

# Febrile Neutropenia Management (Adults) Clinical Guideline

Version No.: 1.0  
Approval date: 10 October 2017

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### **Disclaimer**

This guideline provides advice of a general nature. 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.

Information in this statewide guideline is current at the time of publication.

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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 ensuring 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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## Introduction

This guideline aims to assist and guide prescribers towards best practice in the initial management of febrile neutropenia in adult patients.

The guideline helps Medical Officers to:

- > Determine probable febrile neutropenia
- > Stabilise the patient
- > Order the relevant investigations
- > Consider the need for ICU consultation or transfer to a tertiary centre
- > Prescribe appropriate initial antibiotic therapy

Ongoing therapy and duration of therapy should be determined by the patient's response, isolation of a pathogen, and rate of neutrophil recovery.

## Background

Febrile neutropenia is a medical emergency requiring rapid assessment and prompt initiation of antibiotics. This guideline has been developed by the South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR), based on the Therapeutic Guidelines: Antibiotic Version 15 [1] and current recommendations and treatment strategies used in South Australian Local Health Networks.

## Definitions and acronyms

<b>BP</b>	Blood Pressure
<b>CVC</b>	Central Venous Catheter
<b>DIC</b>	Disseminated Intravascular Coagulation
<b>DRESS</b>	Drug reaction with eosinophilia and systemic symptoms
<b>Empirical treatment</b>	Treatment initiated prior to a confirmed diagnosis and microbiology laboratory finding
<b>Febrile</b>	Having or showing the symptoms of a fever (>38 degrees Centigrade)
<b>Febrile Neutropenia emergency letter</b>	A referral letter providing instruction for emergency departments regarding prompt assessment and treatment of patient at risk (see <a href="#">Appendix 1</a> )
<b>IV</b>	Intravenous
<b>MBA20</b>	Multiple Biochemical Analyses – 20 tests
<b>MC&amp;S</b>	Microscopy, Culture and Sensitivity
<b>Neutropenia</b>	The presence of abnormally few neutrophils in the blood, leading to increased susceptibility to infection (Neutrophils <1.0x10 <sup>9</sup> /L)
<b>O<sub>2</sub> sats</b>	Oxygen saturation
<b>PCR</b>	Polymerase Chain Reaction
<b>PICC</b>	Peripherally Inserted Central Catheter
<b>SJS</b>	Stevens-Johnson Syndrome
<b>TENS</b>	Toxic epidermal necrosis

## Standards

The following National Safety and Quality Health Service Standard (NSQHSS) standards apply:

### **Standard 3 – Preventing & Controlling Healthcare Associated Infections**

- > Criterion 3.14 – Developing, implementing and regularly reviewing the effectiveness of the antimicrobial stewardship system.

### **Standard 4 – Medication Safety**

- > Criterion 4.1 – Developing and implementing governance arrangements and organisational policies, procedures and/or protocols for medication safety, which are consistent with national and jurisdictional legislative requirements, policies and guidelines.

## Principles of the standards

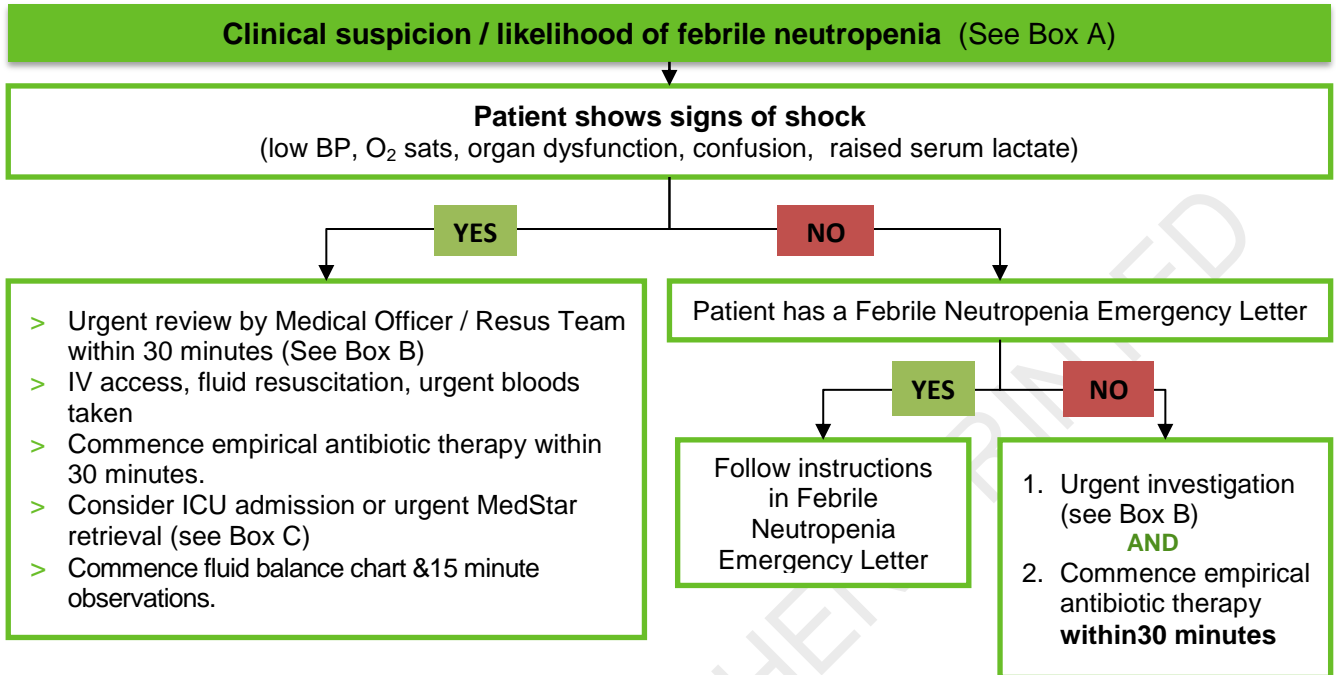
Standard 3 aims to prevent patients from acquiring preventable healthcare associated infections and effectively manage infections when they occur by using evidence-based strategies that are based on the risk to both patients and staff.

Standard 4 aims to ensure competent clinicians safely prescribe, dispense and administer appropriate medicines to informed patients and carers.

## Pathway / Protocol

### Empirical antimicrobial treatment of febrile neutropenia (adult patients)

For patients presenting to the Emergency Department with suspected febrile neutropenia



#### Box A: Probable Febrile Neutropenia

Consider febrile neutropenia if:

- > Up to 3 months post stem cell or bone marrow transplant; **OR**
- > Prescribed long term steroids for Graft vs. Host Disease; **OR**
- > Presents with a 'febrile neutropenia emergency letter' (see Appendix 1); **OR**
- > Has had recent chemotherapy e.g. last 4 weeks; **OR**
- > Is known to be neutropenic: neutrophils  $<1.0 \times 10^9/L$ ; **AND**
- > Has recorded temperature  $\geq 38^\circ C$  (or is not febrile but shows signs of shock – consider sepsis without fever)

**TO AVOID SEPTIC SHOCK, IV ANTIBIOTICS NEED TO BE ADMINISTERED WITHIN 30 MINUTES. DO NOT WAIT FOR BLOOD RESULTS**

#### Box B: Investigations

##### Urgent Investigations:

Complete the following within 30 minutes:

##### Septic Screen:

- > Blood cultures from peripheral vein and CVC / PICC (if present) prior to antibiotics **IF ABLE**
- > MBA20
- > Lactate (if available)
- > Lactate (if available)
- > Lactate (if available)
- > Lactate (if available)

##### Non Urgent Investigations:

Complete within 1-2 hours:

- > Chest x-ray
- > Respiratory viral PCR if indicated clinically
- > Sputum and urine specimen for MC&S
- > Other swabs (for culture / viral PCRs) as clinically indicated e.g. mouth, wounds, or lesion(s)

#### Box C: Considerations for ICU admission or urgent MedStar retrieval

Not responding to resuscitation

- > Altered conscious state
- > Hypoxia not corrected by oxygen therapy
- > Clinical deterioration in any other form
- > Lactate remains  $> 2\text{mmol/L}$  despite intervention

## Empirical antibiotic therapy for Febrile Neutropenia <sup>[1-4]</sup>

<b>No Penicillin / Cephalosporin Allergy</b>	<b>Moderate risk penicillin allergy</b> History suggestive of moderate/low risk (delayed rash which is NOT urticarial or DRESS/SJS/TEN)*
<p>&gt; <b>Piperacillin/tazobactam 4.5g IV every six hours</b></p> <p>Note: Continue piperacillin/tazobactam as mono-therapy in stable patients</p> <p>See additional information below for patients with known or suspected MRSA colonisation/infection</p>	<b>High risk penicillin / cephalosporin allergy</b> History suggestive of high risk (e.g. anaphylaxis, angioedema, bronchospasm, urticarial, DRESS/SJS/TEN)
	<p>&gt; <b>Cefepime 2g IV every eight hours</b></p> <p>Note: Continue cefepime as mono-therapy in stable patients See additional information below for patients with known or suspected MRSA infection/colonisation</p>
	<p>&gt; <b>Vancomycin 25mg/kg IV (Actual Body Weight) up to a maximum of 3g for initial dose</b> (See Table 2 in the <a href="#">Statewide Vancomycin Dosing Guidelines</a> for subsequent doses)</p> <p style="text-align: center;"><b>PLUS</b></p> <p>&gt; <b>Ciprofloxacin 400mg IV every twelve hours</b> Note: Continue vancomycin and ciprofloxacin as dual-therapy in stable patients.</p> <p style="text-align: center;"><b>ADD</b></p> <p>&gt; <b>Metronidazole 500mg IV every twelve hours</b> in patients with features of intraabdominal infection (e.g. diverticulitis/typhlitis or perineal abscess/collection)</p>
<p><b>NOTE:</b> Unless specifically stated antibiotic doses in this guideline reflect recommendations for patients with NORMAL RENAL FUNCTION. Refer to Therapeutic Guidelines or AMH for dose adjustments in patients with renal impairment.</p>	

### Additional considerations:

<p><b>Gentamicin:</b></p> <p><b>If the following apply:</b></p> <ul style="list-style-type: none"> <li>&gt; severe sepsis or shock SBP &lt; 90 mmHg or lactate &gt; 2mmol/L OR</li> <li>&gt; onset of sepsis 48 hours after admission to hospital OR</li> <li>&gt; previous resistant gram negative isolates,</li> </ul> <p><b>THEN ADD</b></p> <p><b>Gentamicin 7mg/kg (CrCl &gt; 60ml/min) or 5mg/kg (CrCl &lt; 60ml/min) ideal body weight IV for initial dose. If CrCl &lt; 40ml/min, contact consultant to consider alternative treatment</b></p> <p>REFER TO <a href="#">STATEWIDE AMINOGLYCOSIDE GUIDELINES</a> FOR FURTHER DOSING if required</p>
<p><b>Vancomycin</b></p> <p><b>If the patient is not already on vancomycin AND:</b></p> <ul style="list-style-type: none"> <li>• has severe sepsis or septic shock or skin/soft tissue/catheter related infection or clinical deterioration (whilst receiving 1st line <math>\beta</math>-lactam therapy); OR</li> <li>• is known or suspected to be colonised with methicillin-resistant Staphylococcus aureus (MRSA); OR</li> <li>• is not responding to 1st line <math>\beta</math>-lactam therapy with central venous access PLUS culture negative PLUS low index of suspicion for fungal infection; <b>THEN</b></li> </ul> <p><b>ADD vancomycin</b> to empiric regimen: <b>Vancomycin<sup>#</sup> 25mg/kg (Actual Body Weight) up to a max of 3g</b> for initial dose (see table 1 in Appendix 2).</p> <p>For subsequent doses refer to table 2 in the <a href="#">Statewide Vancomycin Dosing Guidelines</a> and cease after 3 days if no evidence of gram positive infection.</p> <p><sup>#</sup> <i>If allergic to vancomycin CONTACT Infectious Diseases/Microbiology Specialist for advice</i></p>
<p>Review therapy if culture positive or no improvement after 48 hours</p>
<p>*Moderate risk cephalosporin allergy: History suggestive of moderate/low risk (delayed rash which is not urticarial or DRESS/SJS/TEN) → consult ID/micro for advice</p>
<p>“DRESS/SJS/TEN are systemic drug reactions with skin involvement ( DRESS - Drug Rash With Eosinophilia and Systemic Symptoms, SJC- Stevens-Johnson syndrome, TEN -toxic epidermal necrolysis)”</p>

## Appendix 1 – Template for Febrile Neutropenia Emergency Letter

Treating team: Haematology/Oncology/other (circle)		Attach patient details sticker before giving this letter to your patient
Treating consultant contact details:		
Diagnosis:	Date:	

**Allergies:**

Dear Doctor / Triage nurse:

### Medical emergency – risk of febrile neutropenia

This patient is currently receiving \_\_\_\_\_ chemotherapy and is presenting with a recorded temperature greater than or equal to 38°C.

- > **He/She is likely to be profoundly neutropenic – at least priority 2 triage**
- > **Administer empiric antibiotic therapy within 30 minutes of presentation** (see below) to avoid septic shock. Do not wait for blood results.
- > Take blood cultures **before** starting antibiotics.

<p><b>Investigations:</b></p> <p><b>Step 1</b> (within 30 minutes of presentation)</p> <ul style="list-style-type: none"> <li>&gt; Septic screen:                             <ul style="list-style-type: none"> <li>• Blood cultures from peripheral vein and CVC / PICC (if present) <i>prior to antibiotics</i> IF ABLE.</li> <li>• Complete blood count</li> <li>• MBA20</li> <li>• Lactate (if available)</li> </ul> </li> <li>&gt; Secure IV access/fluid resuscitation</li> </ul> <p><b>Step 2</b> (within 1-2 hours of presentation)</p> <ul style="list-style-type: none"> <li>• Chest X-ray</li> <li>• Sputum and urine specimen for MC&amp;S</li> <li>• Respiratory viral PCR if indicated clinically</li> <li>• Other swabs (for culture / viral PVRs) as clinically indicated e.g. mouth, wounds, or lesion(s)</li> </ul> <p>&gt; Notify Haematology/Oncology registrar during working hours or on-call registrar/RMO after hours</p>	<p><b>Additional Clinical Information:</b></p> <p><b>Please provide any additional relevant clinical information for this patient:</b></p>
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**Initial therapy will need to be reviewed once results of investigations and blood cultures are available.**

#### Empirical antibiotic therapy for Febrile Neutropenia [1-4]

No-Penicillin-/Cephalosporin-Allergy <sup>a</sup>	Moderate-risk penicillin-allergy <sup>†</sup>
<p>&gt;→ <b>Piperacillin/tazobactam 4.5g IV every six hours</b></p> <p>Note: Continue piperacillin/tazobactam as mono-therapy in stable patients</p> <p>See additional information below for patients with known or suspected MRSA colonisation/infection<sup>a</sup></p>	<p>History suggestive of moderate/low risk (delayed rash which is NOT urticarial or DRESS/SJS/TEN)<sup>a</sup></p> <p>&gt;→ <b>Cefepime 2g IV every eight hours</b></p> <p>Note: Continue cefepime as mono-therapy in stable patients</p> <p>See additional information below for patients with known or suspected MRSA infection/colonisation<sup>a</sup></p>
	<p>History suggestive of high-risk (e.g. anaphylaxis, angioedema, bronchospasm, urticarial, DRESS/SJS/TEN)<sup>a</sup></p> <p>&gt;→ <b>Vancomycin 25mg/kg IV (Actual Body Weight) up to a maximum of 3g for initial dose</b></p> <p>(See Table 2 in the <a href="#">Statewide Vancomycin Dosing Guidelines</a> for subsequent doses)</p> <p style="text-align: center; color: green;"><b>PLUS</b></p>
	<p>&gt;→ <b>Ciprofloxacin 400mg IV every twelve hours</b></p> <p>Note: Continue vancomycin and ciprofloxacin as dual-therapy in stable patients.</p> <p style="text-align: center; color: green;"><b>ADD</b></p>
	<p>&gt;→ <b>Metronidazole 500mg IV every twelve hours</b> in patients with features of intraabdominal infection (e.g. diverticulitis/typhilitis or perineal abscess/collection<sup>a</sup></p>
<p><b>NOTE:</b> Unless specifically stated antibiotic doses in this guideline reflect recommendations for patients with NORMAL RENAL FUNCTION. Refer to Therapeutic Guidelines or AMH for dose adjustments in patients with renal impairment<sup>a</sup></p>	



## Appendix 2 – Dosing guide for gentamicin and vancomycin

1. Additional gentamicin dosing (subsequent to loading dose)

If follow up dosing is required for **gentamicin**, refer to the Statewide Clinical Guideline [Aminoglycoside: recommendations for use, dosing and monitoring in adult patients](#) for further information.

2. Vancomycin loading dosing

Based on the currently available evidence, clinical data support a loading dose of **25mg / kg (actual body weight)** [1]. A loading dose may facilitate more rapid attainment of therapeutic target range [1, 5].

**Table 1: Vancomycin loading dosing**

Actual body weight (kg)	Loading dose (grams)
40-44	1g
45-54	1.25g
55-64	1.5g
65-79	2g
80-119	2.5g
<b>OR</b> ≥120kg and GFR < 59mL/min	2.5g
≥120kg and GFR ≥ 60mL/min	3g (maximum dose)

For subsequent doses refer to the [Statewide Vancomycin Dosing Guidelines](#).

## References

1. Antibiotic Expert Groups, *Therapeutic Guidelines: Antibiotic. Version 15*. 2014, Melbourne: Therapeutic Guidelines Limited.
2. Tam, C.S., et al., *Use of empiric antimicrobial therapy in neutropenic fever*. Internal Medicine Journal, 2011. **41b**: p. 90-101.
3. Lingaratnam, S., et al., *An Australian survey of clinical practices in management of neutropenic fever in adult cancer patients 2009*. Internal Medicine Journal, 2011. **41**(110-120).
4. Lingaratnam, S., et al., *Introduction to the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients, 2010/2011*. internal Medicine Journal, 2011. **41**: p. 75-81.
5. Reardon, J., T.T.Y. Lau, and M.H.H. Ensom, *Vancomycin Loading Doses: A Systematic Review*. Annals of Pharmacotherapy, 2015. **49**(5): p. 557-565.

## Document Owner & History

**Document developed by:** South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR)

**File / Objective No.:** 2017-01524 | eA987706

**Next review due:** 10/10/2022

**Policy history:** Is this a new policy (V1)? **Y**  
Does this policy amend or update an existing policy? **N**  
If so, which version?  
Does this policy replace another policy with a different title? **N**  
If so, which policy (title)?

Approval Date	Version	Who approved New/Revised Version	Reason for Change
10/10/17	V1	Safety & Quality Strategic Governance Committee	Original approved version.