, HIV status, place of residence, presence of an indwelling device, comorbidities (prematurity or burns), duration of hospital stay, ICU admission and place of infection.

Table 3. Risk factors for mortality

Risk factors	Univariate model	Multivariate model
	OR* (95% CI)	aOR (95% CI)
Female gender	2.35 (0.96 - 5.82)	
Severe malnutrition	10.25 (2.11 - 49.84)*	
Moderate malnutrition	2.41 (0.21 - 28.13)	
Ward (haematology-oncology)	6.90 (1.15 - 41.25)*	
Ward (neonates)	12.08 (3.43 - 42.53)*	
MRSA	8.48 (3.36 - 21.40)*	
Place of infection (hospital)	13.09 (4.62 - 37.10)*	8.70 (1.55 - 48.77)*

OR = odds ratio; aOR = adjusted odds ratio; MRSA = methicillin-resistant *S. aureus*.
*p-value<0.05.
The multivariate model adjusted for nutritional status, ward of admission and, place of infection.

SSTIs (n=102/226, 45.1%) were the most common clinical presentation for children with MSSA in our study, and septic wounds (n=25/60, 41.7%) constituted the most common presenting condition in those with MRSA infection. That septic wounds were the most common clinical presentation in children with MRSA infection in our study speaks to inadequate attention to infection prevention and control practices in our setting. Pneumonia and bacteraemia without a focus occurred in 12% and 10% of children, respectively. Infective endocarditis was an uncommon clinical presentation of *S. aureus* infection in our study, similar to findings from other centres, but had a high case-fatality rate.[6,7]

Other South African studies have shown higher rates of MRSA in children who are HIV infected.[7,8,16,20] In our case series, 36.1% of HIV-infected patients had MRSA, whereas only 13.3% of the HIV-uninfected children had MRSA infections; however, on multivariate analysis, HIV infection status was not identified as being a risk factor for MRSA infection.

The problem of limited availability of cloxacillin has arisen as a major challenge to targeted therapy of MSSA infections in the past five years, and reflects a global shortage of supply of this key anti-staphylococcal agent. In children hospitalised with infectious syndromes, such as SSTI or bone and joint infections likely to be caused by *S. aureus*, alternative antibiotic agents with anti-staphylococcal activity, e.g. co-amoxiclav, cefazolin or ceftriaxone, is justified.

Children with hospital-acquired infections had 9 times greater adjusted odds of dying compared with those with community-acquired infections. The overall case fatality rate in the study was 7.7% – slightly lower in comparison with case fatality rates of 8.8% and 8.6% in Cape Town and New Zealand, respectively.[6,7] The reason for the lower case fatality rate in our study is probably related to the inclusion of local cellulitis cases, and not only SAB cases as in the other studies. The substantially higher case fatality in patients with hospital-acquired infections observed in our study of 17/72 (23.6%) is similar to findings from other South African studies.[7,16]

The present retrospective analysis has limitations, foremost of which is the lack of availability of archived records, and by inconsistent or incomplete clinical documentation in those cases in which record review was possible. Nevertheless, the data presented in this study are important in improving the management and outcome of paediatric *S. aureus* infections at institutional, national and regional levels, particularly in low- to middle-income settings. The data presented in this study are from patients admitted in 2013, and may not reflect the current situation. However, this study contributes to a deeper understanding of the epidemiology of paediatric *S. aureus* infections in South Africa, and bridges the gap between older studies and studies which will be conducted in future.

Conclusion

Acquisition of infection in hospital was the only risk factor associated with MRSA infection and mortality in multivariate logistic regression analyses in our study. Efforts must be made to reinforce optimal infection prevention and control practice in order to prevent infection with hospital-acquired organisms. We would also support the use of empiric vancomycin for patients with clinical features indicative of HA-MRSA infection. Clinical syndrome, culture results and response to antibiotic therapy should guide duration of treatment. Surgical intervention should be sought timeously in cases with empyema, SSTI, bone or joint infections, or for source control in cases with persistently positive blood cultures.

Declaration. The research was done in fulfilment of the requirements for PR's Master of Medicine degree at the University of the Witwatersrand.
Acknowledgements. The authors acknowledge the support of the National Health Laboratory Services at the Chris Hani Baragwanath Academic Hospital during data collection.
Author contributions. PR and KLP conceptualised the study and study design. PR did the data collection. PR and DPM performed statistical analysis of the data. JW offered data collection support from the National Health Laboratory Services at Chris Hani Baragwanath Academic Hospital. All the authors (PR, JW, DPM and KLP) contributed to writing and reviewing the manuscript.

Funding. None.

Conflicts of interest. None.

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Accepted 7 February 2023.