

Staphylococcus aureus
Bacteraemia (SAB)
Management
Clinical Guideline

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Disclaimer

This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion, with consideration to antibiotic resistance epidemiology in South Australia. In facilities where the prevalence of multi-resistant organisms may differ, local hospital guidelines may take precedence. Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation. If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- Discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary,
- Advising consumers of their choice and ensure informed consent is obtained.
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct and
- Documenting all care in accordance with mandatory and local requirements.

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1. Introduction

Staphylococcus aureus bacteraemia (SAB) is one of the most frequent causes of hospital-acquired and community-acquired blood stream infections, and is associated with high morbidity and mortality [1].

Treatment needs to commence promptly with appropriate empirical therapy and clinical investigations as described in this guideline.

2. Background

Hospital or Community-acquired

Staphylococcus aureus blood stream infections can stem from community or hospital origin, with a 2009 Australian/New Zealand study reporting 61% of cases were contracted in the community environment [2]. The most recent report of the Australian Staphylococcal Sepsis Outcome Programme (ASSOP 2014) reported that of 2,206 cases of SAB identified at 27 laboratories in Australia, 73% (1615 cases) were community onset. 18.8% of the 2,206 SAB cases identified in the ASSOP 2014 report were methicillin-resistant, slightly lower than the 19.1% identified in the 2013 report [1, 3]. An increasing number of methicillin-resistant cases in Australia are of community origin [4]. Of the 1615 community-acquired cases in the ASSOP 2014 report, 240 (14.9%) were methicillin-resistant [1].

Mortality

Published mortality rates due to SAB vary significantly (2.5% - 40%) however the risk is dependent upon a patient's age, clinical manifestation and co-morbidities. Methicillin-resistance is an independent risk factor for mortality in SAB. Recent Australian data reported the 30-day all-cause mortality associated with methicillin-resistant SAB to be 23.4%, compared to 14.4% mortality associated with methicillin-sensitive SAB [1].

Complications

SAB is associated with significant complications such as infective endocarditis and metastatic deep tissue infection. Complications such as left-sided endocarditis, device infection with a secondary focus, pneumonia/empyema and sepsis syndrome result in increased mortality [5-7].

3. Definitions / acronyms

ABW	Actual body weight
CBE	Complete blood examination
CrCl	Creatinine clearance
CRP	C-reactive protein
CXR	Chest X-ray
DRESS	Drug reaction with eosinophilia and systemic symptoms
IV	Intravenous
LFT	Liver function tests

MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
PO	Per oral
QID	Four times daily
SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
TOE	Trans-oesophageal echocardiogram
TTE	Transthoracic echocardiogram

4. Diagnosis & removal of foci / detection of metastatic complications

Isolation of *Staphylococcus aureus* in blood cultures should not be regarded as a 'contaminant' without proper clinical assessment. All patients with suspected SAB should be evaluated and empiric antibiotic treatment commenced immediately (see Appendix 1: SAB management flowchart). On-call infectious diseases physicians or clinical microbiologists are readily available to assist with the interpretation of culture results. It is estimated that only 1.5% of blood cultures positive for *Staphylococcus aureus* are due to contamination [8].

The potential source of infection should be actively sought and the removal or drainage of infectious foci should be undertaken whenever possible. Retention of an infected intravenous catheter has been shown to be the strongest independent risk factor for a relapse of SAB [5, 9]. Removal of infected prosthetic heart valves, prosthetic joints, permanent pacemakers or implantable cardiac defibrillators improves outcomes [8, 10, 11]. Common sites of metastatic infection include heart valves, bone and joints (particularly when prosthetic material is present), intervertebral discs, the epidural space, and intra-abdominal sites such as kidneys, liver and spleen [6, 12].

Deep-seated infections such as vertebral osteomyelitis or deep tissue abscess are likely to relapse if therapy duration is insufficient. Further investigations (based on clinical signs and symptoms) may include MRI of the spine (pain or tenderness of spine), bone scan (bone/joint or muscular pain), CT of brain or abdomen (focal neurology, seizures, abdominal pain) and ultrasound-guided aspiration of swollen, tender joints.

All patients should receive investigatory echocardiogram [7, 13]. A trans-thoracic echocardiogram (TTE) is a rapid, non-invasive test with good specificity but lower sensitivity for detecting cardiac vegetations [14, 15]. A trans-oesophageal echocardiogram (TOE) is superior in quality and improves sensitivity, however is more invasive and is not readily available at some sites [14, 15]. Investigations via TOE should be used in specific patient subgroups – see Box 3 of management flowchart.

5. Antibiotic choice

Mortality rates in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection are higher if treated with vancomycin instead of an appropriate β -lactam such as flucloxacillin [2, 8, 16]. However, if the isolate is methicillin resistant (MRSA), appropriate antibiotic cover with vancomycin is required from outset.

It is therefore suggested that dual therapy be commenced empirically, reducing therapy to a single agent when sensitivities are determined (usually within 48 hours after initial isolation).

- > Cease vancomycin if the *Staphylococcus aureus* is methicillin sensitive (MSSA)

- > Cease flucloxacillin or cefazolin if *Staphylococcus aureus* is methicillin resistant (MRSA).

All penicillin and cephalosporin class antibiotics are contraindicated in patients with a history suggestive of high risk β -lactam allergy such as anaphylaxis, urticaria, angioedema, bronchospasm, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). Treatment should be with vancomycin alone.

In patients with a history of moderate risk penicillin allergy (e.g. delayed rash which is not urticarial or DRESS/SJS/TEN), replace flucloxacillin with cefazolin.

For patients with a history of 'moderate risk' allergy to cefazolin (delayed rash which is not urticarial or DRESS/SJS/TEN), seek advice from Infectious Diseases / Clinical Microbiology. A history of allergy to a specific cephalosporin should not rule out the use of other cephalosporins unless the reaction was anaphylaxis or a severe cutaneous adverse reaction [17].

6. Duration of therapy

The duration of IV therapy for SAB should be at least 14 days [8]. Continued review is essential to detect relapse or metastatic infection. Complicated infections (e.g. positive follow up blood cultures, community-acquired infection, and/or fever for more than 72hrs) will require longer courses of antibiotic treatment, with a minimum of four weeks therapy (see table on management flowchart) [12, 18]. In staphylococcal endocarditis, antibiotics should be administered intravenously for the total duration of therapy. In osteomyelitis, oral therapy may need to continue for many months [18]. It is strongly recommended that advice is sought from an infectious diseases physician or on-call clinical microbiologist to assist in choosing antibiotic duration and treatment plan.

7. Dosing and monitoring of antibiotics in renal impairment


For patients on dialysis, please consult the Therapeutic Guidelines: Antibiotic or other appropriate renal dosing reference. Refer to Appendix 2 of this guideline for guidance on the dosing and monitoring of antibiotics in renal impairment.

8. Special populations

For patients with clinical conditions that alter pharmacokinetic parameters (volume of distribution and clearance), such as pregnancy, burns, critical illness, low weight or obesity, refer to Appendix 3 of this guideline for guidance on the dosing and monitoring of antibiotics in special populations.

9. Safety, quality and risk management

National Safety and Quality Health Service Standards

 National Standard 1 Clinical Governance	 National Standard 2 Partnering with Consumers	 National Standard 3 Preventing & Controlling Healthcare-Associated Infection	 National Standard 4 Medication Safety	 National Standard 5 Comprehensive Care	 National Standard 6 Communicating for Safety	 National Standard 7 Blood Management	 National Standard 8 Recognising & Responding to Acute Deterioration
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11. Document Ownership & History

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12/07/19	V1.2	Director Communicable Disease Control Branch	Minor formatting amendments.
7/06/18	V1.1	Safety and Quality Strategic Governance Committee (SQSGC)	Formally reviewed in line with 2-year scheduled timeline for review. Reformatted in new template.
14/10/14	V1.0	Safety and Quality Strategic Governance Committee (SQSGC)	Original SQSGC approved version.

Antimicrobial guidelines Staphylococcus aureus Bacteraemia (SAB) Management Guideline (Adult)

Appendix 1: SAB Management flowchart

Suspected or confirmed *Staphylococcus aureus* bacteraemia

Take and send blood cultures then commence antibiotics immediately

NO PENICILLIN / CEPHALOSPORIN ALLERGY

Flucloxacillin* 2 grams IV 6-hourly
PLUS vancomycin# 25mg/kg IV (actual body weight, maximum 3g loading dose)

MODERATE RISK PENICILLIN ALLERGY (Delayed rash which is not urticarial or DRESS/SJS/TEN)

Cefazolin* 2 grams IV 8-hourly
PLUS vancomycin# 25mg/kg IV (actual body weight, maximum 3g loading dose)

HIGH RISK PENICILLIN / CEPHALOSPORIN ALLERGY (history suggestive of high risk, e.g. anaphylaxis, urticaria, angioedema, bronchospasm, DRESS/SJS/TEN)

Vancomycin# 25mg/kg IV (actual body weight, maximum 3g loading dose)

For all antibiotics listed above, critically ill patients with severe sepsis (eg in the ICU setting) or infective endocarditis may require higher dosing - seek advice from micro / ID.

Refer to *Vancomycin dosing and monitoring clinical practice guideline* for advice on subsequent dose and frequency. Consult Micro / ID if patient is allergic to vancomycin.

* Refer to 'Dosing & monitoring of antibiotics in renal impairment' section of this guideline for dosing in patients with renal impairment.

NOT

Staphylococcus aureus bacteraemia?

- > Review microbiology results and modify treatment as appropriate
- > Perform investigations as appropriate
- > Consult ID/Clinical Microbiologist if necessary

Confirmed *Staphylococcus aureus* bacteraemia

- > Assess possible focus
- > Assess for metastatic infective complications
- > Perform investigations (Box 1)
- > Remove IV cannula or potentially infected devices
- > Infectious Diseases or Clinical Microbiologist consult strongly recommended
- > Consider patient transfer (Box 2) & need for TOE (Box 3)

Box 1: Investigations to be performed:

1. Trans-thoracic echocardiogram (TTE) on all patients within 7 days and consider TOE (Box 3)
2. If new or worsening back pain, joint or bone pain, consider bone scan +/- MRI
3. Ultrasound and joint aspirate if patient has any joint swelling or suspected joint infection
4. Baseline LFT, CXR, CBE & CRP

Check susceptibility of *Staphylococcus aureus* 24-48 hrs after initial isolation

Flucloxacillin resistant (MRSA)

Cease flucloxacillin (or cefazolin)

Flucloxacillin sensitive (MSSA)

Cease vancomycin (unless high risk penicillin / cephalosporin allergy)

Obtain blood cultures daily for 72 hours after starting treatment. If still positive at 72 hours, discuss further with ID/Micro

BOX 2: Non Tertiary Centres

- > Transfer to a major metropolitan hospital should be considered for ALL patients with *Staphylococcus aureus* bacteraemia
- > Discuss all cases with on-call Clinical Microbiologist
- > Contact numbers:
 - On-call SA Pathology clinical microbiology consultation: 08 8222 3000
 - Medstar: 13STAR (13 78 27)

BOX 3: Who needs a trans-oesophageal echocardiogram (TOE)?

- > All patients with a prosthetic valve or permanent pacemaker (PPM)
- > Patients with persistently positive blood cultures after 72 hours of antibiotic treatment & a negative Transthoracic Echocardiogram (TTE)
- > Patients with clinical features of endocarditis and a negative TTE or who are failing antimicrobial therapy
- > Patients with cardiac failure as a complication of endocarditis
- > Patients with no obvious primary focus who have metastatic infective complications and a negative TTE
- > Community acquired *Staphylococcus aureus* bacteraemia and a negative TTE

Assess duration of therapy based on likelihood of complications

Minimum 2 weeks IV therapy - Uncomplicated catheter-related

Patient must meet ALL of the following criteria:

- > Catheter identified as source of infection and promptly removed after diagnosis
- > No evidence of symptoms suggestive of metastatic infection
- > Fever resolves within 72 hours of antibiotic treatment
- > Blood cultures after 72 hours of antibiotic treatment are negative
- > No prosthetic material present in intravascular space
- > No evidence of valvular abnormality on TTE

Minimum 4 weeks IV therapy - Complicated infections

SEEK ID/MICROBIOLOGY CONSULTATION FOR:

- > Persistent bacteraemia (72 hours) OR slow resolution of fever on treatment
- > Prosthetic infection or presence of foreign material /device
- > Endocarditis
- > Osteomyelitis / septic arthritis
- > Internal organ abscess or infarction
- > CNS infection including epidural abscess
- > Community onset infection

ALL PATIENTS NEED FOLLOW UP FOR RELAPSE

Arrange clinical review 4 weeks following completion of antibiotic therapy

NB: Some infections (e.g. bone & joint) will require ongoing oral therapy after IV treatment completed.

Ensure patient receives Patient Information Leaflet

Appendix 2: Dosing and monitoring of antibiotics in renal impairment

Dosing and monitoring of antibiotics in renal impairment

For patients on dialysis, please consult [Therapeutic Guidelines: Antibiotic](#) or other appropriate renal dosing reference.

B-lactam antibiotics

	CrCl > 50 ml/min	CrCl 10-50 ml/min	CrCl <10 ml/min
Flucloxacillin	2g IV 6 hourly	2g IV 6 hourly	1g IV 6 hourly
	CrCl > 40 ml/min	CrCl 20-40 ml/min	CrCl <20 ml/min
Cefazolin	2g IV 8 hourly	1g IV 8 hourly	1g IV 12 hourly

Estimate CrCl using Cockcroft-Gault formula (see below)

Higher doses may be required in suspected infective endocarditis – consult ID/micro for advice.

Vancomycin

Refer to the *Vancomycin dosing and monitoring clinical practice guideline* for instructions on dose adjustment in renal impairment.

Estimating creatinine clearance

Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation:

Ideal body weight estimation chart

Height		Ideal body weight (kg)	
Feet & inches	Cm	IBW (female)	IBW (male)
5'1	155	48	53
5'3	160	53	57
5'5	165	57	62
5'7	170	62	66
5'10	178	69	73
6'0	183	73	78
6'2	188	78	82
6'4	193	82	87
6'6	198	87	92

IBW (female) = 45.5kg + 0.9kg per cm over 152cm

IBW (male) = 50kg + 0.9kg per cm over 152cm

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW (kg)} \times 0.85 \text{ (for female patients)}}{0.815 \times \text{SeCr (micromol/L)}}$$

- > Use Actual Body Weight (ABW) if this is LESS than IBW
- > If obese (ABW is $\geq 30\%$ above IBW or BMI > 30kg/m²), consider using adjusted body weight (AdjBW) to calculate creatinine clearance [19]:

$$\text{AdjBW} = \text{IBW} + 0.4 \times (\text{ABW} - \text{IBW})$$

Low weight patients: Consider 15mg/kg vancomycin maintenance dosing for patients less than 50kg, appropriately modifying the dose if the patient also has impaired renal function [20].

Obese patients: The volume of distribution is larger and clearance of vancomycin greater in the obese population. Weight-based dosing using total bodyweight (15mg/kg, maximum 2g per dose) is recommended [20-22]. More frequent dosing (8-hourly or continuous infusion in extremely obese patients) may be appropriate to compensate for increased clearance [19, 23-25]. Obese patients (>100kg) and those receiving at least 4g/day of vancomycin have been associated with a higher risk of nephrotoxicity and thus warrant regular creatinine clearance monitoring [25].

Special populations

General Considerations: It is advisable to seek specialist advice for clinical conditions that alter pharmacokinetic parameters (volume of distribution and clearance), such as pregnancy, burns, critical illness and obesity. These conditions also warrant more frequent vancomycin therapeutic drug monitoring [20, 24].

Follow up for relapse post-treatment

Relapse can occur following treatment and all patients with *Staphylococcus aureus* bacteraemia should have a follow-up appointment made one month post completion of antibiotic treatment. Patients should be made aware of the potential for relapse within 3 months of presentation. A patient information leaflet is included with this guideline to assist with detection and management of relapse.

Isolation of *Staphylococcus aureus* in blood cultures should not be regarded as a 'contaminant' – follow-up of positive blood cultures is always required.

Patient information leaflet

Important information for patients diagnosed with *Staphylococcus aureus* bacteraemia

Appendix 3: Patient Information Leaflet

Patient Details:

Name: _____ UR Number: _____

Date of Birth: _____

You were recently diagnosed and treated for a blood stream infection caused by the bacterium *Staphylococcus aureus*.

Staphylococcus aureus is a bacterium (germ) that is normally found on the skin. Usually it causes no medical problems, but occasionally this bacterium can cause a serious infection. The *Staphylococcus* bacteria can get into the body through a break in the skin. Common infections that are caused by *Staphylococcus aureus* include cellulitis (infection of the skin), abscesses or boils. Less common but more serious infections caused by *Staphylococcus aureus* include blood stream infections (bacteraemia), an infection of a joint (septic arthritis) or infection of the heart valves (known as endocarditis).

While the intensive treatment you received in hospital normally cures the infection, there is a small risk that the infection can return within THREE months following completion of antibiotics.

It is important you see your General Practitioner (GP) if you have any of the following symptoms:

- 1) Fever (a recorded temperature greater than or equal to 38°C), chills or shakes
- 2) Unusual backache or pain
- 3) Chest pain and/or shortness of breath
- 4) Headache, dizziness, nausea and/or vomiting

If you are very unwell you should arrange to go directly to the nearest hospital.

This information sheet will provide useful information to the medical staff, so take it with you if you can. Blood tests taken **before** restarting antibiotics (especially a blood culture test) will be helpful in your treatment.

Discuss any concerns regarding your antibiotic treatment with your doctor prior to discharge from hospital. For further information go to www.sahealth.sa.gov.au and search *Staphylococcus aureus*.

For completion by home team prior to discharge:

Hospital treatment details

Doctor's name (print) _____ Treatment hospital _____

Home team _____ Phone / Pager _____

Type of *S.aureus* bacteraemia: MRSA / MSSA (clinician please circle)

Date of initial infection ____/____/____

MRSA = Methicillin Resistant *Staphylococcus aureus*; MSSA = Methicillin Sensitive *Staphylococcus aureus*

Useful contact numbers (patient to complete)

GP _____

Local Hospital _____

