Guideline for the Management of Children with Febrile Neutropenia

Trust Ref:E16/2016

Introduction and Who this Guideline applies to

This CYPICS network guideline has been developed by clinicians from Nottingham Children's Oncology Unit with consultation across the network including from the Leicester Royal Infirmary and has been ratified by the Leicester Children's Hospital guideline process.

This guideline applies to all children and young people under the age of 19 years who are receiving chemotherapy for malignant disease

UHL local Paediatric Oncology specialists are:

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Febrile Neutropenia

Full Title of Guideline:	**1956 - Guideline for the management of children with febrile neutropenia**
Author *(include email and role):*	Sophie Wilne, Consultant Paediatric Oncologist
Division & Speciality:	***Division***: Family Health - Children ***Specialty***: Paediatric Oncology and Malignant Haematology
Scope *(Target audience, state if Trust wide):*	Clinicians and nursing staff caring for children with febrile neutropenia under the care of EMCYPICS (East Midlands Childrens and Young Persons Integrated Cancer Service)
Review date *(when this version goes out of date):*	December 2028

Explicit definition of patient group to which it applies *(e.g. inclusion and exclusion criteria, diagnosis):*	This Guideline applies to all children and young people under the age of 19 years who are assessed as having neutropenic fever including those post autologous stem cell transplant (ASCT).
Changes from previous version *(not applicable if this is a new guideline, enter below if extensive):*	Reviewed and updated. Low risk febrile neutropenia strategy referenced.
Summary of evidence base this guideline has been created from:	NICE Guidelines
This Guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

Document Control

Document Amendment Record

Issue Status	Version	Issue date	Lead Author	Description
	V1		Dr Shaun Wilson SpR	
	V2	Aug 2012	Beverly Harwood and Ghazala Javid, Paediatric Oncology Pharmacists.	
	V3	Aug 2013	Adam Henderson Paediatric Oncology Pharmacists.	Reviewed and updated
	V4	Mar 2015	Beverly Harwood and Ghazala Javid, Paediatric Oncology Pharmacists.	Remove use of gentamicin at presentation unless severe sepsis

	V5 V5b	Mar 2017 Aug 2022	Dr Sophie Wilne	Temperature threshold REDUCED to a single temperature of 38ºC. Routine administration of fluconazole NO LONGER recommended. Agreed extended review date – no significant changes required currently
	V6	April 2023	Dr Sophie Wilne	Reviewed and updated. Low risk febrile neutropenia strategy referenced.
	V7	February 2024	Colin Ward	Empiric antibiotics extended to outline options for patients with penicillin allergy.
	V8	June 2024	Colin Ward and Dr Emma Ross	Maximum dose for teicoplanin removed throughout document antibiotic locks amended to reflect use in Northampton POSCU
	V9	December 2024	Colin Ward	Maximum dose for gentamicin amended to "according to local guidelines" as variation between Trusts Liposomal amphotericin reworded to "Amphotericin B Liposomal (AmBisome® or Tillomed liposomal)" & reference to test dose removed as per marketing authorisations

Introduction

The most commonly encountered cause of neutropenia in the paediatric population is marrow suppression secondary to chemotherapy. Oncology patients are immunosuppressed due to a combination of:

- Neutropenia

- Splenic dysfunction
- T and B-cell dysfunction – quantitative and qualitative dysfunction
- Destruction of normal mucosal barriers
- Alteration of normal body flora

New patients with possible new diagnosis of leukaemia (or relapsed leukaemia) are functionally immunosupressed regardless of their neutrophil count. Any child with a fever should also be started on broad spectrum intravenous antibiotics as below

Neutropenia can also be seen in non-malignant conditions (see table).

Decreased Marrow Production
Congenital – Kostmann's syndrome, Reticular dysgenesis, Fanconi's anaemia Acquired – Sepsis, Post-viral, Drug suppression, Cyclical neutropenia, benign chronic neutropenia, myelofibrosis
Associated with phenotypically abnormal syndromes
Schwachmann's, Chediak-Higashi, Cartilage hair hypoplasia, Dyskeratosis congenita
Increased destruction of neutrophils
Sepsis, endotoxaemia, Autoimmune antibodies, Neonatal isoimmune haemolytic disease
Sequestration of neutrophils
Immune complexes – Viral, SLE, Sjorgen's syndrome Hypersplenism
Associated with immunodeficiency
X-linked hypogammaglobulinaemia Selective immunoglobulin deficiency states
Metabolic Problems
Propionic isovaleric, Methylmalonic acidaemia, Hyperglycinaemia

As the immune system is not working properly, the normal inflammatory responses are muted. This may lead to infection without fever and also a greater tendency to dissemination of pathogens.

The initial management of a child with febrile neutropenia is the same irrespective of the cause of the neutropenia.

The microbiological aetiology of the fever in febrile neutropenic patients is found in only 30 – 40 % of cases. Bacteraemia is present in 10 – 20% of febrile neutropenic patients with neutrophils below 0.1 x 10^9/L. The most likely infective pathogens are endogenous bacteria from skin and gut flora with gram-positive organisms (Streptococci, coagulase-negative Staphylococci, Staphylococcus aureus, Enterococci) now more common agents than gram-negative organisms (Escherichia coli, Klebsiella spp,

Pseudomonas aeruginosa). Fungal infections are always a diagnostic possibility in immunosuppressed patients. These usually occur in patients with prolonged neutropenia (> 7 days) and those who have had a course of broad-spectrum antibiotics.

Prior to empirical antibiotic regimens mortality rates with infections were as high as 80%. Aggressive and early broad-spectrum antibiotic policies have decreased these rates to less than 3%. All febrile neutropenic patients should initially be considered infected, however non-infectious causes that also need to be considered are:

- Malignant process
- Cytotoxics – cytosine, bleomycin
- Blood products
- Allergic reactions

Any child showing signs of infection and considered immunosuppressed should be started on antibiotics and reviewed by a senior staff member regardless of their neutrophil count.

Normal range of neutrophils for children at different ages

AGE	TOTAL WBC ($x10^9$/L) Mean	Range	NEUTROPHILS ($x10^9$/L) Mean	Range
Birth	18	9 – 30	11	6 – 26
1 week	12	5 – 21	5.5	1.5 – 10
1 month	10.8	5 – 19.5	3.8	1.0 – 9
6 months	11.9	6 – 17.5	3.8	1.0 – 8.5
1 year	11.4	6 – 17.5	3.5	1.5 – 8.5
6 years	8.5	5 – 14	4.3	1.5 – 8
16 years	7.8	4.5 – 13	4.4	1.8 – 8

Definitions

Neutropenia:

- Absolute neutrophil count (ANC) less than 0.5 x 10^9/L (<500/ml)

Fever:

- Temperature > 38^o C on one occasion

History on Admission

It is important to pay attention to the following:

1. **Concomitant use of nephrotoxic drugs** (e.g. Cisplatin, Ifosfamide, Vancomycin, Amphotericin, Amiloride, Ciclosporin, Tacrolimus).

2. Relation of symptoms to central line flushing or usage

- Rigors associated within an hour of a line manipulation is strongly suggestive of a line infection

3. **All patients that have received prolonged or intensive chemotherapy and repeated courses of antibiotics (e.g. patients with relapsed cancer) should be discussed with senior medical staff.** More aggressive empiric antibiotic cover (e.g. meropenem) may be required as first line therapy.

4. **History of previous resistant Gram Negative bacteria,** e.g. especially those with resistant E Coli or Klebsiella, Enterobacter, Citrobacter, Morganella. Discuss these patients with Microbiology – consider use of meropenem as first line therapy.

5. **History of other bacteria,** e.g. history of MRSA, VRE or Clostridioides difficile. Discuss patient with Microbiology.

Examination on Admission

All patients with a temperature need a detailed and full examination. Areas that need special attention are:

1. **Mouth** – teeth, gums, pharynx, consider herpetic stomatitis or gingival candidiasis.
2. **ENT** – especially examining for tenderness over the sinuses and mastoid sites in older children. Take a nasopharyngeal aspirate (NPA) or nose and throat swab in viral transport medium for patients with coryzal symptoms
3. **Respiratory** – respiratory rate and oxygen saturations and requirements must be recorded and documented. Hypoxaemia / signs of respiratory distress and normal auscultation may be associated with Pneumocystis Jiroveci pneumonia (PJP).
4. **Cardiovascular** – Blood pressure must be documented.
5. **Upper gastrointestinal** – painful swallowing may be suggestive of herpetic or candidal oesophagitis.
6. **Abdominal tenderness +/- diarrhoea or bowel stasis** – right lower quadrant pain / tenderness / distension may suggest typhilitis (neutropenic colitis), as well as appendicitis. Consider whether AXR and erect CXR are required to look for perforation (NB steroids may mask

signs) or abdominal USS indicated. If diarrhoea send stool for Clostridioides difficile (C. Diff) toxin– discuss with experienced registrar / consultant. Consider surgical review.

7. **Perineum** – symptoms of perianal discomfort or pain should **always** be asked about. If there are symptoms, the perineum should be inspected.
8. **Skin lesions** – look for petechiae and purpura (evidence of thrombocytopenia or DIC), consider Pseudomonas, herpetic, fungal aetiology
9. **Central venous line (CVL) sites** – erythema, swelling, tenderness are suggestive of infection tracking along the line
10. **Procedure sites** – e.g. Gastrostomy sites, lumbar puncture, bone marrow (posterior superior iliac crests).

Patients with following signs/symptoms need antibiotics to be commenced immediately AND URGENT assessment by a senior staff member (specialist registrar or consultant) regardless of neutrophil count:

- **Shock**
- **Respiratory distress**
- **Coagulopathy**
- **More than one organ system involvement**

Use PEWS Scoring System for monitoring

Investigations on Admission

All patients with a temperature on admission need:

1. Temperature/fever confirmed
2. Full blood count – differential to confirm neutropenia
3. Biochemistry – U+E's, Bone profile, LFTs if jaundiced, septic or hepatomegaly, CRP
4. Blood cultures – each sample must be labelled from where it is taken (e.g. red lumen)
    a. 1 culture from each lumen of the CVL (red and white) – ideal volume 5ml each
    b. If no CVL – 1 peripheral culture

Investigations to perform if any clinical indications:

1. CXR if signs or symptoms of respiratory disease

2. Nasopharyngeal aspirate if signs or symptoms of respiratory disease or coryza. Nose and throat swab in a viral transport medium is an alternative. Request extended respiratory virus panel.

3. Stool culture if diarrhoea – MC+S, enteric viruses , Clostridioides difficile toxin

4. Coagulation screen if septic – APPT, INR, fibrinogen

5. Urine culture – clean catch for urine dipstick and urgent MC+S

5. Throat swab – bacterial (in charcoal) and viral PCR (in viral transport medium)

6. Skin lesions:

   a. Bacterial skin swab

   b. CVL site

   c. Gastrostomy site

7. Abdo X ray / USS if signs of abdominal distension / tenderness

Subsequent Investigations

1. FBC – repeated at least twice weekly

2. Biochemistry as clinically indicated

3. At 48 hours and still febrile – **Discuss patient with Experienced Registrar or Consultant**

   a. Repeat examination, including perianal region

   b. Repeat blood cultures

4. At 96 hours and still febrile – **Discuss patient with Experienced Registrar / Consultant**

   a. Repeat full clinical examination, including perineum

   b. Repeat blood cultures

   c. Discuss performing echocardiogram of heart and line tip

   d. Discuss abdominal ultrasound for fungal lesions in liver and spleen plus serum beta-D- glucan and galactomannan.

   e. If serological markers of fungal infection raised may need MRI brain and sinuses and chest CT – consultant decision.

General measures

If the duration of neutropenia is predicted to be prolonged, preventative measures need to be instituted:

- Stop immunosuppressive agents if appropriate
- Do not routinely give any medication via PR route
- Support haematological requirements appropriately
- Do not routinely use NSAIDs as an anti-pyretic
- Good mouth care and dental hygiene
- Prophylaxis against pneumocystis jiroveci (Co-trimoxazole) in patients expected to have prolonged myelosuppression (particularly lymphopenia) - to continue throughout treatment (caution in close relation to high dose methotrexate – see specific treatment protocol for details)
- If exposed to building/construction work there is an increased risk of mould infections. If this exposure cannot be avoided, fungal prophylaxis should include an agent active against Aspergillus species.
- GCSF – institution of GCSF therapy is a consultant decision.

EMPIRICAL ANTIBIOTIC REGIMEN

IF AT ANY TIME DURING ADMISSION A CHILD APPEARS SEPTIC, DISCUSS THE CONDITION WITH THE ONCOLOGY/HAEMATOLOGY CONSULTANT ON-CALL

Antibiotics must be administered within ONE HOUR of arrival to hospital. Decision to change antibiotics at any time will be a Consultant decision.

Prescribe paracetamol 15mg/kg every six hours alongside antimicrobials to control fever

First line antimicrobials:

No penicillin allergy AND not receiving high dose methotrexate

IV piperacillin/tazobactam 90mg/kg every 6 hours (max 4.5 grams every 6 hours)
Use meropenem if meningitis suspected - 40mg/kg every 8 hours if body weight up to 50 kg. 2g every 8 hours if patient over 12 or body weight 50kg and above

IV Gentamicin 7mg/kg (max according to local guidelines) stat dose **only if patient shows signs of sepsis (rigors, temp>39.5ºC, hypotension, hypoxia) -** prescribe on front of drug chart If unsure whether indicated then discuss with paediatric oncology/haematology consultant on call (if out of hours) and to discuss with microbiology consultant during working hours as needed.
If pre-existing renal impairment, then consider dose reduction – see local gentamicin guideline
After senior review if gentamicin is to continue then levels should be taken according to local guidelines

Additional to first line antibiotics:

Add **IV Teicoplanin** (a glycopeptide) 10mg/kg every 12 hours for 3 doses, then once daily as first line agent if one or more of:

- CVL related infection suspected (line or tunnel infection)
- Pain/inflammation around an endoprosthesis
- Severe mucositis
- Previous MRSA isolate

Consider using antibiotic locks (according to local guidelines) for gram positive line infections – instill appropriate volume into each lumen and aspirate after 24hours

- vancomycin 20mg in 2ml for Gram positive organisms
- gentamicin 3mg in 2ml for Gram negative organisms (always in liaison with a medical microbiologist)
- line removal strongly recommended for infections caused by Staph. aureus, MRSA, Coliforms, Pseudomonas and Candida species

Mild penicillin allergy (No anaphylaxis, angioedema or immediate onset urticarial)
OR
Receiving high dose methotrexate

Meropenem - 40mg/kg every 8 hours if body weight up to 50 kg. 2g every 8 hours if patient over 12 or body weight 50kg and above.

IV Gentamicin 7mg/kg (max accordingly to local guidelines) stat dose **only if patient show s signs of sepsis (rigors, temp>39.5ºC, hypotension, hypoxia) -** prescribe on front of drug chart If unsure whether indicated then discuss with paediatric oncology/haematology consultant on call (if out of hours) and to discuss with microbiology

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- line removal strongly recommended for infections caused by Staph. aureus, MRSA, Coliforms, Pseudomonas and Candida species

Severe penicillin allergy
IV Teicoplanin 10mg/kg every 12 hours for 3 doses, then once daily
IV Metronidazole 7.5mg/Kg (Max 500mg) every 8 hours
and
Oral Ciprofloxacin 20mg/Kg (Max. 750mg) every 12 hours. If high risk sepsis or unable to take oral, give IV 10mg/kg (Max 400mg) every 8 hours. See MHRA restriction https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-must-now-only-be-prescribed-when-other-commonly-recommended-antibiotics-are-inappropriate

IV Gentamicin 7mg/kg (max according to local guidelines) stat dose **only if patient shows signs of sepsis (rigors, temp>39.5°C, hypotension, hypoxia) -** prescribe on front of drug chart If unsure whether indicated then discuss with paediatric oncology/haematology consultant on call (if out of hours) and to discuss with microbiology consultant during working hours as needed.
If pre-existing renal impairment, then consider dose reduction – see local gentamicin guideline
After senior review if gentamicin is to continue then levels should be taken according to local guidelines

Second line antibiotics
If febrile at 48 hours – Discuss possible second line antibiotics with Paediatric Oncology/Haematology Consultant & seek microbiology support during normal working hours

Consider adding **IV Teicoplanin** 10mg/kg every 12 hours for 3 doses, then once daily, if not already prescribed

Third line antibiotics

If febrile at 96 hours – Discuss possible third line antibiotics with Paediatric Oncology/

Haematology Consultant: Consider empirical treatment for possible fungal infection (Experienced Registrar / Consultant decision only):

IV Amphotericin B Liposomal (Gilead (previously known as AmBisome®) or Tillomed liposomal)
Dose 3 mg/kg once daily. Test dose is not required. Monitor the patient carefully for signs of hypersensitivity EVERY TIME amphotericin liposomal is administered
Increase to 5 mg/kg once daily if fever does not settle or high suspicion of fungal infection

Discuss change of antibiotic with Paediatric Oncology/Haematology Consultant on call or consultant of the day:
IV meropenem 40mg/kg every 8 hours if body weight up to 50 kg. 2g every 8 hours if patient over 12 or body weight 50kg and above, if not already prescribed.

Discharge

Patients can be considered for discharge once 36 hour cultures are reported if **ALL** of the following criteria are met:

1. No signs of sepsis
2. Blood cultures negative at 36 hours
3. Afebrile for at least 24 hours and clinically well.
4. Experienced Registrar / Consultant is aware of plan and agrees to discharge

Discharge medications:

Some children may be sent home on oral antibiotics as part of the low risk febrile neutropenia pathway.

Refer to the local SOP for management of low risk febrile neutropenia admissions.

This is an Experienced Registrar / Consultant decision only.

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Summary of Guideline for Immediate Management of Suspected or Confirmed Febrile Neutropenia in Children and Young People

Suspicion of Neutropenia (neutrophil count <0.5 10^9/L) defined as:

Any systemic anticancer therapy (SACT) that has the potential to cause neutropenia' within the last 4 weeks. NOTE: Patients who have received G-CSF are still at risk.

Neutropenic sepsis can be fatal if not treated promptly, give antibiotics BEFORE blood results are obtained

Neutropenia/Suspicion of Neutropenia and Fever

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Take Blood Cultures (2 sets)

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Check Allergy Status, review previous microbiology for risk of multi-resistant Gram negative infection and GIVE FIRST DOSE OF ANTIBIOTIC(S) IMMEDIATELY

Fever defined as:
Temp >38°C on 1 occasion recorded before or during admission
Or
Rigors, feeling cold/shivery
Or
Clinical signs of high risk sepsis

Temp 37-38°C repeat after 1 hour

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No penicillin allergy AND not receiving high dose methotrexate

Piperacillin/Tazobactam 90mg/Kg (Max 4.5g) IV every 6 hours

Plus for patients who are known or previous MRSA positive or suspected line infection: **IV Teicoplanin** 10mg/kg every 12 hours for 3 doses, then once daily

Plus a single dose of IV Gentamicin (7mg/kg (max according to local guidelines) stat dose) if patient has high risk red sepsis or blood pressure fails to respond to initial fluid bolus.

Patient with NON-SEVERE penicillin allergy (no anaphylaxis, angioedema or immediate onset urticaria) or on HIGH DOSE METHOTREXATE

Meropenem (40mg/kg if body weight up to 50 kg. 2g if patient over 12 and body weight 50kg and above) IV every 8 hours

Plus for patients who are known or previous MRSA positive or suspected line infection: **IV Teicoplanin** 10mg/kg every 12 hours for 3 doses, then once daily

Plus a single dose of IV Gentamicin (7mg/kg (max according to local guidelines) stat dose) if patient has high risk red sepsis or blood pressure fails to respond to initial fluid bolus.

Patient with SEVERE penicillin allergy

IV Teicoplanin 10mg/kg every 12 hours for 3 doses, then once daily
and
IV Metronidazole 7.5mg/Kg (Max 500mg) every 8 hours
and
Oral Ciprofloxacin 20mg/Kg (Max. 750mg) every 12 hours. If high risk sepsis or unable to take oral, give IV 10mg/kg (Max 400mg) every 8 hours.

Plus a single dose of IV Gentamicin (7mg/kg (max according to local guidelines) stat dose) if patient has high risk red sepsis or blood pressure fails to respond to initial fluid bolus.

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Please then contact Paediatric Haematology/Oncology Consultant on call to inform them of patient and for advice / further guidance. Patients should have a senior review within 24 hours of admission and with result of neutrophil count

Assessment at 24-48 hours – microbiology will ring through any positive blood cultures identified at this stage.

NEUTROPENIC and NOT clinically improving

Continue IV antibiotics.

Check FBC and U&Es daily. Assess daily for signs of localised infection. Repeat blood cultures if temperature spikes.

At 24-48 hours, review all microbiology samples. If cultures have shown no growth and the patient's condition has not improved on first line antibiotics, try and determine a likely source or another cause of fever (e.g. underlying disease).

Discuss with SpR/consultant who may wish to seek further advice from microbiology. The empiric antibiotic regime should not be changed unless there is clinical deterioration or a microbiological indication

If there is no response beyond 48-72 hours

Discuss with an experienced oncology trainee or consultant before contacting microbiology. Non-response to treatment may be due to numerous factors- see full text guideline

NEUTROPENIC but clinically improving

Continue IV antibiotics. Check FBC and U&Es daily.

Assess daily for signs of localised infection. Repeat blood cultures if temperature spikes.

At 36-48 hours, review microbiology samples.

If cultures have shown no growth and the patient's condition has improved, switch to oral antibiotics in the morning, with consideration of discharge later in the day.

Not-improving

Improving

NEVER/NO longer neutropenic

Is a bacterial infective cause likely? Review micro results

Yes

If a probable focus of infection is identified treat as per the relevant Trust guideline

No

No identifiable focus of infection AND patient is not severely septic – consider stopping antibiotics.

Consider discharge if patient is low risk and is otherwise well with normal bloods.

If not well enough for discharge and on IV antibiotics switch to oral after 24-48 hours in patients whose risk of developing septic complications is considered low. Check FBC and U&Es daily. Assess daily for signs of localised infection. Repeat BCs if temperature spike.

If a source of infection has been identified prescribe oral antibiotic in accordance with relevant Trust guideline.

UHL Education and Training

None

UHL Monitoring and Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Antibiotics prescribed and administered later than an hour of arrival to hospital	Via datix	Specialist Pharmacist/Ward Sister	Six monthly	CYPICS CPM
Type of antibiotics used in patients treated for febrile neutropenia	Audit	Specialist Pharmacist	Yearly	CYPICS CPM
Antibiotic prescribing and administration errors	Via Datix	Specialist Pharmacist/Ward Sister	Six monthly	CYPICS CPM

Key Words

Neutropenia, Febrile, Children, Young People, Paediatrics, Oncology, Malignancy, Fever

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Emma Ross; Consultant Paediatric Oncologist	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review:	