



**GUIDELINE**

**Fever and Suspected or Confirmed Neutropenia: Empiric Guidelines**

**Scope (Staff):** Clinical Staff – Medical, Nursing , Pharmacy

**Scope (Area):** Perth Children’s Hospital (PCH)

**Child Safe Organisation Statement of Commitment**

The Child and Adolescent Health Service (CAHS) commits to being a child safe organisation by meeting the National Child Safe Principles and National Child Safe Standards. This is a commitment to a strong culture supported by robust policies and procedures to ensure the safety and wellbeing of children at CAHS.

**This document should be read in conjunction with this [DISCLAIMER](#)**

**Aim**

To provide a guideline for the management of presumed bacteraemia/sepsis in an immunocompromised child greater than one month of age.

**Key Points**

- All oncology patients presenting with fever should receive initial management according to this guideline. Do NOT wait for blood results before initiating treatment.
- These recommendations may also apply to non-oncology patients with confirmed or suspected neutropenia.
- Rapid Central Venous Access Device (CVAD) or intravenous (IV) access is critical to facilitate prompt empiric antimicrobial therapy (as soon as possible, ideally within 30 minutes of triage). DO NOT ACCESS INFUSAPORT IF INSERTED WITHIN LAST 5 DAYS unless under instruction of Oncology Fellow.
- All oncology patients must be discussed with the on-call oncology fellow at PCH
- The Oncology ward provides a Patient Summary Sheet to the ED nurse co-ordinator for patients presenting to the Emergency Department. This summarises patient diagnosis, allergies, alerts, treatment regimen, CVAD details and recent weight.

**Definitions**

**Fever:** Temperature  $\geq 38.5^{\circ}\text{C}$  once or  $\geq 38.0^{\circ}\text{C}$  on two sequential occasions in a 12 hour period

**Neutropenia:** Absolute Neutrophil Count (ANC)  $< 0.5 \times 10^9/\text{L}$  OR  $0.5\text{-}1 \times 10^9/\text{L}$  and likely to fall further in next 48h.

**High risk of infection patients:**

- Haematopoietic Stem Cell Transplantation (HSCT) pre-engraftment or with significant myelo/immunosuppression
- Acute Myeloid Leukaemia (AML)
- Relapsed Acute Lymphocytic Leukaemia (ALL) on re-induction chemotherapy
- Infant ALL during intensive chemotherapy

**Standard risk of infection patients:**

- All oncology patients who do not meet the high risk (of infection) criterion above

**Systemic compromise:**

- Haemodynamic compromise
- Significant tachypnoea, increased work of breathing or oxygen saturation <90% on room air
- Confusion or decreased consciousness
- End organ dysfunction including renal or hepatic dysfunction, coagulopathy

**Initial Assessment**

All febrile oncology patients presenting to the emergency department should be triaged as ATS 2

1. Obtain prompt CVAD or IV access in all patients; **AND**
  2. Send initial investigations; **AND**
  3. **\*\*Administer empiric antibiotics (Table 1) within 30 minutes of arrival\*\*** **AND**
  4. Discuss patient with the on call oncology fellow at PCH.
- The same approach is recommended in non-oncology patients with suspected or confirmed neutropenia presenting with fever

**A) Initial investigations:**

- Blood culture from each lumen of CVAD (or peripheral IV if no CVAD access)
- Full blood count
- C-reactive protein
- Urea electrolytes and creatinine
- Liver function tests
- Venous blood gas and lactate (if any concern regarding haemodynamic compromise)

**Table 1 – Antibiotics for febrile oncology patient / non-oncology patient with suspected or confirmed neutropenia**

CLINICAL SCENARIO	DRUGS/DOSES			
	Standard Protocol	Known or Suspected MRSA <sup>a</sup>	Low risk Penicillin allergy <sup>b</sup>	High risk Penicillin allergy <sup>b</sup>
<b>Variations may apply to some patients (e.g. resistant organism colonisation<sup>c</sup>) please refer to the patient summary sheet for specific recommendations</b>				
Standard risk of infection patient	IV <a href="#">cefepime</a> 50mg/kg/dose (to a maximum of 2g) 8 hourly	As per standard protocol AND <b>consider</b> <a href="#">vancomycin</a> <sup>d</sup>	As per standard protocol	Discuss with ID or Microbiology service
High risk of infection patient (see definitions above)	IV <a href="#">cefepime</a> 50mg/kg/dose (to a maximum of 2g) 8 hourly <b>AND</b>	As per standard protocol	As per standard protocol	Discuss with ID or Microbiology service
Skin infection or erythema over CVAD or fever/rigors following accessing CVAD	IV <a href="#">vancomycin</a> <sup>d</sup> 15mg/kg/dose (to a maximum initial dose of 750mg) 6 hourly			
Fever with sepsis <sup>f</sup> or septic shock <sup>g</sup>	IV <a href="#">cefepime</a> 50mg/kg/dose (to a maximum of 2g) 8 hourly <b>AND</b> IV <a href="#">vancomycin</a> <sup>d</sup> 15mg/kg/dose (to a maximum initial dose of 750mg) 6 hourly <b>AND</b> Stat dose of IV <a href="#">gentamicin</a> <sup>e</sup>  for all patients admitted to ICU contact the Infectious Diseases service for advice regarding additional therapy and follow the <a href="#">Sepsis and Bacteraemia Guideline</a>	As per standard protocol	As per standard protocol	Discuss with ID or Microbiology service

**B) History**

- New site-specific symptoms
- Underlying diagnosis and phase of therapy (to anticipate the degree and anticipated duration of immunosuppression).
- Is the patient considered high risk of infection? (see definition above)
- Unwell contacts, colonisation with multi-resistant organisms, micro alerts.
- Previous infectious and non-infectious complications of therapy.

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- Central venous access device (CVAD).
- Current medications including antimicrobial prophylaxis.

### **C) Examination**

- Be aware that clinical signs of inflammation may be subtle depending on phase of therapy and/or in the presence of neutropenia and become evident upon neutrophil recovery.
- Abnormal vital signs:
  - Haemodynamic compromise – hypotension, tachycardia, capillary refill time  $\geq 2$  seconds, wide pulse pressure
  - Tachypnoea, increased work of breathing or hypoxia
- Ears, nose and throat for mucositis or local infection.
- Abdomen for signs of colitis/typhlitis (generalised or localised tenderness) or organomegaly.
- Skin examination including flexural regions, nail beds and sites where the skin integrity has been breached e.g. bone marrow aspirate, lumbar puncture sites for signs of localised infection
- CVAD exit sites and subcutaneous tunnel for signs of infection.
- Central nervous system (CNS) for signs of confusion or impaired consciousness, meningism and focal neurological deficits.
- Perineum must be examined in all patients.

### **D) Additional investigations as clinically indicated:**

- Respiratory symptoms: Chest X-Ray, Floq swab (preferable in thrombocytopenia) for respiratory virus PCR.
- Urinary symptoms, back pain, vomiting: urinalysis, urine M/C/S
- Diarrhoea or abdominal pain: Stool (M/C/S), viral studies, *Clostridioides difficile* antigen and toxin assay, abdominal ultrasound
- Skin rash and/or mouth ulcers: bacterial/fungal swab (M/C/S), Viral swab of mouth ulcers and vesicular lesions for HSV/VZV/enterovirus PCR
- CNS symptoms or signs: CNS imaging and lumbar puncture

## **Management**

- Empiric antibiotics as per Table 1 (administer within 30 minutes of arrival)
- Fluid resuscitation as required if signs of haemodynamic compromise
- For patients requiring ICU admission contact infectious diseases or clinical microbiology for urgent advice and follow the [Sepsis and Bacteraemia Guideline](#)
- Variations from these recommendations may apply – discussion with Infectious Diseases recommended for patients with:

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- known colonisation with multi-resistant gram negative bacteria (e.g. ESBL colonisation - variations recorded in MOSAIQ and the patient summary sheet provided to ED)
  - suspected intra-abdominal focus of infection
  - suspected meningoencephalitis
- Discuss all patients with the on call oncology fellow at PCH

## Subsequent Assessment and Management

### Re-evaluation during treatment

- Physical examination and assessment at least once daily.
- Daily full blood count.
- Daily blood culture with ongoing fevers (maximum of one blood culture per day, for up to 72 hours) and additionally if clinical deterioration occurs or if fevers recur after being afebrile for ≥ 24 hours).
- Repeat blood culture following positive blood culture to confirm clearance of bacteraemia.
- Drug levels e.g. [gentamicin](#), [vancomycin](#) as indicated.
- Additional investigations depending on progress of symptoms. If febrile neutropenia is prolonged >96 hours, in high risk patients, investigations for invasive fungal infection should be considered including serum galactomannan titre and appropriate imaging<sup>h</sup>.

**Table 2 – Modification of antimicrobials in fever in oncology patients**

Alteration of Antimicrobial Cover	
Blood culture positive - gram negative bacteria	ADD a stat dose of <a href="#">gentamicin</a> <sup>e</sup> to standard therapy and contact Infectious Diseases or clinical microbiology for urgent advice.
Blood culture positive - gram positive bacteria	ADD <a href="#">vancomycin</a> <sup>d</sup> to standard therapy, if already on vancomycin empirically, continue same. Contact infectious diseases or clinical microbiology for urgent advice.
Persistent fever 24 to 96 hours AND Negative culture to date AND clinically stable.	No change to therapy
Persistent fever 24 to 96 hours AND Negative culture to date AND clinically unstable.	Contact Infectious Diseases for advice regarding modifications to therapy. Consider formal consult. Consider adding <a href="#">vancomycin</a> <sup>d</sup> +/- <a href="#">gentamicin</a> <sup>e</sup> For patients requiring ICU admission contact Infectious Diseases or clinical microbiology for urgent advice and follow the Presumed Bacteraemia/Sepsis Guideline.
Persistent fever > 96 hours of antibacterial therapy	Consider imaging <sup>h</sup> and testing serum galactomannan titre AND empiric antifungal therapy <sup>i</sup> in high risk patients with expected prolonged neutropenia >10 days.


Rationalisation of Antimicrobial Cover	
Blood culture negative at 24-48 hours AND clinically stable AND no signs of skin infection <sup>j</sup>	Stop vancomycin (and gentamicin if commenced)
Non-neutropenic oncology patient AND clinically stable at 24 hours	Discuss with Infectious Diseases regarding rationalising or ceasing antibiotics

- a. Children known or suspected to be colonised with MRSA may need to have their therapy/prophylaxis modified. Children suspected of having MRSA include:
  - i. Children previously colonised with MRSA
  - ii. Household contacts of MRSA colonised individuals
  - iii. In children who reside in regions with higher MRSA rates (e.g. Kimberley and the Pilbara) a lower threshold for suspected MRSA should be given
  - iv. Children with recurrent skin infections or those unresponsive to  $\geq 48$  hours of beta-lactam therapy. For further advice, discuss with Microbiology or ID service.
- b. Refer to the [ChAMP Beta-lactam Allergy Guideline](#):
  - Low risk allergy: a delayed rash ( $>1$ hr after initial exposure) without mucosal or systemic involvement (without respiratory distress and/or cardiovascular compromise).
  - High risk allergy: an immediate rash ( $<1$ hr after exposure); anaphylaxis; severe cutaneous adverse reaction {e.g. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens – Johnson syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)} or other severe systemic reaction.
- c. Children known to be colonised with ESBL / CRE organism need to have their therapy modified. Discuss with infectious diseases or microbiology.  
ESBL – extended-spectrum B-lactamase, CRE – carbapenem-resistant enterobacteriaceae.
- d. IV [vancomycin](#) **15mg/kg/dose** (to a maximum initial dose of 750mg) 6 hourly. Therapeutic drug monitoring required for all patients.
- e. IV [gentamicin](#) Children  $\geq 1$  month old to 10 years old **7.5mg/kg/dose** (to a maximum of 320mg) once daily. Children  $>10$  years to 18 years old **6-7mg/kg/dose** (to a maximum of 560mg) once daily. Therapeutic drug monitoring required for all patients.
- f. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- g. Septic shock is a subset of sepsis in which circulatory and cellular/metabolic abnormalities are profound and substantially increase mortality. It is characterised clinically by hypotension requiring vasopressor support and an elevated serum lactate level despite adequate volume resuscitation.
- h. CT imaging of the chest and targeted imaging of other clinically suspected areas of infection (e.g. abdomen/pelvis, brain, musculoskeletal imaging)
- i. IV [AmBisome](#)<sup>®</sup> 3mg/kg/dose once daily OR IV [caspofungin](#)- refer to monograph for dosing
- j. In case of signs of skin infection consider swabs for MRSA culture – if no growth of MRSA consider ceasing vancomycin.

**Related internal policies, procedures and guidelines**[Antimicrobial Stewardship Policy](#)[ChAMP Empiric Guidelines](#)[PCH ED Guideline – Fever - Oncology Patient](#)[MicroAlert Policy](#)**References**

1. Antibiotic Writing Group. Therapeutic Guidelines - Antibiotic. West Melbourne: Therapeutic Guidelines Ltd; 2019. Available from: <http://online.tg.org.au.pklibresources.health.wa.gov.au/ip/>.
2. Expert opinion – Paediatric Infectious Diseases Physicians
3. Singer M, Deutschman CS, Seymour CS, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315(8): 801-810
4. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, Carlesse F, Groll AH, Haeusler GM, de Pablo S, Elena M. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. American Society of Clinical Oncology.

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