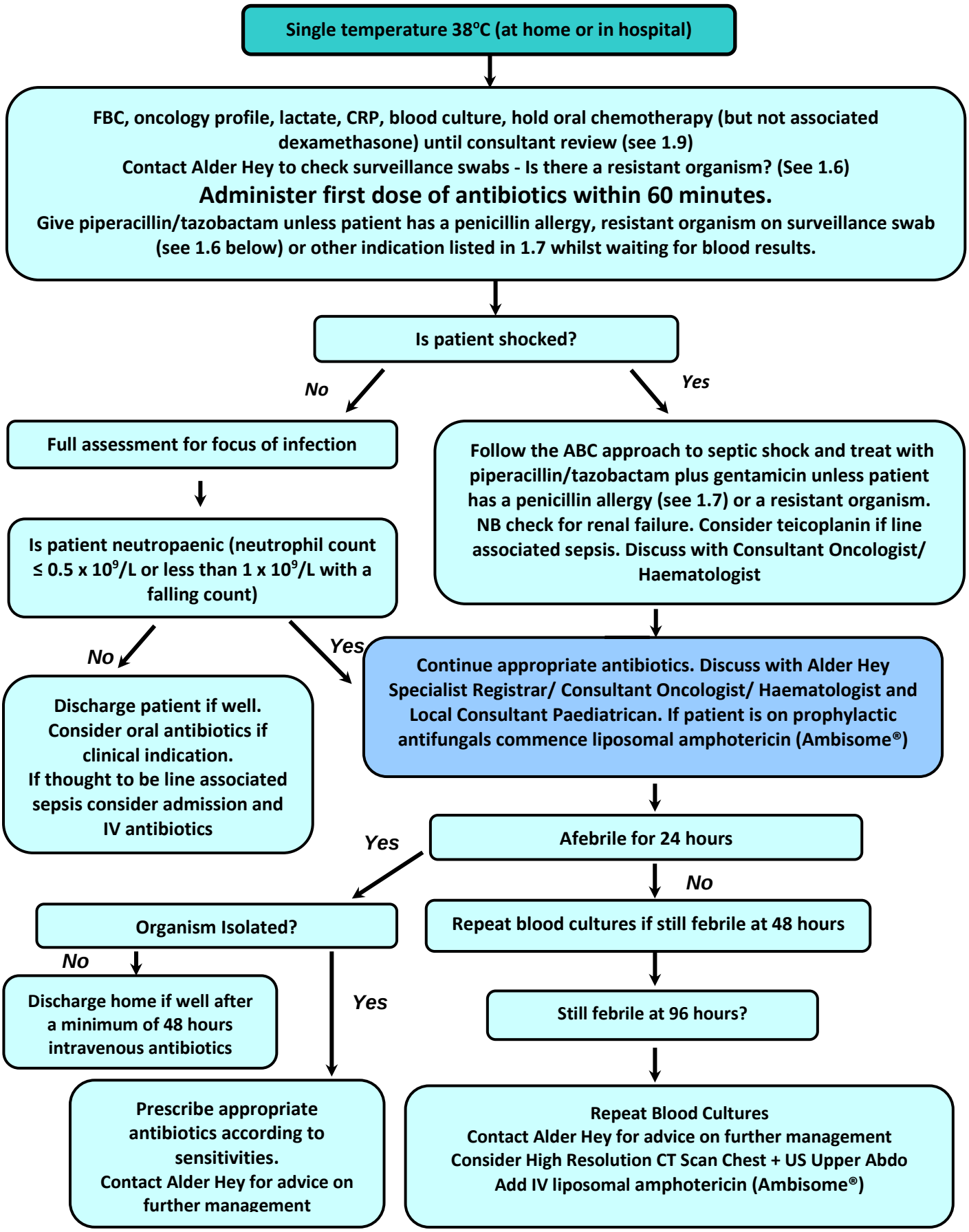
Alder Hey Children's
NHS Foundation Trust

GUIDELINES FOR THE MANAGEMENT AND PREVENTION OF INFECTION IN ONCOLOGY AND HAEMATOLOGY PATIENTS

FOR SHARED CARE CENTRES

Contents

Summary of the Management of the Febrile Patient



1 INITIAL MANAGEMENT OF FEVER IN ONCOLOGY AND HAEMATOLOGY PATIENTS

1.1 Introduction

Life threatening infections may develop rapidly in immunocompromised patients. It is **imperative** to start antibiotic treatment within 60 minutes for patients who are likely to be neutropaenic, even if a full blood count result is not available. Such patients should be reviewed and treated as a **priority**.

1.2 Suspected Septic Shock

a) Follow the "A, B, C" approach to septic shock as per Advanced Paediatric Life Support (APLS) guidelines. See section 1.8 for further information. For fluid bolus give 20ml/kg sodium chloride 0.9%.

b) In addition to normal investigations (see below) check coagulation, renal and liver function.

c) PICU should be informed of any deteriorating septic patient, or if a second 20ml/kg bolus is to be given.

d) Inform Local Consultant and Alder Hey Oncology/Haematology consultant of admission and clinical condition of patient.

1.3 Examination

Examine for focal infection, including finger prick areas, line, gastrostomy site, anus, bone marrow and lumbar puncture sites. Measure pulse, BP and capillary refill.

1.4 Investigations

a) FBC, Oncology Profile (ONC), lactate & CRP. Take central (or peripheral if no central line) blood cultures. If a double lumen central line, take one sample from each lumen.

b) Take swabs from rectum and any focal lesion, including from the exit site of the central line if appears infected.

c) Chest X-ray and nasopharyngeal aspirate (NPA) should be performed in patients with respiratory symptoms or signs. If productive of sputum, send for C&S and respiratory viruses.

1.5 Blood Culture Volumes

In patients with central lines the first volume of blood taken from the line ('discard blood') will be used for blood culture.

Blood Culture Volumes	
< 5kg	2ml
5-10kg	3ml
>10kg	5ml

1.6 Surveillance Cultures

Review microbiology "surveillance cultures" and whether any resistant organisms have been isolated in the last 6 months. In cases of carriage with a resistant Gram-negative organism, inform Local Consultant Paediatrician. If any questions regarding sensitivities contact Microbiology/ Infectious Diseases.

Contact Alder Hey Ward 3B to confirm if patient has resistant organisms on surveillance cultures.

1.7 Start IV Antibiotics

Start IV antibiotics if a single temperature of 38°C has been recorded (at home or in hospital). **Do not wait for the blood count result**. In general piperacillin/tazobactam should be used as first line treatment, unless any of the following are present:

a) Penicillin allergy: meropenem

b) Septic shock (give piperacillin/tazobactam AND gentamicin, see 1.8)

c) Surveillance cultures have identified a resistant organism (see 1.6)

d) If patient presents with a rigor following a CVL flush commence piperacillin/ tazobactam, gentamicin and teicoplanin. (Check surveillance cultures to identify any resistant organism.) Review antibiotics when blood cultures are available.

e) Patient has recently received high dose methotrexate and folinic acid rescue has not been completed (see 1.10)

f) Patients with relapsed ALL or receiving prophylactic antifungals should also commence liposomal amphotericin (Ambisome®) 3mg/kg on admission (stop other antifungals). See 5.2 and 5.4.

g) If patient has no venous access, check platelets and contact on call Local Consultant Paediatrician. Consider giving:

Febrile neutropaenia in oncology/haematology children without IV access	
Routine	**β lactam allergy**
IM ceftriaxone If unwell* *or* carriage of ceftriaxone resistant organism (e.g. ESBL, *Pseudomonas spp*.): add IM amikacin	*Unwell*:* IM teicoplanin and IM amikacin
	Well, on ciprofloxacin prophylaxis: Oral clindamycin and IM amikacin
	Well, not on ciprofloxacin prophylaxis: Oral levofloxacin
*** If circulatory compromise or significant clinical concern, oral or IM doses should not be relied upon and urgent IV or IO access must still be obtained**	

1.8 Definition of Septic Shock

Use septic shock antibiotic regimen in sick children i.e. if capillary refill >2 seconds, or have given a fluid bolus, or if systolic BP <5th centile (see chart below, hypotension is a pre-terminal sign in children). If in doubt, discuss with on call Consultant Haematologist/Oncologist. The need for additional doses of gentamicin will be reviewed on the next Consultant ward round.

Age (Years)	Systolic BP (mmHg) 5th Centile	Systolic BP (mmHg) 50th Centile
<1	65-75	80-90
1-2	70-75	85-95
2-5	70-80	85-100
5-12	80-90	90-110
>12	90-105	100-120

Ref: Advanced Paediatric Life Support: A practical approach to emergencies. 5th Ed. 2016

1.9 Review Chemotherapy

Hold oral chemotherapy but not associated dexamethasone. Only restart oral chemotherapy after consultation with the Consultant Oncologist/ Haematologist.

1.10 Intravenous Antibiotics

- ***For neonates and for patients with renal impairment please refer to pharmacist for dose and monitoring.***
- ***Oncology and Haematology patients may be at increased risk of developing a drug-induced kidney injury. This is because they may:***
  - ***Be receiving nephrotoxic chemotherapy***
  - ***Have a history of acute kidney injury***
  - ***Have a reduced glomerular filtration rate (GFR) i.e. corrected GFR below 90ml/min/1.73m^2***
  - ***Require renal replacement therapy***
- ***If there is any doubt about the risk of drug-induced kidney injury, contact Alder Hey Ward 3B to check if the patient is on the Renal List.***
- ***It is essential to monitor renal function daily, maintain strict fluid balance (input, output and weight), maintain adequate hydration and minimise nephrotoxic drugs as much as possible.***
- ***Refer to Alder Hey Guidelines for further information*** www.alderhey.nhs.uk/aki

Intravenous Antibiotic	Dose	Notes
AMIKACIN*	20mg/kg once daily. Maximum 1200mg (≥60kg) Refer to guidelines for dosing advice in renal impairment. NB If child is obese: base dose on ideal body weight: Contact Oncology Pharmacist	(Monitor levels – see section 3.1 and 3.2) Follow aminoglycoside dosing and monitoring guidelines Caution: in patients on high dose methotrexate until hydration and folinic acid rescue is complete due to nephrotoxicity risk Dilute to at least 10 ml with sodium chloride 0.9% and infuse over 20 minutes
CIPROFLOXACIN*	Child ≥ 1 month 10 mg/kg every 8 hours. Maximum 400mg every 8 hours Reduce dose in renal impairment	Caution: ciprofloxacin may reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete IV infusion over 60 minutes **Refer to BNFC for MHRA Important Safety Information**

FLUCLOXACILLIN*	50mg/kg every 6 hours. Maximum 2g every 6 hours Reduce frequency in severe renal impairment Caution in hepatic impairment	**Caution**: penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete IV bolus (concentration 50mg/ml) or infuse in dextrose 5% or sodium chloride 0.9% over 15 to 30 minutes
GENTAMICIN*	7mg/kg once daily. Maximum: 420mg (≥60kg) Refer to guidelines for dosing advice in renal impairment If child is obese: base dose on ideal body weight: Contact Oncology pharmacist	(Monitor levels – see section 3.1 and 3.2) Follow aminoglycoside dosing and monitoring guidelines Caution: in patients on high dose methotrexate until hydration and folinic acid rescue is complete due to nephrotoxicity risk Dilute to at least 10ml with sodium chloride 0.9% and infuse over 20 minutes
MEROPENEM	20mg/kg every 8 hours. Maximum 1g every 8 hours Reduce dose in renal impairment Increase to 40mg/kg (max 2g) every 8 hours in selected cases (e.g. CNS infection or less sensitive organisms. Discuss with Infectious Diseases)	IV Bolus over 5 minutes or infuse in dextrose 5% or sodium chloride 0.9% over 15 to 30 minutes
PIPERACILLIN/ TAZOBACTAM*	**Intermittent Dosing** 90mg/kg every 6 hours Maximum - 4.5g every 6 hours Reduce dose in renal impairment	**Caution** : penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete IV infusion in dextrose 5% or sodium chloride 0.9%, dilute to at least 90mg/ml and give over 30 minutes, although it may be administered as neat IV bolus in exceptional circumstances (e.g. fluid restriction, compatibility issues or time constraints)

TEICOPLANIN	<2months 16mg/kg loading dose followed 24 hours later by 8mg/kg once a day > 2 months 10mg/kg (maximum 800mg) every 12 hours for 3 doses then 10mg/kg (maximum 800mg) once a day starting 24 hours after the final loading dose Reduce dose in renal impairment	For neonates and infants up to 2 months dose must be infused over 30 minutes Slow IV bolus over 3 to 5 minutes or infuse over 30 minutes. Teicoplanin levels may be available in exceptional circumstances – discuss with pharmacy
VANCOMYCIN*	Over 44 weeks corrected gestational age and up to 6 months: 10mg/kg every 6 hours Over 6 months old: 15mg/kg every 6 hours Maximum starting dose - 500mg every 6 hours Refer to guideline for dosing advice in renal impairment	(Monitor levels – see section 3.3) Follow vancomycin dosing and monitoring guidelines Caution: in patients on high dose methotrexate until hydration and folinic acid rescue is complete due to nephrotoxicity risk Dilute 50 mg/ml reconstituted solution at least 10 times and infuse over at least 1 hour Doses greater then 600mg - administer at a maximum 10mg per minute

***Caution**: Penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete. Nephrotoxic drugs must also be avoided. When methotrexate has cleared consider switching back to usual first line antibiotics – discuss with consultant.

1.11 Intramuscular Antibiotics

NB – Exceptional use - for indication see 1.7

- ***For neonates and for patients with renal impairment please refer to pharmacist for dose and monitoring***.
- ***Oncology and Haematology patients may be at increased risk of developing a drug-induced kidney injury. This is because they may:***
  - ***Be receiving nephrotoxic chemotherapy***
  - ***Have a history of acute kidney injury***
  - ***Have a reduced glomerular filtration rate (GFR) i.e. corrected GFR below 90ml/min/1.73m^2***
  - ***Require renal replacement therapy***
- ***If there is any doubt about the risk of drug-induced kidney injury, contact Alder Hey Ward 3B to check if the patient is on the Renal List.***
- ***It is essential to monitor renal function daily, maintain strict fluid balance (input, output and weight), maintain adequate hydration and minimise nephrotoxic drugs as much as possible.***
- ***Refer to Alder Hey Guidelines for further information*** www.alderhey.nhs.uk/aki

Intramuscular Antibiotic	Dose	Notes
CEFTRIAXONE	50mg/kg once daily by deep intramuscular injection. Maximum 2g (At consultants discretion dose may be increased to 100mg/kg once daily by deep intramuscular injection, for severe cases. Maximum 4g). Consider reducing dose in severe renal impairment.	IM Administration Max strength for IM injection is 350mg/ml. Add 2.2ml 1% lidocaine (lignocaine) to a 1 g vial to give a final concentration of approx. 350 mg/ml. Volume may require administration at more than 1 site. Usually maximum 2ml at a single site. (On rare occasions 5ml has been given in a single site to adult patients.) Consider splitting into two divided doses for large volumes. Discuss with consultant.
AMIKACIN	Dosing and additional information as per IV – section 1.10	Give neat 250mg/ml
TEICOPLANIN	Dosing and additional information as per IV – section 1.10	Reconstitute 400mg vial – 400mg/3ml

1.12 Oral Antibiotics

NB – Exceptional use (See 1.7).

Oral Antibiotic	Dose	Notes
CLINDAMYCIN	≥ 1 month 6mg/kg four times daily (maximum single dose 450mg)	An unlicensed special liquid is available 75mg/5ml Capsules may be opened and mixed in water, squash or food and taken immediately. Only suitable for full capsule dosing.
LEVOFLOXACIN	≥ 1 month 10mg/kg once a day (maximum 500mg)	250mg tablets can be halved. Cannot be crushed. If dose required cannot be given consider oral clindamycin plus IM amikacin. **Refer to BNFC for MHRA Important Safety Information**

2 ONGOING MANAGEMENT OF FEVER

Neutropaenic refers to neutrophils ≤ 0.5 x 10^9/L or less than 1 x 10^9/L with a falling count.

2.1 Not Neutropaenic

a) Discharge if well. Consider oral antibiotics if there is a clinical indication to do so.

b) If thought to be line associated sepsis, admit and start IV antibiotics.

2.2 Neutropaenic

a) If patient scores a PEW of 4 or above a blood gas must be taken.

b) In patients in whom no organism is isolated from blood cultures, continue antibiotic/s until afebrile for 24 hours and for a minimum of 48 hours.

c) If patient remains febrile at 48 hours, repeat blood cultures (or earlier if clinically indicated).

d) If an organism is isolated, repeat blood cultures and prescribe appropriate antibiotics according to sensitivities. Contact Consultant Oncologist/ Haematologist for further advice if required. Patients with positive blood cultures will generally require at least 7 days of intravenous antibiotics. If there is any doubt as to the appropriate antibiotic therapy, then a Consultant Oncologist/ Haematologist at Alder Hey should be contacted.

e) Children who carry extended spectrum beta-lactamase producing organisms (ESBL) should be given antibiotics to which these are sensitive.

2.2.1 Fever Unresolved at 96 Hours

If fever unresolved at 96 hours:
Contact Alder Hey Oncology/Haematology Registrar or Consultant.

a) Add in IV liposomal amphotericin (Ambisome®) 1mg/kg (see section 5.4)
b) Perform CT of chest and ultrasound abdomen (liver and spleen).

In some high risk patients (e.g. AML, HSCT patients, prolonged steroid use), IV liposomal amphotericin (Ambisome®) may be started earlier than 96 hours – discuss with Haematology/Oncology Consultant.

3 ANTIBIOTIC LEVEL MONITORING

External central lines and subcutaneous ports can be used for drug sampling provided the line is flushed well after administration. High levels should be checked from a peripheral vein or finger prick.

3.1 Aminoglycosides for Patients with Normal Renal Function

For additional information see Aminoglycoside Dosing and Monitoring Guidelines.

Aminoglycosides in Normal Renal Function	Trough Level
GENTAMICIN	<1mg/L (18-24 hours)
AMIKACIN	<3mg/L (18-24 hours)

3.2 Aminoglycosides for Patients with Renal Impairment

Contact pharmacist for advice for patients with renal impairment

Aminoglycosides in Renal Impairment	Levels
GENTAMICIN	Pre < 2mg/L One hour post 5-10mg/L
AMIKACIN	Pre 2-5mg/L One hour post 15-25mg/L

3.3 Vancomycin

For additional information see Vancomycin Dosing and Monitoring Guidelines.

Drug	Trough Level	Additional Information
VANCOMYCIN	10-15 mg/L (just before 4th dose)	For all oncology/haematology patients (Higher levels 15-20mg/L may be appropriate in some patients).

3.4 Interpretation of Levels

The following factors may account for higher or lower levels than expected and should be considered before altering dosage:

Higher than expected level	Lower than expected level
Incorrect dose	Incorrect dose
Renal impairment	Missed dose
Level taken from administration site	Inadequate flushing
Drug level taken too early	Drug level taken too late
Dehydration	Abnormal collection of body fluid
	Exchange transfusions
	Hydration

PHARMACY IS AVAILABLE TO ADVISE ON ANY PROBLEMS WITH THERAPEUTIC DRUG MONITORING. CONTACT YOUR WARD OR ON-CALL PHARMACIST.

4 CENTRAL VENOUS CATHETER (CVC) – ASSOCIATED BACTERAEMIA

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Bacteraemia may arise following translocation of bacteria across mucosal barriers or following contamination of a device such as a CVC. At present, there is no satisfactory test for the immediate diagnosis of CVC–associated bacteraemia.

These infections should be suspected when there is fever or rigor following use of the CVC, or persistently positive blood cultures despite the use of appropriate antibiotics.

In the case of suspected CVC–associated bacteraemia, management should be discussed with the Consultant Oncologist/Haematologist and a member of the Microbiology/ Infectious Diseases team.

4.1 General Principles of Management

In such cases, it is very important to consider:

a) Whether the CVC should be removed.

b) The use of antibiotic lock therapy (as well as systemic antibiotics).

There is increasing evidence that antibiotic lock therapy improves the outcome of CVC–associated bacteraemia including increasing the chances of saving the CVC. This particularly applies to treating CVC colonisation with organisms such as coagulase negative staphylococci that proliferate within a biofilm reducing the effectiveness of antibiotic therapy. Antibiotics can be locked into the catheter lumen for as long as possible, during periods when the catheter is not being used. The antibiotic lock should be aspirated before the line is used for other infusions.

The same antibiotic should not be used both as a line-lock and given intravenously (unless recommended by the Microbiology/ Infectious Diseases or Oncology/Haematology Team). This is to reduce the risk of accidental overdose.

Antibiotic locks are administered as a volume of 3 ml per lumen (both external catheters and ports) Concentrations should be selected using the table below:

Antibiotic Line-Lock	Concentration
Vancomycin	5mg/ml
Gentamicin	1mg/ml
Amikacin	2mg/ml
Ciprofloxacin	2mg/ml

Higher concentrations of gentamicin (2mg/ml) and amikacin (5mg/ml) line-locks are available for use at the discretion of the Microbiology/ Infectious Diseases or Oncology/Haematology team.

The duration of antibiotic lock therapy should be discussed with the Consultant Oncologist/Haematologist and a member of the Microbiology/ Infectious Diseases team.

If there is prolonged fever after starting appropriate antibiotics, look for evidence of disseminated infection (metastatic spread) e.g. endocarditis or septic thrombi. If CVC related infection is complicated by endocarditis, septic thrombosis and osteomyelitis, the CVC should be removed and 4-6 weeks of antibiotic therapy given.

4.2 Organism Specific Issues

4.2.1 Gram Positive Organisms

Coagulase Negative Staphylococcus and *Enterococcus Spp.*
Intravenous teicoplanin PLUS vancomycin line locks for at least 7 days following the first negative blood culture.

Remove CVC if there is clinical deterioration/persistent bacteraemia.

Staphylococcus aureus
The threshold for line removal is low because of the risk of complications such as endocarditis.

Need to complete up to 14 days of treatment in total following the first negative blood culture.

If MSSA – use flucloxacillin PLUS vancomycin line locks.

If MRSA - use IV teicoplanin PLUS vancomycin line locks.

If the CVC is retained then 14 days of IV treatment should be given following the first negative blood culture.

If the CVC is removed then at least 7 days of IV treatment should be given following the first negative blood culture with the remainder made up of oral treatment depending on sensitivities.

Perform echocardiogram to exclude endocarditis in complicated bacteraemia.

Remove CVC if there is clinical deterioration and/or persistent bacteraemia.

4.2.2 Gram Negative Organisms

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Discuss with a member of the Infectious Diseases/ Microbiology team.

First line antibiotics (piperacillin/tazobactam) +/- amikacin line locks generally for at least 10 days if trying to keep the CVC.

For patients colonised with Extended Spectrum Beta-Lactamase producing organisms (ESBL) treat with intravenous meropenem.

Remove CVC if there is clinical deterioration and/or persistent bacteraemia (there should be a low threshold for removal of CVC with Gram negative CVC–associated bacteraemia). Discuss with Microbiology/Infectious Disease Consultant the length of treatment required following CVC removal.

4.2.3 Candida

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Remove CVC –There is a high morbidity and mortality associated with candidaemia and it is very difficult to sterilise a CVC colonised with candida.

Repeat blood culture and start intravenous liposomal amphotericin (Ambisome®). Continue intravenous antifungal treatment for at least 10 days after last positive blood culture**. Prompt line removal is recommended if 2 or more positive blood cultures.**

5 ANTI-FUNGAL THERAPY

5.1 Prophylaxis

Only indicated in high risk patients as defined below:

- Patients on AML, HLH, LCH-S, NHL chemotherapy protocols
- Aplastic Anaemia
- Patients on FLAG Chemotherapy
- Allogeneic Stem Cell Transplant patients.
- Patients with severe GVHD

Notes:

- Patients on the HR-NBL-1 protocol who are receiving myeloablative therapy and an autograft are not permitted to receive prophylactic azole antifungals. Cover with prophylactic liposomal amphotericin (Ambisome®) through transplant
- Patients on relapsed ALL protocols – see section 5.2
- Previous significant fungal infection - discuss with consultant Oncologist/Haematologist

5.1.1 Initial Prophylaxis – Liposomal Amphotericin (Ambisome®)

Patients should receive intravenous liposomal amphotericin (Ambisome®) at a dose of 1 mg/kg three times a week on Monday, Wednesday and Friday.
Refer to section 0 for test dose and 5.4 for administration details.

5.1.2 Oral Options at Consultant Discretion

5.1.2.1 First Line - Itraconazole

Fungal Prophylaxis	Age ≥ 1 month	Comment
Itraconazole (liquid 10mg/ml)	2.5mg/kg twice daily	Liquid preparation preferable, due to better absorption. Chilling liquid in the fridge and mixing with Coca-Cola may aid palatability. Take on an empty stomach at least one hour before food. Itraconazole level monitoring may be required (see below).

Drug Interactions:

- Itraconazole will affect and be affected by drugs that are inducers, inhibitors or substrates of the cytochrome P450 enzymes. Avoid concomitant use with vincristine. NO patient should receive vincristine within 48 hours of a dose of itraconazole, due to the risk of development of SIADH. Stop itraconazole for a minimum of 2 days before and 2 days after vincristine.
- Avoid in patients who have busulfan as part of high dose conditioning and do not use concomitantly with cyclophosphamide and gemtuzumab ozogamicin.
- Reduce ciclosporin dose if patient on itraconazole as it will significantly increase ciclosporin levels. Contact clinical pharmacist for advice.
- For details of other drug interactions refer to BNFC and discuss with clinical pharmacist.

Monitoring Itraconazole Levels

Itraconazole levels are not routinely required for patients receiving prophylaxis but may be considered for exceptionally high-risk patients such as those with severe aplastic anaemia and patients with relapsed ALL. Discuss with consultant Oncologist/ Haematologist.

It takes one to two weeks for itraconazole to reach steady state; therefore levels should be taken after two weeks unless toxicity is suspected earlier than this.

1ml of serum is required (2ml of whole blood) in a plain serum tube. Blood samples should be taken 4 hours after an oral dose (no pre-dose necessary). The sample should be sent from the ward to microbiology. Alder Hey does not have the facility to measure these levels, but they will send the sample to a centre that does.

Itraconazole levels between 5 and 15mg/L are satisfactory.

5.1.2.2 Second Line – Voriconazole (for patients unable to tolerate itraconazole)

Voriconazole is associated with a risk of phototoxicity, skin squamous cell carcinoma (SCC) and liver toxicity. It is therefore important to adhere to the advice on the precautions against phototoxic reactions, monitoring for SCC and liver toxicity given in the product information. Prescribers must complete the Health Care Professional checklist when treatment is initiated or reviewed, counsel the patient on the risks and give them an alert card.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON418519

- Children (2 to <12 years) and young adolescents (12 to 14 years and <50kg)

	Intravenous	**Oral (suspension*)**
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg every 12 hours	9 mg/kg every 12 hours (maximum dose 350 mg twice daily)

*These oral dose recommendations for children are based on studies in which voriconazole was administered as oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a paediatric population. It is therefore recommended to use the oral suspension formulation in children aged 2 to <12 years.

- Adults and adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight)

	Intravenous	**Oral (Tablets or Suspension)**	
		Patients over 40kg	Patients under 40kg
Loading Dose Regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg every 12 hours	200 mg every 12 hours
Maintenance Dose (after first 24 hours)	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

Refer to pharmacy if patient is unable to tolerate treatment.

Monitoring voriconazole levels

- Voriconazole levels should be done at least once in all patients. Discuss with consultant Oncologist/Haematologist.
- Measure an initial trough level on day 4 or 5.
- If required thereafter measure twice a week until therapeutic levels are achieved. The serum sample must be taken immediately pre-dose.
- Alder Hey does not have the facility to measure these levels, but they will send the sample to a centre that does. The centre will advise on the therapeutic range.
- The usual therapeutic range for the serum level of voriconazole is 1.3 to 5.7mg/L.
- Levels should be repeated 4 or 5 days after any change in the dose of voriconazole and for stable patients, levels should be repeated every 4 weeks unless the clinical situation demands otherwise.

Drug Interactions

See under Itraconazole

5.2 Antifungal Prophylaxis for Patients on Relapsed ALL R3

All patients require liposomal amphotericin (Ambisome®) prophylaxis during induction.

- **1mg/kg three times a week on Monday, Wednesday and Friday**
- **Continue for 5 weeks or until count recovered**
- **Refer to 0 for test dose and 5.4 for administration details**

Patients on the ALL R3 protocol who are receiving prophylactic systemic antifungal therapy (generally until the end of week 13/14) admitted for febrile neutropaenia must be started on empirical anti-fungal therapy with liposomal amphotericin (Ambisome®) at 3mg/kg/day in addition to the necessary antibacterial therapy. In this case stop any other antifungal.

5.2.1 Standard/Intermediate Risk

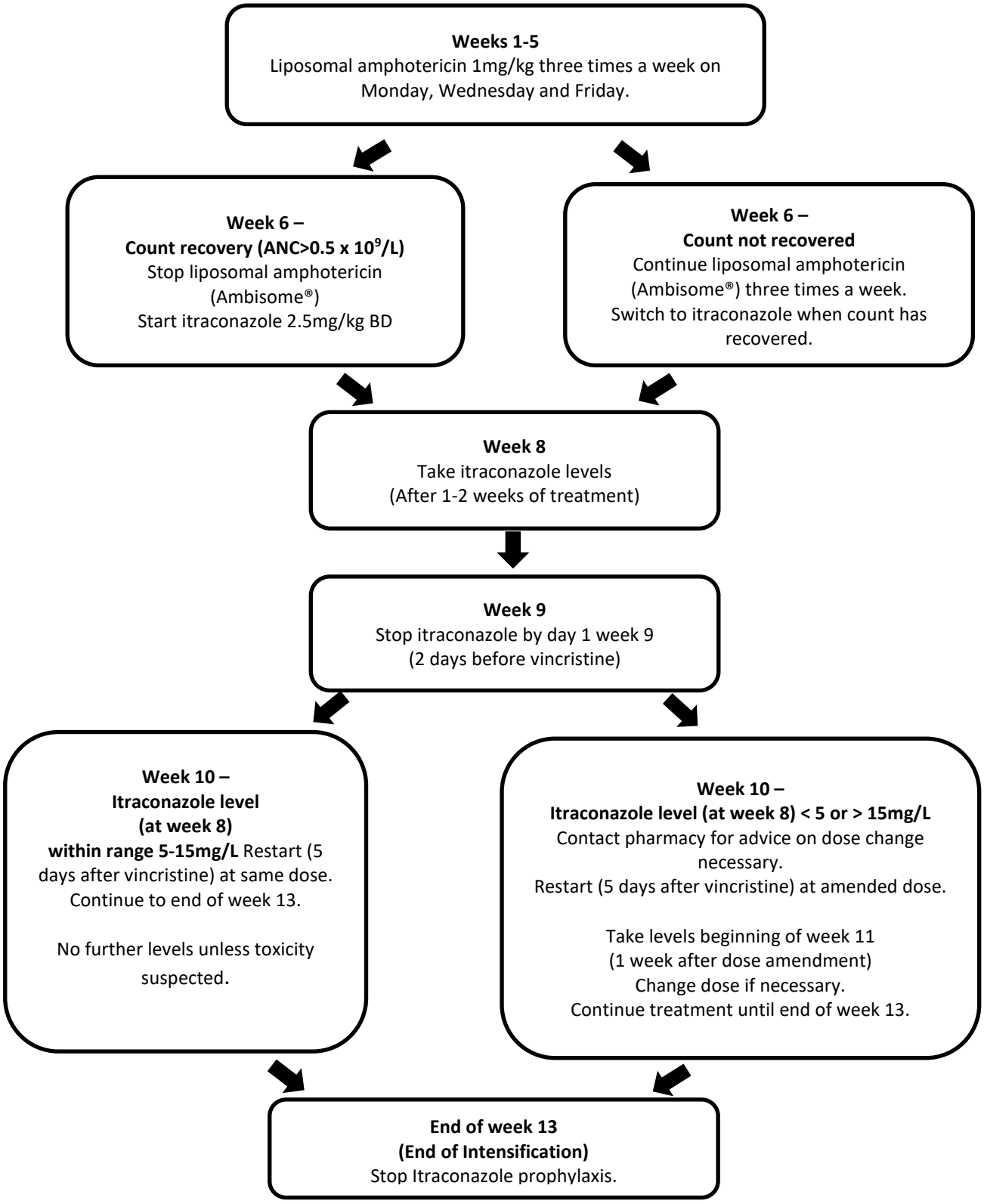
At Week 6: if counts have recovered (ANC > 0.5 x 10^9/L) - stop liposomal amphotericin (Ambisome®) and start oral itraconazole suspension at a dose of 2.5mg/kg twice a day. Levels are needed (see 5.1.2.1) and LFTs should be monitored weekly. If counts have not recovered continue with liposomal amphotericin (Ambisome®) as above until count recovery.

As there is a possible drug interaction between itraconazole and vincristine, which may increase the risk of vincristine neurotoxicity, itraconazole must be stopped 2 days prior to, and restarted 5 days after, any vincristine dose. Hence stop itraconazole at the beginning of week 9 (vincristine due day 3 week 9) and restart at the beginning of week 10.

5.2.1.1 Itraconazole Levels

- It takes one to two weeks for itraconazole to reach steady state; therefore levels should be taken at the beginning of **week 8** unless toxicity is suspected earlier than this. See 5.1.2.1 for further details.
- Itraconazole should be continued to the end of week 13. If no dose adjustment has been necessary based on levels at week 8, no further levels are needed unless toxicity is suspected. If the levels taken at week 8 necessitated a dose adjustment, levels should be re-done at the beginning of week 11.

SUMMARY OF ANTI-FUNGAL PROPHYLAXIS FOR UKALL R3



Itraconazole liquid must be used due to better absorption
ALL R3 patients receiving prophylactic antifungal therapy admitted for febrile neutropaenia must be started on liposomal amphotericin (Ambisome®) at 3mg/kg/day in addition to the necessary antibacterial therapy.

5.3 Treatment of Oral Candidiasis

5.3.1 Mild Oral Candidiasis Infections

	Age 1 month to 2 years	Age ≥ 2 years	Comment
Miconazole Gel	1.25ml four times daily	2.5ml four times daily	Use after food and retain as long as possible
	OR for a localized lesion smear a small amount of gel onto the affected area up to four times a day. Continue for 48 hours after lesions have healed.		

5.3.2 Moderate or Severe Oral Candidiasis Infections

	Age ≥ 1 month	Comment
Oral Fluconazole (Or IV if necessary)	3 mg/kg once daily (maximum 150mg)	Fluconazole is completely orally absorbed, so the IV dose is equivalent to the oral dose. Oral absorption is not affected by food. Higher dose maybe used at consultant discretion

Drug Interactions:
Fluconazole is a moderate inhibitor of CYP3A4. Fluconazole may increase vincristine toxicity. Ideally fluconazole should be omitted for 48 hours before and after vincristine. Concomitant use should be discussed with a consultant.

5.4 Empiric Therapy for Invasive Fungal Infection

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Generally for patients who are neutropaenic and remain febrile after 96 hours, empiric therapy should be prescribed only on discussion with an Oncology/Haematology Registrar or Consultant Oncologist/Haematologist.

Empiric Therapy	Dose	Comments
Liposomal Amphotericin (Ambisome®)	1mg/kg* once daily	Test dose required (see 0) Dilute to 0.2-2mg/ml in glucose 5% Administer over 30-60 minutes Do not filter

*Note patients with relapsed ALL or already receiving prophylactic antifungals should be started on liposomal amphotericin (Ambisome®) 3mg/kg on admission.

5.4.1 Test Dose

A test dose is required for all new courses of liposomal amphotericin (Ambisome®) – if patients have had previous courses that have stopped within the previous week a test dose is not necessary.

Test Dose	< 10kg	≥ 10kg	Comments
Liposomal Amphotericin (Ambisome®) test dose	0.1mg/kg	1mg	Dilute to 0.2-2mg/ml in glucose 5% Do not filter Infuse test dose over 10 minutes. Observe patient for at least 30 minutes

5.4.2 Monitoring

The patient should have baseline creatinine, U+Es, FBC and LFTs measured. Creatinine and U+Es should be measured daily; FBC and LFTs twice weekly, or more frequently in unstable patients.

5.5 Patients with Suspected Deep Seated or Systemic Fungal Infections

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Patients with suspected deep seated or systemic fungal infections must be treated with liposomal amphotericin (Ambisome®).

Suspected Deep Seated or Systemic Infection	Dose	Comments
Liposomal Amphotericin (Ambisome®)	3mg/kg once daily	Test dose required (see 5.4.1) Dilute to 0.2-2mg/ml in glucose 5% Administer over 30-60 minutes Do not filter

5.6 Patients with Proven Deep Seated Fungal Infection

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

Patients with suspected deep seated or systemic fungal infections must be treated with liposomal amphotericin (Ambisome®).

Proven Deep Seated or Systemic Infection	Dose	Comments
Liposomal Amphotericin (Ambisome®)	3mg/kg once daily	Test dose required (see 5.4.1) Dilute to 0.2-2mg/ml in glucose 5% Administer over 30-60 minutes Do not filter

Obtain and review drug sensitivities of fungus if possible.

Treatment of CNS fungal infections should generally include the use of IV voriconazole. Discuss with Consultant Oncologist/ Haematologist and Microbiology/ Infectious Diseases Consultant.

Failure to respond to first line anti-fungal therapy for strongly suspected or proven deep-seated fungal infection must be discussed with a Consultant Oncologist/ Haematologist and Microbiology/ Infectious Diseases Consultant.

Duration of treatment should be discussed with Consultant Oncologist/ Haematologist and Microbiology/ Infectious Diseases Consultant.

Treatment options include the use of:

- IV voriconazole
- IV micafungin
- Oral posaconazole – contact pharmacy for advice (data limited in children. Posaconazole tablets and oral suspension are not directly interchangeable)
- IV liposomal amphotericin (Ambisome®) in higher doses should be considered for mucormycosis at consultant discretion.
- IV/oral fluconazole in higher doses for invasive candida infections

Refer to Summary of Product Characteristics for further information.

6 VIRAL INFECTIONS

6.1 Varicella Zoster Virus

6.1.1 Prophylaxis after Contact with Chickenpox or Shingles

A clinical history of past infection and the Varicella-Zoster IgG antibody (VZV IgG) status should be ascertained before the start of chemotherapy.

Children with solid tumours, who have VZV IgG detected at diagnosis, suggesting previous infection, do not require aciclovir prophylaxis following significant contact with chickenpox or shingles.
Children with leukaemia require aciclovir prophylaxis regardless of their VZV IgG status.

- Oncology/Haematology patients VZV IgG status can be obtained by contacting Ward 3B at Alder Hey Children's NHS Foundation Trust

Solid tumour patients who are VZV IgG negative and all leukaemia patients who are on active treatment and for 6 months following the completion of chemotherapy always require prophylaxis with aciclovir where there has been significant contact with chickenpox or shingles (except where IVIG has been given in the previous 3 weeks). Patients who have had HSCT should receive prophylaxis for 12 months following the completion of treatment or longer if they are still on immunosuppressive therapy.

The VZV IgG level should be re-checked 4 weeks after contact with chickenpox or shingles.

Significant contact with chickenpox = play or direct contact for more than 15 minutes during the infectious period from 2 days prior to the onset of the rash until crusting of all the vesicles.

Significant contact with shingles = direct contact with exposed lesions only.

Aciclovir prophylaxis must be started immediately after a significant contact or gross exposure with sibling or other household member, and given for 21 days because of the ongoing risk of exposure.

Aciclovir prophylaxis must be started 7 days after a significant contact with friends, at school, playgroup, or on holiday and be continued for 7 days.

Prophylaxis after chickenpox contact	**Age ≥ 1 month**	**Comments**
Aciclovir oral	10mg/kg four times daily	Use dispersible tablets where possible. Round to nearest tablet size 200mg, 400mg or 800mg. For obese patients - calculate dose based on ideal body weight

6.1.2 Treatment of Chickenpox or Widespread Shingles

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

In a child with a vesicular rash – send virology swab of vesicle fluid for VZV PCR except in cases of classical dermatomal shingles where the diagnosis of VZV infection may be made on clinical grounds alone.

IV aciclovir should be started in immunosuppressed patients developing chickenpox or disseminated shingles regardless of prior VZV immune status.

Treatment of Chickenpox or disseminated shingles	Age < 3 months	Age 3 months to 12 years	Age > 12 years	Comment
Aciclovir IV	20 mg/kg three times daily	500 mg/m^2 three times daily	10mg/kg three times daily	Dilute to 5mg/ml in sodium chloride 0.9% and administer over one hour. Reduce dose in renal impairment
	For obese patients - calculate dose based on ideal body weight			

For patients who can swallow tablets:
If chickenpox or widespread shingles follows normal course, treatment should generally be continued IV for at least 2 days. The patient may stop IV aciclovir after two days and be discharged home on oral valaciclovir providing that:

- The patient is clinically generally well
- There have been no new VZV lesions within 24 hours
- There are no significant complications of VZV infection
- They are able to swallow tablets or dispersed tablets

If there continues to be VZV lesions – then intravenous aciclovir should be continued for a minimum of 48 hours.

IV aciclovir should be followed by oral valaciclovir treatment to complete a 10 day course:

Continuation treatment for Chickenpox or widespread shingles	Patient Weight 4 – 12 kg	Patient Weight 13 – 21 kg	Patient Weight 22 – 29 kg	Patient Weight > 30 kg
Valaciclovir oral tablets	250 mg three times daily	500 mg three times daily	750 mg three times daily	1000 mg three times daily

For patients who cannot swallow tablets these may be crushed, dispersed in water and taken immediately. The vessel should be rinsed with water (in case any particles remain) and contents swallowed. For patients who cannot swallow the dispersed tablets:

If chickenpox or widespread shingles follows normal course, treatment should generally be continued IV for at least 4 days and until no new lesions have developed within a 48 hour period and the patient is afebrile. However some patients with mild disease may be discharged earlier at Consultant Oncologist/Haematologist's discretion.

IV aciclovir should be followed by oral treatment to complete a 10 day course:

Continuation treatment for Chickenpox or widespread shingles	Age 1 month to 2 years	Age 2 to 6 years	Age > 6 years	Comment
Aciclovir oral	200 mg four times daily	400 mg four times daily	800 mg four times daily	Use dispersible tablets where possible

In severe cases or if new lesions develop, continue with IV therapy as appropriate and discuss with Consultant Haematologist/ Oncologist.

6.1.3 Ocular Lesions

Ocular lesions should be assessed as an emergency (by an ophthalmologist) and topical aciclovir 3% eye ointment prescribed and administered 5 times a day without delay as well as IV aciclovir. Continue for at least 3 days after complete healing.

6.1.4 Treatment of Localised Shingles

Patients with localised shingles may receive treatment with oral valaciclovir or aciclovir (doses as per continuation therapy above). If no response or progression of shingles then intravenous therapy should be commenced as for Chickenpox or widespread shingles.

6.2 Herpes Simplex Virus

6.2.1 Treatment of Localised HSV Infection for all Haematology/Oncology Patients

6.2.1.1 Oral Aciclovir for Mild, Localised (Oral/Perianal) Disease

Mild, localised (oral/perianal) HSV disease	Age 1 month to 2 years	Age > 2 years	Comment
Aciclovir oral	200mg four times daily for 5 days	400mg four times daily for 5 days	Use dispersible tablets where possible
	Continue for longer if new lesions appear of if healing incomplete		

6.2.1.2 IV Aciclovir for Severe, Localised (Oral/Perianal) Disease

Severe, localised (oral/perianal) HSV disease	Age < 3 months	Age 3 months to 12 years	Age > 12 years	Comment
Aciclovir IV	20 mg/kg three times daily for 5 days	500 mg/m^2 three times daily for 5 days	10mg/kg three times daily for 5 days	Dilute to 5mg/ml in sodium chloride 0.9% and administer over one hour. Reduce dose in renal impairment
	For obese patients - calculate dose based on ideal body weight			

NB Ocular lesions should be treated as an emergency. See 6.1.3.

6.2.2 Treatment of Disseminated HSV Infection Including HSV Encephalitis

If disseminated HSV infection is suspected or proven – transfer patient to Alder Hey Children's NHS Foundation Trust.

6.3 Measles

6.3.1 Measles Prophylaxis (After Measles Contact)

All immunosuppressed patients are at risk of severe measles and should be considered for intravenous immunoglobulin (IVIG) following any exposure to measles.

After measles exposure, assess the child's degree of immune suppression using the PHE Guidelines on Post-Exposure Prophylaxis for measles (Groups A, Bi or Bii);
https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis

Group A - individuals who should develop and maintain adequate Measles IgG antibody from past exposure or vaccination

- Patients receiving or within six months of completing immunosuppressive chemotherapy or radiotherapy for malignant disease, (other than those with ALL, a lymphoproliferative disorder or who have had HSCT).
- Patients receiving systemic high-dose steroids, or who have received high dose steroids in the past three months. This would include: Children who receive prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2mg/kg/day for at least one week, or 1mg/kg/day for one month.
- Patients receiving high doses of non-biological oral immune modulating or other types of immunosuppressive drugs (alone or in combination with steroids) or who have received such therapy in the past three months. This would include: methotrexate, azathioprine, 6-mercaptopurine, ciclosporin, cyclophosphamide and leflunomide.

Group Bi – individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination

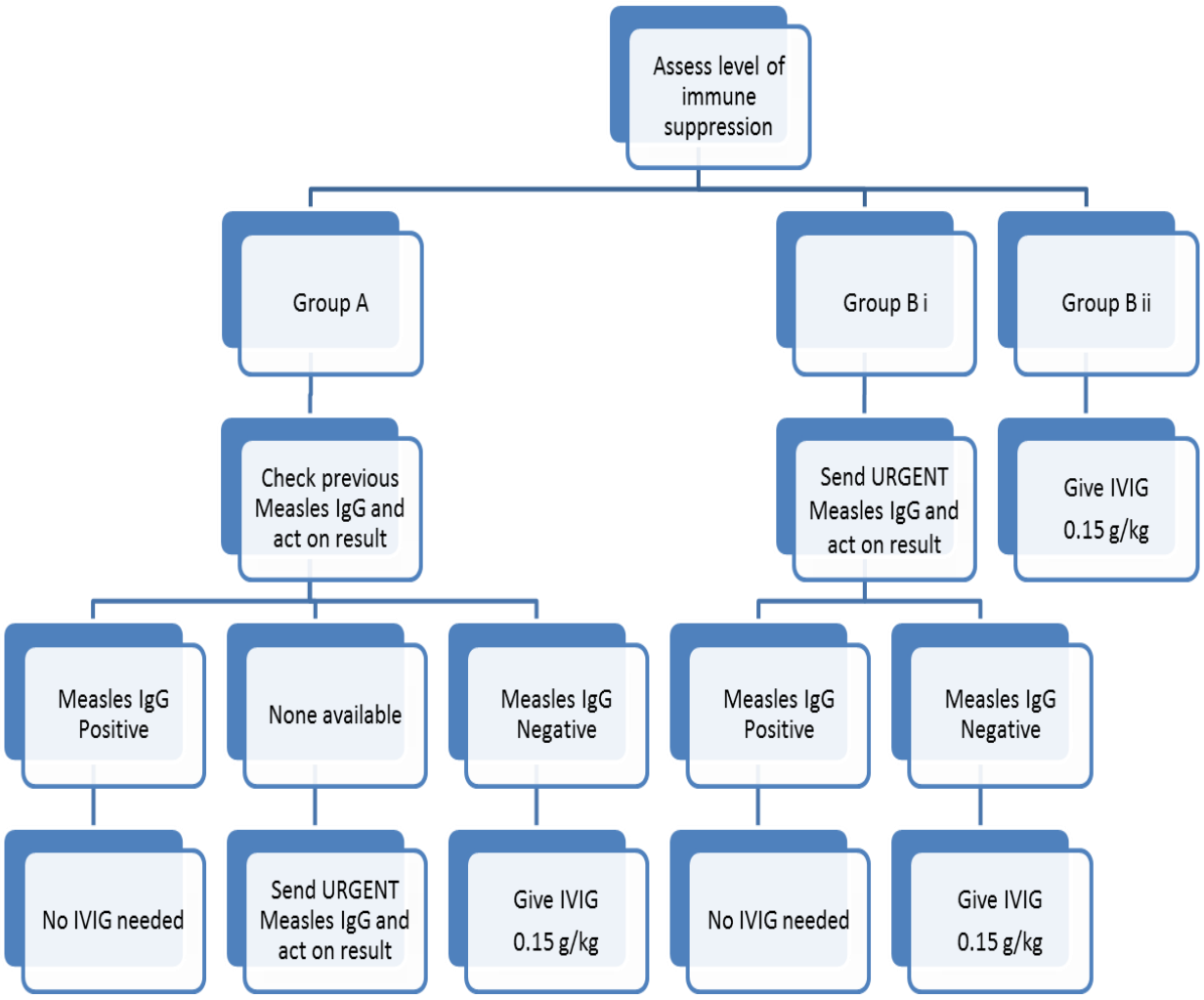
- Patients on or after completion of immunosuppressive chemotherapy for acute lymphoblastic leukaemia (ALL).

- Patients with lymphoproliferative disorders (including haematological malignancies such as indolent lymphoma, leukaemia and plasma cell lymphoma).
- Patients who have received a solid organ transplant.
- Patients more than 12 months after receiving a haematopoietic stem cell transplant (HSCT).
- Patients receiving or within six months of completing biological therapies (alone or in combination with steroids). These include:
    - monoclonal antibodies e.g. alemtuzumab, ofatumumab and rituximab
    - cytokine inhibitors e.g. etanercept.

Group Bii – individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination

- Patients who have received a haematopoietic stem cell transplant (HSCT) within the past 12 months

Immunosuppressed Measles contacts: PHE guidance



- For Group A and Group Bi if unable to get Measles IgG result within 72 hours give IVIG
- For Group Bii give IVIG as soon as possible after exposure, ideally within 72 hours.

Post-Exposure Prophylaxis for Measles	**All Ages**	**Rate of administration**
IV Immunoglobulin	150mg/kg as a single dose	Refer to Immunoglobulin Guidelines for details of brand to be used
Consultant Oncologist/Haematologist must authorise use and usage must be in accordance with the Trust Immunoglobulin Guidelines. IVIG Panel approval is required in discussion with PHE.		

6.3.2 Measles Treatment

In cases of suspected or proven measles infection - patient must be transferred to Alder Hey Children's NHS Foundation Trust for management.

Measles in the immunocompromised child is severe, protracted and usually fatal. It mostly presents as Giant Cell pneumonia or encephalitis. Rash may be sparse or absent, but Koplicks spots are present for a number of days.

6.4 Adenovirus

In cases of suspected or proven adenovirus infection - Patient must be transferred to Alder Hey Children's NHS Foundation Trust for Management.

6.5 Cytomegalovirus

In cases of suspected or proven cytomegalovirus infection - Patient must be transferred to Alder Hey Children's NHS Foundation Trust for Management.

6.6 Respiratory Syncytial Virus (RSV)

Discuss with Oncology/Haematology Consultant – Patients with RSV Pneumonia must be transferred to Alder Hey Children's NHS Foundation Trust for Management.

Respiratory Syncytial Virus (RSV) infection after infancy is usually confined to the upper respiratory tract but can lead to a devastating viral pneumonia in immunocompromised paediatric patients. Deaths occur in children with RSV lower respiratory tract infections before or after haematopoietic stem cell transplant or who are < 2 years of age and receiving treatment for acute myeloid leukaemia.

The morbidity and mortality of RSV infection can be significantly reduced if spread to the lower respiratory tract is prevented. As infection is often secondary to asymptomatic carriage prior to HSCT, a nasopharyngeal aspirate (NPA) should be obtained in all patients on the day of admission.

Unfortunately pneumonia may be the first manifestation of RSV infection in up to 25% of patients and even with antiviral therapy the mortality is greater than 80% in most series. RSV is highly contagious and may spread rapidly throughout a transplant unit. Aggressive policies for the prevention of nosocomial infection have been shown to reduce the incidence of RSV disease during outbreaks in major units.

6.7 Influenza

All immunocompromised children and their immediate families should have influenza immunisation annually (See Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients).

All strains of influenza viruses have a predilection to cause severe disease in the young and immunocompromised. Prompt antiviral therapy reduces severity, duration and complications.

6.7.1 Investigation

Influenza should be looked for in children with 'flu like illness' during the influenza season. The preferred samples are NPA or sputum. Throat and nasal swabs can be sent but are inferior. If a swab is sent it must be placed in Remel Microtest viral transport medium – traditional green viral swabs are not suitable for the test.

6.7.2 Treatment of Influenza

All immunocompromised children with positive influenza on PCR should be treated with oseltamivir for at least 5 days. Treatment should be continued when an immunocompromised child remains symptomatic and discussed with a Respiratory, Infectious Diseases or Microbiology physician. The patient should be isolated in a single room and droplet precautions should be used when caring for the patient, especially if performing suctioning.

Consider antiviral resistance in patients with influenza who fail to improve after five days of oseltamivir treatment or deteriorate after a reasonable period of treatment.

Consult Microbiology/ Infectious Diseases for advice if there is a degree of renal failure, as it may be appropriate to use zanamavir in some cases. Guidance on reduced doses of oseltamivir for renal impairment can be found in the BNF for Children, consult pharmacy for further dosing advice.

6.7.2.1 Oseltamivir (Tamiflu®) Dosing

Treatment of Influenza for Patients Over 1 year				
Age	1 year to under 3 years	3 year to under 7 years	7 year to under 13 years	>13 years
Weight	< 15 kg	15 to 23 kg	23 to 40 kg	> 40 kg
Oral Oseltamivir	30mg twice daily	45mg twice daily	60mg twice daily	75mg twice daily
If patient is not within the weight range expected for the age band in the prescribing table, then use the dose appropriate for the weight band, not the age band. E.g. if a six-year-old child is known to be >23 kg, use the dose for the 23-40 kg body weight band (7-13 years of age). Duration of treatment 5 days. Available as 30 mg, 45 mg and 75 mg capsule and 6mg/ml suspension. Capsules may be opened and contents poured into a suitable, small amount (1 teaspoon maximum) of sweetened food.				

Treatment of Influenza for Patients Under 1 year			
Age	0 to 1 month*	> 1 month to 3 months	> 3 months to 12 months
Oral Oseltamivir	2 mg/kg twice daily	2.5 mg/kg twice daily	3 mg/kg twice daily
Duration of treatment 5 days. * There is no data available regarding the administration of oseltamivir to infants less than one month of age. Administration of oseltamivir to infants less than one year of age should be based upon the judgment of the physician after considering the potential benefit of treatment versus any potential risk to the infant. There is a commercially available oseltamivir suspension (6mg in 1 ml) for patients under 1 year. In the event of stock shortages pharmacy can prepare a suspension from the capsules.			

6.7.3 Prophylaxis of Influenza

The most important things are:

1) Ensure maximal uptake of annual influenza vaccine prior to flu season. (Refer to CCLG Guideline 'Vaccinations for Paediatric Patients Treated with Standard-Dose Chemotherapy and Haemopoietic Stem Cell Transplantation (HSCT) Recipients').
2) Appropriately investigate flu-like illness in patients, with prompt treatment if necessary.

Oseltamivir should be considered for the post-exposure prophylaxis of influenza, for people who fulfil ALL the following criteria:

- at-risk people (e.g. immunocompromised)
- not protected by vaccination (note chemotherapy may negate prior vaccination)
- exposed to someone with a flu-like illness
- able to begin prophylaxis within 48 hours of exposure
- when influenza is circulating in the community

Prophylaxis of Influenza for Patients Over 1 Year				
Age	1 year to under 3 years	3 year to under 7 years	7 year to under 13 years	>13 years
Weight	< 15 kg	15 to 23 kg	23 to 40 kg	> 40 kg
Oral capsules Oseltamivir	30mg once daily	45mg once daily	60mg once daily	75mg once daily
If patient is not within the weight range expected for the age band in the prescribing table, then use the dose appropriate for the weight band, not the age band. E.g. if a six-year-old child is known to be >23 kg, use the dose for the 23-40 kg body weight band (7-13 years of age). **Duration of prophylaxis: 10 days for post exposure prophylaxis; or for up to 6 weeks during an epidemic**				

Prophylaxis of Influenza for Patients Under 1 year			
Age	0 to 1 month*	> 1 month to 3 months	> 3 months to 12 months
Oral Oseltamivir	2 mg/kg once daily	2.5 mg/kg once daily	3 mg/kg once daily
Duration of prophylaxis: 10 days for post exposure prophylaxis			

Contact pharmacy or refer to the Health Protection Agency Website for further information: www.hpa.org.uk

7 REFERRALS FOR RESPIRATORY OPINION ± BRONCHOSCOPY

Patients with a severe or atypical respiratory infection should be transferred to Alder Hey Children's NHS Foundation Trust for further management.

8 PNEUMOCYSTIS JIROVECII PNEUMONIA (PJP) PROPHYLAXIS AND TREATMENT

Pneumocystis jirovecii Pneumonitis (PJP) (previously called *Pneumocystis carinii* Pneumonitis) occurs most commonly in children with defects of cell-mediated immunity as a result of chemotherapy, organ transplantation, primary immune deficiency (SCID or Hyper IgM) or HIV infection.

8.1 Prophylaxis of PJP

PJP prophylaxis is indicated in Acute Lymphoblastic Leukaemia, other types of leukaemia and certain solid tumours according to treatment protocols.

Post HSCT from recovery of neutrophils (>0.5 $x10^9$/L) and platelets (>50$x10^9$/L) to Day 100 in autologous transplants and until the recovery of CD4+ cells (>0.5$x10^9$/L) in allogeneic transplants.

Prophylaxis should also be considered in patients at risk of long-term immunosuppression or neutropaenia. Prophylaxis should be prescribed according to protocol.

8.1.1 First Line Prophylaxis

Co-trimoxazole is given TWICE DAILY on Saturday and Sunday only, as follows (unless otherwise specified in a chemotherapy protocol).

First Line PJP Prophylaxis	Co-trimoxazole Dose
< 0.5m^2	450mg/m^2 twice daily – Saturday/Sunday only
0.5-0.75m^2	240mg twice daily – Saturday/Sunday only
0.76-1m^2	360mg twice daily – Saturday/Sunday only
>1m^2	480mg twice daily – Saturday/Sunday only

Co-trimoxazole should usually be stopped one week before and during high dose methotrexate therapy. Contact Alder Hey for advice.

8.1.2 Second Line Prophylaxis

Oral dapsone at Consultant Oncologist/Haematologist's discretion.

Dose: refer to BNF for Children
Note: should be avoided in G6PD deficiency.

8.2 Treatment of PJP

Patients with suspected or proven PJP must be transferred to Alder Hey Children's NHS Foundation Trust for further management

8.2.1 Diagnosis

Clinical features of PJP in children are; shortness of breath on exertion, fever, tachypnoea, dyspnoea, cough and hypoxia.

The severity of these signs and symptoms may vary from child to child.

Onset can be abrupt or insidious with non-specific symptoms (e.g. mild cough, dyspnoea, poor feeding, and weight loss). Some children may not be febrile, but almost all patients will have tachypnoea by the time pneumonitis is observed on chest radiograph.

The majority of children with PJP have significant hypoxia which is often overlooked.

8.2.2 Investigations

- Oxygen saturation check (NOT blood gas analysis)
- Chest X-ray
- Bronchoscopy

CXR most commonly shows bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance, but CXR may be normal or show only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally before reaching the apical portions of the lung. Rarely, lobar, cavitating, nodular or miliary lesions, pneumothorax, or pneumomediastinum are seen.

9 CLOSTRIDIUM DIFFICILE AND OTHER GASTROINTESTINAL INFECTIONS

9.1 Gastrointestinal Infections – General Principles

9.1.1 Investigation

Patients with acute uncomplicated diarrhoea should not have stool samples sent for infection investigation.

Investigations may be requested based on clinical judgement & discussion with Microbiology/Infectious Diseases Consultant:

- Bacterial culture
- Viral faeces PCR
- *Clostridium difficile* toxin (CDT)

In certain cases e.g. persistent diarrhoea - discuss with Microbiology/ Infectious Diseases Consultant.

9.1.2 Isolation

Patients with diarrhoea require isolation until 48 hours after the last loose stool, whether or not an organism is isolated from the stool.

There is no need to request repeat tests on positive stools for the purpose of infection control: the requirement for source isolation is determined by the presence of symptoms (e.g. diarrhoea) and not the presence of an organism in the child's stool.

9.1.3 Treatment

In general patients with infective diarrhoea do not require specific treatment.
Therapy may be needed in exceptional circumstances (bacterial enteritis, *C difficile*, CMV etc.) – discuss with Oncology/Haematology/Infectious Disease Consultant.

9.1.4 Retesting

In general, repeat stool samples are not required in patients with infective diarrhoea.

Guidelines for retesting Oncology/Haematology patients will, in general, be in line with current Trust policy i.e:

- Following a positive virus test, no further testing will be undertaken within 14 days. Furthermore, requests for repeat testing after 14 days should be clinically indicated (e.g. persistence or recurrence of symptoms). Viruses such as rotavirus are shed in large amounts in stool and more frequent testing is generally unnecessary.

- Following a negative virus test, one further virus test will be undertaken, upon request, within a 7 day period.

9.2 Clostridium Difficile Toxin Positive Patients

Refer to Local Trust Policy on the Management of *Clostridium difficile*

STOP systemic antibiotic therapy if possible

Discuss with Consultant Oncologist/ Haematologist at Alder Hey Children's NHS Foundation Trust

It is unclear if *C. difficile* is a significant pathogen in paediatric oncology/haematology patients.
The epidemiology of *C. difficile* in children is divided into two groups. In neonates and infants less than 2 years *C. difficile* is often asymptomatic, whereas in those >2 years, the epidemiology of *C. difficile* may be similar to that of adults.

9.2.1 Neonates and Infants < 2 Years

The significance of *C. difficile* toxin in this age group is unclear. Colonisation rates vary between 20 and 50% in healthy infants. *C. difficile* toxin may be identified in the stool in as much as one-half of asymptomatic colonised infants, suggesting that toxigenic *C. difficile* may be part of their indigenous flora. It is possible that receptors to *C. difficile* toxins may be decreased or absent in younger children.

9.2.2 Oncology/Haematology Children > 2 Years

C. difficile toxins are found in oncology/haematology children with diarrhoea as often as they are found in those without diarrhoea. This suggests *C difficile* is of limited significance in older paediatric oncology/haematology patients. Look for other pathogens (bacterial and viral).

9.2.3 Testing for *C. difficile* Toxin (CDT)

Children with persistent diarrhoea and negative bacterial and viral tests should be tested for *Clostridium difficile* toxin (CDT).
Stools in children <2 years old will only be tested for CDT following discussion with one of the Microbiology/ Infectious Diseases consultants.
Formed stools will not be tested for CDT (stool must "take the shape of the container").
A two-step test will be carried out by an appropriate method (as recommended by HPA).

9.2.4 When to Treat C. difficile

Consider treating children who are *C difficile* toxin positive **and** have; fever, abdominal pain and any bowel wall thickening > 4 mm detected by ultrasound or CT scan. If these features are present in a child with neutropenia also consider treatment for neutropaenic enterocolitis (typhlitis); including systemic antifungal therapy.

9.2.5 Treatment

STOP systemic antibiotic therapy if possible.
Antimicrobial therapy: As per NICE Guidance NG199 – first line therapy is oral vancomycin (dosing as per BNFC). Seek advice from Infectious Diseases team.
Oral therapy is the preferred route in order to achieve high concentrations in the GI tract. If the patient cannot tolerate oral medication, then the antibiotic should be given via a nasogastric tube.

9.2.6 Retesting

Clearance specimens are not necessary, the toxin may remain in the stool after symptoms have resolved.

Stools will not be re-tested for *C. difficile* Toxin within 28 days of the original positive test. If symptoms resolve and then recur within 28 days, discuss re-testing with Microbiology/ Infectious Diseases Consultant.

10 ANTI-INFECTIVE DRUG DOSES IN RENAL IMPAIRMENT

Certain anti-infectives require dose adjustment in renal impairment.
This should be discussed with the Pharmacy Department.

11 ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis with ciprofloxacin is recommended in patients at high risk of Gram negative infections. These include:

- Stem cell transplant
- AML
- Relapsed ALL
- Children with Downs syndrome and ALL (see note below)
- Children with HLH
- GVHD patients on prolonged steroids

Prophylaxis of gram negative infection	Age ≥ 1 month	Comment
Oral ciprofloxacin	5 mg/kg/dose (maximum 250mg) every 12 hours unless otherwise specified in the protocol	Stop when broad spectrum antibiotics started

Note:
Children with Down syndrome and acute lymphoblastic leukaemia should receive ciprofloxacin during induction, Regimen B and C consolidation and delayed intensification. Give ciprofloxacin 10 mg/kg orally twice daily as per protocol.

11.1 Functional Hyposplenism

This includes patients post:

- Splenectomy
- Splenic radiotherapy
- TBI

Lifelong antibiotic prophylaxis is essential. See tables below for choice of antibiotic.

Note: Patients with chronic GVHD may also have functional hyposplenism.

Hyposplenism > 5 years	Age 5 to 12 years	Age ≥ 12 years	Comment
Phenoxymethylpenicillin oral (Penicillin V)	250 mg twice daily	500 mg twice daily	An hour before or two hours after food

Hyposplenism < 5 years	1 month – 5 years	Comment
Amoxicillin oral	125mg twice daily	Switch to phenoxymethylpenicillin at age 5 years

Hyposplenism with Penicillin Allergy	**Age < 2 years**	**Age 2 to 8 years**	**Age ≥ 8 years**
Erythromycin oral	125 mg once daily	250 mg once daily	500 mg once daily

12 USE OF OCTENILIN WOUND GEL IN ONCOLOGY/HAEMATOLOGY PATIENTS

12.1 Product Description and Properties

Octenilin wound gel contains the active ingredient octenidine 0.05g per 100g gel.

Octenidine is a broad spectrum antimicrobial that has good skin and mucous membrane tolerability. It is both bactericidal and fungicidal.

Octenilin wound gel is available from pharmacy in 20ml containers.

The bottle is sterile when sealed and must be discarded 6 weeks after opening.

12.2 Indication

Topical application to wounds (e.g. visible signs of inflammation at central venous line exit site, PEG site etc.).

12.3 Side Effects

No side effects have been observed.

12.4 Method of Application

Ensure swab taken for microbiology prior to initial application.
Apply to affected area daily and cover with appropriate dressing.

12.5 Duration of Treatment

Once daily for five days.
If no improvement after five days, repeat swabs and discuss with Infectious Diseases Team.

13 ABBREVIATIONS

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APLS	Advanced Paediatric Life Support
ASU	Aseptic Services Unit
ATG	Antithymocyte globulin
AUS	Australia-UK-Swiss score
BNFC	British National Formulary for Children
CMV	Cytomegalovirus
CNS	Central Nervous system
CRP	C Reactive Protein
CT	Computerised Tomography
CVC	Central Venous Catheter
EBV	Epstein Barr Virus
ED	Emergency Department
ESR	Erythrocyte sedimentation rate
FBC	Full Blood Count
FLAG	Fludarabine, cytarabine, GCSF
GCSF	Granulocyte Colony Stimulating Factor
GVHD	Graft versus host disease
HSCT	Haemopoeitic stem cell transplantation/rescue (BMT, PBSCT, umbilical cord blood transplantation)
HLH	Haemaphagocytic Lymphohistiocytosis
HSV	Herpes Simplex Virus
IPV	Inactivated polio vaccine
LCH	Langerhans cell Histiocytosis
MSSA	Methicillin – Sensitive Staph. Aureus
MRSA	Methicillin – Resistant Staph. Aureus
NPA	Naso-Pharyngeal Aspirate
PBSCT	Peripheral blood stem cell transplantation/rescue
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PTLD	Post-transplant lymphoproliferative disease
RSV	Respiratory Syncytial virus
SCID	Severe Combined Immune Deficiency
SIADH	Syndrome of inappropriate antidiuretic secretion
TBI	Total Body Irradiation
VZV	Varicella Zoster Virus

MANAGEMENT AND PREVENTION OF INFECTION IN ONCOLOGY AND HAEMATOLOGY PATIENTS FOR SHARED CARE CENTRES	
Version:	11
Ratified by:	Medicines Management and Optimisation Committee (MMOC)
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Name of originator/author:	Liz Evans (Senior Oncology Pharmacist) & Barry Pizer (Consultant Oncologist)
Name of responsible committee:	Chemotherapy Group & Antimicrobial Stewardship Group
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Version Control Table				
Version	Date	Author(s)	Status	Comment(s)
1-5	Pre 00-Sep 11	Caroline Osborne, Dr Barry Pizer	Archived	
6	11th Jan 13 cbCA	Caroline Osborne, Dr Barry Pizer	Archived	
7	Jun 13	Karen Selwood (ANP - Oncology), Caroline Osborne, Dr Barry Pizer	Archived	
8	Jun 16	Karen Selwood, Caroline Osborne Elizabeth Evans David Sharpe	Archived	
8.1	August 2016	Karen Selwood Caroline Osborne Professor Pizer	Archived	
9	September 2018	Caroline Osborne James Hayden Andrew Taylor Andrew Riordan Mark Caswell Barry Pizer	Archived	
10	November 2020	Liz Evans Barry Pizer	Archived	
11	July 2023	Jen Edwards	Current	C Diff treatment updated

Review and Revision(s) Log *Record of revision(s) made to guidelines since Version 9*			
Section Number	Page Number	Revision(s) made	Reason for revision(s)
		Reformatted throughout	
	5	Flowchart updated	In line with changes to text below
1.3	6	Examination to include bone marrow and lumbar puncture sites	In line with current advice
1.5	7	Blood culture volumes added	For clarification
1.6	7	Review surveillance cultures changed to 6 months from 3 months Contact Alder Hey for results of surveillance swabs	As per ID advice To ensure appropriate choice of first line antibiotics
1.7f	7	New point	To clarify antifungal treatment
1.7g	8	Indication for IM amikacin updated to include ceftriaxone resistant organism	As per ID advice
1.8	8	More recent reference	Updated
1.10	9	Risk of drug induced kidney injury highlighted	For safety purposes
1.10	9 10	Refer to BNFC for ciprofloxacin MHRA safety information Meropenem dosing updated	Updated MHRA safety information Higher dose for selected infections
1.11	12	Risk of drug induced kidney injury highlighted	For safety purposes
1.12	13	Refer to BNFC for levofloxacin MHRA safety information	Updated MHRA safety information
2	14	Ongoing management separated from Section 1	For clarity
2.2	14	Discharge at 24 hours afebrile instead of 48 hours (antibiotics must continue for a minimum of 48 hours)	In line with national change in febrile neutropaenia management
4.2.1	18	Systemic teicoplanin instead of vancomycin (CNS and MRSA)	Low threshold for line removal in MRSA. Systemic and lock therapy to be different antibiotics
6.3.1	33	IVIG Panel approval required in discussion with PHE	As per most recent DH Immunoglobulin Guidance
6.7.2	35	Link to renal.org deleted	Unavailable. Details in BNFC.
6.7.2.1	35	Details of oseltamivir suspension updated	As per SmPC
9.2.5	42	Classification of IVIG indication updated	As per most recent DH Immunoglobulin Guidance
11.1	44	Hyposplenism section updated for non-HSCT patients	For clarification
11.2	41	9.2.5 C Diff treatment updated	As per NICE guidance