Trust Guideline for the use of Antifungals in Adults

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V4	July 2024	Consultant Microbiologist, Specialist Pharmacist, Antimicrobials	Reviewed and updated

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None	Not applicable

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:

- All consultant Microbiologists, NNUH
- Mr Jack Johnson, Highly Specialist Pharmacist, CF
- Dr Chandan Saha, Consultant Haematologist
- Mr Matthew Schneiders, Consultant Opthalmologist
- Antimicrobial Subgroup Committee

Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline applicable to the NNUH; please refer to local Trust's procedural documents for further guidance, as noted in Section 5.

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1. Introduction

1.1. Rationale

The purpose of this guideline is to provide guidance on the selection of antifungal therapy for serious invasive fungal infections. It is based upon current published evidence at the time of writing. It is not intended to be a comprehensive clinical pathway or a substitute for consultation with Microbiology.

1.2. Objective

The objective of the guideline is to

- Provide empirical antifungal choice for serious invasive fungal infections.

1.3. Scope

This guideline provides information on the selection of antifungal therapy for adult patients (16+ years old).

1.4. Glossary

The following terms and abbreviations have been used within this document:

Term	Definition

2. Responsibilities

2.1. Medical staff

Medical staff are responsible for prescribing antifungals according to this guideline

2.2. Nursing staff

Nursing staff are responsible for administering antifungals according to this guideline

2.3. Pharmacists

Pharmacists are responsible for auditing compliance and checking prescriptions and administration against this guideline

3. References

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4. Monitoring Compliance

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
Antifungals prescribed in accordance with this guideline	Audit	Antimicrobial Subgroup committee/ Microbiology	Antimicrobial Subgroup committee/Microbiology	Yearly

The audit results are to be discussed at relevant governance meetings to review the results and recommendations for further action. Then sent to the Antimicrobial

Subgroup Commitee who will ensure that the actions and recommendations are suitable and sufficient.

5. Appendices

There are no appendices for this document.

6. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	All	**Department**	Pharmacy
Name of person completing form	Caroline Hallam	**Date**	13.5.24

Equality Area	Potential Negative Impact	Impact Positive Impact	Which groups are affected	Full Impact Assessment Required YES/NO
Race	No	No	No	No
Pregnancy & Maternity	No	No	No	No
Disability	No	No	No	No
Religion and beliefs	No	No	No	No
Sex	No	No	No	No
Gender reassignment	No	No	No	No
Sexual Orientation	No	No	No	No
Age	No	No	No	No
Marriage & Civil Partnership	No	No	No	No
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?	No effect on equality/diversity			

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.

1. Introduction

The purpose of this guideline is to provide guidance on the selection of antifungal therapy for serious invasive fungal infections. It is based upon current published evidence at the time of writing. It is not intended to be a comprehensive clinical pathway or a substitute for consultation with Microbiology.

Risk factors

There are several risk factors associated with developing invasive candidiasis including:

- Abdominal surgery, particularly recurrent anastomotic leaks, or perforations
- Acute necrotising pancreatitis
- Haematological malignancy and haematopoietic stem cell transplant
- Solid organ transplant
- Solid organ tumour
- Total parenteral nutrition
- Haemodialysis
- Steroid use
- Chemotherapy
- Candida colonisation at non-sterile sites
- Central venous catheter
- Broad spectrum antibiotic use
- Severe systemic illness, trauma or burns.
- Patients immunocompromised due to HIV-infection.

Definitions

Proven infection:
Positive blood cultures or culture from a sterile site with clinical or radiological abnormality OR histology/cytochemistry showing yeasts/hyphae from a biopsy with evidence of tissue damage.

Probable and possible infection:
Combinations of host factors (fever, neutropenia, corticosteroid use (>3 weeks), or persistent fever unresponsive to broad-spectrum antibacterials) plus clinical, microbiological and radiological criteria.

Positive Candida line tip

The management of patients with positive Candida line tip cultures in the absence of a positive blood culture remains uncertain. The lack of prospective trials prevents any firm recommendation of treatment. As a transient

candidaemia cannot be excluded we recommend that antifungal treatment should be commenced, and a surveillance blood culture should be performed.

Invasive aspergillosis and mucormycosis

Aspergillus species are an important cause of life-threatening conditions mainly in immunocompromised patients (eg patients with prolonged neutropenia, allogenic hematopoietic stem cell transplants, inherited or acquired immunodeficiencies, steroid use, the use of biologic agents and solid organ transplants, respiratory diseases, and critical illness, such as following a respiratory viral infection like influenza or COVID-19.).

The most common infecting species is *Aspergillus fumigatus* complex, but other species complexes that are common causes of disease include *A. flavus, A. terreus*, and *A. niger*. Less common species, such as *A. nidulans, A. calidoustus, A. lentulus,* and many others, have been reported to cause infection in highly immunosuppressed patients.

Invasive aspergillosis (IA) includes invasive pulmonary aspergillosis (IPA), Aspergillus sinusitis, disseminated aspergillosis and several types of single organ invasive aspergillosis.

General points

- Doses advised are for adult patients with normal renal and liver function. If these are impaired consult pharmacist for advice.
- Always refer to the BNF and individual data sheets to check possible drug interactions
- IV antifungals should be reviewed daily to confirm the need for continuation and to assess whether an alternative antifungal (oral or systemic) can be used.
- Therapeutic drug monitoring should be performed where indicated (see section 7).
- All antifungals should be ‘stepped down’ as details on the site and type of infection become evident where appropriated.
- See monographs (see section 7) for specific advice about each antifungal agent

Investigations for Invasive Aspergillosis

- Radiographic imaging: high resolution computed tomography (HRCT), MRI for sinus or CNS disease
- Tissue and bronchial lavage (BAL)/ wash specimens should be send for histopathologic /cytologic and culture examination.
- BAL for Galactomannan (GM).
- Serum for GM* and 1-3 Beta-D-Glucan antigen detection test

  1-3 beta-D-glucan, is present in the cell wall of many types of fungi and can be positive in patients with a variety of invasive fungal infections, including Aspergillosis, candidiasis and *Pneumocystis jirovecii*.It is typically negative in patients with mucormycosis or cryptococcosis. As it is not specific for Candida it should not be used as a definitive diagnosis of invasive candidiasis.

CANDIDAEMIA			
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**

Proven Candidaemia (non neutropenic) Positive Candida blood culture prior to sensitivities	**Anidulafungin IV** (200mg on first day and then 100mg once daily) until speciation and sensitivities are available (usually around 72 hours) and then treat according to sensitivities. If intolerance, echinocandin resistant organism, CNS involvement or infection with C.*parapsilosis* is suspected **AmBisome** (Liposomal Amphotericin) 3-5 mg/kg IV per day ***Take a surveillance blood culture at 48 hours after starting treatment***	**Targeted Treatment once sensitivities are available (48-72hrs)** If patient is haemodynamically stable and responding and the isolate is sensitive to fluconazole: Switch to **Fluconazole IV** loading dose 800mg, (12mg/kg) IV on first day and then 400mg (6mg/kg) IV once daily onwards.	Uncomplicated infection should be treated f oral treatment combined) after the last docu blood culture and resolution of signs and sy infection. **ORAL SWITCH:** Step down to orals if the fo are met: Patient has had 5-7 days IV treatm clinically stable and can tolerate and absorb patient has *Candida* susceptible to fluconaz voriconazole, source of sepsis has been ide related infection,line has been removed. 1st choice **Fluconazole PO** 400mg (6mg/kg 2. **Voriconazole PO** (if resistant to fluconaz (6mg/kg) bd for 2 doses then 200mg (3mg/k
Presumed Candidaemia (non neutropenic) In adult non-neutropenic patients: consider empirical antifungal treatment in patients with unexplained clinical features of infection (e.g fever, increasing or raised WCC, haemodynamic instability, severe sepsis) and the presence of risk factors listed above such as TPN, candida colonisation, initial surgery etc	**Anidulafungin IV** (200mg on first day and then 100mg once daily)	**AmBisome** (Liposomal Amphotericin) 3-5 mg/kg IV per day **OR** **Voriconazole** Loading dose of 400mg PO (for patients ≥ 40kg)	

		or 6 mg/kg IV every 12 hours for 2 doses (24hrs), then maintenance dose of 200mg (for patient ≥ 40kg) PO every 12 hours or 4mg/kg IV every 12 hours	
Proven or Presumed Candidaemia (Neutropenic)	Refer to Trust policy 8330 Trust Docs (nnuh.nhs.uk)		

MUCOSAL CANDIDIASIS (ORAL, OESOPHAGEAL, GENITAL)			
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**
Vulvovaginal candidiasis (uncomplicated)	**Clotrimazole 500mg** vaginal tablet STAT OR clotrimazole cream 1% topically bd –tds until symptoms settle.	Fluconazole 150mg PO single dose.	
Vulvovaginal candidiasis (Severe acute)	**Fluconazole** 150 mg every 72 hours for 3 doses		
Vulvovaginal candidiasis (recurrent)	**Fluconazole,** initially 150 mg every 72 hours for 3 doses, then 150 mg once weekly for 6 months.		
Oropharyngeal (mild disease) **Oropharyngeal (moderate/severe disease)**	**Nystatin** suspension 100,000 units/ml - 1ml qds PO for 7-14 days **Fluconazole** loading dose: 200 mg PO OD the first day and then subsequent dose: 100-200mg PO daily. Treat for 7-14 days or for 48 hours after lesions have resolved.	For fluconazole refractory disease Itraconazole solution 100 - 200mg BD	Maximum treatr days, except in immunocompro (up to 28 days)
Oesophageal	**Fluconazole** loading dose 400 mg	Speak to Microbiology	14-21 days

	IV/PO OD the first day and then subsequent dose 200-400mg IV/PO OD.		
URINARY TRACT CANDIDIASIS			
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**
Candida UTIs **Asymptomatic candiduria**	Treatment is NOT indicated unless high risk patients eg neutropenic patients or patients undergoing urological procedures. High-risk patients, should be treated with similar regimens as patients with candidaemia eg **Fluconazole** if C. albicans or Candida sp. susceptible on testing 800mg loading dose IV/PO, then 400mg IV/PO daily. Patients undergoing urologic procedures: **Fluconazole** 6mg/kg (400mg) od for several days before and after the procedure	If resistant to fluconazole contact Microbiology	Review at 7 day
Symptomatic cystitis	**Fluconazole** 200mg (3mg/kg) PO OD for 14 days (If C. albicans or Candida sp. susceptible on testing)	If resistant to fluconazole contact Microbiology	See individual recommendatio
Pyelonephritis	**Fluconazole** 200 mg (3mg/kg) to 400mg (6mg/kg) PO OD for 14 days (If C. albicans or Candida sp susceptible on testing and patient haemodynamically stable)	If resistant to fluconazole contact Microbiology	See individual recommendatio

OCULAR CANDIDIASIS				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Ocular candidiasis: chorioretinitis or endophthalmitis ie with vitritis (endogenous) *Usually results from candidaemia which may be persistent or transient. Blood culture might be negative at time of diagnosis.*	Discuss all cases with a Consultant Microbiologist. If sensitivities unknown or Fluconazole/Voriconazole resistant isolates: **AmBisome (Liposomal Amphotericin B)** 3-5 mg/kg IV OD +/- **5-flucytosine** (5-FC) 25 mg/kg PO/IV every 6 hours (If isolate susceptible) For Fluconazole susceptible isolates: **Fluconazole** IV, loading dose, 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) OD Urgent ophthalmological assessment and consideration of intravitreal therapy such as voriconazole (100 µg/0.1 mL of sterile water) or amphotericin B deoxycholate (5 µg/0.1 mL) +/- surgical intervention e.g. vitrectomy is	For fluconazole resistant, voriconazole susceptible isolates: **Voriconazole** IV, loading dose 400mg (6 mg/kg) intravenous twice daily for 2 doses, then 300mg (4 mg/kg) BD	At least 4-6 weeks or until intraocular infection has resolved as determined by repeated ophthalmological examinations. Discuss with Microbiology for IV to oral switch at 5-7 days	**An urgent referral to ophthalmology is required** ***For complicated keratitis and exogenous ocular candidiasis contact a consultant microbiologist.***

	recommended.			

BONE AND JOINT INFECTIONS				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Osteomyelitis/ spondylodiscitis	if susceptible isolate, **Fluconazole** 400mg (6mg/kg) IV/PO OD for 6-12 months (if pt is unstable start with IV and switch to oral when stable).	**Anidulafungin** 200mg STAT then 100 mg daily. Discuss with Microbiology for oral switch after 14 days. **OR** **AmBisome** (Liposomal Amphotericin B) 3–5 mg/kg daily. Discuss with Microbiology for oral switch after 14 days.	Usual duration 6-12 months Duration is depending on clinical response and normalization of inflammatory markers.	
Septic Arthritis	If susceptible isolate, **Fluconazole** 400mg (6mg/kg) IV/PO OD for minimum 6 weeks	**Anidulafungin** 200mg STAT then 100 mg daily. Discuss with Microbiology for oral switch after 14 days. **OR** **AmBisome** (Liposomal Amphotericin B) 3–5 mg/kg daily. Discuss with Microbiology for oral switch after 14 days.	Total duration including oral minimum 6 weeks	Surgical debridement/wash out is strongly recommended.
Prosthetic joint infections	If susceptible isolate- **Fluconazole** 400 mg (6mg/kg, max. per dose 800 mg) PO/IV OD	**Anidulafungin** 200mg STAT then 100mg daily or **AmBisome** (Liposomal amphotericin B) 3-5 mg/kg OD Discuss with Microbiology for oral switch option	Duration of treatment is at least 12 weeks after the resection arthroplasty and at least 6 weeks after prosthesis implantation.	Removal of prosthesis is strongly recommended. Two stage procedure is preferred. If prosthesis cannot be removed consider chronic suppression therapy eg fluconazole 400mg (6mg/kg) OD if isolate susceptible. Discuss with Consultant Microbiologist.

CANDIDA ENDOCARDITIS				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Candida Endocarditis	**Anidulafungin** IV 200mg OD (high dose) Discuss with Consultant Microbiologist **Fungal blood cultures should continue to be taken for at least the first 2 weeks of therapy or if any clinical deterioration occurs**	**AmBisome** (Liposomal amphotericin B) IV 3-5 mg/kg OD +/- **5-flucytosine** (5-FC) 25 mg/kg PO every 6 hours (If isolate susceptible) **Fungal blood cultures should continue to be taken for at least the first 2 weeks of therapy or if any clinical deterioration occurs**	Surgical valve replacement is highly desirable: treatment should be continued for at least 6 weeks after surgery and for a longer duration for patients with complications.	Initial treatment should be modified once species and susceptibility profile are known. Long term suppression should be considered in patients with native valve infective endocarditis who can't undergo valve replacement and with prosthetic valve endocarditis.

CNS CANDIDIASIS				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Central nervous system candidiasis	**AmBisome (Liposomal amphotericin B)** IV 5 mg/kg +/- Flucytosine IV 25mg/kg qds Oral step down after the patient has responded to initial treatment, usually after several weeks. Fluconazole, 400–800 mg (6–12 mg/kg) PO OD	Discuss with Consultant Microbiologist	For oral step down after the patient has responded to initial treatment. Discuss with Consultant Microbiologist. Treatment should be continued until all signs, symptoms, CSF and radiological abnormalities have resolved.	All CNS devices should be removed, if feasible.
Cryptococcus neoformans Meningitis **(non pregnant patients with HIV)**	**Induction Therapy: dual therapy is essential.** Assess clinical response daily. Repeat LP after 14 days of induction therapy to confirm CSF sterilisation. **AmBisome (Liposomal amphotericin B)** IV 4mg/kg OD + Flucytosine PO 25mg/kg qds for a minimum of 14 days **OR (2nd line)** Fluconazole 800mg -1200mg PO OD + Flucytosine PO 25mg/kg qds for a minimum of 14 days **OR** If no Flucytosine is available **AmBisome (Liposomal amphotericin B)** IV 4mg/kg OD + Fluconazole 1200mg PO OD for a minimum of 14 days **Consolidation Therapy** Pts with a clear response to treatment can transition to fluconazole pending the results of the CSF culture. Treatment should be initiated with Fluconazole 800mg and can be reduced to 400mg/day to complete the 8 week course if all of the following criteria are met • The pt received induction therapy with Ambisome + Flucytosine for 14 days • CSF cultures obtained after 14 days of induction therapy are negative • ART has been started Fluconazole 800mg PO/IV OD for a minimum of 8 weeks **Maintenance Therapy** Minimum duration should be at least 1 year. Maintenance therapy can then be discontinued if			All cases should be managed in conjunction with an infectious diseases specialist. Antifungal therapy involves 3 phases: induction therapy, followed by consolidative therapy and then maintenance. In some cases, secondary prophylaxis and/or suppressive therapy should be considered. In non HIV patients' maintenance therapy could be potentially stopped after 12 months.

	pt on ART and a CD4 cell counts ≥ 100 cells/microL and have achieved an undetectable viral load on ART for more than 3 months Fluconazole 200mg PO OD for a minimum of 1 year	

INTRA-ABDOMINAL FUNGAL INFECTION				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Intra-abdominal Fungal Infection	**Fluconazole IV** (loading dose 800mg IV on first day and then 400mg IV once daily onwards).	If not sensitive or patient not clinically responding continue on anidulafungin or treat according to sensitivities in discussion with microbiologist **Anidulafungin*** IV (200mg on first day and then 100mg once daily)	The duration of therapy should be determined by adequacy of source control and clinical response . When patients are stable and not candidaemic, PO administration can be considered : PO Fluconazole 400mg (6mg/kg) OD for up to 14 days	Empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection/perforation and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis that does not respond to empirical antibiotic treatment. Treatment of intra-abdominal candidiasis should include source control, with appropriate drainage and/or debridement The choice of antifungal therapy is empirical and can further be tailored according to blood culture results, if available.

Respiratory Fungal Infections in Cystic Fibrosis and Chronic Respiratory Diseases in Adults				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Scedosporium **(*Scedosporium apiospermum* and Lomentospora *prolificans*)**	Voriconazole 400mg PO bd for 2 doses and then 200mg PO bd (depending on serum concentration) *Lomentospora prolificans* is a very drug resistant mould. Combination therapy with **terbinafine 250 mg once/ twice daily po and voriconazole 400mg PO bd for 2 doses and then 200mg PO bd** may be considered in discussion with the consultant microbiologist. [Meletiadis *et al* 2003]. Dosing and duration of treatment may depend on clinical response and should be discussed with microbiologist.	Itraconazole PO (with TDM) 200mg bd		*Scedosporium* (*Scedosporium apiospermum* and Lomentospora *prolificans*) are common saprophytic moulds often found in the environment including soil, sewage, polluted water, and decaying vegetation. S. apiospermum and S. prolificans are colonizers of abnormal airways caused by bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease, or lung transplantation. Scedpsporium spp. are one of the most frequently isolated moulds (second only to *Aspergillus* spp) found in CF. In the majority of cases the isolation represents colonization. However, in patients with repeated positive sputum or BAL culture and deteriorating lung function *Scedosporium* infection may need to be considered and treated. Lung transplant patients and other severely immunocompromised patients are also particularly susceptible to invasive *Scedosporium* infection.
Isolation of candida in respiratory secretions	*Candida* isolated from the sputum without clinical signs of oral thrush indicates colonisation which is very common in hospitalised patients and does not warrant treatment. Candida in the sputum is also not an			

	indicator for *Candida* pneumonia which is an extremely rare infection and if suspected should be discussed with a Consultant Microbiologist.			

Invasive Aspergillosis and Mucormycosis				
	ANTIFUNGAL	**ALTERNATIVE**	**DURATION**	**ADDITIONAL INFORMATION**
Confirmed invasive aspergillosis including pulmonary, tracheobronchial, chronic necrotizing pulmonary, sinus, CNS, heart, osteomyelitis, septic arthritis, cutaneous and peritonitis	Voriconazole 6mg/kg IV bd for 1 day then 4mg/kg IV bd Switching between IV and oral administration is appropriate when clinically indicated. Please measure pre-dose voriconazole levels 5 days after switching from IV to oral formulation	AmBisome (Liposomal amphotericin B) 3-5mg/kg/day.	Minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease	Early treatment of IA and reversal of immunosuppression are important components of successful treatment
Suspected invasive aspergillosis	AmBisome (Liposomal amphotericin B) IV 5mg/kg/day.	Discuss with Microbiology		
Aspergilloma	Asymptomatic patients with a single aspergilloma and no progression of the cavity size over 6–24 months should continue to be observed	Patients with symptoms, especially significant hemoptysis, with a single aspergilloma, should have it resected, assuming that there are no contraindications Peri-/postoperative antifungal therapy is not routinely required, but if the risk of surgical spillage of the aspergilloma is moderate (related to location and morphology of the cavity), antifungal therapy with voriconazole (or another mold-active azole) or an echinocandin is suggested to prevent *Aspergillus* empyema.		

		Voriconazole IV 6mg/kg bd for 1 day then IV 4mg/kg bd		
Allergic bronchopulmonary aspergillosis	Posaconazole 300mg BD day 1 then 300mg OD	Voriconazole PO 400mg bd 2 doses then 200mg bd		
Mucormycosis	AmBisome (Liposomal amphotericin B) IV 5mg/kg/day.	Discuss with Microbiolgy		Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy

Drug Monographs

	Fluconazole	**Itraconazole**	**Ambisome (Liposomal Amphotericin B)**	**Voriconazole**
Formulary Status	No restrictions	No restrictions	No restrictions	As per Trust Guideline for the Use of Antifungals in Adults, or after the recommendation of a Consultant Microbiologist
Dosage	PO: 50mg-400mg od depending on indication IV: 50mg-400mg od depending on indication Maximum dose 800mg od for PO or IV in severe infection	IV or Oral Dose depending on indication	Test dose1mg over 10 minutes and then 3mg/kg-5mg/kg od depending on severity of infection	Po->40kg 400mg bd for 2 doses, then 200mg bd increased if necessary to 300mg bd. <40kg 200mg bd for 2 doses, then 100mg bd, increased if necessary to 150mg bd IV: 6mg/kg bd for 2 doses, then 4mg/kg bd (reduced to 3mg/kg bd if not tolerated)
Activity	Fungistatic	Fungistatic	Fungicidal	Fungicidal against *Aspergillus* spp. Fungistatic against *Candida* spp.
CSF penetration	Excellent (~80%)	Poor (<10%)	Poor (<2.5%)	Good (40-60%)
Elimination Route	Renal	Hepatic	Unknown	Hepatic
Renal dose adjustment	Yes	No (Avoid use of IV formulation in CrCl<30ml/min Accumulation of cyclodextrin component)	No	No

Hepatic dose adjustment	No	Yes	No	Yes
Toxicities (not a comprehensive list, see BNF for further details)	Hepatoxicity (high doses and prolonged therapy)	Negative inotropic effect – caution in pts at high risk of heart failure. See BNF for full warning. Hepatotoxicity GI	Nephrotoxicity Infusion related reactions Electrolyte abnormalities	Hepatoxicity, cholestasis and fulminant hepatic failure reported uncommonly usually in first 10 days, risk increased in pts with haematological malignancy. Monitor LFTS before treatment starts and during Possible QT interval prolongation Rash Hallucinations Visual disturbances
Potential Drug Interactions (consult BNF for further details)	+	+++	–	+++

	Caspofungin	**Anidulafungin**	**Posaconazole**
Formulary Status	Restricted Serious proven infections in haematology patients. CCC according to candida guidelines Other indications on advice of a consultant microbiologist	Restricted	Restricted
Dosage	IV: 70mg IV on first day then 50mg IV od (70mg od if >80kg)	200mg IV on day 1 and then 100mg od	200mg qds /400mg bd
Activity	Fungicidal against *Candida* Fungistatic against *Aspergillus*	Fungicidal against *Candida* Fungistatic against *Aspergillus*	Fungistatic
CSF penetration	No	No	Yes
Elimination Route	Hepatic	Hepatic	Hepatic

Renal dose adjustment	No	No	No
Hepatic dose adjustment	Yes	No	No – but use with caution
Toxicities (not a comprehensive list, see BNF for further details)	Nausea, diarrhoea, vomiting,dyspnoea, headache, hypokalaemia, arthralgia, rash, pruritus, injection site reactions	Diarrhoea, nausea, vomiting, flushing, convulsion, headache, coagulopathy, hypokalaemia, raised serum creatinine, rash, pruritus	GI disturbances, blood disorders, dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia,electrolyte disturbances, dry mouth, rash
Potential Drug Interactions (consult BNF for further details)	+	-	++

Guidelines for Antifungal Drug Monitoring

Antifungal assays are not processed onsite and are sent to the Mycology Reference Laboratory. The results of these tests can take several days before they are available

Antifungal agent	Time of sample	Reference range	Comment

Voriconazole (oral and IV)	pre-dose after 3-5 days	Trough Prophylaxis: >1 mg/L Treatment: >2 mg/L NB: Levels above 5.5 mg/L are more likely to lead to liver toxicity and encephalopathy. Levels above 10 mg/L should be avoided.	• The absorption and metabolism of voriconazole will vary from patient to patient and there are no established recommendations. • Toxicity can manifest itself as visual disturbances, liver dysfunction, skin reactions and neurotoxicity. • Repeat assay after 4-8 days of treatment
Itraconazole (IV or oral)	pre-dose after 4-	Trough Prophylaxis:0.5-1 mg/L Treatment:1.0-2.0 mg/L	• Liver function tests should be monitored during prolonged courses. • Repeat assay after 4-8 days of treatment

	7 days		
Posaconazole (oral)	pre-dose after 3-8 days	Trough Prophylaxis: 0.7-1.5 mg/L Treatment: 1.0-3.75mg/L	• The absorption and metabolism of posaconazole will vary from patient to patient, there are no established recommendations. • QDS dosing compared with BD dosing may result in increased trough levels. • Posaconazole absorption is significantly increased when administered after a high fat meal • Repeat assay after 4-8 days of treatment
Flucytosine (oral)	pre-dose a	Trough: 20-40 mg/L Post dose: 50-100 mg/L NB: Trough concentrations < 20 mg/L have been associated with treatment failure and emergence of resistance. Post dose levels >100 mg/L are considered toxic.	• Monitor for bone marrow toxicity • Repeat assay after 4-8 days of treatment • Consider using adjusted body weight in obese patients

	nd 2 hours post-dose after 2 days		
Flucytosine (IV)	pre-dos		

	e a n d 3 0 m i n s p o s t - d o s e a f t e r 2 d a y s		
Caspofungin	N o t r		

	e c o m m e n d e d		
Amphotericin B (including Fungizone and AmBisome)	M e a s u r e m e n t i s n o t o f t e n i n d i c		• Monitoring of blood concentrations of amphotericin B during treatment is rarely indicated. The optimum serum concentrations of the drug for particular fungal infections have not been determined. • Toxicity is assessed by monitoring renal function.

	ated		
Fluconazole	Measurement is not often indicated		