

Infants and Children: Initial Management of Fever/Suspected Sepsis in Oncology /Transplant Patients

Summary This guideline is aimed at achieving optimal paediatric care throughout New South Wales for a unique group of children with a significantly elevated risk of severe infection, namely those undergoing therapy for cancer or stem cell transplantation.

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INFANTS AND CHILDREN: INITIAL MANAGEMENT OF FEVER OR SUSPECTED INFECTION IN ONCOLOGY AND STEM CELL TRANSPLANTATION PATIENTS

PURPOSE

The *Infants and Children: Initial Management of Fever or Suspected Infection in Oncology and Stem Cell Transplantation Patients, first edition* Clinical Practice Guideline has been developed to provide direction to clinicians and is aimed at achieving the best possible paediatric care in all parts of the state. The Clinical Practice Guideline was prepared for the NSW Ministry of Health by an expert clinical reference group under the auspice of NSW Kids and Families.

KEY PRINCIPLES

This guideline applies to all facilities where paediatric patients are managed. It requires the Chief Executives of all Local Health Districts and specialty health networks to determine where local adaptations are required or whether it can be adopted in its current Clinical Practice Guideline format in all hospitals and facilities required to manage infants and children undergoing therapy for cancer or stem cell transplantation presenting with fever or suspected infection.

The clinical practice guideline reflects what is currently regarded as a safe and appropriate approach to the management of fever or suspected infection in infants and children undergoing therapy for cancer or stem cell transplantation. However, as in any clinical situation there may be factors which cannot be covered by a single set of guidelines. This document should be used as a guide, rather than as a complete authoritative statement of procedures to be followed in respect of each individual presentation. **It does not replace the need for the application of clinical judgement to each individual presentation.**

USE OF THE GUIDELINE

Chief Executives must ensure:

- Hospitals and facilities either adopt this protocol or adapt local protocols to comply with the *Infants and Children: Initial Management of Fever or Suspected Infection in Oncology and Stem Cell Transplantation Patients, first edition* Clinical Practice Guideline
- Local protocols are in place in all hospitals and facilities likely to be required to manage paediatric oncology and stem cell transplantation patients with fever or suspected infection
- Ensure that all staff treating paediatric patients are educated in the use of the locally developed paediatric protocols.

Directors of Clinical Governance are required to inform relevant clinical staff treating paediatric patients of this new guideline.

REVISION HISTORY

Version	Approved by	Amendment notes
October-2015 (GL2015_013)	Deputy Secretary, Population and Public Health	New Guideline

ATTACHMENT

1. Infants and children: Initial Management of Fever or Suspected Infection in Oncology and Stem Cell Transplantation Patients, first edition Clinical Practice Guideline.

INFANTS AND CHILDREN

+ Initial Management of Fever or Suspected Infection in Oncology and Stem Cell Transplantation Patients

CLINICAL PRACTICE GUIDELINE

1st edition

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1 BACKGROUND

1.1 Purpose

This guideline is aimed at achieving optimal paediatric care throughout New South Wales for a unique group of children with a significantly elevated risk of severe infection, namely those undergoing therapy for cancer or stem cell transplantation. For the purpose of this guideline, paediatric oncology patients refer to patients (less than 18yrs of age and /or under care of paediatric oncologists) with cancer or undergoing Stem Cell Transplantation (SCT) for any disease.

The guideline should be used with the relevant clinical input and judgment of the managing professionals.

Infection in paediatric oncology/SCT patients presents most commonly with fever. Some patients with serious infection may present without fever or with hypothermia.

Prompt administration of antibiotics (within 60 minutes of presentation) will reduce morbidity and mortality.

Parental concern and judgment are extremely important and are valid triggers for commencing this clinical practice guideline irrespective of the child's clinical condition.

Respecting the difference – be aware of cultural differences of Aboriginal people. Refer to your local Aboriginal liaison or for further information see [NSW Health Communicating positively – A guide to appropriate Aboriginal terminology](#).

1.2 Overview

Infection in paediatric oncology patients (including patients undergoing immunosuppressive SCT) is a common complication and a major source of morbidity and mortality. Fever may be the only indication of a severe underlying infection, as signs and symptoms of inflammation (pain, erythema, and swelling) are typically attenuated in this group of patients. In these patients severe infection may also occur in the absence of fever or neutropenia.¹ Guidelines have been developed for management of febrile neutropenia (mainly in adults), all highlighting the importance of early administration of antibiotics.²⁻⁷

Prompt assessment, initiation of antibiotics and supportive care is essential to minimizing adverse outcomes. ***The aim of this guideline is to ensure that paediatric oncology patients (including patients undergoing immunosuppressive SCT) at risk of infection receive appropriate treatment within 60 minutes or less of presentation to a NSW health care facility.*** Standardisation of treatment practices through clinical guidelines and pathways allows monitoring and evaluation of patient outcomes and helps promote compliance with optimal treatment strategies.⁸ Minimizing and eliminating the variability in the management of fever and neutropenia

in paediatric oncology patients presenting in different acute care settings across NSW is essential to achieve the best standard of care.

The timely and accurate identification of children at risk for infection (e.g. patients on chemotherapy, patients with central venous access devices, recent neutropenia) is essential. Clinical judgment and observations are important in the assessment and management of fever in these children. For paediatric oncology patients presenting with fever, reported fever (temperature $\geq 38^{\circ}\text{C}$), suspected infection without fever, or unwell, the time taken for clinical assessment and observation as well as results of specific investigation must not delay the initiation of antibiotic and supportive care. It is important to note that in the setting of fever and neutropenia, clinical judgment cannot reliably distinguish those with and without serious infection at the time of presentation.

These guidelines are designed to provide assistance within the critical first 60 minutes of presentation to healthcare facility and provide further guidance for the following 24 hours. Continued re-evaluation of these patients is critical to their successful outcome. The child's treating oncologist or oncologist on call should be contacted as soon as practicable after initiation of treatment. ***Decisions regarding subsequent changes to and duration of antibiotic therapy are beyond the scope of this guideline and are the responsibility of the treating oncologist within the scope of local antimicrobial stewardship programs.***

1.3 Summary

The single most important advance in infectious diseases oncology supportive care leading to improved survival has been the prompt initiation of empiric antibiotics when the neutropenic cancer patient becomes febrile. Justification for the prompt administration of antibiotics includes the potential for rapid progression of infection and the inability to distinguish those with and without serious infection at the time of initial evaluation. Before this approach was instituted in the early 1970s, the mortality rate from gram-negative infections especially that of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, approached 80%. With the widespread use of effective empiric antibiotics, the overall mortality has declined significantly.¹

Infection still remains a major cause of morbidity and mortality in paediatric oncology patients. Infection was responsible for 30% of early deaths in a cohort of paediatric acute leukaemia patients from Canada (Cheng et al 2013).⁹ In a recent study by Fletcher M, et al time to administration of antibiotic (>60 minutes vs. < 60 minutes) emerged as a significant risk factor for poor outcome in paediatric patients with febrile neutropenia (Fletcher et al 2013).¹⁰

A review of incidents relating to fever and neutropenia notified within the Incident Information Management System (IIMS) of the Sydney Children's Hospitals Network highlighted the following:

- Clinician unfamiliarity with correct protocol for drug, dose, route and frequency for febrile neutropenic children
- Failure to record adequate observations at triage and/or during admission
- Inadequate procedures for transfer from a rural/regional ED to a tertiary facility

Other important management issues identified are:

- Obtaining accurate weight to ensure drug dose is appropriate
- Accurate recording of dose route and frequency of medications
- Medication reconciliation – recording current medications

This guideline has been developed to assist clinicians unfamiliar with and/or uncertain of best practice in the management of febrile or acutely sick paediatric oncology patients presenting to a healthcare facility emergency department or paediatric ward. This may also include the appropriate transfer procedures for such children within rural or regional areas.

1.4 Key Points in the Recognition and Management

- **Fever and Neutropenia:** In the literature different definitions of fever are used clinically and in paediatric febrile neutropenia research settings.^{11,12} For the purpose of this guideline the working party has agreed to the following definitions of fever and neutropenia:
 - Fever - a single temperature ≥ 38.0 °C by any route (axillary, oral, at home or on presentation). Tympanic temperatures are not recommended due to inaccuracy.
 - Neutropenia - a Neutrophil count $< 1.0 \times 10^9/L$ (= 1000/mm³)
- Do not wait for topical anaesthetic to take effect to access port-a-cath or insert a peripheral cannula
- Do not wait for laboratory test results before starting antibiotics
- Central Venous Access Devices (CVAD) with or without neutropenia are a significant source of infection
- Patients who become febrile within 12 hours of CVAD access should be considered at high risk of infection/sepsis
- The full blood count can change rapidly within 24-48 hours if patient is receiving chemotherapy
- Results of blood counts taken more than 24 hours prior to presentation may not be indicative of the degree of neutropenia
- Mucositis commonly co-exists with fever and neutropenia
- Fever in paediatric oncology patients may be secondary to drugs (Cytarabine, Bleomycin), transfusion of blood products or viral infection. It is not possible to rule out bacterial infection in these patients and hence prompt administration of antibiotics is indicated in such situations
- Fever may be absent in some paediatric oncology patients with infection, particularly those with profound neutropenia and those receiving corticosteroids. The presence of infection in this setting may be detected only by attention to seemingly minor complaints from the patient or by subtle physical findings.

For example:

- abdominal pain may signify an evolving intra-abdominal infection (enterocolitis, appendicitis)
- erythema and tenderness along a subcutaneous catheter tunnel track may indicate the presence of a deep seated soft-tissue infection
- diarrhoea may be the only symptom of infection

- fainting may be the sole manifestation of sepsis
- Children with sepsis may on occasion present with hypothermia
- Some children present with history of fever at home, but are afebrile on presentation to the hospital. These patients must be treated in the same way as patients with fever.
- After accessing the CVAD and administration of antibiotics there may be acute deterioration due to septic shower/endotoxin release. It is vital that the child is closely observed and monitored for deterioration.

Neutropenic patients may not show usual signs of infection or inflammation.

2 SCOPE

- These guidelines are designed to provide assistance in the initial 60 minutes of presentation to the Emergency Department or designated inpatient setting in the management of the following patients presenting with fever or reported fever $> 38.0^{\circ}\text{C}$ or who are unwell :
 - Patients on treatment for cancer
 - Patients who ceased treatment for cancer within the last 3 months
 - Recipients of Stem Cell Transplantation (SCT) within the last 12 months or on immunosuppressive therapy
 - Oncology or SCT patients with Central Venous Access Device (CVAD) in situ
- The guideline then provides further guidance for the following 24 hours
- The majority, but not all, will present with fever
- It is important to note that most paediatric oncology patients have a CVAD in situ which is a potential source of infection irrespective of neutrophil count
- Not all patients are at the same risk of acquiring significant infections during episodes of neutropenia. Clinical assessment and judgement of patients at presentation may not, with complete accuracy, discriminate those with and without significant infection. Patients are divided in two groups:
 1. **Patients with Fever and Neutropenia:** The majority of paediatric oncology patients present with fever and neutropenia and usually do not have an obvious focus of infection. For such patients the morbidity and mortality is reduced with prompt administration of empiric antibiotic therapy.
 2. **Unwell Oncology/SCT patients regardless of temperature or neutrophil count:** Patients may have significant infections without fever and/or neutropenia. In this group clinical significance may not be recognised, leading to inappropriate or delayed management. These guidelines recommend that these patients are managed initially in the same way as febrile patients who are neutropenic.
- The treatment plan for these patients must always incorporate an initial assessment and physical examination but, administration of antibiotics should not be delayed.

- Choice of antibiotics:
 - Monotherapy (use of single antibiotic) with an anti-pseudomonal beta-lactam is recommended by the Australian Therapeutic guidelines – antibiotic 2015 for paediatric oncology patients presenting with fever without severe sepsis or shock. In the *2015 Australian Therapeutic Guidelines*, the addition of A second Gram – negative agent (e.g. Aminoglycosides) or glycopeptide is reserved for patients who are clinically unstable or when a resistant infection is suspected or for centres with high rate of resistant pathogens.^{13,14,15, 21}
 - For the purpose of this clinical practice guideline, which includes paediatric oncology and bone marrow transplant patients presenting to an acute care facility at any NSW hospital managed by staff with varying levels of experience, the working party has pragmatically decided to include a single dose of Gentamicin in addition to Piperacillin +Tazobactam as initial antibiotic therapy for clinically stable patients. This decision was motivated principally by the potential inexperience in recognising severe sepsis in this population. The decision regarding continuation of Gentamicin must be made after discussing with the treating oncologist, but is generally discouraged in stable patients due to the lack of proven benefit and potential for toxicity.
- **Decisions regarding subsequent changes to and duration of antibiotic therapy are beyond the scope of this guideline and are the responsibility of the treating oncologist within the scope of local antimicrobial stewardship programs.**

3 ALGORITHM

See next page:

Key for Algorithm:

^Indications for Vancomycin: Obviously infected intravascular devices (erythema/tenderness along subcutaneous track or purulent exit site discharge), MRSA carriers with clinical instability, high dose cytarabine recipients (>2gm/m²) with clinical instability

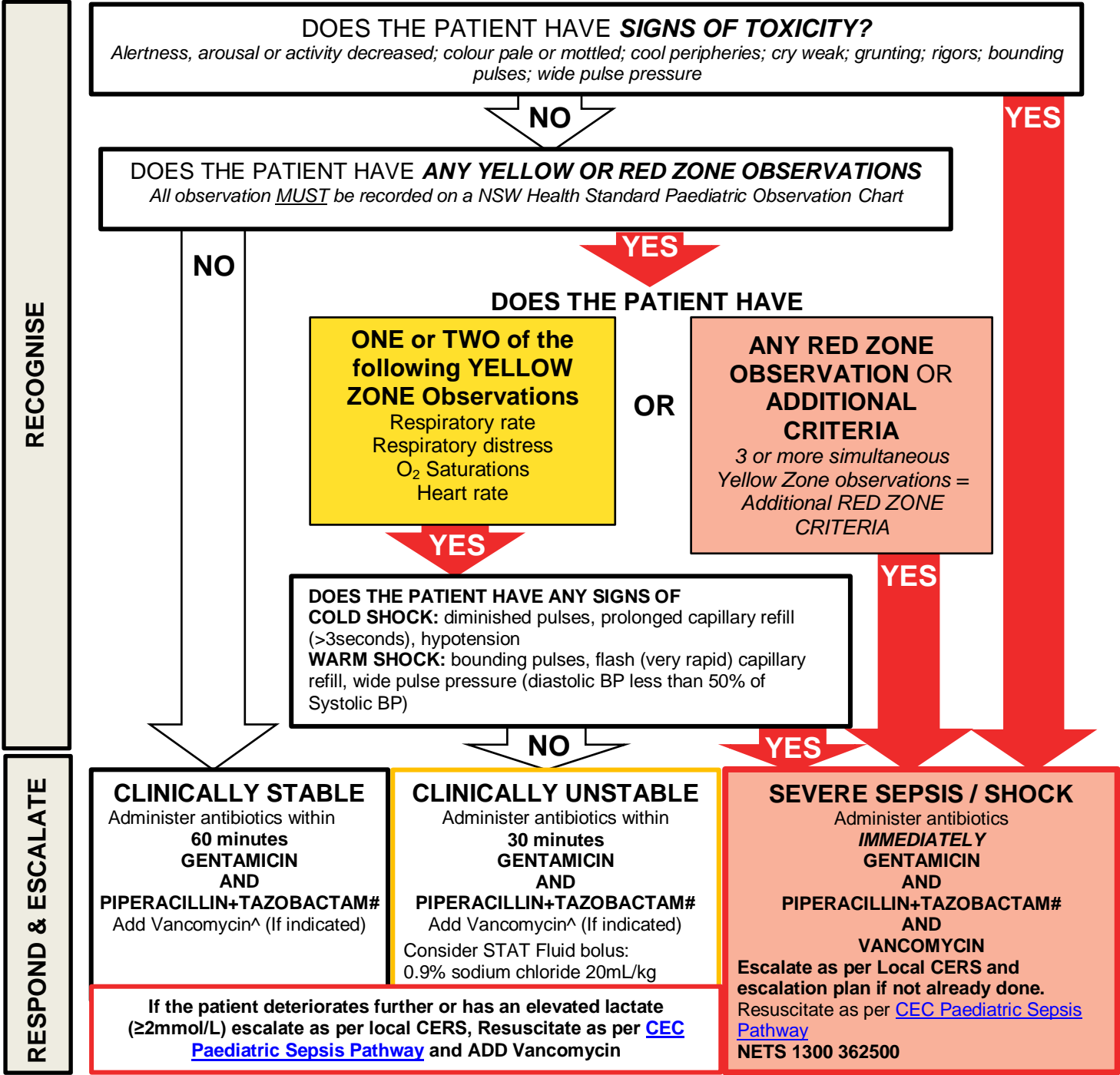
#Patients with penicillin allergy: refer to table 1 for first antibiotic choice

Minimum Triage Category 2 for patients presenting to the ED
If an *inpatient* or presenting directly to the ward activate a RAPID RESPONSE as per local CERS

For the following patients with fever or reported fever $\geq 38.0^{\circ}\text{C}$ or who are unwell

- Patients on treatment for cancer
- Patients who ceased treatment for cancer within the last 3 months
- Recipients of Stem Cell Transplantation (SCT) within the last 12 months or on immunosuppressive therapy
- Oncology or SCT patients with Central Venous Access Device(CVAD) in situ

Do Not Wait for local anaesthetic to take effect. (E.g. to access port or insert peripheral line)
 Access CVAD or establish peripheral IV and collect Blood cultures, FBC, VBG (Lactate & glucose) EUC, LFT
DO NOT WAIT FOR BLOOD RESULTS TO START ANTIBIOTICS



Discuss the management plan with the patient and family
 Inform Paediatrician as per local CERS and Oncologist on call as soon as possible

TABLE 1: FIRST DOSE OF EMPIRICAL ANTIBIOTICS

TREATMENT		Clinically Stable	Clinically Unstable	Severe Sepsis/Shock
EMPIRICAL ANTIBIOTIC REGIMEN*		<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV (max. dose 320 mg) Single dose only</p> <p>then</p> <p>Piperacillin+Tazobactam 100 mg/kg/dose IV 6 hourly (max. dose 4 g Piperacillin component) ADD</p> <p>Vancomycin[^] if clinically indicated</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg)</p> <p>then</p> <p>Piperacillin+Tazobactam 100 mg/kg/dose IV 6 hourly (max. dose 4 g Piperacillin component) ADD</p> <p>Vancomycin[^] if clinically indicated</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg)</p> <p>then</p> <p>Piperacillin+Tazobactam 100 mg/kg/dose IV 6 hourly (max. dose 4 g Piperacillin component)</p> <p>AND Vancomycin 15 mg/kg/dose IV 6 hourly (max. dose 750 mg)</p>
ALLERGY	Non-life threatening penicillin hypersensitivity	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV Single dose only (max. dose 320 mg)</p> <p>AND</p> <p>Cefepime 50 mg/kg/dose IV 8 hourly (max. dose 2 g)</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg).</p> <p>AND</p> <p>Cefepime 50 mg/kg/dose IV 8 hourly (max. dose 2 g) OR Meropenem 40 mg/kg/dose IV 8 hourly (max. dose 2 g)</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg).</p> <p>AND</p> <p>Cefepime 50 mg/kg/dose IV 8 hourly (max. dose 2 g) OR Meropenem 40 mg/kg/dose IV 8 hourly (max. dose 2 g)</p> <p>AND Vancomycin 15 mg/kg/dose IV 6 hourly (max. dose 750 mg)</p>

	TREATMENT	Clinically stable	Clinically unstable	Severe sepsis/shock
ALLERGY	Life-threatening Penicillin Hypersensitivity not known to tolerate Cephalosporins/ Meropenem safely	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV Single dose only (max. dose 320 mg)</p> <p>AND</p> <p>Ciprofloxacin 10 mg/kg/dose IV 8 hourly (max. dose 400 mg)</p> <p>AND</p> <p>Vancomycin 15 mg/kg/dose IV 6 hourly (max. dose 750 mg)</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg)</p> <p>AND</p> <p>Ciprofloxacin 10 mg/kg/dose IV 8 hourly (max. dose 400 mg)</p> <p>AND</p> <p>Vancomycin 15 mg/kg/dose IV 6 hourly (max. dose 750 mg)</p>	<p>Gentamicin (dose based on lean body weight for obese patients) 7.5 mg/kg/dose IV 24 hourly (max. dose 320 mg)</p> <p>AND</p> <p>Ciprofloxacin 10 mg/kg/dose IV 8 hourly (max. dose 400 mg)</p> <p>AND</p> <p>Vancomycin 15 mg/kg/dose IV 6 hourly (max. dose 750 mg)</p>
MODIFICATIONS		<p>Add Metronidazole 12.5 mg/kg/dose IV 8 hourly (max. dose 500 mg) if Cefepime or Ciprofloxacin used AND evidence of abdominal/perineal infection</p>	<p>Use Meropenem rather than Cefepime or Piperacillin+Tazobactam if colonised with a multi-resistant GNR (e.g. ESBL)</p> <p>Add Metronidazole 12.5 mg/kg/dose IV 8 hourly (max. dose 500 mg) if Cefepime or Ciprofloxacin used and evidence of abdominal/perineal infection</p>	<p>Use Meropenem rather than Cefepime or Piperacillin+Tazobactam if colonised with a multi-resistant GNR (e.g. ESBL)</p> <p>Add Metronidazole 12.5 mg/kg/dose IV 8 hourly (max. dose 500 mg) if Cefepime or Ciprofloxacin used AND evidence of abdominal/perineal infection</p>

All Antibiotic doses are based on actual body weight except Gentamicin.

Gentamicin: Dose based on lean body weight for obese patients – see *appendix 3* for method for calculating lean body weight in obese children. **Administer over 5 minutes.** Ensure that line is flushed with 10-20 mL following Gentamicin and prior to any further doses of antibiotics.

Piperacillin+Tazobactam: Administer over 20- 30 mins.

Vancomycin: Administer over at least 60 mins. If patient has previously experienced ‘red man syndrome’ administer over 2 hours.

^ **Indications for Vancomycin:** Obviously infected vascular devices (erythema/tenderness along subcutaneous track or purulent exit site discharge), MRSA carriers with clinical instability, High dose Cytarabine (>2gm/m²/day) recipients with clinical instability.

For clinically stable patients the decision to continue Gentamicin beyond the first dose must be made in consultation with treating oncologist. Continuation of gentamicin for clinically stable patients is not recommended by the Australian Therapeutic Guidelines – Antibiotic 2015 due to the lack of proven benefit and potential for toxicity.

*Subsequent antibiotic choice/dose (i.e. after first dose) may need modification based on patient’s renal function, clinical stability and history of colonisation with multi-drug resistant organisms. These decisions must be made after discussing with treating oncologist.

For patients continuing Gentamicin, drug level must be monitored just prior to second dose.

For patients continuing Vancomycin, drug level must be monitored just prior to 5th dose.

4 ASSESSMENT

Initial Assessment

Fever or suspected infection in paediatric oncology patients is considered a medical emergency and therapy must be initiated promptly. **All patients presenting to an Emergency Department must be triaged urgently, at least category 2. A Rapid Response call (as per local CERS) MUST be made for all inpatient oncology patients with a new fever or suspected infection.** Children who have received stem cell transplantation (SCT) within the previous 12 months and those who remain on immunosuppressive therapy (e.g. Cyclosporine, steroids, Tacrolimus) should be considered at risk of infection regardless of their blood count.

*Parental concerns must always be considered.
Remember that not all septic patients will be febrile.
If parents are concerned the child should be clinically assessed and
discussed with a senior medical officer.*

Assessment^{17, 18}

Initial priority must be rapid assessment of the following:

Airway

Breathing: Respiratory rate, effort, SpO₂, colour

Circulation: Heart rate, rhythm and pulse strength, blood pressure, capillary refill, colour, consider cardiac monitoring if appropriate

Disability: Mental status, (GCS/AVPU), pain assessment

Exposure: Axillary temperature (tympanic temperatures are not accurate in children), rashes

Fluid: Hydration status inclusive of urine output, mucous membranes

Glucose: Blood glucose level

The selection of a management pathway most appropriate for the patient is done by rapid clinical assessment. This includes looking for signs of toxicity (Alertness, arousal or activity decreased; colour pale or mottled; cool peripheries; cry weak; grunting; rigors; bounding pulses; wide pulse pressure) and recording patient parameters on standard paediatric observation chart/paediatric emergency department observation chart.¹⁵

After initial rapid assessment patients are classified in 3 groups as follows:

Clinically stable	Clinically Unstable	Severe Sepsis/Shock
<p><u>ALL of the following</u></p> <p>1. No signs of toxicity</p> <p>AND</p> <p>2. <u>No Yellow or Red Zone</u> criteria</p>	<p><u>ALL of the following</u></p> <p>1. No signs of toxicity</p> <p>AND</p> <p>2. <u>One or two</u> of the following in <u>Yellow Zone</u>: respiratory rate, respiratory distress, O² saturation, heart rate</p> <p>AND</p> <p>3. Normal blood pressure, capillary refill and level of consciousness</p> <p>4. If any signs of cold or warm shock elevate to severe sepsis/shock pathway</p>	<p><u>ANY ONE of the following</u></p> <p>1. Any sign of toxicity</p> <p>2. <u>Three or more</u> of the following in <u>Yellow Zone</u>: respiratory rate, respiratory distress, O² saturation, heart rate</p> <p>3. <u>Any parameter in Red Zone</u></p> <p>4. <u>Signs of cold shock</u>: diminished pulses, prolonged capillary refill (>3seconds), hypotension</p> <p>5. <u>Signs of warm shock</u>: bounding pulses, flash (very rapid) capillary refill, wide pulse pressure (diastolic BP less than 50% of systolic BP)</p>

Hypotension is not necessary for the clinical diagnosis of septic shock; however, its presence in a child with clinical suspicion of infection is confirmatory.¹⁸

- Complete physical assessment from oral mucosa to peri-rectal area with attention to CVAD exit site and primary complaints
- Request the oncology diary/folder from parents

NOTE: The absence of Neutrophils can mask the classic signs of infection

5 INITIAL MANAGEMENT

All paediatric oncology patients presenting with fever, reported fever or unwell following chemotherapy should be managed as if they have neutropenic fever and receive prompt empiric antibiotics.

- Aerobic and anaerobic blood cultures should be collected from each lumen of the CVAD (if present) or peripheral vein but antibiotic administration should not be delayed because of technical difficulties (e.g. inability to withdraw blood from CVAD)
- Antibiotic commencement should **NOT** be delayed for confirmation of neutrophil count. Antibiotic management can be subsequently modified if neutrophil count is normal.

TABLE 2: TIME TO ADMINISTRATION OF FIRST DOSE OF ANTIBIOTIC

Clinically stable	Clinically Unstable	Severe Sepsis/shock
Patients should receive antibiotics within 60 minutes of presentation after collection of blood cultures	Patients should receive their first antibiotic dose within 30 minutes of presentation after the immediate collection of blood cultures and administration of fluid support.	Patients should receive their first antibiotic dose immediately and resuscitation as per CEC paediatric sepsis pathway . ¹⁹

- Administration of antibiotics must not be delayed for results of laboratory investigations or radiological studies
- If patients classified as “Clinically Stable or Clinically Unstable” have an elevated lactate level (≥ 2 mmol/L) or show signs of further deterioration they should be treated as severe sepsis/shock category. This includes the IMMEDIATE administration of 3 antibiotics (Gentamicin, Piperacillin+Tazobactam and Vancomycin), escalation as per local CERS and resuscitation as per [CEC paediatric sepsis pathway](#).

Supportive care interventions

- Access CVAD or insert an intravenous cannula. Do not wait for topical anaesthetic creams to take effect
- Obtain both aerobic and anaerobic blood cultures from each central venous catheter lumen, port-a-cath or peripheral venepuncture if CVAD access is not available
- Obtain additional blood for:
 - Full blood count
 - Venous Blood Gas (Lactate & glucose)
 - Electrolytes
 - Liver function tests.
- Urine analysis or urine culture if indicated
- Swab any sites of concern for culture
- Administer antibiotics promptly as per algorithm, using alternating lumens, commencing with aminoglycoside due to inactivation by penicillins. For Vancomycin administration, if patient has previously had ‘red man syndrome’ (histamine release) reaction, administer dose over **no less** than 2 hours
- If fever persists, administer antipyretics. Do not administer antipyretics rectally. Rectal medications are not administered to neutropenic patients due to the increased risk of bacteraemia with enteric pathogens and possible bleeding
- Non-steroidal anti-inflammatory drugs (NSAIDs) are not to be given to paediatric oncology patients as they increase the risk of bleeding

- Assess for pain using age appropriate paediatric pain assessment tool and offer analgesia as required. Refer to Management of Acute and Procedural Pain in the Emergency Department Clinical Practice Guideline
- Perform observations at a minimum of hourly or more frequently to identify deterioration of condition
- Commence strict fluid balance to monitor patient's fluid status
- Assess the effectiveness of nursing interventions and general patient comfort
- Communicate laboratory results to medical staff as soon as they are available
- Discuss with the patient and parents the reason for the tests and procedures as well as the ongoing treatment plan
- Inform the patient's treating team, when appropriate, of the patient's condition.

Do not give medications via the rectal route, non-steroidal anti-inflammatory drugs or aspirin to a paediatric oncology patient.

6 FIRST DOSE EMPIRIC ANTIBIOTIC REGIMEN AND MODIFICATION

First dose antibiotic therapy for all patients is as per Table 1²⁰⁻²²

- First dose antibiotic therapy for all clinically stable and unstable patients includes 2 antibiotics (Gentamicin and Piperacillin+Tazobactam)
- First dose antibiotic therapy for all patients with severe sepsis/shock includes 3 antibiotics (Gentamicin and Piperacillin+Tazobactam and Vancomycin)
- Subsequent doses of Gentamicin will be based on patient's clinical stability, blood culture result, and renal function. The treating oncologist MUST be consulted in the ongoing antibiotic therapy
- As described in the Table 1 and in the following paragraphs, the first dose of antibiotic for some patients may be different from Gentamicin, Piperacillin+Tazobactam and Vancomycin due to allergy or history of colonisation with multidrug resistant organisms. It is very important that a clear documented plan and communication occurs between tertiary hospital and local hospital, as part of discharge planning, to ensure availability of these antibiotics at the local hospital.

6.1 Modification to First Dose Empiric Therapy for Patients with Vancomycin Allergy:

Some patients may need modification of the therapy as follows:

- Non-life-threatening penicillin hypersensitivity (i.e. rash): Usually **Cefepime** (in specific circumstances **Meropenem** may be substituted) and **Gentamicin**.
 - ✓ ADD Metronidazole if features of abdominal or perineal infection and Cefepime is selected
- Life-threatening/immediate hypersensitivity reaction to penicillin: **Ciprofloxacin + Vancomycin and Gentamicin**
 - ✓ ADD Metronidazole if features of abdominal or perineal infection

- Non-life-threatening Vancomycin allergy (i.e. rash): If Vancomycin would otherwise be indicated, replace with **Teicoplanin** (10mg/kg/dose IV 12 hourly (max. dose 400mg) for 3 doses followed by 10mg/kg/dose IV 24 hourly (max. dose 400 mg))
- Life-threatening Vancomycin allergy: If Vancomycin would otherwise be indicated, consult an infectious diseases physician or clinical microbiologist and oncologist urgently. Options include **Linezolid** (1 month - 12 years 10mg/kg/dose IV 8 hourly (max. dose 600 mg), (greater than 12 years 600mg IV 12 hourly) or **Daptomycin** (no paediatric dose currently established. Adult dose is 6-10 mg/kg IV once daily).

6.2 Modification to First Dose Antibiotics for Patients with History of Colonisation with Drug Resistant Organisms

- If a clinically unstable (severe sepsis/shock) patient is known to be colonised with a multi-drug resistant gram negative bacilli (such as an ESBL producing gram negative bacilli) use **Meropenem**
- If the patient is known to be colonised with a Carbapenem-resistant gram negative bacilli (e.g. MBL-enterobacteriaceae) seek urgent infectious disease/microbiology advice and use the aminoglycoside **Amikacin instead of Gentamicin**
- If the patient is known to be colonised by a Van-B type Vancomycin-resistant enterococci (VRE), replace the Vancomycin with **Teicoplanin**. If the VRE is Van A type consult an infectious disease physician/clinical microbiologist urgently. Options include **Linezolid** or **Daptomycin**.

6.3 Indications for Vancomycin use

- Severe sepsis/shock
- Obviously infected CVAD (erythema/tenderness along subcutaneous track, or purulent exit site discharge) pending cultures
- MRSA carriers who are clinically unstable
- If the episode follows treatment with high dose cytarabine ($\geq 2\text{gm/m}^2/\text{day}$) and patient is clinically unstable

6.4 Patients with Features of Abdominal or Perineal Infection

- ADD Metronidazole (if receiving Cefepime or Ciprofloxacin as first line)
- Piperacillin+Tazobactam or Meropenem will provide adequate anaerobic cover, if required, other than for suspected or proven *Clostridium difficile*-associated diarrhoea or colitis

6.5 Antifungal Therapy

- Antifungal therapy in the first 24 hours is rarely indicated unless the patient is already receiving antifungal therapy, in which case it should be continued.

Subsequent modifications to the regimen will depend on clinical response and isolates which is beyond the scope of this guideline.

7 INFECTION PREVENTION CONTROL ISSUES

Paediatric oncology/SCT patients are to be located in a single room if available. If a single room is unavailable they should **NOT** be placed immediately adjacent to other patients with evidence of potential infectious conditions (such as upper respiratory symptoms, diarrhoea, or fever with rash).

Multidrug resistant organisms:

Some patients will have a history of colonisation with multidrug resistant organisms. These may include, but are not limited to Vancomycin resistant enterococci (VRE), Methicillin resistant Staphylococci (MRSA), Extended spectrum beta lactamase producing gram negative bacilli (ESBL) and Metallo-beta lactamase producing gram negative bacilli (MBL).²³⁻²⁶

Standard precautions, which include meticulous hand hygiene, must be observed in all patients.

Additional contact precautions may be used according to local policies for patients colonised with VRE, ESBL, MBL, MRSA. They are designed to reduce the risk of transmission by direct contact with the patient or by indirect contact with environmental surfaces or patient care items in the environment. These include

- Single room if available or cohort with carrier of same organism and follow local contact guidelines
- Wear isolation gown or apron during contact with patient and/or their environment
- Wear non-sterile gloves during contact with patient and/or their environment
- Wash hands after patient contact and gown/apron removal or perform hand hygiene with 2% alcoholic chlorhexidine hand rub.

Patients with Respiratory signs/symptoms:

In patients who have respiratory symptoms like runny nose, standard AND droplet precautions must be observed.

Patients with Varicella or Measles Infection:

Patients with varicella (Chickenpox) or herpes zoster (Shingles) or measles must be nursed in a negative pressure single room (if available) under airborne precautions by immune staff.

8 CLINICAL PRESENTATION

The most common initial manifestation of infection in paediatric oncology patients is fever. The NSW Health Standard Paediatric Observation Charts Yellow Zone trigger for high temperature starts at 38.5°C. As 'Fever' within this patient population is defined as a single temperature of 38°C or more by any route these patients should be escalated as per local CERS at this lower threshold.

Fever may be the first and only manifestation often without any localising symptoms.

It is important to recognise that the “usual” presenting symptoms and signs of infection in paediatric oncology patients may not be obvious in the absence of an inflammatory response. Furthermore fever in this group of patients may be secondary to drugs (Cytarabine, Bleomycin), blood products or viral infection (usually respiratory viruses). It is not possible to rule out bacterial infection in these patients and hence prompt administration of antibiotics is indicated in them.

Localized infection (pain and signs of inflammation) may occur in the absence of fever. For example, neutropenic patients with intra-abdominal sepsis may complain only of localized pain despite significant intra-abdominal pathology (e.g. perforated bowel). Thus, in an afebrile patient with local pain, hemodynamic instability, prompt initiation of empiric antibacterial therapy is indicated.

Clinical scenarios of localized infection which require prompt antibiotic administration include (but not limited to) the following¹:

Local Infection of CVADs: This can present as

- Warmth, tenderness, erythema at exit site, and/or
- Swelling and fluctuation around the subcutaneous catheter hub with signs of inflammation or cellulitis of the overlying skin, and/or
- Tunnel infection which is characterized by spreading cellulitis in the subcutaneous tissues along the tunnel tract of the catheter.

Ear infection: Paediatric oncology patients can develop the same repertoire of infectious disease as immune-competent patients. Clinical findings suggesting an ear infection range from the classic complaints (e.g. ear pain, drainage, fever, irritability) to minimal findings (e.g. slight tympanic erythema) in profoundly neutropenic children.

Lower respiratory tract infection: These patients may present with cough, respiratory distress, hypoxia with or without fever. Initial chest x-ray changes could be minimal due to the absence of neutrophils.

Intra-abdominal infection: e.g. typhlitis (also known as neutropenic enterocolitis) can present with abdominal pain, diarrhoea with or without fever in profoundly neutropenic patients.

Infectious meningitis in paediatric oncology patients is uncommon but is associated with significant morbidity and mortality. Symptoms may not include headache or photophobia. Neck stiffness may be absent. Meningitis in paediatric oncology patients can be subtle in presentation and signs and symptoms of CNS dysfunction should alert the clinician to this possibility. Children with intra-ventricular shunts and CSF access reservoirs are at high risk for development of CNS infection and early CSF collection for microscopy and culture should be considered.

Management of patients with suspected meningitis should be according to the [Infants and Children: Acute Management of Bacterial Meningitis Clinical Practice Guideline](#).²⁷

Urinary tract infection in patients may not present with the typical symptoms of frequency, dysuria or abdominal pain. When possible a clean catch urine sample should be obtained, preferably before starting antibiotics. Urine collection should not delay administration of antibiotics.

Initial (first dose) antibiotic management of these patients (except for patients with suspected meningitis) will include Piperacillin+Tazobactam and Gentamicin with or without Vancomycin. Subsequent choice of antibiotic will depend on the nature of underlying infection.

9 DIAGNOSTIC TESTS

The following laboratory tests are crucial at initial presentation to assess the aetiology of the episode and guide further treatment. HOWEVER antibiotics administration should NEVER be delayed beyond 30-60 minutes if there are difficulties collecting the required samples.

Blood culture and full blood count are the most important tests at initial presentation.

1. **Blood Culture:** The majority of paediatric oncology patients have a central venous access device (double or single lumen Hickman/Broviac line or Port-a-Cath) in situ. These patients must have all the lumens of the line cultured. Aerobic and anaerobic blood cultures should be collected. If blood volume for culture is limited, aerobic cultures are the first priority. Peripheral cultures may be helpful in selected patients with a CVAD to help distinguish between true bacteraemia and line luminal colonisation/contamination, but are not routinely performed. In patients who do not have CVAD's peripheral blood culture should be obtained, but should not delay administration of antibiotics²⁸⁻³⁰
2. **Blood lactate level:** Blood sample for lactate measurement must be processed as soon as possible as lactate may appear falsely elevated in stored samples. Patients with high levels of lactate (≥ 2 mmol/L) are at high risk of mortality and hence must be managed as per severe sepsis/shock pathway irrespective of other features^{31,32}
3. **Full blood count (FBC):** The full blood count can change rapidly within 24-48 hours if patient is receiving chemotherapy. Results of blood counts more than 24 hours prior to presentation may not be indicative of degree of neutropenia. In infants absolute neutrophil count could be very low in the presence of normal or high total white cell count, with lymphocytes accounting for the majority of white cells
4. **Electrolytes/urea/creatinine (EUC):** Collect as baseline and to serve as a guide to modify subsequent doses of antibiotics
5. **Liver function tests (LFT):** Baseline collection. Abnormalities may be due to chemotherapeutic agents, infectious causes or may be a sign of severe sepsis (hypotension)
6. **Blood glucose level:** (BGL) Sepsis may present with hypoglycaemia in infants

7. **Urine microscopy and culture:** When indicated, clean catch urine sample should be obtained, preferably before starting antibiotics. Urine collection should not delay administration of antibiotics³³
8. **Chest x-ray:** Chest x-rays are not routinely recommended in asymptomatic children. Even in symptomatic children initial chest x-ray findings could be minimal due to lack of neutrophils. Initial antibiotics administration must not be delayed for obtaining chest x-ray^{34,35}

10 PSYCHOSOCIAL NEEDS OF THE FAMILY

- Ensure that the patient and parents/carers receive appropriate education on recognition of the unwell child, the signs of infection and when to seek medical attention
- Commence treatment promptly with the aim that the patient will recover from the infectious episode with minimal complications
- Discuss with the patient and parents/carers the ongoing treatment plan
- Refer the family to the social worker if available.

11 TRANSFER OF THE PATIENT TO TERTIARY REFERRAL CENTRE

NETS-NSW is a state-wide emergency service for medical retrievals between hospitals in NSW and ACT.³⁷

- For patients obviously or probably needing a medical escort for safe transfer to an appropriate hospital, NETS should be called first by the treating doctor. A destination hospital, paediatric ICU or ED and Oncology can be connected in telephone conference to discuss optimal management simultaneously. In parallel, appropriate urgent arrangements for deploying a team can be made.
- For patients referred to an oncologist or regional paediatrician who is thought might require a medical escort, it is recommended to truncate that initial call so that a clinical conference call can be set up. This avoids repetition of information and advice, delay in mobilising resources and inefficiency for the local clinicians treating the patient.

If an infant or child's condition is critical escalate as per local Paediatric Clinical Emergency Response System (CERS)

Contact NETS on 1300 36 2500

12 APPENDICES

12.1 Appendix 1: Bibliography

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12.2 Appendix 2: Glossary

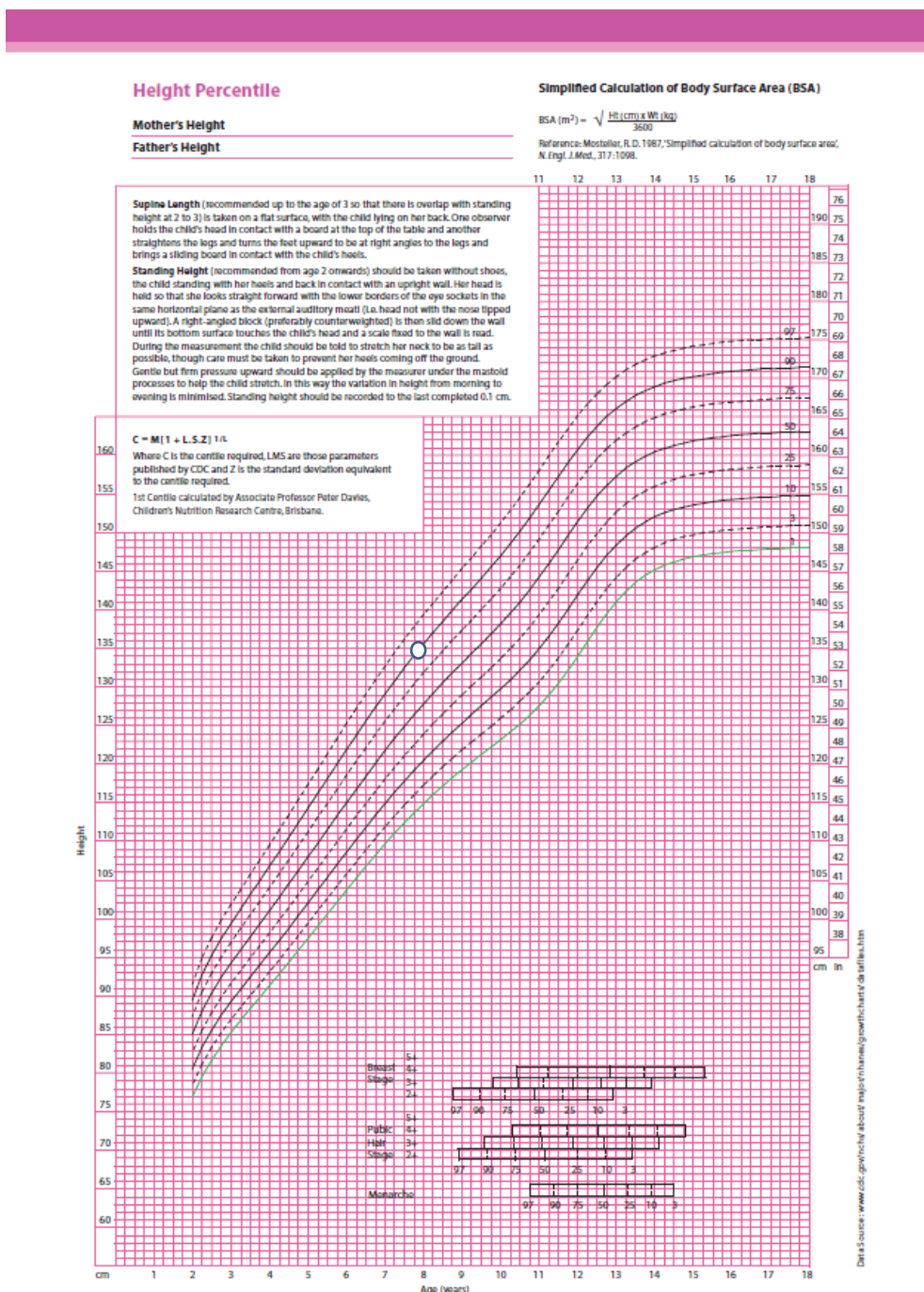
- **ANC:** Absolute neutrophil count
- **BTF:** Between the Flags
- **CERS:** Clinical Emergency Response System
- **CVAD:** Central Venous Access Device (CVAD): refers to CVC (tunnelled and non-tunnelled), PICC and IVAD/TID. CVAD is an intravascular device whose catheter tip is situated in the superior vena cava, inferior vena cava or right atrium
- **EUC:** Electrolyte, Urea and Creatinine
- **ESBL:** Extended Spectrum Beta Lactamase producing gram negative bacilli
- **FBC:** Full blood count
- **F+N:** Fever + Neutropenia. Fever is defined as single temperature of 38° C or more by any route. Neutropenia is defined as Absolute neutrophil count < 1X10⁹/L
- **Lean body weight:** For obese patients lean body weight is used to calculate dose of Gentamicin. *See Appendix 3 for calculation of lean body weight using weight for height method.*
- **LFT:** Liver function test
- **MBL:** Metallo-Beta Lactamase producing gram negative bacilli
- **MRSA:** Methicillin Resistant Staphylococcus aureus
- **PICC:** Peripherally Inserted Central Catheter
- **IVAD/TID:** Implantable Venous Access Device or Totally Implantable Device, otherwise known as ports or portacath (type of CVAD)
- **SCT:** Stem cell transplantation, includes Autologous or allogeneic bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSC) and umbilical cord blood cell transplantation
- **VRE:** Vancomycin resistant enterococci
- **VBG:** Venous Blood Gas

12.3 Appendix 3: Calculating Lean Body Weight for Obese Children

Weight for height method

In this example an eight-year-old girl has a weight of 55 kg, and height of 135 cm which is on the 90th percentile for age. Her predicted weight for height is obtained by determining what weight corresponds to the 90th percentile for an eight-year-old girl, and here it is 33 kg. Therefore, her doses should be calculated using 33 kg, rather than 55 kg.

- Actual weight and height
- Predicted weight for height

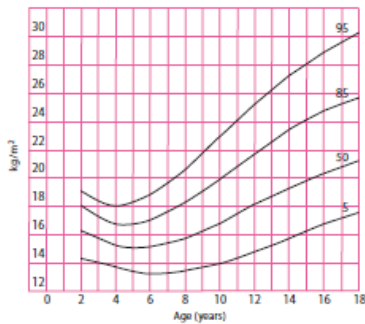




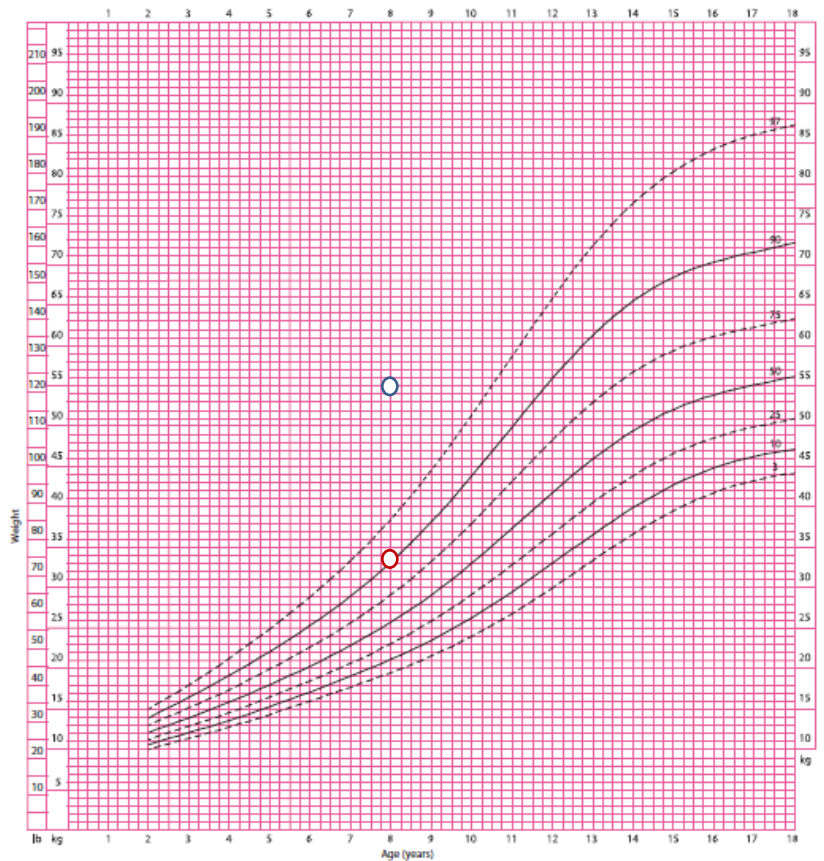
Weight Percentile

Weight should be taken in the nude, or as near thereto as possible. If a surgical gown or minimum underclothing (vest and pants) is worn, then its estimated weight (about 0.1 kg) must be subtracted before weight is recorded. Weights are conventionally recorded to the last completed 0.1 kg above the age of six months. The bladder should be empty.

Body-Mass Index



PUBERTAL STAGES							
DATE	AGE	HEIGHT	WEIGHT	HEAD CIRCUM.	BREAST	PUBIC HAIR	MENARCHE



Adapted from: Sean Beggs, 2008, *Paediatric analgesia*, Australian Prescriber, Volume 31, No.3, June 2008 pge 63

12.4 Appendix 4: Expert Working Group

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