Introduction

Patients undergoing chemotherapy for haematological malignancy are at high risk of invasive fungal infection (IFI). Duration and severity of neutropenia are the main risk factors. Treatment of IFI is difficult because of the lack of diagnostic tests, the toxicity of some antifungal agents and also their significant cost. This policy has been developed to ensure the appropriate treatment and prophylaxis of fungal infections in haematology patients across NHS Tayside. Further details on these agents, such as doses and interactions, are in the Appendix.

Treatment

Empirical IFI treatment

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

Second-line treatment
Liposomal Amphotericin B (Ambisome) IV

Proven/Probable/Possible IFI

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. In practice the use of ‘Probable’ IFI 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 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 now recommended as first line treatment in 2008 guidance from the Infectious Diseases Society of America (6) and the ECIL (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 in Glasgow (contact Ninewells Microbiology beforehand to arrange).

First-line treatment
Voriconazole IV

Second-line treatment
Liposomal Amphotericin B (Ambisome) IV
Other options are Caspofungin IV or Posaconazole PO

Posaconazole is available as liquid and tablets but dosing for each formulation is very different. Always state the formulation on the prescription and check the dosage is correct.

Voriconazole is active against Fusarium spp and Scedosporium spp but not the group causing zygomycosis (also known as mucormycosis). 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.

**Follow-on oral treatment**
Duration of treatment is variable in these infections, but in general at least 2 weeks is required. Oral voriconazole can be used if patients are well enough to be treated as outpatients because its oral bioavailability is very high (96%).

**Prophylaxis**
The choice of antifungal prophylaxis in haematology is risk dependent (8). Itraconazole and fluconazole are the main agents used, with posaconazole also now licensed. Low-dose amphotericin is used in ALL induction. Voriconazole is also licensed for HSCT recipients but is not recommended for use in Scotland by SMC.

_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 high risk of IFI;

Autologous BMT
ALL
AML
Lymphoma (high-dose chemotherapy)
Myeloma (high-dose chemotherapy)

_Posaconazole_ is given orally, is generally well-tolerated and is active against a wide range of fungi. It was found to be superior to either itraconazole or fluconazole in preventing IFI in high risk patients in two trials (10,11). Patients who are intolerant of itraconazole should be prescribed posaconazole.

Posaconazole is available as liquid and tablets but dosing for each formulation is very different. Always state the formulation on the prescription and check the dosage is correct.

_Fluconazole_ is active against most yeasts and reduces invasive infection with _Candida albicans_ in neutropenic patients. It is used for low-risk patients ie. patients not in the above categories who are having inpatient chemotherapy.

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 (Posaconazole is available as liquid and tablets but dosing for each formulation is very different. Always state the formulation on the prescription and check the dosage is correct).

**References**


Dr William Olver
Consultant Medical Microbiologist
May 2013
Approved by AMG May 2013
Review May 2015
Updated Nov 2014 (posaconazole formulation/voriconazole license)
Appendix

CASPOFUNGIN (CANCIDAS®) 50mg and 70mg vials

Available from CIVAS service Mon-Fri

Dose

For the purposes of this protocol the doses are; 70mg loading dose on day 1, then 50mg daily thereafter. If patient >80kg, use 70mg daily dose.

Reconstitution (if not available from CIVAS)

Reconstitute each vial with 10.5ml water for injections and add to 250ml bag of sodium chloride 0.9%. This should be used immediately.

CASPOFUNGIN IS INCOMPATIBLE WITH GLUCOSE – do not use solutions of glucose to prime or flush the line.

Infusion Rate

Give infusion over 60mins

Dosage adjustments

Renal Impairment - For elderly patients (>65 years) or patients with any degree of renal impairment no dosage adjustments required

Hepatic Impairment - Mild-no dosage adjustments
Moderate-initial loading dose 70mg, daily dose of 35mg thereafter
Severe-no data available

Use under 18 years of age not recommended

Cautions/Contraindications/Side effects

Consult the BNF and Data Sheet – www.medicines.org.uk

Fever, injection site reactions, headache, tachycardia, altered LFT’s and U+E’s - consult product literature (www.medicines.org) for full list

Interactions

Ciclosporin increases levels of caspofungin - monitor LFT’s
Tacrolimus levels can be reduced
Efavirenz, nevirapine, rifampcin, dexamethasone, phenytoin and carbamazepine may result in reduced caspofungin levels. When co-administering with enzyme inducers as listed above, a daily dose of 70mg should be used.
LIPOSOMAL AMPHOTERICIN (AMBISOME®)

Available from CIVAS service Mon-Fri

Dose

For the purposes of this protocol the recommended dose is 3mg/kg (consider rounding to the nearest 50mg).

Reconstitution

Reconstitute a 50mg vial with 12ml of WATER FOR INJECTION ONLY. This will provide a solution of 4mg/ml.
Infusion concentrations should be between 0.2 to 2mg/ml in glucose (dextrose) 5%. In practice for doses between 50mg and 400mg dilute into a 250ml glucose (dextrose) 5%.
AMBISOME IS INCOMPATIBLE WITH NaCl 0.9% (Normal Saline)- do not use solution of Sodium Chloride to prime or flush the lines.

Infusion Rate

30 – 60 minutes.

Dosage Adjustments

Renal Impairment - no dosage adjustment recommended
Liver Impairment - can cause raised alkaline phosphatase and bilirubin. In patients with pre-existing liver failure or changes in liver function test consult the pharmacist.

Caution/Contraindication/Side Effects.

Consult the BNF and Data Sheet – www.medicines.org.uk

Can cause severe allergic reaction, monitor U&E’s & LFT’s - hypokalaemia and hypomagnesaemia are common.

Drug Interactions

Azole antifungals
Caution with other renally toxic drugs
Caution with antiarrythmics where there are concurrent electrolyte disturbances.
Corticosteriods can complicate further electrolyte disturbances
Consult pharmacist for more information.
VORICONAZOLE (VFEND®) INFUSION 200MG AND TABLETS 50MG+200MG

Note: Due to the high oral bioavailability (96%), the IV route should only be used if the oral route is unavailable.

Dose

**IV route**
Loading dose 6mg/kg every 12 hours for 2 doses
Maintenance dose 4mg/kg twice a day (can be reduced to 3mg/kg if not tolerated)

Oral route
>40kg: loading dose 400mg every 12 hours for 2 doses.
Maintenance dose 200mg twice daily (300mg twice daily if response inadequate)
<40kg: loading dose 200mg every 12 hours for 2 doses
Maintenance dose 100mg twice daily (150mg twice daily if response inadequate)

Reconstitution

Reconstitute vial with 19ml water for injection. Add to normal saline 0.9% or glucose 5% to give final concentration of 0.5-5mg/ml (see table)
i.e. 70kg patient at 6mg/kg loading dose (420mg). Give in 100ml NaCl 0.9% over 2 hrs then 4mg/kg maintenance dose (280mg). Give in 100ml NaCl 0.9% over 1.5hrs

**Required Volumes of 10 mg/ml VFEND Concentrate**

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<th>Body Weight (kg)</th>
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<td>40 ml (2)</td>
<td>60 ml (3)</td>
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</table>

Infusion Rate

**Maximum rate of 3mg/kg/hour over 1-2 hours**

Dosage Adjustments

**Elderly (>65yrs)** - **No adjustments**

Renal Impairment - **Moderate to severe -switch to oral therapy if possible to avoid accumulation of excipients. If use IV, monitor serum creatinine.**

Hepatic Impairment - **No dosage adjustments for acute hepatic injury (↑ALT, AST) - mild to moderate hepatic impairment, standard loading dose, half maintenance dose**
Cautions/Contraindications/Side Effects

Consult the BNF and Data Sheet – www.medicines.org.uk

- **Most side effects transient. Include rash, fever, vomiting, diarrhoea and headache. Visual disturbances most common which are mild and reversible with majority spontaneously resolving within 60 minutes**
- **Monitor LFT’s**
- Contraindicated with Terfenidine, Rifampicin, Carbamazepine, Phenobarbital and Anti-retrovirals. Consult product literature for full list (www.medicines.org)

Interactions

**Omeprazole-half dose of omeprazole**
Warfarin-monitor INR
Phenytoin-increase IV maintenance dose of voriconazole to 5mg/kg. Increase oral maintenance dose to 400mg bd (>40kg) and 200mg bd (<40kg) Monitor phenytoin levels and avoid use together if possible.
Ciclosporin-doses should be halved of ciclosporin and monitor levels of ciclosporin
ITRACONAZOLE LIQUID 10mg/ml (SPORANOX™)

Only the Liquid preparation should be used.

Dose

Prophylaxis – 5mg/kg twice daily.

Dosage Adjustments

Renal Impairment - Avoid in severe renal impairment due to propylene glycol in solution.
Liver Impairment - Metabolised in the liver. Caution in patients with pre-existing liver failure - consult the pharmacist. Itraconazole can cause hepatotoxicity - consult the pharmacist and review SPC. If a causal relationship is suspected stop itraconazole.

Caution/Contraindication/Side Effects

Consult the BNF and Data Sheet – www.medicines.org.uk

Patients with sensitivities to itraconazole or other Azoles. Regularly monitor LFT’s. CAN RARELY CAUSE CONGESTIVE HEART FAILURE.

Drug Interactions

Calcium Channel Blockers – increased risk of CCF
Clarithromycin increases plasma level of itraconazole.
Warfarin effects enhanced
Phenytoin decreases itraconazole levels
Care with antipsychotics
Markedly increased and prolonged sedation with midazolam.
Digoxin levels increased.
Ciclosporin levels increase
Atorvastatin, simvastatin and lovastatin – stop these drugs as increased risk of myopathy
PPI’s and histamine H2 antagonists reduce absorption
Vincristine metabolism inhibited increased risk of neurotoxicity
Busulphan metabolism inhibited increased risk of toxicity.
Methylprednisolone metabolism inhibited
Reduces effects of amphotericin
Dose

Prophylaxis – 50mg daily or 100mg if poor absorption anticipated.

**Dosage Adjustments**

Renal Impairment - In mild to moderate renal failure 50mg can be used as a maximum dose daily. In severe renal failure consult the pharmacist - rarely changes in electrolytes have been seen with fluconazole therapy of uncertain clinical significance.

Liver Impairment - In patients with pre-existing liver failure consult the pharmacist. Fluconazole can cause hepatotoxicity - if a causal relationship cannot be excluded fluconazole should be stopped and advice sort regarding alternative therapy.

**Caution/Contraindication/Side Effects**

Consult the BNF and Data Sheet – [www.medicines.org.uk](http://www.medicines.org.uk)

Patients with sensitivities to fluconazole or other Azoles. Regularly monitor LFT’s.

**Drug Interactions**

Warfarin effects increased.
Phenytoin levels reduced.
Ciclosporin & tacrolimus increased
Markedly increased levels of midazolam.
Reduces effects of amphotericin