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**UNIVERSITY OF CAPE TOWN**

**Study Title**

Evaluation of adherence to an evidence-based bundle of care for the treatment of staphylococcus aureus bacteraemia at Groote Schuur Hospital

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**Funding**

None

**Declaration**

I, Elizabeth Marguerite Gatley, declare that this dissertation/ thesis is my own original work (except where acknowledgements indicate otherwise). It is being submitted for the degree of Masters of Medicine (MMed) in Medicine. Neither the whole work nor any part of it has been, or is being submitted for another degree in this or any other university. This work has not been reported or published prior to registration for the above-mentioned degree. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. Full ethics approval has been granted by the local ethics committee.

Signed _____

On this 1st (day) of March 2022

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**Evaluation of adherence to an evidence-based bundle of care for the treatment of staphylococcus aureus bacteraemia at Groote Schuur Hospital**

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**Abstract**

**Background**

*Staphylococcus aureus* bacteraemia (SAB) is associated with high hospital mortality. Improvements in outcome have been described with standardised bundles of care.

**Objectives**

To study adherence to a standardised bundle of care (BOC) recommendations using a consultation proforma, for all patients admitted with SAB to Groote Schuur hospital over a year. To describe in-hospital and 90-day mortality in these patients

**Methods**

A retrospective audit of all unsolicited infectious disease consultations for patients with SAB admitted to Groote Schuur hospital during 2018. Adherence to recommendations of a standard care bundle were audited.

**Results**

Eighty six patients were included; 61 (71%) with healthcare-associated infection and 25 (29%) with community associated infection. Over 80% of adherence to treatment recommendations was achieved regarding antibiotic (including vancomycin) usage, source control and use of echocardiography as required. In-hospital mortality was 16% while overall 90-day mortality was 18%, with only age an independent predictor of mortality. No association with adherence to the recommendations and outcome was seen.

**Conclusion**

Adherence to a simple BOC is good, when using standardised a proforma as a communication tool. SAB mortality may be reduced by such an approach.

**Keywords**

*Staphylococcus aureus* bacteraemia, blood stream infections, infectious disease consultation, bundle of care, adherence

## Background

*Staphylococcus aureus* bacteraemia (SAB) remains one of the most common causes of both community- and healthcare-associated blood stream infections (BSI) globally. It is associated with a significant burden of morbidity and mortality and an increased cost of treatment.[1-4] To improve outcomes in SAB, much emphasis has been placed on the benefit of infectious disease consultation (IDC), as well as on a bundle of care (BOC) package to guide treatment of SAB.[5-9]

In 2013 the Division of Infectious Diseases at Groote Schuur Hospital (GSH) started a process of reviewing all cases of SAB admitted to the hospital. Outcomes of the first 100 cases have been published, showing a high mortality of 47.0%. [10] That survey specifically identified non-optimal antibiotic usage and poor adherence to recommendations on source control as possible contributors to mortality. On 1 September 2015 the Division expanded their scope to provide unsolicited IDC on all cases of SAB using a newly created bundle of care. This bundle of care was drawn up by a panel of ID specialists at GSH and agreed upon in accordance with best practice guidelines described in a 2011 Lancet review [11] and a 2014 JAMA review on the management of SAB [12] and included an agreed-to standardised approach to treatment and a standardised proforma to improve communication regarding recommendations to the treating team (*Appendices 1&2*). The focus was to ensure adherence to key quality of care indicators (QCIs), including correct definitive antibiotic use with dose, dosing interval and length of treatment and in the case of vancomycin use, correct initial loading dose and use of therapeutic drug monitoring required to adjust dosing. Further QCIs included early source control, performance of 72 hours blood cultures and appropriate use of echocardiography in specific clinical scenarios.

In this study, we aimed to retrospectively evaluate adherence to the specific QCIs and review the impact on patient mortality.

## Methods

*Study setting and population*

The data for this study was collected from patients admitted to Groote Schuur Hospital which serves as a secondary level hospital for its local drainage area and a tertiary referral centre for the entire West of the Cape Town Metro.

*Recruitment and Enrolment*

We retrospectively analysed records of all patients with SAB seen by the ID Division in 2018, following implementation of the new, routine, bundle of care *(Appendix 1).* The care bundle consisted of the following: all blood cultures for admitted patients that are positive for *staphylococcus aureus* (*S aureus)* are routinely reported to clinicians in the Division of Infectious Diseases, who provided an unsolicited consultation to the treating team within 24 hours or the first day after a weekend. Suggestions for management of the patient were conveyed to the managing team via a proforma that was stapled into the patient's confidential file with clear recommendations, including the need for echocardiography, source control, recommendations with regards to antibiotic choice, dose, dosing interval and length of treatment. (*Appendix 2).* When relevant, this included a dedicated vancomycin prescription chart which provided information on vancomycin dosing and therapeutic drug monitoring *(Appendix 3).* All patients with SAB were seen weekly by the ID team, or more frequently if required, until discharge from hospital.

*Inclusion criteria*

Patients were included in the study if aged >18 years, and *S aureus* was isolated from one or more blood culture regardless of clinical signs of systemic infection.

*Exclusion criteria*

Patients in whom *S aureus* was isolated as part of a mixed growth of organisms were excluded, as were patients who died within 48 hours of admission and thus not subject to the intervention, and those in whom the therapeutic strategy was one of palliation rather than active intervention.

*Definitions*

Community associated SAB (CA-SAB) was defined as a blood culture positive for *S aureus* taken on or within 48 hours of admission. Hospital associated SAB (HA-SAB) was defined as a blood culture positive for *S aureus* taken after 48 hours following admission or in a patient with a positive blood culture within 48 hours of admission who had: 1) received intravenous antibiotics in the preceding 30 days; 2) attended hospital or received haemodialysis in the previous 30 days; or 3) a patient who resides in a long-term care facility. Death was considered SAB related if there were persistent signs and symptoms of bacteraemia or a persistently positive blood culture at the time of death. Optimal definitive antibiotics include correct dose, dosing interval and length of treatment and consisted of the following: methicillin-susceptible Staphylococcus aureus (MSSA) bacteraemia was treated with either Cefazolin or Cloxacillin depending on what was available in pharmacy and whether there was evidence of endocarditis, meningitis or osteomyelitis. Cefazolin 2g 8hourly or cloxacillin 2g 6hourly was considered acceptable treatment for MSSA bacteraemia unless the patient was deemed to have infective endocarditis or osteomyelitis. The recommendation for those patients was Cloxacillin 3g 6hourly. Those with meningitis were treated with Ceftriaxone 2g 12hrly. Methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia was treated with Vancomycin. Patients required

an initial loading dose of 25-35 mg/kg followed by 15-20mg/kg 12-hourly. Ongoing dosing was dependent on therapeutic drug monitoring. A Vancomycin dosing and monitoring chart was stapled into the patient's treatment chart. Length of treatment was based on local and international accepted guidelines. [13] Uncomplicated SAB was treated for 14 days. Complicated infection was defined as: 1) persistently positive blood culture >72 hours after initiating treatment with an appropriate definitive antibiotic; 2) infective endocarditis; or 3) evidence of metastatic infection eg. discitis or deep seated abscesses. These patients required treatment for >28 days. The 72 hour blood culture was considered correctly performed if it was taken within 48-96 hours following initiation of definitive antibiotics that the cultured organism was sensitive to.

*Data management*

All data were anonymously collected into a RedCap® database. Only members of the research team and ID Division had access to records to maintain patient confidentiality. All data management programmes used were password protected.

*Statistical analysis*

Data management and statistical analysis were conducted in SPSS Statistics version 27 (IBM, USA). Descriptive statistics were used to summarise patient data, namely frequency and percentage for categorical data and mean with standard deviation for continuous data. Kaplan-Meier estimates were used to generate cumulative risks and Cox proportional hazards models were used to determine the effect of the intervention on the outcome and to estimate HRs and 95% CIs. Variables included in the Cox-model were selected based on best evidence. For all statistical tests, a p-value of 0.05 was considered significant.

*Ethics approval*

This study was approved by the Human Research and Ethics Committee at the University of Cape Town (Ref 766/2018).

## Results

There were 119 SAB infections recorded that were subject to the bundle of care intervention during 2018 of which a total of 86 cases were included in this analysis. Cases were excluded for the following reasons: incomplete data, 17; age < 18, 3; multiple organisms on blood culture, 5; and palliative care only provided, 8.

*Patient and infection characteristics*

Baseline characteristics, stratified by place of acquisition of infection, are listed in **Table 1.** Overall, of the 86 patients 57 (66%) were male. The mean age was 46.1 ± 16.3 years. Patients had a wide range of comorbidities, the commonest being hypertension, diabetes mellitus, chronic kidney disease and underlying malignancy. Nine patients were HIV positive with 8 of those on ARV's; the median CD4 count in the was 400 cells/mcL (Range: 13 to 669).

Twenty-five patients (29%) were admitted with a CA-SAB and sixty-one (71%) with HA-SAB. All 25 cases of CA-SAB were MSSA. Of the HA-SAB, 11 (18%) were MRSA with 50 (82%) being MSSA. Of the HA-SAB episodes, 33 (54%) were due to line related infections: 'definite peripheral line sepsis' in 12 (20%), 'probable peripheral line sepsis' in 10 (16%), dialysis catheter related infections in 5 (8%) and other central line related infections in 6 (10%). Skin and soft tissue infection was the primary source of infection in 25 (29%) patients overall and were more common in patients with CA-SAB.

*Adherence to Quality of care indicators (QCIs)*

Adherence to the five QCIs indicators are listed in **Table 2**. Of the 86 patients treated, 100% overall adherence was only achieved in 45 of the cases (52%), and under 50% adherence seen in nineteen patients (22%). Adherence to the 5 separate QCIs comprising the SAB bundle of care showed adherence of greater than 80% in four out of the five QCIs, with the 72-hour blood culture performing worst having taken place at the correct time in only 56 (65%) of cases. Source control was required in 40 cases, of which it was correctly adhered to in 34 (85%). Echocardiography was recommended in 31 (36%) and was performed in 26 (83.8%). Of interest only 3 patients (9.6%) had evidence of infective endocarditis with vegetations visible on at least one valve. Thirteen cases were not adequately treated with antibiotics - 8 (62%) were based on too short a course of intravenous antibiotics while the remainder were deemed inadequate due to subtherapeutic vancomycin levels or incorrect dosing of alternate antibiotics. Of the 11 patients treated with vancomycin, 10 (90%) received a loading dose. Therapeutic drug monitoring with trough levels were performed at least once in all 11 patients but only noted to be therapeutic in 9 (81% n=11). Nine out of the eleven patients (81%) had both a loading dose and therapeutic vancomycin levels noted. While vancomycin use may be considered a subsection of antibiotic use it was analysed separately due to the extra nuance required in correct administration.

*Outcomes*

Overall inpatient mortality was 16% (14 patients). Of these deaths, 11 (78%) were attributable to SAB and the remaining 3 considered unrelated. Two further patients died following discharge, thus increasing the 90-day mortality to 18%. Neither of the 2 outpatient deaths were considered SAB related. Of the 11 deaths secondary to SAB, there was 1 MRSA and 10 MSSA episodes. Six patients had CA-SAB and 5 had HA-SAB. Patient and infection characteristics

for the cohort as a whole, stratified by 90-day outcome, are shown in **Table 3**. Patients who died were significantly older, and more were hypertensive or had a stroke.

There was no effect of adherence to the SAB bundle on survival, both with adherence expressed as a continuous variable or as a categorical "100% adherence" vs not. The unadjusted survival estimates for those with 100% adherence vs those without are shown in **Figure 1a**, and with age as an interaction term in **Figure 1b**. Univariate predictors of death in Cox regression included age and community-acquired infection; on multivariable analysis only age was an independent predictor of outcome **(Table 4).**

**Discussion**

Our study was able to demonstrate that with a clear and structured BOC intervention, adherence to key QCI for the treatment of SAB was possible, even in a lower resourced setting. Four out of the five identified QCI achieved adherence rates of greater than 80%. The one QCI that performed worse than 80% was the blood culture at 72 hours. Of note follow up blood cultures were done in all patients, it is merely the timing that was incorrect. While this falls into the noncomplicant category it is worth noting that this most likely had the most modest effect on outcomes compared to the other QCI. While similar interventions have been introduced in multiple hospitals worldwide, this is the first study to our knowledge, evaluating a BOC for the treatment of SAB both within South Africa and Africa. Overall in-patient mortality for this study population was approximating that of best international practice at 16% overall; however we could not show that better adherence to the QCI was associated with improved survival.

There is already a significant body of evidence that shows improved patient outcomes when an ID specialist is involved in the management of patients with SAB. This evidence is so compelling that Tong and Fowler suggest it should be 'the standard of care where ID physicians are available'. [6-9] The mechanism of this improved outcome is likely aggressive application of standard of care treatment guidelines including early localization of septic foci, source control, use of ECHO and early initiation of appropriate antibiotic therapy. This has led to a focus on a BOC for the treatment of SAB and the impact it may have on patient outcomes. Lopez-Cortes et al detailed the introduction of a BOC across 12 tertiary hospitals in Spain. The structured bundle showed an increased adherence to 6 evidence-based QCI they had identified through the literature and was associated with a reduction in mortality.[8] In 2014 a small 200 bed community hospital in Germany was able to show a significant reduction in in-patient mortality from 44% to 10% with the introduction of a structured BOC. [14] ID specialists were available at the hospital and did consult on all SAB cases following the intervention. In 2016 Townsend et al showed a significant improvement in adherence to standard guidelines for the treatment of SAB and a decrease in the 90-day relapse rate with a trainee- initiated and run intervention in a large public hospital serving many uninsured patients with significant comorbidities in Texas. [15] Of note this was achieved by developing an institutional protocol for the treatment of SAB which was distributed to health care providers in multiple formats. This intervention was entirely trainee run. This is a crucial step towards greater care for more patients with SAB and not just those in large institutions with access to IDC. In 2017 a study from Japan evaluated patients with SAB who survived 14 days in hospital and assessed adherence to QCI and the effect on mortality. [16] An increase in adherence to at least 4 out of 5 QCI rose from 47.5% to 79.3% with a decreasing mortality from 10.0% to 3.4% over an 8 year period. In 2018 a similar mortality benefit was seen with a BOC for catheter-related infections due to MSSA. In this cohort adherence of >55% to the BOC already showed an

improvement in 30-day all-cause mortality. [17] In 2020 an evaluation of outcomes in a New Zealand tertiary hospital following the introduction of a BOC for treatment of SAB again showed a significant impact on patient outcomes. [18] While 30 day mortality rates were not significantly different in the two arms, relapse rates and thus morbidity were significantly decreased in the post intervention arm with increased adherence to treatment guidelines.

In terms of data out of South Africa there are some early studies describing epidemiology and risk factors associated with SAB and poorer outcomes. The rates of MRSA vary widely between institutions; generally higher in private institutions and are more often health care associated. Mortality rates range from 23 to 47% in various cohorts [19-21] A previous paper from this institution, describing a sequential 100 admisisons with SAB, found a 90-day mortality rate of 47% and described problems with overall care. [10] Prescription of definitive antibiotics were inadequate in a quarter of all study participants and up to a third of those with MRSA. Early source control was poorly adhered to with less than 60% of those requiring this intervention receiving it. After introduction of the BOC, we describe ideal antibiotic usage and adherence to recommendations on source control of over 80%, similar to that reported in the above international studies. It is tempting to speculate that the reduced in-patient mortality of 16% we describe was at least partly due to better adherence to the standard QCI, with patient and infection charcteristics being comparable to the earlier cohort. However direct comparison is unfortunately not possible due to differing inclusion and exclusion criteria.

A major strength of this study was the ability to accurately capture and evaluate all episodes of SAB in a single hospital. A simple tick sheet was easy to implement and to use for standardising recommendations to treating clincians. There are a number of important limitations, including the small sample size and its retrospective nature. Patients not subject to the BOC intervention

were not included in this analysis and thus a true in-patient mortality rate is unclear. Documentation of an illness severity score on admission was not possible due to the retrospective design but may have helped in understanding those excluded from treatment vs those included in the final cohort. This BOC included specialist consultation by ID specialists and can this not be generalized to hospitals without such support.

In conclusion, we show that a BOC for SAB in-hospital care, that includes routine, unsolicited ID consultation with a proforma for recommendartions and a vancomycin loading dose chart resulted in good adherence to standard guideline recommendations and a good outcome for patients in our setting. Future studies should attempt to prospectively study the impact of a similar BOC intervention for SAB in hospitals without ID specialist support .

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**Conflict of Interest:** None

**Author Contributions:** EG, TB and SW conceived of the study and collected the data. EG and PJR wrote the first draft. All authors reviewed the data and provided input into the different verisons.All authors read and approved the final version.

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## Tables and Figures

**Table 1. Characteristics of patients admitted to Groote Schuur Hospital with Staphylococcal bactaraemia over the 12 month period**

| | **Healthcare-associated** n = 61 | **Community-acquired** n = 25 | **Total** n = 86 |
|---|---|---|---|
| **Age, years** | 46.0 (16.8) | 46.4 (15.1) | 46.1 (16.3) |
| Age > 60yrs | 15 (25%) | 5 (20%) | 20 (23%) |
| **Male sex** | 41 (67%) | 16 (64%) | 57 (66%) |
| **Comorbidities** | | | |
| *Any* | 41 (67%) | 20 (80%) | 61 (72%) |
| Hypertension | 16 (26%) | 4 (16%) | 20 (23%) |
| Diabetes mellitus | 13 (21%) | 6 (24%) | 19 (22%) |
| Chronic kidney disease | 9 (15%) | 2 ( 8%) | 11 (13%) |
| Chronic respiratory disease | 3 (5%) | 1 (4%) | 4 (5%) |
| Stroke | 2 (3%) | 4 (16%) | 6 (7%) |
| Seizure disorder | 4 (7%) | 2 (8%) | 6 (7%) |
| Other neurological condition | 4 (7%) | 3 (12%) | 7 (8%) |
| Cardiological condition | 7 (12%) | 1 (4%) | 8 (9%) |
| Urological condition | 4 (7%) | 2 (8%) | 6 (7%) |
| Dermatologic condition | 3 (5%) | 1 (4%) | 5 (6%) |
| HIV | 3 (5%) | 6 (24%) | 9 (11%) |
| Malignancy | 9 (15%) | 3 ( 12%) | 12 (14%) |
| **Type SAB** | | | |
| MRSA | 11 (18%) | NA | 11 (13%) |
| MSSA | 50 (82%) | 25 (100%)* | 75 (88%) |
| **Source of infection** | | | |
| Line related infections (all) | 33 (54%) | NA | 33 (38%) |
| Peripheral line (definite) | 12 (20%) | NA | 12 (14%) |
| Peripheral line (probable) | 10 (16%) | NA | 10 (12%) |
| Central line | 6 (10%) | NA | 6 (7%) |
| Dialysis catheter | 5 (8%) | NA | 5 (6% |
| SSTI | 11 (18%) | 14 (56%)* | 25 (29%) |
| Pneumonia | 2 (3%) | 2 (8%) | 4 (5%) |
| Surgical site | 7 (11%) | NA | 7 (8%) |
| UTI | 5 (8%) | 1 (4%) | 6 (7%) |
| Intravenous drug use | NA | 1 (4%) | 1 (1%) |
| Other | 3 (5%) | 3 (12%) | 10 (12%) |

Data are mean (SD), n (%). * No characteristic differed significantly between the study groups (P 0.05 at baseline according to Fisher's exact test for categorical data or the Wilcoxon rank- sum test for continuous data), with the exception of Type of SAB ($p = 0.029$) and the presence of skin and soft tissue infections ($p = 0.001$).
HIV, Human immunodeficiency virus infection; MRSA, Methicillin resistant Staphylococcus aureus; MSSA, Methicillin sensitive Staphylococcus aureus, HCA-SAB, Healthcare associated Staphylococcus aureus bacteraemia; CA-SAB, Community acquired Staphylococcus aureus bacteraemia; SSTI, Skin and soft tissue infection; UTI, Urinary tract infection.

## Table 2. Adherence to Quality Care Indicators

| Component | Adherenence |
|---|---|
| | n/required ( % ) |
| 72 hour bloodculture | 56/86 (65.1%) |
| Source control | 34/40 (85.0%) |
| ECHO | 26/31 (83.9%) |
| Vancomycin administration | 9/11 (81.8%) |
| Antibiotic appropriateness | 73/86 (84.9%) |

ECHO – Echocardiography performed when recommended.

**Table 3. Patient and clinical characteristics of patients who survived compared to those that died with SAB.**

| | **Alive (n=70)** | **Dead (n=16)** |
|---|---|---|
| **Age, years** | 42.8 (14,9) | 60.5 yrs (14.4)* |
| Age > 60yrs | 10 (14) | 10 (63)* |
| **Male sex** | 48 (69) | 9 (56) |
| **Comorbidities** | | |
| *Any* | 46 (66) | 15 (94)* |
| Hypertension | 13 (19) | 7(44)* |
| Diabetes mellitus | 13 (19) | 6 (38) |
| Chronic kidney disease | 7 (10) | 4 (25) |
| Chronic respiratory disease | 4 (6) | NA |
| Stroke | 2 (3) | 4 (25)* |
| Seizure disorder | 5 (7) | 1 (6) |
| Other neurological condition | 4 (6) | 3 (19) |
| Cardiological condition | 6 (9) | 2 (13) |
| Urological condition | 5 (7) | 1 (7) |
| Dermatologic condition | 3 (4) | 2 (13) |
| HIV | 7 (10) | 2 (12) |
| Malignancy | 8 (11) | 4 (25) |
| **Type SAB** | | |
| MRSA | 9 (13) | 2 (13) |
| MSSA | 61 (87) | 14 (88) |
| HA-SAB | 53 (76) | 8 (50) |
| CA-SAB | 17 (24) | 8 (50) |
| **Source of infection** | | |
| Line related infections (all) | 28 (40) | 5 (31) |
| Peripheral line (definite) | 9 (13) | 3 (19) |
| Peripheral line (probable) | 9 (13) | 1 (6) |
| Central line | 5 (7) | 1 (6) |
| Dialysis catheter | 5 (7) | NA |
| SSTI | 20 (29) | 5 (31) |
| Pneumonia | 3 (4) | 1 (6) |
| Surgical site | 6 (9) | 1 (6) |
| UTI | 6 (8) | NA |
| Intravenous drug use | 1(1) | NA |
| Other | 4 (6) | 2 (13) |

Data are mean (SD), n (%). * No characteristic differed significantly between the study groups (P 0.05 at baseline according to Fisher's exact test for categorical data or the Wilcoxon rank- sum test for continuous data), with the exception of age or age > 60 ($p < 0.001$) and the presence of hypertension ($p = 0.048$) and stroke ( $p = 0.01$)

HIV, Human immunodeficiency virus infection; MRSA, Methicillin resistant Staphylococcus aureus; MSSA, Methicillin sensitive Staphylococcus aureus, HCA-SAB, Healthcare associated Staphylococcus aureus bacteraemia; CA-SAB, Community acquired Staphylococcus aureus bacteraemia; SSTI, Skin and soft tissue infection; UTI, Urinary tract infection.

**Fig 1. Survival curves for patients with SAB**

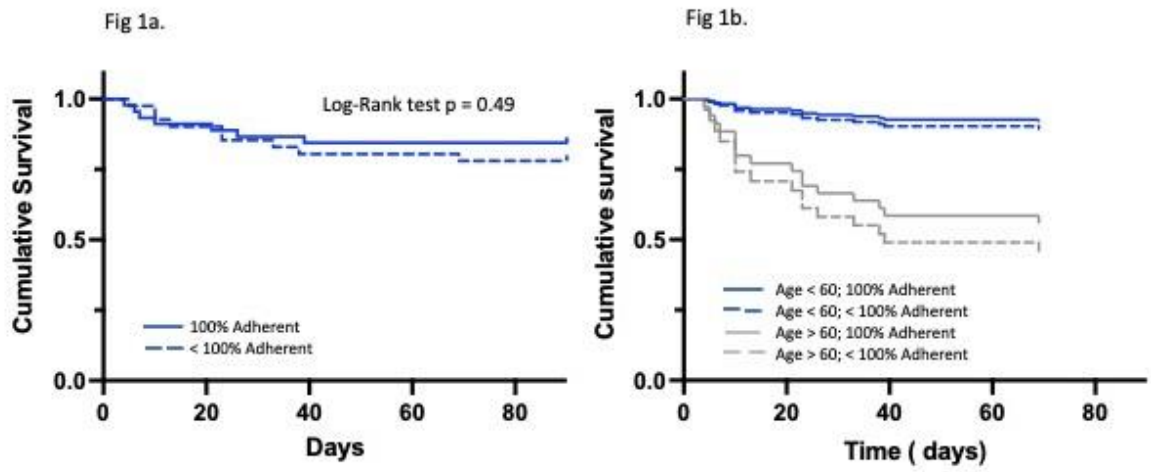


Fig 1a. Kaplan-Meier Curve for pateints with full vs < 100%adherence

Fig 1b. Cox proportional hazards regression stratified by age and adherence.

**Table 4. Cox regression analysis to predict 90-day mortality in patients with SAB**

| | Univariate | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Age ( +1 year) | 1.07 | 1.035-1.107 | < 0.001 | 1.071 | 1.033-1.111 | < 0.001 |
| Male sex | 0.654 | 0.243 - 1.755 | 0.399 | | | NS |
| Comorbidity (any) | 6.659 | 0.879 - 50.427 | 0.066 | | | NS |
| MRSA | 0.876 | 0.199-3.855 | 0.861 | | | NS |
| Community-acquired infection | 2.712 | 1.017-7.234 | 0.046 | | | NS |
| Full adhenrece to bundle | 0.726 | 0.270-1.949 | 0.525 | | | NS |

**Appendix 1.**

**Infectious Diseases and Microbiology consensus document for treatment of Staphylococcus aureus bacteraemia**

It is intended that all patients at Groote Schuur with Staphylococcus bacteraemia (SAB) are seen by an Infectious Diseases consultant at least once either as a solicited or as an unsolicited consultation. This document seeks to clarify a unified approach to investigating and managing patients with SAB.

Definitions-

All patients >13 years old with a single blood culture growing *Staphylococcus aureus* are considered to have SAB.
Definitions are consistent across a number of publications stating that low risk patients have ALL of the following-

- Nosocomial acquisition
- Sterile blood cultures approximately 72 hrs after starting effective therapy
- No permanent intra-cardiac device or vascular graft material
- Are not dialysis dependent
- No peripheral signs of endocarditis
- No cardiac murmur
- No clinical signs of metastatic foci of infection

Investigations-

In line with multiple guidelines and publications from respected authorities all patients should undergo a repeat blood culture after 72 hours of antibiotic therapy and if positive repeat cultures every 72hours until negative. They should also have a chest X-ray and focused imaging, to determine foci of infection, depending on clinical features

Echocardiography

- All patients with prosthetic heart valves or implantable cardiac devices should be referred to cardiology for opinion on the need for transoesophageal echocardiograph (TEE) unless (all below are met)
    - There is an obvious treatable source
    - There is resolution of bacteraemia and sepsis syndrome within 72 hours
    - The clinical suspicion (signs) of IE is low

Patients defined as low risk do not require routine transthoracic echocardiography (TTE)
All patients **not** defined as low risk should have a TTE (this includes all patients with a murmur)
Other than as stated above, TEE is reserved for patients in whom TTE is technically difficult and adequate views cannot be obtained e.g. obesity, ICU patients
Repeat TTE after 2 weeks of treatment may be appropriate in certain cases where endocarditis is still considered
Infectious diseases may discuss other indications for TEE with cardiology on a case by case basis

Initial antibiotics

Initial therapy for methicilin-sensitive *Staphylococcus aureus* (MSSA) is cloxacillin 2g i.v. 6 hourly increased to 3g for endocarditis, meningitis and osteomyelitis.
Penicillin allergic patients should have vancomycin in the first instance. Cefazolin can be considered in patient with a non-type 1 hypersensitivity to penicillin. Referral to clinical immunology may be appropriate.
Initial therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) is vancomycin including a loading dose.
Patients with prosthetic heart valves or an implantable cardiac device should be referred immediately to cardiology and are likely to require TEE. Rifampicin 300mg 12 hrly and gentamicin 3mg/kg 8 hrly should be added to standard therapy.

Source control

All intravascular lines should be removed or replaced immediately. Surgical source control should be performed at the earliest opportunity.

Duration of therapy

The IDSA definition of uncomplicated SAB when all the criteria below are met-

- Endocarditis has been excluded
- There are no implanted prostheses
- Follow-up blood cultures performed on specimens obtained 2–4 days after the initial set do not grow *S aureus*,
- Defervescence of fever occurs within 72 h of initiating effective therapy
- No evidence of metastatic infection is present on examination.

All patients with uncomplicated SAB should have 14 days i.v. therapy from date of first negative blood culture. [1]
Patients with complicated SAB should be treated for 4-6 weeks. These cases can be discussed on an individual basis between ID and micro when a switch to oral therapy may be considered in selected cases.
N.B. Being at high risk doesn't necessarily mean having complicated SAB. For example patients with community acquired infection or cardiac murmurs can be treated as uncomplicated if they fulfil the criteria above.
Guy Thwaites' 2011 LID paper[2] discusses the lack of evidence for switching to oral therapy after initial intravenous therapy although there is some observational data suggesting it may be safe in complicated SAB after at least 2 weeks of intravenous therapy.
Generally linezolid is not recommended for the treatment of SAB. However, it has been used successfully as an oral option following vancomycin in patients with *Staph aureus* infections. There is a lack of direct evidence in uncomplicated MRSA bacteraemia but it may be reasonable to switch patients with who have a good clinical response to vancomycin to linezolid to facilitate hospital discharge

Follow-up

All patients will be seen weekly until discharge or more frequently if required.

Selected references

(1) Holland TL, Arnold C, Fowler VG,Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA 2014 Oct 1;312(13):1330-1341.

(2) Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Torok ME, et al. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect.Dis. 2011 Mar;11(3):208-222.

**Appendix 2.**

# Unsolicited infectious diseases consultations to improve outcomes of patients with *Staph. aureus* bacteraemia

In line with International best practice the Infectious Diseases service is providing unsolicited evidence-based recommendations for the management of all patients with *Staphylococcus aureus* bacteraemia (SAB).

Patient sticker Date:

Date Index blood culture MSSA/MRSA

Vancomycin MIC

**Recommendations:** HA/CA

| | | |
|---|---|---|
| Likely source | | Date and time completed |
| Date and time of next blood culture | | |
| Line removal | | |
| Imaging & source control | | |
| Echocardiography | High risk if any of; CA, persistent bacteraemia, chronic dialysis murmur, signs of IE, metastatic infection | |
| Antibiotics, choice, dose, route, levels | | |
| Estimated duration of antibiotics | | |
| Comments | | |

Consultant name: Review date:

Consultant signature:

Contact on call ID registrar for queries regarding this case

**Appemdix 3. Vancomycin dosing and monitoring chart**



# Vancomycin Prescription Chart

| Name | | Indication | | Loading dose / time/ date | | MIC | eGFR | Weight |
|---|---|---|---|---|---|---|---|---|
| | | Signature | | Contact | | Ward | | |
| Date | | | | | | | | |
| Time | | | | | | | | |
| Dose | | | | | | | | |
| Signature | | | | | | | | |
| Trough level | | | | | | | | |

ALL patients should be weighed and GFR estimated

ALL patients should receive a loading dose of 25-30mg/kg (irrespective of renal function)

ALL subsequent doses should be 10-15 mg/kg/dose (unless inadequate trough levels achieved)

See table for dosing interval and measurement of trough concentrations

| eGFR (ml/min) | Dosing interval (hrs) | Measurement of trough concentrations |
|---|---|---|
| >80 | 12 | Before 3rd dose |
| 50-79 | 24 | Before 3rd dose |
| 35-49 | 36 | Before 2nd dose |
| 25-34 | 48 | Before 2nd dose |
| <25 or haemodialysis or CAPD | When trough level <15 | 3 days after loading dose |

**Notes**

Aim for trough concentration of 10-20 except in osteitis or endocarditis or if MIC >1 when trough should be 15-20

If trough is too low increase dose (seek advice from micro / ID if unsure how much to increase)

If trough too high increase dosing interval (seek advice from micro /ID if unsure how much to increase)

There is no maximum dose but rate of infusion should not exceed 1g per hour (ie at least 2 hrs for a 2 g infusion)

Vancomycin is not significantly removed by conventional intermittent haemodialysis. Dosing and monitoring as for those with GFR <25 ml/min

If vancomycin administered as continuous I.V infusion, the target trough concentation should be 25-30 mcg/ml

A therapeutic plasma concentration is important. If you are uncertain about dose adjustment, contact the clinical pharmacologist on call

**Contact numbers:**

**Clinical pharmacology: speed dial 77 294**

**Microbiology: speed dial 76 652**

# Appendix 4: Data collection form

## Data collection form: SAB

| Patient sticker |
|---|
| |

### Demographics and admission data

| | |
|---|---|
| Date of admission at GSH | |
| Referred from peripheral center? | Yes No Unknown |
| | If yes: Where from:<br><br>Date of admission at peripheral center: |
| Date of Birth | |
| Sex | Male Female |
| Comorbidities:<br>(eg. CCF, DM, AI disease, CRF, immunosuppressive drugs, TB, Chronic respiratory disease) | Yes No. Unknown<br><br>1.<br>2.<br>3.<br>4. |
| HIV | Yes No Unknown |
| | **If Yes:**<br>ARVS: Yes. No Unknown<br><br>Last CD4: Date: Unknown |
| Presenting problem | 1. Drip site sepsis<br>2. Cellulitis<br>3. Endocarditis<br>4. Sepsis<br>5. Osteomyelitis<br>6. Pneumonia<br>7. Other |
| Palliative care for terminal conditions | Yes No Unknown |
| Seen by ID department | Yes No |

## Microbiology

| | | | |
|---|---|---|---|
| Initial Blood culture: | Date:<br>Time (registered at lab):<br>Incubation time: | | |
| MRSA Vs. MSSA | | | |
| Vancomycin MIC | | | |
| Resistance profile (document all) | Antibiotic | Resistence Profile | |
| | Penicillin | R | S |
| | Clindamycin | R | S |
| | Moxifloxacin | R | S |
| | Fusidic Acid | R | S |
| | Rifampicin | R | S |
| | Cotrimoxazole | R | S |
| Result notification: | Time:<br>Date: | | |

## Risk factors for complicated disease

| | | |
|---|---|---|
| Source of infection | • Drip site definite (active drip site sepsis in last 30days)<br>• Drip site probable (HCA SAB in a pt with current or recent (<30 days) IV line and no other clinical focus of infection<br>• Dialysis catheter<br>• CVP<br>• Pneumonia<br>• UTI<br>• Skin & Soft Tissue Infection<br>• Surgical Site Infection<br>• IDU<br>• Other<br>• Unknown | |
| <u>Community Acquired</u><br><br>Positive blood culture taken on or within 48 hrs of admission | <u>Health Care Associated</u><br><br>Positive blood culture after 48hrs following admission<br>OR<br>Blood culture within 48 hrs of admission BUT<br>• Pt received IV antibiotics within previous 30 days<br>• Patient attended hospital or received haemodialysis in previous 30 days<br>• Patient resides in long term care facility | Unknown |
| Clinical endocarditis | Yes No. Unknown | |
| Metastatic foci: (circle all present) | 1. Endocarditis<br>2. Pulmonary<br>3. Bone<br>4. Deep abscess<br>5. Meningitis<br>6. Other<br>7. None | |
| Prosthetic material: (circle if present) | 1. Joint<br>2. Endovascular<br>3. Other | |

## Therapeutic interventions

## ECHO

| | | | |
|---|---|---|---|
| Was ECHO recommended | Yes | No. | Unknown |
| Date performed | | | |
| TTE VS. TOE | | | |
| Endocarditis | Yes | No | Unknown |

## Antibiotics

| | | | | |
|---|---|---|---|---|
| Empiric therapy<br><br>(Antibiotics started at time of index blood culture) | Antibiotic:<br>Dose:<br>Date started:<br>Date ended: | | | |
| Definitive therapy:<br><br>(antibiotic started after results of +BC with staph aureus called out by lab) | Cloxacillin<br>Cefazolin<br>Vancomycin<br>Other | Dose and frequency | Start Date | Start Time |
| | | | | |
| Vancomycin Loading dose | Yes | No | N/A | |
| Vancomycin trough level monitoring | Yes | No | N/A | |
| End Date | | | | |
| Complications of treatment | 1. Nephrotoxicity<br>2. Hepatotoxicity<br>3. Allergic reaction<br>4. Thrombophlebitis | | | |

## Source control

| | | | |
|---|---|---|---|
| Source control | source control needed: Yes | No | Unknown |
| | source control performed: Yes | No | Unknown |

## Blood culture monitoring

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Date | | | | | |
| Time | | | | | |
| SA cultured (Y/N) | | | | | |

## Outcomes

| | | | |
|---|---|---|---|
| Relapse ( within 30 days)<br>Patient with new positive blood culture for SA with the same sensitivity profile, following at least 1 negative culture within 30 days of initial treatment | Yes | No | Unknown |
| Alive at discharge | Yes | No | Unknown |
| Alive at 90 days | Yes | No | Unknown |
| Cause of death | | | |
| Death SAB related<br>(if persistent signs and symptoms of SAB or if bacteraemia still present at time of death) | Yes | No | Unknown |
| Date of death or discharge | | | |

## Appendix 5: UCT HREC approval for study

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room E53-46 Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021]-404 7682
**Email:** suraya.basterman@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

15 January 2019

**HREC REF: 766/2018**

**Dr Tom Boyles**
Infectious Diseases and HIV Medicine
G-16.68
NGSH

Dear Dr Boyles

**PROJECT TITLE: THE IMPACT ON OUTCOMES OF PATIENTS WITH STAPHYLOCOCCUS AUREUS BACTERAEMIA MANAGED WITH AN EVIDENCE BASED BUNDLE OF CARE APPROACH AT GROOTE SCHUUR HOSPITAL (Master's Candidate - Dr E Gatley)**

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 09 January 2019.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 January 2020.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

***The HREC acknowledge that the student, Dr Elizabeth Gatley will also be involved in this study.***

***Yours sincerely***

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

HREC 766/2018

## Appendix 6: South African Medical Journal Instructions to Authors

Article written in accordance with guidelines set out for the South African Medical Journal. Guidelines available at http://www.samj.org.za/index.php/samj/about/submissions