Guideline for the prophylaxis and treatment of fungal infections in Haematology patients

University Hospitals of Leicester NHS
NHS Trust

Trust ref: B6/2017

1. Introduction

This guideline sets out the recommended assessment and management process for prophylaxis and treatment of fungal infections in adults with haematological malignancy. Invasive fungal infections in patients with a malignancy are associated with high levels of morbidity and mortality.

2. Scope

This guideline applies for use on all adult haemato-oncology patients who are at risk of fungal infection. It is intended for use by any medical, nursing and pharmacy staff treating these patients.

3. Recommendations for the prophylaxis and treatment of fungal infections

Please see page 3 and 4 for prophylaxis and treatment flow chart

4. Education and Training

Guideline is part of induction for junior doctors joining the department. It is a working document for the senior medical and pharmacy teams

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
Training of junior medical staff	Inclusion in induction for Osborne Juniors	Four monthly	Haematology training lead

6. Supporting Documents and Key References

See pages 3 and 4 for a summary of the guidelines. They are presented in a way that is easy to follow and fits on to 2 sides of a single sheet A4 for ease of use in an emergency. Further information is given in appendices 1 to 3.

The guideline is informed by EORTC guidance 2019 (https://doi.org/10.1093/cid/ciz1008)

7. Key Words

Antifungal, Anti-fungal, neutropenic, Ambisome, Caspofungin, Posaconazole, Voriconazole, isavuconazole, Itraconazole, Fluconazole, Micafungin.

This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Dr Perera/ Dr Hodgson/ A Delpozo	**Job Title:** Cons Micro/Cons Haem/ Haem Pharmacist
Reviewed by:	Dr Perera/ Dr Hodgson/ A Delpozo	
Approved by:	Anti-microbial working party	**Date Approved: 17.5.24 PGC (v3)**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
2024	V6	Dr Perera/Dr Hodgson/A Delpozo	Removal of CQUIN and change of pharmacist involved.
2021	V5	Dr Perera/Dr Hodgson/V Dulobdas/AWP	Clarity of preference of treatment antimicrobials Simplification of flow charts Removal of EORTC definition as appendix Insertion of antifungal spectrum of activity as appendix
2015	V4	Dr Perera/Dr Hunter/Z Ayub	Change to PAGL format

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**

University Hospitals of Leicester NHS
NHS Trust

Please go to page 3

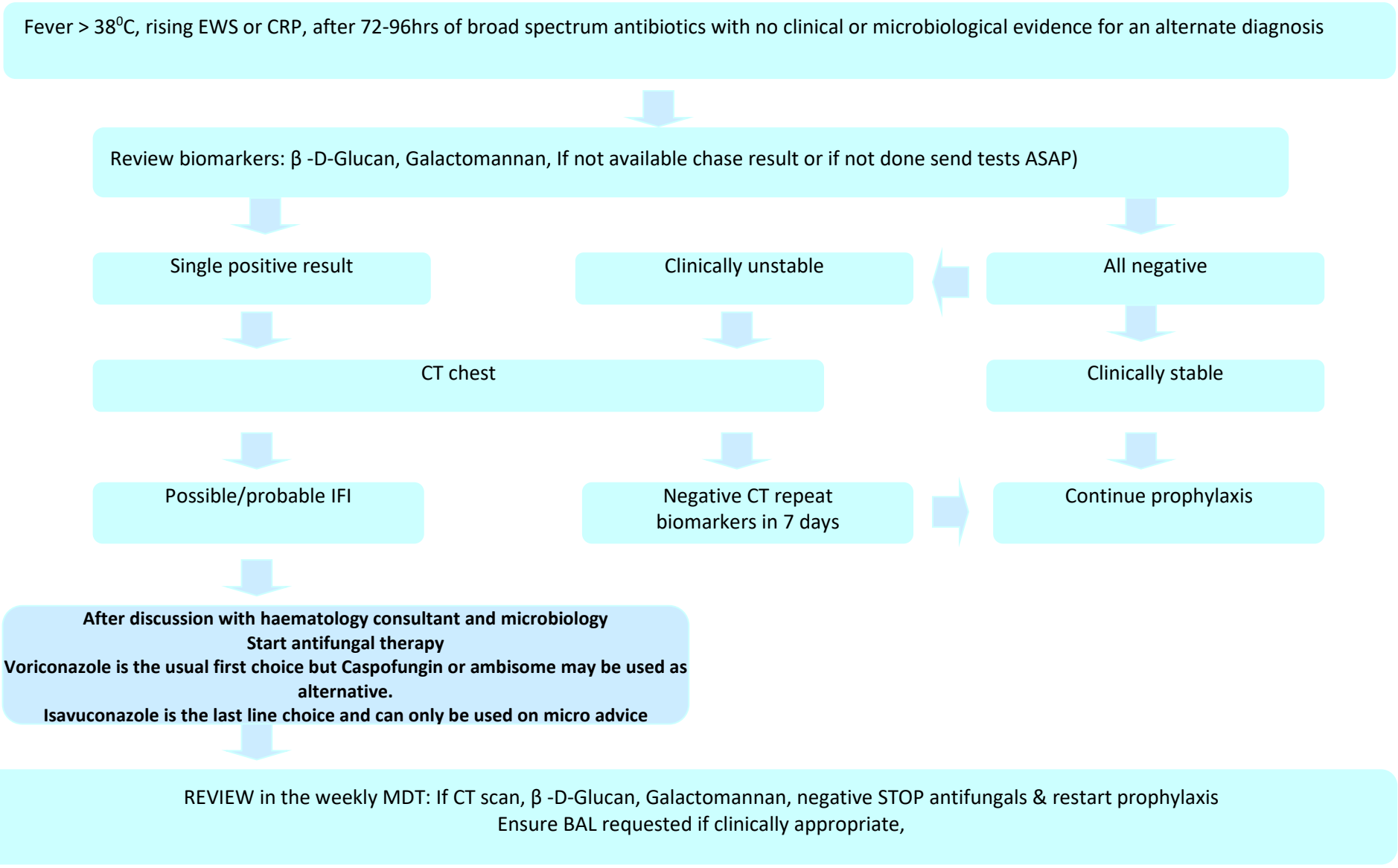
Risk category for invasive fungal infections and antifungal prophylaxis

Disease	Prophylaxis
High risk	
Allogeneic haematopoietic stem cell transplant until 100 days post transplant Graft vs host disease on steroids dose > 0.5mg/kg Severe Aplastic Anaemia	POSACONAZOLE TABLETS 300mg BD for 1 DAY then 300mg OD* + hepafiltered room
Previous proven / probable fungal infection Acute Myeloid Leukaemia on ambulatory care	POSACONAZOLE TABLETS 300mg BD for 1 DAY then 300mg OD
Standard risk	
Autologous haematopoietic stem cell transplant Acute myeloid leukaemia or myelodysplastic syndrome on intensive chemotherapy Acute lymphoblastic leukaemia NOT on vincristine	FLUCONAZOLE 200mg OD + hepafiltered room (consider POSACONAZOLE TABLETS 300mg BD for 1 DAY then 300mg OD* if HEPA filtration not available)
Acute lymphoblastic leukaemia on intensive chemo on Vincristine	AMBISOME 1mg/kg ** 3 times per week + hepafiltered room or ISAVUCONAZOLE 200mg TDS for 48hrs then 200mg OD**
R-CODOX-M/R-IVAC for High Grade Lymphoma	ISAVUCONAZOLE 200mg TDS for 48hrs then 200mg OD***
High dose steroids > 1mg/kg for > 21 days	FLUCONAZOLE 200mg OD
Low risk	
Lymphoma Myeloma	NO PROPHYLAXIS NECESSARY

* Posaconazole liquid dose 200mg TDS
**Round ambisome dose to 50mg eg for 75kg patient total daily dose= 225mg prescribed 250mg & 200mg on alt days.

***Loading dose 200mg every 8 hrs for 48hrs (6 doses in total) then maintenance 200mg od (maintenance dose to be started at least 12 hrs after the last dose loading dose).

Flow chart for antifungal treatment in Haematology patients



Appendix 1: Investigations in patients with suspected Invasive Fungal Disease (IFD)

Routine:

- Examination (skin, mouth (remove dentures), perianal, chest, Hickman line exit site etc)
- Standard and high risk patients: Weekly β -D-Glucan, Galactomannan.
-

If fever >38°C, rising EWS or CRP

- Blood cultures – central and peripheral (taken simultaneously)
- MSU for cultures
- Sputum for cultures
- Oral swabs for cultures in the presence of mouth ulcers / mucositis
- CXR
- Ensure posaconazole level documented
- Send β -D-Glucan and Galactomannan and confirm positive results with a second sample

Continuing fever >38°C, rising EWS or CRP in spite of broad spectrum antibiotics for 72-96 hours and negative blood cultures

- CT (and or CTPA) chest (preferably before commencing antifungal therapy)
- Bronchoscopy and Bronchoalveolar lavage (BAL) if CXR/CTPA is abnormal
- CT sinuses if symptomatic
- Patients with positive blood cultures for candida species should have a
- CT upper abdomen to rule out hepatosplenic candidiasis, echocardiography to exclude endocarditis and an ophthalmic examination to rule out endopthalmitis
- Standard and high risk patients: Increase surveillance of β -D-Glucan, Galactomannan to twice weekly.

Microbiological tests for the diagnosis of invasive fungal disease

- Culture isolation of fungi from Blood, MSU, Broncho-alveolar lavage, sputum, throat swabs skin biopsies etc
- Species identification of Yeasts and common moulds
- Anti-fungal susceptibility testing for candida species
- Aspergillus galactomannan testing in serum and broncho-alveolar lavage fluid
- β-D-glucan testing in serum
- Cryptococcal antigen testing in serum and csf

Appendix 2: Antifungal Treatment for Patients with Risk(s) for Invasive Fungal Disease (IFD) (This appendix should be read in conjunction with the 2019 EORTC criteria)

For patients with a fever > 38^0C, rising EWS or CRP, despite 72-96hrs of broad spectrum antibiotics and no clinical or microbiological evidence for an alternate diagnosis, consider the possibility of invasive fungal disease and the need for antifungal treatment.

Review biomarkers (β -D-Glucan, Galactomannan,). If there is a single positive result, the tests have not been requested or are negative and the patient is clinically unstable, request CT chest (and or CTPA).

Treatment with antifungals should only be initiated after discussion with a consultant haematologist and after obtaining a microbiology code.

Evidence of Host criteria only (Biomarkers/ CT chest negative) - Do not start empirical antifungal treatment

Review prophylaxis and send blood for serum levels of antifungals if appropriate
Investigate for microbiological and other clinical criteria – i.e. bronchoscopy and mycological diagnostic tests available locally (Refer to microbiological tests in Appendix 1)

Evidence of Host criteria and CT chest suggestive of lower respiratory tract fungal disease (Possible IFD)
Stop prophylaxis, commence Voriconazole 6mg/kg BD IV (loading) followed by 4mg/kg BD IV or Ambisome 3mg/kg/day[#] (Caspofungin / Isavuconazole may be considered on microbiology advice).

Consider Voriconazole 400mg BD orally (loading) followed 200mg BD orally for de-escalating treatment OR Posaconazole 400mg BD orally (liquid), 300mg BD for 1 day then 300mg od thereafter (tablet or intravenous)

Avoid using combination of antifungal agents in the treatment of IFD

Investigate for microbiological and other clinical criteria – i.e. bronchoscopy and mycological diagnostic tests available locally (Refer to Appendix 1)

Evidence of Host criteria, CT chest suggestive of lower respiratory tract fungal disease and mycological criteria (Probable IFD)

Stop prophylaxis, commence Voriconazole 6mg/kg BD IV (loading) followed by 4mg/kg BD IV or Ambisome 3mg/kg/day[#] (Caspofungin / Isavuconazole may be considered on microbiological advice).
Consider Voriconazle IV for central nervous system infections.

Consider Voriconazole 400mg BD orally (loading) followed 200mg BD orally for de-escalating treatment OR Posaconazole 400mg BD orally (liquid) 300mg BD for 1 day then 300mg od thereafter (tablet or intravenous)

Avoid using combination of antifungal agents in the treatment of IFD

Investigate further for other microbiological and clinical criteria i.e. bronchoscopy and mycological diagnostic tests available locally (Refer to Appendix 1)

Evidence of Proven IFD

Stop prophylaxis and commence antifungal therapy:
Yeast - Caspofungin 70mg loading 50 mg OD (weight up to 81kg). 70mg OD (body weight 81kg and above)
Consider Fluconazole 400mg BD or 800mg OD IV if proven fluconazole susceptible Candida blood stream infections
Aspergillus infection – Voriconazole 6mg/kg BD IV (loading) followed by 4mg/kg BD or Ambisome 3mg/kg/day[#]
Consider Voriconazole 400mg BD orally (loading) followed 200mg BD orally for de-escalating treatment OR Posaconazole 400mg BD orally (liquid) 300mg BD for 1 day then 300mg od thereafter (tablet or intravenous)

Mucor infection – Ambisome 5mg/kg/day[#]
Consider Isavuconazole 200mg orally 8H for 48hrs (loading) followed by 200mg OD orally for de-escalating treatment OR Posaconazole 400mg BD orally (liquid) 300mg BD for 1 day then 300mg od thereafter (tablet or intravenous)

Cryptococcal infection – Ambisome 3mg/kg/day[#]
Consider Voriconazole 6mg/kg BD IV (loading) followed by 4mg/kg BD IV for central nervous system infections
Avoid using combination of antifungal agents in the treatment of IFD

DURATION OF TREATMENT

Do not commence antifungals without discussion with a consultant haematologist and a microbiology verification code.
If at 5 days there is no supportive clinical and or mycological criteria antifungal then treatment should be stopped
Treatment should have a documented senior review (Consultant Haematologist / Consultant Microbiologist) Every reasonable attempt should be made to include a diagnosis of IFD.
Every reasonable attempt should be made to exclude an alternative aetiology

Proven:
Yeast infections minimum 2 weeks from last positive blood culture– if line infection likely; line removal is strongly advised
Hepatosplenic candidiasis 6 weeks
Mould infections – minimum 6 weeks – 3 months

Probable:
Total 2 weeks – 6 weeks (consider de-escalation to oral voriconazole / posaconazole)

Possible:
Total 2 weeks (consider de-escalation to oral voriconazole / posaconazole)

[#] Ambisome dose should be rounded to give full 50mg vials. A different dose can be given on alternate days to accommodate this. Eg for 75kg patient total daily dose= 225mg prescribed 250mg and 200mg on alternate days.

Appendix 3: Spectrum of activity of antifungals

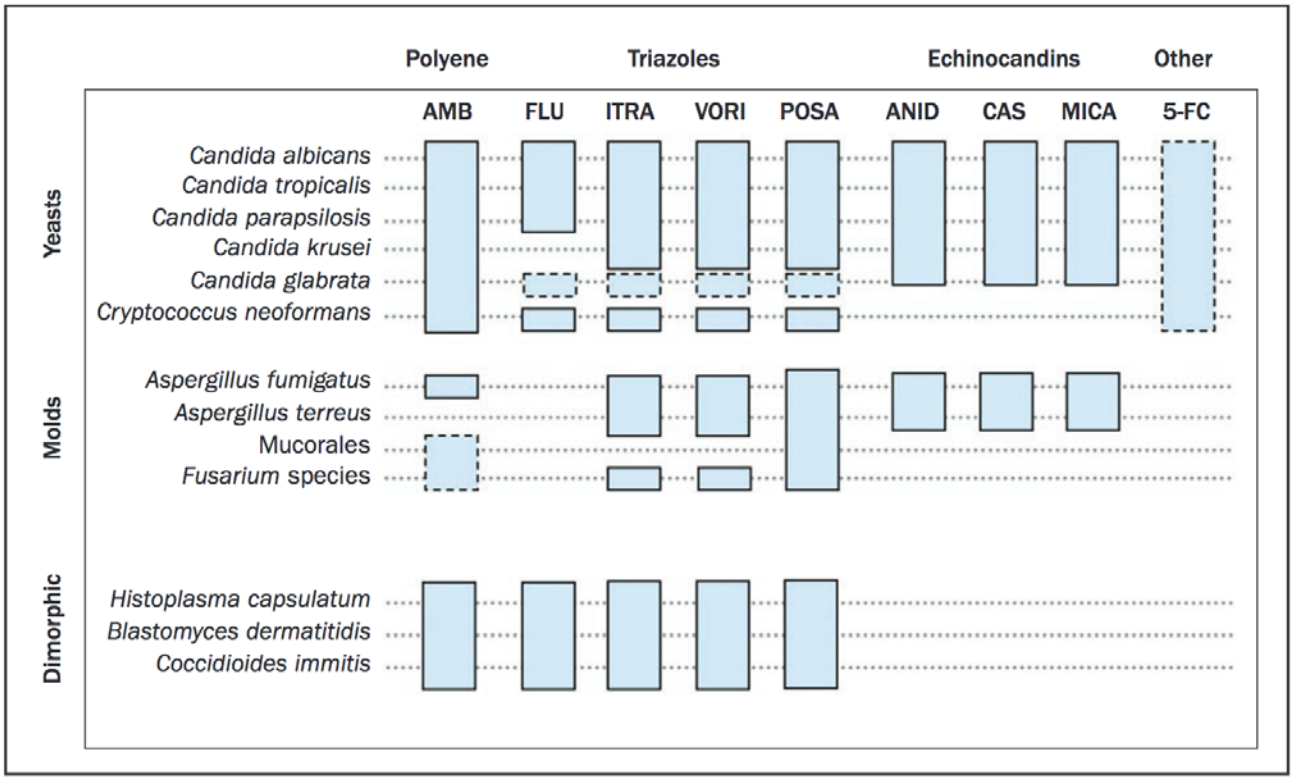


FIGURE 3. Spectrum of action of systemic antifungal agents. Solid blocks represent species in which the antifungal agent has demonstrated microbiological and clinical efficacy. Blocks with dotted lines indicate fungal genera/species in which resistance is common. AMB = amphotericin; ANID = anidulafungin; CAS = caspofungin; 5-FC = flucytosine; FLU = fluconazole; ITRA = itraconazole; MICA = micafungin; POSA = posaconazole; VORI = voriconazole.

Isavuconazole has the same spectrum of activity as posaconazole.

R. E. LEWIS (2011) Current concepts in Antifungal Pharmacology [Image]. *Mayo Clinic Proceedings*, 86(8): 805–817. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146381/. [Accessed 02/07/20]