GUIDELINES FOR THE MANAGEMENT AND PREVENTION OF INFECTION IN ONCOLOGY PATIENTS (Including Immunisation Guidelines)

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SUMMARY OF THE MANAGEMENT OF THE FEBRILE PATIENT

Single temperature 38°C

FBC, Oncology profile, CRP Blood Cultures

Is patient shocked?

- Yes
  - Check surveillance swabs
  - Is there a resistant organism?
    - Yes
      - Follow the ABC approach to septic shock and treat with Piperacillin/Tazobactam plus gentamicin unless patient has a penicillin allergy (see 1.6) or a resistant organism
    - No
      - Prescribe appropriate antibiotics according to sensitivities. Discuss with Specialist Registrar/Consultant Oncologist/Haematologist

- No
  - Afebrile for 48 hours
    - Yes
      - Organism Isolated?
        - Yes
          - Discharge home if well
        - No
          - Prescribe appropriate antibiotics according to sensitivities. Consultant to decide duration of treatment
    - No
      - Repeat Blood Cultures if still pyrexial
       - Continue Piperacillin/Tazobactam until afebrile for 48 hours
       - Still pyrexial at 96 hours?
         - Yes
           - Repeat Blood Cultures
           - High Resolution CT Scan Chest + Upper Abdo
           - Add IV Liposomal Amphotericin
           - Consultant to decide duration of treatment

Discuss with Consultant if child is unwell

- Patients with relapsed ALL should also be given Liposomal Amphotericin 3 mg/kg/day (week 1-13)
1. MANAGEMENT OF PYREXIA IN ONCOLOGY PATIENTS

1.1 Life threatening Infections may develop rapidly in immunocompromised patients. It is imperative to start antibiotic treatment as soon as possible 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 In cases of suspected septic shock:
   a) Follow the “A, B, C” approach to septic shock as per Advanced Paediatric Life Support (APLS) guidelines. For fluid bolus give 20ml/kg 0.9% saline
   b) In addition to normal investigations (see below) check coagulation, renal & liver function and inform the on-call consultant oncologist/haematologist.
   c) PICU should be informed of any deteriorating septic patient, or if a second 20ml/kg bolus is to be given.

1.3 Examination:
   Examine for focal infection, including finger prick areas, line & gastrostomy site and anus. Measure pulse, BP and capillary refill.

1.4 Investigations:
   a) FBC, Oncology profile (ONC) & 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 naso-pharyngeal aspirate (NPA) should be performed in patients with respiratory symptoms or signs. If productive of sputum, send for C&S and respiratory viruses. (Meditech Order for respiratory viruses – VIR – RESPVIRUS)

1.5 Review microbiology “surveillance cultures” and whether any resistant organisms have been isolated in the last 3 months. In cases of carriage with a resistant Gram-negative organism, inform Specialist Registrar/Consultant oncologist/haematologist. If any questions regarding sensitivities contact Infectious Diseases

1.6 Start IV antibiotics if a single temperature of 38.0°C has been recorded. 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 (use vancomycin + ciprofloxacin (+/- gentamicin))
   b) Septic shock (Give Piperacillin/Tazobactam AND Gentamicin, see note (1.7) below)
   c) Surveillance cultures have identified a resistant organism (see 1.9d)
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 received high dose methotrexate see 1.9

1.7 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.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Systolic BP (mmHg) 5th Centile</th>
<th>Systolic BP (mmHg) 50th Centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>65 -75</td>
<td>80 - 90</td>
</tr>
<tr>
<td>1 - 2</td>
<td>70 – 75</td>
<td>85 - 95</td>
</tr>
<tr>
<td>2 - 5</td>
<td>70 – 80</td>
<td>85 - 100</td>
</tr>
<tr>
<td>5 - 12</td>
<td>80 – 90</td>
<td>90 - 110</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>90 – 105</td>
<td>100 - 120</td>
</tr>
</tbody>
</table>

Ref: Advanced Paediatric Life Support: The practical approach. 5th Ed. 2011

1.8 Continuing treatment:

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

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

c) 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 an Infectious Diseases Consultant should be contacted.

d) If fever unresolved by 96 hours:

i. Add in IV Liposomal Amphotericin (Ambisome®) 1mg/kg (see section 4.4), or 3mg/kg if relapsed ALL (see section 4.2).

ii. Perform High Resolution CT of Chest + CT Upper Abdomen (Liver and Spleen).

In some high risk patients (e.g. AML, HSCT patients, prolonged steroid use), IV Liposomal Amphotericin may be started earlier than 96 hours – discuss with Haematology/Oncology Consultant.
e) Children who carry extended spectrum beta-lactamase producing organisms (ESBL) should be given antibiotics to which these are sensitive - GENERALLY MEROPENEM. *These organisms are marked on Meditech by having an E at the end of the organisms' abbreviated name (i.e. KLEPPE, ESCCOE, ENBCLE).*

1.9 Intravenous Antibiotics

*NB - For neonates and for patients with renal impairment please refer to pharmacist for dose and monitoring.*

| AMIKACIN (Monitor levels – see section 2) | 20mg/kg Once Daily.  
| Maximum: 1200mg (>60Kg)  
| Reduce dose in renal impairment  
| Dilute to at least 10 ml with sodium chloride  
| 0.9% and infuse over 20 minutes.  
| If child is obese: base dose on ideal body weight: Contact Oncology pharmacist. |

Follow aminoglycoside pathway

| CIPROFLOXACIN | Child ≥ 1 month  
| 10 mg/kg every 8 hours.  
| Maximum 400mg every 8 hours  
| Reduce dose in renal impairment.  
| IV infusion over 60 minutes |

| FLUCLOXACILLIN* | 50mg/kg every 6 hours.  
| Maximum 2g every 6 hours  
| Caution in hepatic impairment. Reduce frequency in severe renal impairment  
| IV Bolus (concentration 50mg/ml) or infuse in dextrose 5% or Sodium chloride 0.9% over 15 to 30 minutes  
| Caution: penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folic acid rescue is complete |

| GENTAMICIN (Monitor levels – see section 2) | 7mg/kg Once Daily.  
| Maximum: 420mg (>60Kg).  
| Reduce dose in renal impairment  
| Dilute to at least 10ml with sodium chloride  
| 0.9% and infuse over 20 minutes.  
| If child is obese: base dose on ideal body weight: Contact Oncology pharmacist. |

Follow aminoglycoside pathway
| **MEROPENEM** | 20mg/kg every 8 hours.  
Maximum 1g every 8 hours  
Reduce dose in renal impairment.  
IV Bolus over 5 minutes or infuse in dextrose 5% or Sodium chloride 0.9% over 15 to 30 minutes |
| --- | --- |
| **PIPERACILLIN/TAZOBACTAM*** | 90mg/kg every 6 hours  
Maximum - 4.5g every 6 hours  
Reduce dose in renal impairment.  
IV infusion in dextrose 5% or Sodium chloride 0.9%, diluted to at least 90mg/ml and give over 20 to 30 minutes, although it may be administered as neat IV bolus in exceptional circumstances (e.g. fluid restriction, compatibility issues or time constraints).  
Caution : penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete |
| **TEICOPLANIN** | 10mg/kg (maximum 400mg) every 12 hours for 3 doses then 10mg/kg (maximum 400mg) once a day  
Reduce dose in renal impairment  
Slow IV bolus over 3 to 5 minutes |
| **VANCOMYCIN**  
(Monitor levels – see section 2) | 15mg/kg every 8 hours  
Maximum starting dose - 660mg every 8 hours. Reduce dose or frequency in renal impairment.  
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  
follow vancomycin pathway |

*Caution: Penicillins reduce methotrexate excretion and should be avoided in patients on high dose methotrexate until hydration and folinic acid rescue is complete*
2. **ANTIBIOTIC LEVEL MONITORING**

External central lines and Port-a-Caths (Ports) can be used for drug sampling provided the line is well flushed after administration.

High levels should be checked from a peripheral vein or finger prick.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trough level</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENTAMICIN</td>
<td>&lt;1mg/l (18-24hrs)</td>
<td></td>
</tr>
<tr>
<td>AMIKACIN</td>
<td>&lt;3mg/l (18-24hrs)</td>
<td></td>
</tr>
</tbody>
</table>

If renal impairment – need to use an adjusted dose, monitor pre and post levels and aim for the following ranges:

- Gentamicin Pre < 2mg/mL and one hour post 5-10mg/L
- Amikacin Pre 2 to 5mg/L and one hour post 15 to 25mg/L

For additional information on Dosing and Monitoring of Gentamicin and amikacin see aminoglycoside pathway.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trough level</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>VANCOMYCIN</td>
<td>15 to 20 mg/L (just before 4th dose)</td>
<td>For all oncology patients.</td>
</tr>
</tbody>
</table>

For additional information on Vancomycin Dosing and Monitoring Guidelines see vancomycin pathway.

Interpretation of levels

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

<table>
<thead>
<tr>
<th>Higher than expected level</th>
<th>Lower than expected level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect dose</td>
<td>Incorrect dose</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Missed dose</td>
</tr>
<tr>
<td>Level taken from administration site</td>
<td>Inadequate flushing</td>
</tr>
<tr>
<td>Drug level taken too early</td>
<td>Drug level taken too late</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Abnormal collection of body fluid</td>
</tr>
<tr>
<td></td>
<td>Exchange transfusions</td>
</tr>
<tr>
<td></td>
<td>Hydration</td>
</tr>
</tbody>
</table>

PHARMACY IS AVAILABLE TO ADVISE ON ANY PROBLEMS WITH THERAPEUTIC DRUG MONITORING. CONTACT YOUR WARD OR ON-CALL PHARMACIST
3. CENTRAL VENOUS CATHETER (CVC) – ASSOCIATED BACTERAEMIA.

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 Infectious Diseases team.

General Principles of Management

In such cases, it is very important to consider:

1) Whether the CVC should be removed.

2) 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 as a line-lock and given intravenously (unless recommended by the Infectious Diseases or Oncology 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:

<table>
<thead>
<tr>
<th>Antibiotic Line-lock</th>
<th>Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>5mg/ml</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1mg/ml</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2mg/ml</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2mg/ml</td>
</tr>
</tbody>
</table>
Higher concentrations of gentamicin (2mg/ml) and amikacin (5mg/ml) line-locks are available for use at the discretion of the Infectious Diseases or Oncology team. The duration of antibiotic lock therapy should be discussed with the Consultant oncologist/haematologist and a member of the Infectious Diseases team.

If there is prolonged fever after starting appropriate antibiotics look for 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.

**Organism Specific Issues**

**Gram positive organism**

*Coagulase Negative Staphylococcus and Enterococcus Spp.*

Intravenous teicoplanin or vancomycin for at least 7 days following the first negative blood culture PLUS vancomycin line locks.

Remove CVC if there is clinical deterioration/persistent bacteraemia.

*Staphylococcus aureus*

Need to complete 14 days of treatment in total following the 1st negative blood culture.

If MSSA – use Flucloxacillin PLUS vancomycin line locks.

If MRSA - use IV vancomycin 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 persistent bacteraemia.

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

**Gram negative organisms**

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 Infectious Disease Consultant the length of treatment required following CVC removal.

**Candida**

**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.**
4 ANTI-FUNGAL THERAPY

4.1 FUNGAL PROPHYLAXIS

Only indicated in high risk patients as defined below:

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

Notes –

- Patients in the HR-NBL-1 trial who are receiving myeloablative therapy and an autograft are not permitted in the trial to receive prophylactic azole antifungals. Cover with prophylactic Liposomal Amphotericin (Ambisome®) through transplant

- Patients on relapsed ALL protocols – see section 4.2

- Previous significant fungal infection - discuss with consultant oncologist/haematologist

a) First choice – Itraconazole

<table>
<thead>
<tr>
<th>Fungal prophylaxis</th>
<th>Age ≥ 1 month</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole oral (liquid 10mg/ml)</td>
<td>2.5mg/kg twice daily</td>
<td>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 levels monitoring may be required (see below).</td>
</tr>
</tbody>
</table>

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.

- Reduce ciclosporin dose if patient on itraconazole as it will significantly increase ciclosporin levels. Contact clinical pharmacist for advice

- For details of other drug interaction 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.

1 ml of serum is required (2 ml 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

b) Voriconazole - Second choice for patients unable to tolerate itraconazole

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

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Oral (suspension*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading Dose Regimen (first 24 hours)</strong></td>
<td>9 mg/kg every 12 hours</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Maintenance Dose (after first 24 hours)</strong></td>
<td>8 mg/kg twice daily</td>
<td>9 mg/kg twice daily (maximum dose 350 mg twice daily)</td>
</tr>
</tbody>
</table>

*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)**

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Oral (Tablets and Suspension)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Patients over 40 kg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Patients under 40 kg</strong></td>
</tr>
<tr>
<td><strong>Loading dose regimen(first 24 hours)</strong></td>
<td>6 mg/kg every 12 hours</td>
<td>400 mg every 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg every 12 hours</td>
</tr>
<tr>
<td><strong>Maintenance dose (after first 24 hours)</strong></td>
<td>4 mg/kg twice daily</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg twice daily</td>
</tr>
</tbody>
</table>
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

c) Liposomal Amphotericin

May be used as an alternative in patients unable to tolerate itraconazole or voriconazole because of liver toxicity and/or deranged LFTS

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 4.4 for test dose and administration details

4.2 ANTI-FUNGAL PROPHYLAXIS FOR PATIENTS ON RELAPSED ALL R3

All patients require Liposomal Amphotericin (Ambisome®) during induction.

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 at 3mg/kg/day in addition to the necessary antibacterial therapy. In this case stop any other antifungal

**Induction.** All patients should receive intravenous Liposomal Amphotericin (Ambisome®) at a dose of 1 mg/kg three times a week on Monday, Wednesday and Friday. This should continue for 5 weeks (count recovery is required). Refer to section 4.4 for test dose and administration details.
4.2.1 Standard/Intermediate Risk

**At Week 6.** If counts have recovered (ANC > 0.5 \( \times \) \( 10^9 \)/L) - stop Liposomal Amphotericin and start oral Itraconazole suspension at a dose of 2.5mg/kg twice a day. Levels are needed (see below) and LFTs should be monitored weekly. If counts have not recovered continue with Liposomal Amphotericin 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.

**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.

1ml of serum is required (2 ml of 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 15 mg/L are satisfactory**

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

**Weeks 1-5**
Liposomal Amphotericin 1mg/kg three times a week on Monday, Wednesday and Friday.

**Week 6 – Count recovery (ANC>0.5)**
Stop Liposomal Amphotericin
Start Itraconazole 2.5mg/kg/BD

**Week 6 – Count not recovered**
Continue Liposomal Amphotericin three times a week.
Switch to Itraconazole when count has recovered.

**Week 8**
Take Itraconazole levels (After 1-2 weeks of treatment)

**Week 9**
Stop Itraconazole by day 1 week 9
(2 days before Vincristine)

**Week 10 – Itraconazole level (at week 8)**
Within range 5-15mg/L
Restart (5 days after Vincristine) at same dose.
Continue to end of week 13.
No further levels unless toxicity suspected.

**Week 10 – Itraconazole level (at week 8)**
< 5 or > 15mg/L
Contact pharmacy for advice on dose change necessary.
Restart (5 days after Vincristine) at amended dose.
Take levels beginning of week 11
(1 week after dose amendment)
Change dose if necessary.
Continue treatment until end of week 13.

End of week 13
(End of Intensification)
Stop Itraconazole prophylaxis.

Itraconazole liquid must be used due to better absorption

Patients on the ALL R3 protocol who are receiving prophylactic systemic antifungal therapy (generally until the end of week 13) admitted for febrile neutropaenia must be started on empirical anti-fungal therapy with Liposomal Amphotericin at 3mg/kg/day in addition to the necessary antibacterial therapy.
4.2.2 High Risk

Patients receive antifungal prophylaxis (Liposomal Amphotericin (Ambisome®) or itraconazole liquid /voriconazole) until the end of week 14.

Choice is dependent on the timing of Vincristine doses. Avoid itraconazole and voriconazole for at least 48 hours before and after a vincristine dose.

Where vincristine is given weekly (e.g. week 7 to 9) use Liposomal Amphotericin (Ambisome®).

4.3 TREATMENT OF ORAL FUNGAL INFECTIONS

Mild Infections

Miconazole

<table>
<thead>
<tr>
<th>Mild oral fungal infection</th>
<th>Age 1 month to 2 years</th>
<th>Age 2 to 6 years</th>
<th>Age ≥ 6 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miconazole Gel</td>
<td>2.5 ml twice daily</td>
<td>5 ml twice daily</td>
<td>5 ml four times daily</td>
<td>Use after food and retain as long as possible.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moderate/severe Infections

Fluconazole

<table>
<thead>
<tr>
<th>Moderate/severe oral fungal infection</th>
<th>Age ≥ 1 month</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Fluconazole (Or IV if necessary)</td>
<td>5 mg/kg once daily (maximum 150mg)</td>
<td>Fluconazole is completely orally absorbed, so the IV dose is equivalent to the oral dose. Oral absorption is not affected by food.</td>
</tr>
</tbody>
</table>
4.4  EMPIRIC THERAPY FOR INVASIVE FUNGAL INFECTION

Generally for patients who are neutropaenic and remain pyrexial after 96 hours, empiric therapy should be prescribed only on discussion with an Oncology SpR or Consultant oncologist/haematologist.

**IV Liposomal Amphotericin (Ambisome®): 1 mg/kg/day.**

**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.

A test dose of 1mg Liposomal Amphotericin (Ambisome®) in 5ml Dextrose 5% is given over 10 minutes. The patient should be carefully observed for at least a further 30 minutes. Patients <10kg should receive 0.1mg/kg as a test dose.

**Ordering**
Liposomal Amphotericin (Ambisome®) is prepared by the CIVAS unit. Please inform them of your intention to use it at the earliest possible time. Outside CIVAS working hours refer to the “Liposomal Amphotericin Use” guidelines on the intranet for preparation on the ward.

**Administration**
The recommended concentration for intravenous infusion is 0.2mg/ml to 2mg/ml in Dextrose 5%. Liposomal Amphotericin is administered over 30-60 minutes. Do not mix with any other IV drugs except Dextrose 5% and do not filter.

**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.

4.5  PATIENTS WITH SUSPECTED DEEP SEATED OR SYSTEMIC FUNGAL INFECTIONS
Patients with suspected deep seated or systemic fungal infections must be treated with Liposomal Amphotericin (Ambisome®).

**IV Liposomal Amphotericin (Ambisome®): 3 mg/kg/day**

4.6  PATIENTS WITH PROVEN DEEP SEATED FUNGAL INFECTION.

**IV Liposomal Amphotericin (Ambisome®): 3 mg/kg/day**

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 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 Infectious Diseases Consultant.

Duration of treatment should be discussed with Consultant oncologist/ haematologist and Infectious Diseases Consultant.

Treatment options include the use of:

- IV Voriconazole
- IV Micafungin
- Oral Posaconazole – Contact pharmacy for advice (data limited in children)
5. **VIRAL INFECTIONS**

5.1 **VARICELLA ZOSTER VIRUS (VZV)**

5.1.1 **Prophylaxis after contact with Chickenpox or Shingles**

The clinical history of past infection and the varicella antibody status should be ascertained before the start of chemotherapy.

At the present time, children who have varicella IgG detected at diagnosis, suggesting previous infection, do not require aciclovir prophylaxis following significant contact with chickenpox or shingles.

- Oncology patients VZV antibody status can be found on Meditech under virology - SEROLOGY

Patients who are antibody negative 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 HCST 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 is given either

- **For 7 days** following significant contact with friends, at school, playgroup, on holiday
- **For 21 days** following significant contact or gross exposure with sibling or other household member, because of the ongoing risk of exposure.

<table>
<thead>
<tr>
<th>Prophylaxis after chickenpox contact</th>
<th>Age 1 month to 2 years</th>
<th>Age 2 to 6 years</th>
<th>Age ≥ 6 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir oral</td>
<td>200 mg four times daily</td>
<td>400 mg four times daily</td>
<td>800 mg four times daily</td>
<td>Use dispersible tablets where possible</td>
</tr>
</tbody>
</table>
5.1.2 Treatment of Chickenpox or widespread Shingles

In a child with a vesicular rash – send virology swab of vesicle fluid for VZV PCR (on meditech as “vesicle 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.

<table>
<thead>
<tr>
<th>Treatment of Chickenpox or disseminated shingles</th>
<th>Age &lt; 3 months</th>
<th>Age 3 months to 12 years</th>
<th>Age &gt; 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir IV</td>
<td>20 mg/kg three times daily</td>
<td>500 mg/m² three times daily</td>
<td>10mg/kg three times daily</td>
<td>Dilute to 5mg/ml in sodium chloride 0.9% &amp; administer over one hour. Reduce dose in renal impairment</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Continuation treatment for Chickenpox or widespread shingles</th>
<th>Patient Weight 4 – 12 kg</th>
<th>Patient Weight 13 – 21 kg</th>
<th>Patient Weight 22 – 29 kg</th>
<th>Patient Weight &gt; 30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valaciclovir oral tablets</td>
<td>250 mg three times daily</td>
<td>500 mg three times daily</td>
<td>750 mg three times daily</td>
<td>1000 mg three times daily</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Continuation of treatment for Chickenpox or widespread shingles</th>
<th>Age 1 month to 2 years</th>
<th>Age 2 to 6 years</th>
<th>Age &gt; 6 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir oral</td>
<td>200 mg four times daily</td>
<td>400 mg four times daily</td>
<td>800 mg four times daily</td>
<td>Use dispersible tablets where possible</td>
</tr>
</tbody>
</table>

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

All patients:

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.

5.1.3 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.
5.2 HERPES SIMPLEX VIRUS

5.2.1 Prophylaxis for HSV infection – HSCT Patients

Aciclovir is started routinely at D+1.

<table>
<thead>
<tr>
<th>Prophylaxis for HSV infection – HSCT Patients</th>
<th>Age 1 month to 2 years</th>
<th>Age &gt; 2 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Aciclovir</td>
<td>100 mg to 200 mg four times daily</td>
<td>200 to 400 mg four times daily</td>
<td>Use dispersible tablets where possible</td>
</tr>
</tbody>
</table>

If oral aciclovir is not tolerated give intravenous aciclovir converting back to oral when tolerated.

<table>
<thead>
<tr>
<th>Prophylaxis for HSV infection – HSCT Patients</th>
<th>Age &lt; 3 months</th>
<th>Age 3 months to 12 years</th>
<th>Age &gt; 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Aciclovir</td>
<td>10mg/kg every 8 hours</td>
<td>250mg/m² every 8 hours</td>
<td>5mg/kg every 8 hours</td>
<td>Dilute to 5mg/ml in sodium chloride 0.9% &amp; administer over one hour. Reduce dose in renal impairment</td>
</tr>
</tbody>
</table>

Duration of Therapy

For Autografts continue until at least 3 months post transplant
For Allografts continue until completed immunosuppressive therapy and CD4⁺ > 0.5 x 10⁹/L

5.2.2 Treatment of localised HSV infection for all haematology/oncology patients

a) **Oral Aciclovir** is used for mild, localised (oral/perianal) disease

<table>
<thead>
<tr>
<th>Mild, localised (oral/perianal) HSV disease</th>
<th>Age 1 month to 2 years</th>
<th>Age &gt; 2 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Aciclovir</td>
<td>200mg four times daily for 5 days</td>
<td>400mg four times daily for 5 days</td>
<td>Use dispersible tablets where possible</td>
</tr>
</tbody>
</table>

Continue for longer if new lesions appear or if healing incomplete
b) **IV Aciclovir** is used for severe, localised (oral/perianal) disease

<table>
<thead>
<tr>
<th>Severe, localised (oral/perianal) HSV disease</th>
<th>Age &lt; 3 months</th>
<th>Age 3 months to 12 years</th>
<th>Age &gt; 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Aciclovir</td>
<td>20mg/kg every 8 hours for 5 days</td>
<td>500mg/m² every 8 hours for 5 days</td>
<td>10mg/kg every 8 hours for 5 days</td>
<td>Dilute to 5mg/ml in sodium chloride 0.9% &amp; administer over one hour. Reduce dose in renal impairment</td>
</tr>
</tbody>
</table>

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

5.2.3 **Treatment of disseminated HSV infection including HSV encephalitis**

IV aciclovir should be used for 21 days

**Shared care patients should be transferred to Alder Hey for further management.**

<table>
<thead>
<tr>
<th>Disseminated HSV infection including HSV encephalitis</th>
<th>Age &lt; 3 months</th>
<th>Age 3 months to 12 years</th>
<th>Age &gt; 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Aciclovir</td>
<td>20mg/kg every 8 hours for 21 days</td>
<td>500mg/m² every 8 hours for 21 days</td>
<td>10mg/kg every 8 hours for 21 days</td>
<td>Dilute to 5mg/ml in sodium chloride 0.9% &amp; administer over one hour. Reduce dose in renal impairment</td>
</tr>
</tbody>
</table>
5.3 MEASLES

5.3.1 Measles Prophylaxis (after measles contact)

Contact requires action regardless of antibody status for all patients on active treatment and 6 months following the completion of chemotherapy. Patients who have had HCST should receive prophylaxis for 12 months following the completion of treatment or longer if they are still on immunosuppressive therapy.

**Significant contact** = play or direct contact for more than 15 minutes with an individual with virologically confirmed measles during the infectious period from up to 4 days before to 4 days after the onset of the rash.

Every effort should be made to confirm the diagnosis of measles in the index case, but this may not always be possible.

In the event of contact with clinically diagnosed but virologically unproven measles, passive immunisation is warranted if the clinical diagnosis seems plausible.

If within 7 days (most effective if within 72 hours) from contact give IV immunoglobulin.

**Consultant oncologist/haematologist must authorise use and usage must be in accordance with the Trust Policy to Implement Demand Management Plan for Immunoglobulin use. This is classified as a grey indication, approved for use at Alder Hey in advance of need (post-exposure prophylaxis for viral infection if intramuscular injection contraindicated).**

<table>
<thead>
<tr>
<th>Measles prophylaxis after measles contact.</th>
<th>All Ages</th>
<th>Rate of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Immunoglobulin OCTAGAM 10% (usual brand)</td>
<td>150mg/kg as a single dose</td>
<td>0.6mL/kg/hour for 30 minutes then 1.2mL/kg/hour for 30 minutes then 2.4mL/kg/hour until the prescribed dose has been administered.</td>
</tr>
</tbody>
</table>

If a child is receiving 150-400 mg/kg IV immunoglobulin every three weeks for any other condition and are in contact with measles, they do not need any further IVIG.

5.3.2 Measles Treatment

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.

Discuss diagnosis and treatment with a consultant oncologist/haematologist and the Infectious Diseases team.
**Consider intravenous ribavirin.** Requires consultant oncologist/haematologist approval (and preparation in CIVAS).

<table>
<thead>
<tr>
<th>Measles treatment</th>
<th>Age 1 month to 18 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ribavirin</td>
<td>Initial loading dose of 33 mg/kg, followed 6 hours later by 16 mg/kg every 6 hours for 4 days, followed 8 hours after the last dose by 8mg/kg every 8 hours for 3 days.</td>
<td>Dilute dose to 15mL with dextrose 5% or sodium chloride 0.9% and given over 15 minutes Contact pharmacy for advice in the case of renal or hepatic impairment The last dose level may be prolonged if deemed appropriate by the treating physician, based upon the patient’s response to treatment.</td>
</tr>
</tbody>
</table>

Isolate the child for the duration of the illness.
5.4 ADENOVIRUS

Adenovirus can be a cause of severe disseminated infection in the T-cell deficient. The following guidance is for allogeneic HSCT patients primarily. A few other non-HSCT patients may be considered as at high risk on an individual basis.

Currently there is no established effective prophylaxis for adenovirus infections.

**Clinical manifestations:**
- gastroenteritis
- pneumonia
- hepatitis - usually with raised GGT and transaminases rather than hyperbilirubinaemia. Rapidly progresses to fulminant hepatitis and liver failure - nearly always fatal in the absence of functioning T cells
- encephalitis
- haemorrhagic cystitis

These clinical features are not diagnostic of adenovirus infection and virological diagnosis is always required. It is important to take appropriate samples from the sites of disease e.g. if pneumonitis, obtain a respiratory sample.

5.4.1 Adenovirus Infection

For all patients in high risk groups send weekly blood for adenovirus PCR

If adenovirus infection suspected e.g. on basis of symptomatology (see above) or if adenovirus detected in other samples: Send blood for urgent adenovirus PCR and other appropriate samples for virology PCR (Discuss with Consultant Haematologist).

- If blood positive on one occasion: request second urgent blood PCR
  - consider samples from other sites for virology PCR, such as respiratory NPA and urine
  - AND – send stool for adenovirus PCR. Can be found on meditech as "faeces viral PCR"

- Inform Haematologist on-call – who will decide if treatment is required depending on individual patient circumstances.

- If first blood PCR positive and no symptoms – treatment can be deferred pending results of subsequent samples

- If first blood PCR positive and symptomatic – treatment would generally be started

- If second blood PCR positive – Consider treatment. If patient asymptomatic and PCR log value falling and immunosuppression withdrawal an option, treatment can be deferred pending further results. Monitor blood positivity with weekly blood PCR. LFTs should be monitored closely
• 1st Line = cidofovir

(cidofovir is a cytotoxic drug - should be prepared in the cytotoxic preparation unit).

**Cidofovir cannot be made on call. If there is any possibility this may be required after 4 pm contact the oncology or CIVAS pharmacist to arrange preparation.**

The following schedule has been used (Cidofovir is not licensed in children or for this indication)

<table>
<thead>
<tr>
<th>Cidofovir 5mg/kg/dose once a week for two weeks then every two weeks, given over 1 hour in sodium chloride 0.9%. Probenecid given with each dose</th>
</tr>
</thead>
</table>

**For renal compromised patients:** Doses of Cidofovir 1mg/kg 3 times a week may be required with probenecid given with each dose. Contact pharmacy for advice in the case of renal impairment. Consultant to decide on dosage.

Cidofovir is given with oral Probenecid and intravenous hydration with sodium chloride 0.9% to reduce renal toxicity.

| T = 0hrs | Probenecid orally as per chart below |
| T = 2hrs | Prehydration with 15ml/kg (maximum 1000ml) 0.9% sodium chloride over 1 hour |
| T = 3hrs | Ondansetron 5mg/m² oral or IV (max 8mg) |
| T = 4hrs | Cidofovir 5mg/kg in 100ml sodium chloride 0.9% (can be concentrated if required, discuss with pharmacist) over 1 hour |
| T = 6hrs | Post hydration with 15ml/kg (maximum 1000ml) 0.9% sodium chloride over 2 hours |
| T = 12hrs | Probenecid orally as per chart below |

**Weight (kg) | Probenecid dose (500 mg tablet, suspension can be made by Pharmacy on request, 250 mg/5 mL)**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>T = 0 hrs (3hrs pre Cidofovir)</th>
<th>T = 6 hrs (2hrs after end of Cidofovir infusion)</th>
<th>T = 12 hrs (8hrs after end of Cidofovir infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20kg</td>
<td>500mg</td>
<td>250mg</td>
<td>250mg</td>
</tr>
<tr>
<td>21 – 40kg</td>
<td>1g</td>
<td>500mg</td>
<td>500mg</td>
</tr>
<tr>
<td>41 – 60kg</td>
<td>1.5g</td>
<td>750mg</td>
<td>750mg</td>
</tr>
<tr>
<td>&gt;61kg</td>
<td>2g</td>
<td>1g</td>
<td>1g</td>
</tr>
</tbody>
</table>

**Side Effects of Cidofovir:**

Renal damage is a major therapy limiting toxicity related to cidofovir.

- Urea and electrolytes must be closely monitored for the duration of therapy
- Consider stopping concurrent nephrotoxic drugs including Aciclovir.
- Probenecid may affect the metabolism and tubular secretion of other drugs e.g. Aciclovir, Methotrexate and Penicillin

**Consider giving IV immunoglobulin**

**IV immunoglobulin** at a dose of 500mg/kg weekly (See 5.3.1 measles prophylaxis for rate of administration)
Consultant oncologist/haematologist must authorise use and usage must be in accordance with the Trust Policy to Implement Demand Management Plan for Immunoglobulin use. This is classified as a grey indication, approved for use at Alder Hey in advance of need (infection following allogenic HSCT).

- Consider reducing immunosuppression - decision to be made by Consultant Haematologist if lack of response to first line therapy i.e. PCR still positive after 2 weeks with PCR log value static or rising and lack of symptomatic response

- **2nd line** = **Consider adding intravenous ribavirin.** Requires consultant approval. Refer to section 5.3.2 (measles treatment) for dose and administration details. Contact pharmacy for advice in the case of renal or hepatic impairment

- Intravenous immunoglobulin (if not already receiving), see above

- Consider reducing immunosuppression - decision to be made by Consultant Haematologist

- In the absence of T cell recovery, consider donor lymphocyte infusion.

- Adenovirus specific Cytotoxic T lymphocytes (CTLs) have been described but are not likely to be available.

**Other considerations for treatment:**

- adenovirus with significant symptoms
- adenovirus in patients on high dose steroids

### 5.4.2 Adenovirus Pneumonia

The use of nebulised Ribavirin in adenovirus pneumonia is unproven. Currently recommendations are:

Adenovirus on NPA, clinically asymptomatic –

- Generally no treatment
- Request blood adenovirus PCR and viral faeces PCR which incorporates adenovirus.
- CXR

Adenovirus on NPA and clinically symptomatic -

- Request blood adenovirus PCR and viral faeces PCR which incorporates adenovirus.
- CXR
- Respiratory opinion
- Consider bronchoscopy/BAL
- Generally treat with cidofovir (see doses/administration details in 5.4.1 above)
5.5 CYTOMEGALOVIRUS

Cytomegalovirus used to be one of the major infectious complications during the post-engraftment period, but better prophylaxis has reduced its prevalence. CMV may still have a broad impact in transplantation even in the absence of overt disease. CMV disease including pneumonitis can be seen in other immune compromised patients. There are three main mechanisms of acquisition:

- Primary infection via donor cells in a previously seronegative recipient
- Reactivation of endogenous virus
- Reinfection with a different strain of CMV in a previously seropositive child

Interstitial pneumonitis is the most serious manifestation of CMV infection and carries a mortality of over 50% during the post-engraftment period. The clinical presentation includes fever, progressive dyspnoea with dry cough associated with hypoxia and pulmonary infiltrates. The respiratory team should be consulted.

During course of HSCT perform weekly monitoring; CMV PCR on blood. Ordered on the meditech as “blood virus PCR”, which incorporates adenovirus, CMV and EBV.

If coryzal: Send NPA for V-RESP. If negative consider NPA for CMV PCR (discuss with Consultant Haematologist)

If productive of sputum: Send sputum for CMV PCR and V-RESP as well as routine microbial culture.

In both scenarios repeat blood CMV PCR

A dry non-productive cough is a classical symptom of CMV pneumonitis. A physiotherapist assisted sputum collection (arrange via respiratory physiotherapists, ext 2430) should be arranged urgently and sent for CMV PCR. This may require sodium chloride 0.9% nebulisation to be prescribed.

Consider bronchoscopy for BAL if insufficient specimens or symptoms persist despite negative results.

5.5.1 Preemptive CMV therapy in HSCT

Stratify risk:

- Recipient and donor CMV seronegative = Low Risk
- Recipient or donor or both CMV seropositive = High Risk
- Excreting CMV (PCR positive) prior to HSCT = Very High Risk

Very High Risk Patients

- Consider delaying the transplant in very high risk patients
Very High Risk Patients where transplant cannot be delayed.

NB: Remember to discontinue aciclovir if any of the therapy below is initiated.

First choice - Ganciclovir

<table>
<thead>
<tr>
<th>CMV treatment for very high risk patients only</th>
<th>Age ≥ 1 month</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ganciclovir</td>
<td>5mg/kg/dose IV infusion every 12 hours up to day -1 of transplant, do not give on Day 0. Restart aciclovir and consider restarting ganciclovir (or foscarnet) after day 6 depending on clinical symptoms and viral load. Doses and duration at consultant’s discretion.</td>
<td>Handle as a cytotoxic Dilute to a maximum concentration of 10mg/ml in sodium chloride 0.9% or Glucose 5% and administer over one hour. Reduce dose in renal impairment, contact pharmacy for advice</td>
</tr>
</tbody>
</table>

Ganciclovir cannot be made on call. If there is any possibility this may be required after 4 pm contact the oncology or CIVAS pharmacist to arrange preparation. Remember to stop aciclovir

High risk patients; especially CMV mismatch.

Consider IV immunoglobulin 500mg/kg every 2 weeks post-transplant.

Low Risk Patients

No routine CMV prophylaxis required. For HSV prophylaxis refer to section 5.2.1.

Other Patients- discuss with consultant haematologist.

- PCR positive and asymptomatic- await repeat PCR-PCR positive and symptomatic treat as below; first choice IV Ganciclovir.

- Consecutive positive PCRs consider pre-emptive treatment with IV Ganciclovir-

First choice - Ganciclovir

<table>
<thead>
<tr>
<th>Pre-emptive CMV treatment</th>
<th>Age ≥ 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ganciclovir</td>
<td>Start Ganciclovir 5mg/kg/dose IV infusion every 12 hours for 14 days. See above for administration details. If the PCR becomes negative the drug may be stopped after 2 weeks and aciclovir restarted. If the PCR remains positive at the end of 2 weeks ganciclovir therapy then maintenance therapy should be continued at 5 mg/kg/dose IV infusion once a day. For rising PCR levels then full treatment doses might have to be used again. Add IV G-CSF (lenograstim) 5 microgram/kg as a single daily dose if</td>
</tr>
</tbody>
</table>
ganciclovir myelosuppression (neutrophil count < $1 \times 10^9$/L) to support counts. Consider valganciclovir in suitable patients at consultants discretion

**Second choice – convert to foscarnet**

If ganciclovir myelosuppression (neutrophil count < $1 \times 10^9$/L) continues despite IVIG-CSF support or if CMV viral load remains > $10^4$ copies/mL, clinical deterioration or failure to improve.

<table>
<thead>
<tr>
<th>Age ≥ 1 month</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Foscarnet</td>
<td>Foscarnet 60mg/kg/dose IV infusion every 8 hours for 14 days. Pre-hydrate at 125ml/m²/hr for 1 hour with 0.9% sodium chloride. Continue hydration alongside foscarnet infusion and for 1 hour afterwards. Dilute to 12mg/ml in 0.9% sodium chloride or 5% dextrose for administration via peripheral line. Can be given neat via central line.</td>
</tr>
<tr>
<td></td>
<td>If the PCR becomes negative the drug may be stopped after 2 weeks and aciclovir restarted. Dose must be individualised for renal function contact pharmacy for advice.</td>
</tr>
<tr>
<td></td>
<td>If the PCR remains positive at the end of 2 weeks of foscarnet therapy then maintenance therapy should be continued 90mg/kg as a single daily IV infusion. Monitor urea, electrolytes and LFTs daily.</td>
</tr>
<tr>
<td></td>
<td>For rising PCR levels then full treatment doses might have to be used again.</td>
</tr>
</tbody>
</table>

**3rd line**

Change to Cidofovir 5mg/kg/dose once a week for two weeks then every two weeks. Duration at consultant’s discretion - dependent on PCR response.

For administration details see section 5.4 adenovirus

**Oral Valganciclovir therapy**

Valganciclovir is the prodrug of ganciclovir. There is limited information on its use following transplantation but it has been used in both adult and paediatric patients. Patients may be given oral valganciclovir at the consultant’s discretion.

<table>
<thead>
<tr>
<th>CMV Prophylaxis for high Risk &amp; very high risk patients</th>
<th>Age ≥ 1 month</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valganciclovir</td>
<td>520mg/m² once daily (maximum 900mg)</td>
<td>Available as a 450mg tablet Liquid preparation available 250mg/5mL If Creatinine Clearance &lt;80ml/min adjust dose - contact Pharmacy for advice.</td>
</tr>
</tbody>
</table>
5.5.2 Treatment of CMV Pneumonitis

NB: Remember to discontinue aciclovir if any of the therapy below is initiated.

1st line

**Ganciclovir** 5mg/kg/dose IV infusion every 12 hours for 14 to 21 days followed by 5mg/kg/dose once daily for at least 3 to 4 weeks (or until day 100 after HSCT (duration at consultants discretion). See section 5.5.1 for administration details.

Add IV GCSF (lenograstin) 5 microgram/kg as a single daily dose if ganciclovir myelosuppression (neutrophil count < 1 x 10^9/L) to support counts

Plus

**Intravenous immunoglobulin** 500mg/kg/dose given as a single dose every other day for 2 weeks followed by once a week for the duration of ganciclovir treatment. See section 5.3.1 (measles prophylaxis for rate of administration)

Consultant must authorise use. Usage must be in accordance with the Trust Policy to implement Demand Management Plan for Immunoglobulin use. This is classified as a red (available at all times because of risk to life) indication.

2nd line

**Change to Foscarnet** if ganciclovir myelosuppression (neutrophil count < 1 x 10^9/L) continues despite IV GCSF support or if CMV viral load remains > 10^4 copies/mL, clinical deterioration or failure to improve.

Foscarnet 60mg/kg/dose IV every 8 hours for 14 days followed by 90mg/kg as a single daily dose for 2 weeks plus IV GCSF (duration at consultant’s discretion).

3rd line

**Change to Cidofovir** 5mg/kg/dose once a week for two weeks then every two weeks (duration at consultant’s discretion). For administration details see section 5.4.1 adenovirus

Treatment strategies should be reviewed and changes should be implemented based on clinical status and viral load.

In refractory cases with rising viral load despite treatment, consider CMV specific CTLs. These are anti-CMV T cells that have been shown to have some effect. CTL therapy is in an early stage of development and may not be available for many patients.
5.6 RESPIRATORY SYNCYTIAL VIRUS (RSV)

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 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.

Treatment Guidelines

Pre HSCT conditioning:

- **RSV on NPA** (naso-pharyngeal aspirate) – consider postponing the transplant if possible.

During conditioning / peri transplant

- **RSV on NPA** -

  - **Treat with intravenous ribavirin.** Requires consultant approval. Refer to section 5.3.2 (measles treatment) for dose and administration details. Contact pharmacy for advice in the case of renal or hepatic impairment.

- Consider giving IV immunoglobulin

<table>
<thead>
<tr>
<th>IV immunoglobulin</th>
<th>at a dose of 500mg /kg weekly (See 5.3.1 measles prophylaxis for rate of administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant must approve use and usage must be in accordance with the Trust Policy to Implement Demand Management Plan for Immunoglobulin use. This is classified as a grey indication, approved for use at Alder Hey in advance of need (Infection following allogeneic HSCT)</td>
<td></td>
</tr>
</tbody>
</table>
5.7 INFLUENZA

All immunocompromised children and their immediate families should have influenza immunisation annually (See Immunisation guidelines).

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.

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. Request VIR VRESP on Meditech.

Treatment
All immunocompromised children admitted to hospital because of suspected or proven severe influenza or its complications 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 pandemic H1N1 (2009) influenza who fail to improve after five days of oseltamivir treatment or deteriorate on after a reasonable period of treatment. (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152289698)

Consult 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. Guidance on reduced doses of Oseltamivir where there is a degree of renal failure is available from pharmacy and the BAPN website: (http://www.bapn.org/assets/clinical_standards/Antivirals%20in%20children%20with%20renal%20failure.pdf)

Dosing of Oseltamivir (Tamiflu)

<table>
<thead>
<tr>
<th>Treatment of influenza</th>
<th>Age 1 to 13 years - body weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year to under 3 years</td>
</tr>
<tr>
<td></td>
<td>3 year to under 7 years</td>
</tr>
<tr>
<td></td>
<td>7 year to under 13 years</td>
</tr>
<tr>
<td></td>
<td>&gt;13 years</td>
</tr>
<tr>
<td>&lt; 15 kg</td>
<td>15 to 23 kg</td>
</tr>
<tr>
<td>23 to 40 kg</td>
<td>&gt; 40 kg</td>
</tr>
<tr>
<td>Oral Oseltamivir</td>
<td>30mg twice daily</td>
</tr>
<tr>
<td></td>
<td>45mg twice daily</td>
</tr>
<tr>
<td></td>
<td>60mg twice daily</td>
</tr>
<tr>
<td></td>
<td>75mg twice daily</td>
</tr>
</tbody>
</table>

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 (seven-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

Infants below 12 months of age:

<table>
<thead>
<tr>
<th>Oral Oseltamivir</th>
<th>0 to 1 month*</th>
<th>&gt; 1 month to 3 months</th>
<th>&gt; 3 months to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/kg twice daily</td>
<td>2.5 mg/kg twice daily</td>
<td>3 mg/kg twice daily</td>
<td></td>
</tr>
</tbody>
</table>

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 an Oseltamivir suspension 6mg in 1 ml. In a Pandemic situation, contact Pharmacy to confirm strength of suspension.

Prophylaxis of Influenza

THE MOST IMPORTANT THINGS ARE:

1. Ensure maximal uptake of annual Influenza vaccine prior to flu season.
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

<table>
<thead>
<tr>
<th>Prophylaxis of influenza</th>
<th>Age 1 to 13 years - body weight:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year to under 3 years</td>
</tr>
<tr>
<td></td>
<td>&lt; 15 kg</td>
</tr>
<tr>
<td>Oral capsules Oseltamivir</td>
<td>30mg once daily</td>
</tr>
</tbody>
</table>

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 (seven-13 years of age).

Duration of prophylaxis:
10 days for post exposure prophylaxis; or for up to 6 weeks during an epidemic.
<table>
<thead>
<tr>
<th>Prophylaxis of influenza</th>
<th>Infants below 12 months of age:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 1 month*</td>
</tr>
<tr>
<td>Oral Oseltamivir</td>
<td>2 mg/kg once daily</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 month to 3 months</td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg once daily</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 months to 12 months</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg once daily</td>
</tr>
</tbody>
</table>

**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](http://www.hpa.org.uk)
5.8 **BK VIRUS**

BK virus has been associated with late-onset hemorrhagic cystitis after haematopoietic stem cell transplant.

BK virus infects almost all children in early childhood. Primary infection is generally asymptomatic but the virus can remain latent in many sites, most notably the kidney. BK virus can become reactivated and cause disease, if there is cellular immunodeficiency.

**Investigation**

If a child has hemorrhagic cystitis after haematopoietic stem cell transplant send urine for virus detection. Contact the microbiology laboratory (ext 2268) and ask them to send the urine for BK virus PCR and adenovirus detection. If the urine is positive a blood sample should be sent for BK PCR.

**Treatment.**

- Consider treatment if haemorrhagic cystitis persists with high BK viral load in urine and particularly if blood BK PCR positive,
- Increase IV fluids to ensure good urine output
- Keep platelets >50 and higher if still bleeding
- Urology input may be required
- Tranexamic acid can be considered but needs to be discussed with consultants increases VOD risk

- **Consider giving Cidofovir**

  Cidofovir 1 mg/kg once weekly. For administration details see section 5.4.1 adenovirus.

Monitor clinical symptoms and BK PCR in urine. Should get at least a one log reduction in urinary BK viral load after the first dose of cidofovir. The blood BK PCR should be followed closely and aim for a reduction in log value.
5.9 MANAGEMENT OF EPSTEIN-BARR-VIRUS (EBV) REACTIVATION

5.9.1 Background

- Reactivation of EBV may occur following transplant
- EBV reactivation may progress to a lympho-proliferative disease (LPD).
- LPD is a major cause of mortality.
- Patients are considered at higher risk following T cell depletion with ATG and Campath or after matched unrelated donor transplants or with reduced intensity conditioning.
- Pre-emptive treatment of EBV reactivation results in an improved prognosis.
- EBV reactivation is most commonly asymptomatic but may present as a rapidly progressing lymphadenopathy, acute respiratory illness or encephalopathy indicating the development of post-transplant lymphoproliferative disease.

5.9.2 Treatment of EBV Reactivation

All at risk transplant patients must have EBV PCR sent weekly until Day 100 or CD4+ recovery (>0.5 x 10^9/l). This is ordered on Meditech as "blood viral PCR", and also incorporates CMV and adenovirus. Continue monitoring for longer if prolonged immunosuppression or previously required treatment.

Clinical suspicion and EBV PCR rising - discuss with Consultant Haematologist and Infectious Diseases Consultant.

Any positive results should be repeated urgently and discussed with Haematology and Infectious Diseases Consultants.

Treatment regimen

Start treatment where there is evidence of clinical disease or in the presence of two positive PCRs and either an viral load > 40,000 copies/ml whole blood or a rapidly rising level

- Reduce or withdraw immunosuppression if possible and monitor closely for symptoms of Post transplant lympho-proliferative disease (PTLD)
- Treat with Rituximab

<table>
<thead>
<tr>
<th>EBV reactivation</th>
<th>Dose and infusion rates</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Rituximab</td>
<td>Rituximab 375mg/m^2 IV infusion weekly for up to 4 weeks dependent on weekly PCR results. Administer at a rate of 25 mg/hour, then increase after each subsequent 30 minutes by 25 mg/hour to a max of 200 mg/hour). (These are half the rates recommended by the manufacturer). If faster rates required contact the pharmacist for advice. Hydrocortisone should be written up PRN dose.</td>
<td>Premedicate with chlorphenamine and paracetamol 30 minutes prior to infusion. Rituximab is prepared in the CIVAS unit. The dose will be made in CIVAS to give a final concentration of 4mg/ml in sodium chloride 0.9% or dextrose 5%.</td>
</tr>
</tbody>
</table>
Monitoring:
- Renal profile. LFTs, CRP and immunoglobulins prior to each infusion.
- Check immunoglobulins and T and B subsets prior to first and 4th infusion.
- Monitor temperature, pulse, blood pressure prior to treatment and every 30 minutes for the first two hours then hourly for remainder of infusion.

Adverse effects:
Usually occur during the first infusion and include fever, chills, rigor, urticaria/rash, dyspnoea, bronchospasm, flushing, vomiting, nausea, headache and transient hypotension (consider stopping antihypertensives 12 hours prior to administration). For severe bronchospasm give IV hydrocortisone.

In the event of an infusion related adverse event, stop infusion and recommence at half the previous rate once symptoms have resolved. Incidence of infusion related side effects decreases with subsequent infusions.
- Following clearance of EBV after Rituximab therapy give IVIG replacement until B cell recovery (>0.5 x10⁹/l). (T and B subsets)
- Continue to monitor EBV PCR every 4 weeks until CD4 count >0.5 x10⁹/l

IV immunoglobulin at a dose of 500 mg/kg as a single dose every three weeks. (See 5.3.1 Measles prophylaxis for rate of administration) Consultant oncologist/haematologist must approve use and usage must be in accordance with the Trust Policy to Implement Demand Management Plan for Immunoglobulin use. This is classified as a red (available at all times because of risk to life) indication, (Low serum IgG levels following HSCT for malignancy)
6. REFERRALS FOR RESPIRATORY OPINION +/- BRONCHOSCOPY

For respiratory opinion please bleep the Respiratory SpR, Monday to Friday 9am to 5pm. There is no on-call or out-of-hours respiratory service. SpR opinion can usually be given the same day. Consultant opinion depends upon urgency and workload.

A respiratory opinion is not a prerequisite for a bronchoscopy referral.

Respiratory Consultants Dr Kevin Southern and Dr Calum Semple provide a bronchoscopy service by arrangement. Bronchoscopy is subject to their availability. There is no on-call or out-of-hour’s bronchoscopy service. Both may be contacted via switchboard. Early referrals will greatly ease the logistical problems of organising an urgent bronchoscopy and facilitate prompt results.

The oncology team will be responsible for organising investigations and checking results for samples to be taking in the oncology unit. The bronchoscopists will be responsible for organising investigations for samples taken in theatre.

From a practical point of view it is worth noting:

1. If a request is made in the early morning, an urgent bronchoscopy can often be arranged for the same day.

2. KS or CS should be contacted as soon as the need for bronchoscopy is identified, even if that means one member of the oncology team breaking away from the ward round to make the referral.

3. Parents/Guardians should remain on the ward. They need to be present to help with the history and give written consent!

4. The patient should be fasted on the presumption that we will be able to arrange bronchoscopy on the acute list that same day.

5. Ensure that when platelets are required they are ordered and ready.

Bronchoalveolar lavage (BAL) Samples and Results

The Respiratory Team will order the relevant BAL tests and liaise with Alder Hey Microbiology and Alder Hey Histology who will co-ordinate the distribution of samples.

Results of urgently requested investigations are often telephoned directly to wards by technical staff from reference laboratories. An isolated negative result may not be sufficient reason for cessation of a prescribed therapy. It is crucial that interpretation of BAL results is made by senior oncology staff in liaison with the respiratory and ID consultants.

Samples of BAL are sent for Cytology, Microbiology and Virology. Specific tests depend upon the history, presentation, radiology and other risk factors such as duration of immune suppression. These tests will be ordered by the Respiratory Team at the time of Bronchoscopy. Sample volume and quality may limit the tests that can be sent so labs must not be confused by redundant MEDITECH orders made in advance by others albeit with the best of intentions.
This table relates to tests done on BAL:

| Cytology | Gross cytology reports on any cellular inflammatory response and can *indicate* the presence of viral, bacterial and fungal infection.  
Specific stains can identify Aspergillus and Pneumocystis Jeroveci (formally known as *Pneumocystis carinii*).  
The presence of lipid laden macrophages on BAL *and* characteristic changes seen on bronchoscopy indicates reflux aspiration. |
|----------|---------------------------------------------------------------------------------------------------------------|
| Microbiology | Routine bacterial and fungal culture. (Alder Hey, Micro Lab)  
Extended culture for mycobacterium |
| Virology | Respiratory viral PCR  
Respiratory viral PCR (RLUH)  
Polymerase Chain Reaction  
CMV (RLUH)  
Other PCRs that can be arranged on request  
*Pneumocystis jiroveci* (formally known as *Pneumocystis carinii*)  
Aspergillus (Manchester Virology)  
Herpes Simplex Virus, EBV (RLUH) |

**Chasing Results.**

BAL tests will have been ordered as **urgent** and the labs will normally phone the results to the patient’s ward and the Alder Hey Microbiology Lab.  
Contact telephone numbers for “chasing results” when results are overdue are:

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Royal Liverpool Hospital, Cytology, Dr Turnbull 0151 706 4496</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology</td>
<td>Alder Hey internal 2268</td>
</tr>
<tr>
<td>Virology</td>
<td>Alder Hey internal 2268</td>
</tr>
</tbody>
</table>
7 PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP) PROPHYLAXIS AND TREATMENT

INTRODUCTION
Pneumocystis Jiroveci Pneumonitis (PCP) (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.

7.1 PROPHYLAXIS OF PCP

In Acute Lymphoblastic Leukaemia and certain solid tumours according to protocol.

Post HSCT from recovery of neutrophils (>0.5 x10⁹/l) and platelets (>50x10⁹/L) to Day 100 in autologous transplants and until the recovery of CD4+ cells (>0.5x10⁹/L) in allogeneic transplants.

Prophylaxis should also be considered in certain other patients at risk of long-term immunosuppression or neutropaenia.

1st Line Prophylaxis

COTRIMOXAZOLE

Cotrimoxazole is given TWICE DAILY on Saturday and Sunday only, as follows (unless otherwise specified in a Chemotherapy protocol).

<table>
<thead>
<tr>
<th>Surface area (m²)</th>
<th>Cotrimoxazole dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5</td>
<td>450 mg/m² twice daily - Saturday/Sunday only</td>
</tr>
<tr>
<td>0.5-0.75</td>
<td>240 mg twice daily - Saturday/Sunday only</td>
</tr>
<tr>
<td>0.76-1.0</td>
<td>360 mg twice daily - Saturday/Sunday only</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>480 mg twice daily - Saturday/Sunday only</td>
</tr>
</tbody>
</table>

Co-Trimoxazole must always be stopped one week before and during high dose methotrexate therapy

2nd Line Prophylaxis

Consider using nebulised Pentamidine or Oral Dapsone at Consultant oncologist/haematologist’s discretion.

NEBULISED PENTAMIDINE

Nebulised Pentamidine is less effective than Cotrimoxazole but may be indicated if the latter is not tolerated.

Dose: Child> 1 month – 300mg every 4 weeks. (Limited information on use in children < 5 years).

Note: Treatment with Salbutamol aerosol metered dose inhaler (dose as per BNF for children) via a large volume spacer may alleviate coughing in some patients. If
bronchoconstriction (wheeze) may be contributing to hypoxia and discomfort nebulised Salbutamol should be considered as per BNF for children.

**ORAL DAPSONE**

**Dose:** Refer to BNF for children  
**Note:** Should be avoided in G6PD deficiency. Other therapy options for prophylaxis to be discussed with medicines information.

**7.2 TREATMENT OF PCP**

Patients with suspected or proven pneumocystis pneumonia treated at Shared Care centres must be transferred to Alder Hey for further management.

**Diagnosis**

Clinical features of PCP 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 PCP have significant hypoxia that is often overlooked.

**Investigations**

- Oxygen saturation check (NOT blood gas analysis).
- Chest X-ray
- Bronchoscopy with PCR for *P. jiroveci*.

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.

**Bronchoscopy**

Bronchoscopy with bronchoalveolar lavage (BAL) is the diagnostic procedure of choice. The Bronchoscopy service should be contacted without delay.

(Respiratory Consultants Dr Kevin Southern and Dr Calum Semple provide a bronchoscopy service by arrangement. Bronchoscopy is subject to their availability. There is no on-call or out-of-hours bronchoscopy service. Both may be contacted via switchboard. Early referrals will greatly ease the logistical problems of organising an urgent bronchoscopy and facilitate prompt results).
Sensitivity for PCP in BAL ranges from 55%-97% and can be positive for 72 hours after treatment has been initiated. Treatment may need to start before bronchoscopy can be arranged. Treatment should not be delayed while awaiting the results of BAL.

BAL samples will be sent for other pathogens.

**Grading of severity of Pneumocystis Jiroveci Pneumonia**

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms &amp; signs</td>
<td>Exertional dyspnoea with or without cough and sweats</td>
<td>Dyspnoea on minimal exertion, occasional dyspnoea at rest, fever with or without sweats</td>
<td>Dyspnoea at rest, tachypnoea at rest, persistent fever, cough</td>
</tr>
<tr>
<td>Blood Oxygen</td>
<td>Normal $\text{SaO}_2/\text{PaO}_2$ falling on exercise</td>
<td>$\text{SaO}_2 &lt; 93%$, $\text{PaO}_2 60-80 \text{ mmHg}$</td>
<td>$\text{SaO}_2 &lt; 93%$, $\text{PaO}_2 &lt; 60 \text{ mmHg}$</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Normal or minor perihilar shadowing</td>
<td>Diffuse interstitial shadowing</td>
<td>Extensive interstitial shadowing with or without diffuse alveolar shadowing (“white out”) sparing costophrenic angles and apices</td>
</tr>
</tbody>
</table>


**DRUG THERAPY**

**1st Line Treatment**

**COTRIMOXAZOLE AND METHYLPREDNISOLON**

First line treatment includes IV Cotrimoxazole, with IV Methylprednisolone added for children with moderate or severe hypoxia ($\text{SaO}_2 < 93\%$ in air or $\text{PaO}_2 < 70$ mm Hg or an alveolar-arterial gradient of 135 mm Hg). To ensure maximum benefit Methylprednisolone should be started within 72 hours of initiating anti-pneumocystis treatment.

<table>
<thead>
<tr>
<th></th>
<th>Cotrimoxazole</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>IV for first 10 to 14 days then oral if tolerated</td>
<td>IV methylprednisolone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Convert to oral Prednisolone if tolerated</td>
</tr>
</tbody>
</table>
### Dose

| Day 1-5: | 1 mg/kg twice daily |
| Day 6-10: | 0.5 mg/kg twice daily |
| Day 11-21: | 0.5 mg/kg once daily |

If using oral prednisolone, do not exceed the maximum dose of 60mg per day. May be stopped earlier on day 16 at consultants discretion.

**Duration:** 21 days

**Monitoring:**
- Blood counts - 3 times/week
- Renal function - 2 times/week
- LFTs – 2 times/week

**Additional notes:**
- Mild rashes do not necessarily warrant discontinuation.
- Discuss with consultant.

**2nd Line Treatment**

Some patients on 1st line treatment may deteriorate before showing a response. This deterioration usually occurs between days 3-5 of initial treatment and is due to the marked pulmonary inflammation produced by PCP treatment. Poor response may also be seen in children with co-infections (e.g. CMV).

Second line treatment should be reserved for patients intolerant to Cotrimoxazole or who demonstrate clinical treatment failure after 5-7 days of Cotrimoxazole therapy. However when a poor response has been shown to 1st line therapy it is unusual to see a good response to alternative regimes.

**IV PENTAMIDINE** is the 2nd line treatment of choice. There is no clinical benefit in using combination treatment with Cotrimoxazole. However it takes 2-4 days for Pentamidine to reach therapeutic levels in the lungs so Cotrimoxazole therapy should be continued for this period.

**Dose:** Refer to BNF for children

**Administration:** Intravenous infusion over 60-90 minutes

**Duration:** 14-21 days

Daily monitoring: U&Es and creatinine, blood count, blood glucose and blood pressure. Baseline LFTs required followed by weekly monitoring.

**Additional note:** Arrhythmias may occur and an ECG may be indicated. Pancreatitis may also rarely occur.

**NEBULISED PENTAMIDINE** is inappropriate for the treatment of PCP since it may be associated with a fall in \( \text{PaO}_2 \), and IV therapy is more effective.
**3rd Line Treatment**

If there is no response to the above treatments the following therapy may be considered. (Further information is available from the Pharmacy Medicines Information Service).

- Dapsone and trimethoprim
- Clindamycin and primaquine
- Atovaquone

**Atovaquone** Data are limited for children; dosage is 30-40 mg/kg/day in 2 divided doses given orally with fatty foods. Infants aged 3-24 months might require a higher dosage of 45 mg/kg/day. Most adverse reactions occur after the first week of therapy. Skin rashes (10%-15%), nausea, and diarrhoea can occur.

**Clindamycin/primaquine** data for children are not available. Primaquine is contraindicated among patients with glucose-6-dehydrogenase deficiency associated with the possibility of inducing haemolytic anemia. The usual paediatric dose of clindamycin is 10 mg/kg every 6 hours, and the paediatric dose of primaquine equivalent to an adult dose of 30mg base (when used for malaria) is 0.3 mg/kg of the base daily. 21 days of treatment is recommended. Adverse reactions include skin rashes, nausea, and diarrhoea.

**Dapsone/trimethoprim** administered for 21 days is effective in treatment of mild-to-moderate PCP among adults (BI); data on toxicity and efficacy among children are not available. Dose for Dapsone is detailed in the BNF for children. The associated paediatric dose of Trimethoprim is 5 mg/kg every 8 hours. The primary adverse reaction is reversible neutropaenia; other reactions include skin rashes, elevated serum transaminases, anaemia, and thrombocytopenia.
8. CLOSTRIDIUM DIFFICILE AND OTHER GASTROINTESTINAL INFECTIONS.

8.1 GASTROINTESTINAL INFECTIONS – GENERAL PRINCIPLES

Investigation

Patients with diarrhoea should have stool samples sent for:

- Bacterial culture including microscopy for Cryptosporidium spp.
- Viral faeces PCR (incorporates adenovirus, sappovirus, rotavirus, norovirus and astrovirus) If patient has persistent diarrhoea and negative microbiology and virology, then test for Clostridium difficile toxin (CDT).

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

Investigation with imaging (e.g. AXR/USS) depends on clinical examination

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 rotavirus in the child’s stool.

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/Infectious Disease Consultant.

Retesting

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

Guidelines for retesting Oncology 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).

Following a negative virus test, one further virus test will be undertaken, upon request, within a 7 day period. Viruses such as rotavirus are shed in large amounts in stool and more frequent testing is generally unnecessary.
8.2 CLOSTRIDIUM DIFFICILE TOXIN POSITIVE PATIENTS

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

STOP systemic antibiotic therapy if possible.

It is unclear if *C. difficile* is a significant pathogen in paediatric oncology 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.

Neonates and infants less than 2 years,
The significance of *C. difficile* toxin in this age group is unclear. Colonization 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 colonized 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.

Oncology Children > 2years
*C. difficile* toxins are found in oncology 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 patients. Look for other pathogens (bacterial and viral).

When to test 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 yrs old will only be tested for CDT following discussion with one of the 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)

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.

Treatment.

STOP systemic antibiotic therapy if possible.

**FIRST LINE** Metronidazole orally

<table>
<thead>
<tr>
<th></th>
<th>Age 1 month to12 years</th>
<th>Age ≥ 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole Oral</td>
<td>7.5mg/kg (max. 400mg)</td>
<td>400mg every 8 hours</td>
<td>By mouth for 10 days.</td>
</tr>
<tr>
<td></td>
<td>every 8 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SECOND LINE Vancomycin orally

<table>
<thead>
<tr>
<th>Age 1 month to 5 years</th>
<th>Age 5 to 12 years</th>
<th>Age ≥ 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5mg/kg (maximum 62.5mg) four times daily</td>
<td>62.5mg four times daily</td>
<td>125mg four times daily</td>
<td>By mouth 10 days</td>
</tr>
<tr>
<td>Vancomycin ONLY to be used in cases where there is severe intolerance to Metronidazole or if not responding to Metronidazole. (Vancomycin therapy may lead to development of resistance in Enterococcus sp.)</td>
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<td></td>
</tr>
</tbody>
</table>

NB. Relapse is common and should be treated in the same way as the initial episode. 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 naso-gastric tube.

In severe colitis (with abdominal or radiological signs) not responding to oral vancomycin, high-dose oral vancomycin 10 mg/kg/dose (maximum 500mg) four times daily, if necessary administered via a nasogastric tube +/- intravenous metronidazole 7.5mg/kg/dose (maximum 500mg) three times daily is recommended.

The addition of oral rifampicin 10mg/kg/dose (maximum 300mg) twice daily or intravenous immunoglobulin 400mg/kg as a stat dose may also be considered. **Infectious diseases Consultant must authorise use. Usage must be in accordance with the Trust Policy to implement Demand Management Plan for Immunoglobulin use. This is classified as a blue indication.** (Treatment for patients in whom alternative therapies have been used where appropriate. Proof of efficacy for long-term therapy. Reduced use in times of shortage)

**Retesting for *C difficile* toxin (CDT)**

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 Infectious Diseases Consultant.
9. ANTI-INFECTIVE DRUG DOSES IN RENAL IMPAIRMENT

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

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

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

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

Note: Children with Downs syndrome and acute lymphoblastic leukaemia should receive ciprofloxacin during induction, Regimen B and C consolidation and both delayed intensifications. Give ciprofloxacin 10 mg/kg orally as a single dose once a day as per protocol.

The duration of ciprofloxacin should be discussed with the patient’s Haematology Consultant.
11. IMMUNISATION

The degree of compromise of immune function during and after treatment for malignant disease in childhood is determined by:

1. The nature of the disease.
2. The degree and nature of treatment induced immuno and myelosuppression.
3. Whether the spleen has been irradiated or removed.

Chemotherapy is the principle cause of the immunocompromised state, along with other treatment modalities e.g. radiotherapy, monoclonal antibody therapy and underlying malignancy e.g. Hodgkin’s Disease.

GENERAL PRINCIPLES

- Avoid all LIVE VACCINES in patients actively receiving chemotherapy and radiotherapy and for at least 6 months following completion of treatment.

- INFLUENZA VACCINE recommended annually in the autumn for all patients, family members and close contacts/carers. 2 letters will be given to all patients at this time, for the family and their General Practitioner.

11.1 STANDARD CHEMOTHERAPY

A. IMMUNISATIONS DURING AND UNTIL 6 MONTHS AFTER COMPLETION OF CHEMOTHERAPY

NO LIVE VACCINES

INFLUENZA VACCINE recommended annually in the autumn for all patients, family members and close contacts/carers.

We do not routinely administer any other non-live vaccines during this time, as it is likely that responses will be sub-optimal, although some patients may achieve protective antibody levels.

In case of higher than usual risk of tetanus exposure e.g. dirty, extensive wounds – please discuss with patient's consultant oncologist/haematologist.

B. IMMUNISATIONS 6 MONTHS AND LATER AFTER COMPLETION OF TREATMENT

IN ALL PATIENTS < 10 years give additional booster of:

- High dose diphtheria vaccine (D)
- Tetanus
- Acellular Pertussis
- IPV
- Hib
- Meningococcal C
- MMR
• 2 doses of Pneumococcal conjugate vaccine 1 month apart (Prevenar 13 ®)

Available vaccines
High dose Diphtheria, Tetanus, acellular Pertussis, IPV and Hib (Pediacel ®) DTaP/IPV/Hib
Or without Hib
High dose Diphtheria, Tetanus, acellular Pertussis and IPV (IPV®) DTaP/IPV
Men C (Neisvac C ® or Meningitec ®)
Hib/Men C (Menitorix ®)
MMR (Priorix ® or MMR II ®)

IN ALL PATIENTS >10 years give additional booster of
• Low dose diphtheria vaccine (d)
• Tetanus
• Acellular Pertussis
• IPV
• Hib
• Meningococcal Group C
• MMR
• 2 doses of pneumococcal conjugate vaccine 1 month apart (Prevenar 13 ®)

Available vaccines
Low dose diphtheria, Tetanus, acellular Pertussis, IPV (Repevax) dTaP/IPV
Low dose diphtheria, Tetanus, IPV (Revaxis) dT/IPV
Hib/Men C (Menitorix ®)
MMR (Priorix ® or MMR II ®)

Subsequent routine booster (e.g. Pre School) will not be necessary if it is scheduled to be given within 1 year of this additional dose.

Patients not previously vaccinated at all will require a complete course of the above immunisations.

Bacille Calmette Guerin (BCG)
The Department of Health has issued new guidelines for the use of BCG vaccination. (July 2005).

Routine BCG vaccination is not recommended for children aged 10-14 years

From 1st September 2005 BCG is offered to
• All infants (aged 0 to 12 months) living in areas where the incidence of TB is 40/100,000 or greater.
• All infants (aged 0 to 12 months) with a parent or grandparent who was born in a country where the incidence of TB is 40/100,000 or greater.
• New immigrants from a country where the incidence of TB is 40/100,000 or greater.
• Healthcare professionals should opportunistically identify unvaccinated children older than four weeks and younger than two years at increased risk of TB who would have qualified for neonatal BCG and provide Mantoux testing and BCG (if Mantoux negative).
11.2 SIBLING VACCINATIONS

Certain general principles apply to vaccination of siblings and other close family contacts of patients undergoing chemotherapy, radiotherapy and after completion of treatment.

Vaccines which can be used for siblings and other close family contacts as part of their own vaccination program:

- IPV
- Hib
- Acellular Pertussis
- Diphtheria (High dose (D) for <10 years old and Low dose (d) for >10 years old)
- Tetanus
- Meningococcal Group C
- Pneumococcal conjugate
- Human Papilloma virus
- MMR - even though this is a live vaccine, transmission has not been reported.

It is strongly recommended that siblings should be given MMR to reduce the patient’s risk of exposure to wild measles.

11.3 INTENSIVE CHEMOTHERAPY AND HAEMOPOIETIC STEM CELL TRANSPLANTATION/RESCUE (HSCT)

Following HSCT the degree and speed of immune function recovery is determined by:

1. The original disease.
2. The type of conditioning regimen.
3. Whether autologous or allogeneic haemopoietic stem cells were used and the source of these stem cells (bone marrow, peripheral blood, umbilical cord blood.)
4. The degree of HLA disparity between allogeneic donor and recipient (particularly the use of an unrelated or mismatched related donor.)
5. Whether T cell depletion (in vivo or in vitro) was performed.
6. The engraftment status.
7. The time elapsed since transplantation.
8. The presence or absence of chronic GVHD and of continued immunosuppressive treatment.

It is assumed that all intensive chemotherapy is followed by HSCT, so separate recommendations for intensive chemotherapy alone are not given.

GENERAL PRINCIPLES

As per all chemotherapy patients-

But applied until the patient is:

1. At least 12 months post HSCT.
2. Off all immunosuppressive treatment for at least 12 months.
3. CD4 + > 0.5 x 10^9/L
4. Has no evidence of active GVHD.
**Every Autumn administer Influenza vaccine**

This should be given every year for as long as the patient remains clinically immunocompromised or is considered to be at increased risk from influenza virus infection.

In patients who received standard chemotherapy/radiotherapy, influenza vaccine is recommended for 1 autumn/winter season following the completion of treatment.

**DECISIONS RE IMMUNISATION FOLLOWING ANY TRANSPLANT PROCEDURE MUST BE MADE BY THAT PATIENTS CONSULTANT**

**11.3.1 Autologous HSCT**

All children should be considered for a re-immunisation program as above, starting 12 months after autologous transplant.

The frequency and severity of loss of immunity appears to be lower in children who have received an autologous HSCT, but 70% patients may have absent tetanus antibodies after autologous HSCT and 50% after autologous PBSCT.

**11.3.2 Allogeneic HSCT**

**Background**

1. It is assumed that all children are at very considerable risk of losing their natural or immunisation-derived protective antibodies.

2. All children who have received an allogeneic HSCT should be considered for a re-immunisation programme.

3. It is difficult to predict the extent of immune recovery in individual children and to interpret specific antibody levels.

4. The use of live vaccines is **potentially dangerous** until the child has been off all immunosuppressive treatment for **at least 12 months** and has **no evidence** of active GVHD.

5. Chronic GVHD and its treatment cause considerable and often prolonged immunosuppression.

However, they are at high risk of infectious complications due to their immunosuppressed condition and the use of non-live vaccines is recommended if the patient is not receiving IVIg, even if it is considered the response may be sub optimal.

**HLA IDENTICAL DONOR, ALLOGENEIC OR SYNGENEIC HSCT**

The immune system post HSCT should be considered as <10 years old and therefore the high dose diphtheria should be used.

**AT 12 MONTHS POST HSCT administer**
• DTaP/Hib/IPV - at monthly intervals for 3 doses
• Men C - at monthly intervals for 2 doses
• HPV – Girls 12 years and older – 3 doses at 12, 13 and 18 months

**AT 15 MONTHS POST HSCT administer**
• Prevenar 13 ®(conjugate Pneumococcal vaccine) - 2 doses at monthly intervals

**AT 18 + 24 MONTHS POST HSCT administer**
• MMR
  2 doses should be given with a minimum 6 month interval. If measles outbreak, the 2nd dose can be given 4 weeks after the 1st.

**AT 24 MONTHS POST HSCT administer**
• Pneumovax (Polysaccharide Pneumococcal vaccine) – 1 dose
• Hib booster
• Men C booster

**ANY OTHER ALLOGENEIC HSCT /MUD**
Re-immunisation schedule as above starting 18 months post HSCT.

**Bacille Calmette Guerin (BCG)**
There is a lack of evidence about the safety of BCG immunisation after HSCT.
**IT SHOULD THEREFORE BE AVOIDED**

Varicella Zoster Vaccination is not routinely given post HSCT. This is currently under national discussion and may be recommended in the future.

**Wounds likely to engender a risk of tetanus after HSCT**

Patients suffering wounds likely to engender a risk of tetanus and who have not been immunised yet should be considered non-immune and should receive a first dose of tetanus vaccine.

Tetanus immunoglobulin (250-500 units IM) should also be given along with wound toilet and prophylactic antibiotics where applicable.

**11.4 MEASLES AND VARICELLA CONTACT AFTER HSCT**

**Significant contact** with varicella zoster.
Oral aciclovir as per section 5.1.1.is indicated until at least 12 Months post Sib/Auto SCT, 18 Months post other SCT and are 1 year off all immunosuppressive treatment.

Significant contact with measles

Passive immunisation with IVIG as per section 5.3.1 indicated for patients who have not yet received the second MMR in their revaccination schedule.
11.5 HYPOSPLENISM FOLLOWING HSCT

Patients who receive TBI are assumed to have functional hyposplenism.

Lifelong antibiotic prophylaxis with penicillin V is essential.

Patients with chronic GVHD may also have functional hyposplenism.

<table>
<thead>
<tr>
<th></th>
<th>Age 5 to 12 years</th>
<th>Age ≥ 12 years</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxyethylpenicillin orally</td>
<td>250 mg twice daily</td>
<td>500 mg twice daily</td>
<td>An hour before food or on an empty stomach</td>
</tr>
</tbody>
</table>

For patients less than 5 years of age give amoxicillin until the patient reaches 5 years old – then switch to Phenoxyethylpenicillin.

Amoxicillin – Age 1 month to 5 years: 125 mg twice daily

In the case of penicillin allergy - give erythromycin

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 2 years</th>
<th>Age 2 to 8 years</th>
<th>Age ≥ 8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin orally</td>
<td>125 mg once daily</td>
<td>250 mg once daily</td>
<td>500 mg once daily</td>
</tr>
</tbody>
</table>

11.6 HUMAN PAPILLOMA VIRUS VACCINE

HPV vaccine has been routinely recommended for girls aged 12-13 years (School year 8) since September 2008.

Girls with immunosuppression should be considered for HPV vaccine. However, individuals who are immunosuppressed may not develop a full antibody response. Clinical trials to study the effectiveness of HPV vaccination in immunosuppressed individuals are in progress.

Re-immunisation should be considered after treatment is finished and/or recovery has occurred.

GARDASIL Child 9–18 years 3 doses of 0.5 mL, the second 2 months and the third 6 months after the first dose
12 USE OF OCTENILIN WOUND GEL IN ONCOLOGY 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 Disease Team.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>AML</td>
<td>Acute Myeloid leukaemia</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>APLS</td>
<td>Advanced Paediatric Life Support</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette Guerin (TB vaccine)</td>
</tr>
<tr>
<td>BNFC</td>
<td>British National Formulary for Children</td>
</tr>
<tr>
<td>CIVAs</td>
<td>Central Intravenous Additive Service</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous system</td>
</tr>
<tr>
<td>CRP</td>
<td>C Reactive Protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>CVC</td>
<td>Central Venous Catheter</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein Barr Virus</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>FLAG</td>
<td>Fludarabine, cytarbine, GCSF</td>
</tr>
<tr>
<td>GCSF</td>
<td>Granulocyte Colony Stimulating Factor</td>
</tr>
<tr>
<td>GVHD</td>
<td>Graft versus host disease</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenza type b (vaccine)</td>
</tr>
<tr>
<td>HSCT</td>
<td>Haemopoeitic stem cell transplantation/rescue (BMT, PBSCT, umbilical cord blood transplantation)</td>
</tr>
<tr>
<td>HLH</td>
<td>Haemaphagocytic Lymphohistiocytosis</td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes Simplex Virus</td>
</tr>
<tr>
<td>IPV</td>
<td>Inactivated polio vaccine</td>
</tr>
<tr>
<td>LCH</td>
<td>Langerhans cell Histiocytosis</td>
</tr>
<tr>
<td>MeningoC</td>
<td>Meningococcal group C conjugated vaccine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles, mumps, rubella vaccine</td>
</tr>
<tr>
<td>MSSA</td>
<td>Methicillin – Sensitive Staph. Aureus</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin – Resistant Staph. Aureus</td>
</tr>
<tr>
<td>NPA</td>
<td>Naso-Pharyngeal Aspirate</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral polio vaccine</td>
</tr>
<tr>
<td>PBSCT</td>
<td>Peripheral blood stem cell transplantation/rescue</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PTLD</td>
<td>Post-transplant lymphoproliferative disease</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial virus</td>
</tr>
<tr>
<td>SCID</td>
<td>Severe Combined Immune Deficiency</td>
</tr>
<tr>
<td>SDD</td>
<td>Selective Decontamination of the Digestive Tract</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of inappropriate antidiuretic secretion</td>
</tr>
<tr>
<td>TBI</td>
<td>Total Body Irradiation</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella Zoster Virus</td>
</tr>
</tbody>
</table>
**MANAGEMENT AND PREVENTION OF INFECTION IN ONCOLOGY PATIENTS**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author(s)</th>
<th>Status</th>
<th>Comment(s)</th>
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<td>1-5</td>
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<td>Caroline Osborne, Dr Barry Pizer</td>
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**Review and Revision(s) Log**

*Record of revision(s) made to guidelines since Version 1*

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**Version Control Table**

**Key search words:** Management, Prevention, Infection, Oncology