Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust

South Yorkshire and Bassetlaw

Antifungal Guidelines for adult patients

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Introduction

This guideline is divided into 3 sections

1. Prophylactic therapy aimed at preventing fungal infection in patients deemed to be at sufficient risk
2. Empiric therapy in patients suspected but not confirmed to have fungal infection including guidance as to appropriate laboratory tests to confirm or refute the diagnosis
3. Targeted therapy when fungal infection has been confirmed

This guideline is intended to be a living document replacing local trust guidelines where possible but reviewing and integrating changes to regional guidelines as and when they occur. Any such remaining or new antifungal guidelines should have a member of the antifungal stewardship team on the authorship or review panel to ensure consistency between documents across the trust.

Interim annual review of this guideline will be performed by the antifungal stewardship team with full review on a 3-yearly basis or earlier where significant change dictates.

Antifungal advice can be sought from the Infection Team

Therapeutic drug monitoring is essential for management in instances with the hyperlink TDM. Details can be found in appendix 3.[1]

Many of the antifungal agents, particularly the azoles, have multiple important drug interactions. Please consider these where relevant when prescribing.

Dose adjustments for hepatic and renal dysfunction are detailed in appendix 4

Contents

Drug Susceptibility considerations

Candida

Approximately 75% of confirmed invasive Candida infections locally are due to the species *C. albicans, C. dubliniensis, C. parapsilosis* or *C. tropicalis,* which are usually susceptible to fluconazole unless the patient has received antifungals in the recent past. Where other species are isolated from significant infections please liaise with the Infection Team if necessary to determine the appropriate therapeutic strategy.

Mould infections

The majority of confirmed mould infections are due to *Aspergillus spp.* The vast majority of clinical isolates in the UK remain susceptible to mould active azoles (e.g. voriconazole, posaconazole, isavuconazole) but reduced susceptibility has been noted in up to 25% of isolates in the Netherlands and is also more common in patients with a long history of exposure to mould-active azoles. Susceptibility testing is performed by the reference laboratory – please contact Infection Team at the time of sample acquisition/culture confirmation to discuss if drug resistance is a concern.

Invasive infections caused by non-aspergillus moulds are rare and, where suspected, management should occur in conjunction with the Infection Team.

Pneumocystis jirovecii

Co-trimoxazole remains first line therapy for *Pneumocystis*. Although strains with reduced susceptibility have been recognised, evidence suggests that this resistance is overcome by the high doses of drug used in this context. Routine susceptibility testing is not possible due to the non-cultivable nature of *P. jirovecii.*

1. Prophylaxis

A consensus antifungal prophylaxis risk table developed on behalf of NHS England can be found in appendix 2.

1.1 Antifungal prophylaxis in Haematology patients[2]

Clinical Indication	Drug dose and route	Duration
Autologous stem cell transplant	Fluconazole 100mg PO od	Days –1 up to Day +100. Continue if ongoing neutropenia.
Allogeneic stem cell transplant	Mould active prophylaxis (see below)	Days-1 to+100 or while on immunosuppression for Graft vs Host Disease whichever is the longest
Graft vs Host Disease requiring steroids or other immunosuppression	Mould active prophylaxis (see below)	Duration of Immunosuppression
Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS) during induction and salvage chemotherapy	Mould active prophylaxis (see below)	Until neutrophil count recovery AND complete remission
AML and MDS during consolidation chemotherapy	Consider Mould active prophylaxis (see below)	During consolidation chemotherapy
Acute Lymphoblastic Leukaemia (ALL) induction	Prophylaxis not routinely indicated – alternate day caspofungin may be considered in some patients by lymphoid malignancy consultant	No prophylaxis
ALL salvage	Mould active prophylaxis (see below)	During salvage chemotherapy
Intensively treated Chronic Myeloid Leukaemia (high dose Thymidine Kinase Inhibitor or AML type regimens)	Mould active prophylaxis (see below)	During chemotherapy
Severe aplastic anaemia (as per British Society for Haematology definition)	Mould active prophylaxis (see below)	Until neutrophil count recovery
Intensive or dose-escalated chemotherapy for lymphoma	Prophylaxis not routinely indicated. Fluconazole 100mg PO od may be considered in some patients by lymphoid malignancy consultant	For duration of chemotherapy

Mould active prophylaxis

1st line

- Posaconazole tablets 300mg twice daily on the first day then 300mg daily thereafter. N.B tablets and suspension dose are not interchangeable

Alternatives

- Posaconazole suspension – 200mg tds. Therapeutic drug monitoring is mandatory.[TDM]
- Alternate day caspofungin is occasionally used in patients intolerant or unable to receive azoles but its evidence base is currently slim.

1.2 Antifungal prophylaxis in Oncology

Clinical Indication	Drug dose and route	Duration
Specified docetaxel containing regimens	Fluconazole 50mg PO od	7 days duration from day 5 of chemotherapy

1.3 Antifungal prophylaxis in Surgical patients[3]

Clinical Indication	Drug dose and route	Duration
Severe Acute Pancreatitis (modified Glasgow score of 3 or greater) or CT evidence of necrosis	Fluconazole 800mg (or 12mg/kg) on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od.	10 days
Oesophageal rupture	Fluconazole 800mg (or 12mg/kg) on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od.	5 days post drainage/repair assuming clinical stability
GI perforation or anastomotic leak in the context of recent antibacterial therapy (usually repeat laparotomy)	Fluconazole 800mg (or 12mg/kg) on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od.	5 days post washout/repair assuming clinical stability

The requirement for antifungal prophylaxis in this context will be reviewed if in-house beta-D-glucan testing becomes available

1.4 Antifungal prophylaxis in Hepatology[4]

Clinical Indication	Drug dose and route	Duration
Acute liver failure with encephalopathy requiring ITU admission	Fluconazole 400mg (6mg/kg to a maximum of 800mg) IV od	Duration of requirement for level 3 care for encephalopathy

1.5 Antifungal prophylaxis in Immunology patients

Patients with a variety of uncommon or rare primary and secondary immune deficits are at risk of fungal disease. Decisions about prophylaxis in this group should align with guidelines in other groups and will be made on the recommendation of an Immunology Specialist on consultation with the Infection Team where required.

1.6 *Pneumocystis jirovecii* prophylaxis

Pneumocystis jirovecii prophylaxis is recommended in those patients with an estimated risk of disease of >3%. A lower threshold for prophylaxis may be adopted in patients with previous *Pneumocystis* pneumonia

Clinical Indication	Drug dose and route	Duration
Pneumocystis jirovecii prophylaxis	1st line Co-trimoxazole 480mg PO bd three times a week on Mondays, Wednesdays and Fridays OR 480mg PO od. 2nd line Pentamidine 300mg monthly by nebuliser 3rd line Atovaquone 750mg PO bd*	Duration of immunocompromise – suggested durations in common clinical contexts listed below.

*Prophylactic use of atovaquone is an unlicensed indication.

Duration of *Pneumocystis* prophylaxis:

- HIV with CD4 count <200x10^6/L
- Steroid therapy equivalent to 20mg prednisolone per day for >4 weeks
- Renal Transplant patients for 6 months after transplant (or 1 year if total lymphocyte count <1x10^9/L at 6 months)
- Acute Lymphoblastic Leukaemia on chemotherapy (excluding during high dose methotrexate)
- During and for 6 months following completion of purine analogue therapy
- Ibrutinib or Idelalisib therapy- consider on case by case basis.
- During treatment with CAMPATH
- Autologous transplants = 3 months
- Autologous transplant + TBI = 6 months
- Allogeneic transplant = 12 months
- Post donor lymphocyte infusions = 3 months
- GVHD whilst active GVHD or on treatment for GVHD
- Multiple Myeloma patients receiving bortezomib therapy
- Small cell and non-small cell lung cancer patients receiving concurrent chemoradiotherapy

2. Empiric therapy

2.1 Empiric antifungal therapy in patients with neutropenic sepsis[2]

Clinical Indication	Drug dose and route	Notes
Neutropenic sepsis without clear focus and with persisting fever after ~96hrs antibacterials	Caspofungin 70mg IV loading dose, then 50mg od IV if ≤80kg or 70mg od IV if >80kg	• Request HRCT scan within 24 hours • Consider bronchoscopy • Send fungal serology (BD Glucan and Galactomannan) • Discuss with Infection Team

2.2 Empiric antifungal therapy in suspected invasive candidiasis[5]

Clinical Indication	Drug dose and route	Notes
Suspected **non-urinary tract** invasive candidiasis. Consider especially in: • Abdominal disease and recent broad spectrum antibiotic use • Invasive devices who have failed to respond to broad spectrum antibiotics	If no recent fluconazole use and not in shock and not on CRRT* Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od If recent fluconazole use **OR** patient in septic shock **OR** on CRRT* Anidulafungin 200mg IV on day 1 then 100mg IV od	• Send blood cultures and BD glucan • Consider appropriate imaging and source control • Discuss with Infection Team
Suspected urinary tract source invasive candidiasis	Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od	Other azoles and echinocandins DO NOT penetrate urinary tract well • If fluconazole resistant Candida UTI suspected (see above) contact Infection Team • Send blood cultures, urine and BD glucan • Consider urinary tract imaging

*CRRT = Continuous Renal Replacement Therapy

2.3 Empiric therapy in suspected invasive mould infection[6]

The majority of invasive mould infections occur in profoundly immunocompromised Haemato-oncology patients but a smaller number of cases are diagnosed in other patient groups including critically ill patients with influenza or COVID-19

Clinical Indication	Drug dose and route	Notes
Suspected invasive aspergillosis (consistent clinical picture and consistent changes on CT)	Voriconazole 6mg/kg IV bd on day 1 then 4mg/kg bd. Therapeutic drug monitoring is mandatory. TDM Monitor LFT See below if voriconazole not tolerated	• Bronchoscopy where possible including fungal culture and BAL galactomannan • Send serum galactomannan • Liaise with Infection Team about sampling and about alternatives if prior azole exposure • Monitor LFT
If invasive non-Aspergillus mould infection suspected	Liaise with Infection Team or the anti-fungal stewardship team	

Where patients are critically ill with presumed invasive aspergillosis, it may be reasonable to add anidulafungin or caspofungin to the voriconazole until therapeutic levels are attained – discuss with Infection Team or the antifungal stewardship team.

2nd line mould active agents

If voriconazole not tolerated due to adverse effects, or if therapeutic levels difficult to achieve then consider:

- Isavuconazole 200mg tds (IV/PO) for 6 doses then 200mg od. The infusion requires the use of a filter.
- Liposomal amphotericin B (Ambisome) 3mg/kg IV od (higher doses of up to 10mg/kg used if suspected mucoraceous mould (zygomycete) infection). A test dose of 1mg to be given over 10 minutes is advisable before giving the first dose to ensure no allergic reaction.
- Posaconazole 300mg tablets twice daily on the first day then 300mg daily thereafter. TDM N.B tablets and suspension dose are not interchangeable.

3. Treatment of confirmed infection

For treatment of dermatophytosis and complex organ-specific fungal infection (e.g. CNS, eye, endovascular, bone and joint, endocarditis) contact the Infection Team.

3.1 Candidiasis[5]

3.1.1 Oral and oesophageal candidiasis

Clinical Indication	Drug dose and route	Duration and notes
Oral candidiasis	Nystatin 100 000 units qds PO OR Topical miconazole oral gel 2%, 2.5mL QDS	7 days
Oral candidiasis with failed response to nystatin or in heavily immunocompromised	Fluconazole 100mg od PO. OR Fluconazole 150mg stat PO may be used in a palliative care context.	7 days. • Consider swab • Contact Infection Team if confirmed/suspected fluconazole resistant organism
Oesophageal candidiasis	Fluconazole 200-400mg od PO	14-21 days • Contact Infection Team if confirmed/suspected fluconazole resistant organism

3.1.2 Genital candidiasis

Clinical Indication	Drug dose and route	Duration and notes
External genital candidiasis	Clotrimazole 1% cream applied to affected area 2-3 times daily	7 days
Vaginal candidiasis	Clotrimazole pessary 200mg nightly PV	3 nights
Genital candidiasis with failed response to clotrimazole	Fluconazole 150mg stat PO	Stat dose • Consider swab if recurrent • Contact Infection Team if confirmed/suspected fluconazole resistant organism
Recurrent vulvovaginal candidiasis	Nystatin 100 000 unit pessaries nightly for 14 days Boric acid 600mg pessaries nightly for 14 days Suppressive therapy with Fluconazole 150mg 3x/week	Consider alternative dermatological differential diagnoses e.g. lichen sclerosus or contact dermatitis and systemic predisposing factors such as HIV, diabetes mellitus or iron deficiency anaemia

	then weekly for 6 months if fluconazole susceptible	Advise avoidance of irritants e.g. soaps or perfumes

3.1.3 Urinary tract candidiasis

Clinical Indication	Drug dose and route	Duration and notes
Asymptomatic candiduria	Treatment not usually indicated	Often represents contamination or colonisation of catheter if present. If treatment indicated e.g. due to forthcoming surgery then follow UTI guidance below
Lower UTI - Fluconazole susceptible isolate	Fluconazole 200mg od	7-14 days Other azoles and echinocandins DO NOT penetrate urinary tract well.
Lower UTI - Fluconazole resistant isolate	Contact Infection Team.*	
Upper UTI - Fluconazole susceptible isolate	Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od	At least 14 days Other azoles and echinocandins DO NOT penetrate urinary tract well
Upper UTI - Fluconazole resistant isolate	Contact Infection Team*	

* Options include fluconazole dose increase; addition of second systemic agent, 5-flucytosine alone or in combination or conventional amphotericin depending on patient and organism factors.

3.1.4 Respiratory tract candidiasis

Respiratory tract candidiasis is extremely uncommon and most isolates from sputum or BAL fluid represent contamination by oral flora. Please contact Infection Team if genuine infection suspected.

3.1.5 Abdominal candidiasis related to surgery or perforated viscus

Clinical Indication	Drug dose and route	Duration and notes
Fluconazole susceptible isolate	Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od. Oral step-down on advice of Infection Team	At least 14 days depending upon effectiveness of source control and clinical progress. Monitoring of BD glucan may be helpful
Fluconazole resistant isolate	Anidulafungin 200mg IV on day 1 then 100mg IV od Oral step-down where possible on advice of Infection Team	

3.1.6 Candida bloodstream infection

Clinical Indication	Drug dose and route	Duration and notes
Treatment of Candida bloodstream infection before species known	Anidulafungin 200mg IV on day 1 then 100mg IV od	14 days treatment after first negative blood culture • Repeat blood cultures on alternate days until negative • Remove all intravenous lines • Exclude endocarditis and endophthalmitis (echocardiogram and ophthalmology review)
Treatment of Candida bloodstream infection due to fluconazole susceptible isolate	Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od. Oral step-down on advice of antifungal stewardship team	
Treatment of Candida bloodstream infection due to fluconazole resistant isolate	Anidulafungin 200mg IV on day 1 then 100mg IV od Oral step-down where possible on advice of Infection Team	

3.1.7 Candida from line tips

Culture of Candida species from intravascular line tip samples can represent genuine infection or contamination of the sample from the exit site on withdrawal.

Clinical Indication	Drug dose and route	Duration and notes
Fluconazole susceptible isolate	Fluconazole 800mg (or 12mg/kg) IV on day 1 then 400mg (or 6mg/kg to a maximum of 800mg) IV/PO od. Oral step-down on advice of Infection Team	Send blood culture and beta-d-glucan. Treatment can be stopped at 7 days if culture and BD glucan negative.

Fluconazole resistant isolate	Anidulafungin 200mg IV on day 1 then 100mg IV od Oral step-down where possible on advice of Infection Team	If either culture or BD glucan positive then treat as candidaemia, above.

3.1.8 Candida endocarditis

Clinical Indication	Drug dose and route	Duration and notes
Empirical therapy for presumed Candida endocarditis	Anidulafungin 200mg IV daily **OR** Liposomal amphotericin (Ambisome) 3mg/kg od IV +/- 5-flucytosine 25mg/kg qds IV/PO (i.e. total 100mg/kg/d). A test dose of 1mg Ambisome to be given over 10 minutes is advisable before giving the first dose to ensure no allergic reaction. Therapeutic drug monitoring is essential for efficacy and safety TDM of flucytosine.	Management should be in liaison with the Infection Team and the South Yorkshireinfective endocarditis MDT. Treatment should be for at least 6 weeks, generally requires valve replacement and is often followed by long term suppressive therapy

3.1.9 Disseminated candidosis (formerly "hepato-splenic candidiasis") in Haematology patients

Clinical Indication	Drug dose and route	Notes
Disseminated candidosis (AKA hepato-splenic candidiasis)	Caspofungin 70mg IV loading dose, then 50mg od IV if ≤80kg or 70mg od IV if >80kg	• Monitor BD glucan

3.2 Cryptococcal meningitis[7]

Clinical Indication	Drug dose and route	Duration/Notes
Cryptococcal meningitis	INDUCTION Liposomal amphotericin (Ambisome) 4mg/kg od IV **PLUS** 5-flucytosine 25mg/kg qds IV/PO (i.e. total 100mg/kg/d) Therapeutic drug monitoring is essential for efficacy and safety TDM of flucytosine. A test dose of 1mg Ambisome to be given over 10 minutes is advisable before giving the first dose to ensure no allergic reaction. MAINTENANCE Fluconazole 400 mg od PO	Induction course of at least 2 weeks as determined by clinical response and rate of CSF sterilisation. Maintenance 10 weeks Secondary prophylaxis may be indicated if ongoing immunocompromise

3.3 Aspergillus infection[6]

Clinical Indication	Drug dose and route	Duration/Notes
Invasive pulmonary or sinus aspergillosis	Voriconazole 6mg/kg IV bd on day 1 then 4mg/kg bd. Therapeutic drug monitoring is mandatory. TDM Conversion to PO on discussion with Infection Team	6-12 weeks Monitor LFT Combination echinocandin therapy may be considered initially until levels adequate Consider surgery, especially for sinus disease Consider reducing immunosuppression where possible Secondary prophylaxis may be indicated if ongoing immunocompromise
CNS aspergillosis	Voriconazole 6mg/kg IV bd on day 1 then 4mg/kg bd. Therapeutic drug monitoring is mandatory. TDM	6-12 weeks Monitor LFT Consider surgery Consider reducing immunosuppression where possible Secondary prophylaxis may be indicated if ongoing immunocompromise
Chronic cavitatory pulmonary aspergillosis	• Itraconazole 200mg bd solution PO. Therapeutic drug monitoring is mandatory. TDM **OR** • Voriconazole 400mg bd PO for 2 doses then 200mg bd.	6 months Monitor LFT

	Therapeutic drug monitoring is mandatory. TDM	
Saprophytic aspergilloma	Initial observation and no therapy if not enlarging If Surgical resection performed and concern re: potential for spillage: Voriconazole 6mg/kg IV bd on day 1 then 4mg/kg bd. Therapeutic drug monitoring is mandatory. TDM	Perioperative treatment only Monitor LFT
Allergic bronchopulmonary aspergillosis	• Itraconazole 200mg bd solution PO. Therapeutic drug monitoring is mandatory. TDM **OR** • Voriconazole 400mg bd PO for 2 doses then 200mg bd. Therapeutic drug monitoring is mandatory. TDM	Where antifungal treatment is indicated under supervision of respiratory specialist.

2nd line mould active agents

If voriconazole not tolerated due to adverse effects, or if therapeutic levels difficult to achieve then consider:

- Isavuconazole 200mg tds (IV/PO) for 6 doses then 200mg. The infusion requires the use of a filter.
- Liposomal amphotericin B (Ambisome) 3mg/kg IV od (higher doses of up to 10mg/kg used if suspected mucoraceous mould (zygomycete) infection). A test dose of 1mg to be given over 10 minutes is advisable before giving the first dose to ensure no allergic reaction. During working hours to be made by the pharmacy aseptics unit.
- Posaconazole 300mg tablets twice daily on the first day then 300mg daily thereafter. TDM N.B tablets and suspension dose are not interchangeable.

3.4 Other mould infection

Contact Infection Team to discuss management of non-Aspergillus mould infection

3.5 *Pneumocystis jirovecii* pneumonia

Clinical Indication	Drug dose and route	Duration/Notes
Pneumocystis jirovecii pneumonia	1st line Co-trimoxazole 30mg/kg qds IV/PO (120mg/kg total daily dose). Dose can be reduced to 90mg/kg/d total from day 4) 2nd line Clindamycin 600mg qds + primaquine 30mg od (**Exclude G6PD deficiency**) 3rd line (mild-moderate disease) Atovaquone 750mg bd	• 21 days total therapy • Consider steroids if hypoxic. (Prednisolone 40mg bd for 5 days, then 40mg od for 5 days, then 20mg od for 11 days if initial pO2 is <9.3kPa on air) • Consider addition of caspofungin as synergistic therapy (70mg load then 50mg od if ≤80kg; 70mg od if >80kg) • Exclude G6PD deficiency before prescribing primaquine • Primaquine is not licensed within the UK. • Secondary prophylaxis may be indicated if ongoing immunocompromise

Appendix 1 - NHS England consensus antifungal prophylaxis risk 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		

14

Appendix 2: Therapeutic Drug Monitoring [1]

Send a clotted sample of blood (usually a gold top tube) Please ensure Infection Team are aware if the patient is on more than one antifungal as some of these drug levels are measured by bioassay

Antifungal	Timing	Sampling Commencement and Frequency	Target Levels/Comments
Itraconazole (oral)	Random **Essential for management of invasive disease**	*Commence:* only after steady state has been reached i.e.1-2 weeks on oral therapy. *Frequency:* dependent on patient and levels achieved - seek advice	A level of greater than 0.5mg/L is likely to be effective. Contact Infection Team for advice in patients on IV therapy
Voriconazole	Pre-dose (i.e. 12 hours post-dose for standard bd regimens) **Essential in all cases**	*Commence:* on day 4 of therapy *Frequency:* until therapeutic levels obtained. Repeat if a dose change, interaction or a question of poor compliance and 2-4 weekly thereafter	A **trough** concentration between 2.0 and 6.0mg/L is likely to be effective and non-toxic. If dosage changes are required, discuss with Infection Team Due to the non-linear kinetics of the drug, informed clinical judgement regarding target range is not possible on any sample except pre-dose samples
Posaconazole	Random **Essential for management of invasive disease.**	*Commence:* only after steady state has been reached i.e.1-2 weeks on oral therapy *Frequency:* once or twice early in course. Repeat if required to check compliance, or if possible drug interaction	Steady state reached after 1-2 weeks on oral therapy, with little variation throughout the day Target concentration: Prophylaxis: >0.7mg/L Treatment: >1mg/L
Isavuconazole	Pre-dose	Test if clinical concern about drug exposure (e.g.malabsorption), or failure of response. Commence after 3 days of therapy Discuss subsequent testing with Infection Team	Target levels not yet established and informed clinical judgement is required for dose adjustments. • Normal range on standard 200mg od therapy at steady state is 2-4 mg/L • Dose escalation is advised for any level less than 1 mg/L

5-Flucytosine	**Pre- and post- (2 hours post oral or 30 mins post IV) dose** **Essential in all cases**	Within 72 hours of therapy initiation then repeated at least weekly. Repeat within 72 hours of dose adjustment or modification of interacting drugs or renal function	Pre-dose 20-40mg/l Post-dose <100mg/l

Appendix 3 – Dose adjustments for hepatic and renal dysfunction

FLUCONAZOLE

Patients with Renal Failure
Severe renal failure only (CrCl < 10ml/ min): **HALVE the maintenance dose.**

Patients on Renal Replacement Therapy
Clearance of fluconazole by continuous renal replacement techniques is highly variable.
In patients on CRRT, use anidulafungin (hepatic elimination) instead to ensure therapeutic antifungal levels are obtained throughout the treatment period.

ANIDULAFUNGIN

Patients with Renal Failure
No dosing adjustments are required for patients with any degree of renal insufficiency, including those on renal replacement therapies.

Patients with Liver Failure
No dosing adjustments are required for patients with mild, moderate, or severe hepatic impairment.

VORICONAZOLE

Patients with Renal Failure
Moderate to severe renal dysfunction (CrCl < 50 ml/min): accumulation of the intravenous vehicle from the IV preparation occurs. **Use Oral/ enteral voriconazole if absorbing unless an assessment of the risk/benefit justifies use of IV voriconazole. Monitor serum creatinine level closely**

Patients with Liver Failure
Moderate to severe liver failure: **reduce maintenance dose to 100mg PO/ enteral twice daily.** [TDM]

FLUCYTOSINE

Patients with Renal Failure
Creatinine clearance of 10-20 ml/min**, halve the usual dose**. [TDM]
CrCl <10 ml/min: **initial single dose of 50 mg/kg; then 25mg/kg daily.** [TDM]

Patients on Renal Replacement Therapy
CVVH 35ml/kg/hour regime - loading dose of 50mg/kg, then 25mg/kg TDS. [TDM]
CVVH 80ml/kg/hour regime - loading dose of 50mg/kg, then 25mg/kg QDS. [TDM]

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