Initial Management of Febrile Neutropenia or Suspected Bacterial Infection

Reference: CG854
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Review Due: December 2017

Intended Audience

These guidelines have been produced to inform the management of children who are receiving “standard dose” chemotherapy. They were updated in 2005 following a review of bacterial isolates from patients on M3 and to be compatible with the Standard Operating Procedure regarding the antimicrobial prophylaxis and management of neutropenic fever in children undergoing haemopoietic transplantation. This SOP (HSCT/038) should be referred to if the child in question has undergone a haemopoietic stem cell transplant procedure.

The guidelines have been reviewed in relation to the NICE guidelines and a local service evaluation of febrile neutropenia admissions. The outcome of the review is that no changes should be made to our local policy.

There is ongoing review of bacterial isolates from patients on M3 and if appropriate the guidelines may be changed prior to the planned review date.

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1. Introduction

Children receiving cytotoxic drugs are at risk from infection, particularly bacterial. This risk is greatest in those children undergoing intensive treatment such as bone marrow transplantation, high dose chemotherapy with stem cell support or during leukaemia induction treatment. Where leukaemia is concerned the problems tend to be more severe in children with AML than ALL.

Children with solid tumours can also become severely pancytopenic, although in general this is for a shorter period. In the majority of these children the blood count nadir usually occurs 10 to 14 days after a course of treatment, and recovery has occurred by day 21.

Prophylactic antibiotics (amoxicillin/co-amoxiclav and ciprofloxacin, +/- fluconazole) are given to children who are expected to have a prolonged period of neutropenia. This includes patients with AML and those undergoing transplantation procedures. Other children are not routinely given prophylactic antibiotics, but may occasionally be prescribed these on an individual basis.

This guideline gives advice on the initial investigation and management of patients presenting with fever or suspected bacterial infection (sepsis can present with normo- or hypothermia). The majority of patients will be febrile and neutropenic, but the management of an unwell child is the same regardless of actual or anticipated neutrophil count and should not be delayed whilst waiting for laboratory results. All severely unwell patients and any patient who deteriorates after initial improvement must be discussed urgently with a consultant.

Information about viral or fungal infection can be found in subsequent sections of the Haematology/Oncology Ward M3 Guidelines, Section 6: Infection, 856 Management of suspected fungal infection (M3/06/856) and 857 Management of suspected viral infection (M3/06/857). Additional specific guidelines are also available for the management of patients undergoing bone marrow transplantation (HSCT 038).

2. Febrile Neutropenia

Any suggestion of infection in children at risk must be urgently investigated and treated. Children who have recovered normal haematopoiesis after completing all their chemotherapy and radiotherapy whose central line has been removed should be investigated according to SC(NHS)FT medical guidelines and treated accordingly.

Fever

Single temperature ≥38.5°C, or >38.0°C on two occasions more than 1 hour apart.

Sepsis can present with normal or low temperature (overwhelming sepsis, steroids, Trisomy 21)

Neutropenia

Absolute neutrophil count of ≤0.5 x 10^9/L.

If neutrophils between 0.5 x 10^9/L but < 1.0 x 10^9/L, management is determined by the overall condition of the child, and also whether the white cell count is likely to still be falling or is expected to rise very soon

Any child receiving chemotherapy who appears unwell but is not febrile or neutropenic may still need treating with antibiotics. If in any doubt as to whether antibiotics should be given it is usually preferable to err on the side of caution and give them. Discuss with more senior colleague if you are not sure.
3. Telephone Advice

If a child at home becomes febrile a parent will usually phone the ward for advice. These calls are usually handled by the nursing staff, but if you take a call it should always be documented on the communication sheets in the Telephone Advice folder. Please do not ask patients to contact their GP without first discussing with a more senior colleague whether this is appropriate advice. Although most febrile patients will require review, this may not be necessary in all cases e.g. well patient with known normal count and known rhinovirus on NPA. Any decision not to review a febrile patient must be taken in discussion with a senior doctor from the Haematology/Oncology Team.

4. Initial Management

All patients should undergo a rapid clinical assessment to determine whether they are “well” or “unwell”. A full history and examination should then be completed, alongside immediate treatment if required. Be sure to specifically document any symptoms such as diarrhoea or cough or the presence of focal signs of infection such as skin sepsis. There is a proforma for admissions with suspected febrile neutropenia which should be used – ask the nursing staff if you do not know where these are kept.

Well children with a history of fever at home, but who are afebrile on admission may be observed for a period pending results of initial bloods to help decide whether antibiotics are required. However if there is additional history suggestive of bacterial infection, e.g. diarrhoea, rigors or productive cough, then antibiotics should be started once cultures obtained. Antibiotics should be started after appropriate cultures have been obtained in well children with neutrophils ≤0.5 x 10^9/L even in the absence of any other signs or symptoms.

Children with central lines are at risk from "line infections" even when they are not neutropenic. Immunocompromised children with diarrhoea are at particular risk from gram negative bacteraemia.

Unwell children should ALWAYS be given antibiotics irrespective of their count. Unwell children may have tachycardia, tachypnea or poor perfusion. Hypotension is a late sign and suggests critical illness. This is not an exhaustive list – if your overall impression or gut feeling suggests the patient is unwell, treat them as such.

Remember that nursing staff on M3 know the patients well and are used to providing fairly high dependency nursing; if they feel a child is significantly unwell they will tell you and you should take note, ensuring a rapid and thorough assessment is undertaken.

Initial management should proceed as per PLS/APLS guidelines with the early involvement of senior members of the Haematology/Oncology team. Escalation to PCCU may be required immediately, or following inadequate response to resuscitation and should be arranged in line with current hospital guidelines.

If you are unfamiliar with the resuscitation of critically ill children you should not be managing a septic Haem/Onc patient on your own – get senior help immediately.

Whilst they are on their way ensure the following actions are being taken:

- Administer high flow oxygen via an appropriate mask
- Give 20ml/kg bolus of 0.9% Sodium Chloride if haemodynamically compromised (e.g. tachycardia not explained by fever, delayed capillary refill, hypotension)
- Ensure appropriate cultures obtained (providing no delay)
- Start “first line” antibiotics unless alternative documented on Medic alert in front of notes (e.g. drug allergy, known to be colonised with resistant organism)
Initial Management of Febrile Neutropenia or Suspected Bacterial Infection

Severely unwell patients should be given antibiotics prior to collection of blood cultures if the central line will not bleed back. Peripheral cultures should be taken when a cannula is sited. Central cultures can be attempted again when the patient has been resuscitated. Do not wait for urine cultures in unwell children.

Ongoing management

- Monitor vital signs including urine output closely. Catheterisation may be required.
- Further fluid boluses should be given as required. Discuss with PCCU if a second bolus is required and they are not already aware of the patient.
- Beware of children who remain cardiovascularly unstable or who deteriorate after initial improvement. Antibiotics should be changed to Meropenem and Teicoplanin to cover the possibility of resistant organisms, without waiting for culture results.

5. Initial Investigations

<table>
<thead>
<tr>
<th>Blood Cultures</th>
<th>From central line (all lumens individually)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ideally aerobic and anaerobic set (blue and purple) or combined (yellow)</td>
</tr>
<tr>
<td></td>
<td>Label samples from multiple lines / lumens correctly</td>
</tr>
<tr>
<td>Urine</td>
<td>Send for M,C+S. Do not delay antibiotics waiting for this if unwell</td>
</tr>
<tr>
<td>Stool</td>
<td>If history of diarrhoea. Send for MC+S, C. difficile, virology</td>
</tr>
<tr>
<td>NPA/Throat swab</td>
<td>If upper or lower respiratory symptoms</td>
</tr>
<tr>
<td>Swabs</td>
<td>All clinically infected lesions</td>
</tr>
<tr>
<td></td>
<td>Remember to check line site (bacterial swab)</td>
</tr>
<tr>
<td></td>
<td>Look for rash esp. vesicular (bacterial and viral swabs)</td>
</tr>
<tr>
<td></td>
<td>Look inside mouth for candida, HSV, ulceration (bacterial and fungal, viral)</td>
</tr>
<tr>
<td>CRP</td>
<td>Can be stored and analysed in working hours.</td>
</tr>
<tr>
<td></td>
<td>Only useful for subsequent management; not required for decision making</td>
</tr>
<tr>
<td>CXR</td>
<td>Not required on admission unless respiratory signs/symptoms</td>
</tr>
<tr>
<td>Other</td>
<td>Under 5’s with ALL should have adenovirus screening as per Ward M3 guidelines (M3/06/857 – Management of Suspected Viral Infection).</td>
</tr>
<tr>
<td>LP</td>
<td><strong>Not to be performed unless requested by Haem/Onc Consultant</strong></td>
</tr>
</tbody>
</table>
6. First Line Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>75mg/kg 12 hourly (150mg/kg/day)</td>
<td>Max daily dose 9 grams</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Once daily dose see Appendix I for details</td>
<td>NB serum level monitoring</td>
</tr>
</tbody>
</table>

Patients who have previously grown multi-resistant gram negative bacteria may require alternative first line antibiotics. This will usually be Meropenem. If an alternative first line antibiotic regime is required this will be documented on the Medic Alert sheet at the front of the patient’s notes. Other antibiotics may be also be given in the presence of specific focal signs, e.g. clarithromycin or high dose co-trimoxazole, if there are respiratory signs – discuss with a senior colleague.

Prophylactic antibiotics (other than co-trimoxazole which should always continue) are stopped if IV antibiotics are given.

7. Subsequent Management – See Appendix II

<table>
<thead>
<tr>
<th>12-24 hours after starting antibiotics</th>
<th>Check gentamicin level. Refer to Appendix I for further details.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If afebrile and well at 48 hours, and all cultures negative</td>
<td>If child well, stop antibiotics and discharge home. If continuing concerns, observe for a further 24 hours.</td>
</tr>
<tr>
<td>If still febrile at 48 hours but cultures negative</td>
<td>Stop gentamicin and start teicoplanin.</td>
</tr>
<tr>
<td>If still febrile at 96 hours</td>
<td>Start caspofungin. See Section 6.4 “Management of suspected Fungal infection” for details</td>
</tr>
<tr>
<td>If cultures positive (may take up to 48 hours to confirm)</td>
<td>Change antibiotics if necessary as dictated by cultures. Gentamicin may be stopped if appropriate alternative available – discuss with microbiologist. Systemic antibiotics should be given for a minimum of 5-7 days – discuss with microbiologist. In some situations, e.g. if <em>S.aureus</em> isolated, a more prolonged course of systemic antibiotics will be needed. Consider removal of central line if <em>S. aureus</em> or <em>Candida</em> isolated. Antibiotic “locks” may be needed after a course of systemic antibiotics, e.g. if <em>coagulase negative staphylococcus</em> repeatedly isolated from central line. (See Appendix III)</td>
</tr>
<tr>
<td>In case of acute deterioration after a period of stabilisation</td>
<td>Change to Meropenem and Teicoplanin to cover resistant organisms. Consider early addition of Antifungals and Aciclovir</td>
</tr>
</tbody>
</table>
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NB Consider need for daily blood cultures in children who remain febrile.

For advice about appropriate antibiotics for a child with continuing fever and negative cultures, discuss with Consultant Microbiologist. If a source of suspected bacterial infection is strongly suspected, then appropriate antibiotics should be added to ensure adequate cover of possible organisms. Consult the hospital antibiotic policy (section 2.3 Medical Staff Guidelines) in consultation with microbiology. DO NOT ASSUME THE CAUSE OF INFECTION; always continue broad spectrum antibiotics until a positive culture is isolated or they have been afebrile and well for at least 24 hours.

8. Second Line or Additional Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Administration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teicoplanin</td>
<td>10mg/kg</td>
<td>12 hourly IV x 3 doses then every 24 hrs</td>
<td>If treating a line infection can change to vancomycin “lock” after 48 hrs Maximum single dose 400mg</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15mg/kg</td>
<td>8 hourly IV Infusion over 1 hour (rate not &gt; 10mg/min)</td>
<td>Monitor drug levels Reduce doses if renal impairment Maximum starting dose 2g/day Total daily dose may be increased if indicated by drug levels</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>75mg/kg</td>
<td>12 hourly IV bolus or short infusion</td>
<td>Maximum dose 2.5g 12 hourly</td>
</tr>
<tr>
<td>Meropenem</td>
<td>20mg/kg</td>
<td>IV 8 hourly</td>
<td>40 mg/kg if life threatening sepsis Maximum dose 2g 8 hourly Adjust dose if renal impairment</td>
</tr>
<tr>
<td>(1g if &gt; 50kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.5mg/kg</td>
<td>IV 12 hourly Infuse over 1 hour</td>
<td>Maximum dose 500mg 12 hourly Do not give as a bolus</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>7.5mg/kg</td>
<td>8 hourly IV Infuse over 20-30 minutes</td>
<td>Maximum dose 500mg 8 hourly</td>
</tr>
</tbody>
</table>

9. Patients on Oral Chemotherapy

Many patients will be taking oral chemotherapy, including mercaptopurine, methotrexate, tioguaine, procarbazine, temozolamide, procarbazine, etoposide or imatinib, at home.

When admitted to hospital with possible infection the decision whether to suspend or continue these drugs will need to be made by a senior member of the Haem/Onc team (ST4+ or Consultant).

Oral chemotherapy drugs are only given during the day. Patients admitted in the evening prior to that days dose should be discussed at time of admission. Patients admitted after they have taken their evening dose or overnight should be identified at handover for discussion with the relevant consultant on the morning ward round prior to the drug being written up or administered. See Haematology/Oncology Ward M3 guidelines, Section 4: Chemotherapy Administration section for further information.
Initial Management of Febrile Neutropenia or Suspected Bacterial Infection

10. Oral Antibiotics

Patients at low risk of developing serious bacterial infection can be considered for oral antibiotic therapy. In practice, identifying appropriate patients is difficult and the majority will receive parenteral therapy for 48 hours.

Potentially eligible patients must be:

- Clinically well with normal BP, capillary refill time and urine output
- In low risk diagnostic group (ALL in first remission unless on Reg C, most solid tumours)
- WCC >0.5 x 10^9/l but <1.0 x 10^9/l and rising or expected to rise very soon

The following patients are not eligible for consideration of oral antibiotic therapy

- AML
- Relapsed ALL
- Patients with Trisomy 21
- Transplant patients (including solid tumour patients following Autograft)
- Patients with focal signs of infection
- Patients with previous admissions for serious bacterial or fungal infection
- Patients unwilling or unable to take oral antibiotics (refusal, mucositis, allergy etc…)

Treatment is with a combination of Ciprofloxacin and Amoxycillin

All patients being considered for oral antibiotic therapy must be discussed with a senior doctor from the Haematology/Oncology Team.
11. Advice for Shared Care Centres

All patients and their parents are asked to contact Ward M3 if they become unwell. Parents will usually be advised to bring their child to the ward for review, but if they are felt to be severely unwell parents will be asked to dial 999 and request an emergency ambulance. On occasion parents may also dial 999 without contacting M3 first and in both these situations the patient is likely to be taken to Accident and Emergency at their local hospital.

These guidelines have therefore been written to be equally applicable to Haematology/Oncology patients who present to designated shared care centres (or other referring district general hospitals within our cancer network).

The following additional advice for Shared Care centres should also be noted:

- Ensure early liaison with the Consultant on Call for paediatric Oncology
- If haemodynamic compromise present or develops contact EMBRACE urgently
- Avoid rectal route of drug administration in neutropenic patients
- Use peripheral access if nobody immediately available to access central line. Take peripheral blood cultures if possible when cannula is sited, and label as such. Central line cultures can be obtained later. Do not delay treatment waiting for them.

12. References


Guideline for once daily gentamicin in infants and children. SCH guidelines. 2013 Laboratory Handbook


Appendix I: Administration of Once Daily Gentamicin

(Note: this is not the full SC(NHS)FT Gentamicin Policy)

Dosage and Monitoring

Dose: 35 weeks gestation to 1 month = 5mg/kg per dose
       1 month to 12 years = 6mg/kg per dose
       > 12 years = 5mg/kg per dose
If obese, calculate dose based on ideal weight for height
e.g. if height 90th centile use 90th centile weight

Administration: Slow IV infusion over 15 – 20 minutes
Dilute with sodium chloride 0.9% or glucose 5% (volume not critical)

Monitoring:

- Initially prescribe one dose only (on the regular medication section of
  the treatment chart), wait for levels before further doses are
  prescribed
- Only **trough** levels should be monitored
- Take level **12 – 24 hours** after the start of the infusion
- Record the following on the drug card and laboratory request form
  (labels available):
  1. Exact time dose given
  2. Exact time sample taken

Thereafter take level:

- twice weekly if stable, 12 - 24 hours after last dose
- if renal function fluctuating, take level 12 to 24 hours after each
dose
- Whenever possible, send levels to microbiology during normal
  working hours, always mark request forms with ‘**Once daily**’
gentamicin

Renal function:

- Monitor serum creatinine when starting gentamicin and then daily
  thereafter
- If renal function impaired, consider alternative treatment
- If gentamicin used must seek guidance from Microbiology or
  Pharmacy

Contra-Indications and Warnings

- The narrow spectrum of activity of gentamicin must be kept in mind as used alone it
  provides no cover for streptococci or anaerobes.
- Patients should be well hydrated during therapy.
- Extra caution in neonates with urinary outflow problems (bladder obstruction, urinary
  retention) in case of renal impairment, dehydration or concomitant nephrotoxic
  chemotherapy (including high dose methotrexate and platinum agents). Discuss with
  consultant on call if unsure.

Side Effects

Nephrotoxicity and ototoxicity can occur if optimum blood levels are exceeded.

- Monitor renal function in **all** children receiving gentamicin.
- Extra caution in child receiving other nephrotoxic drugs e.g. ciclosporin,
  ifosfamide or cisplatin.

(See over for “Interpretation of Gentamicin Levels”)

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Interpretation of Gentamicin Levels:

- **Normal Level**
  - Dose every 24 hours

- **Potentially Toxic Level**
  - Repeat level 36 hours after start of infusion

- **Less than 0.5mg/L**
  - Dose every 36 hours
  - Consider alternative antibiotic; consult Microbiology or Pharmacy

- **More than 0.5mg/L**

**NB.** The dosage and monitoring regimen in this protocol are different from those in ‘BNFc’ and decisions regarding changes in therapy should follow the recommendations above. Any deviations from the protocol should only be made on the advice of senior medical staff, microbiology or pharmacy and these should be documented.
Appendix II: Summary of Management of Neutropenic Fever

FEVER or UNWELL

Blood cultures from all lumens of central line, urine culture, stool culture + others as clinically indicated

Well child
No haemodynamic compromise

• Consider ALL CR1 (except Regimen C)/solid tumours for oral antibiotics if well without focal signs.

All others:
• Intravenous Ceftazidime + Gentamicin
  Unless known allergy or previous growth of multi resistant gram negative bacteria (check Medic Alert sheet in notes)
• Stop prophylactic antibiotics (apart from co-trimoxazole)
• Consider addition of
  a) Clarithromycin, high dose Cotrimoxazole or antifungals if respiratory signs
  b) Metronidazole if mucositis or gut symptoms

Reassess at 48 hrs

Culture positive

All cultures negative

STILL FEBRILE

Continue Ceftazidime
Stop Gentamicin
Start Teicoplanin

If still febrile at 96 hours add antifungal therapy

Unwell +/- Haemodynamic compromise

• Inform SpR/Consultant
• O₂ to maintain saturation
• Fluid challenge if required
• Intravenous antibiotics
• Escalate to PCCU as per hospital guidelines

NB. Change antibiotics to Meropenem & Teicoplanin if remains unstable or worsens after initial improvement

AFEBRILE AND WELL

Stop antibiotics and discharge

• Discuss with microbiologist
• Gentamicin may be stopped depending on sensitivities
• Continue appropriate antibiotics for 5-7 days

NB: If cultures remain positive despite adequate trial of antibiotic therapy consider removal of central line
Appendix III  Antibiotic Locks

If a line infection is suspected, i.e. organism such as *coagulase negative Staphylococcus* cultured, or there is repeated infection with the same organism then it may be helpful to use an antibiotic lock once the child has received systemic treatment for a minimum of 48 hours (longer if the child is neutropenic or unwell).

If there is a further episode of suspected infection within 1 month of a proven infection, the line should be treated with urokinase 5000 units in 2ml 0.9% sodium chloride for 2 hours each day for 3 days to remove any fibrin sheath from within the line. See Ward M3 Guidelines, section 7: Central Line Care, 986 Central Venous Access Device Management (M3/07/986).

Antibiotic locks are prepared by pharmacy in pre-filled syringes, except for gentamicin for which there is insufficient stability data. The lock should be diluted to a volume of 2mls with sodium chloride 0.9% (whether for a Broviac line or portacath). This gives a concentration well above the systemic concentration achieved with systemic drug dosages used on the ward. Normally both lumens are treated in children with double lumen central access even if only one has a positive culture, to ensure that cross contamination from sampling has not occurred.

Drugs that are normally administered by IV bolus injection do not need to be removed before the next lock is administered, e.g. ceftazidime, teicoplanin, unless the child is under 1 year or 10kg when the dose could become significant. Drugs normally administered slowly or by infusion should be aspirated before flushing, e.g. vancomycin, gentamicin or ciprofloxacin.

The line should then be flushed with 2-5mls sodium chloride 0.9% before the next lock is applied. Antibiotic locks are to be used for a minimum of 7 days and usually treatment is given for 14 days in the case of *Staph albus* infections and for up to 21 days for gram negative organisms.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency of application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>20mg/2ml</td>
<td>Once daily</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100mg/2ml</td>
<td>Once daily</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3mg/2ml</td>
<td>Once daily</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4mg/2ml</td>
<td>Once daily</td>
</tr>
<tr>
<td>Meropenem</td>
<td>40mg/2ml</td>
<td>8 hourly*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Unstable after 8 hours at 37°C.</td>
</tr>
</tbody>
</table>

Flucloxacillin and teicoplanin are not suitable for preparing line locks. To prepare gentamicin locks dilute 0.3mls of the paediatric injection (20mg/2ml) to 2mls with 0.9% sodium chloride immediately before use.