Antifungal therapy guidelines

Background
Invasive fungal infections (IFI) can cause significant morbidity and mortality among patients with haematological malignancies. There is good evidence for the use of antifungal prophylaxis in high risk patients. This guideline aids clinical decision making about which group of patients should receive prophylaxis and the choice of antifungal agents.

The possibility of invasive fungal infection must be considered in patients with neutropenic fever, which is persistent despite broad spectrum antibiotic treatment. The diagnostic and treatment strategy in these patients should be discussed with the ID/Microbiology team.

This document is divided into seven sections:

1. Risk stratification
2. Prophylaxis
3. Treatment/Diagnosis
4. Treatment: Patients NOT on mould-active prophylaxis. First line, second line.
5. Treatment: Patients ON mould-active prophylaxis. First line, second line.
6. Ongoing management
7. Drug interactions

Section 1: Risk stratification

Risk stratification and prophylactic agents
Some patients are at higher risk of invasive fungal infection and should receive antifungal prophylaxis.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient group</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• Acute myeloid leukaemia including acute promyelocytic leukaemia (APML) receiving intensive chemotherapy.</td>
<td>Mould-active prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Neutropenic myelodysplastic syndrome (MDS) being considered for bone marrow transplant (BMT).</td>
<td>1st line: Voriconazole</td>
</tr>
<tr>
<td></td>
<td>• Allogeneic BMT: including the following BMT conditioning regimes: Myeloablative, Cord blood, Single antigen mismatch, Haploidentical, or any patient with previous history of Aspergillus.</td>
<td>2nd line: Posaconazole</td>
</tr>
<tr>
<td></td>
<td>• Acute/Chronic graft versus host disease (GvHD): steroid dependent or refractory, grade 3 or 4.</td>
<td>Alternative agents see below</td>
</tr>
<tr>
<td>Low</td>
<td>• Allogeneic BMT: Reduced intensity conditioning (RIC) with no previous history of aspergillus</td>
<td>Anti-candida prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Lymphoma: Intensive/dose escalated therapy.</td>
<td>1st line: Fluconazole 50mg od.</td>
</tr>
<tr>
<td></td>
<td>• Autologous BMT.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Myeloid malignancy: with neutropenia(&lt;1.0)</td>
<td></td>
</tr>
<tr>
<td>Very</td>
<td>• Lymphoma: standard therapy.</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>low</td>
<td>• Chronic myeloid leukaemia (CML).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other myeloproliferative malignancy</td>
<td></td>
</tr>
</tbody>
</table>

Commencement and duration of prophylaxis for patient groups identified above:
• Inpatient chemotherapy/BMT: Neutropenia<0.5 or Prednisolone≥20mg/day, until count recovery (N > 1.0) or end of Prednisolone course.   
• Outpatients: On commencement of chemotherapy or Prednisolone≥20mg/day until end of course.
Section 2: Prophylaxis

First line
Voriconazole (for patients with expected treatment duration <6 months)
Oral administration is first line. Only consider intravenous administration if oral route is unavailable or absorption may be impaired and benefits outweigh risks.

<table>
<thead>
<tr>
<th>Voriconazole prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong> (Tablets/ Oral Suspension)</td>
</tr>
</tbody>
</table>
| Body weight > 40 kg:  
  Loading dose 400 mg 12 hourly for 2 doses, then maintenance 200 mg bd. |
| Body weight <40 kg:  
  Loading dose 200 mg 12 hourly for 2 doses, then maintenance 100 mg bd. |
| **Intravenous infusion** |
| Loading dose 6mg/kg 12 hourly for 2 doses then maintenance 4mg/kg bd. |
| If not tolerated, dose can be reduced to 3mg/kg bd.  
  Maximum rate of 3 mg/kg per hour. |

Refer to IV drug monograph

Notes:

Drug interactions
- Voriconazole is associated with many clinically significant drug interactions, of note Busulfan. See Drug interaction section.

Oral
- Use oral Voriconazole unless impaired absorption (e.g. severe mucositis), in which case IV initially.
- Tablets are to be taken at least one hour before, or one hour after a meal.
- Oral suspension is to be taken at least one hour before, or two hours after a meal.
- Visual disturbance may occur throughout the course of treatment.

Intravenous infusion
- Electrolyte disturbances such as hypokalemia, hypomagnesaeemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation or during Voriconazole therapy.
- The vehicle can accumulate in patients with moderate or severe renal impairment (creatinine clearance <50mg/ml), therefore renal function should be monitored closely. Consideration should be given to change to oral Voriconazole.

Therapeutic drug monitoring (TDM) with voriconazole prophylaxis should be considered for
- Suspected toxicity associated with high plasma concentration, e.g. visual disturbance
- Patient taking concurrent medications that affect CYP450 enzymes metabolism

Dose Adjustment
- Trough level < 1 mg/L: increase dose by 1mg/kg bd rounded to tablet size.
- Trough level 1mg/L – 5 mg/L: continue current dose.
- Trough level > 5mg/L: consider discontinuation and recommencement at lower dose.
Second line
Posaconazole
Oral administration is first line. Only consider intravenous administration if oral route is unavailable or absorption may be impaired and benefits outweigh risks.

<table>
<thead>
<tr>
<th>Posaconazole prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
</tr>
<tr>
<td><em>Tablets</em>: Loading dose 300mg 12 hourly for 2 doses, followed by 300mg od.</td>
</tr>
<tr>
<td>Taken with or without food.</td>
</tr>
<tr>
<td><em>Suspension</em>: 200mg TDS. Taken with or immediately after food.</td>
</tr>
<tr>
<td><strong>Intravenous infusion (Non-formulary)</strong></td>
</tr>
<tr>
<td>Loading dose 300mg 12 hourly for 2 doses, followed by 300mg od.</td>
</tr>
<tr>
<td>Administer via central line, over 90 mins, if a central line is not available, a single infusion may be given peripherally over 30 mins.</td>
</tr>
<tr>
<td>Refer to IV drug monograph</td>
</tr>
</tbody>
</table>

Notes:
- Where possible, Posaconazole tablets should be used in preference to the suspension because the tablets have a higher bioavailability.
- The suspension is not interchangeable with the tablets on a milligram-for-milligram basis, consult a pharmacist for advice.
- Posaconazole has the potential for a number of drug interactions, consult a pharmacist for advice.
- For intravenous formulation, the vehicle can accumulate in patients with moderate or severe renal impairment (creatinine clearance < 50mg/ml), therefore renal function should be monitored closely.
- In the setting of possible malabsorption or other drug interaction, please discuss with microbiology.
- Therapeutic drug monitoring (TDM) for Posaconazole is not recommended.

Indications for alternative prophylaxis
Micafungin prophylaxis: Patients intolerant of azoles (including patients on vinca alkaloids).
Ambisome® prophylaxis: Mainly for use in ALL induction.

<table>
<thead>
<tr>
<th>Micafungin prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose:</td>
</tr>
<tr>
<td>Body weight &gt; 40kg: 50mg IV od</td>
</tr>
<tr>
<td>Body weight ≤ 40kg: 1mg/kg/day IV</td>
</tr>
<tr>
<td>Administer by infusion over 1 hour.</td>
</tr>
<tr>
<td>Refer to IV drug monograph.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liposomal amphotericin B/Ambisome® prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose: 7.0mg/kg IV weekly.</td>
</tr>
<tr>
<td>Administer by infusion over 2 hours.</td>
</tr>
<tr>
<td>Indication: Mainly for use in ALL induction</td>
</tr>
<tr>
<td>Refer to IV drug monograph.</td>
</tr>
</tbody>
</table>

Notes:
- Test doses are required.
- There are serious risks if different brands are confused therefore please state the following on any prescription for amphotericin: Patient weight in Kg, indication and dose used in mg/Kg, brand name as well as generic name. (Select with care when prescribing on EPR!).
Section 3: Diagnosis

When to add antifungal treatment
Current approaches are empiric treatment (fever driven), or pre-emptive treatment (diagnostic driven) or a combination of the two depending on the availability of diagnostic tools.

Diagnostic strategies
Neutropenic patients, with fever persisting at 96 hours despite broad spectrum antibiotic treatment.

- Obtain CT thorax (and sinuses).
- If radiological features are suggestive of invasive fungal disease consider:
  - Early bronchoscopy with BAL and commence empirical antifungal therapy. The 'BAL Immunocompromised Careset' should be used for requesting on EPR, and samples should be sent for microscopy and culture, respiratory virus PCR, fungal microscopy and culture, and cytology for PCP and fungi. Biopsies (lung, other tissue) should be sent for microscopy and culture, fungal microscopy and culture, and histology. Additional antigen and molecular studies (galactomannan, beta-D glucan and fungal PCR) should be discussed with the ID/micro team
  - Early discussion with chest medicine, ENT, radiology and infectious diseases/ microbiology as appropriate is advised.
- In the absence of radiological features of invasive fungal infection no empirical antifungal therapy is required and alternative causes for persisting fever should be sought. Consider repeat imaging after one week.

Section 4: Treatment

Patients NOT on mould-active prophylaxis.

First line

<table>
<thead>
<tr>
<th>Voriconazole treatment</th>
<th>Intravenous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (Tablets/ Oral Suspension)</td>
<td>Loading dose 6mg/kg 12 hourly for 2 doses then maintenance 4mg/kg bd.</td>
</tr>
<tr>
<td>Body weight &gt; 40 kg: Loading dose 400 mg 12 hourly for 2 doses, then maintenance 200 mg bd.</td>
<td>If not tolerated, dose can be reduced to 3mg/kg bd. Maximum rate of 3 mg/kg per hour.</td>
</tr>
<tr>
<td>Body weight &lt;40 kg: Loading dose 200 mg 12 hourly for 2 doses, then maintenance 100 mg bd.</td>
<td>Refer to IV drug monograph</td>
</tr>
</tbody>
</table>

Notes:

Drug interactions
- Voriconazole is associated with many clinically significant drug interactions, of note Busulfan. See Drug interaction section.

Oral
- Use oral Voriconazole unless impaired absorption (e.g. severe mucositis), in which case IV initially.
- Tablets are to be taken at least one hour before, or one hour after a meal.
- Oral suspension is to be taken at least one hour before, or two hours after a meal.
- If the patient is unable to tolerate treatment at the higher maintenance doses, reduce the dose by 50 mg steps back to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg), or consider an alternative agent.
That visual disturbance may improve throughout the course of treatment.

**Intravenous infusion**
- Electrolyte disturbances such as hypokalemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation or during Voriconazole therapy.
- The vehicle can accumulate in patients with moderate or severe renal impairment (creatinine clearance <50mg/ml), therefore renal function should be monitored closely. Consideration should be given to change to oral Voriconazole.

Therapeutic drug monitoring (TDM) for Voriconazole is recommended if there is concern as to whether the patient is responding to treatment. TDM is only of benefit after 5 days of treatment.
- Trough level < 1 mg/L: increase dose by 1mg/kg bd rounded to tablet size.
- Trough level 1mg/L – 5 mg/L: continue current dose.
- Trough level > 5mg/L: consider discontinuation and recommencement at lower dose.

**Second line**

Decisions regarding selection of an agent other than Voriconazole for initial empiric antifungal therapy should be made based on clinical and patient specific grounds. The choice of agent is at the discretion of the responsible consultant.

If there is concern about possible mucormycosis then Ambisome® should be used and the dose should be discussed with ID/microbiology. Previous intolerance to Voriconazole may necessitate initial use of an echinocandin; in the OUH Micafungin is the agent on the formulary.

<table>
<thead>
<tr>
<th>Liposomal amphotericin B/Ambisome® treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose: 3mg/kg IV daily initially (max 5mg/kg daily unless otherwise determined by Consultant Haematologist and ID/Microbiology consultant).</td>
</tr>
<tr>
<td>Administer by infusion over 30-60mins.</td>
</tr>
<tr>
<td>Refer to IV drug monograph.</td>
</tr>
</tbody>
</table>

**Notes:**
- Before a new course of Ambisome® patients must first receive a test dose of 1mg over 10 minutes. Stop the infusion and observe the patient for 30 minutes. The infusion of Ambisome® dose can only be continued if there have been no severe allergic or anaphylactic/anaphylactoid reactions
- There are serious risks if different brands are confused therefore please state the following on any prescription for amphotericin: Patient weight in Kg, indication and dose used in mg/Kg. Brand name as well as generic name. (Select with care when prescribing on EPR!)

<table>
<thead>
<tr>
<th>Micafungin treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose: Body weight &gt; 40 kg: 100 mg IV once daily (increased to 200 mg daily if inadequate response) (higher doses of 150mg to 300mg daily can be used)</td>
</tr>
<tr>
<td>Body weight &lt;40 kg: 2 mg/kg IV once daily (increased to 4 mg/kg daily if inadequate response)</td>
</tr>
<tr>
<td>Administer by infusion over 1 hour</td>
</tr>
<tr>
<td>Refer to IV drug monograph.</td>
</tr>
</tbody>
</table>
Section 5: Treatment

Patients ON mould-active prophylaxis, e.g. Posaconazole

First line
(The choice of agent is at the discretion of the responsible consultant)

<table>
<thead>
<tr>
<th>Micafungin treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose: Body weight &gt; 40 kg: 100 mg IV once daily (increased to 200 mg daily if inadequate response) (higher doses of 150mg to 300mg daily can be used). Body weight &lt;40 kg: 2 mg/kg IV once daily (increased to 4 mg/kg daily if inadequate response). Administered by infusion over 1 hour</td>
</tr>
</tbody>
</table>

Refer to IV drug monograph.

<table>
<thead>
<tr>
<th>Liposomal amphotericin B/Ambisome® treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous infusion</strong></td>
</tr>
<tr>
<td>Dose: 3mg/kg IV daily initially (max 5mg/kg daily unless otherwise determined by Consultant Haematologist and ID/Microbiology consultant). Administer by infusion over 2 hour.</td>
</tr>
</tbody>
</table>

Refer to IV drug monograph.

Notes:
- Before a new course of Ambisome® patients must first receive a test dose of 1mg over 10 minutes. Stop the infusion and observe the patient for 30 minutes. The infusion of Ambisome® dose can only be continued if there have been no severe allergic or anaphylactic/anaphylactoid reactions
- There are serious risks if different brands are confused therefore please state the following on any prescription for amphotericin: Patient weight in Kg, indication and dose used in mg/Kg. Brand name as well as generic name. (Select with care when prescribing on EPR!).

Section 6: Ongoing management

Stopping antifungal therapy
- The on-going administration of antifungal therapy should be subject to regular review.
- The diagnosis of invasive fungal infection is unlikely in the absence of radiological infiltrates or positive culture results.
- Antifungal therapy can be discontinued in patients with fever resolution, recovering neutrophils and no subsequent evidence of invasive fungal infection

Continuing anti-fungal therapy
- The on-going administration of antifungal therapy should be subject to regular review.
- Patients with evidence supporting a diagnosis of invasive fungal infection (imaging, histological, culture) should continue treatment. Modification to treatment may be made on the basis of culture, identification and sensitivities.
- Duration of treatment, particularly for invasive mould infections is difficult to precisely define. Treatment of proven or probable aspergillosis should continue until there is clear clinical improvement, accompanied by radiological response and improvement in immune status with an expectation that treatment will continue for a minimum of 6 weeks. Longer treatment durations may be appropriate and should be considered on an individual basis.
- Discharge: Supply 1 week TTO and ensure review in clinic/DTU within that time period.
Future prophylaxis

- Patients who have undergone treatment for invasive fungal (mould) infection are candidates for secondary prophylaxis if they are to undergo further therapy resulting in significant neutropenia or immunosuppression.

**Section 7: Drug interactions**

Antifungals are associated with a number of potential drug interactions, *this list is not conclusive*; please consult the pharmacist for advice.

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Affected Drug(s)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>Ciclosporin, tacrolimus, sirolimus, statins, Rifampicin, Midazolam, Phenytoin (and other anticonvulsants), busulfan, thiopeta</td>
<td>Ciclosporin/Tacrolimus dose adjustments may be required.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Ciclosporin, Phenytoin, rifabutin, rifampicin, efavirenz, busulfan, thiopeta</td>
<td>Ciclosporin/Tacrolimus dose adjustments may be required.</td>
</tr>
<tr>
<td>Ambisome</td>
<td>Increased risk of nephrotoxicity when given with other nephrotoxic drugs i.e. ciclosporin, tacrolimus, aminoglyclosides. Can increase cardiotoxicity of digoxin due to Ambisone-induced hypokalaemia. Increased risk of hypokalaemia when used with corticosteroids and/or diuretics</td>
<td>Monitor renal function and electrolytes including potassium and magnesium levels.</td>
</tr>
<tr>
<td>Micafungin</td>
<td>May increase levels of: Sirolimus, nifedipine or itraconazole</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Warfarin, ciclosporin, tacrolimus, rifabutin, phenytoin, sulphamylureas, theophylline</td>
<td></td>
</tr>
</tbody>
</table>

**Audit:**

1. Dispensing records of all patients receiving broad spectrum antifungal treatment for > 5 days will be maintained by the Pharmacy team.
2. Annual audit of all patients with positive fungal cultures.

OUH Trust approval: Antimicrobial Steering Group, July 2015

**References:**

Freifeld et al, Clinical Infectious Diseases 2011;52(4):e56–e93  
Fleming et al, Internal Medicine Journal 44 (2014)  
Hamada et al, J Infect Chemother 2013, 19:381-392
Department of Clinical Haematology

Authors:
Dr Stephen Chapman (Respiratory Consultant)
Sandy Hayes (Quality manager)
Dr Katie Jeffery (Microbiology Consultant)
Dr Elham Khatamzas (ID/micro SpR)
Dr Jaimal Kothari (Haematology Consultant)
Nadjoua Maouche (Haematology pharmacist).
Dr Andy Peniket (Haematology Consultant)
Dr Karthik Ramasamy (Haematology Consultant)
Prof. Vanderson Rocha (Haematology Consultant)
Prof. Paresh Vyas (Haematology Consultant)

Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandy Hayes, Quality manager</td>
<td>New document</td>
<td>May 2015</td>
<td>1.0</td>
<td>May 2017</td>
</tr>
<tr>
<td>Nadjoua Maouche</td>
<td>Audit Prophylactic Ambisome dose reduced to 7 mg/kg</td>
<td>July 2015</td>
<td>1.1</td>
<td>May 2017</td>
</tr>
<tr>
<td>Sandy Hayes, Quality manager</td>
<td>OUH approval</td>
<td>Sept 2015</td>
<td>1.2</td>
<td>May 2017</td>
</tr>
<tr>
<td>Nadjoua Maouche, Haematology Pharmacist.</td>
<td>Addition of Busulfan voriconazole interaction</td>
<td>Dec 2015</td>
<td>1.3</td>
<td>May 2017</td>
</tr>
<tr>
<td>Sandy Hayes, Quality manager</td>
<td>Clarification of BMT risk stratification, addition of APML</td>
<td>March 2016</td>
<td>1.4</td>
<td>May 2017</td>
</tr>
<tr>
<td>Cheuk-kie Jackie Cheung</td>
<td>Substitution of posaconazole with voriconazole as 1st line prophylaxis</td>
<td>March 2017</td>
<td>1.5</td>
<td>May 2017</td>
</tr>
</tbody>
</table>