Clinical Guideline

MANAGEMENT OF INFECTIONS IN PAEDIATRIC HAEMATOLOGY AND ONCOLOGY PATIENTS

<table>
<thead>
<tr>
<th>SETTING</th>
<th>Bristol Royal Hospital for Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR STAFF</td>
<td>Staff involved in clinical management of children and young adults under the care of the Paediatric Haematology and Oncology team</td>
</tr>
<tr>
<td>PATIENTS</td>
<td>All children, teenagers and young adults, under the care of the Paediatric Haematology and Oncology team. <em>(For Paediatric Bone Marrow Transplant (BMT) patients with infections, please refer to separate standard operating procedure document on DMS)</em></td>
</tr>
</tbody>
</table>

Guidance

1. Introduction

Children undergoing treatment for cancer are at increased risk of infections as a result of their disease as well as its treatment.

This document deals with the management of presumed infection in the immunocompromised child and should serve as a guideline only.

Treatment strategies and some definitions have been amended in line with new NICE guidance on management of febrile neutropenia. Adherence to NICE definitions may vary within the south west shared care network depending on clinical situation and proximity of a patient to their local hospital. We would expect clinical teams in Bristol and across the region to use clinical judgment and adjust the recommendations in the guidance where appropriate.

There are several factors which can influence the risk of infection.

- The disease itself
- Presence of an indwelling central venous line
- Duration and severity of neutropenia
- Length of treatment and prolonged immunosuppression
- Presence of chemotherapy-related toxicity e.g. mucositis

2. Management of Febrile Neutropenia

Treat suspected febrile neutropenia as an acute medical emergency and offer empiric antibiotic therapy immediately. In a neutropenic or immunocompromised patient treat as febrile neutropenia if clinically indicated such as signs or symptoms consistent with clinically significant sepsis.
Definition of Febrile Neutropenia

Diagnose febrile neutropenia in patients having anticancer treatment where:

- Neutrophils ≤ 0.5 x 10⁹/L plus either
- Fever > 38.0°C (assessed by any means)

or

- other signs or symptoms consistent with clinically significant sepsis (e.g. unexplained abdominal pain or generally unwell)

Initial Investigation of the Febrile Neutropenic Patient

Prior to commencing intravenous antibiotics, perform a full clinical examination looking for any site of sepsis. Examination must also include:

- Examination of central venous access device for exit site or tunnel infection
- Examination of mouth for mucositis
- ENT examination
- Assessment of nappy area/perineum

Baseline Investigations must include:

- Full blood count (FBC) + differential
- Routine biochemistry, baseline C-reactive protein (CRP) and lactate
- Blood cultures from each lumen of the central venous line, or peripherally (if no central line or if deemed appropriate).
- Urinalysis in all children aged under 5 years

Also, if clinically indicated:

- Chest X-ray (CXR) if symptomatic or chest signs present
- Computerised tomography (CT) of chest if suspicion of fungal infection (more sensitive than CXR)
- Urine microscopy and culture
- Swabs from sites of clinical infection only
- Clotted blood for viral and atypical serology (please discuss with virology and specify samples required)
- EDTA blood for viral polymerase chain reaction (PCR) (please discuss with virology and specify samples required)
- Throat swab or other respiratory tract sample for viral PCR. If possible, combined throat and nose swab.

For fever with acute diarrhoea and/or vomiting add:

- stool culture and sensitivities
- stool virology, Clostridium Difficile (C. diff) toxin, cryptosporidiosis
- ensure form states that patient is NEUTROPENIC if indicated

For fever with possible or definite respiratory tract infection add:

- Sputum (if produced) or
- Nasopharyngeal aspirate (NPA) - send one sample for bacterial culture and one sample for respiratory virus PCR.
Empirical Treatment of Febrile Neutropenia (all patients)

(For drug doses see separate “Commonly Used Drug Doses” Appendix 1)

Please take care when prescribing potentially nephrotoxic antibiotics in children at increased risk of nephrotoxicity secondary to chemotherapy, for example. The renal team should be consulted if there are any concerns about renal impairment or failure.

At Time (T) =0 hours

Aim that first dose of antibiotics is to be given within 60 minutes of presentation

Commence:

- Piperacillin/tazobactam as monotherapy. Please check if there is a contraindication to start Piperacillin/tazobactam for example a patient on high dose methotrexate.
- If allergy reported to penicillin then see section Patients with documented penicillin allergy.
- Add gentamicin if haemodynamically compromised.
- If a patient is rapidly deteriorating on first line consider possibility of a Tazocin resistant organism and review antibiotic choice with on call consultant
- Do not offer empiric vancomycin to patients with suspected neutropenic sepsis who have central venous access devices unless there is clinical evidence of line sepsis or a tunnel infection, or known previous colonisation with MRSA.
- If consistent illness and influenza circulating, commence appropriate antiviral therapy following discussion with microbiology/virology.

At T=48 hours, reassess.

IF ON GENTAMICIN, STOP AT 48 HOURS – unless clinical or microbiological indication to continue

Blood cultures positive: fever settling

- Treat with appropriate antibiotics for minimum 7 days depending on organism isolated

Blood cultures positive: fever persists

- Clinical review
- Reassess all microbiology results and sensitivities, preferably with a microbiologist
- Repeat blood cultures
- Repeat CRP
- If patient stable do not change antibiotics
- If patient unstable consider changing 1st line antibiotics to 2nd line by swapping Piperacillin/tazobactam to ceftazidime or add Vancomycin (if not already on it) or add antifungal if appropriate (see antifungal guideline)
- Give serious consideration to removing central line, particularly if blood cultures are positive for organisms such as *Staphylococcus aureus, Pseudomonas aeruginosa, Candida sp or other fungal organisms*
Blood cultures negative: fever persists

- Clinical review
- Repeat blood cultures
- Repeat CRP
- If patient needs to remain in hospital, do not change antibiotics unless indicated
- Review regarding potential viral infection

Blood cultures negative: fever settled in the last 24 hours

- If clinically well, stop antibiotics and arrange discharge

At \( T = 96 \) hours, reassess. If fever persists, Blood cultures positive:

Clinical review, repeat blood cultures and CRP Otherwise review cultures and sensitivities and consider:

- Changing antibiotics if appropriate
- Consider adding/changing antifungal therapy (antifungal guideline)
- Consider removing line

Blood cultures negative

- Clinical review, repeat blood cultures and CRP
- Consider removal of line if clinically unstable
- Consider adding antifungal therapy (antifungal guideline)

Patients with documented penicillin allergy: (see penicillin allergy guideline)

<table>
<thead>
<tr>
<th>Anaphylactic allergy (anaphylaxis, urticarial or rash immediately after administration of a beta-</th>
<th>IV Ciprofloxacin* + gentamicin + teicoplanin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-anaphylactic allergy</td>
<td>IV Ceftazidime</td>
</tr>
<tr>
<td></td>
<td>Add in gentamicin if haemodynamically compromised</td>
</tr>
</tbody>
</table>

*for patients on ciprofloxacin prophylaxis (e.g. AML patients), substitute IV ciprofloxacin with IV aztreonam

3. Management of Presumed Fungal Sepsis (see antifungal guideline)

- The most common fungal infections seen are Candidiasis and Aspergillosis.
- Candida may cause skin and or mucosal infection such as oesophagitis, or systemic disease with fever, jaundice and occasionally pulmonary infiltrates.
- Aspergillus usually presents with pulmonary infiltration or rhino-sinusitis and occasionally Central Nervous System (CNS) disease.
Children at greater risk of fungal infection include:

- Children with prolonged periods of neutropenia
- Patients who have received more than one course of intravenous antibiotics
- Children with underlying immunodeficiencies
- Children on “high risk” protocols e.g. high risk Neuroblastoma, Acute Myeloid Leukaemia (AML) or infant Acute Lymphoblastic Leukaemia (ALL)

Investigations

Fungal infection can be difficult to prove as blood cultures are often negative.

- Cultures of blood, urine, sputum and/or Broncho-alveolar lavage (BAL), serology for Candida and Aspergillus should be performed (discuss with mycology).
- CT scan of chest +/- sinuses plus ultrasound scan of abdomen should be undertaken
- Beta-glucan test (G-Test) on serum sample (high negative predictive value, although not for mucormycosis) or BAL
- Galactomannan test if suspect aspergillosis
- Aspergillus specific PCR (still investigational so discuss on individual basis)
- For proven infection with Candida consider Ophthalmology assessment

Treatment – see antifungal guideline

4. STOPPING ANTIBIOTICS AND ANTIFUNGALS

STOPPING ANTIBIOTICS

If patient meet criteria to discontinue antibiotics, they can usually be discharged after stopping antibiotics. Parents should be warned to bring the child back if she/he becomes febrile or unwell.

a) Blood Cultures Positive

- Continue minimum of 7 days appropriate intravenous antibiotics from the start of treatment.
- Certain infections e.g. Staphylococcus aureus, Pseudomonas aeruginosa or Aspergillus/Candida, may require more prolonged treatment and removal of line. Discuss with microbiologist/mycologist as necessary.
- Child should be afebrile for at least 24 hours and well with negative cultures before antibiotics are stopped, preferably with rising neutrophil count and a stable or decreasing CRP

b) Blood Cultures Negative

- Stop antibiotics once afebrile (<37.5°C) for 48 hours.
- Always try to stop aminoglycosides at 48 hours if clinically stable even if still febrile.
- Consider stopping antibiotics if alternative cause for fever identified e.g. respiratory virus.

STOPPING ANTIFUNGALS (see antifungal guideline)

a) Where there is no definitive evidence for fungal infection,
Stop antifungal therapy when patient has been afebrile for 3 days with a rising neutrophil count and discharge (this is usually 24 hours after stopping antibacterials).

b) Where there is clear evidence for fungal infection,
   □ Complete a minimum of 14-21 days of antifungal therapy and reassess sites of disease with appropriate investigations to confirm resolution of infection.

5. FEVERS IN NON-NEUTROPENIC HAEMATOLOGY ONCOLOGY PATIENTS
   □ The child should be assessed and should be treated according to clinical findings.
   □ The minimum investigations are full blood count, routine biochemistry, CRP and blood cultures from all lumens of the central line.
   □ If the child is well and no site of infection is found clinically it may be possible to send him/her home pending culture results.
   □ If line sepsis is suspected, e.g. fever and rigors after flushing line, start empirical antibiotics irrespective of neutrophil count and await cultures.
   □ For central venous access device exit site or tunnel infections, give 7-10 days of treatment depending on the organism isolated.
   □ Well, non-neutropenic children with Gram-positive line infections can often be managed at home with IV teicoplanin (provided sensitivity demonstrated).
   □ Consider *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) in a child with leukaemia or relapsed Hodgkin’s disease who has missed cotrimoxazole prophylaxis. N.B. patients infected with Pneumocystis jirovecii will give a positive beta-glucan test which can help in diagnosis, although as it is non-specific other fungal infections cannot be excluded.

6. MANAGEMENT OF CENTRAL LINE TUNNEL OR EXIT SITE INFECTIONS
   □ Blood cultures should always be taken from both lumens, irrespective of clinical status of the child
   □ Exit site swab should be taken
   □ Ensure that the line is secure to prevent it being accidentally dislodged whilst the area is inflamed and infected.
   □ When giving intravenous antibiotics through the central lines, ensure that alternate lumen are used

Management

a) If the child is AFEBRILE and NOT Neutropenic with exit site infection:
   □ Antibiotics may be given orally, for example Flucloxacillin or Augmentin, if the child is well and blood culture negative and where there is no evidence tunnel infection.

b) If the child is FEBRILE and NOT Neutropenic with exit site infection:
   □ Vancomycin alone could be used as first line, if this was felt to be clinically appropriate and the child required admission.
   □ Broad spectrum antibiotic cover with Piperacillin/tazobactam should be started together with Vancomycin, if the child is clinically unwell
c) If the child is FEBRILE and NEUTROPENIC:

☐ Treatment should be commenced with empiric 1st line monotherapy as outlined in section 2.0 with Piperacillin/tazobactam together with vancomycin.

d) If the child is AFEBRILE and NEUTROPENIC:

☐ Assuming the child is well, Vancomycin alone could be used as first line, if this was felt to be clinically appropriate.

7. SPECIFIC INFECTIONS

7.1 Interstitial Pneumonia

Investigations (discuss with microbiology)

☐ Bacterial cultures
☐ Nasopharyngeal aspirate, sputum or BAL fluid for immunofluorescence and respiratory virus PCR.
☐ Viral and mycoplasma serology.
☐ EDTA blood for viral PCR
☐ Beta-glucan test on serum sample (this has a high negative predictive value for fungal infection – including Pneumocystis jiroveci (previously known as Pneumocystis carinii, PCP)
☐ Otherwise, BAL if suspicion of PCP (NPA and throat swab no good for PCP)
☐ Consider lung biopsy if deteriorating on appropriate treatment

Treatment, consider:

☐ Patients may be already on empirical first line therapy if they are neutropenic and febrile.
☐ Treating for PCP (co-trimoxazole – see BNFC)
☐ Treating for atypical bacterial infections with addition of clarithromycin - do not use clarithromycin if patient is receiving ciprofloxacin (see Empirical Antibiotic Guideline)
☐ Treating for CMV or other viruses (discuss with consultant)
☐ Antifungal therapy (see antifungal guideline)

7.2 Parvovirus B19 infection

Investigations (discuss with microbiology)

☐ Confirm diagnosis by Parvovirus serology and blood PCR.
☐ Bone marrow aspirate may be helpful and show characteristic bizarre giant erythroblasts (can also be tested for Parvovirus by PCR).
☐ IVIg (human immunoglobulin) may be used to treat parvovirus red cell aplasia (see Department of Health (DOH) Clinical Guidelines for Immunoglobulin use). Discuss with consultant. Contact pharmacist for supply.

7.3 Varicella-Zoster (VZV)
See “Immunisation of immunosuppressed haematology and oncology children” and DoH Immunisation Against Infectious Disease: The Green Book
7.4 Measles
See “Immunisation of immunosuppressed haematology and oncology children” and DoH Immunisation Against Infectious Disease: The Green Book

7.5 Cytomegalovirus Infection (CMV)
Discuss with consultant. SOPs are available on the intranet for the medications used in the treatment of CMV. Dosage and administration of ganciclovir, Dosage and administration of cidofovir.

7.6 Clostridium difficile and patient with diarrhoea
- Patients with Clostridium difficile toxin positivity should be treated with ORAL metronidazole and subsequently changed to ORAL vancomycin if there is no response.
- If symptoms are severe give ORAL vancomycin first.
- If complicated or life threatening, then give both oral vancomycin and IV metronidazole.
- See BNFC for doses & discuss with pharmacist if any issues

8. SPECIFIC SITES OF INFECTION

8.1 Perineal Infection
- Have high index of suspicion for Gram negative infection.
- Repeat blood cultures and local swabs.
- Treat with initial empirical antibiotic regimen and consider addition of metronidazole.
- If still febrile at 96 hours, consider antifungal therapy (antifungal guideline)

8.2 Mucositis/Stomatitis (see also Mucositis guideline)
- Secondary to treatment
- Send swabs for bacterial and fungal culture and viral PCR (Herpes simplex virus)
- Metronidazole should not be used empirically in this situation.
- Aciclovir may occasionally be used but it is better to await confirmative virology.

8.3 Severe Rhinosinusitis
- The most common cause is aspergillus, but mucoraceous moulds also can cause this
- Search extensively for organisms.
- Treat early with high-dose AmBisome (and debridement where possible) – see antifungal guideline
- Consider Posaconazole where Zygomycte suspected
- Consider metronidazole if no response or if anaerobes are grown
- Consider imaging sinuses with a CT scan
8.4 Encephalitis

- Multiple viral causes (discuss with virologist to request appropriate investigations)
- Seek advice regarding appropriate combination for treatment
- Patient should be on broad spectrum antibacterials to cover central nervous system infection as well as fungal and viral cover.

8.5 Hepatitis

- Multiple causes (discuss with virologist/microbiologist to request appropriate investigations)
- Send EDTA blood for CMV, EBV and adenovirus PCR, and clotted blood for hepatitis A, B and C testing.

REFERENCES

| REFERENCES | DoH Immunisation Against Infectious Disease: The Green Book |

RELATED DOCUMENTS AND PAGES

| RELATED DOCUMENTS AND PAGES | All Trustwide Antibiotic Documents are available on the Intranet: Gentamicin guideline Antifungal guideline Penicillin allergy guideline Mucositis guideline |

AUTHORISING BODY

| AUTHORISING BODY | Paediatric Haematology, Oncology, BMT Quality Assurance Forum (Quaf) |

SAFETY

| SAFETY | Not applicable |

QUERIES AND CONTACT

| QUERIES AND CONTACT | For clinical concerns please contact any of the following for advice: Paediatric Haematology Registrar: bleep 3495 Paediatric Oncology registrar: Bleep 2950 Ocean unit (8am-6pm): 28145 Starlight ward : 28334 Apollo 35: 28335 For other enquiries please contact Microbiology or Antibiotic Pharmacist |
### Appendix 1

<table>
<thead>
<tr>
<th>DRUG ROUTE</th>
<th>DOSE &amp; FREQUENCY</th>
<th>NOTES/MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/ tazobactam IV¹</td>
<td>90mg/kg to max 4.5grams QDS</td>
<td>Be aware of allergies and contraindications such as High dose MTX</td>
</tr>
<tr>
<td>Gentamicin IV¹,²</td>
<td>5mg/kg OD</td>
<td>See <a href="#">BCH Gentamicin guideline</a></td>
</tr>
<tr>
<td>Ceftazidime IV¹</td>
<td>50mg/kg 8 hourly Maximum 2 gram/dose</td>
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</tr>
<tr>
<td>Vancomycin IV²</td>
<td>see BCH guidelines for intermittent vancomycin infusion – paediatrics or if over 38kg consider using adult guideline.</td>
<td>Use ideal bodyweight for obese patients. Aim for target concentration of 10-15mg/L unless otherwise indicated. follow guidelines for detail on taking levels and dose adjustments</td>
</tr>
<tr>
<td>Meropenem IV¹</td>
<td>20mg/kg 8 hourly Maximum 1 gram/dose</td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>2-11 years 50mg/kg every 6 hours (max 2g QDS) 12-17 years 2 grams QDS</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin IV¹</td>
<td>10mg/kg 8 hourly Maximum 400mg/dose</td>
<td>Treatment dose</td>
</tr>
<tr>
<td>Ciprofloxacin oral treatment¹</td>
<td>20mg/kg 12 hourly Maximum 750mg/dose</td>
<td></td>
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<tr>
<td>Ciprofloxacin oral prophylaxis³</td>
<td>7.5mg/kg 12 hourly Maximum 500mg/dose</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin IV¹</td>
<td>10mg/kg 12 hourly for 3 doses, then 24 hourly</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole oral prophylaxis³</td>
<td>&lt;0.5m² 0.5 – 0.75m² 0.76 – 1m² &gt;1m²</td>
<td>Give doses 12 hourly on Saturdays and Sundays only</td>
</tr>
<tr>
<td>Aciclovir IV Treatment¹ (see BNFC for other indications)</td>
<td>&lt;3 months 3mths -12yrs &gt;12 years</td>
<td>20mg/kg 8 hourly 500mg/m² 8 hourly 10mg/kg 8 hourly</td>
</tr>
<tr>
<td>Valganciclovir oral</td>
<td>See SOPs for dosing</td>
<td>Consult pharmacist for advice and supply. See SOPs for each drug.</td>
</tr>
<tr>
<td>Ganciclovir IV</td>
<td></td>
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<tr>
<td>Foscarnet IV</td>
<td></td>
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<tr>
<td>Cidofovir IV</td>
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<tr>
<td>Ribavirin</td>
<td>Oral – see BNFC (use doses as for hepatitis C)</td>
<td></td>
</tr>
</tbody>
</table>

**References:**
1. BNFC and department current practice
2. Department current practice
3. UKALL 2011 Trial protocol and Interfant trial protocol
4. [BCH Gentamicin Guideline](#)
5. BCH vancomycin guidelines ( paediatric and adult)

- See BNFC latest edition. The doses below are for reference when the BNFC either contains a range of options, or no information.
- Use drug stickers where possible.
- Always be aware that doses may need to be adjusted for renal or liver function – contact pharmacist for more information.