THE CLINICAL SPECTRUM OF *STAPHYLOCOCCUS AUREUS* INFECTIONS IN CHILDREN ADMITTED AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: A RETROSPECTIVE, DESCRIPTIVE STUDY

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Paediatrics.

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DECLARATION

I, Phophi Manenzhe declare that the research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of Witwatersrand. It has never been submitted before for any degree or examination at this or any other university.

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_____day of_____2018

To my parents, husband and siblings.

In memory of my grandmother

Zodwa Kate Mulaudzi

1933 - 2011

PUBLICATIONS AND PRESENTATIONS

Preliminary findings from this research were presented at the University of the Witwatersrand Department of Paediatrics research day on 6th June 2015.

ABSTRACT

Introduction: *Staphylococcus aureus* is a virulent bacterial pathogen which is associated with considerable morbidity and mortality. There are relatively few studies describing invasive *S. aureus* infections in children, particularly in developing countries.

Objectives*:* To define the spectrum of clinical presentation, risk factors, duration of treatment and outcomes of paediatric *S. aureus* infections treated at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa.

Methods*:* A retrospective, descriptive study for the period from January to December 2013 was conducted. Data were sought for all children <14 years of age with *S. aureus* infection.

Results: Four hundred, twenty-two episodes of *S. aureus* infection were identified. Clinical data were obtained for 286 (68%) cases, on which all further analyses were based. Two-hundred, twenty-six (79%) infections were caused by methicillin-susceptible *S. aureus* (MSSA), and 60 (21%) were caused by methicillin-resistant *S. aureus* (MRSA). Clinical presentations for MSSA bacteraemia included skin and soft tissue infection (45%), pneumonia (10%), meningitis (7%), bone/joint infections (5%) and urinary tract infections (4%). Risk factors for MRSA sepsis included burns (OR 38.01; 95%CI 15.33-94.21), prematurity (OR 14.42; 95%CI 5.72-36.34), prolonged hospitalisation (OR 12.26; 95%CI 3.81-40.77), presence of indwelling device (OR 12.08; 95%CI 5.86-24.90) and malnutrition (OR 11.03; 95%CI 3.41-35.74). Five cases of MRSA were attributed to have been community-acquired.

Conclusion: Paediatric *S. aureus* infections are an important cause of morbidity. Most invasive *S. aureus* infections are caused by methicillin-susceptible strains, although MRSA should be considered particularly in the context of hospitalised patients.

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LIST OF ABBREVIATIONS

95%CI	95% confidence interval
CA	community-acquired
CHBAH	Chris Hani Baragwanath Academic Hospital
CSF	cerebrospinal fluid
HA	hospital-acquired
ICU	intensive care unit
IQR	interquartile range
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NHLS	National Health Laboratory Service
PVL	Panton-Valentine leucocidin
RCWMCH	Red Cross War Memorial Children's Hospital
RMPRU	Respiratory &Meningeal Pathogens Research Unit
SAB	*Staphylococcus aureus* bacteraemia
SD	standard deviation
SSSS	staphylococcal scalded skin syndrome
SSTI	skin and soft tissue infection
STSS	staphylococcal toxic shock syndrome
TMP/SMX	trimethoprim-sulfamethoxazole
VATS	video-assisted thoracoscopic surgery
UTI	urinary tract infection

CHAPTER 1

1.0 INTRODUCTION

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

A study conducted in Birmingham, United Kingdom, found that SAB in the paediatric population was significantly different to SAB in the adult population, with more similarities to the clinical spectrum of disease as encountered in the neonatal group [3].

Staphylococcus aureus produces disease in two main ways [2]. Production of toxins leads to specific diseases such as acute gastroenteritis, staphylococcal scalded skin syndrome (SSSS), and staphylococcal toxic shock syndrome (STSS), while direct tissue invasion causes localized folliculitis, abscesses, cellulitis, pyomyositis, osteomyelitis, and septic arthritis [2]. Severe infection can present as overt septicaemia occasionally followed by disseminated secondary infection, including pneumonia, infective endocarditis, and meningoencephalitis [2].

Infections caused by *S. aureus* are often classified in terms of the clinical isolate's antibiotic susceptibility profile as being either methicillin-sensitive (MSSA) or methicillin-resistant (MRSA). MRSA infection can be separated into two major categories: community-acquired or hospital-acquired [4]. According to the Centers for Disease Control and Prevention, patients need to fulfil several criteria before the

clinician can identify an MRSA infection as being community-acquired in nature [4]. Firstly, patients cannot have any medical devices or indwelling catheters that are permanently placed through their skin, and must not have any medical history of MRSA infection [4]. Also, patients cannot have any history of a recent hospitalization, or be resident in a nursing home or other long-term care facility [4].Furthermore, the MRSA infection must be diagnosed in the outpatient environment, or the positive culture for MRSA must be identified within 48 hours of hospital admission [4].

Community-acquired MRSA (CA-MRSA) strains are associated with greater toxin production, compared with nosocomial MRSA strains [5].Many CA-MRSA strains carry the Panton-Valentine leucocidin (PVL) genes, which encode cytotoxins that can cause tissue necrosis and leukocyte destruction [5].

1.1 EPIDEMIOLOGY OF PAEDIATRIC *S. AUREUS* INFECTION

Two recent South African studies, conducted in Soweto and Cape Town, have described the epidemiology of *S. aureus* bacteraemia in children. The first study was a retrospective review of children hospitalized with *S. aureus* bacteraemia at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, between January 2005 and December 2006 [6]. The main focus of that study was community-onset *S. aureus* bacteraemia, and it therefore did not include hospital-acquired isolates [6]. One hundred sixty-one episodes of community-onset *S. aureus* bacteraemia were identified, with an incidence of 26/100 000 [6]. Sixty-three (39%) of the 161 isolates were identified as MRSA, with an incidence if 10/100 000 [6].

At Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, between January 2007 and December 2011, 365 episodes of *S. aureus* bacteraemia were identified [7]. Two-hundred, seventy(74%) had MSSA and 95 (26%)had MRSA [7]. The annual incidence of SAB in Cape Town was 3.28/1000 hospital admissions per year, with a mean frequency of 2.43 MSSA cases and 0.85 MRSA cases per 1000 hospital admissions per year [7]. The place of acquisition of SAB was identifiable in 357/365 (97.8%) episodes; 33% were nosocomial, 16% healthcare associated and 51% community-acquired [7].

An Australian study, conducted in Sydney, described 431 patients with community-associated *S. aureus* infection that were hospitalised in 2008 [8]. Of the 431 patients,19.3% had MRSA [8]. The findings of the Australian study are similar to the South African studies, which showed a predominant occurrence of MSSA in the paediatric group, which was not the case in the adult and neonatal groups [7, 8].

The rates of MRSA have been on an upward trend in these studies, ranging between 10% and 24% [3, 6, 7], with a rise in the incidence of nosocomial SAB described in Cape Town accounting for approximately half of all cases of MRSA SAB in that study [7].

1.2 SPECTRUM OF CLINICAL PRESENTATION

Most cohorts of *S. aureus* infection in children reveal that bone and joint infections, followed by skin and soft tissue infections (SSTI), are the commonest clinical presentations [9]. A study from New Zealand found that SSTI occurred in two thirds of children presenting with *S. aureus* infection [10]. This finding was different from the South African studies.

In the study from Cape Town, SAB without an identifiable source was the most frequently encountered staphylococcal syndrome (33%), followed by pneumonia with or without empyema (22%) [7]. Out of 365 patients at RCWMCH, 17% presented with SSTI, and 12% presented with bone and joint infections. MRSA infections were mainly responsible for SAB without an identifiable source, while bone and joint infections were more likely to be due to MSSA [7]. Furthermore, all central venous catheter-related line infections were of nosocomial origin and were equally likely to be attributable to MSSA or MRSA [7].

In Soweto, there were no statistically significant differences in clinical presentation between MRSA and MSSA [6].The most common diagnoses were pneumonia (35%), gastroenteritis (21%), sepsis (16%), and primary bloodstream infections without a focus (10%) [6].

One of the most dreaded complications of SAB is infective endocarditis, which has been reported to occur in 6-32% of patients from whom *S. aureus* is isolated in blood cultures [11]. The presenting symptoms and clinical findings are non-specific, so it is advisable that echocardiography should be considered as part of the routine evaluation of SAB patients [11].

1.3 CHARACTERISTICS OF PATIENTS WITH *S. AUREUS* INFECTION

At RCWMCH, the median age of patients with SAB was 11 months [7]. Neonates accounted for 10% of episodes and infants represented 52% of paediatric SAB cases [7]. In contrast to this, in a Canadian study of paediatric SAB, the median age of patients was 6.6 years (IQR 1.0 to 11.2 years) [9].

In most studies of paediatric *S. aureus* infection, children with MRSA were significantly younger than those with MSSA [7, 12, 13]. Neonates were more likely to have MRSA as compared to the older children[3].

In New Zealand, males accounted for 60% of cases of SAB, which was similar to the 52% males at RCWMCH [7, 10]. At RCWMCH, children with MRSA were frequently underweight, stunted and HIV infected [7].

1.4 RISK FACTORS FOR *S. AUREUS* INFECTION

Comorbid conditions that are associated with SAB include congenital heart disease, malignancy and chronic skin disorders [3, 9]. Malnutrition and HIV infection were also found to be risk factors for SAB, as described in Kenya and South Africa (Cape Town) [2, 7, 14].With regards to age group, infants were found to be at higher risk of SAB, as compared to older children [3, 7].

1.4.1 RISK FACTORS FOR INFECTION WITH MRSA

Malnutrition and HIV infection have been identified as risk factors for both SAB and MRSA [2, 7, 14]. HIV-infected children were found to be at higher risk for MRSA in Kenya and South Africa [2, 7].This was thought to be likely due to frequent hospitalization of

HIV-infected children, resulting in an increased risk of colonisation with hospital-acquired pathogens and hospital-acquired infections [14].

Other comorbid conditions that were found to be risk factors for MRSA were congenital heart disease and concurrent tuberculosis [7]. Infants were not only at higher risk of SAB in general, but also at higher risk of MRSA [3, 7].

Prolonged hospitalization and residents of long-term facilities were also found to be significant risk factors for MRSA [7].

The presence of an indwelling device, particularly a central venous catheter, was the most commonly identified risk factor for MRSA infection in South Africa and the United Kingdom [3, 7].

1.5 RISK FACTORS FOR MORTALITY

MRSA was found to be the most significant risk factor associated with a high mortality rate amongst children with SAB in South Africa and in the United Kingdom [7, 12]. Infective endocarditis has also been identified as a risk factor for mortality, particularly in children <10 years of age [15]. In a study from Kenya, children with no identified focus of SAB had a higher risk of mortality as compared to those with a focus of infection [2].

1.6 MANAGEMENT OF *S. AUREUS* INFECTIONS

Site of infection and clinical severity should guide the clinician regarding antibiotic choice, route and duration of therapy, and the need for additional interventions. For example, *S. aureus* bone and joint infections have proven to be difficult to treat, usually involving a prolonged course of antibiotics, often with surgical intervention [5].

The Infectious Diseases Society of America recommends systemic antibiotic treatment in addition to incision and drainage in patients with skin abscesses who have severe or extensive disease, including: rapid disease progression, associated cellulitis, signs and symptoms of systemic illness, associated coexisting conditions or immunosuppression, very young or advanced age, an abscess in an area that is difficult to drain, associated phlebitis, or an abscess that does not respond to incision and drainage alone [16].

It is recommended that bone and joint infections are treated for a longer duration, approximately 6-7weeks [13].

At RCWMCH, infective endocarditis, bone or joint infections, and pulmonary infections were treated for a median of 44 days (IQR 39-51 days), 40 days (IQR 32-79 days) and 13 days (IQR 7-23 days) respectively [7]. Overall, the duration of treatment for all the other clinical presentations of *S. aureus* infections was 14 days (IQR 7-29 days) [7].

Recommendations from the Infectious Diseases Society of America are that MRSA bacteraemia should be treated for at least 14 days in the absence of any complicating factors [16].

In addition to antimicrobial therapy, a population-based study recently endorsed recommendations that chest tube drainage is an acceptable first treatment option for most children with empyema [17].

At CHBAH, the current treatment for bone and soft tissue infections includes cloxacillin, cefotaxime and the consideration of fusidic acid. Children are investigated by means of bone scan and echocardiograph if SAB persists despite adequate antibiotics; this is according to the 2006 guidelines for the hospital.

1.7 ANTIMICROBIAL SUSCEPTIBILITY

Most South African studies have looked at antimicrobial susceptibility of the *S. aureus* isolates [7, 18]. Extensive susceptibility testing was performed in Cape Town where most MSSA isolates were susceptible to the majority of antibiotics against which they were tested, including cloxacillin, vancomycin, fusidic acid, moxifloxacin, linezolid, teicoplanin and tigecycline [7]. However, some MSSA isolates were found to be resistant to clindamycin, erythromycin, co-trimoxazole, ciprofloxacin, gentamicin and rifampicin [7]. Only 6% of the MSSA isolates were susceptible to penicillin [7].Most MRSA isolates displayed multidrug resistance, defined as non-susceptibility to at least three classes of antibiotics, however they were all sensitive to vancomycin [7]. Clindamycin resistance rates were noted to be high in Cape Town and KwaZulu-Natal [7, 18].

1.8 OUTCOMES OF *S. AUREUS* INFECTION

Mortality rates associated with *S. aureus* infections were found to vary in developed and developing countries, with higher mortality rates (8.8 to 24.7%) occurring in developing

countries [2, 12, 13, 15]. Lower mortality rates (0.7 to 3.0%) have been described in New Zealand, Australia, England and the USA [12, 13, 15].

MRSA has been associated with higher mortality rates than MSSA in developed and developing countries [2, 7, 12, 13, 15]. At RCWMCH, MRSA accounted for 53% of deaths amongst SAB patients, with a case fatality rate of 8.8% over a five year period [7]. Mortality was substantially higher (24.7%)in Kenya [2]. MRSA infection, HIV and malnutrition contributed to higher mortality at RCWMCH [7].

1.9 SURGICAL INTERVENTION

A survey of paediatric hospitals in the USA revealed that the incidence of empyema in children nearly doubled, from 3.1 to 6.0 per 100 000, between 1997 and 2009 [19]. The introduction of video-assisted thoracoscopic surgery (VATS) in the 1990s introduced a new minimally invasive approach of debridement and drainage of the pleural space, without the need for thoracotomy [19].

Over the years, there has been an increase in the use of chest tube with fibrinolytics, challenging the use of VATS [19, 20]. Both procedures were found to have a similar outcome, with no evidence of one modality being superior to the other [19, 20]. Both procedures are available at CHBAH.

1.10 THE ROLE OF ECHOCARDIOGRAPHY

Infective endocarditis is a dreaded complication of SAB [11]. In a study of paediatric SAB conducted in South Africa, the prevalence of definite infective endocarditis was 12% and

was frequently associated with congenital heart disease and multiple positive blood cultures [21].

CA-MRSA has been increasingly reported recently and has become an emerging pathogen of infective endocarditis in adults, but still rarely reported in children [22]. A case report documented a previously healthy preschool child without any heart anomaly, who developed infective endocarditis and pneumonia with pleural effusion [22]. Blood cultures on this child repeatedly yielded MRSA until 13 days after commencement of a teicoplanin-containing regimen [22].

1.11 IMPACT OF INFECTIOUS DISEASE CONSULTATION

The impact of infectious disease consultation in adults with SAB has been studied [23-25]. Involvement of infectious disease subspecialists in the care of children with SAB has been associated with improved adherence to guidelines, including appropriate and targeted investigation, optimal duration of antibiotic therapy and a reduction in complicated infection, morbidity and mortality [23-25].

A study conducted in England examined the impact of introducing an infectious disease consultation service on the management of SAB in children [26].The findings of the study were that patients who had infectious disease consultations were more likely to have echocardiography performed, a removable focus of infection identified and to receive a longer course of intravenous antibiotic therapy [26].

1.12 PANTON-VALENTINE LEUCOCIDIN-POSITIVE *S.AUREUS* INFECTIONS

Invasive community-onset staphylococcal disease has emerged worldwide associated with PVL toxin [27]. Studies have reported an association between PVL genes and invasive disease, thus using PVL-positivity as a marker of severity [27].Results from observational studies and a metanalysis show that infection with a PVL-positive strain does not predict poor clinical outcome for staphylococcal pneumonia, musculoskeletal disease, or bacteraemia; but patients with PVL-positive skin and soft-tissue disease are more likely to require surgical treatment [27-29].

CHAPTER 2

2.0 AIMS, OBJECTIVES AND METHODS

2.1. AIM

The aim of this study was to describe the clinical spectrum and outcomes associated with *S. aureus* infection in children <14 years of age hospitalized at CHBAH, and to identify risk factors of developing invasive disease.

2.2. OBJECTIVES

The objectives of the study were as follows:

1. To define the spectrum of clinical presentations of *S. aureus* infections treated at CHBAH over a 1 year period, from 01 January to 31 December 2013, in children <14 years;
2. To define the proportion of *S. aureus* infections that are CA-MRSA and which are HA-MRSA in nature;
3. To describe risk factors for *S. aureus* infection, CA-MRSA, HA-MRSA and factors associated with poor outcome;
4. To describe the duration of treatment and outcome of *S. aureus* infection in children at CHBAH.

2.3. METHODS

2.3.1. STUDY DESIGN

This was a retrospective, descriptive analysis of hospital records. All positive fluid cultures on children hospitalised in the general paediatric wards, paediatric surgery and burns wards, and neonatal units at CHBAH from 01 January to 31 December 2013 were obtained, with permission, from the National Health Laboratory Service (NHLS) computerized database. The patients' clinical data and demographic characteristics (as supplied in the laboratory database) were obtained by retrieving and interrogating hospital records. Other clinical data were obtained from the Respiratory &Meningeal Pathogens Research Unit (RMPRU) computerized database.

2.3.2. STUDY POPULATION

The study population included all children <14 years of age who had a positive culture for *S. aureus* from body fluids (blood culture, cerebrospinal fluid, pleural fluid, pericardial fluid, pus, tissue culture, synovial fluid, and urine) at CHBAH during the study time period. The study cohort included children who were admitted in the general paediatric wards, paediatric surgical wards (ENT, surgery, neurosurgery, orthopaedic), paediatric haematology-oncology wards, neonatal unit and paediatric intensive care unit. There were no exclusion criteria.

2.3.3. ETHICAL CONSIDERATIONS

Although patient identifiers (name and hospital number) were required for retrieval of hospital folders and data capture, these were deleted from the database on which all analyses were conducted. Ethics approval was obtained from the University of the Witwatersrand Committee for Research of Human Subjects (Ethics Clearance Certificate number: M140729) (Appendix A).

1. ***Staphylococcus aureus* infection** was defined as the isolation of *S. aureus* from any fluid culture specimen, including blood culture, and/or culture from cerebrospinal fluid, pleural fluid, pericardial fluid, pus, tissue culture, synovial fluid, and urine, in a child that had clinical features of infection.

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

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

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

5. **Malnutrition** was classified according to the 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 [30].

6. **HIV infection** was confirmed by the presence of a positive HIV PCR in children less than 18 months of age, and a positive HIV ELISA in children above 18 months of age.

2.3.5. DATA COLLECTION

All positive *S. aureus* fluid cultures for the study period were obtained from the NHLS computer database, with permission. Data obtained from the NHLS also included the antimicrobial susceptibility profiles of the isolates. The demographic and clinical data of the patients were obtained by retrieving and interrogating hospital records. All information was captured on a standardised data collection sheet (Appendix C).

Additional patient information was obtained from the RMPRU computerized database and the electronic patient management system used by the hospital (Medicom).

Information captured on the data collection sheet included:

Demographic information: gender, age, date of birth, place of residence, date of hospitalization and date of outcome.

Clinical outcome: The outcome was classified as discharged, demised, refused hospital treatment or transferred to another hospital.

Clinical data: HIV status, nutritional status, co-morbid disease, presence/absence of an indwelling device, ward to which admitted, history of previous hospitalization, clinical presentation, and whether or not the patient was admitted to the intensive care unit.

Treatment (Medical and Surgical): Information on inpatient and outpatient antimicrobial therapy and duration of therapy. Surgical interventions of particular interest included intercostal drain insertion, VATS, incision and drainage and laparotomy.

Antimicrobial susceptibility: Information on antimicrobial susceptibility was obtained. These antimicrobials included; cloxacillin, fusidic acid, amoxicillin-clavulanate,

erythromycin, azithromycin, clindamycin, trimethoprim-sulfamethoxazole, amikacin, gentamicin, cefotaxime/ceftriaxone, linezolid, vancomycin, ciprofloxacin and rifampicin.

2.3.6. STATISTICAL ANALYSIS

Data were captured on a customized data collection sheet (Appendix C) and entered into Microsoft Excel for analysis. Data were interpreted by means of frequency tables, graphs, percentages and SD using Microsoft Excel and Stata version 12.0 (SataCorp, College Station, Texas, USA).

Descriptive statistics presented continuous variables as means and SD for normally distributed data, and as medians with interquartile ranges (IQR) for skewed data. For normal data, the Student's *t*-test was used to compare means; for skewed data, the Mann-Whitney U test was used to compare medians. A two-sided p-value <0.05 was considered significant.

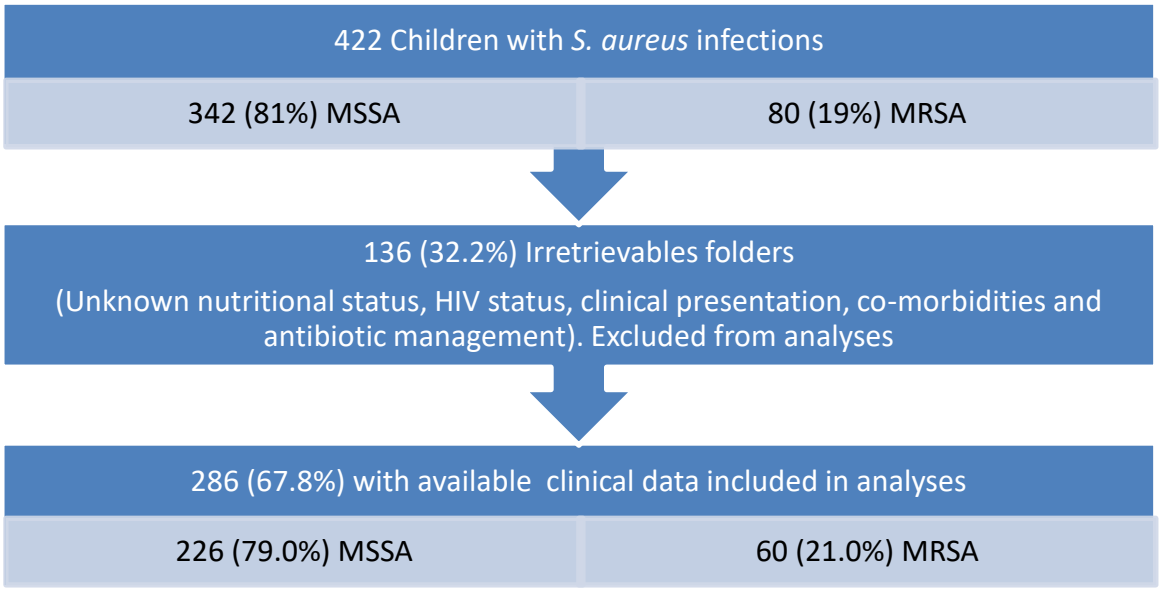
Risk factors for *S. aureus* infection were deduced by performing univariate and multivariate analyses. Odds ratios and 95% confidence intervals (95%CI) were used to describe disease risk factors.

CHAPTER 3

3.0 RESULTS

Between January and December 2013, 422 episodes of *S. aureus* infection were identified amongst paediatric patients <14 years of age treated at CHBAH. Of the 422 patients, 342 (81%) had MSSA and 80(19%) had MRSA; ward of origin and antibiotic susceptibility profile data were available for all clinical isolates. Sections 3.1 (specimen which cultured the isolate), 3.2 (ward of origin) and 3.3 (antimicrobial susceptibility pattern) highlight the results of the analyses done on the full complement of 422 patients in whom S. aureus was isolated from clinical specimens.

Clinical data was obtained for 286 (67.7%) patients (Figure 3.1). The subsequent analyses (Sections 3.4 through 3.10) highlight the results of the analyses done on the 286 patients who had both NHLS data and retrievable clinical folders (Figure 3.1).



Abbreviations: MSSA= methicillin-susceptible *S. aureus*; MRSA= methicillin-resistant *S. aureus*

FIGURE 3.1 DISTRIBUTION OF *S. AUREUS* EPISODES

Table 3.1 highlights the comparison of clinical characteristics between children with *S. aureus* infection whose clinical data were retrievable through review of clinical folders, and those whose clinical folders were not available for review. There were no statistically significant differences between the groups, indicating that the sub-group of 286 on which most of the analyses have been based, is likely to be a representative sample of all of the children from whom *S. aureus* was isolated during the study period.

Table 3.1 Comparison of the characteristics of the 422 children with the 286 children with available folders

	All children (n=422)	**Children with available hospital folders (n=286)**	**P-value***
Median age in months (IQR)	16.1 (1.0–75.4)	11.3 (0.6–60.3)	0.482^
Gender (%)			
Male	52.1%	55.6%	0.365
Female	47.9%	44.5%	0.365
Ward of origin (%)			
General Paediatric wards	46.7%	52.5%	0.132
Surgical	35.3%	31.5%	0.261
Neonatal	10.6%	8.0%	0.245
Orthopaedic	4.9%	4.5%	0.793
Haematology-oncology	2.4%	3.5%	0.375
MRSA (%)	19.0%	21.0%	0.508
MSSA (%)	81.0%	79.0%	0.508

* P-values derived using Pearson Chi-Square test, unless otherwise stated
^ Mann-Whitney test used to compare medians

3.1 SITE OF *S. AUREUS* CULTURE

The site of S. *aureus* culture was known for all 422 isolates (Fig 3.2). Of the 422 isolates, 226 (53.6%) cultured S. *aureus* from pus, 149 (35.3%) from blood, 20 (4.7%) from sputum, 17 (4%) from cerebrospinal fluid, 8 (1.9%) from urine and 2 (0.5%) from pleural fluid (Fig 3.2).

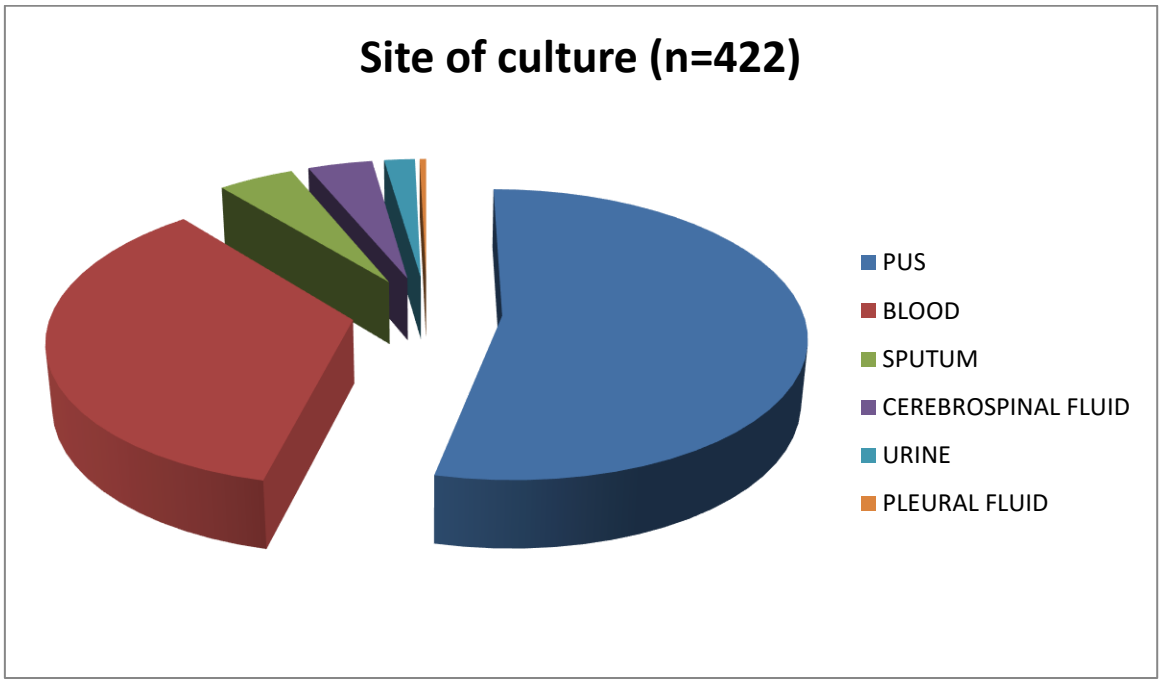


FIGURE 3.2 SITE OF *S. AUREUS* CULTURE

3.2 WARD OF ORIGIN

The ward of origin was known for all the 422 *S. aureus* isolates. Of the 422 patients, 212 (50.2%) originated from the general paediatric wards, 134 (31.8%) from the paediatric surgical wards (general surgery, neurosurgery and ENT) and burns unit, 45 (10.7%) from the neonatal unit, 21 (4.9%) from the orthopaedic ward and 10 (2.4%) from the haematology-oncology ward (Figure 3.3, page 32).

Most (188/342: 55%) MSSA isolates were from patients treated in the medical wards, whereas the majority of MRSA isolates (48/80: 60%) were from patients managed in the surgical setting. Children treated in the surgical wards and neonatal unit had a 4.5-fold (95% CI, 2.69-7.41) and 5.2-fold (95% CI, 2.77-10.1) greater odds of having MRSA rather than MSSA infection, respectively (Table 3.5, page 40). Forty (83.3%) of the 48 children diagnosed as having MRSA infection in the surgical wards, were being treated in the burns unit.

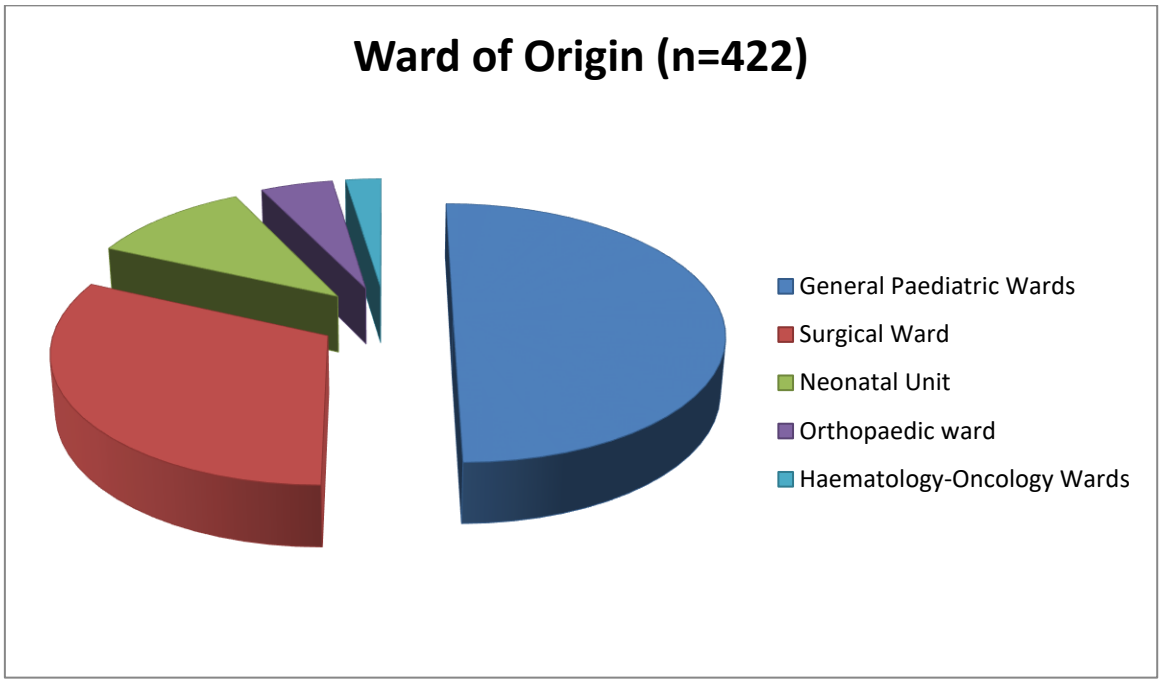


FIGURE 3.3 WARD OF ORIGIN OF THE *S. AUREUS* EPISODES

3.3 ANTIMICROBIAL SUSCEPTIBILITY

Data relating to antimicrobial susceptibility were available for all 422 *S. aureus* isolates. The MSSA isolates were susceptible to most antimicrobials against which they were tested. These antimicrobials included cloxacillin, fusidic acid, amoxicillin-clavulanate, erythromycin, azithromycin, clindamycin, trimethoprim-sulfamethoxazole, amikacin, gentamicin, cefotaxime/ceftriaxone, linezolid, vancomycin, ciprofloxacin and rifampicin.

Three (1.1%) MSSA isolates were sensitive to penicillin and 5 (1.9%) were sensitive to ampicillin. All of the MRSA isolates were susceptible to vancomycin (Table 3.2).

Table 3.2 Antimicrobial susceptibility results for all 422 *S. aureus* isolates

Antibiotic	**MSSA (n=342)**	**MRSA (n=80)**
	Number of susceptible isolates/number tested (%)	**Number of susceptible isolates/number tested (%)**
Penicillin	3/267 (1.1%)	0/59 (0%)
Ampicillin	5/267 (1.9%)	0/59 (0%)
Cloxacillin	342/342 (100%)	0/80 (0%)
Erythromycin/Azithromycin	33/33 (100%)	2/19 (10.5%)
TMP/SMX	29/32 (90.6%)	1/14 (7.1%)
Vancomycin	3/3 (100%)	80/80 (100%)
Ciprofloxacin	3/3 (100%)	1 /4 (25%)
Gentamicin	1/1 (100%)	NT
Rifampicin	1/1 (100%)	NT
Fusidic acid	6/6 (100%)	NT
Clindamycin	30/30 (100%)	2/6 (33.3%)
Linezolid	2/2 (100%)	2/2 (100%)
Cefotaxime/ceftriaxone	1/1 (100%)	NT
Chloramphenicol	6/6 (100%)	0/4 (0%)
Amoxicillin-clavulanate	15/15 (100%)	1/3 (33.3%)

Abbreviations: NT= Not tested; TMP/SMX = Trimethoprim-sulfamethoxazole

3.4. CHARACTERISTICS OF CHILDREN WITH *S. AUREUS* INFECTION

The median age of the 286 patients from whom *S. aureus* was isolated was 11.3 months (IQR 0.6-60.3 months) (Table 3.3, page 39). There were 159 (55.6%) boys and 127 (44.5%) girls, with a male to female ratio of 1.25:1.

3.4.1 HIV INFECTION STATUS

Of the 286 patients, 165(57.7%) patients were HIV-negative, and 36(12.6%) were HIV-positive. Eighty-five (29.7%) of the 286 patients had undefined HIV infection status (Figure 3.4). Of the 36 patients who tested HIV- positive, 13 (36%) had MRSA (Figure 3.4).

In patients with MSSA, (143/226, 63.3%) tested HIV-negative, 23 (10.2%) were HIV-positive and 60(26.5%) had undefined HIV status. Thirteen (21.7%) of the 60 children with MRSA infection were HIV positive (Table 3.3, page 39).

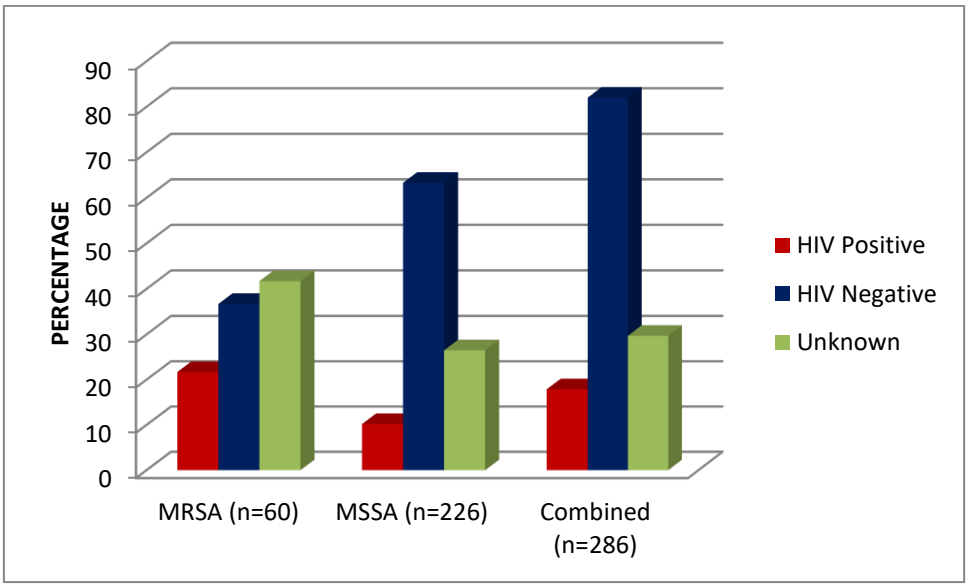


FIGURE 3.4 HIV INFECTION STATUS OF CHILDREN WITH *S.AUREUS* INFECTION

3.4.2 ANTIRETROVIRAL THERAPY

Nineteen (52.8%) of the 36 patients who were HIV-positive were on antiretroviral therapy. The date of initiation of antiretroviral therapy could be determined for all of the 19 patients who had been on treatment. Fourteen of the 19 (73.7%) patients had been on antiretroviral therapy for more than 6 months, while the remaining 5 (26.3%) patients were on antiretroviral therapy for less than 6 months (Figure 3.5).

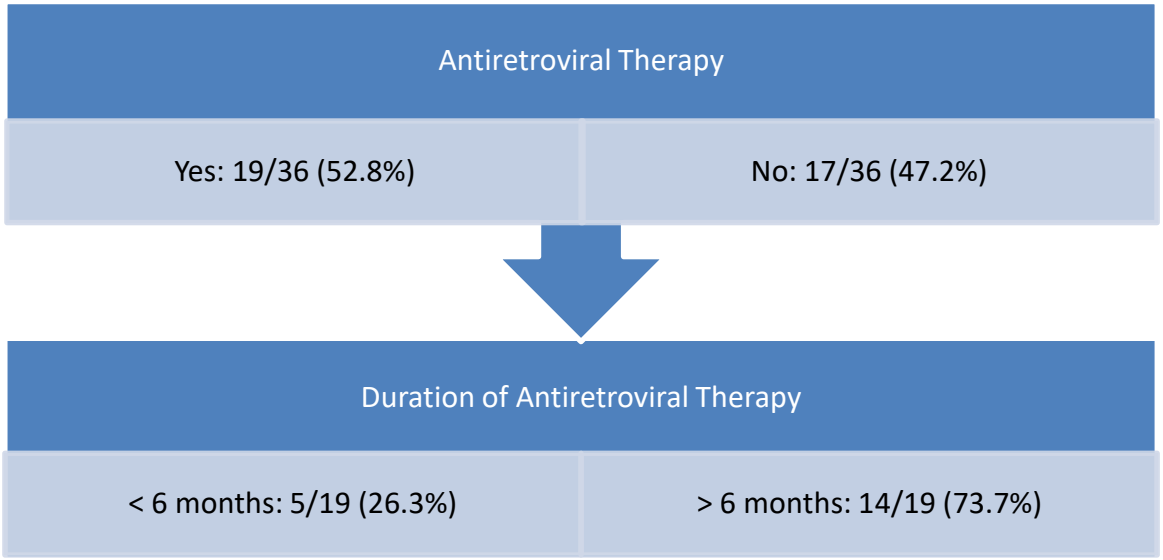


FIGURE 3.5 ANTIRETROVIRAL THERAPY IN HIV-POSITIVE PATIENTS

3.4.3 NUTRITIONAL STATUS

Nutritional status could be determined for 147 (51.3%) of the 286 patients included in the analysis. Of the 147 patients with determined nutritional status, 84 (57.1%) had normal nutritional status, 45 (30.6%) were severely malnourished and 18 (12.2%) were moderately malnourished according to the WHO classification (Figure 3.6, page 36).

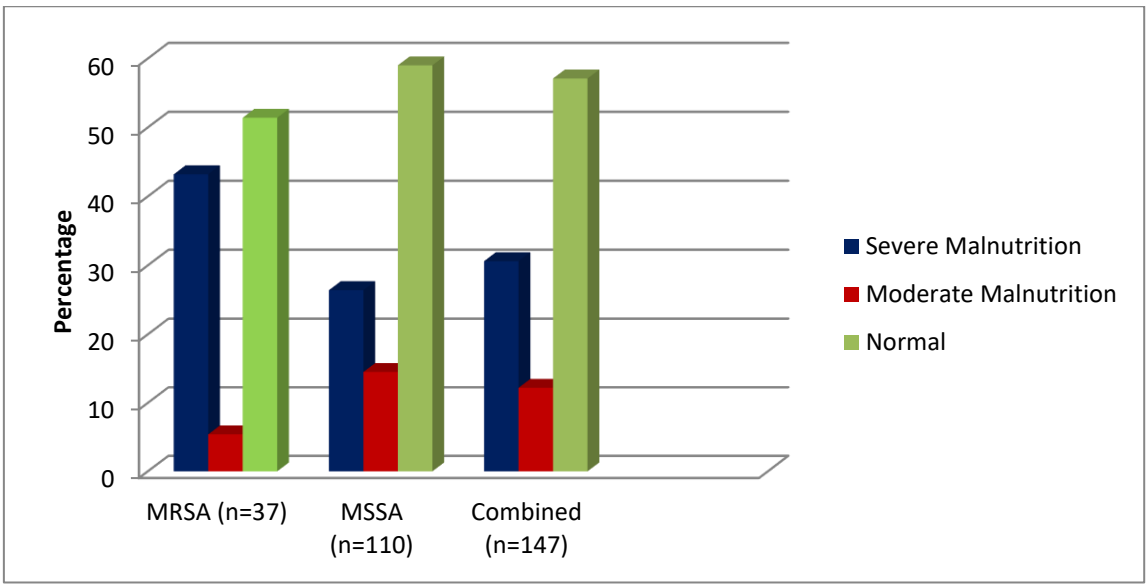


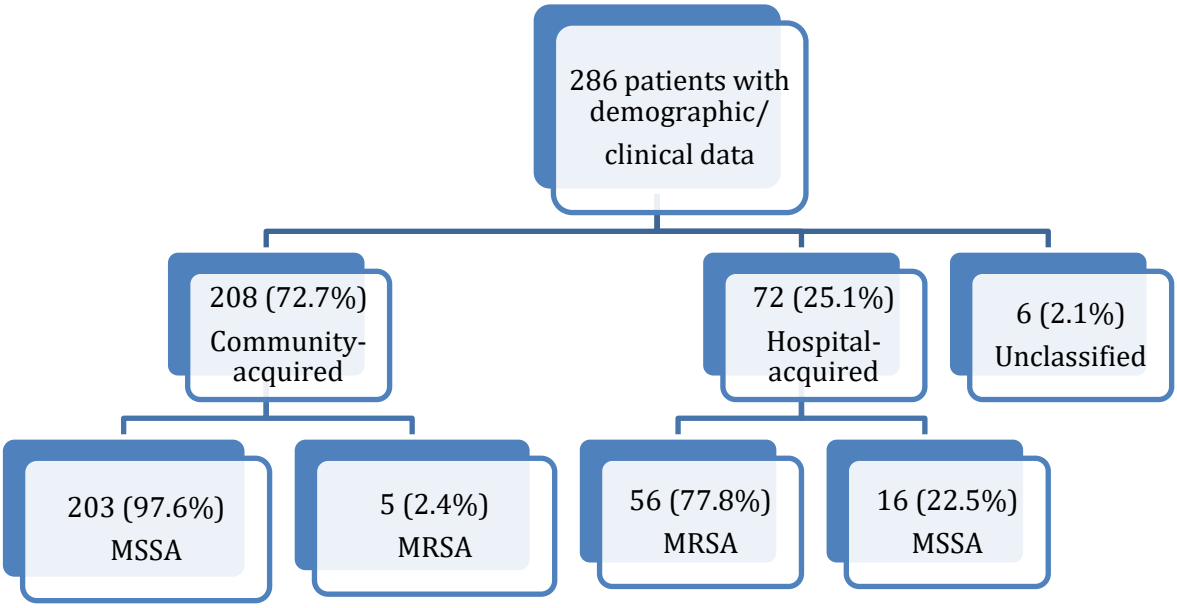
FIGURE 3.6 NUTRITONAL STATUS OF CHILDREN WITH *S.AUREUS* INFECTION

3.4.4 SETTING IN WHICH *S. AUREUS* INFECTION WAS ACQUIRED

Two-hundred and nine (73.1%) of the 286 patients with available demographic and/or clinical data had community-acquired infections and 72 (25.2%) had hospital-acquired infections (Figure 3.7, page 37). Of the 208 patients who had community-acquired infections, 203 (97.6%) had MSSA. Five (2.4%) of the 208 children deemed to have community-acquired infections had infection caused by MRSA, and were therefore classified as having CA-MRSA. Clinical and/or demographic data was obtainable for 3 (60%) of the 5 children with CA-MRSA (Table 3.4, page 40). Of the 72 patients who had hospital-acquired infections, 56 (77.8%) had MRSA and 16 (22.5%) had MSSA (Figure 3.8, page 37).

Six (2.1%) of the 286 children with available demographic and/or clinical data had *S. aureus* infections which could not be classified in terms of whether they were community- or hospital-acquired. This was because the dates of hospitalisation were unknown for these patients, thus the timing of sample collection in relation to hospitalisation could not be determined. Of these six children, 4 (66.7%) had MSSA and

2 (33.3%) had MRSA. HIV status was documented for 6 of these patients, and all were HIV-negative.



Abbreviations: MSSA= methicillin-susceptible *S. aureus*; MRSA= methicillin-resistant *S. aureus*

FIGURE 3.7 DISTRIBUTION OF MSSA AND MRSA EPISODES

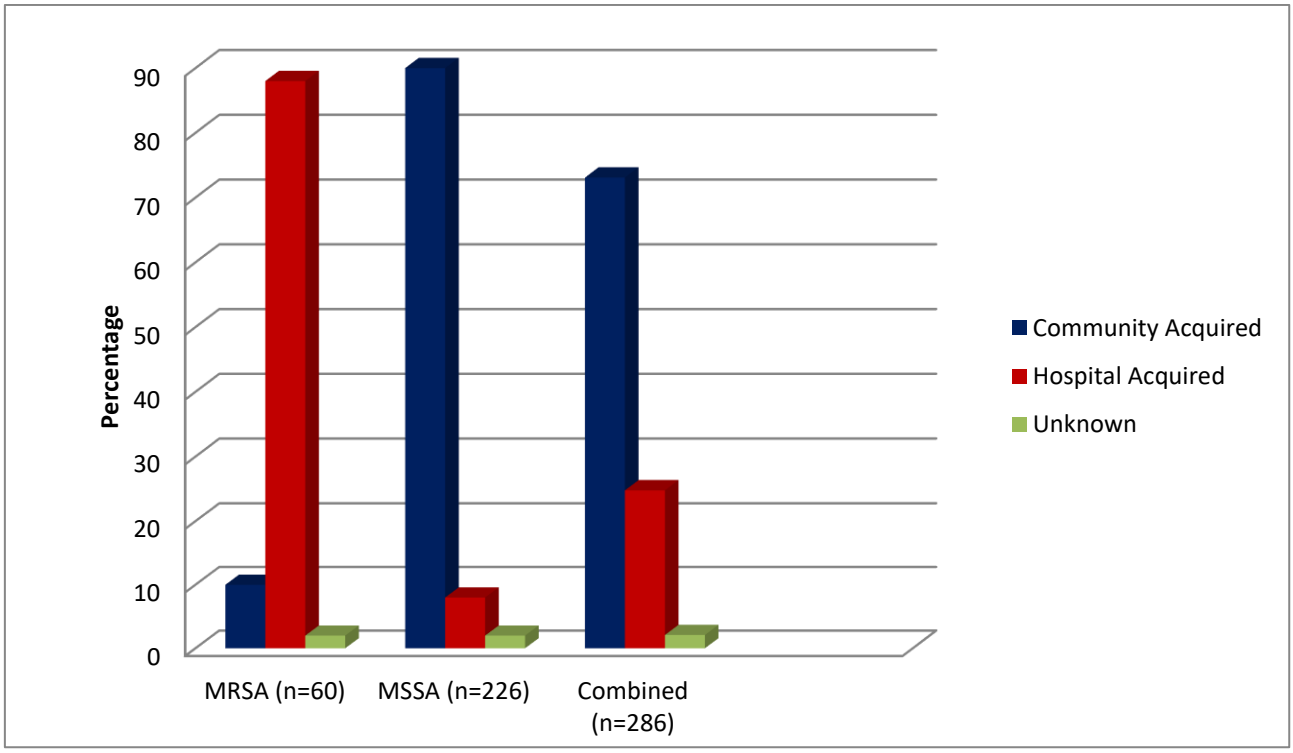


FIGURE 3.8 PLACE OF ACQUISITION OF INFECTION OF THE *S. AUREUS* EPISODES

3.4.5 DURATION OF HOSPITALISATION

Of the 286 patients with available demographic and/or clinical data, the median duration of hospital stay was 11 days (IQR 5-24 days). The duration of hospital stay was significantly longer (35 days; IQR 24-65 days) in those with MRSA infection compared to those with MSSA infection (8 days; IQR 4-18 days), $p<0.001$ (Table 3.3, page 39).

Table 3.3 Characteristics of the 286 patients with available demographic/clinical data

	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)	0.471
Age stratification				
<1 month	69 (24.1%)	20 (33.3%)	49 (21.7%)	0.061
1-11 months	72 (25.2%)	10 (16.7%)	62 (27.4%)	0.088
>12 months	145 (50.7%)	30 (50.0%)	115 (50.9%)	0.903
Gender				
Male	159 (55.6%)	36 (60.0%)	123 (54.4%)	0.439
Female	127 (44.5%)	24 (40.0%)	103 (45.6%)	0.439
Nutritional status (n=147)				
Severe Malnutrition	45/147 (30.6%)	16/37(43.2%)	29/110 (26.4%)	**<0.001**
Moderate Malnutrition	18/147 (12.2%)	2/37 (5.4%)	16/110 (14.5%)	0.288
Normal	84/147 (57.1%)	19/37 (51.4%)	65/110 (59.0%)	0.660
HIV Infection				
HIV-positive	36 (12.6%)	13 (21.7%)	23 (10.2%)	**0.017**
HIV-negative	165 (57.7%)	22 (36.7%)	143 (63.3%)	**<0.001**
HIV-unknown	85 (29.7%)	25 (41.7%)	60 (26.5%)	**0.023**
Place of residence				
Long term facility	15 (5.2%)	11 (18.3%)	4 (1.8%)	**<0.001**
Home	271 (94.8%)	49 (81.7%)	222 (98.2%)	**<0.001**
Indwelling device	44 (15.4%)	28 (46.7%)	16 (7.1%)	**<0.001**
Co-morbidities				
Prematurity	30 (10.5%)	15 (25.0%)	15 (6.6%)	**<0.001**
Tuberculosis	17 (5.9%)	2 (3.3%)	15 (6.6%)	0.539
Congenital Heart Disease	6 (2.1%)	1 (1.7%)	5 (2.2%)	1.000^
Chronic Kidney Disease	1 (0.4%)	0 (0.0%)	1 (0.4%)	1.000^
Malignancies	7 (2.5%)	1 (1.7%)	6 (2.7%)	1.000^
Burns	40 (13.9%)	29 (48.3%)	11 (4.9%)	**<0.001**
No co-morbidity	185 (64.7%)	12 (20.1%)	173 (76.5%)	**<0.001**
Duration of stay (median, IQR)	11 (IQR 5–24)	35 (IQR 14-65)	8 (IQR 4-18)	**<0.001**
Place of infection				
HA	72 (25.7%)	54 (90%)	18 (7.9%)	**<0.001**
CA	208 (74.3%)	5 (8.3%)	203 (89.8%)	**<0.001**
Unknown	6 (2.1%)	1 (1.7%)	5 (2.2%)	1.000^
Previous Hospital Admission	42 (14.7%)	7 (11.7%)	35 (15.5%)	0.457
ICU Admission	48 (16.8%)	30 (50.0%)	18 (7.9%)	**<0.001**

* P-values derived by using the Mann Whitney test (comparing medians) and Pearson Chi-Square test (comparing proportions), comparing the MRSA and MSSA groups, used unless otherwise indicated.
^ Fisher's exact test. Abbreviations: CA = community-acquired; HA = hospital-acquired; ICU = intensive care unit; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus.*

Table 3.4 Clinical characteristics of children with CA-MRSA

	PATIENT 1	PATIENT 2	PATIENT 3
Age	2 months	4 months	55 months
Gender	Male	Male	Male
HIV Status	Positive	Negative	Negative
Nutritional status	Normal	Normal	Normal
Co-morbidities	No defined co-morbidity	No defined co-morbidity	No defined co-morbidity
Clinical presentation	Pneumonia	Skin and soft tissue infection	Septic wound
Antibiotic choice	Amoxicillin-Clavulanate	Cloxacillin	Vancomycin
Duration of treatment	7 days	21 days	10 days
Outcome	Discharged	Discharged	Discharged

Table 3.5 Comparison of MRSA and MSSA infection in respective wards for all 422 *S. aureus* isolates

Ward	MSSA (N=342)	MRSA (N=80)	OR (95%CI)*	p-value
Paediatric medical	203 (59.4%)	9 (11.3%)	0.09 (0.04-0.18)	**<0.001**
Paediatric surgical	86 (25.1%)	48 (60%)	4.47 (2.69-7.41)	**<0.001**
Paediatric orthopaedic	21 (6.1%)	0	-	**0.019 (exact)**
Haematology-oncology	9 (2.6%)	1 (1.3%)	0.47 (0-2.92)	0.695 (exact)
Neonatal Unit	23 (6.7%)	22 (27.5%)	5.23 (2.77-10.10)	**<0.001**

* Comparisons reflecting the odds of having MRSA rather than MSSA infection in each of the ward settings.

3.5. SPECTRUM OF CLINICAL PRESENTATION FOR CHILDREN WITH *S. AUREUS* INFECTION

One-hundred and seven (37.4%) of the 286 patients with available clinical information presented with SSTI, which was the commonest clinical presentation amongst those with MSSA infection. Thirty-four (11.9%) patients presented with pneumonia, two thirds (23/34, 67.6%) of which had MSSA infection (Table 3.6, page 42).

Twenty-nine (10%) patients had bacteraemia without a focus. Seventeen (5.9%) patients presented with meningitis and 13 (4.5%) presented with bone and joint infections. MSSA was significantly associated with SSTI, whereas MRSA was associated with septic (surgical/burns) wounds (Table 3.6, page 42). All bone and joint infections were associated with MSSA. The commonest clinical presentation for CA-infection was SSTI, and children with HA-infection presented mainly with septic (surgical/burns) wounds and bacteraemia without focus (Table 3.7, page 43).

Other clinical presentations included: urinary tract infections in 8 (2.8%), conjunctivitis in 6 (2.1%), STSS in 5 (1.7%), acute gastroenteritis in 4 (1.4%), SSSS in 3 (1.0%), and empyema in 2 (0.7%). All of these less common clinical presentations were associated with MSSA. One (0.3%) patient presented with infective endocarditis, which was a HA-infection associated with MRSA (Table 3.7, page 43).

Table 3.6 Spectrum of clinical presentation for the 286 patients with available folders

Clinical Spectrum	All patients	MRSA (n=60)	MSSA (n=226)	p-value*
SSTI	107 (37.4%)	5 (8.3%)	102 (45.1%)	**<0.001**
Septic wounds	39 (13.4%)	25 (42.4%)	14 (6.2%)	**<0.001**
Pneumonia	34 (11.9%)	11 (18.5%)	23 (10.2%)	0.083
Bacteraemia without a focus	29 (10.1%)	6 (10.2%)	23 (10.2%)	0.968
Meningitis	17 (5.9%)	2 (3.3%)	15 (6.7%)	0.336
Bone and joint infections	13 (4.6%)	2 (3.4%)	11 (4.9%)	0.612
Urinary tract infection	8 (2.8%)	0 (0.0%)	8 (3.6%)	0.211^
Conjunctivitis	6 (2.1%)	0 (0.0%)	6 (2.7%)	0.349^
STSS	5 (1.8%)	2 (3.4%)	3 (1.3%)	0.282^
Acute gastroenteritis	4 (1.4%)	1 (1.7%)	3 (1.3%)	1.000^
SSSS	3 (1. 1%)	0 (0.0%)	3 (1.3%)	1.000^
Omphalitis	3 (1.1%)	2 (3.3%)	1 (0.4%)	0.112^
Empyema	2 (0.7%)	0 (0.0%)	2 (0.9%)	1.000^
Endocarditis	1 (0.4%)	1 (1.7%)	0 (0.0%)	0.209^
Others	9 (3.2%)	4 (6.8%)	5 (2.2%)	0.096^
Unknown	6 (1.4%)	0 (0.0%)	6 (1.8%)	0.349^

* P-values derived using Pearson Chi-Square test, unless otherwise stated, comparing the MRSA and MSSA groups.
^ Fisher's exact test
Abbreviations: SSSS = staphylococcal scalded skin syndrome; SSTI = skin and soft tissue infection; STSS = staphylococcal toxic shock syndrome.

Table 3.7 Clinical presentation of community-acquired and hospital-acquired *S. aureus* infections in 280 children whose place of acquisition of *S. aureus* infection could be determined

Clinical Presentation	All	Community-acquired (n=209)	Hospital-acquired (n=71)	p-value*
SSTI	107 (37.4%)	100 (47.9%)	7 (9.9%)	**<0.001**
Septic wounds	39 (13.4%)	8 (3.8%)	31 (43.7%)	**<0.001**
Pneumonia	34 (11.9%)	21 (10.1%)	13 (18.3%)	0.066
Bacteraemia with a focus	29 (10.1%)	16 (7.7%)	13 (18.3%)	**0.011**
Meningitis	17 (5.9%)	15 (7.2%)	2 (2.8%)	0.184
Bone and joint infections	13 (4.6%)	11 (3.9%)	2 (2.8%)	0.397
Urinary tract infections	8 (2.8%)	8 (3.8%)	0 (0.0%)	0.209^
Conjuctivitis	6 (2.1%)	6 (2.8%)	0 (0.0%)	0.343^
STSS	5 (1.8%)	3 (1.4%)	2 (2.8%)	0.604^
Acute gastroenteritis	4 (1.4%)	4 (1.9%)	0 (0.0%)	0.575^
SSSS	3 (1.0%)	3 (1.4%)	0 (0.0%)	0.574^
Omphalitis	3 (1.1%)	3 (1.4%)	0 (0.0%)	0.574^
Empyema	2 (0.7%)	2 (0.9%)	0 (0.0%)	1.000^
Endocarditis	1 (0.4%)	0 (0.0%)	1 (1.4%)	0.254^
Others[$]	9 (3.2%)	9 (4.3%)	0 (0.0%)	0.112^

* P-values derived using Pearson Chi-square test, unless otherwise stated, comparing the MRSA and MSSA groups;
^ Fisher's exact;
[$] Others = Bursitis (n=5), dacrocystitis (n=4);

Abbreviations: SSSS = staphylococcal scalded skin syndrome; SSTI = skin and soft tissue infection; STSS = staphylococcal toxic shock syndrome.

3.6. RISK FACTORS FOR MRSA INFECTION

Univariate and multivariate analyses were done to determine risk factors for MRSA infection. Univariate analysis showed that severe malnutrition, being a resident of a long term facility, presence of an indwelling device, prematurity, burns, treatment in the intensive care unit (ICU), hospital-acquired infection and prolonged hospitalization were risk factors for MRSA infection. In the multivariate analysis model, only acquisition of infection in hospital retained its significance as a risk factor for MRSA infection (Table 3.8).

Table 3.8 Risk factors for MRSA infection for the 286 patients with available folders

RISK FACTORS	Univariate Analysis	Multivariate Model#
	OR* (95% CI)	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)	1.01 (0.99 – 1.02)
ICU Admission	11.22 (5.60-22.45)	
Place of infection (hospital)	99.62 (37.68 – 263.36)	125.55 (11.67 – 1350.68)

* OR = Odds ratio; ^aOR = Adjusted odds ratio. # The multivariate model adjusted for HIV status, nutritional status, comorbidities, place of residence, place of infection, duration of hospital stay, and presence of an indwelling device.

3.7 ANTIBIOTIC MANAGEMENT FOR THE 286 PATIENTS WITH AVAILABLE FOLDERS

Antibiotic management was determined for 250 (87.4%) of the 286 patients with available demographic and/or clinical data. One hundred and eighty-six (78.4%) of these patients had community-acquired infection and 64 (21.6%) had hospital-acquired infection.

There were 28 (43.8%) patients who had septic wounds and cultured *S. aureus* on pus swabs, but were systemically well and were not given systemic antibiotic therapy. These patients were from the group with hospital-acquired infection and were treated with topical antiseptic dressings only. These patients had septic burn wounds and septic drip site ulcers and were all based in the surgical wards.

Data on antibiotic therapy was based on review of prescription charts. Directed therapy was mainly cloxacillin, vancomycin, and amoxicillin-clavulanate. Beta-lactam antibiotics were commonly used for the empiric therapy of community-acquired infections. Of the 186 patients who had community-acquired infections, 101 (54.3%) were treated with cloxacillin alone, 53 (28.5%) were treated with amoxicillin-clavulanate, and 27 (14.5%) were treated with a combination of cloxacillin and a third generation cephalosporin. Five (2.7%) patients, all of them with persistent *S. aureus* bacteraemia as evidenced by the presence of two or more positive blood cultures, were treated with cloxacillin and fusidic acid.

Vancomycin was the antibiotic of choice for the children with hospital-acquired infections. This was also based on directed antimicrobial therapy. Thirty-four (53.1%) patients with hospital-acquired infections were treated with vancomycin, and 2 (3.1%) were treated with linezolid.

3.7.1 DURATION OF ANTIBIOTIC THERAPY PER *S. AUREUS* SYNDROME

The duration of inpatient and outpatient antibiotic treatment varied in accordance with 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). 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 11 days (IQR 5 – 24 days). There were 3 patients who had documented persistent SAB who were treated with a combination of cloxacillin and fusidic acid. The duration of antibiotic therapy in these patients ranged from 14 to 21 days.

In addition to antibiotic therapy, two patients who presented with empyema had intercostal drain insertion, and subsequently underwent VATS.

3.8 OUTCOME

One-hundred and eighty-nine (90.4%) of the 209 children with community-acquired *S. aureus* infection were discharged, ten (4.8%) were transferred to other hospitals, five (2.4%) died, and the parents of one (0.5%) child refused hospital treatment. Of the 5 patients who died, 3 had sepsis and 2 had bacteraemic pneumonia. The outcome was unknown for four (1.9%) patients with community-acquired *S. aureus* infection.

Amongst the 71 children with hospital-acquired *S. aureus* infection, 48 (67.6%) were discharged, 17 (23.9%) died, and 4 (5.6%) patients were transferred to other hospitals. Of the 17 patients who died, 10 had septic wounds, 4 had bacteraemic pneumonia, 2 had SAB and 1 had infective endocarditis. The outcome was unknown for two (2.8%) patients with hospital-acquired *S. aureus* infection.

The odds of dying was 13-fold (95% CI, 4.61 to 37.10) greater in children with MRSA infection as compared to infection caused by MSSA.

Four (4/22, 18.2%) of the patients who died, 3 with MRSA and 1 with MSSA infection, were not initiated on any antimicrobial therapy before time of death. The remaining 18 (18/22, 81.8%) patients who died were on antimicrobial therapy for a median duration of 6 days (IQR 5- 14 days) before time of death.

Table 3.9 Case fatality rates per clinical syndrome for the 17 patients who died

Clinical Syndrome	Number of cases	Number of deaths	Case Fatality Rate
Infective Endocarditis	1	1	100%
Septic wounds	39	10	25.6%
Bacteraemic Pneumonia	34	4	11.8%
SAB/Bacteraemia without a focus	29	2	6.9%

Abbreviations: SAB = *Staphylococcus aureus* bacteraemia

3.9 ADMISSION TO THE INTENSIVE CARE UNIT

Of the 286 patients with available clinical data, 48 (16.8%) were admitted to ICU, with HA-infections accounting for 87.5% of those patients and CA- infections accounting for 12.5%. The clinical presentation amongst patients who were admitted to ICU included septic wounds (54.2%), pneumonia (25.0%), STSS (8.3%), bacteraemia without a focus (6.3%), septic arthritis (4.2%) and infective endocarditis (2.1%).

3.10 RISK FACTORS FOR MORTALITY

On univariate analysis amongst patients with hospital-acquired infections, the following were associated with higher mortality: malnutrition, infection caused by MRSA, haematology-oncologic conditions, and neonates with prematurity. Neonates treated in the general paediatric wards appeared to have a better outcome as the majority of them were not preterm. On multivariate analysis, acquisition of infection in hospital was the only factor independently associated with a higher mortality (Table 3.10, page 49).

Table 3.10 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# The multivariate model adjusted for nutritional status, comorbidities, place of residence, place of infection, duration of hospital stay and presence of an indwelling device.

CHAPTER 4

4.0 DISCUSSION

Paediatric *S. aureus* infections are an important cause of morbidity. Most invasive *S. aureus* infections in our setting are caused by methicillin-susceptible strains, although MRSA should be considered, particularly in the context of hospitalized patients. Community-onset MRSA infections appear to be uncommon in our setting.

4.1 GENDER PREFERENCE

According to previous publications, *S. aureus* infections appear not to have a specific gender preponderance [7, 9]. In this study, there was no significant gender preponderance for *S. aureus* infections, with a male: female ratio of 1.25:1. This is consistent with the Cape Town and Canadian studies, which showed male: female ratios of 1.1:1 and 1.3:1 respectively [7, 9].

4.2 AGE PREFERENCE

Staphylococcus aureus infections appear to affect different age groups according to the different populations studied [7, 9, 10].South African studies show a predilection of *S. aureus* infections in the younger age groups, whereas international studies show a predilection of older children [7, 9, 10]. In this study, the median age was 11.3 months (IQR 0.6 - 60.3); which was similar to that observed in a Cape Town study of SAB, in which the median age was 11.3 months (IQR 3.8 - 42.3) [7]. In New Zealand, the mean age was 74 months (0.25 - 168 months); and in Canada the median age was 6.6 years (IQR 1.0 - 11.2 years) [9, 10]. The reason for the age difference can be explained by the social determinants of health which affect developing countries.

4.3 RISK OF MRSA

Increasing rates of MRSA infection have been observed in England and in the USA [31, 32]. There has been an upward trend of MRSA infection over the past four decades, from 2% in 1974, to 18% in 1992, and 26% in the study done in Cape Town [7, 31, 32]. In the current study, 19% of patients had MRSA infections. A large proportion (88%) of the MRSA isolates were nosocomial or healthcare associated. As reported in other studies, MRSA appears to be common in neonates and infants as compared to the older age group [31, 33].

A study in the USA looked at the reasons why neonates are particularly vulnerable to colonization and infection with MRSA, and identified low birth weight, prematurity and multiple gestations to be important risk factors [34]. Procedures and devices, such as endotracheal intubation, mechanical ventilation, percutaneous central venous catheterization and surgery, that neonates in ICU often required during their hospital stay were also found to be associated with higher risk of MRSA infection[34]. Feeding methods, including gavage feedings and receipt of parenteral nutrition have also been associated with a higher risk of MRSA infection [34].

In this cohort, children treated in the surgical and neonatal wards had a 4.5 and 5.2-fold greater odds of having *S. aureus* infection caused by MRSA, rather than MSSA (Table 3.5, page 40). These findings are similar to the findings from Cape Town, which showed increased rates of MRSA infection in patients with prolonged hospitalization[7]. The most common presentation of MRSA infection in the current study was that of septic surgical and burn wounds (Table 3.7, page 43).

Other South African studies have shown higher rates of MRSA in children who are HIV-positive [7, 14]. In this cohort, 36% of patients who were HIV-positive had MRSA, compared to 13% of HIV-negative children that had MRSA, but on multivariate analysis, HIV infection was not seen to be a risk factor for MRSA infection (Table 3.8, page 44). The reason for the different findings in this study as compared to other studies could be due to the number of patients with unknown HIV status. In this study, 47.2% of patients were not on any antiretroviral therapy. Most of the patients who were not on any antiretroviral therapy were not eligible for initiation of treatment, as per the national guidelines for the initiation of antiretroviral therapy at the time. However, more than 50% of patients were on antiretroviral therapy. The new guidelines for initiating antiretroviral therapy are: all children less than 5 years of age; children between 5 and 10 years of age with WHO stage 3 or 4 disease (irrespective of CD4 count), or CD4 count less or equal to 500 (irrespective of WHO stage).

In Cape Town, 20% of patients were HIV- positive and of those patients, 49% had MRSA bacteraemia [7].The reason for the higher proportions of MRSA in HIV-infected children is thought to be due to the fact that they are more often hospitalised compared to immunocompetent children, and are therefore at risk of being colonised with nosocomial pathogens harbouring antibiotic resistance [7].

Similar to the Cape Town study, other risk factors associated with MRSA infection on univariate analysis included malnutrition, being a resident of a long term facility, presence of an indwelling device, prematurity, burns and prolonged hospitalization; however, only hospital-acquired infections were associated with MRSA in the multivariate analysis (Table 3.8, page 44).

4.4 SPECTRUM OF CLINICAL PRESENTATION

Skin and soft tissue infections were the commonest clinical presentation for children with MSSA in this study, accounting for nearly half (45%) of the patients with MSSA (Table 3.5 page 40). This was followed by bacteraemic pneumonia (10.2%) and bacteraemia without a focus (10.2%). MSSA was significantly associated with SSTI, whereas MRSA was associated with septic (surgical/burns) wounds (Table 3.6, page 42). All bone and joint infections were associated with MSSA. In Cape Town, the commonest clinical presentation was bacteraemia without a source [7]. This difference may be explained by the fact that the Cape Town study focused on *S. aureus* bloodstream infections, whereas the current study looked at *S. aureus* cultured from different sites, including pus swabs.

According to this study, pneumonia was a common clinical presentation in 10.2% of the patients. In view of this finding, an antimicrobial with good cover for staphylococcal infections should be considered as part of the first line antimicrobial choices for treating CA-pneumonia.

During this study period, 5.9% of patients presented with meningitis. These patients were treated with a combination of cloxacillin and a third generation cephalosporin. This study did not look at the morbidity associated with meningitis, however, none of the patients with meningitis died. The morbidity associated with meningitis, which includes the development of hydrocephalus, cerebrovascular accidents, seizures, vision and hearing impairment, should be considered as an area of future research.

During this study period, all community-acquired bone or joint infections were caused by MSSA isolates, and the most frequently prescribed empiric antibiotic therapy (in

41.4%) was cloxacillin. This is similar to the findings at RCWMCH, where the empiric antibiotic of choice for osteomyelitis and septic arthritis was cloxacillin [7].

4.5 PLACE OF ACQUISITION OF *S. AUREUS* INFECTIONS

The majority (74.6%) of the patients in this study cohort had community-acquired infections, with hospital-acquired infections comprising one quarter of the episodes. This is similar to the national and international studies which show that most paediatric *S. aureus* infections are community-acquired [3, 7].

Five (2.9%) of the 209 children with MRSA infection and enough information on which to base the place of origin of the infection, were classified as having CA-MRSA. All the patients with CA-MRSA who had obtainable clinical/demographic data had a good clinical outcome and were discharged from the respective wards. This is similar to a meta-analysis conducted on CA-MRSA, which showed a good clinical outcome [27-29].

4.6 ECHOCARDIOGRAPHY IN *S. AUREUS* INFECTIONS

One patient was found to have infective endocarditis during the period under review for the current study. Echocardiography was not done routinely, but was performed in patients who had multiple positive blood cultures and underlying congenital heart disease, as per hospital guidelines [36]. At RCWMCH, 2.4% of patients were diagnosed with endocarditis [7]. According to published data, S. *aureus* infective endocarditis is a life-threatening disease associated with a high rate of complications and a high mortality, warranting all patients with SAB to undergo echocardiographic screening in order to minimize the risk of missing this potentially lethal diagnosis [11, 21]. This study did not assess the number of patients who had echocardiography. Assessing the number

of SAB patients who have echocardiography will assist in the development of standardised universal guidelines for managing patients with SAB and to reduce the morbidity associated with *S. aureus* infective endocarditis. This can be an area of future research.

4.7 ANTIBIOTIC MANAGEMENT

The antibiotic management was known for 250 patients (87%). Cloxacillin was the preferred antibiotic of choice for the targeted therapy of patients with MSSA in this study. Patients treated with cloxacillin were mainly those who presented with SSTI, bone and joint infections, pneumonia and bacteraemia without a focus. Patients who had meningitis were treated with a combination of cloxacillin and a third generation cephalosporin, either cefotaxime or ceftriaxone. Other antibiotics used for the treatment of MSSA included amoxicillin-clavulanate, ceftriaxone/cefotaxime, and fusidic acid in combination with cloxacillin. The duration of treatment was 6weeks (IQR 3 – 8 weeks) for bone and joint infections and infective endocarditis in this study. Patients with meningitis were treated for 3 weeks (IQR 2- 6 weeks). The total median duration of inpatient treatment for all other groups of *S. aureus* infection was 11 days (IQR 5-24 days). According to this study, cloxacillin was the preferred antibiotic of choice for SSTI, bone and joint infections, bacteraemic pneumonia and bacteraemia without a focus in patients with MSSA, which was similar to the findings in Cape Town [7].

The combination of cloxacillin and fusidic acid was used in patients who had persistent bacteraemia or complicated SAB, i.e. patients who had two or more positive blood cultures. This was in accordance with the CHBAH guidelines for treating *S. aureus* infections [36]. According to the clinical practice guidelines by the Infectious Disease Society of America, the use of single agents and combination therapy should be

individualized and local epidemiology should be considered when decisions are made about antibiotic therapy for *S. aureus* infections [16]. Children with local disease, i.e. skin and soft tissue infections, have had good outcomes on single agents, however, some groups of patients with invasive disease have benefited from combination therapy [16].

Antibiotic therapy used in the management of this cohort was not documented for 36(12.5%) of the 286 patients, and a further 27(9.4%) did not receive any antibiotics. Children who did not receive antibiotics included those who had septic wounds with *S. aureus* cultured from pus swabs, but were systemically well and were treated with antiseptic dressings. Four (4/22, 18.2%) of the patients who were not initiated on any antimicrobial therapy demised. The failure of initiation of antimicrobial therapy on these patients appears to be the cause of this poor outcome. Reasons for failure to initiate appropriate therapy in these patients were not clearly documented. Factors affecting appropriate initiation of antimicrobial therapy amongst clinicians should be considered as an area of future research.

MRSA was significantly associated with hospital-acquired infections in this cohort, which justified the use of vancomycin as the empirical antimicrobial of choice when treating healthcare associated infections. Thirty-two (53.3%) of the patients with hospital-acquired infection were treated with vancomycin, and two (3.1%) were treated with linezolid. The choice of vancomycin as the preferred antimicrobial for the directed therapy of hospital-acquired MRSA infections was in accordance with the clinical practice guidelines proposed by the Infectious Diseases Society of America [16]. Clindamycin and linezolid have been recommended in cases of persistent MRSA bacteraemia, and in instances where vancomycin treatment fails [15]. In this cohort, none of the patients with hospital-acquired MRSA were treated with clindamycin [16].

In this study, the MSSA episodes were susceptible to most antimicrobials against which they were tested. However, similar to findings in Cape Town, there was a high prevalence of MSSA strains resistant to penicillin and ampicillin [7]. This is in keeping with other South African antimicrobial susceptibility studies in children [7, 18, 35].

4.8 OUTCOME OF PATIENTS WITH *S. AUREUS* INFECTION

Patients with community-acquired infections had a better outcome compared to those who had hospital-acquired infections. Hospital-acquired infections were associated with a higher mortality, with a case fatality rate of 24%. In addition, children with hospital-acquired infections had a 13-fold greater odds of dying compared to those with community-acquired infection. The case fatality rate of patients with MSSA infection in this study was 2.4%.

The overall case fatality rate in the study was 7.7%, slightly lower in comparison to case fatality rates of 8.8% and 8.6% in Cape Town and New Zealand, respectively [7, 10]. The reason for the lower case fatality rate in this cohort is likely related to the inclusion of local cellulitis cases, while other studies focused on the invasive cases. The higher mortality in patients with hospital-acquired infections observed in our study is similar to findings from other South African studies [6, 7].

Of the 286 patients, 48 (16.8%) were admitted to ICU, with hospital-acquired infections accounting for 87.5% of those patients and community-acquired infections accounting for 12.5%. Some of the patients might have acquired the infection in ICU, following admission for a different pathology that is not caused by *S. aureus* infection. The findings

in this study suggest that hospital-acquired infections are associated with a higher rate of ICU admissions, as compared to community-acquired infections. This was not the case in a study conducted in New Zealand wherein 94.8% of the children who required admission to ICU had community-acquired infection [10]. The high rate of ICU admissions associated with hospital-acquired infections could be prevented through strict adherence to good infection control practice and use of universal precautions.

The outcome of patients after discharge and the number of patients who might have returned to hospital after discharge was not known, as this was not part of the objectives of this study.

CHAPTER 5

CONCLUSION

Staphylococcus aureus appears to be a common pathogen in paediatric bacterial infections. Most invasive *S. aureus* infections are caused by methicillin-susceptible strains, although MRSA should be considered, particularly in the context of hospitalised patients. Community-onset MRSA infections appear to be uncommon in our setting.

Paediatric *S. aureus* infections appear to affect different age groups according to the different populations studied. South African studies show a predilection of *S. aureus* infections in the younger age groups, whereas international studies show a predilection of older children.

Clinical presentations for MSSA bacteraemia include skin and soft tissue infection, pneumonia, meningitis, bone/joint infections and urinary tract infections. Infective endocarditis was not a common occurrence in our study, however, it was associated with a high mortality.

Risk factors for MRSA sepsis include burns, prematurity, prolonged hospitalisation, presence of indwelling device and malnutrition.

Children with hospital-acquired infections had a 13-fold greater odds of dying, which warrants an urgent need to look at ways to limit infection. These factors include addressing the social determinants which predispose patients to burns; good antenatal care to reduce prematurity; and adherence to strict infection control practices when inserting lines in the ICU setting.

Cloxacillin or amoxicillin-clavulanate remain the antimicrobials of choice for MSSA, whereas vancomycin remains the antimicrobial of choice for MRSA.

From this study, it appears that patients with methicillin-susceptible strains have a better outcome as compared to those with methicillin-resistant strains. Patients with MSSA displayed a good response to cloxacillin or amoxicillin-clavulanate. .

5.1 RECOMMENDATIONS

- Current practice at CHBAH is for children with SAB to receive 14 days of targeted antibiotic therapy, as per international guidelines.
- Involvement of infectious disease subspecialists in the care of children with SAB has been associated with good outcomes and should be practiced across different centres.
- Due to the high mortality associated with hospital-acquired infections, strict infection control measures such as handwashing should be emphasized. Strict observance of infection control practice would be expected to impact favourably on the rates of MRSA infection at our hospital and would be expected to ease the pressure on ICU bed occupancy.
- An improvement in the social determinants of health may contribute to the reduction of MRSA through decreasing the numbers of premature infants being born and requiring care at the overburdened CHBAH Neonatal Unit, and by limiting the numbers of children presenting with burns to the Burns Unit.
- Good antenatal services will contribute to the reduction of premature deliveries, which were associated with an increased risk of MRSA in this study.
- Neonates receiving care in the Neonatal Unit, or with a history of recently being treated in the Neonatal Unit, and residents at long-term care facilities should be treated with vancomycin as part of their empiric antibiotic cover for putative

MRSA infections, and antibiotic treatment should be rationalised once an isolate is cultured and its antibiotic susceptibility profile is determined.

- The need for invasive lines should be reassessed in the ICU setting and their prolonged use should be avoided.
- All inpatients in both surgical and medical wards should have age appropriate HIV testing performed on admission or prior to discharge.

5.2 AREAS FOR FUTURE RESEARCH

Based on this study, paediatric *S. aureus* appears to be a common cause of paediatric bacterial infections. Although CA-MRSA infections do not appear to cause a large burden of disease in our setting, continued surveillance for potential CA-MRSA infection is warranted.

Additional risk factors for complicated SAB should be investigated, in addition to HIV infection and malnutrition. This will help in determining the choice of empiric antibiotics for patients at risk. The local epidemiology of *S. aureus* infection should be researched further.

The failure of initiation of antimicrobial therapy resulted in the mortality of some patients with *S. aureus* infection. Factors contributing to the failure of initiation of antimicrobial therapy were unclear. Factors affecting appropriate initiation of antimicrobial therapy amongst clinicians should be considered as an area of future research.

Very few South African studies have looked at *S. aureus* infections in the ICU setting; this is an area that warrants further research.

An update on the prevalence of S. *aureus* infective endocarditis in developing countries needs to be conducted, which will assist in the development of universal guidelines on the role of routine echocardiography in SAB. The current recommendations are based on European studies.

The outcome of patients with S. *aureus* infection who receive a short duration of antimicrobial therapy needs to be researched further. This will assist in more aggressive treatment of such patients, with an awareness of the outcome.

CHAPTER 6

LIMITATIONS

Due to the retrospective nature of this study, there were some limitations.

- Poor documentation in patients' hospital folders resulted in a number of patients with unknown nutritional status.
- The lack of availability of clinical folders might have resulted in study bias.
- The relationship between HIV infection and MRSA could not be established in this study as compared to other studies. This was due to the lack of confirmed HIV status in some patients.
- Information on the outpatient antibiotic management was not assessed as part of this study.

APPENDIX A: Chris Hani Baragwanath Academic Hospital Medical Advisory Committee Clearance Certificate for this study

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 8th September 2014

TITLE OF PROJECT:
THE CLINICAL SPECTRUM OF *STAPHYLOCOCCUS AUREUS* INFECTIONS IN CHILDREN ADMITTED AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: A RETROSPECTIVE. DESCRIPTIVE STUDY

UNIVERSITY: Witwatersrand

Principal Investigator: DR P MANENZHE

Department: PAEDIATRICS

Supervisor : DR K L PETERSEN
DR D P MOORE

Permission Head Department (where research conducted): **Yes**

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 25/09/2014

.....
Approved/Not Approved
Hospital Management
Date: 19/09/14

APPENDIX B: University of the Witwatersrand Human Research Ethics Committee (Medical) Clearance Certificate for this study

M14049 Dr Phoph Manenzhe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140729

NAME: (Principal Investigator)	Dr Phophi Manenzhe
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Clinical Spectrum of Staphylococcus Aureus Infection in Children Admitted at Chris Hani Baragwanath Academic Hospital: A Retrospective, Descriptive Study
DATE CONSIDERED:	25/07/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Karen Peterser and Dr David Moore
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/07/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: Data collection sheet

DATA COLLECTION SHEET

Demographic Information

File Number:

Gender:

Male ☐

Female ☐

Date of hospitalization (dd/mm/yy): ☐☐☐☐☐☐

Date of birth (dd/mm/yy): ☐☐☐☐☐☐

Age:

< 1 month ☐

1-3 months ☐

4-11 months ☐

12-23 months ☐

24-59 months ☐

5-14 years ☐

Place of residence:

At home (i.e. with family) ☐

At long term Care Facility ☐

Indwelling Device: Yes ☐ No ☐

If Yes, type of device: _____

HIV Status:

Positive ☐

Negative ☐

Unknown ☐

HIV on ART: Yes ☐ No ☐

ART start date (dd/mm/yy) ☐☐☐☐☐☐

HIV duration on ART< 6 months ☐

HIV duration on ART > 6 months ☐

CD4 count within 3 months of the *S. aureus* admission episode:

Date of CD4 count (dd/mm/yy): ☐☐☐☐☐☐

Absolute CD4 count (cells/mm^3): ☐☐☐☐. ☐☐

CD4 Percent (%): ☐☐. ☐

Nutritional Status (WHO classification):

Weight (kg): ☐☐. ☐

Height (cm): ☐☐☐. ☐

Oedema: Yes ☐ No ☐

Weight-for-height (Z-scores):

< -2SD ☐

< -3SD ☐

Co-Morbid Disease:

Prematurity/ ex-premature ☐

Congenital Heart Disease ☐

Tuberculosis ☐

Chronic Kidney Disease ☐

Other 1: ☐ _____

Other 2: ☐ _____

Other 3: ☐ _____

Other 4: ☐ _____

Previous Hospital Admission:

Yes ☐

No ☐

Date of previous Hospital Admission (dd/mm/yy): ☐☐☐☐☐☐

Date of previous Hospital Discharge (dd/mm/yy): ☐☐☐☐☐☐

Diagnosis at previous Hospital Discharge:

1: _____

2: _____

3: _____

4: _____

Current Hospital Admission:

Hospital Department in Which Child was treated during the current *S. aureus* hospitalization: ☐

Neonatal: ☐

Paediatric: ☐

Paediatric Surgical: ☐

Adult Surgical: ☐

Paediatric Orthopaedic: ☐

Adult Orthopaedic: ☐

Neurosurgical:

Other: ☐ _____

Duration of Antibiotics in current admission:

Date Antibiotics started (dd/mm/yy) ☐☐☐☐☐☐

Date Antibiotics stopped (dd/mm/yy) ☐☐☐☐☐☐

Antibiotic	Route	Date Started (dd/mm/yy)	Date Completed (dd/mm/yy)	Date of culture positive result (dd/mm/yy)
1.	iv / oral			
2.	iv / oral			
3.	iv / oral			
4.	iv / oral			
5.	iv / oral			
6.	iv / oral			
7.	iv / oral			

S. aureus Culture Site:

Blood ☐

Cerebrospinal Fluid ☐

Pus ☐

Pleural fluid ☐

Urine ☐

Other 1: ☐ _____

Other 2: ☐ _____

S. aureus antibiotic susceptibility profile:

Antibiotic	Susceptible	Intermediate resistance	Resistant	E-test Result
Penicillin				
Ampicillin				
Cloxacillin/ Methicillin				
Amoxicillin-clavulanate				
Cefuroxime				
Cefotaxime/ Ceftriaxone				
Ciprofloxacin				
Erythromycin				
Clindamycin				
Vancomycin				
Tetracycline				
Rifampicin				
Linezolid				
Daptomycin				

Clinical Presentation/Diagnosis:

Pneumonia ☐

Empyema ☐

Cellulitis ☐

Infective Endocarditis ☐

Meningitis ☐

Arthritis ☐

Osteomyelitis ☐

Staphylococcal Scalded Skin Syndrome ☐

Other 1: ☐ _____

Other 2: ☐ _____

Treatment:

Conservative (antibiotics only): Yes ☐ ☐ No

Surgical: Yes ☐ No ☐

If Yes, surgical intervention required:

Intercostal drain insertion: Yes ☐ No ☐

Date ICD inserted (dd/mm/yy): ☐☐☐☐☐☐

Date ICD removed (dd/mm/yy): ☐☐☐☐☐☐

Incision and Drainage: Yes ☐ No ☐

Laparotomy: Yes ☐ No ☐

Other surgery 1: Yes ☐ No ☐ _____

Other surgery 2: Yes ☐ No ☐ _____

Intensive Care Admission: Yes ☐ No ☐

Date ICU admission (dd/mm/yy): ☐☐☐☐☐☐

Date ICU discharge (dd/mm/yy): ☐☐☐☐☐☐

Outcome:

Date of outcome (dd/mm/yy): ☐☐☐☐☐☐

Discharged home ☐

Transfer to other hospital ☐

Refused hospital treatment ☐

Follow-up ☐

Demised ☐

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