Clinical Guideline

Health
Hunter New England
Local Health District

Staphylococcus aureus Bacteraemia Management

Sites where Clinical Guideline applies	Acute Network Hospitals District Hospitals and Community Networks
This Clinical Guideline applies to:	
1. Adults	Yes
2. Children up to 16 years	Yes
3. Neonates – less than 29 days	No Approval gained from the Children, Young People and Families Network on 21 August 2023
Target audience	All clinicians who treat *Staphylococcus aureus* bacteraemia (SAB).
Description	This document provides guidance for the investigation and management of patients with SAB. Infectious Diseases (ID) consultation is recommended for all patients with SAB and has been shown to result in improved clinical outcomes (1-5). Adherence to this guideline will reduce mortality, morbidity and relapse of disease. While not requiring mandatory compliance, staff must have sound reasons for not implementing the practices set out within the guideline.

Go to Guideline

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Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNELHD Document, Professional Guideline, Code of Practice or Ethics:

- Therapeutic Guidelines: Antibiotic. Version 16. Melbourne: 2019:

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Glossary

Acronym or Term	Definition
AMO	Attending medical officer
BMI	Body Mass Index
CAP	Clinical Applications Portal (HNELHD patient electronic medical record system) http://cap/concerto/Login.htm
CRP	C-reactive protein
FBC	Full blood count
ICU	Intensive Care Unit
ims+	Statewide incident management system
ID	Infectious Diseases
IPS	Infection Prevention Service
IV	Intravenous
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
PICC	Peripherally inserted central (venous) catheter
PSSA	Penicillin-susceptible *Staphylococcus aureus*
SAB	*Staphylococcus aureus* bacteraemia or bloodstream infection documented by a positive blood culture
TOE	Trans-oesophageal echocardiogram
TTE	Trans-thoracic echocardiogram

Purpose And Risks

SITUATION

In 2022, there were 83 healthcare-associated SAB cases with 8% due to methicillin-resistant *Staphylococcus aureus* (MRSA) and age-adjusted 30-day mortality of 9.3%. SAB relapse within 15-90 days (2019 – 2022) occurred in 1.8% of adult events and 0% of paediatric events.

Over the same period, 264 community acquired SAB events were documented with 12% due to MRSA and 30-day age-adjusted mortality of 6.9%. SAB relapse within 15-90 days (2019 – 2022) occurred in 1.3% of adult events and 0% of paediatric events.

Isolation of *Staphylococcus aureus* from blood cultures should always be considered as significant until proven otherwise[1].

For detailed analyses, see the Intranet Infection Control Indicators webpage, report.

From that report, the most common principal sites of SAB in 2022 were:

A. Healthcare-associated events

- Vascular access device (e.g., intravenous cannula, central venous catheter, arterial line, tunnelled central line, subcutaneous port) – 53% (n=44), of which, 61% were peripheral cannulas (n=27)
- Skin and soft tissue infection (e.g., abscess, boil, post-operative wound infection) – 20%
- Primary blood stream infection with no apparent primary source or clear focus – 7%

B. Community-acquired events

- Primary blood stream infection with no apparent primary source or clear focus – 30%
- Skin and soft tissue infection (e.g., abscess, boil, deep abscess) -27%
- Joint infection or spinal osteomyelitis – 14%
- Pneumonia – 9%
- Infective endocarditis – 7%

Key clinical care required of all patients with SAB

1. Commence intravenous (IV) high dose flucloxacillin AND vancomycin (unless allergies) immediately, pending results of S.aureus PCR testing or susceptibilities.
2. Remove any removable foci of infection (change IV lines, drain abscesses).
3. Evaluate for complicated SAB using the criteria defined below (section 2.3).
4. Repeat blood cultures between 48 and 72 hours after the start of treatment.
5. Monitor full blood count (FBC), C-reactive protein (CRP), electrolytes and liver enzymes every 3 days for 2 weeks and then weekly for the duration of IV antibiotic treatment.
6. Arrange trans-thoracic echocardiogram (TTE) in all adults and in selected children between days 5 and 7. Progress to trans-oesophageal echocardiogram (TOE) if indicated (section 2.1).
7. Except in renal dialysis patients, arrange or insert a peripherally inserted central catheter (PICC) line once blood cultures have become negative.

8. Consult the Infectious Diseases on-call consultant or contact the on-call Clinical Microbiologist for ALL patients with SAB (by phone if necessary – (02) 4921 3000 for ID physician or (02) 4921 4000 for Clinical Microbiologist).

9. Give adult patients 2 to 6 weeks of intravenous (IV) antibiotics (section 2.3)

Provide verbal and written advice to the patient and their family about the symptoms of relapse and the need for early review if problems occur.

Risk Category*:* Clinical Care & Patient Safety

GUIDELINE

While not requiring mandatory compliance, staff must have sound reasons for not implementing standards or practices set out within guidelines issued by HNELHD, or for measuring consistent variance in practice.

1. Evaluation

1.1 Assessment by the treating team

All patients should have a thorough evaluation to identify the likely source and assess for complications of SAB.

Initial history

Recent inoculating injury, surgery, peripheral lines or prosthetic devices; comorbidities such as immunosuppression, diabetes. History of boils or soft tissue infection. Renal haemodialysis treatment.

Previous history of MRSA – check laboratory data and patient alert section on the Clinical Access Portal (CAP) system.

Initial examination

Assess for metastatic foci, prosthetic material, and evidence of endocarditis. **NB**. Prosthetic joints commonly become seeded during SAB (6).

Ongoing assessment

- Daily clinical assessment for metastatic foci (including for peripheral signs of endocarditis, cardiac auscultation for new murmurs, vertebral percussion for tenderness, abdominal palpation, and examination of large joints/long bones).
- Repeat blood cultures between 48 and 72 hours after initiation of appropriate antibiotics**. N.B**. Persistent positive blood cultures on treatment should prompt further discussion with ID or Clinical Microbiology service.
- Imaging (if clinically indicated) for deep-seated abscess or osteoarticular infection. Routine imaging in the absence of localising symptoms or signs is not required.
- **Echocardiography (7)**: All adults with SAB require trans-thoracic echocardiography (TTE). Not all children require TTE, however those with structural heart disease, clinical suspicion of endocarditis or prolonged bacteraemia (>72 hrs) should have echocardiography. The sensitivity of echocardiography for endocarditis is maximal at 5-7 days after onset of bacteraemia (8, 9). Initial investigation should be TTE, however, where safe and available, trans-oesophageal echocardiography (TOE) should be performed in patients in the presence of:
    - a high clinical suspicion of endocarditis but a negative TTE.
    - a complicated SAB with a negative TTE.
    - a prosthetic cardiac valve.
    - sub-optimal images on TTE.

Intravascular devices

Patients with pre-existing intravascular devices should have these removed regardless of whether there are signs of infection (the infection often relates to luminal colonisation), as retention of such devices is a strong predictor of treatment failure (10, 11).

In instances where this is difficult (e.g., pacemaker/defibrillator or difficult vascular access issues, especially in dialysis patients), ID advice should be sought. Where necessary, involve interventional radiology to scope future IV access options.

Monitoring

Monitor FBC, CRP, electrolytes, and liver enzymes every 3 days for 2 weeks from the beginning of treatment and then weekly for the duration of IV antibiotic treatment.

These tests should also be repeated 1-2 weeks following the end of intravenous antibiotic treatment.

1.2 Infectious Diseases and/or Clinical Microbiology consultation (all patients)

- At John Hunter Hospital, where there is an on-site infectious diseases clinical service, the ID registrar (page 5134) should be contacted. Routine consultation with an ID physician is associated with improved outcomes (1-5).
- At other HNELHD hospitals, all SAB patients should be discussed by telephone with the on-call ID Physician (phone 4921 3000) or the on-call Clinical Microbiologist (NSW Health Pathology phone 4921 4000).
- ID and Clinical Microbiology will record their recommendations in the patient's medical records (JHH patients) a consult document in CAP (others).

1.3 Cardiology and cardiothoracic surgery consultation (selected patients)

- Early cardiology consultation/discussion (cardiologist or suitably experienced general physician) should occur when any question of endocarditis arises. Do not assume that consultation has happened just because the patient has had an echocardiogram (TTE or TOE).
- Cardiothoracic surgical consultation is required in all patients when a diagnosis of endocarditis has been confirmed.

2. Antibiotic management

All patients require immediate treatment of SAB.

2.1 Empirical therapy

For suspected (i.e., initial blood culture Gram stain showing Gram positive cocci in clusters) or proven SAB, prior to the availability of GeneXpert or antimicrobial susceptibility results, patients should receive an appropriate β-lactam antibiotic AND vancomycin to cover both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA). Rates of MRSA among SAB were 11% across HNELHD in 2022.

Use

Flucloxacillin 2 g (child: 50mg/kg up to 2 g) IV, 6-hourly

(For patients with suspected endocarditis, septic shock or requiring ICU support, use a 4-hourly dosing interval)

PLUS

Vancomycin 25 mg/kg IV as a loading dose, followed by appropriate maintenance dosage
(see Appendix 1 for intermittent maintenance dosing of vancomycin in adults. In children, refer to the Children's Hospital Westmead vancomycin dosing guideline).

Notes

- The combination of flucloxacillin and vancomycin for longer than 48 hours is potentially nephrotoxic (12). If sensitivity testing is not available beyond this duration of empirical therapy seek expert advice.
- ALL penicillin AND cephalosporin class antibiotics are contraindicated in patients with a history of drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome or documented past immediate allergy (anaphylaxis or angioedema). Treatment should be with vancomycin alone.
- Where there is a history of non-immediate β-lactam allergy (e.g., rash) replace flucloxacillin with *cefazolin 2 g (child less than 12 years 50 mg/kg up to 2g) 8 hourly IV. (For adults with septic shock or requiring ICU support, use a 6-hourly dosing interval)*
- Vancomycin should be infused slowly, at a rate not normally exceeding 10 mg/minute (in children dose should be infused over at least 60 minutes).

2.2 Directed therapy once susceptibilities known

For haemodialysis patients, see section 3.2 below.

Penicillin susceptible *Staphylococcus aureus* (PSSA), *use*

Benzylpenicillin 1.8 g (Child less than 12 years: 50 mg/kg up to 1.8 g) IV, 4-hourly.

Methicillin-susceptible (but penicillin resistant) *Staphylococcus aureus* (MSSA), *use*

Flucloxacillin 2 g (child: 50 mg/kg up to 2 g) IV, 6-hourly. (For patients with suspected endocarditis, septic shock or requiring ICU support, use a 4-hourly dosing interval)

Notes*:*

- ALL penicillin AND cephalosporin class antibiotics are contraindicated in patients with history of drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome or documented past immediate allergy (anaphylaxis or angioedema). Treatment should be with vancomycin alone see below.
- Where there is a history of non-immediate β-lactam allergy (e.g., rash) then replace flucloxacillin with cefazolin 2 g (child: 50 mg/kg up to 2 g) 8 hourly IV. (For adults with septic shock or requiring ICU support, use a 6-hourly dosing interval)
- In the absence of a contraindication, vancomycin should not be used for MSSA as it has been associated with inferior outcomes compared to β-lactams (13).

Methicillin-resistant *Staphylococcus aureus* (MRSA), *use*

Vancomycin IV, see Appendix 1 for dosing advice in adults.

Notes

- Vancomycin should be infused slowly, at a rate not exceeding 10mg/minute (in children, dose should be infused over at least 60 minutes).

2.3 Duration of antibiotic therapy

The treatment plan should be discussed with the ID service and documented in the clinical record.

Complicated SAB (adults): Give at least 4 weeks of intravenous therapy; extend to 6 weeks if response to therapy is slow or if indicated by the specific complication.

Complicated SAB (paediatrics): A longer duration of therapy is generally required for complicated infection. Seek expert advice.

Complicated SAB is defined as the presence of ANY of the following features (14):

- Persistent bacteraemia at 48-72 hours following initiation of appropriate antibiotics.
- Persistent fever for >72 hours following initiation of appropriate antibiotics.
- Abnormal valvular morphology or evidence of valvular lesions, regurgitation, or endocarditis on a technically adequate echocardiogram.
- No identifiable focus of infection or an identifiable focus that has not been removed (removable foci include intravascular lines, skin and soft tissue abscesses that have been drained and simple skin lesions).
- Metastatic foci (e.g., endocarditis, vertebral osteomyelitis, visceral abscesses).
- Intravascular prosthetic material (e.g., prosthetic cardiac valve, pacing wires, pacemaker, implanted defibrillator, prosthetic arteriovenous graft).

Patients have uncomplicated bacteraemia if they meet NONE of these criteria.

Uncomplicated SAB (adults)

Give 14 days of intravenous therapy.

Uncomplicated SAB (paediatrics): There are few data to inform the duration of therapy for SAB in children. For MSSA, at least 7 days of intravenous therapy after the first negative blood culture is recommended. For MRSA, a minimum duration of 14 days of intravenous therapy is recommended.

3. Adult haemodialysis patients

These patients require different dosing of antibiotics due to renal impairment, as detailed below.

Vancomycin is not removed by low-flux dialysis membranes (infrequently used), but high-flux membranes can reduce plasma levels by up to 50%.

There is no additional requirement for vascular access in these patients, as antibiotics are given at the time of dialysis or by competency-trained haemodialysis staff via a patient's established access (arteriovenous fistula, arteriovenous graft or central venous indwelling catheter or Vas-Cath) if antibiotics are needed prior to dialysis.

Durations for therapy are as per section 2.3 above.

3.1 Empirical therapy in adult haemodialysis, *use*

Cefazolin: 2 g IV post-dialysis on dialysis days only

PLUS

Vancomycin: Loading dose of 25 mg/kg, rounded up to the nearest 500 mg, up to 2 g IV.

Notes:

- ALL penicillin AND cephalosporin class antibiotics are contraindicated in patients with history of drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome or documented past immediate allergy (anaphylaxis or angioedema). Treatment should be with vancomycin alone.
- See Appendix 2 for advice on vancomycin dosing and administration.

3.2 Directed therapy in adult haemodialysis.

Once susceptibilities known, *use:*

Methicillin-susceptible *Staphylococcus aureus* (MSSA)*, use*

Cefazolin 2 g IV post dialysis on dialysis days only (13, 15, 16).

- Unless there is major beta-lactam allergy (below), vancomycin should not be used for MSSA as it has been associated with inferior outcomes compared to beta-lactams (13).

Methicillin-resistant *Staphylococcus aureus* (MRSA), *use*

Vancomycin 25 mg/kg, rounded up to the nearest 500 mg, up to 2 g IV.

- Dosing of vancomycin in patients receiving continuous renal replacement therapy in ICU is complex. Seek advice from an ID physician and/or the Intensive Care Unit (ICU) pharmacist.
- See Appendix 2 for advice on vancomycin dosing and administration.

4. Outpatient intravenous (IV) therapy

Consenting patients with SAB may be appropriate for management through an outpatient IV service. These patients must meet the following criteria:

- Resolution of signs of infection (e.g., fever, tachycardia, hypotension) and been clinically stable for > 48 hours.
- Review by the ID or outpatient intravenous therapy service (phone or face-to-face consult).
- Have a functioning PICC line or other long-term vascular access device.
- Come from a stable home situation with support person and access to a telephone and transport.

5. Patient information

- Every patient with SAB requires education about the risk of relapse and the need for early medical attention for possible symptoms of relapse.

  Every patient should receive medical review one month after completion of treatment.

Implementation, Monitoring and Audit

- Clinical microbiology will phone the treating doctor immediately when a blood culture signals positive with SAB and advise the doctor to follow the recommendations 1-9 from the summary in this document.
- Recommendations arising out of ID consultation or Clinical Microbiology contact are placed either on a consult document associated with the patient's record within the CAP system or in the specimen notes in the laboratory database. These recommendations are also conveyed directly to the medical staff caring for the patient.
- Each healthcare-associated SAB event is investigated by the HNELHD Infection Prevention Service (IPS) to identify preventable factors that may have been neglected.
- Healthcare-associated SAB are reported on the Incident Information Management System (IIMS) at a minimum SAC level of 2. The AMO's team should enter this IIMS report. Events associated with mortality within 30 days are escalated by IPS for consideration by the District Patient Safety Officer for a Reportable Incident Brief and a Root Cause Analysis.

IIMS, SAC2 events are subject to a London Protocol investigation using an agreed District template.

Evaluation plan

- The guideline will be reviewed following consultation with key stakeholders every 2 years.

Relapse and mortality rates due to SAB will be evaluated at the time of guideline review by the IPS.

Consultation With Key Stakeholders

- Infectious Diseases and Microbiology services
- Nephrology
- Children, Young People and Families Network
- District Pharmacy Service
- District Antimicrobial Working Group

Appendices

Appendix 1: Vancomycin dosing in adults (non-dialysis)

Appendix 2: Vancomycin dosing in haemodialysis patients

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FEEDBACK

Any feedback on this document should be forwarded to the Contact Officer listed on the front page.

Appendix 1: Vancomycin Dosing in Adults (non-dialysis)

1. **Vancomycin loading dose.**

Based on pharmacokinetic data, Actual Body Weight (ABW) should be used for calculation of vancomycin loading dose, as it is an accurate descriptor for vancomycin volume of distribution and will provide rapid attainment of therapeutic serum levels.

The loading dose should be administered independent of renal function.

2. **Loading dose:** *Vancomycin 25 mg/kg (actual body weight) intravenously. The dose should be infused slowly, at a rate not exceeding 10 mg/minute.* **Intermittent maintenance dosing of vancomycin**

For intermittent vancomycin dosing in non-obese adults, an appropriate initial maintenance dosage is 15 to 20 mg/kg (actual body weight, rounded to nearest 50 mg) with frequency of dosing determined by renal function:

Creatinine clearance (mL/min)	Dose (mg/kg) (actual body weight)	Frequency
>60	15	12 hourly
40-60	20	24 hourly
20-40	15	24 hourly
<20	15	48 hourly
Haemodialysis	See Appendix 2 below	

For patients treated with vancomycin for more than 48 hours, dosage adjustments are based on plasma concentration. There are two methods available for therapeutic drug monitoring of vancomycin within HNE Health:

- "Traditional" method – this is the default for most patients.
    - Trough levels (i.e., 30 minutes prior to dosing) to be taken
    - Dosing adjusted to aim for a target trough concentration of 15 to 20 mg/L
    - As per HNE DQUMC FACT SHEET: Vancomycin IV (adults)
- Bayesian AUC-based method- for selected patients as directed by JHH ID team.
    - Managed by the JHH ID team – ideally will be used for patients receiving vancomycin as directed therapy for SAB and where the ID team is involved in the patient's care.
    - Utilises Bayesian software to calculate the AUC
    - Vancomycin level may be drawn at any time in the dosing interval, ideally 6 to 18 hours after a dose. Time of collection and time of actual dose administration must be well documented.
        - Ensure actual time of administration, rather than scheduled time of administration is documented; this can be checked by hovering mouse over the administration tick in MedChart
    - Dosing is adjusted to aim for a target AUC of 350 to 450 mg/L.h

- This should be repeated weekly, or more often in those with unstable renal function, changing volume of distribution (e.g., resolving sepsis) or if target attainment is yet to be reached/optimised.

In most settings, this will be adjusted based on trough levels unless otherwise notified by the JHH ID team. Management of vancomycin using trough levels (including when to take the first level and how to adjust doses according to levels) is described in HNE DQUMC FACT SHEET: Vancomycin IV (adults)

3. **Vancomycin dosing in obese adults** (Body Mass Index (BMI) >35)

Loading dose

A weight-based loading dose is recommended because volume of distribution and clearance of vancomycin correlate with actual body weight. *Use:*

Vancomycin 25 mg/kg (actual body weight) intravenously, as a loading dose.

Maintenance dosing

Maintenance vancomycin doses based on actual body weight may result in high plasma concentrations, and increased rates of nephrotoxicity. For obese patients with a BMI of 30 to 35 kg/m^2, initial vancomycin dosing can be as for non-obese patients (i.e., a 15 to 20 mg/kg actual body weight-based dose). For patients with BMI >35 kg/m^2, seek expert advice.

Appendix 2: Vancomycin dosing in adult haemodialysis patients

Methicillin-resistant *Staphylococcus aureus* (MRSA), use:

- Vancomycin: Give loading dose of 25 mg/kg, rounded up to the nearest 500 mg, up to 2 g IV
- Vancomycin should be infused slowly, at a rate not exceeding 1 g/hour (for adult haemodialysis patients only).
- Blood for vancomycin concentration should be drawn immediately prior to dialysis and sent to pathology as an urgent request in order to guide further dosing, which should be calculated according to the Table below.
- Patients' vancomycin levels should be monitored closely for at least 1 week in a facility where the level can be ascertained prior to the next dosing.
- Once the patient is discharged to a community dialysis unit, the last vancomycin level can be used to guide the first dose, and for the subsequent doses, the blood for vancomycin concentration should be drawn at the beginning of dialysis to guide the next dosing.

Vancomycin concentration (mg/L)[4]	**Next vancomycin dose**
<5	2000 mg
5-15	1500 mg
16-20	1000 mg
21-25	500 mg
>25	0