SOUTHAMPTON Children's Hospital

Wessex Paediatric Oncology Supportive Care Guidelines: Management of Febrile Neutropenia

Scope
This guideline applies to all paediatric oncology patients in the region. It does not apply to neonates on neonatal units.

Purpose
Children receiving treatment at the Southampton Paediatric Oncology Principal Treatment Centre (PTC) have open access to the designated Paediatric Oncology Ward at either the PTC or their Paediatric Oncology Shared Care Unit (POSCU) Hospital. Their parents/carers will be in possession of contact details for these wards and have been instructed to contact them for any medical problems that arise while they are receiving treatment. These Guidelines are intended for the use of the medical teams at the PTC or POSCU. If one of the Paediatric Oncology patients presents to a medical service outside of the PTC or POSCU, please contact the medical teams at the PTC or POSCU for advice.

Chapter Authors:
1) Dr Mary Morgan (Consultant Paediatric Haematologist, UHS NHS FT)
2) Dr Sanjay Patel (Consultant Paediatric Infectious Diseases, UHS NHS FT)
3) Prof Juliet Gray (Associate Professor/ Consultant Paediatric Oncologist, UHS NHS FT)
4) Ms Claire Fosbrook (Paediatric Oncology Pharmacist, UHS NHS FT)
Adapted from version 1, written by Dr Sheila Bevin Retired Associate Specialist. Updated from Dec 2015 version changed wording regarding non-neutropenic fever.

Edited by: Dr Amy Mitchell (Paediatric Oncology Grid SpR, UHS NHS FT)
Valid from 24/03/16

Contents

1.1. General principles 3
1.1.2 Septic shock....3
1.1.3. Anti-pyretic use in Paediatric Oncology Patients 3
1.2. Management of suspected febrile neutropenia 4
Table 1: Initial screening Investigations in Suspected Febrile Neutropenia 5
Table 2: Risk assessment of severity (at onset and 48 hrs) - *Modified Alexander score:*....6
1.2.1 Initial Treatment of suspected febrile neutropenia: See Flowchart 1....7
1.2.2. Table 3. Specific Antibiotic Considerations: -....8
1.2.3 Antibiotic Prescribing whilst on protocols containing High dose IV methotrexate....9
1.2.4 Ongoing management of (suspected) febrile neutropenia....10
1.3 Duration of antibiotic treatment....11
1.4.1 Positive blood cultures....11
Table 5. Antibiotic plans for children with positive blood cultures....11
1.4.2 In Patient 96 hours Reassessment See Flowchart 4....11
1.5 Early discharge for low risk children on oral antibiotics See Flowchart 5....11
Table 6: Discharge Antibiotic Plans....12
1.5.1 Early Discharge Plan (see Flowchart 5)....12
1.6 Non-neutropenic Fever in immuno-suppressed patients. See Flowchart 2....13
1.7 Line infections....14
1.8 Antibiotic locks.....15
1.9 Line site infections....17
1.10 Antibiotic and Antifungal Prophylaxis....18
1.11 C. Difficile diarrhoea....18
Table 8: Spectrum of Antibiotic Activity....18
References and Further Reading....19
Table 9. Paediatric Oncology Pharmacy Approved Anti-biotic doses for use in Wessex Paediatric Oncology Patients (alphabetical order)....**Error! Bookmark not defined.**
Table 10. Paediatric Oncology Pharmacy Approved Anti-fungal doses for use in Wessex Paediatric Oncology Patients (alphabetical order)....**Error! Bookmark not defined.**
Table 11. Paediatric Oncology Pharmacy Approved Anti-viral doses for use in Wessex Paediatric Oncology Patients (alphabetical order)....**Error! Bookmark not defined.**

1.1. General principles

This section has been updated incorporating recommendations based on the 2012 NICE clinical guideline 151 – Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients http://guidance.nice.org.uk/cg151. Children with cancer are particularly susceptible to life-threatening infections. Chemotherapy affects the body's normal defences against infection by causing bone marrow and immune-suppression. Patients who have had total body or splenic irradiation are likely to have hyposplenism. Chemotherapy may disrupt mucosa in the mouth and gut increasing the risk of Gram-negative sepsis. Central lines and bone marrow sites are a potential focus of infection.

The term "febrile neutropenia" or "neutropenic sepsis" includes a spectrum of patients from those who are haemo-dynamically stable with no obvious focus of infection, to those in septic shock. Patients treated with chemotherapy may also have a significant infection without fever (particularly younger ones or when receiving steroids), or when not neutropenic. Children with fever, rigors or tachycardia and poor perfusion shortly after a central venous access device (CVAD) has been used should be considered to have a line infection, until proven otherwise. Blood cultures should be taken from the CVAD and antibiotics commenced.

All the doses for antibiotics/anti-virals/anti-fungals we recommend are now to be found in the appendix in the drug tables. **Please check drug doses against current version BNF for children or access www.emc.medicines.org.uk.** See Tables 9/10/11.

1.1.2 Septic shock

Details of treatment of severe sepsis/septic shock including useful emergency drug calculator may be found on PICU page on UHS NHS FT extranet website (guidelines found via "retrievals" or www.sort.nhs.uk). These guidelines should be followed except for antibiotic choice which is as detailed below.

Please notify consultant on call of any critically ill child, or if not responding appropriately to treatment. POSCU consultants please discuss with UHS consultant any child not responding appropriately to treatment, or with ongoing sepsis, poor renal function, hypotension, respiratory problems requiring oxygen or severe abdominal pain. Consider early central line removal if severe sepsis which is thought to be line related and child not improving (discuss with UHS consultant first).

1.1.3. Anti-pyretic Use in Paediatric Oncology Patients

Outpatients and children at home

Anti-pyretics (e.g. paracetamol, ibuprofen) should not be used in patients who are likely to be neutropenic (Neutrophils of 0.5 x 10^9/l or less) as they may mask fever. Blood counts may fall quickly and be unpredictable, and therefore even if the child has had a good neutrophil count measured recently, it should not be assumed to be the same. Children who are at risk of developing mucositis or who are likely to have pain for another reason (e.g. line insertion) should be discharged home with a supply of oral morphine in anticipation of pain. Once a decision to start antibiotics has been made (e.g. parent has phoned to say child is on their way to hospital having spiked a fever), then paracetamol may be given as needed.

In patients

For neutropenic patients who are in hospital, and having regular observations and medical assessment, paracetamol may be given for pain at the discretion of the treating medical team. This should be avoided in patients at high risk of neutropenic sepsis (e.g. those with AML or post autograft), who should be given an opioid as first line treatment for any pain. For patients receiving IV antibiotics, paracetamol may be given as needed for control of fever. Paracetamol should be stopped prior to discharge in patients who are likely to be neutropenic once discharged home, and parents should understand that it should not be given to the child at home whilst they are neutropenic.

Ibuprofen should be used with caution in thrombocytopenia as it affects platelet function; but there will be occasions when it will be beneficial. It must be avoided in patients receiving iv methotrexate (as interferes with excretion) and should be avoided in patients receiving mifamurtide as it may reduce efficacy).

1.2. Management of suspected febrile neutropenia

Definition of neutropenia and fever

Neutrophil count is 0.5 x 10^9/L or lower, and either
- Temperature ≥ 38 °C **or**
- Signs or symptoms consistent with clinically significant infection

"Any patient with a low neutrophil count who appears unwell with or without a fever should be treated with intravenous antibiotics, even if they do not quite fit the definition of febrile neutropenia"

Treat **suspected** febrile neutropenia as a medical emergency and offer empiric antibiotics immediately, after prompt assessment and appropriate investigations. i.e. start treatment if you suspect patient is neutropenic and has temperature ≥ 38°C or have other signs or symptoms of infection: don't wait for neutrophil count confirmation. **Antibiotics MUST be administered within 60 minutes of arrival to hospital.**

- Children with leukaemia are usually neutropenic at presentation or relapse.
- Those receiving treatment for acute lymphoblastic leukaemia (ALL) are likely to be neutropenic **during delayed intensification and during consolidation in Regimen B and C**.
- Suspect neutropenia in children receiving chemotherapy for solid tumours **7-10 days after start of chemotherapy**.

In children on maintenance treatment for ALL or Langerhan Cell Histiocytosis (LCH), if not neutropenic on the most recent FBC, it is appropriate to wait for the result of the FBC which should be marked urgent, unless unwell. However always consider that non-neutropenic children can still develop central line infections, which can be as potentially life-threatening as febrile neutropenia. (see flowchart 1 for overview of management)

History
Ask about symptoms of URTI or LRTI, pain around line site, abdominal pain, diarrhoea, fluid intake, urine output, rigors, relation of fever to CVAD use. Children with mucositis are more likely to acquire Gram negative infections

Examination
In addition to standard examination, check **line entry and exit site** and any recent bone marrow or lumbar puncture sites. Assess peripheral perfusion, pulse rate, blood pressure, respiratory rate, oxygen saturation, mental status. Rigors and reduced mental status are associated with more significant infection and severe sepsis. **Be alert to signs of warm shock**, (flash capillary refill, bounding peripheral pulse, warm peripheries, wide pulse pressure) as well as cold shock (capillary refill > 3 seconds, reduced peripheral pulses, cool mottled extremities, narrow pulse pressure).

Signs of warm shock	Signs of cold shock
Flash capillary refill, **Bounding peripheral pulse,** **Warm peripheries,** **Wides pulse pressure.**	**Capillary refill >3 seconds,** **Reduced peripheral pulses,** **Cool mottled extremities,** **Narrow pulse pressure.**

Hypotension is not necessary for diagnosis of septic shock – child may compensate for some time. Use early warning signs system to monitor (eg PEWS in Southampton). Measure ongoing fluid losses (which may be considerable) and urinary output.

Table 1: Initial screening Investigations in Suspected Febrile Neutropenia

Assessment for all patients	
Detailed history and examination	To include ears, mouth and throat for mucositis, line site for exit site or tunnel infections, endo-prosthesis for local infection, peri-anal area, any recent lumbar puncture/bone marrow sites.
Scoring system (see Table 2)	To assess patient's risk of septic complications
Blood Cultures	From each lumen of central line take at least 1-2mls (max 4 mls), peripheral culture if no central linetake 4mls for children > 36 mths, >1ml for 1-36mths and >0.5mls if less than 1 month.
Bloods	Urgent FBC, Renal function, LFT's including albumin, CRP, blood gas and lactate.
Urinalysis	If <5yrs or has urinary symptoms ideally pre commencing antibiotics but don't delay antibiotics in an unwell child.
Assessments to consider	
Chest X-ray	If symptoms or signs
Stool	If diarrhoea virology for rotavirus, adenovirus, c.difficile toxin, MC&S (will detect fungus in addition to bacteria, specifically request cryptosporidium), If prolonged diarrhoea and culture negative, look for norovirus - this usually needs discussion with virology.)
Sputum/NPA/viral throat swab	If signs of respiratory tract infection
Swabs for culture	From sites of clinical infection, look for areas of redness and tenderness: NB pus not usually present when neutropenic.

Table 2: Risk assessment of severity (at onset and 48 hrs) - *Modified Alexander score:*

	Are any of the following risk factors present:	**Initial assessment** Date: Time: Completed by:	**48 hr assessment** Date: Time: Completed by:
History	Inpatient at onset of FN Down Syndrome PICU during last FN episode		
Age	< 1 year		
Diagnosis / treatment	ALL (except maintenance) Infant ALL AML Intensive B-NHL protocols Anaplastic lymphomas Stage IV neuroblastoma PBSCT pre engraftment Ewing's Aplastic anaemia		
Clinical features	Shock or compensated shock Haemorrhage Dehydration Metabolic instability Altered mental status Pneumonitis Significant mucositis Respiratory distress/compromise Perirectal infection Soft tissue abscess/infection (other than minimal redness around line site) Rigors Irritability/meningism Organ failure		
Compliance with out-patient treatment	Inability to take oral medicines Poor compliance Social or family concerns		
48 hr assessment	Neuts < 0.1 Positive blood cultures Not clinically 'well'		

If none of the above features present, may be considered for conversion to oral antibiotics at 48hrs, or stopping antibiotics altogether if afebrile.

1.2.1 Initial Treatment of suspected febrile neutropenia: See Flowchart 1

The mainstay of treatment of febrile neutropenia is early use of empiric antibiotics, appropriate supportive care and regular review. Most children with febrile neutropenia will appear very well, but still need early treatment with antibiotics as infection could progress rapidly. The early use of empiric broad spectrum antibiotics in febrile neutropenia, before any pathogen is identified, has reduced morbidity and mortality rates. Previous NCEPOD reports (2008) have recommended administration of antibiotics within 30 minutes of presentation to patients with suspected neutropenic sepsis and shock, and NCAG (2009) that **antibiotics are administered within 60 minutes of arrival to patients with suspected febrile neutropenia.** A step down policy is also recommended, so that patients at low risk of septic complications, may be safely discharged from hospital earlier (Table 2). Children colonised with resistant bacteria should be started on a patient-specific antibiotic regimen that reflects their resistant organisms.

Empirical antibiotic treatment of febrile neutropenic in patients who are relatively well
Single agent Piperacillin/tazobactam*

- Child 1 month-18 years 90 mg/kg (max. 4.5 g) 6 hourly
- < 1 month 90 mg/kg 8 hourly

*unless patient specific or local microbiological indications

Empirical antibiotic treatment of febrile neutropenic patients with signs of severe sepsis eg poor peripheral perfusion, rigors, altered mental status or hypotension
Dual agent Piperacillin/Tazobactam & Gentamicin*

Age	Piperacillin/tazobactam	Age	Gentamicin
< 1 month	90 mg/kg 8 hourly	**> 7days – 1month**	5 mg/kg od*
child 1 month-18 years	90 mg/kg (max. 4.5 g) 6 hourly	**child 1 month -18 years**	7 mg/kg od* *Trough level before 2nd dose (do not delay administration of 2nd dose by waiting for result unless known renal dysfunction)

*unless patient specific or local microbiological indications

NICE guidance advises against the routine use of empiric glycopeptide antibiotics (e.g .teicoplanin or vancomycin) for patients with CVAD unless specific indications to do so (eg tracking CVL site infection or soft tissue infection not responding to initial antibiotics, pain and redness at site of metal prosthesis). If patient on prophylactic antibiotics, continue co-trimoxazole prophylaxis, but stop ciprofloxacin.

Rationale
Empiric antibiotics need to cover gram-negative infections such as E.coli, other coliforms and pseudomonas aeruginosa, and gram positive such as staphylococcus aureus and streptococci. Pseudomonads and other environmentals are increasingly common. Anaerobes are infrequent. Yeasts and fungi are rarely grown in blood cultures.

Dual therapy is associated with more toxicity overall than monotherapy. As many patients have no infection, it is important to reduce toxicity of empiric treatment. Toxicity should be limited by short and considered use of gentamicin. Patients showing signs of severe sepsis need dual therapy until cultures and sensitivities known, and 48 hours of gentamicin is recommended. Gentamicin is good for treating bacteraemia, but has poor tissue penetration and not usually indicated for prolonged systemic use. Trough level should be taken before 2nd dose. If any renal deterioration after 1st dose always check level before 2nd dose administered.

1.2.2. Table 3. Specific Antibiotic Considerations: -

Penicillin Allergy	If history of penicillin allergy treat with meropenem +/- gentamicin if unwell pending allergy testing or clarification. Most historical reports of penicillin allergy are not confirmed.
Previous growth of ESBL	Meropenem is usually indicated
Previous positive blood cultures	Discuss with microbiology regarding sensitivities
Receiving High dose IV Methotrexate	Treat febrile neutropenic episodes with meropenem because piperacillin/tazobactam (penicillins) are contraindicated. If not neutropenic could treat with cephalosporins or Teicoplanin depending on clinical indication.
Bone tumours with endo-prosthesis	Consider adding teicoplanin to empiric piperacillin/tazobactam if focal signs.
Patients on cisplatin chemotherapy	Generally aim to avoid gentamicin in these patients as together have prolonged effect on renal tubules. Can be considered for use when off cisplatin treatment for some months But should not be withheld if child is septic and unwell (but stop as soon as possible)
Renal Impairment	Use gentamicin with caution in renal impairment – always get result of level before 2nd dose in this case: can often take level at 18 hours.
Mucositis	Piperacillin/tazobactam and meropenem have good anaerobic cover, and so metronidazole not usually needed in addition to either of these antibiotics. Consider adding metronidazole for abdominal / perineal infection.
Pneumonia	Consider adding IV clarithromycin or oral azithromycin to treat atypical pneumonia. Consider pneumocystis, viral infections (especially in flu season) and fungal infections.
Colonised with MRSA	Piperacillin/tazobactam alone as first line antibiotics for uncomplicated febrile neutropenia. Low threshold for adding vancomycin if fever doesn't settle. Add vancomycin to piperacillin/tazobactam and gentamicin if unwell/septic.

1.2.3 Antibiotic Prescribing whilst on protocols containing High dose IV methotrexate
Patients receiving high dose methotrexate must not be prescribed high dose penicillins, aminoglycosides, ciprofloxacin, co-trimoxazole or tetracycline during administration and excretion of the drug, as they will interfere with excretion (eg ALL on protocol M or M-A, osteosarcoma, Burkitt's NHL, ALCL). (see chemotherapy section of full guidelines)

Table 4. Drugs to avoid during administration and excretion of high dose methotrexate

high dose penicillins
aminoglycosides i.e. gentamicin
ciprofloxacin
co-trimoxazole
tetracycline
aciclovir
vancomycin
ibuprofen
omeprazole

During high dose methotrexate administration, treat febrile neutropenic episodes with meropenem. If not neutropenic could treat with cephalosporins or teicoplanin depending on clinical indication. **Avoid ibuprofen as antipyretic or analgesic as this will have major impact on drug excretion.**

- UKALL 2011 also recommends avoiding aciclovir, vancomycin, oseltamivir and suspending co-trimoxazole throughout protocol M or M-A.
- UKALL 2011 regimen C patients on Capizzi interim maintenance. These patients have increasing doses of intermediate dose methotrexate**. UKALL 2011 advice is to avoid penicillins during Capizzi**. For febrile neutropenia recommend meropenem. However, if patient has been given penicillin, discuss with PTC to plan further treatment and change of antibiotics if needed
- Avoid treating superficial infections with penicillins; where possible, use a cephalosporin or teicoplanin, for example. If however, a patient has been given penicillin, need to allow for 5 doses to be omitted, in order to allow for drug excretion prior to giving methotrexate.
- Patients with osteosarcoma and lymphoma may receive tazocin and other penicillins in between cycles of chemotherapy, but **must stop 36-48 hours before next cycle**. If gentamicin has been used, this would need to be stopped for longer, but it is likely that this will have been given for 48 hours only.

1.2.4 Ongoing management of (suspected) febrile neutropenia

- If patient started on antibiotics and subsequently found not to be neutropenic, have a low threshold for reviewing and stopping at 48 hours unless clinically indicated. See Wessex antibiotic guidelines and **see Flowchart 2**. If patient otherwise well with no other signs of significant sepsis, not neutropenic and not likely to be imminently neutropenic, consider discharge after discussion with senior.
- If patient significantly unwell and febrile, whether following CVAD use or not, continue with antibiotics pending culture results.
- A healthcare professional with experience in managing complications of anti cancer treatment should assess patient's risk of developing septic complications within 24 hours of admission to secondary or tertiary care, using validated system (modified Alexander score), and should be assessed daily.
- Continue to monitor FBC, renal, liver function, CRP every 24-48 hours (and lactate if indicated). Repeat blood cultures every 48 -72 hours if patient remains febrile.
- We do not advise routinely changing empiric antibiotics, even if fever not settling, unless clinical deterioration or microbiological indication.
- We do not recommend adding in teicoplanin or vancomycin, unless specific indication.
- If patient's condition clinically deteriorating consider changing to meropenem, but do not change just because of ongoing fever. Discuss with microbiologist.
- If patient at low risk of developing complications, consider early discharge on oral antibiotics (**see Flowchart 5**). For standard risk patients continue iv antibiotics until temperature has settled, unless another cause of fever is likely (**see Flowchart 3/4**). If patients has shown signs of severe sepsis, then a longer treatment course is warranted (e.g. 5 days if blood cultures negative, 10-14 days id positive depending on organism and microbiology advice. See Table 4)
- **Repeat investigations if symptoms do not settle** – dramatic changes can appear as the patient develops neutrophils and collections of pus or changes on X-ray may only become apparent at this stage.
- **Remember to seek advice on complicated patients from microbiology/virology department.**
- **Consider CT chest / USS abdo +/- echo if persists more than 5 days**

1.3 Duration of antibiotic treatment

- Patients with febrile neutropenia and consolidation on CXR should have 10-14 days treatment – duration of IV antibiotics would depend on clinical progress and count recovery.
- Line tunnel infection should be treated for 10 -14 days (shorter duration may be considered if central line removed – discuss with microbiology team).
- Other areas, depends on site, count recovery, speed of resolution of symptoms.
- Yeasts and fungi are rarely grown in blood cultures, therefore clinical decision as when to stop anti-fungals. BNF recommends after patient is afebrile for 3 days if no evidence fungal infection; however, anti-fungals will need to be continued for longer if high index of suspicion of a fungal infection and may need to be continued longer if patient still very cytopenic.

1.4.1 Positive blood cultures

The following Table gives an indication of the action required in case of blood culture growth, if in doubt discuss with consultant and/or microbiology.

Table 5. Antibiotic plans for children with positive blood cultures (all should be discussed with local microbiologist)

Type of Growth	Notes
coagulase negative staphylococcus (CONS) isolation from 1 bottle	Repeat blood cultures, and decide clinically whether teicoplanin should be added. If starting teicoplanin treat for 10-14 days.
coagulase negative staphylococcus (CONS) infection is genuine (in at least 2 bottles ± temperature)	Treat with teicoplanin (confirm sensitivities) for 10 –14 days.
coagulase positive staphylococcus	Give at least 2 weeks IV treatment then 2-4 week course orally to reduce risk of subsequent deep-seated infection.
for other organisms	Depending on count recovery and microbiology advice.
candida	Treat for 14 days after last positive culture. Usually remove CVAD.
stenotrophomonas	Almost always need to remove CVAD.

1.4.2 In Patient 96 hours Reassessment See Flowchart 4

If temperature not settling at 96 hours and no focus of infection, repeat FBC, blood cultures, chemistry, CRP. Do CXR if not already done.

Consider adding in **AmBisome.** If child well and blood count is anticipated to recover imminently (particularly in low risk group), may hold off AmBisome. If starting AmBisome ensure CT chest, abdo USS, Echo and fungal blood sample for Beta glucans taken.

1.5 Early discharge for low risk children on oral antibiotics See Flowchart 5

It has been demonstrated that it is safe to discharge selected children home early on oral antibiotics, following initial inpatient treatment of febrile neutropenia with IV antibiotics, provided patients are appropriately assessed and managed. (PINE study). Use the Modified Alexander Score (see Table 2) at admission and again at 48 hours to **ensure no exclusion criteria are present**. Patient must be discussed with POSCU or PTC Consultant before being discharged.

The low risk protocol for oral antibiotics after 48 hours of IV antibiotics is applicable only to the following patients:

1) no exclusion criteria on admission or at 48 hours
2) negative blood cultures at 48 hours.
3) clinically well
4) Neutrophils ≥0.1 x 10^9/L at 48 hours
However fever at 48hours does not exclude from low risk protocol

Table 6: Discharge Antibiotic Plans

Child's status		Plan of action
If child is afebrile (<37.5°C) for 48 hours by time of discharge, all blood cultures negative, clinically well.	**And** provided count regenerating, or not anticipated that neutrophils will fall to ≤ 0.1 x 10^9/l.	Consider if suitable for discharge without any antibiotics.
If child is afebrile for 48 hours by time of discharge.	**And** uncertain whether neutrophils are stable	Consider need for oral antibiotics for further few days pending repeat FBC.
If patient still febrile but otherwise fulfils all other criteria for early discharge.	Take repeat cultures prior to discharge	Discharge on Co-amoxiclav usually, or if penicillin allergic use clarithromycin/ azithromycin or ciprofloxacin. Patient should take first dose in hospital (to check if will take orally).
If patient has only grown coagulase negative staphylococcus in blood cultures but is otherwise well and afebrile.	Repeat blood cultures	Start Teicoplanin and consider discharge with Teicoplanin locks after being loaded for 24hrs.

1.5.1 Early Discharge Plan (see Flowchart 5)

- **Before discharge** ensure 72 hr (from onset of fever) and 96 hr follow up confirmed and with whom.
- If patient is discharged early, parents should record twice daily temperature at home.
- **@ 72 hours from onset of fever**. Telephone contact should be made the morning after discharge and hospital review arranged if any concerns.
- At any point, patient should be readmitted for IV antibiotics if there is clinical deterioration or parental concern, or patient is unable to tolerate oral antibiotics.
- **@96 hours** or **day 5** from onset of fever, (96 hours – or morning after for practical reasons) child should be seen on ward or in community
- Any child still febrile at home on day 5 of febrile neutropenic episode (not 5 days after discharge) **must** be reviewed in hospital. FBC should be repeated, vital signs recorded and home temperature recordings reviewed.
- If child remains well and temperature < 38°C they could return home after hospital review. Discontinue antibiotics when temperature < 37.5 °C for 48 hours.
- If clinical deterioration, or if temperature ≥ 38°C at 96 hours or beyond, child must be re-admitted.
- If any stage blood cultures become positive, child should be re-admitted (unless coagulase negative staphylococcus and remains afebrile and well)
- If child has been completely afebrile at home and completely well, does not need to be seen routinely in hospital at day 5, but could be managed over the phone with community FBC as needed. If patient still neutropenic at discharge from hospital, or if count not regenerating, before discharge make arrangement to repeat FBC around day 5 either at home or in community.
- If child needs re-admission, then restart IV antibiotics as per initial treatment plan (usually piperacillin/tazobactam) if culture negative. Adjust antibiotic choice if cultures positive.

1.6 Non-neutropenic Fever in immuno-suppressed patients. See Flowchart 2

Non-neutropenic patients with fever do not all need to receive antibiotics routinely but each should be assessed individually and treated according to clinical findings. Although many fevers in non-neutropenic patients do not represent serious infection, in one series 25% of deaths occurred in children who were not neutropenic at presentation. Unwell, immuno-compromised patients with an in-dwelling line should receive tazocin and an aminoglycoside within 1 hour of presentation irrespective of the neutrophil count.

In addition to standard paediatric assessment for infection, clinician should examine any central venous catheters, shunts or endo-prosthesis in situ. Examine along central venous catheter and exit site to look for tunnel infection or cellulitis. Minimum investigations are full blood count and blood culture from central venous access device. Send micro swabs of any potentially infected areas and discuss with PTC if needed.

Factors which need to be considered include:

- ***Is the child unwell or septic?*** Treat with IV antibiotics as per febrile neutropenic protocol

- ***Is there a CVL in situ?*** Strongly consider empirical IV antibiotics, even if the child is well, if there is definite fever and no clear focus of infection.

- ***Does the child have a VP shunt or endo-prosthesis that could be infected?*** There will usually some clinical signs of symptoms if infected. Discuss with PTC if concerned.

- ***Is the neutrophil count likely to be falling?*** If patient has just received chemotherapy, and is likely to be neutropenic soon, then consider admission for antibiotics.

- ***How far away do the family live, and will they be able to bring the child back if unwell?***

- ***Has the child had a stem cell transplant within last 6 months?*** These children remain significantly immune-compromised and admission for IV antibiotics is usually warranted – discuss with PTC team.

If child is febrile but well, then it may be reasonable to admit and observe, holding off antibiotics unless the child becomes unwell or a focus of infection becomes evidence. If the child remains well and temperature is settling then can be discharged with plan for review if recurrent fevers. *Every parent will have a different idea of what 'unwell' means, so parents need clear parameters of when they need to bring the child back.*

If in doubt about the need for antibiotics in non-neutropenic patients, then please discuss with PTC. Discuss with microbiology and/or PTC if blood cultures are positive or previous Gram negative isolates resistant to Piptazobactam or Aminoglycosides. Adjust antibiotics as appropriate.

Consider PCP in a child with leukaemia or Hodgkin's disease who has missed co-trimoxazole prophylaxis.

1.7 Line infections

- Rigors, pyrexia or mottling shortly after a line flush are suggestive of infection in the line. If rigors or episodes of poor perfusion Gram-negative more likely than Gram-positive infections. Often these patients will be perfectly well before line flush. Even if not-neutropenic, they can deteriorate very rapidly. Coagulase negative staphylococci, staph aureus, aerobic Gram-negative bacilli and candida albicans are the most common catheter related bloodstream infections.

- Take blood cultures from the line (use the first few mls which would normally be discarded) and check the line site. **In the case of a double lumen line remember to take cultures from both lumens.**

- Management of infection depends on the certainty of infection and symptoms.

- If the child is extremely well when seen and has only had a transient pyrexia which may or may not have been related to line flushing and which has settled without paracetamol, culture line and wait for culture results before starting antibiotics. Ensure child stays on ward for 1 hour to ensure there is no deterioration in condition after line use.

- If the cultures are positive, appropriate IV antibiotics are required.

- Many line infections will be caused by coagulase negative staphylococcus. Under these circumstances, it is often possible for these children to be treated either with teicoplanin at home, or attend daily for treatment. Discuss each family with the nursing staff before offering home administration to parents.

- Colonisation of lines with Pseudomonads and other environmental pathogens appears to be increasing, which may give rise to more problems. These children will need hospital admission, initially at least until organism and sensitivities identified and clinical condition stabilised.

- If the child has had a rigor, mottling or is poorly perfused following line flush – admit, culture line and start tazocin and gentamicin (unless contraindicated).

1.8 Antibiotic locks.

Microbial colonisation of a central venous line can trigger catheter related bloodstream infections (CRBSI) and may spread from the catheter to the bloodstream. CRBSIs occur most commonly from migration of pathogens from skin flora or from contamination of the catheter hub but can also occur from seeding from a secondary site infection or from injection of a contaminated infusate. CRBSIs often require catheter removal for effective treatment; however catheter salvage may be attempted. CRBSIs can be particularly complicated to treat if the catheter is not removed as bacterial biofilms can develop in the catheter which can be resistant to the penetration of anti-bacterials and need much higher concentrations of antibiotics than those given systemically.

The decision to salvage the line is a complex one and should be made on an individual basis taking into account factors such as clinical condition of the patient, the continuing need for the central line, the pathogen(s) involved and response to treatment. If the line is no longer required, it should be removed. If the line is removed the tip should be sent for culture.

Where attempts at catheter salvage are unsuccessful i.e the blood cultures remain positive at 72 hours after the initiation of appropriate antimicrobial therapy, fever does not resolve, or the patient deteriorates, the line should be removed.

Where line salvage is attempted it is recommended that both systemic and antibiotic line locks are used concurrently.

The most common pathogens implicated in CRBSI are:

- Coagulase-negative staphylococci (in particular *S.epidermis*) – most common
- *Staphylococcus aureus*
- *Candida*
- *Enterococci*
- Gram negative *bacilli*

Antibiotic line locks allow much higher concentrations of antibiotics to be applied directly to the catheter without associated systemic effects.

- The decision to start a patient on line locks should be in conjunction with microbiology.
- The **volume** of the lock will only be enough to fill the lumen of the line i.e. **2mL maximum (see Table 7)**
- Ideally the lock should be left in place for 24 hours, and then aspirated. Rotate lumens to allow effective dwelling time of lock.
- Treat both lumens of a double lumen line, even if cultures were only positive from one lumen.
- Treatment duration is normally for between 7-14 days but seek microbiological advice.

Antibiotic	Concentration	Diluent
Vancomycin	10mg/mL	0.9% sodium chloride
Gentamicin	5mg/mL	0.9% sodium chloride
Teicoplanin	10mg/mL	0.9% sodium chloride

Theoretically there is the potential for the antibiotic in the line to leach out into the systemic circulation, however although the concentration of antibiotic in the line lock is high, the total amount given in the line lock is generally only a small fraction of a systemic dose.

Taurolock

Taurolock is a commercially available lock that contains taurolidine and citrate. Taurolidine has been shown to have broad spectrum antimicrobial activity and citrate is used an anticoagulant, but may also enhance antimicrobial activity. At present the majority of evidence for Taurolock line locks is for the prevention of CRBSIs rather than treatment. Used once weekly - can be considered for prophylactic use following treatment of a line infection.

Table 7. Central Venous Catheter Volumes:
NB Only the Groshong will necessarily be of this length. Leadercuff and Hickman lines are cut to length so may well have a smaller volume.

Catheters – internal volumes		
Groshong 3.5 Fr		0.13 ml
Groshong 5.5 Fr		0.4 ml
Groshong 7.0 Fr		0.7 ml
Groshong 8.0 Fr		0.9 ml
Groshong 8.0 Fr extra long		1.2 ml
Groshong 5.0 Fr DL	Red (distal)	0.42 ml
	White (proximal)	0.35 ml
Groshong 9.5 Fr DL	Red (distal)	0.83 ml
	White (proximal)	0.52 ml
Groshong 9.5 Fr DL (Extra long)	Red (distal)	0.94 ml
	White (proximal)	0.57 ml
Leadercuff		1.1 ml
Hickman SL	9.6F	1.65 ml
Hickman DL	7 F	0.7 ml and 1.1 ml
	9 F	0.7 ml and 1.6 ml
	9.5 F	1.3 ml and 1.3 ml
Broviac	6.6 F	1.1 ml
	5.0 F	0.7 ml
	4.2 F	0.35 ml
Sitimplant ports Adult	1.11 ml	
Paediatric	0.89 ml	
Gripper needles	0.3 and 0.5 ml	
Bionectar hub	0.02 ml	
Bionectar "octopus"	0.4 ml each lumen	

1.9 Line site infections

- May be indicated by redness, soreness ± discharge around the exit site ± pain on moving arm. Some patients tend to have some mild redness around the line site most of the time, others produce a lot of crusting: this is not necessarily abnormal. Parents will always be your best guide for assessing change in appearance of line site.

- If the patient is well and not neutropenic localised site infections can usually be treated successfully with oral antibiotics. Take a swab if any discharge and empirically start oral **flucloxacillin*** (unless penicillins contraindicated due to concomitant IV Methotrexate or penicillin allergy).

- Ensure patient can take orally before discharge home. Remember to arrange review in 1-2 days, with a plan to return sooner if worse. If flucloxacillin is not tolerated, co-amoxiclav, cefalexin, cefaclor are alternatives but if staph aureus is isolated flucloxacillin is the gold standard.

- Coag negative staphylacoccus from swab may represent normal skin colonisation rather than infection, so treat clinically, if the child has improved on flucloxacillin this should be continued, they do not need to change to teicoplanin routinely, only if failing to respond to flucloxacillin.

- If the patient is neutropenic, take blood cultures from the line as well as swabbing the exit site. If well, start oral flucloxacillin and review in the next 1-2 days. If deteriorating, will need admission and IV antibiotics (either IV flucloxacillin if staph aureus isolated and compliance of oral medication the main issue, or if unwell need tazocin +/-gentamicin +/-teicoplanin to broaden spectrum) and +/- line removal. Remember the need for early line removal in septic patients.

- Extensive redness and swelling, or tracking along the line is more serious. Check for associated lymphadenopathy. Admission and antibiotics are needed - flucloxacillin IV if non-neutropenic, but if patient profoundly neutropenic treat with broad spectrum antibiotics (tazocin) in the first instance pending culture results. Take blood cultures from the line and a swab from the exit site (and entry site if inflamed) prior to starting antibiotics. Tunnel infections will usually need line removal, but will certainly need 10-14 days systemic antibiotics minimum if trying to salvage.

- If site infection does not respond to tazocin, then flucloxacillin will add very little to this, add in teicoplanin (or vancomycin if previous teicoplanin resistance). It may be appropriate to change tazocin to flucloxacillin later once culture results known, to narrow down spectrum of cover, again depending on associated factors such as ongoing neutropenia and clinical condition.

- In all cases adjust antibiotics according to culture results. See comment above re CNS. If unsure about what to do - discuss with consultant on call.

1.10 Antibiotic and Antifungal Prophylaxis

See Table 9. for guidance of antibiotics, Table 10. anti-virals and Table 11. anti-fungal therapy.

1.11 C. Difficile diarrhoea

Under most circumstances, consider whether broad spectrum antibiotics can be stopped; if not, usually treated with 7-10 days of metronidazole, oral where possible. Toxin can be detected for months/years after initial infection; its presence does not necessarily mean ongoing infection. If a clinical relapse occurs within this period, usually treat again with metronidazole, but a 3rd and 4th episode should be treated with oral vancomycin. Refer to staffnet or local guidelines.

Table 8: Spectrum of Antibiotic Activity

	staphylococcus aureus (not MRSA)	streptococci	enterobacter-iaceae (G-ves)	pseudomonads	anaerobes
Aztreonam	-	-	+ not all	+	-
Co-amoxiclav	+	+	+ not all	-	+
Ceftazidime	-	±	+ not all	+	-
Ceftriaxone	+	+	+	-	-
Ciprofloxacin	±	-	+	+	-
Clarithromycin	+	+	-	-	-
Clindamycin	+ not all	+ not all	-	-	+ not all
Gentamicin	+ esp in synergy with ß-lactams	-	+	+	-
Meropenem	+	+	+	+	+
Metronidazole	-	-	-	-	+
Piperacillin/ tazobactam	+	+	+ not all	+	+
Teicoplanin	+	+	-	-	-

Coagulase negative staphylococci generally sensitive to teicoplanin although need for treatment should be assessed on an individual basis. Vancomycin use should be limited to where necessary due to increasing vancomycin resistant enterococci.

References and Further Reading

- *National Institute for Health and Clinical Excellence. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. CG151 London: National Institute for Health and Clinical Excellence, 2012 http://guidance.nice.org.uk/CG151.*
- *Phillips R, Selwood K, Lane SM, et al. Variation in policies for the management of febrile neutropenia in United Kingdom Children's Cancer Study Group centres. Arch Dis Child 2007;92:495–8.*
- *Gibson F, Chisholm J, Blandford E, et al. Developing a national 'low risk' febrile neutropenia framework for use in children and young people's cancer care. Support Care Cancer 2012 Dec 20.*
- *Bate J, Gibson F, Selwood K, et al. A re-audit of current febrile neutropenia practice in UK paediatric oncology centres prior to implementation of NICE guidance. Arch Dis Child 2013;98:315–16.*
- *Dommett R, Geary J, Freeman S, et al. Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropenia in a UK, multicentre, shared care setting. Eur J Cancer 2009 Nov;45(16):2843-9.*
- *Guidelines for the management of intravascular catheter related infections. CID 2001; 32: 1249-72.*
- *Guidelines for the retrieval and management of severe sepsis and septic shock in infants and children PICU web page UHS NHS FT extranet. www.sort.nhs.uk.*
- *Bevin et al. Audit of positive blood cultures in paediatric oncology patients 2006.*
- *Guidelines on the management of invasive fungal infections during therapy for haematological malignancy BCSH 2008.*
- *UHS NHS FT Extranet department of infection website A-Z of bugs and drugs.*

Drug Tables have been removed.

To access up to date information of recommended antibiotics, please go to the Microguide web viewer or download the Microguide app from the Apple App Store, Google Play Store or Windows App Store.