GUIDELINE

Fever in the Oncology patient (or non-oncology neutropenia)

Scope (Staff):	Clinical Staff – Medical, Nursing, Pharmacy
Scope (Area):	Perth Children's Hospital (PCH)

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this disclaimer

Aim

To provide guidance 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.
- This guideline should be read in conjunction with the Emergency Department (ED) guideline: Fever in the oncology patient.
- Some patients may fulfil criteria to follow the low-risk febrile neutropenia pathway. Refer to the Identification and management of children with cancer and low-risk febrile neutropenia (internal link) for eligibility to follow this pathway.
- 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 60 minutes of patient arrival in ED). 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 ≥ 38.5°C once or ≥ 38.0°C on two sequential occasions in a 12 hour period.

Neutropenia: Absolute Neutrophil Count (ANC) < 0.5 x 10^9/L OR 0.5-1 x 10^9/L and likely to fall further in next 48 hours.

High risk of infection patients:

- Allogeneic 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 Australasian Triage Scale (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 60 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**[a]	**Low risk Penicillin allergy**[b]	**High risk Penicillin allergy**[b]
Variations may apply to some patients (e.g. resistant organism colonisation[c]) please refer to the patient summary sheet for specific recommendations				
Low risk febrile neutropenia	Refer to Identification and management of children with cancer and low-risk febrile neutropenia pathway (internal link)			
Standard risk of infection patient	IV cefepime 50mg/kg/dose (to a maximum of 2g) 8 hourly	As per standard protocol AND **consider** vancomycin[d]	As per standard protocol	Discuss with ID or Microbiology service
High risk of infection patient (see definitions above)	IV cefepime 50mg/kg/dose (to a maximum of 2g) 8 hourly **AND** IV vancomycin[d] 15mg/kg/dose (to a maximum initial dose of 750mg) 6 hourly	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				

CLINICAL SCENARIO	DRUGS/DOSES			
	Standard Protocol	**Known or Suspected MRSA**[a]	**Low risk Penicillin allergy**[b]	**High risk Penicillin allergy**[b]
Fever with sepsis[f] or septic shock[g]	IV cefepime 50mg/kg/dose (to a maximum of 2g) 8 hourly **AND** IV vancomycin[d] 15mg/kg/dose (to a maximum initial dose of 750mg) 6 hourly **AND** Stat dose of IV gentamicin[e] for all patients admitted to ICU contact the Infectious Diseases service for advice regarding additional therapy and follow the Sepsis and Bacteraemia Guideline	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.
- 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 ≥ 3 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, FLOQswab® (preferable in thrombocytopenia) for respiratory virus PCR.
- Urinary symptoms, back pain, vomiting: urinalysis, urine microscopy/culture/sensitivity (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 Herpes Simplex Virus/Varicella Zoster Virus/enterovirus polymerase chain reaction (PCR).
- CNS symptoms or signs: CNS imaging and lumbar puncture

Management

- Empiric antibiotics as per Table 1 (administer within 60 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:
  - known colonisation with multi-resistant gram-negative bacteria (e.g. extended spectrum beta lactamase (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.[h]

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 gentamicin[e] to standard therapy and contact Infectious Diseases or Clinical Microbiology for urgent advice.
Blood culture positive - gram positive bacteria	ADD vancomycin[d] to standard therapy, if already on vancomycin empirically, continue the 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 vancomycin[d] +/- gentamicin[e] For patients requiring ICU admission contact Infectious Diseases or Clinical Microbiology for urgent advice and follow the Sepsis and Bacteraemia Guideline
Persistent fever > 96 hours of antibacterial therapy	Consider imaging[h] and testing serum galactomannan titre AND empiric antifungal therapy[i] 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[j]	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 methicillin-resistant Staphylococcus aureus (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, Pilbara and Goldfields) a lower threshold for suspected MRSA should be given
    iv. Children with recurrent skin infections or those unresponsive to ≥ 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 (>1hr after initial exposure) without mucosal or systemic involvement (without respiratory distress and/or cardiovascular compromise).
    - High risk allergy: an immediate rash (<1hr 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 ≥ 4 weeks old to < 10 years old **7.5mg/kg/dose** (to a maximum of 320mg) once daily. Children ≥10 years to 18 years old **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. Computerised Tomography (CT) imaging of the chest and targeted imaging of other clinically suspected areas of infection (e.g. abdomen/pelvis, brain, musculoskeletal imaging)

i. IV liposomal amphotericin (AmBisome®) 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 CAHS internal policies, procedures and guidelines
Antimicrobial Stewardship Policy
ChAMP Empiric Guidelines
PCH ED Guideline – Fever - Oncology Patient
Identification and management of children with cancer and low-risk febrile neutropenia
MicroAlert Policy

References and related external legislation, policies, and guidelines

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 spies 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.

This document can be made available in alternative formats on request.

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