# *Staphylococcus aureus* bacteraemia at two academic hospitals in Johannesburg

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*Objectives and methods. Staphylococcus aureus* bacteraemia (SAB) remains a major problem worldwide. A retrospective study of patients with SAB seen from November 1999 to October 2002 was conducted at two academic hospitals in Johannesburg to determine mortality rates (death within 14 days of submission of blood culture) in patients bacteraemic with methicillin-sensitive (MSSA) and resistant *S. aureus* (MRSA) and to identify risk factors associated with mortality.

*Results*. Of 449 patients with SAB, 104 (23.2%) died within 14 days of clinically suspected SAB. Of the 204 patients who acquired SAB in hospital, 6 patients died within 2 days, 39 between 2 and 14 days, and 41 more than 14 days after onset of SAB. One hundred and five patients (23.4%) had MRSA bacteraemia, 21 (20%) originating from the community. The MRSA bacteraemia rate among patients with hospital-acquired infection was 41.1%, significantly higher ($p < 0.0001$) than the 10.3% community-acquired MRSA bacteraemia.

Thirty-five (33.3%) of the 105 patients with MRSA bacteraemia died within 14 days, compared with 69 (20.1%) of 344 MSSA patients ($p = 0.0048$).

Admission to the intensive care unit (ICU) was significantly associated with mortality ($p < 0.001$) – 30 of 79 patients admitted to ICU died (38%). Among 222 patients whose HIV status was known, 117 (52.7%) were positive, and of these 32 died (27.4%), a rate not significantly higher than that among HIV-seronegative patients (18 of 105 patients, $p = 0.69$).

*Conclusions*. Compared with MSSA, MRSA was shown to be significantly associated with mortality. Stay in ICU and infection with strains resistant to oxacillin, ofloxacin and rifampicin were highly significant predictors for mortality.

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*Staphylococcus aureus* bacteraemia (SAB) is a common disease and continues to be a major problem related to both community-acquired and nosocomial infections. The mortality associated with SAB is high, with estimated rates of 15 - 60%.[1-3] Meta-analyses by Cosgrove *et al*.[3] and Whitby *et al*.[4] comparing the mortality rate of methicillin-resistant *S. aureus* (MRSA) bacteraemia with methicillin-sensitive *S. aureus* (MSSA) bacteraemia found that MRSA bacteraemia is associated with an increased mortality. Other studies have shown no difference in the mortality between MSSA and MRSA bacteraemia.[1,5]

Community-acquired and nosocomial infections caused by resistant pathogens, including MRSA, are increasing.[6,7] Glycopeptide antibiotics have been the treatment of choice for serious infections caused by MRSA. Glycopeptide-resistant *S. aureus* (GISA) was described for the first time in 1997[8] and has been detected in South Africa.[9] Community-acquired MRSA isolates from children in Taiwan showed high prevalences of macrolide resistance, associated with widespread use of this class of antimicrobials.[10]

Some studies[3,11,12] have shown that inadequate antimicrobial therapy for bloodstream infections increases patient mortality. Patients with MRSA bacteraemia may not receive empirical vancomycin therapy, particularly in settings of low prevalence.[3] In addition to greater mortality rates, antibiotic resistance is associated with prolonged hospitalisation, which increases costs.[13]

The mortality rate and outcome associated with SAB in South Africa is unknown. Mortality studies may be useful in determining deficiencies in current medical practice.

We performed a retrospective record review to determine the mortality rate of SAB among patients admitted to two academic hospitals attached to the University of the Witwatersrand, Johannesburg. In addition we compared the mortality rates between MRSA and MSSA.

## Objectives

The objectives of this study were to determine the number of patients presenting with SAB, to determine the proportion of MRSA versus MSSA infections, to determine the mortality rate

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of patients with SAB, to compare the mortality rate of MRSA versus MSSA SAB, and to identify risk factors associated with mortality.

## Methods

### Setting

This study was conducted at two academic hospitals, namely Johannesburg Hospital (JH) and Chris Hani Baragwanath Hospital (CHBH), with 1 180 and 3 000 beds respectively, in the greater metropolitan area of Johannesburg. These hospitals provide primary to tertiary care to patients in Johannesburg and surrounding areas. Both hospitals have trauma, burns, renal and intensive care units as well as trauma, surgical, medical, coronary and general wards.

### Study population

A computer search was used to identify adult patients who had blood culture-confirmed bacteraemia with *S. aureus* during the period November 1999 to October 2002 at the two academic hospitals.

### Design

This study was a retrospective analysis of patient records with SAB. Data were recorded onto a specially designed study recording form. Data were collected on demographics, diagnosis, underlying diseases, complications, clinical and laboratory assessment of the patients at onset of SAB, antibiotic treatment used to treat SAB and outcome.

Outcome was recorded as dead or alive. Death was attributed to staphylococcal infection if a patient died within 14 days of submitting a blood specimen that grew *S. aureus*. As the study was a retrospective record review, to avoid bias no attempt was made to determine if death was directly attributable to SAB.

### Definitions

A patient was considered to have SAB if one or more blood cultures were positive for *S. aureus* in association with clinical and/or laboratory evidence of infection. In the absence of these findings the organism was considered to be not significant and excluded from analysis.

When a blood culture taken within the first 72 hours of admission yielded *S. aureus*, it was considered to denote a community-acquired infection. Positive blood cultures taken after 72 hours from day of admission were considered to provide evidence of nosocomial-acquired bacteraemia.

### Microbiological methods

Blood samples were processed using the BacT/Alert system (Organon Teknika, USA). Two sets of aerobic and anaerobic bottles were inoculated with 5 - 10 ml of blood and submitted to the laboratory. Isolation and identification of *S. aureus* was performed using standard laboratory procedures. Sensitivity patterns of isolates were determined by the disk-diffusion method according to the Clinical Laboratory Standards Institute (CLSI) guidelines.[14]

### Statistical analysis

Patient information was entered into Microsoft Access. Statistical analysis was performed using Stata. Mann-Whitney U-tests were used to test for differences between groups, and logistical regression was used to assess association with risk factors. A $p$-value of $< 0.05$ was considered to be statistically significant.

## Results

From November 1999 to October 2002, 501 patients with SAB were identified from the two academic hospitals, and 449 patients were included for analysis (Fig. 1). A total of 52 patients were excluded because patient data were inadequate or isolates were considered not clinically significant. Of the patients included in the study, a total of 173 (38.5%) died (crude mortality rate); 104 (23.2%) patients died within 14 days, and of these, 21 died within 48 hours of admission, and 83 during the 3 - 14-day period. Sixty-nine patients died on the 15th day, or later.

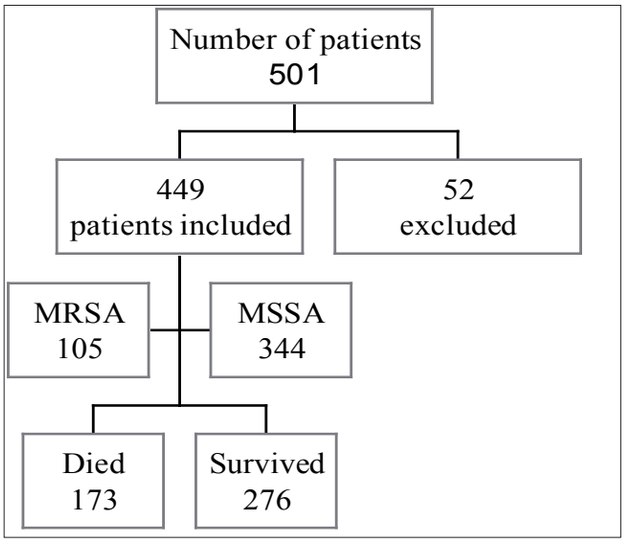


*Fig. 1. Inclusion and mortality of* S. aureus *bacteraemia cases.*

Demographic and clinical characteristics are listed in Table I. The mean age was 41.6 years. The most common predisposing factor was surgery (139/449). HIV seropositive status was detected in 117 of 222 patients tested. Other risk factors in order of frequency were malignancy, diabetes, and burns. The mean albumin level was low at 25.5 g/l. Community-acquired SAB was identified in 204 patients, including 21 with MRSA. A total of 105 patients were identified with MRSA bacteraemia.

Table II characterises the influence of predisposing conditions on 14-day mortality. Of 449 patients, 104 (23.1%) died. The median age of patients who died was 41 years. Thirty-two of



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**Table I. Epidemiological features of patients with SAB**

| Characteristics | Cases (total number) | SD/% |
|---|---|---|
| Mean age (yrs) | 41.6 (437) | 15.8 |
| Male sex | 282 (449) | 63% |
| Underlying conditions | | |
| HIV seropositive | 117 (222)* | 53% |
| Burns | 19 (449) | 4.2% |
| Diabetes | 26 (449) | 5.8% |
| Malignancy | 26 (449) | 5.8% |
| CRF | 4 (449) | 0.9% |
| Other (CVA, renal, liver) | 9 (449) | 2% |
| Laboratory findings | | |
| Mean albumin | 25.5 (222) | 10.6 |
| Mean albumin in female | 26.9 (81) | 13.9 |
| Mean albumin in male | 24.8 (141) | 8.2 |
| Predisposing factors | | |
| Surgery | 139 (449) | 31% |
| Antibiotics at admission | 51 (449) | 11% |
| Previous admission | 91 (449) | 20% |
| MRSA | 105 (449) | 23% |
| Acquisition of infection | | |
| Community acquired | 204 (449) | 45% |

*Patients with known HIV serostatus.
SD = standard deviation.

117 (27.4%) HIV-seropositive patients died as opposed to 18 of 105 (17.1%) seronegative patients ($p = 0.069$). Significant risk factors that contributed to mortality were ICU admission, reflecting more severe disease ($p = 0.0006$), organ dysfunction ($p < 0.0001$), pyogenic complications ($p < 0.00003$), oxacillin resistance ($p = 0.004$), ofloxacin resistance ($p = 0.004$) and rifampicin resistance ($p = 0.0058$).

Comparison of clinical, laboratory and predisposing factors between patients with MRSA and MSSA is presented in Table III.

## Discussion

The SAB mortality rate of 23.1% found in this study is comparable to mortality rates recorded in other studies.[3,4,15] Our study also reaffirms evidence from other reports that MRSA is associated with a higher mortality rate (33.7%) than MSSA (20.3%) ($p = 0.0048$).[3,16]

The rate of community-acquired MRSA SAB in the present study was 20% (no genotypical investigation was performed to demonstrate the possibility of clonal transmission of MRSA in the hospital or in the community). Clinicians working in settings where the prevalence of community-acquired MRSA is known to be high need to be aware that the use of empirical β-lactam antibiotics for suspected *S. aureus* infection may not always be appropriate, especially in critically ill patients.[16] Owing to the established efficacy of glycopeptide antibiotics in treating serious MRSA infections, these agents are the mainstay of treatment in such cases. Newer antimicrobial agents effective in treating MRSA are becoming available, and are alternatives for treating serious MRSA infections. Prudent and appropriate use is advised to avoid the development of resistance.

Unlike other studies[15] older age was not found to be associated with SAB mortality. The median age of patients enrolled in this study was low at 41 years. This may be attributed to the devastating effects of the HIV pandemic South Africa is currently experiencing where most infected patients are young.[17] More than 50% of the 222 patients tested in the present study were seropositive, and the mortality rate

**Table II. Risk factors for SAB 14-day mortality**

| Characteristics | Died 0 - 14 days (*N* (%)) | Survived > 14 days (*N* (%)) | OR (95% CI) | *p*-value |
|---|---|---|---|---|
| Mortality outcome | 104/449 (23.1) | 345/449 (76.8) | NA | NA |
| Median age (yrs) | 41 | 38 | 1.01 (0.99 - 1.02) | 0.419 |
| Males | 67/104 (64.4) | 215/345 (62.3) | 1.09 (0.69 - 1.73) | 0.697 |
| HIV-seropositive | 32/50 (64) | 85/172 (49.4) | 1.82 (0.95 - 3.49) | 0.071 |
| Central line | 29/104 (27.9) | 80/345 (23.2) | 1.28 (0.78 - 2.10) | 0.328 |
| ICU admission | 30/104 (28.8) | 49/345 (14.2) | 2.45 (1.45 - 4.12) | < 0.001 |
| Inatrope support | 30/104 (28.8) | 33/345 (9.6) | 3.83 (2.20 - 6.68) | < 0.001 |
| Intubations | 37/104 (35.6) | 60/345 (17.4) | 2.62 (1.61 - 4.28) | < 0.001 |
| Intravenous catheter | 94/104 (90.4) | 288/345 (83.5) | 1.86 (0.91 - 3.79) | 0.087 |
| Nosocomial | 45/104 (43.3) | 159/345 (46.1) | 0.89 (0.57 - 1.39) | 0.6139 |
| Organ dysfunction | 17/104 (16.3) | 11/345 (3.2) | 5.93 (2.68 - 13.13) | < 0.001 |
| Peritoneal dialysis | 0/89 (0) | 11/345 (3.2) | - | 0.0653 |
| Renal failure | 33/104 (31.7) | 80/345 (23.1) | 1.54 (0.95 - 2.49) | 0.080 |
| Pyogenic complications | 14/104 (13.5) | 13/345 (3.8) | 3.97 (1.80 - 8.75) | < 0.001 |
| Surgery | 35/104 (33.7) | 104/345 (30.1) | 1.18 (0.74 - 1.88) | 0.498 |
| Erythromycin resistance | 40/96 (41.7) | 84/290 (29.0) | 1.75 (1.09 - 2.83) | 0.022 |
| Oxacillin resistance | 35/104 (33.7) | 70/345 (20.3) | 1.99 (1.23 - 3.23) | 0.005 |
| Rifampicin resistance | 24/85 (28.3) | 39/261 (14.9) | 2.24 (1.25 - 4.01) | 0.007 |
| Ofloxacin resistance | 17/78 (21.8) | 31/246 (12.6) | 1.93 (1.003 - 3.73) | 0.049 |

OR = odds ratio; NA = not applicable.



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**Table III. Comparison of clinical features between patients with MRSA and MSSA**

| Features | Number of sensitive/ resistant | MRSA | | MSSA | | *p*-value |
|---|---|---|---|---|---|---|
| | | Mean | SD/% | Mean | SD/% | |
| Laboratory | | | | | | |
| WCC (x $10^9$/l) | 322/100 | 16.6 | 25.5 | 12.4 | 11.5 | 0.1542 |
| Haemoglobin (g/dl) | 342/105 | 9.4 | 8.0 | 9.4 | 3.6 | 0.0292 |
| Platelets (x $10^9$/l) | 321/99 | 262.9 | 188.6 | 234.8 | 136.8 | 0.5144 |
| ESR (mm 1st h) | 66/20 | 64.0 | 36.4 | 63.8 | 39.0 | 0.8700 |
| CRP (mg/l) | 60/21 | 148.7 | 94.0 | 141.4 | 112.4 | 0.6392 |
| Albumin (g/l) | 154/68 | 21.5 | 8.2 | 27.3 | 11.1 | <0.0001 |
| CD4 (cells/$mm^3$) | 48/13 | 267.7 | 355.3 | 157.8 | 244.9 | 0.2016 |
| Clinical | | | | | | |
| Fever | 284/69 | 38.0 | 1.1 | 38.1 | 1.1 | 0.1978 |
| Pulse rate/min | 275/72 | 104.4 | 23.3 | 100.5 | 21.0 | 0.23503 |
| Respiratory rate/min | 210/51 | 23.4 | 6.56 | 23.1 | 6.9 | 0.5528 |

WCC = white cell count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SD = standard deviation.

among HIV-infected patients was higher (37.4%) than among seronegative patients (17.1%), but not significantly so ($p$ = 0.069).

Several studies[2,3] identified risk factors for mortality among SAB patients, such as older age, SAB caused by MRSA, presence of shock, inadequate treatment and underlying disease status. This study defined slightly different risk factors for 14-day mortality, namely ICU admission ($p$ = 0.0006), inatrope support ($p$ = 0.00014), intubations ($p$ = 0.0001), organ dysfunction ($p$ < 0.0001), pyogenic complications ($p$ = 0.0003) (Table II), MRSA ($p$ = 0.0048), quinolone resistance ($p$ = 0.046) and rifampicin resistance ($p$ = 0.0058).

When comparing this study with other mortality studies it is important to note that we defined SAB mortality as death within 14 days of a positive blood being taken. In the present study no scoring system was used to define severity of illness.

## Conclusion

In this study the overall mortality rate for SAB was 23.2%, and for MRSA 33.3%. This is cause for concern and wherever possible efforts should be made to prevent SAB, including appropriate treatment of *S. aureus* infections, eradication of *S. aureus* colonisation before invasive procedures, and appropriate infection control measures in people infected with *S. aureus*, particularly MRSA. Primary treatment regimens should still be with cloxacillin, but in patients at risk for MRSA vancomycin should be considered. Newer antimicrobials available to treat MRSA include linezolid, quinupristin/dalfopristin and daptomycin. These agents should be used prudently as second-line therapy.

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