Management of Fever in a Paediatric Oncology Patient

Febrile Neutropaenia and Febrile Non-neutropaenia

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 neutropaenia and those with known non-neutropaenia 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.

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Related documents

Policy and standard(s)

- CHQ Nursing standard 03453 IVAD - Central Venous Catheters Nursing Care and Management of Tunneled (cuffed and non-cuffed) CVC in Paediatric Patients (QH staff only)
- CHQ Nursing standard 03454 IVAD - Venous Port Device: Nursing Care and Management of Totally Implanted Venous Port Device (Port) in Paediatric Patients (QH staff only)

Procedures, Guidelines, Protocols

- CHQ Procedure 03450 Intravascular Access Device Management of (Peripheral and Central Venous Access Devices) (QH staff only)
- CHQ Procedure 01036 Antimicrobial: Prescribing and Management (QH staff only)
- CHQ Procedure 01000 Medication (QH staff only)
- CHQ Procedure 01001 CHQ Procedure 01001: Medication - Prescribing (QH staff only)
- CHQ Guideline Antifungal Prophylaxis and Treatment in Paediatric Oncology and Immunocompromised (QH staff only)
- CHQ Guideline 01202 CHQ Paediatric Antiibiocard: Empirical Antibiotic Guidelines (QH staff only)
- CHQ Guideline 07449 Sepsis: Recognition and Early Management in Children (QH staff only)

Forms and templates

- CHQ Clinical Pathway Clinical Pathway: Initial Management of Suspected Neutropaenic Sepsis (QH staff only)
Guideline

Febrile Neutropaenia (FN)

Definition

![Image](image)

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 neutropaenia is known as Febrile Neutropaenia (FN). Neutropaenia must be suspected in any oncology patient that has received chemotherapy within the last 10-14 days. Neutropaenia 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 Neutropaenia

Follow the Febrile Neutropaenia antibiotic algorithm (Page 9) unless neutrophil count is known to be > 1.0, then follow the Non Neutropaenic Flow chart (Page 10). Complete the Clinical Pathway: Initial Management of Suspected Neutropaenic Sepsis (QH staff only) if available.

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 (20ml/kg) and oxygen therapy as required.
- Refer to CHQ Guideline 07449  [Sepsis: Recognition and Early Management in Children](QH staff only)

**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 ELFTs (Collect COAG’s only if critically unwell)

**Antibiotic Management:**

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**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 = 100mg/kg (of piperacillin component) IV 6H (maximum 4000mg Piperacillin component per dose)
  - Administer undiluted (200mg/mL of piperacillin component) as an IV bolus over 3-5 minutes via CVAD (can be diluted to 20mg/mL of piperacillin component for infusion over 20 minutes via peripheral IV)

If septic, critically unwell or haemodynamically unstable (see Febrile Neutropaenia Antibiotic Algorithm, Page 9) add Gentamicin and Vancomycin as below.

- **Gentamicin** provides additional gram negative cover including pseudomonas
  - Dose = 1mth to <10years: 7.5mg/kg every 24 hrs (max 320mg); >10years: 6mg/kg every 24 hrs (max 640mg) (Note: PICU sepsis dosing for gentamicin >10years is 7mg/kg every 24 hrs (max initial dose 640mg) and this dose may be used if septic shock requiring PICU)
  - Wait 30 minutes after Piperacillin/Tazobactam dose prior to administering the Gentamicin
  - Infuse IV Gentamicin dose in total volume of 30mL (in sodium chloride 0.9%) over 30 minutes
  - Document time of administration – 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](QH staff only)
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 = 15mg/kg (max dose 750mg) every 6 hrs (perform therapeutic drug monitoring – Vancomycin trough level 30 minutes before 4th or 5th dose)
- Administer once flush following Gentamicin is complete
- Dilute to 5mg/mL or less and infuse over 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 LCCH Paediatric Oncologist

Special considerations:

- Beta lactam delayed hypersensitivity – Use Ceftazidime (50mg/kg/dose IV every 8 hours (max 2 grams/dose)) and single dose of Gentamicin (as above)
- Beta lactam anaphylaxis – Use Meropenem (40mg/kg/dose IV every 8 hours (max 2 gram/dose)) (see ALERT below)
- Antibiotic approvals are required for restricted antibiotic use outside stated protocol. Please refer to the Medication approval process (QH staff only) and the Individual Patient Request form (QH staff only).

ALERT

Restricted antibiotics eg Meropenem, require AMS 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. N.B. Antibiotics MUST be commenced before undertaking other investigations
- Abnormal CXRs should be discussed with the Paediatric Oncologist at the Oncology Services, LCCH

Communication:

ALERT

Discuss all patients with the Regional Paediatrician and on-call Paediatric Oncologist at Oncology Services Group via Lady Cilento Children’s Hospital (LCCH) switch: (07) 3068 1111.
• Prescribe blood products if required and other relevant medications e.g. paracetamol; antiemetics; prophylactic antibiotics, antivirals, and antifungals
• Discuss with the Paediatric Oncologist whether children receiving oral chemotherapy should continue to receive this treatment

**Ongoing Management of Febrile Neutropaenia** (Appendix 3, Page 9)

**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 Neutropaenia:**

**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 iv to oral switch to complete 5-7 days antibiotics

- No evidence of marrow recovery:
  - Continue 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 - 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 - 5 days follow as below.

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**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 iv to oral switch to complete 5-7 days antibiotics

- No evidence of marrow recovery:
  - If afebrile for at least 24 hours, all negative cultures and neutropaenia 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 neutropaenia expected to be prolonged consider completing a 5-7 day course of antibiotics. If stable, these do not need to be intravenous, consider intravenous to oral switch e.g. oral amoxycillin/clavulanate, cephalexin

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 1mg/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 4-5 days:

- Reassess and in consultation with the treating team consider:
  - more invasive investigative procedures and imaging
  - transfer to LCCH 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 3mg/kg/day if high clinical or radiological suspicion of IFD) 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 culture’s at this stage only when clinically indicated/ requested by senior medical staff.

### ALERT

**Antifungals require AMS 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, PIV 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)** III** IV 6H

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

Patient with:
- Suspected gram +ve infection e.g. CVAD OR
- Recent HiDose Cytarabine

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

Admit

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
100mg/kg (max 4g)** III** IV 6H

Gentamicin**
1 month to 10yrs 7.5mg/kg (max 320mg) IV 24hrly
>10yrs 6mg/kg (max 640mg) IV 24hrly
add Vancomycin 15mg/kg (max 750mg) IV 6H

Admit

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

*For sepsis see: CHQ Guideline 07449 Sepsis: Recognition and Early Management in Children
**give Gentamicin 30 minutes after Piperacillin/Tazobactam
***based on Piperacillin component
Febrile non-neutropaenia antibiotic algorithm

Febrile oncology patient – not Neutropaenia

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

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 24hrs to review results, progress and ongoing management.

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

For children who have received Piperacillin/Tazobactam as per the Initial management of suspected febrile neutropaenia but have neutrophils ≥ 1.0:
• Consider a stat dose of Ceftriaxone 100mg/kg (max 4g) IV q24hr prior to discharge OR
• If being admitted, give the Ceftriaxone dose 8hrs post the Piperacillin/Tazobactam dose. Cease Piperacillin/Tazobactam order
Note

Neuroblastoma and recent IL2; additional gram positive cover is not routinely required as ceftriaxone provides good gram positive cover.

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**ALERT**

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

- Clinical suspicion of bacteraemia: hypotension, poor perfusion, rigors, significant tachycardia, tachypnoea, dehydration

- Impending neutropaenia: IV chemotherapy (other than single agent, Vincristine) within the last 10-14 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 Neutropaenia antibiotic algorithm
Febrile neutropenia follow-on management algorithm

Febrile neutropenia – admitted to hospital

Stable patient
- Piperacillin/Tazobactam IV

Positive blood culture
- Repeat blood culture

Septic patient
- Stop Gentamicin and Vancomycin at 48hrs if negative cultures and stable.
  Note: Piperacillin/Tazobactam has gram positive activity, fever alone after 48hrs with negative cultures is not a reasonable indication to continue Vancomycin

Negative blood culture
- Continue antibiotics as appropriate for organism

LOW RISK DISEASE
(Appendix 1)
- Assess at 48 hours

Afebrile: low risk of bacterial disease?
(Appendix 1)

Assess at 72 hours
- Afebrile for 24hrs and completed 3 days IV antibiotics?

HIGH RISK DISEASE
(Appendix 2)

Yes
- Complete 5 days antibiotics

No
- If afebrile for at least 24hrs at completion of 5-7 days of appropriate antibiotics stop antibiotics and discharge home

Stop IV antibiotics. Consider oral antibiotics to complete 5-7 days

Yes
- Continue Piperacillin/Tazobactam IV, reassess, repeat blood culture and review at 72 HOURS. No need for empiric antibiotic change if stable

No
- Continue antibiotics, reassess, repeat blood culture and review at 96 hours. No need for empiric antibiotic change if stable

Afebrile for 24hrs 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/dose. If clinical deterioration or if fever continues, change antibiotics as per guideline.

No
Consultation:

Key stakeholders who reviewed this version:
- Medical Fellow, Oncology Services Group, CHQHHS
- Director Infection Management
- Statewide Educator, QPPHON
- Clinical Nurse, Oncology Services Group, CHQHHS
- Nurse Educator, Oncology Services Group, CHQHHS
- Antimicrobial Stewardship Pharmacist, Lady Cilento Children’s hospital
- Director Paed BMT, Oncology
- SMO Oncology
- Oncology Director and Oncology SMOs

Definition of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<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>
<td></td>
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<tr>
<td>CVL</td>
<td>Central venous line</td>
<td></td>
</tr>
<tr>
<td>IMPS</td>
<td>Infection Management and Prevention Service</td>
<td></td>
</tr>
<tr>
<td>IFD</td>
<td>Invasive fungal disease</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>Acute Myeloid Leukaemia</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukaemia</td>
<td></td>
</tr>
<tr>
<td>HSCT</td>
<td>Haemapoetic stem cell transplant</td>
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<td>HSV</td>
<td>Herpes Simplex virus</td>
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<td>Varicella Zoster Virus</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>EBV</td>
<td>Epstein barr virus</td>
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<tr>
<td>GVHD</td>
<td>Graft versus host disease</td>
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<td>UTI</td>
<td>Urinary tract infection</td>
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References and suggested reading


Guideline revision and approval history

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**Keywords**

Oncology; Fever; Febrile; Neutropaenia; Neutropenic; Non-Neutropenic; Antibiotics; antimicrobial stewardship; sepsis; antifungals, 01249

**Accreditation references**

NSQHS Standards (1-10): 3; 4; 5; 6; 9
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 (e.g. 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 (e.g. CRP >100 mg/L or rising)

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<tr>
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<th>LOW RISK</th>
<th>HIGH RISK</th>
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<td>Absolute neutrophil count</td>
<td>0.1 – 0.5 x 10^9/L</td>
<td>&lt;0.1 x 10^9/L</td>
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<tr>
<td>Duration of neutropaenia</td>
<td>&lt; 7 DAYS</td>
<td>≥ 7-10 DAYS</td>
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<tr>
<td>Co morbidity</td>
<td>None</td>
<td>• Toxic/Shocked</td>
</tr>
<tr>
<td></td>
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<td>• BMT Inpatient</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: Normal range for age specific vital signs

<table>
<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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<tbody>
<tr>
<td>Tem</td>
<td>100-180</td>
<td>60</td>
<td>40-60</td>
</tr>
<tr>
<td>6mth</td>
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<td>1yr</td>
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<tr>
<td>12yr</td>
<td>60-110</td>
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<td>16-25</td>
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<tr>
<td>16yr+</td>
<td>60-100</td>
<td>90</td>
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As per CHQ Guideline 07449 [Sepsis: Recognition and Early Management in Children](QH staff only)