Haematology Antifungal Guidelines

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Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Changed wording of Ambisome to Amphotericin B liposomal (AmBisome or Tillomed liposomal) Updated turn around time information for galactomannan and beta-d glucan Changed antifungal treatment option choices into a tabular format
Summary of evidence base this guideline has been created from:	Expert committee reports or opinions and/or clinical experiences of respected authorities
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

Clinical Guideline for the Prophylaxis and Treatment of Fungal Infections in Haematology Patients

Introduction

Patients with prolonged neutropenia (ie. those who have an absolute neutrophil count of <0.5 x10^9/L or those patients who are receiving chemotherapy regimens which are expected to result in this degree of neutropenia within the following 2-3 days) are at risk of developing both localised fungal infections (mainly mucocutaneous Candida species), and invasive fungal infections (IFI), usually of the respiratory system and sinuses (mainly Aspergillus and Mucor species). Prophylaxis with azole antifungal agents can reduce the risk of Candida infections. Some of the newer third generation azole antifungals have a broader spectrum of activity against moulds including Aspergillus.

- All patients with neutropenic fever who are at risk of invasive fungal infections (see Table 2) should have a chest x-ray (CXR). The criteria for neutropenic sepsis are shown in Table 1. Refer to the Guideline for the Management of Neutropenic Sepsis in Haematology here for more information.
- High resolution CT scanning (HRCT) should be performed if there is CXR shadowing suspicious of fungal infection, if there is unremitting fever following 48-72 hours of broad spectrum antibiotics with no obvious cause or high CRP > 200.
- Galactomannan and beta D glucan screening samples should also be sent for patients with unremitting fever before starting antifungal treatment.

Table 1. Criteria for treatment of neutropenic sepsis. Patients should meet criteria 1 AND 2 or 3

Criteria for Treatment Criteria 1 AND 2 or 3		Comments
1.	**Presence of neutropenia i.e. neutrophils < 1.0 x 10^9/L** **OR** **suspected neutropenia** **OR** **day 0 onwards of autograft or allograft**	**If patient admitted from home and history of recent chemotherapy within past 4 weeks treat as neutropenic sepsis without waiting for full blood count (FBC) result (if not neutropenic downgrade treatment later).** **Some patients may be neutropenic due to their blood disorder without any prior exposure to chemotherapy.**
2.	**Presence of fever**	i.e. temperature ≥ 38°C on one occasion Or a clear history of pyrexia measured by patient prior to admission. If temperature is 37-38°C, repeat after 1 hour to see if the above criteria for treatment are met.
3.	**Clinical signs of sepsis / obvious focus of infection**	i.e. tachycardia, low blood pressure, tachypnoea, chest signs, etc.

Antifungal Prophylaxis According to Risk of Invasive Fungal Infections

Haematology patients can be stratified into three risk categories as shown in the table below, according to the intensity of treatment they are receiving, likely duration of neutropenia and whether or not they have had a previous episode of probable or confirmed invasive fungal infection.

Fungal biomarkers

1,3-βeta-D-glucan (BDG)

BDG is a carbohydrate moiety in the cell walls of many fungi, and is produced in vivo during infection by several important fungal organisms (Aspergillus spp, Candida spp, and P jirovecii, **but not** by Cryptococcus spp or species of the order Mucorales). BDG can be detected from serum.

This test makes use of the high negative predictive value (i.e., excluding infection), but positive results will always necessitate further investigations. False positive results can occur, resulting from gauze dressings, dialysis, and some bacteria.

The test is also useful for diagnosis of pneumocystis pneumonia, especially when a respiratory sample cannot be obtained.

Please note the usual turnaround time for BDG tests is 24 hours Monday to Friday, samples sent at a weekend will be processed on a Monday.

Galactomannan

Galactomannan (aspergillus antigen) detection in body fluids is more sensitive than culture for diagnosis of invasive aspergillosis. In serum, the sensitivity is variable, with the highest sensitivity in patients with haematological disease who are not on anti-mould prophylaxis. Additionally, galactomannan detection can be performed on BAL specimens for invasive pulmonary aspergillosis.

Please note the usual turnaround time for Galactomannan tests is 24 hours Monday to Friday, samples sent at a weekend will be processed on a Monday.

Sputum galactomannan testing can be performed but it is sent to an outside laboratory so turnaround time is longer and there are no clinically validated cut-offs for interpretation of results

Table 2. Antifungal risk categories and recommended prophylaxis:

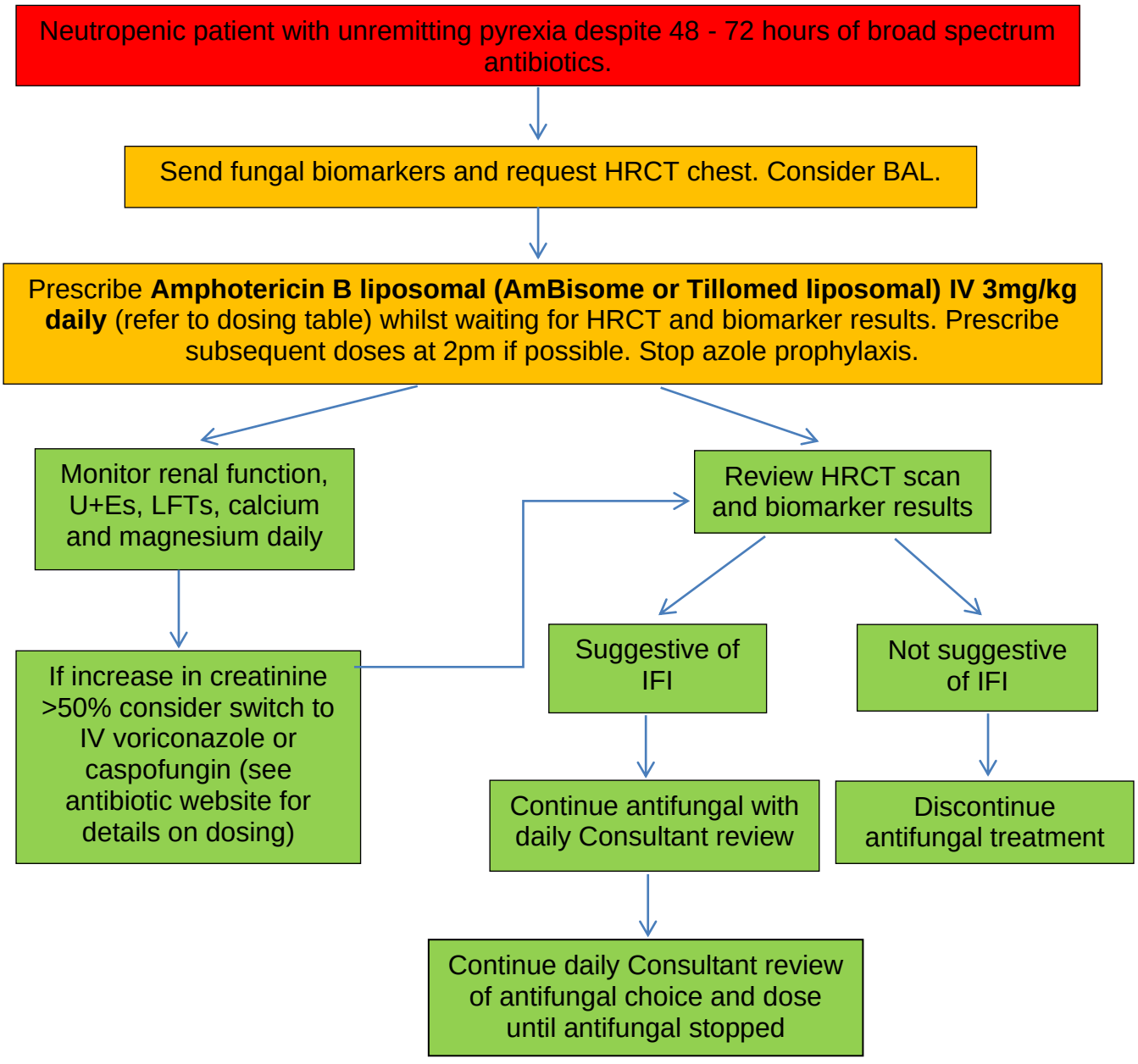
Antifungal Risk Category		
High Risk Patients IV mould active prophylaxis	**High Risk Patients PO mould active prophylaxis**	**Low Risk Patients PO Candida prophylaxis**
• ALL induction chemotherapy including dexamethasone, likely to have prolonged period of neutropenia. Azoles contraindicated due to vincristine interactions – use Amphotericin B liposomal (AmBisome or Tillomed liposomal) prophylaxis • Previously documented confirmed or highly probable IFI undergoing intensive chemotherapy likely to result in prolonged period of neutropenia (>10 days) eg. AML induction chemotherapy • Allogeneic stem cell transplant (SCT) patients	• Intensive or out-patient AML chemotherapy • NB. Azoles must NOT be given to patients receiving Gemtuzumab ozogamicin (Mylotarg) or quizartinib (AC220) – use Amphotericin B liposomal (AmBisome or Tillomed liposomal) prophylaxis • Patients receiving >10mg prednisolone for GvHD • Autologous SCT for the following conditioning regimens: Benda-EAM, BEAM, Etop/Melph	• Autologous SCT EXCLUDING Benda-EAM, BEAM, Etop/Melph • Intensive or out-patient chemotherapy for NHL
Recommended Antifungal Prophylaxis		
ALL induction • Amphotericin B liposomal (AmBisome or Tillomed liposomal) IV 100mg OD on Mon/Wed/Fri Previous IFI, AML induction or Allogeneic SCT • Amphotericin B liposomal (AmBisome or Tillomed liposomal) IV 100mg OD on Mon/Wed/Fri, if not tolerated discuss with Microbiology • Continue until absolute neutrophil count (ANC) >0.5x10^9/L	• Posaconazole gastro-resistant TABLETS 300mg PO BD on day 1, then 300mg PO OD thereafter • Posaconazole LIQUID may be used for swallowing difficulties – see below for dosing*	Autologous SCT EXCLUDING Benda-EAM, BEAM, Etop/Melph • Fluconazole 100mg PO OD Intensive or OP chemotherapy for NHL • Fluconazole 50mg PO OD

*Posaconazole liquid PO 200mg TDS with food (ideally administered with a high fat meal) may be used for patients with swallowing difficulties/NG tube. GvHD patients previously on oral posaconazole should be switched to posaconazole IV 300mg OD if the oral route is no longer available.

Treatment of Invasive Fungal Infections in Neutropenic Patients

- It is important to try and prove that there is an IFI by requesting HRCT scanning, galactomannan/beta D glucan blood tests or BAL prior to initiating antifungals. Antifungal treatment may have to be started before these results are back but may be able to be discontinued early if they are negative
- The preferred antifungal agent depends on the likelihood of an IFI being present and the strength of evidence for this
- Discontinue the patient's azole prophylaxis for the duration of treatment with IV antifungal agents

Empirical and Pre-Emptive Therapy



Treatment Options for Severe Proven or Strongly Suspected Fungal Infections

The choice of antifungal agent should be discussed with the Consultant prior to initiation. All IV antifungal therapy requires daily Consultant review.

AMPHOTERICIN B LIPOSOMAL (AmBisome or Tillomed liposomal)

Indication

Reserved for severe confirmed or highly suspected IFI, or proven cases of Mucor infections resistant to other antifungal agents. Posaconazole can be considered as an alternative, presuming this has not been used as prophylaxis.

Dose

- **IV 3mg/kg OD**, following the weight based dosing table below
- **Prescribe subsequent doses at 2pm if possible**
- Doses of 5mg/kg OD may occasionally be used in severe cases (discuss with consultant prior to dose escalation

Patient Weight	Amphotericin B liposomal (AmBisome or Tillomed liposomal) dose (ONCE DAILY)
40-45kg	150mg/100mg on alt days (150mg on alternate days with 100mg on intervening days)
46-55kg	150mg
56-62kg	200mg/150mg on alt days (200mg on alternate days with 150mg on intervening days)
63-69kg	200mg
70-79kg	250mg/200mg on alt days (250mg on alternate days with 200mg on intervening days)
80-89kg	250mg
90-99kg	300mg/250mg on alt days (300mg on alternate days with 250mg on intervening days)
100kg+	300mg

Administration

Refer to Medusa monograph, patients should be monitored at each administration

Monitoring

- A leak of potassium and magnesium may occur. Monitor levels closely and give IV replacement if necessary (refer to local Haematology electrolyte replacement guideline). Amiloride may be considered as a potassium and magnesium sparer
- Monitor renal function daily. If creatinine increases by 50% then consider switching to another agent:
    - IV voriconazole (avoid if calculated CrCl <50ml/min due to accumulation of the vehicle SBECD)
    - Oral or IV posaconazole (avoid the IV route if calculated CrCl <50ml/min due to accumulation of the vehicle SBECD)
    - IV caspofungin (NB. limited activity against moulds)

VORICONAZOLE	
Indication	An alternative to Amphotericin B liposomal (AmBisome or Tillomed liposomal) for probable or proven fungal infections

Dose	• Loading dose necessary to rapidly achieve therapeutic concentrations of the drug
	• Serious infections (For body weight >40kg):
	  ○ IV loading dose: 6mg/kg IV every 12 hours for 2 doses
	  ○ Followed by 4mg/kg IV twice daily for 7 to 10 days before converting to oral. See antibiotic website for further details.
	• Less severe infections (For body weight >40kg):
	  ○ ORAL loading dose 400mg every 12 hours for 2 doses
	  ○ Followed by 200mg orally twice daily
	Dose escalation to 300mg orally twice daily may be necessary depending on levels (see below

Monitoring	• Monitor LFTs daily due to risk of liver toxicity • Monitor renal function. No dose adjustment is required in renal impairment, however the IV preparation should be used with caution as accumulation of the vehicle may occur • ECG at baseline and subsequent monitoring to check for QTc prolongation • Refer to antibiotic website for information on liver toxicity, renal impairment and phototoxicity

Interactions	• Numerous drug interactions – discuss with ward pharmacist
	  ○ Avoid voriconazole in patients receiving chemotherapy regimens containing vinca alkaloids (eg. vincristine, vinblastine)
	  ○ Patients on ciclosporin should have the dose of ciclosporin halved and levels monitored carefully during voriconazole treatment

Levels	Levels should be taken to guide treatment and determine the need for dose escalation during the oral phase.
	• Do NOT withhold doses pending level results unless overt voriconazole toxicity is suspected
	• The first level should be taken 3-4 days into IV therapy
	  ○ Take a pre-dose level 1 hour prior to the time that the dose is due
	  ○ Send to microbiology in a red plain top (clotted) blood bottle
	• Refer to the antibiotic website for advice on target levels, result interpretation and dosing advice

POSACONAZOLE	

Indications	• **Oral**
	  ○ Considered for patients with suspected Mucor infections (sinus fungal infection)
	  ○ Oral switch from Amphotericin B liposomal (AmBisome or Tillomed liposomal) to complete the course of treatment for confirmed IFI
	• **IV** Posaconazole
	  ○ Considered for treatment of invasive aspergillosis, Fusariosis, Coccidioidomycosis fungal infections in adults who are intolerant, refractory or have had allergic reactions to Amphotericin B liposomal (AmBisome or Tillomed liposomal).
	  ○ Treatment or prophylaxis of IFI in patients with malabsorption of oral posaconazole due to e.g. gut GvHD resulting in sub-therapeutic drug levels

Dose	There are THREE formulations of posaconazole available: tablets, suspension and IV injection. Doses differ according to formulation are not interchangeable. Formulation must be specified when prescribing.
	
	• Gastro-resistant tablet formulation
	  ○ 300mg BD on day 1 (loading dose) followed by 300mg OD thereafter
	  ○ Better absorbed than suspension
	
	• Liquid formulation
	  ○ 400mg BD with food, or 200mg QDS if not tolerated or risk factors for poor absorption (NB. this differs from the prophylactic dose)
	  ○ Prescribed for patients who are unable to swallow tablets
	  ○ Administer with a high fat meal or nutritional supplement to increase bioavailability
	
	• IV formulation
	  ○ 300mg BD on day 1 (loading dose) followed by 300mg OD thereafter
	  ○ Duration of therapy is based on disease severity and clinical response

Monitoring	Monitor LFTs daily due to hepatic metabolism
Interactions	Numerous drug interactions, similar to voriconazole – discuss with ward pharmacist
Posaconazole levels	Levels should be taken for all patients receiving the liquid and IV formulation of posaconazole, both for treatment and prophylactic intent. Patients taking posaconazole tablets should have levels checked if they are on treatment dose, or if they have a higher body weight or reasons for poor absorption e.g. diarrhoea or GvHD. Levels are not routinely required for patients taking posaconazole tablets prophylactically, except in the circumstances described above. • Levels should be taken at least 7 days after the start of therapy • Do not withhold doses pending levels ○ Refer to antibiotic website for further advice on target levels, results interpretation and dosing advice

Caspofungin	
An echinocandin antifungal agent with a different mode of action to azoles and Amphotericin B liposomal (AmBisome or Tillomed liposomal), active against most strains of Candida sp. and Aspergillus sp.	
Indications	• Consider for patients with renal impairment when Amphotericin B liposomal (AmBisome or Tillomed liposomal) or IV voriconazole would be unsuitable • No activity against Mucor sp. If suspected clinically (naso-pharyngeal involvement) then use an alternative agent
Dose	• 70mg IV loading dose on Day 1, followed by 50mg IV OD maintenance dose (70mg if patient >80kg) • No adjustment required for renal impairment
Monitoring	• Monitor LFTs daily. Dose adjustment necessary in moderate hepatic impairment (refer to antibiotic website)

Interactions	• Numerous drug interactions – discuss with ward pharmacist:
	  • Ciclosporin increases exposure to caspofungin, which can lead to increased liver toxicity
	  • Carbamazepine, dexamethasone, nevirapine, phenytoin and rifampicin all decrease the concentration of caspofungin; consider dose adjustment

ISAVUCONAZOLE	
Indication	Used only for the treatment of invasive aspergillosis/mucormycosis when Amphotericin B liposomal (AmBisome or Tillomed liposomal) is inappropriate. It MUST be approved by Microbiology/ID before commencing treatment.
Restrictions	Isavuconazole should only be used if the patient meets the following criteria (1, 2 and 3): 1. The Patient A) Has a proven/probable invasive aspergillosis or proven mucormycosis OR B) Does NOT have a proven/probable invasive aspergillosis or mucormycosis but has clinical suspicion of infection (one of the following criteria below must apply) • *Aspergillosis* species cultured from a non-sterile site • Biomarker positivity in repeat samples (galactomannan and/or PCR) • Imaging suggestive of invasive aspergillosis or invasive mucormycosis with repeated biomarker negativity for invasive aspergillosis 2. The treatment has been discussed with a medical Microbiologist or Infectious Diseases specialist 3. ONE of the following applies to the patient • Has had an incomplete response to treatment (must include voriconazole; liposomal amphotericin is an option for treatment of invasive aspergillosis prior to isavuconazole) • Unable to achieve therapeutic drug levels with initial treatments • Has had significant adverse effects with voriconazole (this includes development of photosensitivity, squamous cell carcinoma, visual disturbances, periostitis, cardiotoxicity and peripheral neuropathy) • Initial treatment options are contraindicated due to significant drug interactions (not manageable by therapeutic drug monitoring and/or dose alteration) or pre-existing co-morbidities (e.g. renal impairment with liposomal amphotericin)
Dose	An IV and oral preparation are available, dosing schedules equivalent. Discuss choice of preparation with Consultant before prescribing. • IV and PO dosing: Loading dose 200 mg every 8 hours for 48 hours (6 administrations in total), then maintenance 200 mg once daily, maintenance dose to be started at least 12 hours after the last loading dose • No dose adjustment necessary in any degree of renal impairment • Not recommended in severe hepatic impairment (Child-Pugh C) unless risk/benefit decision
Administration	• PLEASE NOTE: the infusion requires the use of a filter, refer to antibiotic website for more information, including administration instructions
Monitoring	• Monitor LFTs daily due to risk of liver toxicity • Contraindicated in short QT syndrome
Interactions	• Numerous drug interactions – discuss with ward pharmacist

Continuation Treatment for Proven or Strongly Suspected Fungal infection

Patients who have responded well to IV antifungal therapy, whose counts have regenerated, but there is radiological evidence of residual fungal infection should be started on oral maintenance with voriconazole or posaconazole.

- Oral voriconazole
    - Use if patient has previously received posaconazole prophylaxis
    - Follow dosing guidance above (a higher starting dose of 300mg BD may be required if levels were previously low)
    - Loading dose not required if converting IV voriconazole to oral
    - Levels required during oral treatment as per antibiotic website

- Oral posaconazole
    - May be considered as an oral switch if the patient was not previously on posaconazole prophylaxis
    - Follow dosing guidance above

- Continue oral maintenance for 2 weeks
- If patients cannot tolerate azoles then Amphotericin B liposomal (AmBisome or Tillomed liposomal) IV 3mg/kg once daily Monday to Friday on Haematology Daycase Unit may be considered