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Staphylococcus aureus bacteraemia in Gauteng academic hospitals, South Africa

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SUMMARY

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are responsible for longer hospital stays, increased hospital costs, and poorer outcomes compared to methicillin-sensitive *S. aureus* (MSSA) infections. We aimed to describe the epidemiology of *S. aureus* bacteraemia (SAB) and to determine factors associated with MRSA infection in South Africa.

Methods: Cases of SAB were reported from September 2012 to September 2013 from three sentinel sites. A case was defined as the isolation of *S. aureus* from a blood culture during a 21-day period. Detailed clinical information was collected. Multivariable logistic regression was done to determine factors associated with MRSA infection and mortality.

Results: There were 442 cases of SAB reported; antimicrobial susceptibility testing was performed on 240 isolates (54%). Thirty-six percent (86/240) of cases had an MRSA infection. A longer hospital stay before positive specimen collection (odds ratio (OR) 1.08, 95% confidence interval (CI) 1.02–1.13, $p = 0.004$), hospitalization in the last year (OR 15.7, 95% CI 2.5–99.5, $p = 0.003$), HIV infection (OR 4.9, 95% CI 1.05–22.90, $p = 0.044$), and antibiotic use in the previous 2 months (OR 0.1, 95% CI 0.01–0.68, $p = 0.022$) were independent predictors of MRSA. Older age, and in particular age 25–44 years (OR 22.2, 95% CI 2.7–185.5, $p = 0.004$, compared to those aged < 5 years), was the only independent predictor of mortality amongst cases with SAB. MRSA isolates were non-susceptible to more antimicrobial agents compared to MSSA isolates.

Conclusions: HIV infection was an independent risk factor for MRSA infection. The selection of appropriate empirical antimicrobial treatment is essential in patients with MRSA infections because of non-susceptibility to many other antimicrobial classes.

1. Introduction

Staphylococcus aureus, a Gram-positive bacterium, can cause bacteraemia, amongst a variety of other clinical syndromes. Due to metastatic complications, *S. aureus* bacteraemia (SAB) is strongly associated with a higher mortality compared to other bacterial bloodstream infections.[1] In a Canadian study, the mortality rate of SAB was 4–6 deaths per 100 000 persons.[2] The incidence of SAB and methicillin-resistant *S. aureus* (MRSA) bacteraemia has increased in the USA[3] due to increases in the number of invasive surgeries, use of intravascular devices, and patients with immunodeficiencies.[4] However, in the UK, a decline has been seen in MRSA incidence.[5]

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Few African studies focusing only on SAB have been documented. The prevalence of MRSA bacteraemia varies greatly between African countries, with prevalence as high as 52% in Egypt, 45% in Algeria, 44% in Botswana,[6] and 19% in Morocco.[7] Even in South Africa, the prevalence of MRSA bacteraemia varies depending on the geographical location and population studied.[8–11]

Numerous reports from various countries have shown that MRSA bacteraemia results in a higher mortality compared to methicillin-sensitive *S. aureus* (MSSA) bacteraemia.[12–16] Crude mortality rates for MRSA infection vary from 29%[15] to 63%.[13] Mortality rates vary depending on how mortality is defined, the study population, location, and medical practices. MRSA is also more likely to be resistant to multiple antimicrobial agents compared to MSSA[17] and increases the length of hospital stay and costs.[12] Therefore it is important to determine risk factors that are associated with MRSA infection to assist clinicians in reducing MRSA infections and choosing appropriate empirical therapy.

The aim of this study was to describe the epidemiology of SAB and to determine factors associated with MRSA infection at three sentinel sites in Gauteng Province, South Africa.

2. Methods

2.1. Setting

Enhanced surveillance of SAB was initiated in September 2012. Three public sector sentinel sites in South Africa were involved in the surveillance: Charlotte Maxeke Johannesburg Academic hospital (CMJAH), a 1088-bed tertiary institution, Steve Biko Academic (tertiary) and Tshwane (district) hospitals (SBAH/TSH) with 832 and 197 beds, respectively, and Helen Joseph Hospital (HJH), a tertiary hospital with 700 beds. All of these hospitals are associated with universities and serve an urban population. These hospitals provide care to patients in the city of Johannesburg (approximate population 4.5 million) and the city of Tshwane (approximate population 3 million).

2.2. Study design

A cross-sectional study was conducted from September 2012 to September 2013. Surveillance officers collected demographic and clinical information through an interview and/or medical record review on a standardized case report form (CRF). Data on the following predisposing conditions were collected: chronic lung disease, chronic renal disease, diabetes mellitus, cardiac disease, cerebrovascular disease, malignancies, immunotherapy, previous surgery, aplastic anaemia, organ transplant, prematurity, decubitus ulcer, dementia, and smoking. Informed consent was obtained. CRFs were sent to the National Institute for Communicable Diseases (NICD), Johannesburg where quality checking and data capture occurred. Audits were performed quarterly to ensure complete case ascertainment.

2.3. Case definitions

A case of bacteraemia was defined when *S. aureus* was isolated from a blood culture. A positive blood culture for *S. aureus* obtained ≥21 days after the first positive blood culture was considered a new case of *S. aureus*. For cases with viable isolates, a case was defined as MRSA or MSSA depending on whether the *S. aureus* isolate was non-susceptible (MRSA) or susceptible (MSSA) to oxacillin and/or cefoxitin. A case was defined as hospital-acquired bacteraemia if the first blood culture positive for *S. aureus* was collected ≥3 days after hospital admission. Infection was defined as community-associated if the first blood culture positive for *S. aureus* was collected <3 days after hospital admission and did not fall into the hospital-associated community-onset category. Hospital-associated community-onset infection was defined if the first blood culture for *S. aureus* was obtained <3 days after hospital admission and the patient was hospitalized in the 90 days before SAB and/or had received haemodialysis and/or was a resident in a long-term care facility or nursing home. Acute severe illness was defined as a Pitt bacteraemia score of >4.[18] Empirical treatment was defined as an antimicrobial agent started prior to or less than 3 days following specimen collection. Directed treatment was defined as any antimicrobial agent that was prescribed 3 days or more after a positive specimen was collected. Appropriate antimicrobial therapy was defined as the receipt of any antimicrobial agents to which the organism was susceptible. Inappropriate antimicrobial therapy was defined if the patient received no antimicrobial agents to which the organism was susceptible or if no antimicrobial therapy was received.

2.4. Laboratory methods

Sentinel site laboratories performed initial identification and antimicrobial susceptibility testing. *S. aureus* isolates were submitted on Dorset transport medium (Diagnostic Media Products, Sandringham, South Africa) together with a laboratory report form to the NICD. Vitek 2 (bioMérieux, Durham, NC, USA) was used to confirm the identity of the isolate. Susceptibility testing was done using the MicroScan Walkaway system (Siemens Healthcare Diagnostics Inc., West Sacramento, CA, USA) and Gram-positive minimum inhibitory concentration (MIC) panel type 33. Two different systems were used for identification and antimicrobial susceptibility testing to rationalize time and costs. MICs were interpreted using Clinical and Laboratory Standards Institute guidelines.[19] Isolates not identified as *S. aureus* were excluded.

DNA was extracted from purity plates using a crude boiling method. The isolates were re-suspended in Tris–ethylenediaminetetraacetic acid buffer and boiled at 95 °C for 25 min.

Amplification and detection of *mec*A and *nuc* genes was done by multiplex real-time PCR using the LightCycler 480 II instrument (Roche Diagnostics Ltd, Rotkreuz, Switzerland) and the LightCycler 480 Probes Master kit (Roche Diagnostics, IN, USA).[20] For SCC*mec* typing, MRSA isolates were typed by conventional multiplex PCR using the Qiagen Multiplex PCR kit (Qiagen, Hilden, Germany). The multiplex PCR included 10 loci. Therefore 10 primer sets were used. These were obtained from a previously published study.[20]

2.5. Ethics

Approval was obtained from the Human Research Ethics Committee (Medical) (HREC), University of Witwatersrand, Johannesburg (protocol number M120632) and from the individual facilities.

2.6. Statistical analysis

Data were extracted from Microsoft Access and analysed in Stata 12.0 (College Station, TX, USA). The average incidence of SAB for the study period was calculated for each hospital. The number of *S. aureus* cases for the study period was the numerator and the number of admissions for the same period was the denominator. Incidence was expressed as *S. aureus* cases per 1000 admissions. The incidence of SAB was calculated using all cases (audit cases included). The MRSA incidence was calculated using only the cases where isolates were submitted to NICD, since susceptibility information was not available for audit cases. A descriptive analysis was performed comparing factors between MRSA and MSSA cases. The Chi-square test and Mann–Whitney *U*-tests were performed on categorical and non-parametric continuous data, respectively. A *p*-value of <0.05 was deemed statistically significant.

Categorical data were presented as frequencies, and continuous data as the median and interquartile range (IQR). Meningitis and bone and joint infection categories were collapsed within the unspecified category due to small numbers. The hospital-associated community-onset infection category was excluded and only hospital-acquired and community-onset infection categories were used for further analysis. Two univariate and multivariable logistic regression models were performed. The first to determine factors associated with MRSA cases compared to MSSA cases and the second to determine factors associated with mortality in cases with SAB. Variables with a p-value of <0.2 were selected from the univariate analysis to be evaluated in the multivariable model. The multivariable model was built using a backward selection technique. The log-likelihood test was used to assess the significance of factors included in the model. A log-likelihood p-value of <0.05 was used for inclusion of a variable in the final model. The model's fit was tested using a Hosmer–Lemeshow goodness-of-fit test.

3. Results

During the 13-month study period, a total of 442 SAB cases were reported; 241 (55%) cases had isolates submitted to the antimicrobial resistance reference laboratory at NICD and 201 cases (45%) were detected by audit. There were 240 cases with oxacillin susceptibility results; clinical information was available for 140 (58%) of these. The total number of admissions from September 2012 to September 2013 for CMJAH, HJH, and SBAH/TSH were 58 324, 38 836, and 57 439, respectively. The incidence of SAB was highest at CMJAH at 3.7 cases per 1000 admissions, followed by HJH at 2.7 cases per 1000 admissions and SBAH/TSH at 1.9 cases per 1000 admissions. The proportion of MRSA differed significantly by hospital ($p < 0.001$). CMJAH had the highest proportion of MRSA isolates (58%, 46/79), followed by SBAH/TSH (26%, 20/77) and HJH (24%, 20/84). The overall proportion of MRSA infection was 36% (86/240). The MRSA incidence was the highest for CMJAH at 0.08 cases per 1000 admissions, followed by HJH at 0.05 cases per 1000 admissions and SBAH/TSH at 0.03 cases per 1000 admissions.

3.1. Demographics and clinical characteristics

Persons with MRSA and MSSA bacteraemia were of similar age (Table 1). The greatest proportion of cases of SAB occurred in those aged <5 years (MRSA 38% (32/85), MSSA 33% (50/152)), with cases <1 year old accounting for 27% (23/85) and 25% (38/152) of MRSA

Table 1
Clinical characteristics of patients with MRSA and MSSA infections[a]

Characteristics	MRSA (n = 86) n (%)	MSSA (n = 154) n (%)	p-Value[b]
Age, years, median (IQR)	29 (0.4–45)	32 (1–50)	0.232
Male	48/84 (57%)	86/145 (59%)	0.748
Site of infection			
Bacteraemia without focus	27/51 (53%)	51/89 (57%)	0.054
Lower respiratory tract infection	12/51 (24%)	7/89 (8%)	
Meningitis	2/51 (4%)	1/89 (1%)	
Skin/soft tissue infections	4/51 (8%)	7/89 (8%)	
Bone and joint infection	0/51 (0%)	3/89 (3%)	
Unspecified[c]	6/51 (12%)	20/89 (22%)	
Predisposing factors			
HIV-infected	14/33 (42%)	18/68 (26%)	0.106
CD4 count, cells/μl, median (IQR)	47 (30–56)	200 (169–277)	0.037
Any predisposing condition[d]	36/49 (73%)	46/87 (53%)	0.018
Previous MRSA episode	2/49 (4%)	5/85 (6%)	0.652
Previous hospitalization in last year	17/48 (35%)	19/83 (23%)	0.122
Previous dialysis	2/48 (4%)	5/82 (6%)	0.638
Previous CVC in situ	14/50 (28%)	6/83 (7%)	0.001
Previous long-term facility resident	3/50 (6%)	3/85 (4%)	0.501
Crowded facility	3/48 (6%)	2/84 (2%)	0.263
Treatment			
Antibiotic usage in previous 24 h	17/49 (35%)	24/83 (29%)	0.488
Antibiotic usage in previous 2 months	16/45 (36%)	10/79 (13%)	0.003
Antibiotic use during this admission	47/51 (92%)	74/89 (83%)	0.134
Severity of illness			
Hospital-acquired infection[e]	27/38 (71%)	34/75 (45%)	0.028
Hospital-associated community-onset[f]	2/38 (5%)	4/75 (5%)	
Community-acquired[g]	9/38 (24%)	37/75 (49%)	
Case-fatality rate	24/51 (47%)	22/89 (25%)	0.005
Acute severe illness[h]	1/27 (4%)	3/39 (8%)	0.504
Length of hospital stay, days, median (IQR)	38 (14–64)	19 (7–33)	0.037
Length of hospital stay before positive specimen collection, days, median (IQR)	13 (2–27)	1 (0–12)	<0.001

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; IQR, interquartile range; CVC, central catheter venous catheter.

[a] Due to missing data, the total number of cases for certain variables differs from N = 240 (for age and sex) or N = 140 (other variables obtained from case report forms). Data are expressed as frequencies unless a range is specified. The percentages for all of the data are calculated using the total number of cases unless indicated otherwise. Totals for continuous variables: age (MRSA 85, MSSA 152), CD4 count (MRSA 5, MSSA 10) in HIV-infected individuals, length of hospital stay (MRSA 38, MSSA 74).

[b] A p-value of <0.05 was considered significant.

[c] The site of infection was not specified.

[d] Predisposing conditions included chronic lung and renal disease, diabetes mellitus, malignancy, decubitus ulcer, prematurity, smoking, dementia, cardiac disease, cerebrovascular disease, previous surgery, immunosuppressive conditions such as organ transplant, immunosuppressive therapy, and aplastic anaemia.

[e] Hospital-acquired infection was defined as a positive blood culture collected ≥3 days after admission.

[f] Hospital-associated community-onset (HACO) infection was defined as a positive blood culture collected <3 days after admission in a patient admitted <90 days before and/or a resident in a long-term or chronic care facility and/or a patient who had received haemodialysis.

[g] Community-onset infection was defined as a positive blood culture collected <3 days after admission, not falling into the HACO category.

[h] Acute severe illness: Pitt bacteraemia score >4.

and MSSA cases, respectively. The male to female ratio was slightly higher among all cases of SAB.

The overall HIV prevalence was 32%: 42% among MRSA cases compared to 27% among MSSA cases ($p = 0.106$). HIV status was unknown for 39 cases, of whom 46% had an MRSA infection. Only 15 HIV-infected cases had a CD4 cell count available. Antiretroviral treatment information was available for 29 of the 32 HIV-infected SAB cases. Among HIV-infected MRSA and MSSA cases, there was no difference in the proportion on antiretroviral treatment (67%, 8/12 and 65%, 11/17, respectively).

Sixty percent of all cases had one or more predisposing conditions, of which surgery prior to specimen collection was the most common in both MRSA and MSSA cases. Five cases diagnosed with MSSA infection had a history of previous MRSA infection. The presence of a central venous catheter (CVC) was strongly associated with the length of hospital stay before a positive specimen was collected ($p < 0.001$). Patients who did not have a CVC in situ had a median length of stay before positive specimen collection of 2 days (IQR 0–14) compared to 34 days (IQR12–63) for patients who had an indwelling CVC. Compared to MSSA cases, MRSA cases had a longer hospital stay before positive specimen collection irrespective of the presence or absence of an indwelling CVC (MRSA: CVC in situ, median 57 days (IQR 12–63), no CVC, median 13 days (IQR 0–21); MSSA: CVC in situ, 26 days (IQR 16–54), no CVC, 1 day (IQR 0–9)).

In more than half of MRSA (53%) and MSSA (57%) cases, bacteraemia with no focus was diagnosed. Only six cases were defined with hospital-associated community-onset SAB. Five cases were previously hospitalized <90 days before the SAB episode, of whom two had also received haemodialysis, and one case had received only haemodialysis. Very few cases had severe illness (Pitt bacteraemia score >4). There was no difference in severity of illness between MRSA and MSSA cases.

The following variables had >10% missing information: HIV status (28%), length of hospital stay (20%), severity of illness (53%), antibiotic use in the previous 2 months (11%), and hospital-acquired infection (19%).

3.2. Antimicrobial susceptibility

Among *S. aureus* isolates, 36% were oxacillin non-susceptible (86/240). Non-susceptibility to daptomycin and linezolid was not detected in these isolates (Figure 1). Four isolates were vancomycin and teicoplanin non-susceptible (MIC ≥16 μg/ml). Thirteen cases (6%) had vancomycin at the susceptible breakpoint value MIC 2 μg/ml (five isolates were MRSA and eight isolates MSSA). MRSA isolates were more likely to be non-susceptible to other antibiotic classes compared to MSSA isolates (Table 2).

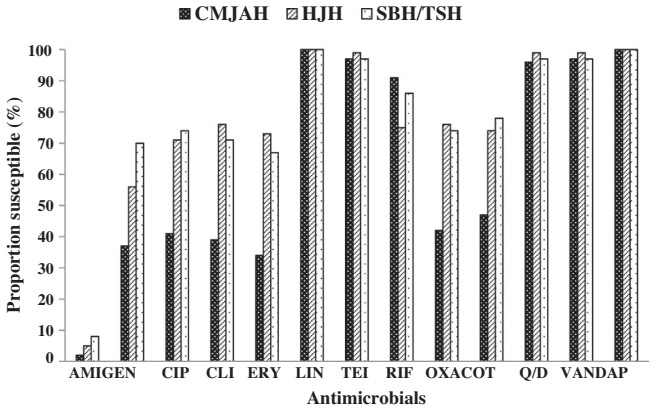

Figure 1. Antimicrobial susceptibility by hospital, September 2012 to September 2013.
CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; HJH, Helen Joseph Hospital; SBAH/TSH, Steve Biko Academic and Tshwane District Hospitals; AMI, amikacin; GEN, gentamicin; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; LIN, linezolid; TEI, teicoplanin; RIF, rifampin; OXA, oxacillin; COT, co-trimoxazole; Q/D, quinupristin/dalfopristin; VAN, vancomycin; DAP, daptomycin.

3.3. Molecular data

SCC*mec* typing was performed on 82 isolates of which nine were non-typeable. Among the MRSA isolates, the most common SCC*mec* type was III at 56% (45/73), followed by SCC*mec* type IV at 29% (23/73). Only four isolates were SCC*mec* type II and no SCC*mec* type I isolates were found.

3.4. Antimicrobial treatment

Eighty-six percent (121/140) of patients with SAB received one or more antimicrobial agents (Table 1). Ninety-five cases received empirical treatment and 42 cases received directed treatment. A greater proportion of MSSA cases (95%, 55/58) received appropriate empirical therapy compared to MRSA cases (57%, 21/37) ($p < 0.001$). All MSSA cases (25/25) and 59% (10/17) of MRSA cases received appropriate directed therapy ($p < 0.001$). Vancomycin was given as empirical treatment in 31% (29/95) of patients with SAB and 49% (18/37) of patients with MRSA. A greater proportion of MRSA cases who did not receive vancomycin died (61%, 14/23) compared to MRSA cases who received vancomycin (38%, 9/24) ($p = 0.018$). Among MRSA cases who did not receive vancomycin ($n = 23$), only three cases received an appropriate antimicrobial agent. Vancomycin was started as directed treatment in 55% (11/20) of MSSA cases; four cases only received vancomycin, one case received concomitant antimicrobial agents (amikacin and meropenem) to which the organism was not susceptible, and six received concomitant antimicrobial agents to which the organism was susceptible.

3.5. Factors associated with MRSA cases compared to MSSA cases

All the variables that were most strongly associated with MRSA infection ($p < 0.2$) in the univariate analysis are presented in Table 3. Age was kept in the multivariable model as a possible confounder. The multivariable analysis showed that length of stay before specimen collection, previous hospitalization in the last year, antibiotic use in the previous 2 months, and HIV infection were significant predictors of the acquisition of MRSA infection (Table 3). HIV infection and length of stay before specimen collection ($p = 0.389$), HIV infection and previous hospitalization

Table 2
Antimicrobial resistance among cases with MRSA and MSSA bacteraemia[a]

Antimicrobial agent	MRSA *n*/*N* (%)	MSSA *n*/*N* (%)	*p*-Value
Amikacin	53/53 (100%)	93/101 (92%)	0.035
Gentamicin	77/86 (90%)	33/154 (21%)	<0.001
Ciprofloxacin	78/86 (91%)	13/154 (8%)	<0.001
Clindamycin	80/86 (93%)	10/154 (6%)	<0.001
Erythromycin	81/86 (94%)	19/154 (12%)	<0.001
Trimethoprim/sulfamethoxazole	66/86 (77%)	15/154 (10%)	<0.001
Linezolid	0/81 (0%)	0/154 (0%)	N/A
Teicoplanin	5/86 (6%)	0/154 (0%)	0.002
Rifampin	30/86 (35%)	9/154 (6%)	<0.001
Quinupristin/dalfopristin	6/86 (7%)	0/154 (1%)	0.001
Vancomycin	4/86 (5%)	0/154 (0%)	0.002
Daptomycin	0/81 (0%)	0/154 (0%)	N/A

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; N/A, Not applicable.
[a] Cases with intermediate resistance according to Clinical and Laboratory Standards Institute guidelines were reported as resistant.

Table 3
Univariate and multivariable analysis of factors associated with MRSA compared to MSSA

Characteristics	Univariate analysis[a]		Multivariable analysis[b]	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Length of hospital stay before positive specimen collection, days	1.04 (1.02–1.07)	0.001	1.08 (1.02–1.13)	0.004
Previous CVC in situ (yes vs. no)	4.99 (1.77–14.05)	0.002		
Antibiotic usage in previous 2 months (yes vs. no)	3.80 (1.55–9.38)	0.004	0.1 (0.01–0.68)	0.022
Hospital-acquired infection[c] (vs. community-onset)	3.14 (1.33–7.43)	0.009		
Any predisposing condition[d] (yes vs. no)	2.47 (1.15–5.28)	0.020		
HIV-infected (yes vs. no)	1.97 (0.77–5.04)	0.158	4.89 (1.05–22.90)	0.044
Previous hospitalization in the last year	1.85 (0.84–4.04)	0.124	15.74 (2.49–99.48)	0.003

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; OR, odds ratio; CI, confidence interval; CVC, central venous catheter.
[a] Only the variables that had a *p*-value of <0.2 in the univariate analysis are shown in the table.
[b] A *p*-value of <0.05 is significant in the multivariable analysis.
[c] Hospital-associated infection was defined as a positive blood culture ≥3 days after admission.
[d] Predisposing conditions included chronic lung and renal disease, diabetes mellitus, malignancy, decubitus ulcer, prematurity, smoking, dementia, cardiac disease, cerebrovascular disease, previous surgery, immunosuppressive conditions such as organ transplant, immunosuppressive therapy, and aplastic anaemia.

($p = 0.164$), HIV infection and antibiotic use in the previous 2 months ($p = 0.944$), and age and HIV infection ($p = 0.552$) were included as possible interaction terms in the model, but none was significant.

3.6. Factors associated with mortality in SAB cases

The factors associated with outcome are shown in Table 4. In the unadjusted model, MRSA bacteraemia was significantly associated with mortality (OR 2.8 95% CI 1.36–5.83, $p = 0.005$) but did not remain significant in the adjusted model (OR 3.7 95% CI 0.50–27.6, $p = 0.197$). The factors that were adjusted for were age, having any predisposing conditions, length of hospital stay before specimen collection, time to start of antibiotic treatment, appropriate empirical therapy, HIV infection, and having a CVC inserted previously. The only factor that was a significant predictor of mortality was older age, and in particular age 25–44 years (OR 22.2, 95% CI 2.7–185.5, $p = 0.004$).

Table 4
Factors associated with outcome among cases with *Staphylococcus aureus* bacteraemia[a]

Characteristic	Died ($n = 47$), *n* (%)	Survived ($n = 94$), *n* (%)	*p*-Value
Age, years			
<5	7 (15%)	43 (46%)	<0.001
5–24	2 (4%)	14 (15%)	
25–44	21 (45%)	17 (18%)	
45–64	13 (28%)	17 (18%)	
≥65	4 (9%)	3 (3%)	
Sex			
Male	26/46 (57%)	48/86 (56%)	0.938
Female	20/46 (43%)	38/86 (44%)	
Methicillin-resistant infection			
Yes	25 (53%)	27 (29%)	0.005
No	22 (47%)	67 (71%)	
HIV-infected			
Yes	16/35 (46%)	16/66 (24%)	0.027
No	19/35 (54%)	50/66 (76%)	
Empirical therapy received			
Appropriate[b]	25/34 (74%)	51/61 (84%)	0.239
Inappropriate[c]	9/34 (26%)	10/61 (16%)	
Any predisposing condition[d]			
Yes	33/43 (77%)	49/93 (52%)	0.008
No	10/43 (23%)	44/93 (47%)	
Time to antibiotic start, days, median (IQR)	1 (−6 to 1)	1 (−1 to 1)	0.254
Length of hospital stay before positive specimen collection, days, median (IQR)	6 (0–20)	4 (0–14)	0.301
Length of hospital stay, days, median (IQR)	18 (7–30)	27 (10–46)	0.102
Previous CVC in situ			
Yes	6/44 (14%)	14/89 (16%)	0.751
No	38/44 (86%)	75/89 (84%)	
Origin of infection			
Hospital-acquired infection[e]	21/33 (64%)	40/74 (54%)	0.355
Community-onset infection[f]	12/33 (36%)	34/74 (46%)	

IQR, interquartile range; CVC, central venous catheter.
[a] Due to missing data, the total number of cases for certain variables differs from the total number of cases who died or survived. Data are expressed as frequencies unless a range is specified. The percentages for all of the data are calculated using the total number of cases unless indicated otherwise.
[b] Appropriate empirical therapy: Antimicrobial agents that were started before or within 3 days of specimen collection of which one or more were effective against the organism.
[c] Inappropriate empirical therapy: Antimicrobial agents that were started before or within 3 days of specimen collection of which all were ineffective against the organism, or no treatment was received.
[d] Predisposing conditions included chronic lung and renal disease, diabetes mellitus, malignancy, decubitus ulcer, prematurity, smoking, dementia, cardiac disease, cerebrovascular disease, previous surgery, immunosuppressive conditions such as organ transplant, immunosuppressive therapy, and aplastic anaemia.
[e] Hospital-acquired infection was defined as a positive blood culture collected ≥3 days after admission.
[f] Community-onset infection was defined as a positive blood culture collected <3 days after admission.

4. Discussion

To our knowledge this is the first study in South Africa that has prospectively collected detailed clinical information on patients with SAB at multiple sites. MRSA and MSSA infection was most common in the <5 years age group. Forty-nine percent of patients with MRSA did not receive vancomycin. We also showed that HIV infection, among other factors, was a risk factor for MRSA infection. Age was the only predictor of mortality in cases with SAB when controlled for other factors.

SAB incidence is hospital-specific. A study conducted in Australia from 1999 to 2002 in 17 hospitals showed that SAB incidence varied from 0.6 to 3.24 cases per 1000 admissions, depending on the type of hospital.[21] Similarly MRSA bacteraemia rates varied from 0 to 0.89 cases per 1000 admissions between hospitals. Our study showed that SAB and MRSA incidence varied from 1.9 to 3.7 cases per 1000 admissions and 0.03 to 0.08 cases per 1000 admissions, respectively.

The proportion of patients with MRSA infection varies by country. High MRSA rates of 52.4%, 48.4%, and 48.2% have been reported from Malta, Portugal, and Cyprus.[22] Very low MRSA prevalence is found in Scandinavian countries, varying from 0% in Iceland to 0.8% in Denmark. Our MRSA prevalence of 36% is comparable to Ireland (38.1%), the UK (35.6%), and Israel (33.5%). Despite the MRSA prevalence in our study being an underestimation, susceptibility testing was done only on viable isolates sent to the reference laboratory; the MRSA prevalence was found to be higher than in a previous study conducted in two Gauteng hospitals in South Africa from November 1999 to October 2002, which showed an MRSA bacteraemia prevalence of 23%.[8] Perovic et al. only looked at adults, while our study focused on all ages. The difference in MRSA prevalence among countries could be due to differences in the types of hospitals involved in surveillance, clinical co-morbidities of patients, infection control practices, and medical practices. In South Africa, it is likely that the incidence of MRSA bacteraemia is increasing in comparison with previous South African publications, but a more in-depth trend analysis is required to verify this.[8]

Risk factors for the acquisition of MRSA infection vary between different studies depending on the study population. In studies that have looked at cases of nosocomial SAB, previous hospitalization, length of stay before positive blood culture, surgery, enteral feeding, the use of intravascular catheters, and age have been found to be independent risk factors for MRSA infection.[23–26] A study that looked at cases with SAB only found previous MRSA infection or colonization to be a risk factor for MRSA infection.[27] We showed similar risk factors for MRSA infection, with previous hospitalization in the last year as the strongest predictor of MRSA infection. In addition, our study showed that cases with HIV infection had almost 5-times higher odds of developing an MRSA infection compared to HIV-uninfected cases. HIV-infected patients have a higher risk of MRSA colonization compared to HIV-uninfected individuals (OR 3.3, 95% CI 1.3–14.7),[28] which could contribute to their higher odds of developing MRSA bacteraemia. Among HIV-infected cases, a low CD4 cell count can increase the risk of MRSA infection.[29] We showed that among HIV-infected cases, the median CD4 cell count was significantly lower in cases with MRSA compared to cases with MSSA. Other factors that could increase the risk of MRSA in HIV-infected individuals are nosocomial infection, prior antibiotic use, previous MRSA infection, and previous hospitalization.[29,30] Earlier initiation of antiretroviral therapy is important to prevent poor immune status and to decrease the risk of MRSA infection.[29]

Compared to cases with MSSA infection, cases with MRSA infection had a higher mortality rate. Reasons for a worse outcome with MRSA could be due to SCC*mec*-associated virulence factors.[31] In addition, 49% of cases with MRSA were not treated with vancomycin, of whom 62% died. Also, vancomycin is known to be less effective in clearing the pathogen due to poor tissue penetration and slower bactericidal activity, which is unrelated to vancomycin MICs in the high susceptible range.[32] Four MRSA isolates had a vancomycin MIC of ≥16 μg/ml. However, reports have shown that infection with heteroresistant vancomycin-intermediate *S. aureus* (hVISA) is not associated with increased mortality.[33]

MRSA infection was not a significant predictor of death after we controlled for possible confounders. There is conflicting evidence regarding whether MRSA infection is a predictor of mortality. Cosgrove et al. found that mortality was higher in patients with MRSA than with MSSA (OR 1.93, 95% CI 1.54–2.42, $p < 0.001$), which remained significant after controlling for potential confounders such as age and severity of illness (OR 1.88, 95% CI 1.33–2.69, $p < 0.001$).[12] Other studies did not find a higher mortality in cases with MRSA infection compared to MSSA cases.[23,24,27,34] Older age was the only predictor of mortality among cases with SAB. Interestingly, only the 25–44 years age group had a significantly higher odds of dying compared to the <5 years age group. Previous reports have shown age to be a significant predictor of mortality in cases with SAB, especially age >65 years, or with every 10-year increase in age.[35,36] Our study had only seven cases aged ≥65 years, which could explain why, in the multivariable model, this age group was not a significant predictor of mortality. Even though we accounted for HIV infection in the multivariable model, the 25–44 years age group remained a significant predictor of mortality, probably because a large proportion (28%) of cases had an unknown HIV status. HIV infected individuals in our study had a worse outcome compared to HIV-uninfected individuals, regardless of oxacillin susceptibility: 50% (16/32) and 28% (19/69) died, respectively ($p = 0.027$).

MRSA isolates were more likely to be resistant to other antimicrobial classes compared to MSSA isolates. This limits the antimicrobial choices when patients are treated empirically. Our study looked at antimicrobial resistance patterns over a 13-month period only, and we were unable to look at changes over time. A study conducted by Marais et al. from August 2005 to November 2006 included 15 public and eight private hospitals across South Africa and analysed antimicrobial resistance in MRSA isolates.[17] In comparison to this study, we found a higher prevalence of non-susceptibility among MRSA isolates from only public sector laboratories to amikacin (29% vs. 100%), gentamicin (86% vs. 90%), erythromycin (71% vs. 94%), clindamycin (17% vs. 93%) and trimethoprim/sulfamethoxazole (71% vs. 77%). Only rifampin resistance was lower in our study (53% vs. 35%). No vancomycin, teicoplanin, or quinupristin/dalfopristin-resistant MRSA isolates were found by Marais et al., whereas the prevalence of non-susceptibility was 5–7% for these three antibiotics in our study. Differences in antimicrobial non-susceptibility could be attributed to the fact that our study included only four hospitals in Gauteng Province, while that of Marais et al. included sites across all nine provinces of South Africa. In addition, all of our MRSA isolates were from blood cultures, whereas only 35.5% of isolates in the study by Marais et al. were from blood.

Thirty-two percent of MRSA isolates had SCC*mec* type IV, which is linked to community-associated infection. Sixty-nine percent of SCC*mec* type IV MRSA isolates were obtained from blood cultures collected ≥3 days after admission, which suggests that community-associated MRSA strains are being transmitted in hospitals. Similarly, a study from Switzerland found that 87% of hospital-associated MRSA cases carried SCC*mec* type IV.[37] It is important to monitor community-associated MRSA because of greater toxin production and tissue necrosis, which can cause higher mortality rates compared to hospital-associated MRSA.[38,39]

The limitations of our study were that very few HIV-infected cases had a documented CD4 count, hence we could not control for it in the multivariable analysis. More than 10% of information was missing for HIV status, length of hospital stay, severity of illness, and origin of infection, but the proportion was similar between MRSA and MSSA cases ($p > 0.05$). Variable blood culture-taking practices could underestimate the true burden of SAB. More than 50% of isolates from one hospital were not viable and susceptibility testing could not be performed. A long hospital stay, a long lag period in sending CRFs to the reference laboratory, and missing hospital folders could have contributed to a large proportion of cases without CRF information. Molecular information was only available for a few isolates. The strength of the study is that detailed clinical information was collected, particularly on antibiotic usage, predisposing conditions, HIV status, and previous hospitalizations among cases with SAB.

In conclusion, HIV infection was a significant predictor of MRSA infection. Being aged 25–44 years was significantly associated with mortality among cases with SAB. MRSA cases were infected with isolates that were non-susceptible to multiple antibiotics. As a public health measure, antimicrobial susceptibility surveillance and antibiotic prescription practices should be monitored. Knowledge of local epidemiology as well as factors predictive of MRSA infection will assist in guiding the use of appropriate empirical treatment.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.10.011.

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