Guideline

Management of Fever in a Paediatric Oncology Patient - Febrile Neutropenia and Febrile Non-neutropenia

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Primary Document			
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HUMAN RIGHTS

This governance document has been human rights compatibility assessed. No limitations were identified indicating reasonable confidence that, when adhered to, there are no implications arising under the *Human Rights Act 2019.*

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.

GUIDELINE

Febrile Neutropenia (FN)

Definition

Fever: ≥ 38.5^0 C on one occasion **or**

≥ 38.0^0 C on two occasions – at least one hour apart **WITH EITHER**

Neutropenia: a neutrophil count of <1 x 10^9/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 10^9/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 (if pseudomonas aeruginosa is cultured, contact CHQ ID SMO on call to discuss rationalizing therapy)
- **Gentamicin Dose (normal renal function):**
- 1 month to 10 years and critically ill/septic shock: 7.5 mg/kg every 24 hrs (maximum initial dose 320 mg);
- More than 10 years and critically ill/septic shock: 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 Vancomycin for patients with suspected CVAD infection or MRSA.
- **In patients treated with high dose cytarabine (HD Ara-C) who have high risk of *S.mitis* and are receiving Teicoplanin prophylaxis (Appendix 3), do not add Vancomycin. Continue Teicoplanin at 15 mg/kg/dose (Maximum 800mg/dose) IV three times a week (Mondays, Wednesdays and Fridays) and review with cultures.**

- **Vancomycin dose (normal renal function)** = 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 (rash)–** Use Ceftazidime IV 50 mg/kg/dose (maximum 2 gram per dose) every 8 hourly
- **Beta lactam anaphylaxis** – Use Meropenem IV 40 mg/kg/dose (maximum 2 gram per dose) every 8 hourly (see ALERT below)
- AMS approvals are required for restricted antibiotic use outside of stated indications and timeframes. Please refer to the CHQ AMS Formulary and CHQ-PROC-01036 Antimicrobial: Prescribing and Management (health.qld.gov.au).

Supplemental Investigations:

ALERT

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

- 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 <u>all</u> 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 ≥ 38^0 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.

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).

<u>Initially stable with suspected Febrile Neutropenia:</u>

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.

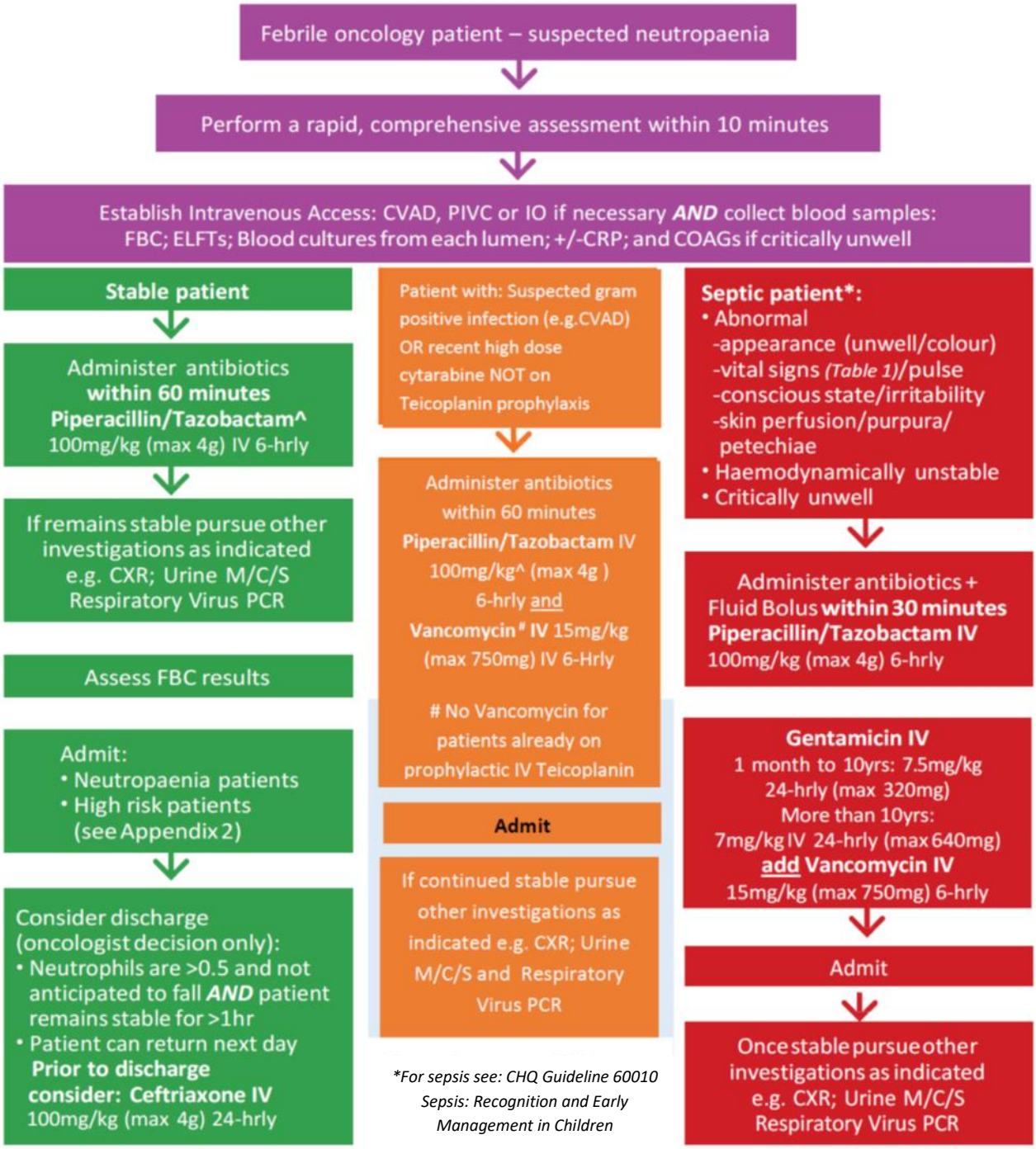
Febrile at 4 to 5 days:

- 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 neutropaenia antibiotic algorithm

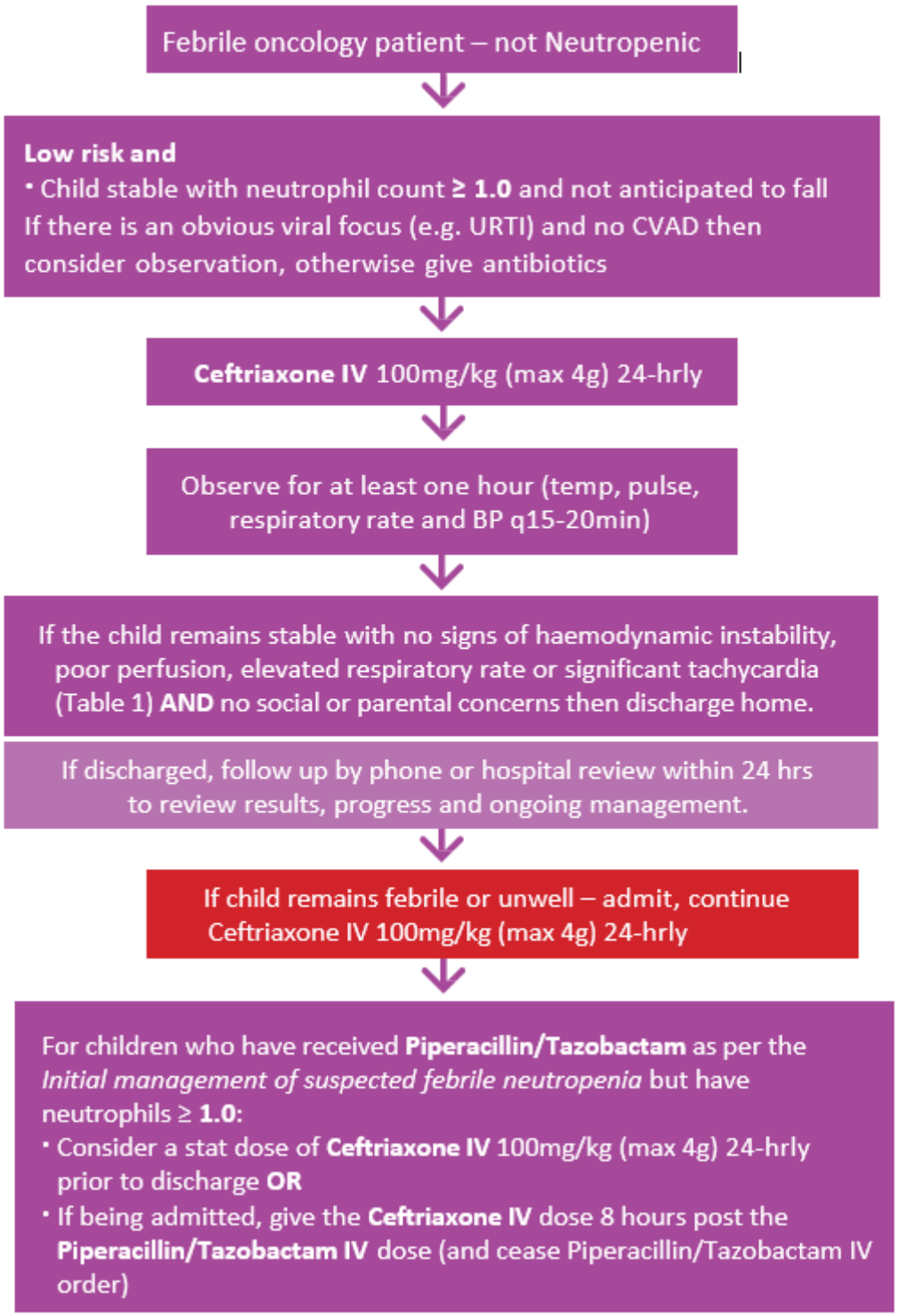


**For sepsis see: CHQ Guideline 60010 Sepsis: Recognition and Early Management in Children*

^ based on Piperacillin component

#AML and infant ALL may already be on teicoplanin (see appendix 3)

Febrile non-neutropenia antibiotic algorithm



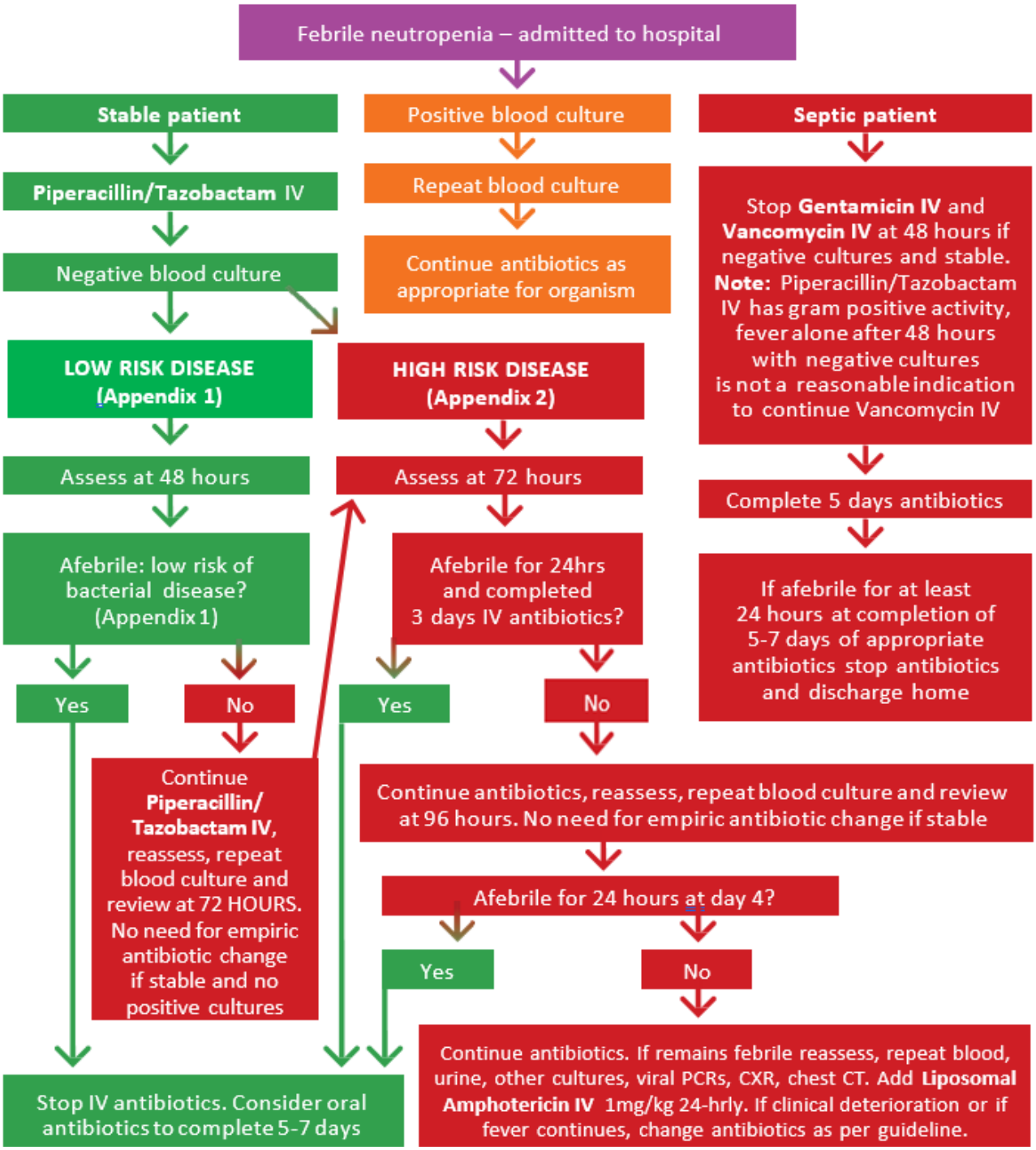
ALERT

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



SUPPORTING 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 Antibiocard: 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
- CHQ-GDL-01249-1 Febrile Oncology – Emergency Management in Children - Flowchart

FORMS AND TEMPLATES

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

CONSULTATION

Key stakeholders who reviewed this version:

• Service Group Director Infection Management and Prevention service, Immunology and Rheumatology • State-wide Oncology Nursing Educator, QPPHON	• Pharmacist Advanced, Antimicrobial Stewardship • Clinical Pharmacist Lead, Oncology • Oncology Director and Oncology SMOs

DEFINITIONS

Term	Definition
CHQHHS	Children's Health Queensland Hospital and Health Service
CVAD	Central venous access device
CVL	Central venous line
IMPS	Infection Management and Prevention Service
IFD	Invasive fungal disease
AML	Acute Myeloid Leukaemia
ALL	Acute Lymphoblastic Leukaemia
HSCT	Hematopoetic stem cell transplant
HSV	Herpes Simplex virus
VZV	Varicella Zoster Virus
CMV	Cytomegalovirus
EBV	Epstein barr virus
GVHD	Graft versus host disease
UTI	Urinary tract infection
CXR	Chest Xray

REFERENCES

No.	Reference
1	Salstrom J et al. Pediatric Patients who receive antibiotics for fever and neutropenia in less than 60 min have decreased intensive care needs. Pediatr Blood Cancer 2015; 62:807-815
2	Fletcher M et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer. 2013 Aug;60(8):1299-306
3	Cometta A et al. Vancomycin versus Placebo for Treating Persistent Fever in Patients with Neutropenic Cancer Receiving Piperacillin-Tazobactam Monotherapy. CID 2003; 37:382-9
4	Lehrnbecher T, Sung L. Anti-infective prophylaxis in pediatric patients with acute myeloid leukemia, Expert Review of Hematology. 2014, 7:6, 819-830, DOI: 10.1586/17474086.2014.965140
5	Botzug H et al. Antibiotic prophylaxis with teicoplanin on alternate days reduces rate of viridans sepsis and febrile neutropenia in pediatric patients with acute myeloid leukemia. Ann Hematol (2017) 96:99–106. DOI 10.1007/s00277-016-2833-5

GUIDELINE REVISION AND APPROVAL HISTORY

Version No.	Modified by	Amendments authorised by	Approved by
1.0	Director Infectious Diseases	Divisional Director of Medicine	Executive Director Clinical Services QCH
2.0 11/06/2020	Director Infectious Diseases	Divisional Director of Medicine	Executive Director Clinical Services QCH
3.0 21/05/2021	Minor update to add flowchart	Director Oncology	Divisional Director of Medicine
4.0 08/03/2023	Pharmacist Advanced - AMS	Director of Infectious Diseases	Executive Director Medical Services
4.1	Pharmacist Advanced - AMS	Director of Infectious Diseases	Executive Director Medical Services
4.2 12/03/2025	Pharmacist Advanced - AMS	Senior Director	Executive Director Clinical Services

Key words	Oncology; Fever; Febrile; Neutropenia; Neutropenic; Non-Neutropenic; Antibiotics; piperacillin/tazobactam, gentamicin, ceftriaxone, vancomycin, teicoplanin, ceftazidime, meropenem, antimicrobial stewardship; sepsis; antifungals, 01249
Accreditation references	NSQHS Standards (1-8): 3; 4; 5; 6

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)

	LOW RISK	**HIGH RISK**
Absolute neutrophil count	0.1 – 0.5 x 10^9/L	≤0.1 x 10^9/L
Duration of neutropenia	< 7 DAYS	≥ 7-10 DAYS
Co morbidity	None	• Toxic/Shocked • BMT Inpatient • AML patients

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

As per CHQ-GDL-60010-Sepsis: Recognition and Early Management in Children

Table 1: Normal range for age specific vital signs

Age	Heart Rate (bpm)	Minimum Systolic BP (mmHg)	Respiratory Rate (bpm)
Term	100-180	60	40-60
6mth	100-180	70	30-50
1yr	100-170	70	20-40
2yr	100-160	70	20-30
4yr	80-130	75	20-30
8yr	70-110	80	16-25
12yr	60-110	90	16-25
16yr +	60-100	90	10-16

APPENDIX 3:

Intervention to reduce *Streptococcus mitis* (and VGS) health care associated blood stream infections (HA BSI) in highly at risk children with cancer

Patient groups: Neutropenic children with AML (including congenital) and infant ALL.

***Streptococcus mitis* Prophylaxis:**

Give Teicoplanin IV 15mg/kg/dose (Maximum 800mg) three times a week (eg. Mondays, Wednesdays and Fridays) (ID approval required)

- When to start: At onset of severe neutropenia, when neutrophil count less than 0.5.
- When to stop: Cease Teicoplanin when neutrophil count is more than or equal to 0.5.
- No loading dose required