Guideline

Management of Fever in a Paediatric Oncology Patient

Febrile Neutropenia and Febrile Non-neutropenia

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<th>Document ID</th>
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**Purpose**

This guideline provides a framework for the treatment of children with cancer and fever from presentation to resolution. Pathways are provided for those with suspected neutropenia and those with known non-neutropenia at presentation.

**Scope**

This guideline applies to staff caring for children with cancer in CHQ HHS and can be used by the Queensland Paediatric Palliative care Haematology Oncology Network and other State-wide services.

**Related documents**

**Procedures, Guidelines, Protocols**

- CHQ Procedure 03450 [Venous Access Device (VAD) Insertion and Management of Peripheral and Central Venous Access Devices](#)
- CHQ Procedure 01036 [Antimicrobial: Prescribing and Management](#)
- CHQ Procedure 01000 [Medication](#)
- CHQ Procedure 01001 [CHQ Procedure 01001: Medication - Prescribing](#)
- CHQ Guideline 01075 [Antifungal Prophylaxis and Treatment in Paediatric Oncology Patients and other Immunocompromised Children](#)
CHQ Guideline 01202  CHQ Paediatric Antibiotic Card: Empirical Antibiotic Guidelines
CHQ Guideline 60010  Sepsis: Recognition and Early Management in Children
CHQ Work Instruction 03468 Central Venous Access Device (CVAD)-Blood Sampling
CHQ Work Instruction 03460 Totally Implanted Venous Port Device (TIVPD)-Needling
CHQ Procedure 03455  Management of Compromised Central Venous Access Device (CVAD)
CHQ Guideline 01069  Fever in a Child with Central Venous Access Device - Management of Suspected Central Venous Access Device (CVAD) Infection in Children
CHQ Guideline 01065  Antibiotic Lock Therapy for Catheter Related Blood Stream Infections

Forms and templates

- CHQ Clinical Pathway  Clinical Pathway: Initial Management of Suspected Neutropaenic Sepsis

Guideline

Febrile Neutropenia (FN)

Definition

Fever: ≥38.5°C on one occasion or
≥38.0°C on two occasions – at least one hour apart WITH EITHER

- Neutropenia: a neutrophil count of <1 x 10⁹/L OR
- Recent Intensive Chemotherapy (within last 14 days) where neutropenia is expected

Fever in children with cancer is a medical emergency as they are at increased risk of developing severe sepsis and septic shock and may progress from fever to severe sepsis rapidly. Fever may be the only sign of underlying infection and children presenting with fever should be rapidly triaged (minimum Cat 2). Fever in a child with cancer or chemotherapy/treatment induced neutropenia is known as Febrile Neutropenia (FN). Neutropenia must be suspected in any oncology patient that has received chemotherapy within the last 10 - 14 days. Neutropenia in CHQ is defined as a neutrophil count of ≤1 x 10⁹/L.

Antibiotics given within 60 minutes of presentation improve outcomes and decrease the need for admission to PICU (1, 2). These children can deteriorate rapidly and progress to septic shock if not managed appropriately.

ALERT

DO NOT wait for blood results before initiating treatment.

Antibiotics should be given within 60 minutes of presentation (or fever spike if inpatient)
Antibiotics MUST be commenced after blood cultures but before undertaking other investigations (e.g. CXR, NPA)

Initial Management of Suspected Febrile Neutropenia

Follow the Febrile Neutropenia antibiotic algorithm (Page 8) unless neutrophil count is known to be
≥ 1.0, then follow the Non Neutropaenic Flow chart (Page 9).

Complete the Clinical Pathway: Initial Management of Suspected Neutropaenic Sepsis if available or IEMR Febrile Neutropenia Oncology Paediatric power plan.

Triage (if presentation through Emergency Department):
- Triage as minimum Australasian Triage Scale (ATS) 2

Initial Management:
- Comprehensive patient assessment should be performed within 10 minutes of presentation
- Haemodynamically unstable or critically unwell
  - ABCD management, including fluid bolus (20 mL/kg) and oxygen therapy as required.
  - Refer to CHQ-GDL-60010-Sepsis: Recognition and Early Management in Children

Intravenous Access:
- Immediately establish intravenous (IV) access - use central venous access device (CVAD) as first option,
  - Insert peripheral line (PIV) if CVAD competent staff unavailable
  - Do not wait for topical anaesthetic
  - Intraosseous access may be required if there are no other options.

Primary Investigations:
- Collect blood samples - Full Blood Count, Blood Cultures from each lumen of CVAD (peripheral blood cultures NOT required), and Chem 20 (Collect COAG’s only if critically unwell).

Antibiotic Management:

**ALERT: Do not delay antibiotic administration whilst waiting for blood results**

If CVAD in-situ and patent, give IV antibiotics through CVAD, not peripherally

- Commence antibiotics as below and commence intravenous (IV) fluids if clinically indicated
- **Piperacillin/tazobactam** has both gram negative and gram-positive cover and is an effective empiric treatment for most common gram positive infections including *S.aureus* (MSSA). Exceptions include enterococcus, coagulase negative staphylococcus, penicillin resistant *S.mitis*.
  - Dose = 100 mg/kg (of piperacillin component) IV 6-hourly (maximum 4000 mg Piperacillin component per dose).
  - Administer undiluted (200 mg/mL of piperacillin component) as an IV bolus over 3 to 5 minutes via CVAD (can be diluted to 20mg/mL of piperacillin component for infusion over 20 minutes via peripheral IV access).

If septic, critically unwell or haemodynamically unstable (see Febrile Neutropenia Antibiotic Algorithm, Page 10) add Gentamicin and Vancomycin as below.
- **Gentamicin** provides additional gram-negative cover including pseudomonas
Dose:

- 1 month to 10 years: 7.5 mg/kg every 24 hrs (maximum initial dose 320 mg);
- More than 10 years: 6 mg/kg every 24 hrs (maximum initial dose 640 mg)
- If critically ill (septic shock) and more than 10 years of age, use 7 mg/kg every 24 hours (maximum initial dose 640 mg)
- Infuse IV Gentamicin dose in total volume of 30 mL (in sodium chloride 0.9%) over 30 minutes.

Document time of administration and if a syringe driver or burette was used for infusion (as well as if line was primed with sodium chloride 0.9% or gentamicin) – may need levels taken at 2 hours and 6 hours after the dose (timed from start of infusion). Please refer to the Tobramycin/Gentamicin Therapeutic Drug Monitoring Guideline.

- Vancomycin provides additional gram positive cover, including MRSA, penicillin resistant S. mitis and coagulase negative staphylococcus. Add for patients treated with high dose cytarabine (HD ARA C) who have high risk of S. mitis, suspected CVAD infection or MRSA.
- Dose = 15 mg/kg (maximum initial dose 750 mg) every 6 hourly (perform therapeutic drug monitoring – Vancomycin trough level 30 minutes before 3rd or 4th dose)
- Administer once flush following Gentamicin is complete
- Dilute Vancomycin dose to 5 mg/mL or less and infuse over at least 120 minutes (2 hours)
- Patients with documented previous Red Man syndrome will require prolonged infusion

Routine addition of vancomycin to the initial empiric regimen within 72 hours does not reduce mortality or time to defervescence and is associated with increased nephrotoxicity.

ALERT

All changes to antibiotics need to be discussed with the on-call QCH Paediatric Oncologist

Special considerations:

- Beta lactam delayed hypersensitivity – Use Ceftazidime IV (50 mg/kg/dose IV every 8 hourly (maximum 2 grams per dose)) and single dose of Gentamicin (as above)
- Beta lactam anaphylaxis – Use Meropenem IV (40 mg/kg/dose IV every 8 hourly (maximum 2 grams per dose)) (see ALERT below)
ALERT

Restricted antibiotics e.g. Meropenem, require Infectious Diseases Consultant approval for use > 48 hours

Supplemental Investigations:

- Request other investigations as clinically indicated i.e. ± CXR, urine/stool M/C/S, Respiratory virus PCR, CRP.
- Note: Antibiotics MUST be commenced before undertaking other investigations
- Abnormal CXRs should be discussed with the Paediatric Oncologist at the Oncology Services, QCH

Communication:

ALERT

For all children presenting to a hospital other than QCH discuss all patients with the Regional Paediatrician and on-call Paediatric Oncologist at Oncology Services Group via Queensland Children’s Hospital (QCH) switch: (07) 3068 1111.

- Prescribe blood products if required and other relevant medications e.g. paracetamol; antiemetics; prophylactic antibiotics, antivirals, and antifungals. Not for rectal medications or Ibuprofen.
- Discuss with the Paediatric Oncologist whether children receiving oral chemotherapy should continue to receive this treatment.
- Patients with a fever ≥ 38°C require observations including temperature, pulse, oximetry, respiration, blood pressure, capillary refill and Children's Early Warning Tool Score (CEWT) hourly until stable and afebrile.
- The decision to reduce the observations are based on the clinical condition of the child. Minimum of 4 hourly observations including temperature, pulse, oximetry, respiration, blood pressure, capillary refill and CEWT score. Daily skin inspection to assess for potential sources of infection including skin, mucous membrane, mouth, perianal area and CVAD should be undertaken.

Ongoing Management of Febrile Neutropenia (Page 11)

Evaluate at 24 hours

- Consider low risk child for HITH antibiotics (Queensland Children’s Hospital only). See Identification and Management of Low-Risk Febrile Neutropenia in Paediatric Oncology Patients Guideline (under development).

Evaluate at 48 hours:

- All culture results should be reviewed, and antibiotics adjusted according to isolates and antibiotic sensitivities (Discuss with Paediatric Oncologist and Infection Management Fellow/Consultant).
Initially stable with suspected Febrile Neutropenia:

Afebrile:
- Evidence of marrow recovery:
  - If afebrile for at least 24 hours with all negative cultures - stop empiric antibiotics.
  - If afebrile for at least 24 hours with negative blood cultures but evidence of resolving local infection (e.g. UTI, skin, soft tissue, chest) and evidence of marrow recovery - consider intravenous to oral switch to complete 5 to 7 days of appropriate antibiotics.
- No evidence of marrow recovery:
- Continue IV antibiotics and review at 72 hours.

Febrile:
- Continue Piperacillin/Tazobactam. Reassess and re-culture. Repeat blood cultures from all lumens of CVAD no more than once within a 24-hour period.

Initially Unwell or Septic (received Piperacillin/Tazobactam, gentamicin and vancomycin):
- Continue Piperacillin/tazobactam; stop Gentamicin and Vancomycin at 48 hrs if negative cultures and patient is stable.
- Complete a 5 to 7-day course of appropriate intravenous antibiotics, unless specific viral cause identified.
- If afebrile for at least 24 hours at completion of 5 days of appropriate antibiotics stop antibiotics and discharge home.
- If remains febrile at 4 to 5 days follow as below.

**ALERT**

Routine addition of vancomycin to the initial empiric regimen within 72 hours does not reduce mortality or time to defervescence.

Evaluate at 72 hours:

Afebrile:
- Evidence of marrow recovery:
  - If afebrile for at least 24 hours with all negative cultures - stop empiric antibiotics.
  - If afebrile for at least 24 hours with negative blood cultures but evidence of resolving local infection (e.g. UTI, skin, soft tissue, chest) and evidence of marrow recovery - consider intravenous to oral switch to complete 5 to 7 days antibiotics.
- No evidence of marrow recovery:
- If afebrile for at least 24 hours, all negative cultures and neutropenia expected to be less than 7 days consider stopping antibiotics and scheduling careful follow up.
- If afebrile for at least 24 hours, all negative cultures and neutropenia expected to be prolonged consider completing a 5 to 7-day course of antibiotics. If stable, these do not need to be intravenous, consider intravenous to oral switch (e.g. oral amoxicillin/clavulanate, cefalexin).

Febrile:
- Continue Piperacillin/tazobactam. Reassess and repeat blood cultures from all lumens of CVAD no more than once within a 24-hour period.
- If there is clinical deterioration, consider change to meropenem or add vancomycin if concern for gram positive infection.
- In children at high risk for invasive fungal disease (IFD) with clinical deterioration consider Liposomal Amphotericin (AmBisome ®) IV 1 mg/kg once daily and investigate as below.

ALERT

Do not switch initial empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

Febrile at 4 to 5 days:
- Reassess and in consultation with the treating team consider:
- more invasive investigative procedures and imaging
- transfer to QCH if patient is in a shared-care service
- In high risk children with persistent fever beyond 96 hours perform evaluation for invasive fungal disease (IFD) e.g. CT scan lung, plus abdominal ultrasound (if LFTs deranged) and other clinically suspected areas of infection.
- Add Liposomal Amphotericin (AmBisome ®) IV 1mg/kg once daily (increase to 3 mg/kg/day if high clinical or radiological suspicion of IFD) – refer to CHQ_GDL_01075_Antifungal_Prophylaxis_and_Treatment_in_Paediatric_Oncology_and_Immunocompromised_Children
- Close monitoring of electrolytes and renal function is essential every 24 hours
- If renal impairment or previous adverse reaction to AmBisome® consider Voriconazole or Caspofungin/Micafungin on Paediatric Infectious Disease (ID) team advice.
- If there is clinical deterioration, consider change to meropenem or add vancomycin if concern for gram positive infection.
- Remember the possibility of viral infection HSV, VZV, CMV, EBV, Adenovirus etc. When indicated, request appropriate viral blood PCRs, swabs, urine, stool or respiratory secretions.
- Daily blood cultures at this stage only when clinically indicated/ requested by senior medical staff.

ALERT

Antifungals require Infectious Diseases Consultant approval for use for more than 72 hours for treatment of presumed Invasive Fungal Disease
Febrile neutropenia antibiotic algorithm

Febrile oncology patient – suspected neutropenia

Perform a rapid, comprehensive assessment within 10 minutes

Establish Intravenous Access: CVAD, PIVC or IO if necessary AND collect blood samples: FBC; ELFTs; Blood cultures from each lumen; +/-CRP; and COAGs if critically unwell

Stable patient

Administer antibiotics within 60 minutes
Piperacillin/Tazobactam* 100mg/kg (max 4g) IV 6-hrly

If remains stable pursue other investigations as indicated e.g. CXR; Urine M/C/S Respiratory Virus PCR

Assess FBC results

Admit:
• Neutropenia patients
• High risk patients (see Appendix 2)

Consider discharge (oncologist decision only):
• Neutrophils are >0.5 and not anticipated to fall AND patient remains stable for >1hr
• Patient can return next day Prior to discharge consider: Ceftriaxone IV 100mg/kg (max 4g) 24-hrly

Patient with:
Suspected gram positive infection (e.g. CVAD) OR recent high dose Cytarabine

Administer antibiotics within 60 minutes
Piperacillin/Tazobactam IV 100mg/kg (max 4g) 6-hrly
Vancomycin IV 15mg/kg (max 750mg) IV 6-hrly

If continued stable pursue other investigations as indicated e.g. CXR; Urine M/C/S Respiratory Virus PCR

Septic patient*:
• Abnormal
  - appearance (unwell/colour)
  - vital signs (Table 1)/pulse
  - conscious state/irritability
  - skin perfusion/purpura/ petechiae
• Haemodynamically unstable
• Critically unwell

Administer antibiotics + Fluid Bolus within 30 minutes
Piperacillin/Tazobactam IV 100mg/kg (max 4g) G-hrly

Gentamicin IV
1 month to 10yrs: 7.5mg/kg 24-hrly (max 320mg)
More than 10yrs: 6mg/kg/IV 24-hrly (max 640mg) add Vancomycin IV 15mg/kg (max 750mg) 6-hrly

Admit

Once stable pursue other investigations as indicated e.g. CXR; Urine M/C/S Respiratory Virus PCR

*For sepsis see: CHQ Guideline 60310 Sepsis: Recognition and Early Management in Children

*based on piperacillin component
Febrile non-neutropenia antibiotic algorithm

Febrile oncology patient – not Neutropenic

Low risk and
- Child stable with neutrophil count ≥ 1.0 and not anticipated to fall
- If there is an obvious viral focus (e.g. URTI) and no CVAD then consider observation, otherwise give antibiotics

Ceftriaxone IV 100mg/kg (max 4g) 24-hrly

Observe for at least one hour (temp, pulse, respiratory rate and BP q15-20min)

If the child remains stable with no signs of haemodynamic instability, poor perfusion, elevated respiratory rate or significant tachycardia (Table 1) AND no social or parental concerns then discharge home.

If discharged, follow up by phone or hospital review within 24 hrs to review results, progress and ongoing management.

If child remains febrile or unwell – admit, continue Ceftriaxone IV 100mg/kg (max 4g) 24-hrly

For children who have received Piperacillin/Tazobactam as per the *Initial management of suspected febrile neutropenia* but have neutrophils ≥ 1.0:
- Consider a stat dose of Ceftriaxone IV 100mg/kg (max 4g) 24-hrly prior to discharge OR
- If being admitted, give the Ceftriaxone IV dose 8 hours post the Piperacillin/Tazobactam IV dose (and cease Piperacillin/Tazobactam IV order)
ALERT

Exclusion criteria for Febrile non-neutropenia antibiotic algorithm outpatient management:

- Clinical suspicion of bacteraemia: hypotension, poor perfusion, rigors, significant tachycardia, tachypnoea, dehydration
- Impending neutropenia: IV chemotherapy (other than single agent, Vincristine) within the last 10 to 14 days
- High risk patients: AML, ALL undergoing intensification or relapse therapy, High risk solid tumours, Down’s Syndrome, infants, Children post HSCT (see Appendix 2)

Admit and follow the Febrile Neutropenia antibiotic algorithm. Discuss all patients with on call oncology consultant.
Febrile neutropenia follow-on management algorithm

**Febrile neutropenia – admitted to hospital**

- **Stable patient**
  - Piperacillin/Tazobactam IV
  - Negative blood culture

- **LOW RISK DISEASE** (Appendix 1)
  - Assess at 48 hours
    - Afebrile: low risk of bacterial disease? (Appendix 1)
      - Yes → Continue Piperacillin/Tazobactam IV, reassess, repeat blood culture and review at 72 HOURS. No need for empiric antibiotic change if stable and no positive cultures
      - No → Stop IV antibiotics. Consider oral antibiotics to complete 5-7 days

- **HIGH RISK DISEASE** (Appendix 2)
  - Assess at 72 hours
    - Afebrile for 24hrs and completed 3 days IV antibiotics?
      - Yes → Continue antibiotics, reassess, repeat blood culture and review at 96 hours. No need for empiric antibiotic change if stable
      - No → Afebrile for 24 hours at day 4?
        - Yes → Continue antibiotics. If remains febrile reassess, repeat blood, urine, other cultures, viral PCRs, CXR, chest CT. Add Liposomal Amphotericin IV 1mg/kg 24-hrly. If clinical deterioration or if fever continues, change antibiotics as per guideline.
        - No → Septic patient

- **Septic patient**
  - Stop Gentamicin IV and Vancomycin IV at 48 hours if negative cultures and stable.
    - Note: Piperacillin/Tazobactam IV has gram positive activity, fever alone after 48 hours with negative cultures is not a reasonable indication to continue Vancomycin IV
  - Complete 5 days antibiotics
    - If afebrile for at least 24 hours at completion of 5-7 days of appropriate antibiotics stop antibiotics and discharge home
Consultation:

Key stakeholders who reviewed this version:

- Director Infection Management
- State-wide Oncology Nursing Educator, QPPHON
- Clinical Nurse, Oncology Services Group, CHQHHS
- Pharmacist Advanced, Antimicrobial Stewardship
- Clinical Pharmacist Lead, Oncology
- Oncology Director and Oncology SMOs

Definition of terms

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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>CHQHHS</td>
<td>Children’s Health Queensland Hospital and Health Service</td>
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<tr>
<td>CVAD</td>
<td>Central venous access device</td>
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<tr>
<td>CVL</td>
<td>Central venous line</td>
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</tr>
<tr>
<td>IMPS</td>
<td>Infection Management and Prevention Service</td>
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<tr>
<td>IFD</td>
<td>Invasive fungal disease</td>
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<tr>
<td>AML</td>
<td>Acute Myeloid Leukaemia</td>
<td></td>
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<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukaemia</td>
<td></td>
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<tr>
<td>HSCT</td>
<td>Haematopoetic stem cell transplant</td>
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References and suggested reading

Guideline revision and approval history

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**Keywords**
- Oncology; Fever; Febrile; Neutropenia; Neutropenic; Non-Neutropenic; Antibiotics; antimicrobial stewardship; sepsis; antifungals, 01249

**Accreditation references**
- NSQHS Standards (1-8): 3; 4; 5; 6
- ISO 9001:2015 Quality Management System (4-10)
Appendix 1:

Risk of serious bacterial infection

Low risk patients:
- Age ≥12 months
- Not on myeloablative treatment or during extremely intensive chemotherapy
- No social or economic conditions that compromise access to care or adherence to treatment
- No other medical conditions requiring hospitalisation
- Evidence of recovering marrow function

Low risk of bacterial infection:
- Not clinically unwell
- No evidence of a significant source of infection (eg pneumonia, soft tissue infection, severe mucositis) requiring IV antibiotics
- No clinically significant positive blood cultures
- Evidence of recovering marrow function (a clinical decision – the consultant should be involved, no evidence for any specific neutrophil cut off to be useful)
- No other clinical features to suggest significant infection (eg CRP >100 mg/L or rising)

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<td>0.1 – 0.5 x 10⁹/L</td>
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<td>&lt;0.1 x 10⁹/L</td>
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<tr>
<td>Duration of neutropenia</td>
<td>&lt; 7 DAYS</td>
<td>≥ 7-10 DAYS</td>
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<td>Co morbidity</td>
<td>None</td>
<td>Toxic/Shocked</td>
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Appendix 2:

High risk disease

AML

ALL: Infant ALL (<1y);
    Induction;
    Delayed intensification

Downs syndrome

Lymphoma: Induction therapy

Neuroblastoma stage IV

Allogeneic transplant: Day -14 to Day +180

Autologous transplant: Day -7 to Day +60

Reinduction therapy for any relapse

If in doubt discuss with Oncology Consultant on call or treat as high risk

Table 1

Table 1: Normal range for age specific vital signs

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<thead>
<tr>
<th>Age</th>
<th>Heart Rate (bpm)</th>
<th>Minimum Systolic BP (mmHg)</th>
<th>Respiratory Rate (bpm)</th>
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<td>60-100</td>
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As per CHQ-GDL-60010-Sepsis: Recognition and Early Management in Children

CHQ-GDL-01249 – Management of Fever in a Paediatric Oncology Patient – Febrile Neutropenia and Febrile Non-Neutropenia