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

BP Blood Pressure
CVC Central Venous Catheter
DIC Disseminated Intravascular Coagulation
DRESS Drug reaction with eosinophilia and systemic symptoms
Empirical treatment Treatment initiated prior to a confirmed diagnosis and microbiology laboratory finding
Febrile Having or showing the symptoms of a fever (>38 degrees Centigrade)
Febrile Neutropenia emergency letter A referral letter providing instruction for emergency departments regarding prompt assessment and treatment of patient at risk (see Appendix 1)
IV Intravenous
MBA20 Multiple Biochemical Analyses – 20 tests
MC&S Microscopy, Culture and Sensitivity
Neutropenia The presence of abnormally few neutrophils in the blood, leading to increased susceptibility to infection (Neutrophils <1.0x10^9/L)
O₂ sats Oxygen saturation
PCR Polymerase Chain Reaction
PICC Peripherally Inserted Central Catheter
SJS Stevens-Johnson Syndrome
TENS 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.
Empirical antimicrobial treatment of febrile neutropenia (adult patients)

For patients presenting to the Emergency Department with suspected febrile neutropenia

**Clinical suspicion / likelihood of febrile neutropenia** (See Box A)

- Patient shows signs of shock (low BP, O₂ sats, organ dysfunction, confusion, raised serum lactate)
  - YES
  - NO

  - Urgent review by Medical Officer / Resus Team within 30 minutes (See Box B)
  - IV access, fluid resuscitation, urgent bloods taken
  - Commence empirical antibiotic therapy within 30 minutes.
  - Consider ICU admission or urgent MedStar retrieval (see Box C)
  - Commence fluid balance chart & 15 minute observations.

  **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 x 10⁹/L; AND
  - Has recorded temperature ≥ 38°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) **MBA20**

- **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 > 2mmol/L despite intervention
Empirical antibiotic therapy for Febrile Neutropenia [1-4]

<table>
<thead>
<tr>
<th>No Penicillin / Cephalosporin Allergy</th>
<th>Moderate risk penicillin allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>History suggestive of moderate/low risk (delayed rash which is NOT urticarial or DRESS/SJS/TEN)*</td>
<td>&gt; Cefepime 2g IV every eight hours</td>
</tr>
<tr>
<td>Note: Continue cefepime as mono-therapy in stable patients</td>
<td>Note: Continue cefepime as mono-therapy in stable patients</td>
</tr>
<tr>
<td>See additional information below for patients with known or suspected MRSA infection/colonisation</td>
<td>See additional information below for patients with known or suspected MRSA infection/colonisation</td>
</tr>
</tbody>
</table>

| > Piperacillin/tazobactam 4.5g IV every six hours | High risk penicillin / cephalosporin allergy |
|Note: Continue piperacillin/tazobactam as mono-therapy in stable patients | History suggestive of high risk (e.g. anaphylaxis, angioedema, bronchospasm, urticarial, DRESS/SJS/TEN) |
| See additional information below for patients with known or suspected MRSA colonisation/infection | > Vancomycin 25mg/kg IV (Actual Body Weight) up to a maximum of 3g for initial dose |
| (See Table 2 in the Statewide Vancomycin Dosing Guidelines for subsequent doses) | PLUS |
| > Ciprofloxacin 400mg IV every twelve hours | Note: Continue vancomycin and ciprofloxacin as dual-therapy in stable patients. |
| > Metronidazole 500mg IV every twelve hours in patients with features of intraabdominal infection (e.g. diverticulitis/typhlitis or perineal abscess/collection |

NOTE: 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.

Additional considerations:

Gentamicin:
If the following apply:
  > severe sepsis or shock SBP < 90 mmHg or lactate > 2mmol/L   OR
  > onset of sepsis 48 hours after admission to hospital   OR
  > previous resistant gram negative isolates,
THEN ADD
  Gentamicin 7mg/kg (CrCl > 60ml/min) or 5mg/kg (CrCl < 60ml/min) ideal body weight IV for initial dose. If CrCl< 40ml/min, contact consultant to consider alternative treatment

REFER TO STATEWIDE AMINOGLYCOSIDE GUIDELINES FOR FURTHER DOSING if required

Vancomycin
If the patient is not already on vancomycin AND:
  • has severe sepsis or septic shock or skin/soft tissue/catheter related infection or clinical deterioration (whilst receiving 1st line ß-lactam therapy); OR
  • is known or suspected to be colonised with methicillin-resistant Staphylococcus aureus (MRSA); OR
  • is not responding to 1st line ß-lactam therapy with central venous access PLUS culture negative PLUS low index of suspicion for fungal infection; THEN
ADD vancomycin to empiric regimen: Vancomycin# 25mg/kg (Actual Body Weight) up to a max of 3g for initial dose (see table 1 in Appendix 2). For subsequent doses refer to table 2 in the Statewide Vancomycin Dosing Guidelines and cease after 3 days if no evidence of gram positive infection.

# If allergic to vancomycin CONTACT Infectious Diseases/Microbiology Specialist for advice

Review therapy if culture positive or no improvement after 48 hours

*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

“DRESS/SJS/TEN are systemic drug reactions with skin involvement (DRESS - Drug Rash With Eosinophilia and Systemic Symptoms, SJS-Stevens-Johnson syndrome, TEN -toxic epidermal necrolysis)”
Appendix 1 – Template for Febrile Neutropenia Emergency Letter

<table>
<thead>
<tr>
<th>Treating team: Haematology/Oncology/other (circle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treating consultant contact details:</td>
</tr>
<tr>
<td>Diagnosis:</td>
</tr>
<tr>
<td>Date:</td>
</tr>
<tr>
<td>Allergies:</td>
</tr>
</tbody>
</table>

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.

**Investigations:**

**Step 1** (within 30 minutes of presentation)

> **Septic screen:**
  - Blood cultures from peripheral vein and CVC / PICC (if present) **prior to antibiotics** IF ABLE.
  - Complete blood count
  - MBA20
  - Lactate (if available)

> **Secure IV access/ﬂuid resuscitation**

**Step 2** (within 1-2 hours of presentation)

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

> Notify Haematology/Oncology registrar during working hours or on-call registrar/RMO after hours

**Initial therapy will need to be reviewed once results of investigations and blood cultures are available.**

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**Empirical antibiotic therapy for Febrile Neutropenia:**

| No-Penicillin / Cephalosporin-Allergy || Moderate-risk penicillin allergy |
|----------------------------------------|---------------------------------|
| History suggestive of moderate-risk (delayed rash which is NOT urticarial or DRESS/SSTEN) |

> **Piperacillin/tazobactam 4.5g IV every six hours**

*Note: Continue piperacillin/tazobactam as mono-therapy in stable patients*  
See additional information below for patients with known or suspected MRSA colonization/infection

> **Cefepime 2g IV every eight hours**

*Note: Continue cefepime as mono-therapy in stable patients*  
See additional information below for patients with known or suspected MRSA colonization/infection

> **Vancomycin 25mg/kg IV (Actual Body Weight) up to a maximum of 3g for initial dose**

*(See Table 2 in the Statewide Vancomycin Dosing Guidelines for subsequent doses)*  
PLUS

> **Ciprofloxacin 400mg IV every twelve hours**

*Note: Continue vancomycin and ciprofloxacin as dual-therapy in stable patients*  
ADD

> **Metronidazole 500mg IV every twelve hours**

*Note: Vancomycin and ciprofloxacin in patients with features of intra-abdominal infection (e.g. diverticulitis, appendicitis, or perineal abscess/collecction)*
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

<table>
<thead>
<tr>
<th>Actual body weight (kg)</th>
<th>Loading dose (grams)</th>
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<tbody>
<tr>
<td>40-44</td>
<td>1g</td>
</tr>
<tr>
<td>45-54</td>
<td>1.25g</td>
</tr>
<tr>
<td>55-64</td>
<td>1.5g</td>
</tr>
<tr>
<td>65-79</td>
<td>2g</td>
</tr>
<tr>
<td>80-119</td>
<td>2.5g</td>
</tr>
<tr>
<td>≥120kg and GFR &lt; 59mL/min</td>
<td>3g (maximum dose)</td>
</tr>
</tbody>
</table>

For subsequent doses refer to the Statewide Vancomycin Dosing Guidelines.
References


Document Owner & History

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

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Does this policy amend or update and existing policy? **N**
If so, which version?
Does this policy replace another policy with a different title? **N**
If so, which policy (title)?

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<td>V1.0</td>
<td>Safety &amp; Quality Strategic Governance Committee</td>
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