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Trust Guideline for the use of Antifungals in Adults

For use in:	All adult clinical areas
By:	Doctors, pharmacists and nurses involved in prescribing/supplying/administering antifungals.
For:	All adult patients that require an antifungal
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This is a Controlled Document

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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.

Invasive fungal infections

Invasive fungal infections are seen mostly in:

1. Intensive care patients, who are not necessarily neutropenic, but are compromised due to:
    - Breaches in their integument e.g. extensive abdominal surgery.
    - Presence of long-term intravascular lines.
    - Receiving parenteral nutrition (PN).
    - Severe systemic illness or burns, or;
    - Prolonged broad-spectrum antibiotic therapy.
2. Patients with prolonged neutropenia or sustained immunosuppression following intensive chemotherapy, bone marrow transplant or solid organ transplantation.
3. 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.

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

2. Candidiasis (in adults)

2.a Mucosal candidiasis

General Guidance:
In all cases of mucosal candidiasis a sample (swab or washing) should be taken prior to treatment and sent to Microbiology to guide specific treatment. Some Candida species are resistant to fluconazole. If the patient fails to respond to treatment please contact microbiologist for advice.

Candida in Sputum:

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.

Oropharyngeal candidiasis:

-Mild disease:

Nystatin oral suspension 100,000U/mL 1ml qds PO.

-For moderate to severe disease or in immunocompromised/neutropenic patients:

Fluconazole l*oading dose: 200 - 400 mg PO OD day 1 and then subsequent dose: 100 mg to 200 mg PO OD.* Treat for 7-14 days or for 48 hours after lesions have resolved.

If nebuliser is in use rinse the unit thoroughly. Clean dentures regularly. Encourage the patient to rinse their mouth after inhaled/nebulised steroid.

Oesophageal candidiasis:

Fluconazole 200-400mg PO OD, for 14-21 days. Longer treatment periods may be indicated in immunocompromised patients. Oral fluconazole is preferred.

If infection is due to non-*C.albicans* or if refractory (no clinical response after ≥ 7 days) to treatment contact microbiologist.

Genital candidiasis (penile or vulvovaginal candidiasis)

-Uncomplicated infection:
Topical: **Clotrimazole 500mg** vaginal tablet STAT OR clotrimazole cream 1% topically bd –tds until symptoms settle.
or
Systemic**: Fluconazole 150mg PO single dose**.

-Recurrent* *Candidia* infection or refractory, re-send swab for culture and susceptibility testing. Treat for up to 6 months (unlicensed). See BNF for treatment regimens. *recurrent is defined as ≥4 episodes of symptomatic vulvovaginal candidiasis within one year caused by the same *Candida* species susceptible to fluconazole.

2.b Treatment of candidaemia in adults

General guidance:

Candida is the most common cause of nosocomial fungal bloodstream infection and contributes significantly to the morbidity and mortality of patients. Particular **risk factors** are intra-vascular lines, total parenteral nutrition, abdominal surgery, intensive care stay, intravenous drug abuse and malignancies. The recommendations are based on national and international clinical guidelines for the management of proven or possible candidaemia.

General guidance on the management of serious invasive *Candida* infections/candidaemia

- Remove intra-vascular lines if feasible or change (but not through guidewires) as early as possible to lower mortality and shorten the duration of infection.
- Candidaemia should be treated with systemic anti-fungal agents unless all treatment has been withdrawn. Treatment should be initiated within 48 hours of candidaemia being documented.
- A surveillance blood culture must be taken at 48 hours after initiation of therapy to enquire and document resolution of fungemia.
- Uncomplicated infection should be treated for two weeks after the last documented negative blood culture and resolution of signs and symptoms of infection.
- The choice of antifungals depends on the clinical status of the patient, the knowledge of the *Candida* species and/or sensitivities, drug toxicity and organ dysfunction.
- A fundoscopy should be performed and documented to exclude fungal endophthalmitis. This is the most common infection related complication and patients may need modifications in their treatment.
- Exclude endocarditis. Document heart sounds and peripheral stigmata in the medical notes. Consider cardiology review to determine if an ECHO required (IVDU and haemodialysis patients have a particularly high risk of Candida endocarditis).
- Patients with complicated *Candida* infections such as endocarditis, central nervous system or other organ involvement may need more than 14 days of anti-fungal treatment possibly in combination with additional anti-fungal agents. Please contact the microbiologist (Ext 4587) for advice.
- Routine antifungal prophylaxis is not warranted in non-neutropenic patients.
- Antifungal prophylaxis may only be prescribed in selected high risk patients (see the prophylaxis section below).
- Certain antifungal agents require **therapeutic drug monitoring** (see section 6.)

General guidance on the susceptibility of known *Candida* species

Acquired resistance of *Candida* to antifungal agents is rare but some species are intrinsically resistant to some antifungals. Speciation and sensitivity testing of non-*C. albicans* species may take up to two weeks if sent to the reference laboratory. Please contact the microbiologist (Ext 4589) for further guidance.

Treatment of Candidaemia in Adults (Cont.)

Empirical first line : (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, renal candidiasis, CNS involvement or infection with C.parapsilosis is suspected
Liposomal Amphotericin 3 mg/kg IV per day

Treat candidaemia 14 days from the last negative surveillance blood culture (which MUST be taken at 48 hours after starting treatment).

***IN NEUTROPENIC PATIENTS** use **Caspofungin** IV (70 mg od first day then 50mg od if <80kg or 70mg od if >80kg)

OR

Liposomal Amphotericin 3/kg IV per day

OR **Voriconazole**

loading dose 6 mg/kg IV BD for 2 doses (24hrs), then maintenance dose of 4mg/kg IV BD, can be used in situations where mould coverage is required (see **monograph 6**). Avoid empirical use of Voriconazole if patient is on Voriconazole, itraconazole or posaconazole prophylaxis.

Targeted treatment: *(once sensitivities/species are available (48-72 hours)*

If patient is haemodynamically stable and responding and the isolate is sensitive to fluconazole:

Switch to **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.

Empirical treatment of suspected candidaemia but NOT proven

Suspected cases of *Candidaemia* but negative blood cultures or awaiting results must be discussed with a Consultant Microbiologist before treatment is initiated.

Step down criteria to oral treatment

Treatment can be stepped down to oral fluconazole (if sensitive to fluconazole) or oral voriconazole (if resistant to fluconazole) if the following criteria are met:

1. Patient has had 5-10 days IV treatment.
2. Patient is clinically stable and can tolerate and absorb the oral agent.
3. Patient has *Candida* susceptible to fluconazole or voriconazole.
4. Surveillance cultures are taken at 48hrs and when again necessary to prove treatment success or failure

5.Source of sepsis has been identified and if line-related line has been removed.

Treat uncomplicated candidaemia 14 days from last documented negative surveillance blood culture.

Fluconazole PO 400mg-600mg od (if sensitive)

Voriconazole PO (for Voriconazole monograph see section 6)
Body weight over 40kg :400mg 12 hourly for 2 doses then 200mg 12 hourly (increased to 300mg 12 hourly if necessary)
Body weight under 40kg – consult BNF

2.c Management of positive *candida* vascular 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 considered and a surveillance blood culture should be performed.

If culture shows *C.albicans* or other *Candida* species susceptible to fluconazole treat with **Fluconazole**: 400mg on first day then 200-400mg PO od for 7 days, IV if oral route or absorption compromised (14 days if clinical signs of infection and raised inflammatory markers).

If *C. glabrata* or fluconazole resistant organisms, discuss with microbiologist.

2d Other Invasive Candidiasis (in adults)

All patients in the below groups should be discussed with a Consultant Microbiologist.

2.d.i Ocular Candidiasis

There are two forms of ocular endogenous candidiasis, chorioretinitis and endophthalmitis.

Chorioretinitis is the inflammation of the choroid and the retina while endophthalmitis is the inflammation of the vitreous body. Treatment is the same for both types but an intravitreal injection is sometimes indicated in endophthalmitis in addition to systemic therapy.

An urgent referral to Ophthalmology is required.

For complicated keratitis and exogenous endophthalmitis contact a consultant microbiologist.

Empirical first line treatment:

Liposomal amphotericin B 3 mg/kg IV od +/- **flucytosine** 25mg/kg IV qds *(Note: flucytosine requires therapeutic drug monitoring, section 6).*

In the case of vitreal involvement **vitrectomy and intravitreal injection** of amphotericin B (5-10 µg) are recommended in addition to systemic therapy.

In susceptible isolates

Less severe cases:
Fluconazole 800mg PO STAT followed by 400mg-800mg PO od
OR
Voriconazole 400mg PO bd for 2 doses then 200mg PO bd (resistant to fluconazole).

Severe cases:

Fluconazole 400mg – 800mg IV od followed by oral
OR
Voriconazole 6mg/kg IV bd for 2 doses, then 4mg/kg IV bd followed by 200mg PO bd (if resistant to fluconazole).

Treatment duration: 2 weeks in less severe cases, 4-6 weeks in severe cases, as defined by ophthalmological review of resolution of infection

2.d. ii Bone And Joint Candidiasis

Candida infections of bones and joints are grouped into osteomyelitis/spondylodiscitis, arthritis and prosthetic joint infection. No randomized clinical trials have been conducted so evidence for the best therapeutic approach is limited.

Usually, cases of *Candida* osteomyelitis are diagnosed by biopsy. Surgical debridement is frequently necessary.

Osteomyelitis or Spondylodiscitis:

Liposomal amphotericin B IV 3 mg/kg od for 2-6 weeks and then **fluconazole PO** 400mg od for 5-11 months*
OR,
if susceptible isolate, **Fluconazole 400mg od (6mg/kg) for 6-12 months** (initially IV then oral).

*duration is depending on clinical response and normalization of inflammatory markers.

Septic Arthritis

Surgical debridement/wash out is strongly recommended.

Liposomal amphotericin B 3mg/kg IV od for 2 weeks then fluconazole 400mg PO od for at least 4 weeks.
OR
If susceptible isolate- **Fluconazole 400mg od** for at least 6 weeks (initially IV then oral).

Prosthetic Joint Infection

Removal of prosthesis plus fluconazole or Liposomal amphotericin B (pending on susceptibility of isolate).

For antifungal use in cement or if prosthesis cannot be removed discuss with Consultant Microbiologist.

2.d. iii Urinary Tract Candidiasis

Candiduria is commonly encountered in hospital patients, particularly those with a urinary catheter.

Change of urinary catheter and re-culture of urine is recommended.

Treatment is often NOT indicated unless there is persistent candiduria combined with symptoms.

Asymptomatic Candiduria

Do not treat.

Symptomatic Cystitis

If isolate sensitive: **Fluconazole 200mg (3mg/kg) PO** od 14 days.

Pyelonephritis

If isolate sensitive and patient haemodynamically stable:

Fluconazole 200mg-400mg (3mg/kg-6mg/kg) PO od for 2 weeks +/- flucytosine (25mg/kg IV qds) *(Note: flucytosine required therapeutic drug monitoring, section 6)*

OR

Liposomal amphotericin B (1mg/kg IV od) +/- flucytosine (25mg/kg IV qds) (if azole intolerant or isolate resistant) *(Note: flucytosine required therapeutic drug monitoring, section 6).*

If fungal balls present surgical intervention and drainage is recommended.

2.d. iv Candida Endocarditis

Refer to the Trust Guideline for the Treatment of Endocarditis and discuss with a Consultant Microbiologist

- Fungal endocarditis comprises 2-4% of all cases of endocarditis. It is most common in IV drug abuse, patients with prosthetic valve endocarditis, neonates and immunocompromised patients.
- The treatment is currently unsatisfactory and usually requires surgical intervention.
- Surgical valve replacement is highly desirable, if technically feasible.
- Treatment should be given for a minimum of 4 weeks but usually much longer and in some circumstances (e.g prosthetic valves) therapy may be life long.
- Susceptibility testing must be undertaken for any fungus causing endocarditis including the determination of minimal fungicidal concentrations.
- Fungal blood cultures should continue to be taken for at least the first 2 weeks on therapy or if any clinical deterioration occurs.

3. Febrile Neutropenia (in adults)

The incidence of severe opportunistic fungal infections in patients with haematological malignancies has increased dramatically over the past 20 years. In neutropenic patients, these infections are a major cause of morbidity and mortality. Between 20-40% of these mycoses are disseminated, and more than 70% are fatal. Candidiasis and aspergillosis are the most common fungi but rarer moulds such as *Fusarium* or mucoraceous moulds should be considered. Invasive aspergillosis commonly affects the lung and may disseminate to other organs such as the brain. Candidiasis often

originates from the gut or intravascular line causing candidaemia or infections of other organs (e.g. liver).

Fungal infections should be suspected in any immunocompromised patient with prolonged pyrexia not responding to broad-spectrum antibiotics, or patients with GvHD. Treatment and investigations (e.g. BAL, HRCT) should be initiated quickly to avoid further deterioration in clinical condition. **These cases should be discussed with a consultant haematologist at all times. Involvement of a consultant microbiologist might be required in difficult cases.**

Prophylaxis

Primary candida prophylaxis for high risk patients:

Fluconazole 50mg po 3 x week or as per individual oncology or heamatology policy.

For risk determination please see following NHS England table:

Consensus between national guidelines for prophylaxis risks

NHS England

High Risk - mould active prophylaxis	Low Risk - candida prophylaxis	Low Risk - no prophylaxis
Allo-HSCT **Intensive treatment for ALL, AML, MDS** **Significant GVHD** –till resolved. **CML intensive chemo** **Severe aplastic anaemia** Duration Allografts to day 75-100 GVHD – 16 weeks or until prednisolone <10mg OD Others – neutrophil recovery	**Auto-SCT** – candida prophylaxis if mucositis or recent excessive chemo until neutropenia resolved **Myeloma** – fluconazole or no prophylaxis **Lymphoma** - intensive/dose-escalated therapy **Solid tumours** – if profound neutropenia and mucositis expected to last for ≥ 7 days in environments with > 10% risk of invasive Candida infection	**MDS** – not undergoing intensive chemo **CML** (treated with TKIs or conventional treatment) **CLL** No prophylaxis (consider in CLL with prolonged neutropenia (>6 months), elderly, advanced and unresponsive disease) **Lymphoma** - standard chemo **Other myeloproliferative neoplasms**
Unclear		
Autograft – mould-active agent if prior IA, neutropenia >2 weeks expected or prolonged neutropenia prior to HSCT **Allo-HSCT** with expected neutropenia <14 days (II, A) **Aplastic anaemia** - Consider prophylaxis for first months after ATG and after HSCT for as long as neutropenia and/or lymphopenia is present **Allogeneic HSCT** with expected neutropenia >14 days Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × 10 9 /L for >1 week Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks High-dose cytarabine Fludarabine use in highly treatment-refractory patients with CLL or low-grade lymphoma Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma		

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Consensus high risk prophylaxis guidelines published by NHS England via consensus of IDSA, ECIL6, Clincial Cancer Network, American Society of Clinical Oncology, Austrialia and New Zealand gudelines as part of the standardisation in optimizing antifungal use in NHS trusts across England

Empirical treatment

<u>Possible</u> fungal infection or neutropenic fever not responding to antibacterial treatment

Urgently investigate (e.g. BAL or 3x sputum, HRCT) to obtain a definitive diagnosis.

Start with **Ambisome IV 1-3mg/kg/ od** for 3 days, then consider changing to oral **Voriconazole** (discuss with senior medical staff).

If patients CRP and fever had responded to Ambisome but deteriorates when on Voriconazole without any other positive bacteriology, the patient may need to be switched back to Ambisome.

Antifungals should be given until three consecutive days of sustained apyrexia or a maximum of 10 days unless new evidence of proven/probable invasive fungal infection.

Probable fungal infection

- Urgently investigate (e.g. BAL or 3x sputum, HRCT) to obtain a definitive diagnosis.
- Start with **Ambisome IV 3-5mg/kg od.**
- If strongly suspicious of aspergillosis, consider **Caspofungin IV.**
- If patient deteriorates on antifungal consider using combination therapy – d/w Consultant Microbiologist.
- **Duration of treatment is unknown and should be guided by clinical and radiological response.**

Targeted Treatment

Proven invasive fungal infection

- Start **Ambisome 3-5mg/kg** IV od, unless fungal isolate suggests otherwise.
- Consider **Caspofungin** if *Aspergillus* species isolated.
- If patient unable to tolerate Ambisome or Caspofungin use **Voriconazole IV.**
- If patient deteriorates on antifungal consider using combination therapy – d/w Consultant Microbiologist .
- In documented mucoraceous mould (formerly zygomycosis) infection **Posaconazole** is the first line for treatment. Second line Ambisome (same as fungal sinusitis section 4.a).
- For proven **cryptococcosis**, Ambisome (>4mg/kg/od) is the drug of choice.
- Flucytosine (75-100 mg/kg/d) should be added if cryptococcal meningitis is present *(Note: flucytosine required therapeutic drug monitoring, section 5).*
- For treatment of invasive candidiasis including candidaemia see section 2.b.

Duration of treatment:

Pulmonary aspergillosis, duration of antifungal therapy for invasive pulmonary aspergillosis is not well defined. In immunosuppressed patients, therapy should be continued throughout the period of immunosuppression and until lesions have resolved (this may take 6-12 weeks).

Cryptococcal meningitis, duration of induction therapy 2 weeks followed by consolidation therapy (fluconazole 400 mg od) for 8 weeks, followed by maintenance therapy fluconazole 200mg/d ≥ 1 year.

Step down criteria to oral treatment

Possible/probable invasive fungal infection:

If empirical treatment started and the patient responding and a fungal infection has not been confirmed switch to oral voriconazole if patient is well enough to tolerate oral agent.

Proven fungal infection
For confirmed invasive fungal infection current national and international guidelines provide no guidance on the step down therapy due to insufficient evidence. Voriconazole po may be considered.

4. ENT Fungal Infections In Adults

4.a Acute Invasive Fungal Sinusitis

Acute invasive fungal sinusitis is an ENT emergency and mostly seen in neutropenic, transplant or diabetic patients. Patients should be under the care of a consultant ENT surgeon and discussed with a Consultant Microbiologist. It is important to send biopsies to histopathology as well as culture.

If causative organism is *Aspergillus*:

1st line: **Liposomal Amphotericin B 3-5mg/kg IV od**
OR
If Amphotericin not tolerated:

2nd line: **Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 hours)**. Switch to oral voriconazole on advice of the Consultant Microbiologist.

If causative organism likely to be due to mucoraceous moulds (formerly zygomycosis):
1st line: **Posaconazole** 200 mg PO qds initially, then 400 mg PO bd after stabilization of disease
OR
2nd line: **Liposomal Amphotericin** B 3-5mg/kg IV od (if posaconazole is not tolerated or oral route not appropriate).

Duration of treatment or step down to oral treatment depends on clinical and radiological response and should be discussed with Consultant Microbiologist.

5. Respiratory Fungal Infections in Adults

4. ### 5.a Fungal infections in cystic fibrosis (CF) and chronic respiratory diseases in adults

5. ### 5.a.i Scedosporium

Scedosporium (*Scedosporium apiospermum* and *Scedosporium 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 immunocompromized patients are also particular susceptible to invasive *Scedosporium* infection.

THERAPY of invasive infection:

S. apiospermum is almost always resistant to Amphotericin B.

Voriconazole 400mg PO bd for 2 doses and then 200mg PO bd (pending on serum

concentration) is the treatment of choice.

S. prolificans is a very drug resistant mould.

Combination therapy with **terbinafine 250 mg twice daily po and voriconazole 400mg PO bd for 2 doses and then 200mg PO bd OR Itraconazole 200mg 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.

5.b Isolation of candida in respiratory secretions

Growth of Candida from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy

6. **6.Intra -abdominal fungal infection**

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.

First line is:

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 200-600mg OD for up to 14 days

7. Therapeutic Drug Monitoring

The pharmacokinetics of anti-fungal agents can vary between patients for various reasons including unpredictable absorption, compliance, metabolism, elimination, or drug-drug interaction leading to inconsistent serum concentrations. Therapeutic drug monitoring (TDM) is therefore recommended for itraconazole in order to monitor therapeutic serum concentrations and for flucytosine and voriconazole to avoid toxicity [Ashbee *et al*. 2013].

There are NO indications for TDM of amphotericin B or the echinocandins.

Voriconazole

Target trough concentration for treatment is > 1 mg/L.

Active dosage adjustment to keep serum concentrations < 5.5 mg/L prevents voriconazole-related toxicity.

Oral therapy can be increased if necessary to 300mg bd.

Measurement of serum trough concentration within 7 days of initiation of therapy or following dose adjustment or if toxicity is suspected.

Flucytosine:

It is recommended that flucytosine is measured in all patients to prevent toxicity. This should be done in the first 72 hours of therapy and regularly thereafter (once per week or after dose adjustments)

For trough concentrations (recommended to be 20-40 mg/L) a serum sample should be taken just before the next (iv or oral) dose is due. For therapeutic peak concentrations (50-100 mg/L) two hours after an oral dose, peak values for iv therapy have not been established.

The dose of flucytosine should be reduced in patients with renal impairment (creatinine clearance <50mL/min). Contact Medicines Information for advice.

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8. Drug Monographs

	Fluconazole	Itraconazole	Ambisome (Liposomal Amphotericin B)	Voriconazole
Formulary Status	No restrictions	No restrictions	No restrictions	Oral Voriconazole -haematology patients in accordance with the protocol for treatment of fungal infections
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 Caution use of IV formulation in CrCl<50ml/min. Accumulation of cyclodextrin component. Use oral route if possible
Hepatic dose adjustment	No	Yes	No	Yes
Toxcities (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)	+	+++	–	+++

Trust Guideline for the Use of Antifungals in Adults

	Caspofungin	Anidulafungin	Posaconazole	Flucytosine
Formulary Status	Restricted Serious proven infections in haematology patients. CCC according to candida guidelines Other indications on advice of a consultant microbiologist	Restricted	Restricted	Always used in combination, never used as a single agent.
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	50mg/kg qds IV usually for not more than 7 days.
Activity	Fungicidal against *Candida* Fungistatic against *Aspergillus*	Fungicidal against *Candida* Fungistatic against *Aspergillus*	Fungistatic	Fungistatic and fungicidal activity pending on species. Enhances fungicidal activity in combination with Amphotericin
CSF penetration	No	No	Yes	Yes
Elimination Route	Hepatic	Hepatic	Hepatic	Renal
Renal dose adjustment	No	No	No	Yes – see BNF
Hepatic dose adjustment	Yes	No	No – but use with caution	No
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	Bone marrow suppression Cardiotoxicity
Potential Drug Interactions (consult BNF for further details)	+	-	++	+