HAEMATOLOGY ANTIFUNGAL GUIDELINE FOR ADULT PATIENTS

For flow chart summary and dosing click here

Introduction

Patients undergoing systemic anti-cancer therapy for haematological malignancy can be at risk of invasive fungal infection (IFI), with the risk determined by diagnosis, age, duration and severity of neutropenia and type of therapy. Treatment of IFI is difficult because of the lack of diagnostic tests, the toxicity of some antifungal agents and also their significant cost. This guideline has been developed to enable the appropriate treatment and prophylaxis of fungal infections in haematology patients across NHS Tayside, but therapy should be tailored to each patient's individual circumstances.

Risk Stratification

The following guidance is for patients at 'high risk' but should be followed for other risk groups if appropriate.

High-risk: severe aplastic anaemia, acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL) and allogeneic stem cell transplant recipients, particularly those receiving allografts from unrelated donors and those with a previous IFI.

Moderate-risk: lymphoma patients undergoing high dose therapy and autologous stem cell rescue

Low risk: all other patients

Notes

- **For flow chart summary and dosing click here**
- ✧Posaconazole is available as IV, liquid and tablets but dosing for each formulation is very different. Always state the formulation on the prescription and check the dosage is correct.
- Refer to voriconazole professional checklist and patient alert card here
- Always check for interactions in SPC or specialist website - http://www.fungalpharmacology.org/tool
- When voriconazole or posaconazole are being used for treatment, ensure pre dose level is checked 5 - 7 days after commencing therapy and when any interacting drugs are commenced / discontinued (12). Ensure Microbiology lab is aware to expect a sample as these have to be sent to a specialist centre.
- Duration of treatment is variable in these infections.
- Patients can be stepped down to oral treatment:
    - if they are clinically improving and scan or other investigation results indicate improvement
    - or for patients on empirical treatment if there is a low index of suspicion of fungal infection after investigation.
- Oral bioavailability is very high for voriconazole, posaconazole and isavuconazole.

Prophylaxis

The choice of antifungal prophylaxis in haematology is risk dependent (8). Itraconazole, fluconazole and posaconazole are the main agents used. Low-dose liposomal amphotericin (Ambisome) is used in ALL induction. Voriconazole is licensed for HSCT recipients but had not been recommended for use in Scotland by the SMC on the grounds of non submission. However, it may be used in other specialist centres and should be continued if the patient is transferred to NHS Tayside.

Primary Prophylaxis

Itraconazole is active against a wide range of yeasts and moulds. It has been shown to significantly reduce *Aspergillus* infections in neutropenic patients when compared to fluconazole (9). Its use is recommended in patients at risk of IFI;

Autologous HSCT for lymphoma
ALL
AML
Severe aplastic anaemia

Posaconazole is given orally, is generally well-tolerated and is active against a wide range of fungi. It was found to be superior to itraconazole and fluconazole in a combined analysis in preventing IFI in high risk patients in two trials (10,11). The study was not powered to detect a difference with itraconazole and the effectiveness of posaconazole and itraconazole appeared to be equivalent. Itraconazole should therefore remain first line prophylaxis for high-risk patients excluding those with a previous IFI. High-risk patients who are intolerant of itraconazole should be prescribed posaconazole.

Fluconazole is active against most yeasts and reduces invasive infection with *Candida albicans* in neutropenic patients. It should be used for autologous HSCT for myeloma and may be considered for other low-risk patients ie. patients not in the above categories who are having inpatient chemotherapy.

Ambisome is given IV three times a week for patients who cannot have azoles due to vincristine interaction e.g. ALL induction.

Secondary prophylaxis

Patients who have had previous treatment for IFI (i.e for 2 weeks or more, not just empirical use until resolution of neutropenic fever) may not have completely cleared the infection at the start of their next course of chemotherapy. They are at high risk of reactivation and should be prescribed oral posaconazole for secondary prophylaxis, even if they have had a breakthrough infection on posaconazole.

Treatment

Empirical IFI treatment

Consideration of empirical antifungal therapy is indicated in neutropenic patients with a pyrexia unresponsive to broad spectrum antibiotics for more than 96 hours and with no focus of infection identified. These patients are at high risk of mould infection (most commonly *Aspergillus*) in the lungs. A multicentre randomised controlled trial in these patients showed caspofungin to be as effective as liposomal amphotericin B, with fewer side effects (1). Voriconazole is not licensed for empirical use in neutropenic fever (2,3).

First-line treatment
Caspofungin IV
Step down to previous antifungal prophylaxis if low index of suspicion of fungal infection otherwise see below proven/probable/possible IFI section.

Second-line treatment OR interactions with Caspofungin
Liposomal Amphotericin B (Ambisome) IV
Step down to previous antifungal prophylaxis if low index of suspicion of fungal infection otherwise see below proven/probable/possible IFI section.

Proven/Probable/Possible IFI

Definitions and diagnosing fungal infections
These are definitions used by the European Organisation for Research in the Treatment of Cancer (EORTC)(4). In summary:

'Proven' IFI is where there is a histological evidence or a fungus cultured from a normally sterile site.
'Probable' IFI in practice this term is not very helpful because without the use of any *Aspergillus* antigen test (e.g serum galactomannan) the microbiological criterion will rarely be fulfilled and Aspergillus PCR on BAL is not mentioned.
'Possible' IFI is defined as a susceptible patient with some clinical evidence of IFI e.g signs on CT chest.

Voriconazole has been shown to be superior (improved survival and clinical response) to amphotericin B in the treatment of invasive aspergillosis, with fewer side-effects, but it must be noted that this was conventional amphotericin B (5). It is licensed for this indication and is recommended as first line treatment in 2016 guidance from the Infectious Diseases Society of America (6) and ECIL-6 (7). Therefore in a patient with CT chest showing a dense, well-circumscribed lesion(s) with or without a halo sign, the air-crescent sign or a cavity (with

no alternative cause found), voriconazole should be used. Where possible a BAL should be performed and sent for Aspergillus PCR (sensitivity 77-80%, specificity 94-95% (13)).

Anti-fungal drugs and *in vitro* activity
Voriconazole is active against some *Fusarium spp* and *Scedosporium spp* but not the group causing zygomycosis (also known as mucormycosis). Isavuconazole is also a triazole antifungal and is licensed for the treatment of invasive aspergillosis and mucormycosis. It has fewer side effects and interactions than voriconazole, in addition, it has activity against *Mucor*. Amphotericin B has the broadest spectrum of activity but may be less active against a few organisms e.g *Aspergillus terreus*. Caspofungin is not active against some fungi, particularly *Cryptococcus spp*, *Fusarium spp* and the group causing zygomycosis. If there is evidence/ suspicion of one of these infections, caspofungin should not be used. Posaconazole has a wide spectrum of activity that includes the zygomycetes. It can be used where specific fungal infections have been refractory to treatment with other antifungals or the patient has been intolerant of other antifungals. Please discuss cases with Microbiology or Infectious Diseases.

Summary of Antifungal Activity

	Aspergillus	Fusarium	Zygomycetes e.g Mucor,Rhizopus
Echinocandins	✓	x	x
Voriconazole	✓	+/-	x
Isavuconazole	✓	+/-	✓**
Posaconazole	✓	+/-	✓
Amphotericin B	✓*	✓	✓

* Except *Aspergillus terreus*
** Overall less active against zygomycetes compared to posaconazole

Key
✓ Antifungal expected to be active against this group of organisms
+/- Antifungal may have activity against this group of organisms – depends on species
x Antifungal not active against this group of organisms and should not be used

First-line treatment (if no previous antifungal prophylaxis or fluconazole only prophylaxis)
Voriconazole IV (check levels see notes above)
Step down to oral voriconazole

Patients who cannot tolerate voriconazole
Isavuconazole IV
Step down to oral isavuconazole
Note: Isavuconazole is not routinely kept in stock – discuss with pharmacy if required

Patients already prescribed itraconazole or posaconazole prophylaxis
Ambisome IV
Initial test dose of 1mg should be given over 10 minutes, stop infusion and observe patient for at least 30 mins, continue if no anaphylactoid/allergic reactions. Test dose has to be repeated at beginning of each new course of treatment. Always prescribe by brand name. Use lean body weight in obese patients.
Step down discuss with Micro/ID

Other options – on Micro/ID advice only
Caspofungin IV or ✧*Posaconazole IV/PO* (check levels see notes above)

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