

Scottish Childrens' Cancer MSN CYPC Febrile Neutropenia Guideline
December 2013, Version 1

NICE guidance 2012 is taken into account but this document includes some alternative recommendations. This is due to local microbiological indications and local preferences which are listed as such throughout the document

Scottish childrens' cancer centres should incorporate this guidance into their own in-house policy.

References

- ¹Treatment of low risk febrile neutropenia in paediatric oncology: a framework document, version 1.1 2008, CCLG/Royal College of Nursing
- ²CATSCAN Febrile Neutropenia Guideline. January 2011
- ³Assessment, Diagnosis & Management of Neutropenic Sepsis. Best Practice Statement, NHS Scotland. September 2011
- ⁴Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropenia in a UK, multicentre, shared care setting Dommett R, Geary J, Freeman S et al. Eur J cancer 2009;45:2843-9
- ⁵NICE clinical guideline 151 Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. Guidance.nice.org.uk/cg151
- ⁶Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance. Phillips,R, Hancock B, Graham J et al. BMJ 2012; 345:7-48
- ⁷Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. Bate J, Gibson F, Johnson E et al Arch Dis Child Educ Pract Ed 2013;98:73-75

Section 1: Febrile Neutropenia Immediate Management

Section 2: Febrile Neutropenia – Ongoing Management

Section 3: Flow Chart

Section 4: Background and Other Detailed Information to Support the Management of Febrile Neutropenia

Section 1: Febrile Neutropenia – Immediate Management

- Any patient on chemotherapy or radiotherapy is at risk
- For patients coming in out of hours, treat all as if they MAY be neutropenic. Adjustments can be made during admission
- Extra vigilance is needed for patients on dexamethasone which can cause severe immunosuppression with normal neutrophil count

Fever: 38.0°C or higher Neutropenia: neuts $<1.0 \times 10^9/l$ (see NICE, page 3)

- Low temperatures $< 36.0^\circ\text{C}$ may also indicate sepsis and the same guidelines should be followed.
- Raised temperature recorded by parents at home IS significant.
- If afebrile on arrival use highest temperature reported by parent at home.
- If in doubt treat as febrile.
- An unwell child with symptoms and/or signs of sepsis but without fever or neutropenia must be treated as for febrile neutropenia.

Immediate First Line:

Piperacillin/tazobactam (Tazocin) + Gentamicin

Tazocin: 90mg/kg 6 hourly, max 4.5g, IV over 30 minutes, PLUS

Gentamicin: 7 mg/kg IV over 30 minutes 24 hourly (see NICE, page 3)

Penicillin allergy – ciprofloxacin 10mg/kg, max 400mg IV over 60 mins 8 hrly + gentamicin

Immediate management of patient – first 15 minutes

Any doctor or 'experienced clinical staff member'³

- Document date and TIME
- History of febrile episode – fever history, brief cancer history
- Vital sign assessment - **seek immediate senior opinion if patient unwell or shocked.**
Refer to local resuscitation guidance
- Prepare to access line/place line according to local policy

Within First 60 minutes - Any doctor

- Access central line or place cannula. Operator defined in local policy
- Central blood cultures (both lumens if double lumen line), peripheral blood culture if no central line, FBC, U+E, creatinine, LFTs, CRP (see NICE page 3), group and save. Other tests as page 4, now or later.
- Do not check coagulation unless specific concern – petechiae commonly due to low platelets. Heparin in line gives prolonged APTT; peripheral sample should be taken if significant concern
- **Do not wait for results of FBC**
- Give **piperacillin/tazobactam**, (ciprofloxacin if penicillin allergy). Gentamicin can be given now or later.
- Examination of patient including mouth, cardiovascular and respiratory systems, abdomen, central line sites, skin, PEG site, perineum
- Clean catch urine or MSU. Do not delay antibiotics waiting for this
- Consider risk of septic complications (see Risk, page 3)
- Check vital signs - **seek immediate senior opinion if patient unwell or shocked. Refer to local resuscitation guidance**

Antibiotic Exceptions:

- Exception 1: Penicillin allergy – use ciprofloxacin + gentamicin
Exception 2: If handover asks for a specific combination (e.g. neonate)
Exception 3: Fever/rigor after recent line flush, add teicoplanin

Risk: High Risk and Low Risk Groups for MSN:

High Risk: AML, Burkitt lymphoma, ALL induction, relapsed ALL, ALL during intensification, ALL in third year, Osteosarcoma, Ewings sarcoma, high risk neuroblastoma, relapsed disease with marrow involvement, progressive disease, post stem cell transplant (up to 6 months)

or any of the following features: hypotension, tachypnoea, or hypoxia <94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason(s) for inpatient treatment, neutrophil count < $0.1 \times 10^9/l$

Low Risk: Maintenance ALL, any disease with no high risk features as above,

(Using Modified Alexander Rule – see below – plus additional factors)

NICE guidance recommendation states^{5, 6, 7}:

- i) 'Neutrophil count < $0.5 \times 10^9/l$.' Comment: In this paediatric population the Scottish MSN review group prefers < $1.0 \times 10^9/l$ as safe practice.
- ii) 'Do not offer aminoglycoside unless there are local microbiological indications' Comment: Scottish MSN review group recommends dual therapy with piperacillin/tazobactam and gentamicin as a local microbiological indication due to levels of piperacillin/tazobactam resistance in Scotland.
- iii) 'Measure CRP and lactate' Comment: lactate not considered necessary by Scottish MSN review group. CRP depends on local policy.
- iv) 'In patients with central lines, peripheral blood cultures should be taken' Comment: Scottish MSN review group considers that the time taken to acquire peripheral blood cultures in children could result in delay in starting antibiotics thus peripheral cultures are not routine.
- v) A specialist should assess the risk of septic complications within the first 24 hours using modified Alexander rule.

Modified Alexander Rule for children and young people <18 yrs old^{5, 6, 7}

'Patients are at low risk of septic complications if:

They are not having treatment for acute myeloblastic leukaemia or Burkitt lymphoma, or the induction phase of treatment for acute lymphoblastic leukaemia; do not have a progressive disease; or are not having treatment for relapsed disease with marrow involvement; or

They do not present with any of the following features: hypotension, tachypnoea, or hypoxia as defined by oxygen saturation <94%, new changes in chest radiography results, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason(s) for inpatient treatment, neutrophil count < $0.1 \times 10^9/l$

Within 90 minutes of fever:

FY2 or equivalent must discuss case with registrar (ST3 or above) who should ALSO see patient as soon as reasonably possible

1. Complete full clerking
2. Do NOT perform RECTAL examination. Do inspect perineum.
3. Swab skin or mouth lesion for bacteriology and virology (into pink viral transport medium, VTM).

4. Throat and nose swabs to bacteriology and virology (VTM)
5. Give **Gentamicin** (local policy may dictate that this can be omitted if known not to be neutropenic, no focus and well)
6. If patient is not neutropenic and well, local policy will discuss the possibility of early discharge home. This should be discussed with the consultant for haematology/oncology.
7. If rigor/fever after line flushed or cellulitis at line exit site consider **teicoplanin, 10mg/kg 12 hourly for first 3 doses then 24 hourly, IV (max 400mg) in addition**
8. CXR/USS/other radiology/imaging if specific indication, eg for focal chest signs and/or reduced oxygen saturation.
9. Give paracetamol and continue all regular medications incl cotrimoxazole and other prophylactics.
10. Omit oral/IV chemotherapy overnight if neutropenic. Decision to continue this can be made the next day if appropriate.
11. Transfuse blood or platelets according to transfusion guideline.
12. If patient shocked i.e. low BP, poor perfusion, needing fluid bolus or **significant** specific focus of infection eg spreading cellulitis, perianal ulceration, the consultant 'On Call' for haematology and oncology **MUST** be informed.
13. **Repeat clinical examination** over the first 24-48 hours as signs may change with time.
14. Ensure that specialist team and/or principal treatment centre are aware of the patient at the earliest convenient opportunity eg the next day if out of hours. For DGH, ensure consultant on call for paediatrics is aware.
15. Consider risk of septic complications. See Risk, page 3

Section 2: Febrile Neutropenia – Ongoing Management

At 24 Hours: Review by specialist team:

Febrile, neutropenic:

Continue all antibiotics

Repeat blood cultures 24 hourly with fever spike

Febrile, not neutropenic:

Low Risk: Consider home with oral coamoxiclav or clarithromycin or azithromycin + follow up

High risk: Consider stopping gentamicin, continue other antibiotic

No fever for most of 24 hours, neutropenic:

Low risk: stop gentamicin, continue other antibiotic

High risk: continue all antibiotics

No fever for most of 24 hours, not neutropenic:

Low risk: Consider home with oral coamoxiclav or clarithromycin or azithromycin

High risk: Consider home with oral coamoxiclav or clarithromycin or azithromycin unless other reason to stay

At 48 hours: Review by specialist team:

Febrile, neutropenic:

Continue antibiotics

Consider second line eg teicoplanin if skin focus or line infection likely

Consider clarithromycin or azithromycin if respiratory focus
Repeat blood cultures 24 hourly with fever spike
DGH/shared care – contact primary treatment centre

Febrile, not neutropenic, high risk, reason to stay in hospital:

Continue antibiotics
Consider second line eg teicoplanin if skin focus or line infection likely
Consider clarithromycin or azithromycin if respiratory focus
Repeat blood cultures 24 hourly with fever spike
DGH/shared care – contact primary treatment centre

No fever for 24 hours, neutropenic:

Continue antibiotics until afebrile for 48 hours and blood cultures negative then stop antibiotics
At 48 hours afebrile, see below

No fever for 48 hours, neutropenic:

Check blood cultures are negative
Check no new focus of infection
Stop antibiotics
Discharge home on no antibiotic unless other reason to stay
If focus of infection, treat accordingly

NB: Positive blood cultures, pyrexial or not: be guided by type of bacteria and sensitivities – d/w Microbiology

At 72-96 hours : Review by specialist team:

Febrile, neutropenic:

CXR + abdominal USS
Consider lung CT
Consider AmBisome® at 3mg/kg (see IV monograph)
Viral DNA detection by PCR on EDTA blood sample
Ensure urine/stool/respiratory/skin samples sent to bacteriology and virology as appropriate
DGH – Consider transfer to Primary treatment centre

Discharge from hospital following febrile neutropenia

- Usually when afebrile for 48 hours with negative blood cultures
- Oral antibiotics at discharge usually NOT given unless specific focus of infection or at discretion of senior medical member of specialist team.
- No fever for 24 hours with rising neutrophil count and negative cultures may be acceptable in low risk patient, especially if positive respiratory viral isolate.

Section 3: see Flow Charts (separate attachment)

Section 4: Background and Other Detailed Information to Support the Management of Febrile Neutropenia

4.1 Background

Febrile neutropenia is common in children receiving cytotoxic chemotherapy for malignancy. If prompt and appropriate treatment is not commenced, septic shock can occur which can be fatal.

The risk and pattern of infection in children with malignancy or other immunosuppressing condition depends on the primary diagnosis and the type, duration and intensity of the treatment. The signs of infection may be minimal or absent in the presence of neutropenia or when patients are on steroids. Since there is no certain way of telling which febrile neutropenic patients have a potentially life-threatening infection, all such patients require investigation and empiric antibiotic therapy. Some or all of the following factors may be important:

4.1.1 General Risk Factors :

Duration and severity of neutropenia - neutrophils $<0.5 \times 10^9/L$ and predicted to continue for > 7 days or rapidly falling neutrophil count

Mucositis and gut toxicity due to chemotherapy or radiotherapy

Radiotherapy

Previously documented *Pseudomonas aeruginosa*

Evidence of serious sepsis - hypotension, shock

Aplastic anaemia with neutrophils $< 0.5 \times 10^9/L$

Autologous or allogeneic bone marrow transplant recipients

Peripheral blood stem cell rescue

Chronic graft versus host disease

Long term immunosuppressive treatment

In-dwelling central venous line or CSF access device or other 'foreign body'

Primary immunodeficiency + chronic neutropenia (non malignant) can also be treated using this guideline

4.1.2 Diseases linked to protocols which predispose to high risk febrile neutropenia:

Acute myeloid leukaemia (AML)

Acute lymphoblastic leukaemia (ALL) in the first 6 months after diagnosis

Relapsed AML or ALL

Stage 4 Neuroblastoma

B cell non Hodgkin lymphoma/Burkitt lymphoma

Osteosarcoma

Ewing's sarcoma

4.1.3 Risk Group assessment will take place at 48 hours by senior members of the specialist team. At this point patients may be assessed as suitable for discharge with or without oral antibiotics. Note the 'Treatment of low risk febrile neutropenia in paediatric oncology: a framework document, version 1.1 2008, CCLG/Royal College of Nursing' states a discharge plan at 48 hours based on improvement of fever, but not complete resolution of fever. The plan allows safe early discharge of low risk children who fulfill certain criteria but

who may still have a fever. These children will be discharged home on oral antibiotics. In Edinburgh, children tend to stay until afebrile for a full 48 hours.

4.1.4 Pyrexia during blood product transfusion

If pyrexia occurs during blood product transfusion in a neutropenic patient it cannot be assumed that the fever is related purely to the transfusion. Patients should be treated as if febrile neutropenic.

4.1.5 Prophylaxis

Patients normally receive regular medication as prophylaxis against organisms which are known to cause problems:

Those at risk of *Pneumocystis jirovecii* pneumonia (ALL, bone marrow transplant, Hodgkin lymphoma, neuroblastoma, peripheral blood stem cell rescue) receive cotrimoxazole on two days per week, Mondays and Tuesdays for leukaemia patients and 3 days per week on Mondays, Wednesdays and Fridays for other patients. The regime for leukaemia patients is to avoid interaction with oral methotrexate which is given weekly on Thursdays.

Cotrimoxazole dosage: BSA: less than 0.5m ² :	120mg twice daily
0.5-0.75m ² :	240mg twice daily
0.76-1m ² :	360mg twice daily
over 1m ² :	480mg twice daily

All patients should receive daily mouthcare as detailed in the Haematology/Oncology mouthcare guidelines.

4.2 Introduction to policy

4.2.1 The current plan in Scotland is to treat all febrile neutropenic children with piperacillin/tazobactam and gentamicin at presentation with fever. A preference is given to keeping patients as in-patients until they are afebrile for 48 hours although early discharge may sometimes occur.

Patients should be seen by an experienced clinical staff member, usually a doctor within 15 minutes of arrival in hospital or within 15 minutes of notification of the fever if already an in-patient. This policy applies to patients who are neutropenic due to cytotoxic chemotherapy and/or radiotherapy Patients who are neutropenic for other reasons and also those receiving immunosuppressing doses of steroids may follow this regime at the discretion of the treating consultant.

4.2.2 For patients admitted from home, there should be a robust and clear pathway for management and treatment in each hospital. If patients are seen by a junior doctor (eg FY2) the case must also be discussed with a more senior doctor at least ST4 or above.

4.2.3 Medical staff should ensure that a FBC is taken and should commence treatment as if neutropenic. The FBC result does not need to be known before starting treatment. This is to avoid delays in starting antibiotics. If the patient is not neutropenic, an adjustment can be made the next morning. If specific instructions have been given at handover to start a different antibiotic regime, follow these.

4.2.4 Neutropenia: neutrophil count <1.0x10⁹/L. (deviation from NICE guidance – see page 3)

- 4.2.5 Fever: One recording 38.0°C or more. Temperature to be recorded using any type of thermometer. If a child presents and does not fulfill the above criteria, consideration should be made to admit the child for observation such that treatment can be started as soon as possible if criteria are fulfilled.

Aural thermometers may record temperatures 0.5 – 1.0°C higher than axillary but raised temperature with any method should be considered significant. Consider individual child's temperature in the context of the entire clinical picture.

Low temperatures < 36.0°C may also indicate sepsis and the same guidelines should be followed as for febrile neutropenia.

- 4.2.6 These are guidelines only and patients may require treatment without fulfilling these fever criteria.

4.3 **Examination**

- 4.3.1 Patients must be fully examined especially mouth (including gums, tongue, teeth and sinuses), cardiovascular system, (especially heart rate, perfusion, blood pressure), respiratory system (especially respiratory rate, oxygen saturation), abdomen, perineum, central line site, skin and gastrostomy site.

- 4.3.2 Do **not** perform rectal examination. This can cause transient bacteraemia.

- 4.3.3 Monitor fluid balance closely.

- 4.3.4 Assess new skin lesions and swab and send to bacteriology and virology. State that the patient is immunosuppressed on the order, especially if the patient is in A+E or on an outlying ward.

- 4.3.5. Consider meningitis/ventriculitis if shunt or access device *in situ*, even if no 'meningism'. If there is genuine concern about a possible central nervous system (CNS) infection, the access device must be tapped by an operator whose name appears on the 'intrathecal register for administration of intrathecal antibiotics' before antibiotics are commenced if there is any possibility of CNS infection (in practice this will be the senior tier 2 registrar). The platelet count should be above 50x10⁹/l before accessing the reservoir.

- 4.3.6 Repeat clinical examination over the first 48 hours is essential. Signs may change with time.

4.4 **Investigations**

- 4.4.1 FBC, blood cultures (both lumens of double lumen line), urea, electrolytes, creatinine, LFT's, group and save.

Lactate and CRP are not measured routinely (deviation from NICE guidance – see page 3)

- 4.4.2 Nose and throat swabs to microbiology and virology in viral transport medium (VTM).

- 4.4.3 Swabs of mouth or skin lesions to microbiology and virology in VTM.

- 4.4.4 MSU or clean catch urine. The start of antibiotics must not be delayed waiting for this.
- 4.4.5 At clinical discretion, CXR +/- abdominal USS may be required early. These are not routine; only if significant specific symptoms and/or signs relating to chest (eg reduced oxygen saturation, focal changes) or abdominal (focal tenderness, guarding, mass) focus of infection.
- 4.4.6 Order tests accurately; all symptoms and signs should be listed. State that the patient has 'neutropenic sepsis and is immunosuppressed' as this may affect which tests are done in the laboratory. State whether a central line is present or not.
- 4.4.7 Blood cultures: These must be taken from each lumen of any central line. Cultures from lines should be taken according to ward protocol by appropriately trained nursing staff wherever possible. Ideally 3-5 ml of blood should be taken for each bottle, but a minimum of 1ml must be taken. Bottles must be labelled accurately. Peripheral blood cultures are considered unnecessary in this patient population unless the patient has no central line in which case a peripheral culture is essential (deviation from NICE guidance – see page 3). The extra time spent taking a peripheral culture is considered to result in undue delay in giving the IV antibiotics.

4.5 Treatment

Antibiotics must be commenced within **60 minutes** of admission or **60 minutes** after documentation of fever if already an in-patient

4.5.1 Empirical 'First Line' antibiotic therapy

Piperacillin/tazobactam 90 mg/kg IV (max 4.5g) over 30 minutes, 6 hourly (ciprofloxacin if penicillin allergy, 10mg/kg, max 400mg, 8 hourly IV) PLUS Gentamicin: 7 mg/kg one dose in sodium chloride 0.9% over 30 minutes. A trough level should be taken at 18 hours post end of infusion. Refer to Extended Interval IV Monograph.

Antibiotic Exceptions:

Exception 1: Penicillin allergy – use ciprofloxacin + gentamicin

Exception 2: If handover asks for a different combination for a specific patient (e.g. neonate)

Exception 3: Fever after recent line flush or soon after new line inserted, add teicoplanin

Risk groups are assigned to each individual patient taking into account The modified Alexander rule and also various other factors such as underlying disease, co-morbidities, treatment protocol, past history of infection, length of hospital stay etc. The final decision regarding risk group allocation lies with the consultant in charge of each patient.

4.5.2 Review in First 24 hours

Clinical review by the specialist team

Continue antibiotics

If patient not neutropenic, could discharge home if clinical condition allows and patient low risk by modified Alexander Rule. Home on oral coamoxiclav or clarithromycin expected.

4.5.3 Review at 48 hours - Second line antibiotic therapy

Ongoing pyrexia at 48 hours

Clinical review by specialist team especially looking for new focus of infection

Consider the addition of teicoplanin if specific indication, not empirically

Continue piperacillin/tazobactam

Consider stopping gentamicin if patient well with no high risk features and no positive blood cultures

Pyrexia settled at 48 hours

Clinical review by specialist team

If afebrile since admission i.e. for 48 hours and negative blood cultures: stop antibiotics. Discharge home without antibiotics unless there is a specific focus of infection or at the specific request of a senior member of the medical specialist team. Coamoxiclav or clarithromycin for 5 further days if required.

If afebrile for less than 48 hours, continue antibiotics until afebrile for 48 hours

4.5.4 Review at 72 hours - Pyrexia at 72-96 hours – Third line therapy

Clinical review by specialist team

Empirical AmBisome® must be considered at 72-96 hours if still pyrexial, ongoing neutropenia and no obvious bacterial source and no positive blood cultures. AmBisome® dose is 3mg/kg once daily over one hour. See IV Monograph for AmBisome® test dose. Prophylactic chlorphenamine and/or hydrocortisone is recommended if the patient has had a previous adverse reaction to AmBisome®. U+E's, magnesium, LFT's should be monitored regularly. If potassium low, use oral amiloride. AmBisome® should be continued until patient is afebrile for 72 hours with no suggestion of fungal infection. Neutrophil count should ideally be $> 0.5 \times 10^9/L$ for 2 days by this time. A small number of patients will be receiving oral antifungal prophylaxis - this should be stopped temporarily whilst receiving systemic antifungals.

CXR and Lung CT scan : look for evidence of focal infection, consolidation, or interstitial changes consistent with opportunistic lung infection.

Abdominal USS : look for evidence of hepatosplenic candidiasis or other focal bacterial or fungal infection

Virology: EDTA Blood should be sent for viral serology/PCR

Continue broad spectrum antibiotics

4.5.5 Positive Blood Cultures

If a positive blood culture is obtained, be guided by microbiologist and by type and sensitivity of bacteria. 7-10 days IV treatment would be expected.

14 days IV treatment is indicated for *Staphylococcus aureus* bacteraemia.

Blood cultures should be taken daily until negative

4.5.6 Discharge Home

Afebrile for 48 hours: Patients can be discharged home if afebrile for 48 hours with no positive blood cultures. Patients are usually discharged home without antibiotics.

A rising neutrophil count is not essential.

Antibiotics would be given if there is a specific focus of infection or at the request of a senior member of the specialist medical team.

Afebrile for 24 hours: Discharge home if afebrile for 24 hours, a low risk of septic complications, with no positive blood cultures, no specific focus of infection and with a rising neutrophil count is possible at the discretion of a senior member of the specialist team.

Oral antibiotics would be more likely in this situation – coamoxiclav or clarithromycin – check with a senior member of the specialist team.

4.5.7 Other Treatments

Paracetamol - every 4-6 hours

Parents are advised not to give paracetamol at home for pain or low-grade fever, except under specific advice from nursing or medical staff (e.g. patients with previous febrile seizures). This could theoretically mask a high fever.

Paracetamol can be given after documentation of significant fever and before cultures taken, once a decision to act has been taken. The doctor must however see the child as soon as possible.

For patients with ALL, stop maintenance chemotherapy e.g. 6-mercaptopurine, oral methotrexate, but continue prophylactic cotrimoxazole. (Check the patient's regimen at the earliest opportunity the next day for further guidance on chemotherapy dosing, for example on regimen C at certain points, chemotherapy should continue unless infection is proven.)

4.6. Investigations – more information

- 4.6.1 Nose/throat swabs: Ideally these are done weekly on all in-patients and sent to microbiology and virology. These can be done twice weekly if symptomatic or if patient has received autologous marrow or peripheral blood stem cell rescue (PBSC rescue). PCR will give a result in 24-48 hours for a range of respiratory viruses and for mycoplasma.
- 4.6.2 Mouth/line/wound/perianal swabs: any possibly infected lesion must be swabbed and sent to microbiology and virology in VTM. For a skin vesicle, swab lesion by squashing and rubbing vesicle and place swab in VTM and send to virology for PCR.
- 4.6.3 Urine: Must be sent to microbiology if any possibility of urinary tract infection. Specify that the patient may be neutropenic. Do not delay the commencement of intravenous antibiotics waiting for a urine sample. Give antibiotics as soon as possible and collect urine later if necessary.
- 4.6.4 Stool: Send to microbiology and virology if patient has diarrhoea (stool which takes the shape of the container). Request *Clostridium difficile* toxin if patient has diarrhoea and *Clostridium difficile* infection (CDI) is considered.
If stools are contaminated with urine they can still be sent for analysis as urine is usually sterile.
- 4.6.5 Sputum: send to microbiology and to virology if significant respiratory symptoms.
- 4.6.6 Nasopharyngeal aspirate (or induced sputum for pneumocystis if patient able to cooperate) to virology if significant respiratory symptoms. Discuss with local virology laboratory.

- 4.6.7 Bronchoalveolar lavage should be considered for ill patients with respiratory symptoms or signs. Send specimens to microbiology (ask specifically for mycobacteria analysis if required), mycology, virology, pathology/cytology. Discuss with laboratories before sending specimens.
- 4.6.8 Chest x-ray + Lung CT scan if significant respiratory symptoms or signs.
- 4.6.9 Abdominal USS if significant abdominal symptoms or signs
- 4.6.10 Repeat blood cultures once every 24 hours with temperature spikes, if patient remains febrile, unless clinical deterioration dictates otherwise
- 4.6.11 If cultures positive and patient becomes afebrile, repeat blood cultures 48 hours after stopping antibiotics (mainly in patients with central lines)
- 4.6.12 Repeat C-reactive protein twice weekly while febrile

4.7. **Monitoring the episode**

- 4.7.1 Monitor temperature, pulse, respirations + BP. Hourly measurements in all patients while febrile. Reduce to 2-4 hourly if patient is afebrile and well.
A HYPOTENSIVE PATIENT IS IN SEPTIC SHOCK until proven otherwise. Discuss early with ITU.
- 4.7.2 Check microbiology results daily
- 4.7.3 Monitor renal function
Monitor U&Es twice weekly whilst on gentamicin. Aminoglycosides are ototoxic. Central lines can be used for levels provided they are adequately flushed. If high levels are obtained consideration should be given to obtaining a peripheral sample. Information on monitoring of gentamicin can be found on IV Monographs. There is an increased risk of nephrotoxicity if patient is on vancomycin and gentamicin; avoid this situation if possible.
- 4.7.4 Alternate daily FBC or daily if indicated
- 4.7.5 Platelet requirements increase significantly in the presence of fever and infection. Give transfusion if platelets < 20 in febrile neutropenic patients.
- 4.7.6 Add metronidazole if severe mucositis, perianal sepsis or *Clostridium difficile* toxin present and diarrhoea. Do not use just for diarrhoea alone.

4.8. **Specific Infections**

4.8.1 **Fungal infection**

The two infections most commonly seen are Candidiasis and Aspergillosis. Patients at risk of systemic fungal infection are those with prolonged severe neutropenia, especially if they have received more than one course of antibiotics, particularly likely in patients with AML, relapsed ALL, B cell NHL, stage 4 neuroblastoma.

Candida can cause skin and/or mucosal infection, oesophagitis, infiltrates in liver, spleen or kidney and occasionally lung.

Aspergillus usually presents with pulmonary infiltration. Sinus infiltration is less common. Rarely, in advanced cases, central nervous system infection can occur.

The diagnosis of systemic fungal infection is difficult to confirm and blood cultures are often negative. Empirical antifungal therapy is essential in patients in whom there is a strong clinical suspicion of infection. A high level of suspicion must be maintained at all times.

Positive blood cultures with fungal organisms always require removal of the central venous line.

Lung CT scan and abdominal USS must be performed if systemic fungal infection at all likely.

‘Maintenance’ therapy with itraconazole, voriconazole or fluconazole after established systemic aspergillus or candida infection respectively can be discussed for specific patients.

Consider antifungal cover up front with first line antibiotics for patients with documented fungal infection on a previous occasion.

4.8.2 Line Infection

Central venous catheters are at risk of colonisation with gram positive, gram negative and fungal pathogens including some bacteria which are normally environmental pathogens eg *Stenotrophomonas*. Introduction of infection can occur during line accessing and from other causes of bacteraemia secondary to breaches in natural barriers to infection eg mouth and gut, during mucositis, or from bacteraemia secondary to a focus of infection eg UTI.

Fever and rigors after line flushing is especially indicative of line infection.

If there is doubt about whether a positive culture is a line infection or a true bacteraemia, peripheral cultures can be taken in addition to central cultures.

If blood cultures from the line grow *Pseudomonas aeruginosa*, klebsiella, *Staphylococcus aureus*, or yeasts eg candida and the child is unwell and septic, the line must be removed as soon as possible. If these organisms are causing actual line infection, the line will never be cleared and must be removed. Gram negative and staphylococcal sepsis can be systemic without actual line infection and a prolonged antibiotic course can be tried but in an unwell child the line must be removed as soon as possible.

For gram positive line infection, teicoplanin (if organism sensitive) would usually be given for a total of 7-10 days. Vancomycin is an alternative.

4.8.3 Interstitial Pneumonia

Pneumocystis jirovecii, cytomegalovirus, common respiratory viruses (influenza, parainfluenza, adenovirus, respiratory syncytial virus, metapneumovirus), mycoplasma are all well recognised causes of pneumonia.

Measles, varicella zoster virus, herpes simplex virus, other atypical organisms (e.g. coxiella, chlamydia) are all rare causes of pneumonia.

An intensive search must be made to identify the pathogen as the treatment varies considerably. CXR and lung CT scan essential.

A bronchoalveolar lavage must be performed for patients with significant respiratory symptoms or signs.

High dose cotrimoxazole IV or oral should be considered, along with broad-spectrum antibiotics and antifungals. Clarithromycin must be considered early.

Consider ganciclovir for cytomegalovirus.

Consider nebulised or IV ribavirin for severe respiratory syncytial virus. Cidofovir can be used for severe infection with adenovirus.

Oral oseltamivir (Tamiflu) or if > 5years of age, inhaled zanamivir (Relenza), can be used for immunosuppressed children with proven influenza A. See current local guidelines for pandemic influenza (eg H1N1 Swine flu 2009).

Pneumocystis jirovecii (pneumocystis pneumonia, PCP): Signs and symptoms are cough, fever, tachypnoea, hypoxia, absence of chest signs on auscultation, bilateral infiltration on CXR. Treatment is high dose co-trimoxazole and steroids. Pentamidine or dapsone are also effective.

4.8.4 **Perineal infection**

High suspicion of gram negative infection (e.g. Pseudomonas) and of anaerobic and fungal infections. Blood cultures, local swabs, stool cultures all essential. Add metronidazole.

4.8.5 **Diarrhoea**

Frequently occurs because of cytotoxic drug side effects and should not be used as the only reason for antimicrobial changes. Stools must be sent to microbiology for *Clostridium difficile* toxin and to virology. Oral metronidazole should be added if there is diarrhoea in the presence of *Clostridium difficile* toxin. Oral vancomycin may also be used in patients not tolerating metronidazole. IV metronidazole can be used only if the enteral route is contraindicated.

4.8.6 **Stomatitis**

Commonest cause is cytotoxic drugs. Send swabs for bacterial, fungal and viral analysis. Do not use metronidazole empirically. Aciclovir may be considered empirically if the mouth is very sore and herpes simplex virus likely but it is better to wait for confirmatory virology. Herpes simplex virus positive stomatitis or if identified from other blister/ulcer lesion, use high dose oral aciclovir (x 5 per day).
Give fluconazole for probable oral candidiasis.

4.8.7 **Sinusitis**

Consider fungal infection e.g. Aspergillus or Mucor. Take nasal and mouth swabs. Contact ENT for advice.

4.8.8 **Encephalitis**

Herpes simplex, adenovirus, Epstein Barr virus, mycoplasma, progressive multifocal leucoencephalopathy (JC virus), varicella zoster virus, HHV6, HHV 7, enteroviruses. Human Immunodeficiency Virus (HIV), mumps. Seek specialist advice.

4.8.9 **Hepatitis**

Consider hepatitis A, B, C, cytomegalovirus, adenovirus, EBV, Parvovirus B19. Check serology/EDTA blood for PCR.

4.8.10 **Haemorrhagic cystitis**

Cyclophosphamide/ifosfamide is the commonest cause but infective causes include adenovirus and BK (polyoma) viruses. Send urine to virology.

4.8.11 **Cytomegalovirus (CMV)**

Symptoms/signs include fever, pancytopenia, hepatosplenomegaly, hepatitis, retinitis, pneumonitis. CMV can be particularly aggressive after BMT.

Check for virus in urine, throat and stool.

Send EDTA blood for PCR

Consider sending nasopharyngeal aspirate or bronchoalveolar lavage specimens (inform laboratory first for any of these).

Ganciclovir may be given.

4.8.12 **Varicella Zoster Virus** – see separate protocol

4.8.13 **Parvovirus B19**

Can cause chronic anaemia in immunosuppressed children. Confirm serologically and also send blood in EDTA for PCR. Can be treated with IV immunoglobulin.

4.9. **Patients known to have neutrophil count greater than $1.0 \times 10^9/L$ in previous 24 hours**

4.9.1 Patients who are febrile but not neutropenic must still be assessed. It is possible to have gram negative septic shock with a normal neutrophil count so this should not lead to a false sense of security.

4.9.2 Out of hours, the advice is to treat as if neutropenic.

4.9.3 If specialist advice is available, the child is well with no significant physical signs, IV coamoxiclav (ciprofloxacin if penicillin allergy) is an alternative but blood cultures must be taken beforehand. Home with oral coamoxiclav or clarithromycin and close follow up is a possibility but only after specialist consultation. Decision to discharge the patient can be taken by the specialist team.

4.9.4 If respiratory symptoms/signs present, send a throat swab to virology for respiratory virus

4.9.5 Any patient with an indwelling central venous line can develop bacteraemia at any time – this is the rationale behind the assessment, investigation and empirical treatment of any patient with fever and a central line.

DOSES

Aciclovir:	IV infusion over 1 hour < 3months: 10mg/kg, 8 hourly 3 months -12 years: 500mg/m ² , 8 hourly > 12 year: 10mg/kg, 8 hourly (dose may need increased towards 500mg/m ² 8 hourly depending on clinical response). IV aciclovir must be given with hydration: 3 L/m ² /day (Max 4L/day) 0.45% sodium chloride/5% glucose
AmBisome®:	3mg/kg is the recommended dose for empirical cover, once daily over one hour. Doses from 1mg/kg once daily can be given at consultant discretion. See IV Monograph for AmBisome® test dose – first day only. Dose can be increased in proven fungal infection.
Ceftazidime:	50mg/kg (max 2g) 8 hourly IV bolus
Ciprofloxacin:	10mg/kg (max 400mg) 8 hourly IV Infusion over 60 minutes
Co-amoxiclav:	30mg/kg (max 1.2g) 8 hourly IV bolus (see BNFC for oral dose)
Fluconazole	1 month-12 yrs: 3-6mg/kg on the first day then 3mg/kg (max 100mg daily) 12-18 yrs: 50mg daily (max 100mg daily) for 7-14 days (max 14 days except in severely immunocompromised patients).
Gentamicin:	>1month of age 7 mg/kg intravenous infusion over 30 minutes in 0.9% sodium chloride, once daily. Refer to Extended Interval IV Monograph Trough to be measured at 18 hours post infusion. Aim for level < 1 mg/l.
Meropenem:	20mg/kg IV (max 1g), 8 hourly
Metronidazole:	7.5 mg/kg (max 500mg) 8 hourly IV infusion over 30 minutes Oral for <i>Clostridium difficile</i> toxin positive: 1 month – 12 years: 7.5 mg/kg (max 400mg) 8 hourly > 12 years 400mg 8 hourly
Piperacillin/ tazobactam:	90mg/kg (max 4.5g) 6 hourly IV infusion over 30 minutes
Teicoplanin:	10mg/kg (max 400mg) 12 hourly for 3 doses then 10mg/kg (max 400mg) 24 hourly
Vancomycin:	IV infusion over 1 hour. 15mg/kg 8 hourly, down alternate lumens if double lumen line. Trough should be taken prior to the fourth dose. Aim for trough 5-10mg/l. 'Red man syndrome' may occur if infusion rate too high i.e. >10mg/minute. Try infusion over 2 hours and if still occurs, change to different antibiotic.