SA Health

Staphylococcus aureus Bacteraemia (SAB) Management Clinical Guideline (Adult)

Version 2.0

Approval date: 27/02/2023

Government of South Australia
SA Health

Disclaimer

This state-wide 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 state-wide 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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Contents

1. Name of guideline

Staphylococcus aureus Bacteraemia (SAB) Management Clinical Guideline (Adult).

2. Introduction

This guideline has been developed by the South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR) to guide the management of *Staphylococcus aureus* bacteraemia (SAB) in adult patients. 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.

Key stewardship points

- Isolation of *Staphylococcus aureus* in blood cultures should never be regarded as a contaminant. Evaluate all patients and commence empirical treatment with an appropriate beta-lactam and vancomycin.
- Reduce to a single antimicrobial agent once sensitivities confirmed.
- Beta-lactams are associated with improved outcomes compared to vancomycin when used to treat methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia.
- A minimum of 2 weeks of IV therapy is required for uncomplicated infections, and a minimum of 4 to 6 weeks for complicated infections.
- Provide **ALL** patients with Patient Information Leaflet *'Important information for patients diagnosed with Staphylococcus aureus bacteraemia'.*

3. 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 [1]. The most recent report of the Australian Staphylococcal Sepsis Outcome Program (ASSOP 2020) reported that of 2,734 cases of SAB identified at 30 laboratories in Australia, 79.7% (2,180 cases) were community onset. Of the 2,734 SAB cases identified in the ASSOP 2020 report, 17.6% were methicillin-resistant, slightly lower than the 18.5% identified in the 2019 report [2, 3]. An increasing number of methicillin-resistant cases in Australia are of community origin [4], with 77% of the methicillin-resistant SAB cases in the ASSOP 2020 report due to community-associated clones [2].

South Australian data from the 1st of July 2021 to the 30th of June 2022 has shown that 22% of all reported healthcare associated SAB infections were methicillin-resistant [5].

Data for community-acquired SAB infections are currently not routinely reported in South Australia.

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 has previously been an independent risk factor for mortality in SAB, however, recent Australian data has reported no significant difference in 30-day all-cause mortality between methicillin-resistant SAB (14.2%) and methicillin-susceptible SAB (13.3%) [2].

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 [6-8].

4. Definitions and acronyms

ABW	Actual body weight
AGEP	Acute generalised exanthematous pustulosis
CBE	Complete blood examination
CNS	Central nervous system
CrCl	Creatinine clearance
CRP	C-reactive protein
CXR	Chest X-ray
DRESS	Drug reaction with eosinophilia and systemic symptoms
Healthcare associated SAB	The episode is considered healthcare associated if the relevant specimen was collected: - greater than 48 hours after admission/delivery at your facility and was not present or incubating on admission, **OR** - within 48 hours of discharge/transfer, **OR** - the episode is epidemiologically linked to a previous admission/intervention at your facility (e.g., within one month of discharge and there is no evidence to link the isolate to another healthcare facility or intervention) [9].
ICU	Intensive care unit
ID	Infectious diseases
IV	Intravenous
LFT	Liver function tests
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
PPM	Permanent pacemaker
SAB	*Staphylococcus aureus* bacteraemia
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
TOE	Trans-oesophageal echocardiogram
TTE	Transthoracic echocardiogram

5. Diagnosis and 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 [10].

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 IV catheter has been shown to be the strongest independent risk factor for a relapse of SAB [6, 11]. Removal of infected prosthetic heart valves, prosthetic joints, permanent pacemakers or implantable cardiac defibrillators improves outcomes [10, 12, 13]. 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 [7, 14].

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 [8, 15]. A trans-thoracic echocardiogram (TTE) is a rapid, non-invasive test with good specificity but lower sensitivity for detecting cardiac vegetation [16, 17]. A trans-oesophageal echocardiogram (TOE) is superior in quality and improves sensitivity, however is more invasive and is not readily available at some sites [16, 17]. Investigations via TOE should be used in specific patient subgroups – see Box 3 of management flowchart.

6. Antibiotic choice

Mortality rates in patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection are higher if treated with vancomycin instead of an appropriate beta-lactam such as flucloxacillin [1, 10, 18]. 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-susceptible (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 beta-lactam allergy such as anaphylaxis, urticaria, angioedema, bronchospasm, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or acute generalised exanthematous pustulosis (AGEP). 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/AGEP), replace flucloxacillin with cefazolin.

For patients with a history of moderate risk allergy to cefazolin (e.g., delayed rash which is not urticarial or DRESS/SJS/TEN/AGEP), 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, or the antibiotics share common side chains [19].

7. Duration of therapy

The duration of IV therapy for SAB should be at least 14 days [10]. 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 72 hours) will require longer courses of antibiotic treatment, with a minimum of four weeks therapy, up to six weeks if response to therapy is slow (see table on management flow chart) [14, 20]. In staphylococcal endocarditis, antibiotics should be administered IV for the total duration of therapy. In osteomyelitis, oral therapy may need to continue for many months [20]. 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.

8. Dosing and monitoring of antibiotics in renal impairment

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

9. Special populations

General considerations: It is advisable to seek specialist advice for patients with clinical conditions that alter pharmacokinetic parameters (volume of distribution and clearance), such as pregnancy, burns, critical illness, low weight, or obesity.

Vancomycin dosing in 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 [21].

Vancomycin dosing in obese patients: The volume of distribution is larger and clearance of vancomycin greater in the obese population. Weight-based dosing using total body weight (15mg/kg, maximum 2g per dose) is recommended [21-23]. More frequent dosing (8-hourly or continuous infusion in extremely obese patients) may be appropriate to compensate for increased clearance [24-27]. 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 [27].

For further information refer to the Vancomycin Dosing and Monitoring in Adults Clinical Guideline for guidance on the dosing and monitoring of vancomycin in low weight and obese patients.

10. Follow up for relapse post-treatment

Relapse can occur following treatment and all patients with SAB 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, and should be provided to all patients.

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

11. Safety, quality and risk management

National Safety and Quality Health Service Standards

 Clinical Governance	 Partnering with Consumers	 Preventing and Controlling Infections	 Medication Safety	 Comprehensive Care	 Communicating for Safety	 Blood Management	 Recognising and Responding to Acute Deterioration
☐	☐	☒	☒	☐	☐	☐	☐

The following actions of the relevant standards are applicable:

Standard 3 – Preventing and Controlling Infections

- Actions 3.18, 3.19: Antimicrobial stewardship – The health service organisation has systems for the safe and appropriate prescribing and use of antimicrobials as part of an antimicrobial stewardship program.

Standard 4 – Medication Safety

- Action 4.01: Integrating clinical governance – Clinicians use the safety and quality systems from the Clinical Governance Standard when implementing policies and procedures for medication management, managing risks associated with medication management, and identifying training requirements for medication management.

12. Priniciples of the standard

National standard 3, *Preventing and Controlling Infections,* aims to reduce the risk to patients, consumers and members of the workforce of acquiring preventable infections; effectively manage infections, if they occur; prevent and contain antimicrobial resistance; promote appropriate prescribing and use of antimicrobials as part of antimicrobial stewardship; and promote appropriate and sustainable use of infection prevention and control resources.

National standard 4, *Medication Safety,* aims to ensure clinicians are competent to safely prescribe, dispense and administer appropriate medicines and to monitor medicine use. To ensure consumers are informed about medicines and understand their individual medicine needs and risk.

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14. Document ownership

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Contact: HealthAntibio@sa.gov.au
Endorsed by: Domain Custodian, Clinical Governance, Safety and Quality
Next review due: 27/02/2025
Title: Staphylococcus aureus Bacteraemia (SAB) Management (Adult) Clinical Guideline
ISBN: 978-1-76083-617-7
CGSQ reference: CG167
CPG history: Is this a new clinical guideline (V1)? **N**
Does this clinical guideline amend or update and existing clinical guideline? **Y**
If so, which version? **Version 1.2**
Does this clinical guideline replace another clinical guideline with a different title? **N**

15. Document history

Version	Date approved	Approved by	Amendment notes
2.0	27/02/2023	Domain Custodian, Clinical Governance, Safety and Quality	Revised as per requirements - guideline has been developed by SAAGAR and approved by SAMAC.
1.2	15/07/2019	Director Communicable Disease Control Branch	Minor formatting amendments.
1.1	07/06/2018	Safety and Quality Strategic Governance Committee (SQSGC)	Formally reviewed in line with 2-year scheduled timeline for review. Reformatted in new template.
V1	14/10/2014	Safety and Quality Strategic Governance Committee (SQSGC)	Original approved.

16. Appendices

16.1 Appendix 1: *Staphylococcus aureus* bacteraemia (SAB) management flowchart

Suspected or confirmed *Staphylococcus aureus* bacteraemia (SAB)
Take and send blood cultures then commence antibiotics immediately

NO PENICILLIN / CEPHALOSPORIN ALLERGY	MODERATE RISK PENICILLIN ALLERGY (e.g., delayed rash which is NOT urticarial or DRESS/SJS/TEN/AGEP)	HIGH RISK PENICILLIN / CEPHALOSPORIN ALLERGY (e.g., anaphylaxis, angioedema, bronchospasm, urticaria, DRESS/SJS/TEN/AGEP)
Flucloxacillin* 2g IV 6-hourly **PLUS** **Vancomycin#** 25mg/kg IV (actual body weight, maximum 3g loading dose)	**Cefazolin*** 2g IV 8-hourly **PLUS** **Vancomycin#** 25mg/kg IV (actual body weight, maximum 3g loading dose)	**Vancomycin#** 25mg/kg IV (actual body weight, maximum 3g loading dose)

For all antibiotics listed above, critically ill patients with severe sepsis (e.g., in the ICU setting) or infective endocarditis may require higher dosing – seek advice from ID/Micro.
* Refer to *'Appendix 3: Dosing and monitoring of antibiotics in renal impairment'* section of this guideline for dosing in patients with renal impairment.
# Refer to Vancomycin Dosing and Monitoring in Adults Clinical Guideline for advice on subsequent dose and frequency, and dosing in patients with renal impairment. Consult ID/Micro if patient is allergic to vancomycin.

NOT *Staphylococcus aureus* bacteraemia?
- Review microbiology results and modify treatment as appropriate
- Perform investigations as appropriate
- **Consult ID/clinical microbiologist if necessary**

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)

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 required**
- **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 to 48 hours after initial isolation

Flucloxacillin **resistant (MRSA)**	Flucloxacillin **sensitive (MSSA)**
Cease flucloxacillin (or cefazolin) continue vancomycin	**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 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 trans-thoracic 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
- No significant immunocompromise

Minimum 4 to 6 weeks IV therapy – Complicated infections
SEEK ID/MICROBIOLOGY CONSULTATION FOR:
- Persistent bacteraemia (72 hours) **OR** slow resolution of fever on treatment (fever >72 hours after starting appropriate antibiotics)
- 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
- No identifiable source of 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 is completed.
Ensure patient receives Patient Information Leaflet.

16.2 Appendix 2: Calculating creatinine clearance

Ideal body weight estimation chart [20]

Height		Ideal body weight (kg)	
Cm	Feet & inches	Female	Male
155	5’1	48	53
160	5'3	53	57
165	5'5	57	62
170	5'7	62	66
175	5'9	66	71
180	5'11	71	75
185	6'1	75	80
190	6'3	80	84
195	6'4	84	89
200	6'6	89	93

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

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

Cockcroft-Gault equation for estimating creatinine clearance

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

^ Use actual body weight (ABW) if this is less than ideal body weight (IBW)

^ **If obese** (BMI ≥ 30 kg/m^2) consider using adjusted body weight (AdjBW) to calculate creatinine clearance [28]:

AdjBW = IBW + 0.4 x (ABW - IBW)

Note: Cautions when using Cockcroft-Gault equation:

- Muscle wasting – CrCl will be overestimated
- Acute renal failure – CrCl may represent non-steady state serum creatinine levels and may underestimate the level of renal impairment
- Elderly – CrCl can overestimate renal function in the elderly

16.3 Appendix 3: Dosing and monitoring of antibiotics in renal impairment

Beta-lactam antibiotics

	CrCl > 50ml/min	CrCl 10-50ml/min	CrCl < 10ml/min
Flucloxacillin	2g IV 6-hourly	2g IV 6-hourly	1g IV 6-hourly
	CrCl > 40ml/min	**CrCl 20-40ml/min**	**CrCl < 20ml/min**
Cefazolin	2g IV 8-hourly	1g IV 8-hourly	1g IV 24-hourly
Estimate CrCl using Cockroft-Gault formula (see Appendix 2)			
For patients on dialysis, please consult *Therapeutic Guidelines: Antimicrobial dosages for adults with impaired renal function* or other appropriate renal dosing reference.			
Higher doses may be required in suspected infective endocarditis – consult ID/Micro for advice			

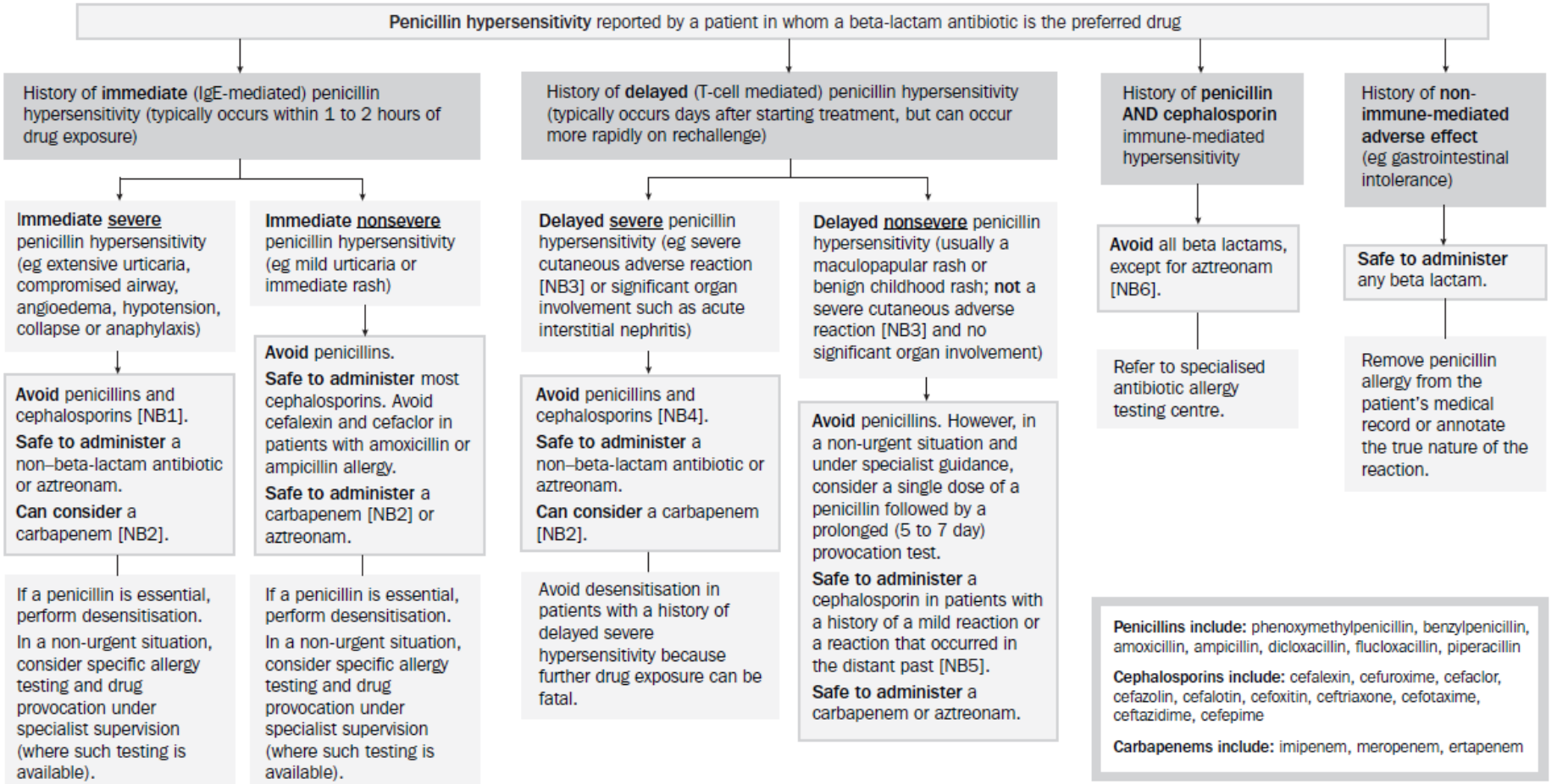
Vancomycin

Refer to the Vancomycin Dosing and Monitoring in Adults Clinical Guideline for instructions on dose adjustment in renal impairment.

16.4 Appendix 4: Assessment of patients who report hypersensitivity to penicillins

Therapeutic Guidelines

Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug



NB1: In a critical situation, a cephalosporin can be considered in this group after undertaking a risk–benefit analysis and assessment of potential side-chain cross-reactivity. Seek expert advice.

NB2: In patients with penicillin hypersensitivity, the rate of immune-mediated cross-reactivity with carbapenems is approximately 1%; therefore, carbapenems can be considered in supervised settings. However, in patients with a history of a severe cutaneous adverse reaction (eg drug rash with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome / toxic epidermal necrolysis [SJS/TEN], acute generalised exanthematous pustulosis [AGEP]), consider a carbapenem only in a critical situation when there are limited treatment options.

NB3: For example DRESS, SJS/TEN, AGEP.

NB4: There is limited evidence on the safety of cephalosporins in patients with a history of penicillin-associated acute interstitial nephritis (AIN). In a critical situation, directed therapy with a cephalosporin can be considered.

NB5: In patients who have had a **recent** reaction, consider avoiding cephalosporins with the same or similar R1 side-chain as the implicated penicillin.

NB6: However, avoid aztreonam in patients hypersensitive to ceftazidime; these drugs have the same R1 side-chain, so there is a risk of cross-reactivity.

Patient information leaflet

Important information for patients diagnosed with *Staphylococcus aureus* bacteraemia

Government of South Australia
SA Health

16.5 Appendix 5: 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 aureus* 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 (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)

General Practitioner: _____ **Local hospital:** _____