HAEMATOLOGY ANTIFUNGAL POLICY

PROPHYLAXIS

Primary Prophylaxis

Patient Group	Primary prophylaxis
Patients receiving intensive remission-induction chemotherapy for Acute Leukaemia (excluding patients receiving vinca alkaloids) or myelodysplastic syndromes expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections	**Posaconazole tablets 300mg once daily (give loading dose of 300mg twice daily on day 1)** **Continue until count recovery post treatment (ANC ≥1.0 x 10^9/L).**
Acute Lymphoblastic leukaemia patients on vinca alkaloids in Phase I induction in ALL management	**Ambisome 3 mg/kg twice weekly.**
Acute Lymphoblastic Lymphoma Patients Phase II induction	**Switch to Posaconazole tablets 300mg once daily (give loading dose of 300mg twice daily on day 1) at start of Phase II induction.**
Burkitt's Lymphoma	**Fluconazole 100mg once daily until end of treatment.** **Consider Ambisome 3mg/kg twice weekly.**
Patients on Alemtuzumab	**Posaconazole tablets 300mg once daily (give loading dose of 300mg twice daily on day 1) until immune reconstitution.**
Patients on ALG	**Posaconazole tablets 300mg once daily (give loading dose of 300mg twice daily on day 1) until immune reconstitution.**
Patients on Methylprednisolone	**Fluconazole 100mg once daily until end of treatment**
Patients receiving intensive chemotherapy where anticipated duration of neutropenia >7 days	**Fluconazole 100mg once daily until end of treatment.** **Consider Posaconazole if further immunocompromised.**
Other Chemotherapy patients	**Consider Fluconazole 100mg once daily if on high dose steroids.**

Secondary Prophylaxis

Patients with previous proven/probable Invasive Aspergillosis

Voriconazole tablets
-Loading *400mg twice daily for two doses*
-Maintenance *200mg twice daily* (If <40kg see SmPC)

Notes:-

- This is an unlicensed indication and should be discussed with the patient and documented in the notes.
- Patients who have had proven/probable IFI (see EORTC criteria) may not have cleared the infection at the start of their next course of chemotherapy and therefore are at high risk of infection reactivation.
- The need for voriconazole prophylaxis must be reviewed regularly and be discontinued promptly when the period of immunosuppression has ended.

Patients with Invasive Fungal Infections (not Aspergillosis)

Consult with microbiology for advice.

TREATMENT

Indications for Empiric Treatment

1. Clinically unwell/unstable regardless of type of prophylaxis.
2. On no antifungal prophylaxis or fluconazole prophylaxis and
- refractory fevers[1] (+/- neutropenia)[2] or
- no on site or timely access[3] to the results of GM-ELISA and /or PCR assay.

3. On posaconazole/ voriconazole / ambisome prophylaxis and refractory fevers[1] (+/-neutropenia)[2] and or clinical signs/symptoms of Invasive Fungal Disease (IFD)[4] and no on site access to therapeutic drug monitoring (TDM) or timely access[3] to TDM results

Recommended Investigations

- Cultures – blood (in all patients) and urine, sputum, faeces, other sites (as clinically indicated).
- HRCT scanning – chest (in all patients) and sinuses, abdomen, other sites (as clinically indicated).
- Serum GM-ELISA and Aspergillus PCR – only in patients on no fluconazole prophylaxis.
- Bronchoscopy or lung biopsy – if radiological abnormality detected on HRCT scan [5]
- Biopsy of other sites as clinically indicated
- Antifungal drug levels (see Appendix 2 for reference levels).

Notes:-
1. Refractory fevers – persistent (daily for 3-5 days) or recurrent (after an afebrile period of 48 hours) despite broad spectrum antibiotics and negative microbiological investigations.
2. Neutropenia = neutrophil count $<0.5x10^9$/l.
3. Timely access = results available within 3-5 days of sampling.
4. Symptoms/signs IFD = cough, chest pain, haemoptysis, dyspnoea, pleural effusion or rub, rhinorrhoea, epistaxis, ulceration or eschar of nasal septum or hard palate, maxillary pain, periorbital swelling, focal neurological signs or symptoms, skin lesions consistent with fungal infections (eg nodules, ulceration or satellitism).
5. Procedure of choice depends on site and nature of lesion and patient's status – all bronchoscopies and biopsies should be performed within 72 hours of initiating emipiric antifungal therapy for maximum yield. All samples should be sent for microscopy, culture, GM-ELISA, fungal PCR testing (biopsy should be sent for histology and all other tests with exception of GM-ELISA) – need fresh specimen as well as formalin to maximise chance of success.

Empiric Treatment of Possible Invasive Fungal Infection (IFI)

First Line – **Caspofungin**

- Loading dose of 70mg on day 1. Followed by a maintenance dose of 70mg (if patient > 80kg) or 50mg (if patient ≤ 80kg).
- Reduce dose if liver function impaired (for a Child-Pugh score 7-9, give 35mg).

Second Line – **Ambisome**

- Dose – 3mg/kg/day.
- Nephrotoxic agent- risk of worsening renal impairment particularly but not exclusively if pre-existing problems and /or concomitant use of another nephrotoxic agent.
- Patients may react to amphotericin and may need pre-medicated with paracetamol, pethidine or hydrocortisone.

Third Line **–** **Posaconazole** tablets

- Dose - 300mg twice daily on day 1 and 300mg/day thereafter.
- Should not be given with vinca alkaloids due to drug interaction.

Treatment of Proven / Probable IFI

Consult microbiology for advice – based on previous exposure to antifungal agents and investigational results.

Treatment of Invasive Aspergillosis.

First Line – Intravenous **Voriconazole**

- Dose – Loading dose of 6mg/kg twice daily on day 1. Followed by a maintenance dose of 4mg/kg twice daily.
- Voriconazole has excellent penetration of the blood brain barrier and is the drug of choice where there is evidence of intracerebral infection.
- Can be switched to an oral formulation on discharge.

Second Line – Consult microbiology for advice.

APPENDICES

Appendix 1 – Definitions of Fungal Infections (EORTC-IFICG and MSG criteria)

1. Criteria for **Probable** and **Possible** Invasive Fungal Infection

PROBABLE INVASIVE INFECTION	**POSSIBLE INVASIVE INFECTION**
At least 1 host criterion	At least 1 host criterion
AND 1 microbiological criterion	AND
AND 1 major OR 2 minor clinical criteria	EITHER 1 microbiological criterion
	OR 1 major OR 2 minor clinical criteria

probable candidaemia - Clinical criteria are not required (no definition for possible)
Chronic disseminated Candida – microbial criteria not required for probable

Microbiological Criteria

- Positive culture of a mould (including Aspergillus spp., Fusarium pp., zygomycetes, scedosporium pp), C Neoformans from sputum or BAL
- Positive culture or cytology/ direct microscopy for moulds from sinus aspirate
- Positive cytology/ direct microscopy for a mould or cryptococcus from sputum, BAL
- Positive Aspergillus antigen in BAL, CSF or >2 blood samples
- Positive cryptococcal antigen in blood
- Positive cytology/ direct microscopy for fungal elements (eg cryptococcus in CSF) in sterile body fluids
- Two positive urine cultures of yeasts in the absence of urinary catheter
- Candida casts in the urine in the absence of urinary catheter
- Positive blood culture of candida spp.

Host Factors

- Neutropenia: PMN <500 $x10^9$/l for >10 days
- Persistent fever for >96 hrs refractory to appropriate broad spectrum antibacterial treatment
- Body temperature either >38^{0}C or <36^{0}C AND any of the following
    - Prolonged neutropenia (>10 days) in the previous 60 days
    - Recent or current use of significant immunosuppressive agents in the previous 30 days
    - Proven or probable invasive fungal infection in a previous episode
    - Coexistence of AIDS
- Signs & symptoms of GVHD, particularly severe (>grade 2) or chronic extensive disease
- Prolonged use of corticosteroids in previous 60 days (>3 weeks)

Clinical Criteria

Should be related to the site of microbiological criteria and temporarily related to current episode

MAJOR	MINOR
Lower Respiratory Tract Infection	
Any of the following new infiltrates on CT imaging; • halo sign, • air-crescent sign • cavity within an area of consolidation	• Symptoms of LRTI (cough, chest pain, haemoptysis) • Physical finding of pleural rub • Any new infiltrate not fulfilling major criterion • Pleural effusion
Sino Nasal Infection	
• Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighbouring structures, extensive base of skull destruction)	• URTI symptoms (nasal discharge etc.) • Nose ulceration or eschar of nasal mucosa or epistaxis • Periorbital swelling • Maxillary tenderness • Black necrotic lesions or perforation of the hard palate
CNS Infection	
• Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, auricular or vertebral processes, intracerebral abscesses or infarcts)	• CSF culture negative for other pathogens & malignant cells by microscopy and culture • Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) • Mental changes • Meningeal irritation findings • Abnormalities in CSF biochemistry and cell count
Disseminated Fungal Infection	
• Papular or nodular skin lesions without any other explanation • Intraocular findings suggestive of haematogenous fungal chorioretinitis or endophthalmitis	
Chronic Disseminated Candidiasis (Probable)	
One host factor **AND** small peripheral target like abscesses (Bull's eye) in liver and or spleen demonstrated by CT, MRI or USS	

2. Criteria for **Proven** Invasive Fungal Infection

DEEP TISSUE INFECTIONS	
Moulds	*Yeasts*
Histo/ cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging)	Histo/ cytopathology showing yeast cells and/or pseudohyphae with evidence of associated tissue damage (either microscopically or unequivocally by imaging) from a needle aspiration or biopsy excluding mucous membranes
OR	OR
Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection	Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses and mucous membranes.
	OR
	Microscopy (india ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF
FUNGAEMIA	
Positive blood culture of fungi excluding Aspergillus spp. And penicillium spp other than P. marneffei, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism	Positive blood culture of candida and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism

Appendix 2 – Antifungal Reference Levels

Drug	**Sample Time**	**Reference level**
Posaconazole	Pre-dose	Prophylaxis (>0.7mg/l) Treatment (>1.3mg/l)
Voriconazole	Pre-dose	Prophylaxis and treatment (1.0 – 4.5mg/l)

Appendix 3 – Treatment Summary.

Primary Prophylaxis

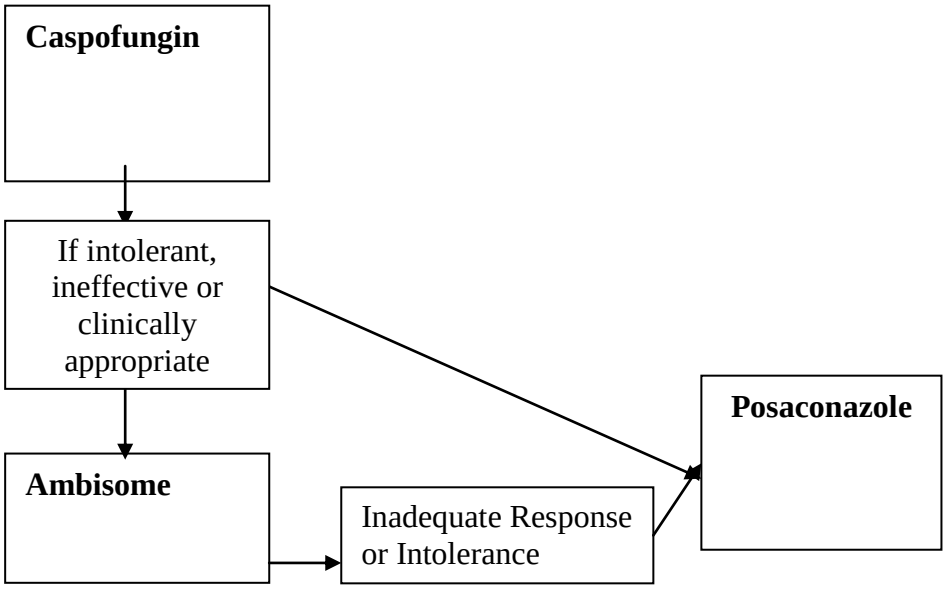
Low risk **Fluconazole**

High Risk **Posaconazole**

Secondary Prophylaxis of Invasive Aspergillosis

Voriconazole tablets

Empiric Treatment of Invasive Fungal Infection



Treatment of Proven / Probable Invasive Aspergillosis

Intravenous **Voriconazole**

REFERENCES

1. Segal BH & Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. Am J Respir Crit Care Med. 2006 Apr 1;173 (7):707-17

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