

Antifungal Guidelines (Adults)

Introduction

This collection of guidelines for prophylaxis, investigation, treatment and audit has been agreed by the Leukaemia and Lymphoma Board and forms the policy for management of all fungal infections in patients with haematological malignancy.

Prophylaxis

Patients receive prophylaxis according to risk category and this in turn influences their empirical therapy. Not all neutropenic patients require prophylaxis and some non-neutropenic ones with other significant risk factors (such as severe graft-versus-host disease) do. Risk is most easily categorised by therapeutic regimen, which allows the majority of associated risk factors to be taken account of. Patients receiving itraconazole should be considered early for the IV formulation if they are intolerant.

Prophylaxis should be continued until recovery of the neutrophil count ($>0.5 \times 10^9 /l$) with no evidence of fungal infection.

For cyclophosphamide-containing regimens, prophylaxis should start on the day of HSCT transplant, at least 48 hours after the end of chemotherapy and continued until the neutrophil count is $\geq 0.5 \times 10^9 /L$.

Regimen	Risk Category	Prophylaxis
Auto PBSC	Low	No
Lymphoma chemotherapy*	Low	No
Adult ALL chemotherapy**	High - Int	For vincristine containing blocks: Ambisome 3mg/kg three times per week for outpatients), followed by itraconazole at least 1 week after last vincristine dose. Otherwise use <u>Itraconazole</u> and oral <u>Amphotericin B</u>
AML chemotherapy	High - Int	Itraconazole and oral Amphotericin B

Allogeneic transplantation	High	Itraconazole and oral Amphotericin B
High-dose Cytarabine (ara-C) or fludarabine regimens	High	Itraconazole and oral Amphotericin B

* HIV positive patients may require prophylaxis according to HIV risk
 ** avoid using itraconazole and voriconazole with vincristine containing regimens.
 Vincristine cannot be given within 5 days of the last itraconazole or voriconazole dose.

Risk factors which may change risk category		
Colonised at > 1 site	High - Int	Itraconazole and oral Amphotericin B
Neutropenia > 5 weeks	High	Itraconazole and oral Amphotericin B
Corticosteroids > 1 mg/kg and neutrophils < 1 for > 1 week	High	Itraconazole and oral Amphotericin B
GVHD requiring steroids	High	Itraconazole and oral Amphotericin B

Graft-versus-host disease and graft rejection/failure

Patients with chronic graft-versus-host disease and those who become neutropenic again as a result of graft rejection/failure are at significant risk of invasive aspergillosis and should receive oral itraconazole prophylaxis. Those with significant gut involvement should have levels measured weekly.

Secondary prophylaxis

Patients with previously documented fungal infection (proven or probable invasive aspergillosis or other mould infections, or fungaemia) must receive secondary prophylaxis during subsequent neutropenia and graft-versus-host disease. This should be oral itraconazole (unless the previous infection broke through itraconazole prophylaxis or was unresponsive to itraconazole). AmBisome 3mg/kg/day three times per week may be given as an alternative. In cases where patients required voriconazole for treatment of the initial infection, this would also be a suitable secondary prophylactic agent.

Abnormal Liver Function Tests

Pre-existing abnormal liver function tests are not a contra-indication to azole prophylaxis, but patients should be monitored carefully and azoles discontinued if there is associated progressive hepatotoxicity.

Management of Neutropenic Fever - Investigations

At onset of fever:

- **Trough itraconazole level**

High-risk patients receiving oral itraconazole prophylaxis who become febrile are commenced on broad spectrum antibiotic therapy and should have itraconazole levels taken. Levels should be taken prior to the next itraconazole dose following the onset of fever. The time of the dose AND the time of the level must be recorded. Assays for itraconazole levels are performed twice weekly, therefore a result should be available at 96 hours to guide subsequent management. If patients have been intolerant of the oral preparation and are receiving IV itraconazole, the level can be assumed to be therapeutic and no assay need be performed.

At 96 hrs of fever:

- **HRCT chest**

If the fever persists despite 96 hours of broad spectrum empirical antibiotic therapy, a high resolution chest CT scan should be performed. If the HRCT is negative and trough itraconazole levels are greater than 500ng/ml or the patient is receiving IV itraconazole then additional antifungal agents are not required. If the HRCT is negative and the trough itraconazole levels are subtherapeutic, then the patient should be switched to IV itraconazole prophylaxis (200mg BD for 48hrs, then 200mg OD).

If there is a delay in performing the HRCT (beyond 120 hours), then patients should be treated with targeted therapy pending the CT. If the CT has features suggestive of fungal infection, then the patient should received targeted therapy.

Ongoing investigations:

- **Serum galactomannan levels twice weekly in high risk patients in centres where available**

High-risk patients should be screened twice weekly for serum galactomannan and the antigen should be assayed in bronchoalveolar lavage samples, when available. Any new respiratory clinical feature should be investigated by CT scanning. All patients developing a new fever which persists despite 96 hours of broad spectrum antibiotic therapy at the end of neutropenia should have an upper abdominal CT scan (to exclude chronic disseminated candidosis).

Two sets of blood cultures should be taken from different sites (including central lines) in patients remaining febrile. An MSU (for fungal culture) should be sent prior to commencement of antifungal therapy and in symptomatic patients.

All patients with blood cultures positive for *Candida* species should have an upper abdominal HR CT scan and an ophthalmological examination of their fundi (for the detection of choroidoretinitis/endophthalmitis).

Other:

Low/low intermediate-risk patients should be managed on clinical or microbiological grounds. Consideration should be given to performing a chest HRCT at 96 hours of fever.

Targeted Therapy

Targeted therapy is given where evidence exists to suggest invasive fungal infection (CT, galactomannan PCR, blood culture), as outlined in the algorithm. This sets out the therapy to be given for the different categories of infection and causative organism and subsequent modification (if necessary) in the case of toxicity or failure of response. All cases should be discussed with the Microbiology Department. Completion of therapy will depend upon the causative organism, the extent of the infection and the response to therapy. It may be possible to switch to an oral azole to complete therapy, in which case the intravenous antifungal should be continued during the 24 hour loading period for the azole.

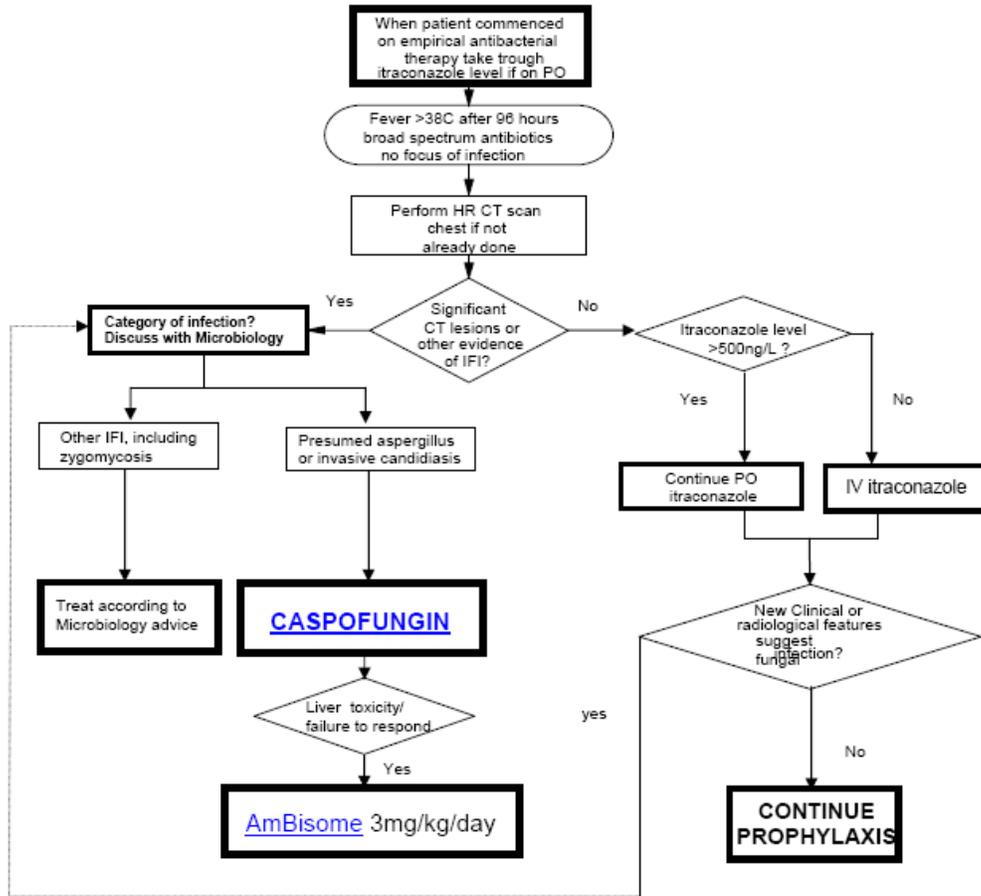
Therapy should be modified as detailed in the algorithm. It should be noted that there is currently no evidence for combining antifungal agents in the management of invasive aspergillosis and this should not, therefore, be done.

Failure of treatment is defined as progression of clinical features (fever, respiratory function, hypotension, haemoptysis or chest pain) **after at least 7 days of adequate antifungal treatment.**

Renal toxicity is defined as a creatinine clearance < 50mls/min (this can be calculated rather than directly measured).

Liver toxicity is defined as an elevation of transaminases and/or bilirubin to at least **3 times the upper limit of normal.**

ANTIFUNGAL THERAPY FOR HIGH INTERMEDIATE/HIGH RISK NEUTROPENIC PATIENTS



LIPOSOMAL AMPHOTERICIN (AMBISOME)

Dose in Adults

Intravenous: 3mg/kg three times per week for prophylaxis (see text and algorithm)
3mg/kg/day for treatment

Give a test dose of 1mg on the first day of treatment.

N.B. Liposomal amphotericin must be infused in glucose 5% with a pre and post flush of glucose 5%.

Dose Adjustment in Renal Impairment

Monitor renal function closely. If renal toxicity supervenes swap to caspofungin or voriconazole, taking the potential for drug interactions into consideration

Dose Adjustment in Liver Impairment

Dose adjustment not required.

ORAL AMPHOTERICIN B

Dose in adults

500mg four times a day, total of 2grams.

Tablets: 5 x 100mg four times a day

or Suspension: 5ml four times a day

CASPOFUNGIN

Dose in Adults

Intravenous: Loading dose of 70mg, then 50mg od thereafter.

NB: If patient weight >80kg: loading dose of 70mg, then 70mg od thereafter.

N.B. Caspofungin must have a pre and post flush with sodium chloride 0.9% and be infused in sodium chloride 0.9%

Dose Adjustment in Renal Impairment

Dose adjustment not required.

Dose Adjustment in Liver Impairment

For mild hepatic insufficiency (Child-Pugh score 5 - 6): no dose adjustment required.

For moderate hepatic insufficiency (Child-Pugh score 7 - 9): loading dose of 70mg, then 35mg od thereafter.

For severe hepatic insufficiency (Child-Pugh score > 9): there is no clinical experience but a higher exposure than in moderate hepatic impairment is expected, so use with caution in these patients.

FLUCONAZOLE

Dose in Adults

Oral: 100mg od for prophylaxis.

Otherwise 400mg OD for systemic candidosis or cryptococcosis

Intravenous: Loading dose of 800mg, then 400mg od.

Dose Adjustment in Renal Impairment

For adults: If CrCl <10ml/min, give a maximum daily adult dose of 150mg.

N.B. If patient established on effective haemofiltration specialist advice should be sought.

Dose Adjustment in Liver Impairment

Dose adjustment not required.

ITRACONAZOLE

Dose in Adults

Oral solution: 200mg bd (if tolerance is a problem od dosing may be appropriate). If still intolerant, give itraconazole IV.

When switching therapy from IV antifungal therapy load with 400mg bd for 24 hours.

Intravenous: 200mg bd for 48 hours then 200mg od

Dose Adjustment in Renal Impairment

Dose adjustment not required.

If CrCl < 30ml/min, intravenous itraconazole should not be used as accumulation of the intravenous vehicle (cyclodextran) occurs and can result in potential toxicity.

Dose Adjustment in Liver Impairment

Itraconazole is predominantly metabolised in the liver. Therefore, in moderate to severe liver dysfunction (Child-Pugh score > 7), consider dose adjustment and only initiate therapy if expected benefits exceed risk of further hepatic injury.

VORICONAZOLE

Voriconazole can cause serious visual disturbances, these affect colour, focus and concentration. These are reversible on discontinuation of the drug.

Dose in Adults

Oral: Patients >40kg: 400mg bd for first 24 hours, then 200mg bd thereafter

Patients <40kg: 200mg bd for first 24 hours, then 100mg bd thereafter

Intravenous: 6mg/kg every 12 hours for first 24 hours, then 4mg/kg bd

Dose Adjustment in Renal Impairment

Dose adjustment is not required, for the oral formulation.

If CrCl <50ml/min, accumulation of the intravenous vehicle (SBECD) occurs, and the oral route should be used, unless the benefits outweighs the risks of intravenous treatment.

Dose Adjustment in Liver Impairment

No dose adjustment necessary in patients with acute hepatic injury, manifested by elevated liver function tests, but continued monitoring is required.

In patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B, or score 5 - 9), the standard loading dose should be used, but the maintenance dose should be halved. Voriconazole has not been studied in severe chronic cirrhosis (Child-Pugh C, or score >10).