Whittington Health NHS

Antifungal Guideline for Invasive Fungal Infections in Adults

Subject:	Antifungals for Invasive Fungal Infections in Adults
Policy Number	N/A
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Designation of Author:	Microbiology and Pharmacy Department
Name of Assurance Committee:	Drugs & Therapeutics Committee
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Target Audience:	All clinical staff involved in prescribing, dispensing and administering antifungals. Doctors, nurses, midwives and pharmacists
Key Words:	Antifungal, fungal, yeast, mould, candida, aspergillus, pneumocystis, PCP, fluconazole, amphotericin, voriconazole, caspofungin, itraconazole

Version Control Sheet

Version	Date	Author	Status	Comment
1.0	Sept 2009	Dr Gauri Godbole (ST2 doctor in Microbiology) Ai-Nee Lim (Lead Pharmacist, Antimicrobials) Dr Michael Kelsey (Consultant Microbiologist)	In-active	First version
1.0	Jan 2012	Ai-Nee Lim	In-active	Date revision
2.0	Sept 2015	Ai-Nee Lim (Lead Pharmacist, Antimicrobials) Dr Michael Kelsey (Consultant Microbiologist)	In-active	Transfer on to new template. Section on pneumocystis jirovieci (carinii) pneumonia and crytococcal meningitis has been updated to reflect national and international guidelines.
3.0	July 2019	Dr Kate David (Microbiology Registrar) Ai-Nee Lim (Consultant Pharmacist, Antimicrobials) Dr Michael Kelsey (Consultant Microbiologist)	Active	Newly added section on investigations, and antifungal monitoring and prescribing guidance.

➢ Criteria for use

Invasive fungal infection

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 and resistance of fever of unknown origin to broad-spectrum antibacterials) plus clinical, microbiological and radiological criteria.

This 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.

➢ Investigation

Laboratory investigations

1. Sterile fluids (and bronchoalveolar lavage (BAL) if respiratory fungal infection suspected):
    - Fungal microscopy, culture and sensitivities
    - Histology
    - Galactomannan on BAL for aspergillus
    - Direct fluorescent antibody staining and PCR for *Pneumocystis jiroveci*

2. Cerebrospinal fluid (CSF):
    - Fungal microscopy, culture and sensitivities
    - *Crytococcus neoformans* antigen (CRAG) testing of all CSF specimens from immunocompromised patients, those with sarcoidosis or cancer, or those who show abnormal concentrations of glucose, protein or leucocytes without an adequate explanation.

3. Sputum:
    - Take at least 3 samples for fungal microscopy, culture and sensitivities

4. Serum:
    - Galactomannan (two times per week) from patients with haematological malignancies at high risk of invasive aspergillosis in those not receiving mould-active prophylaxis
        - high negative predictive value, enabling invasive aspergillosis to be excluded
    - β-D-glucan from patients at high risk of invasive fungal disease
        - negative result has a high negative predictive value, enabling invasive fungal disease to be excluded
    - PCR for aspergillus from patients at high risk of invasive fungal disease
        - a negative result has a high negative predictive value, enabling invasive fungal disease to be excluded
    - CRAG if lumbar puncture contraindicated in suspected cryptococcosis
    - Aspergillus antibodies if pulmonary cavities of uncertain cause (with or without an aspergilloma)
    - Total IgE and aspergillus-specific IgE if suspected allergic bronchopulmonary aspergillosis

Imaging

1. Patients with leukaemia, haemopoietic stem cell or solid organ transplantation **with any of the following** should have a high-resolution (or spiral) or, preferably, multidetector CT thorax within 48 hours:
    i. new respiratory symptoms/signs
    ii. abnormal chest radiograph
    iii. new culture of an Aspergillus spp/other mould
    iv. microscopic evidence of hyphae in any invasive sample
    v. persistent temperature after 5 days of antibiotics +/- antifungals
    vi. positive fungal biomarkers (galactomannan, β-D glucan)

2. All immunocompromised patients with new neurological features or possible or proven meningitis should have MRI of the brain within 48 hours (or if not possible, a contrast-enhanced CT scan).

3. All patients with suspected invasive fungal paranasal sinus infection should have a non-contrast CT scan within 48 hours.

4. Patients undergoing investigation for disseminated fungal infection should have an MR or dual-phase CT scan of the abdomen.

5. In patients not infected with HIV who have possible pneumocystis pneumonia, a CT scan of the chest is important to make differential diagnoses.

- **Empirical antifungal therapy**

1. HIGH RISK INTENSIVE CARE UNIT and SURGICAL PATIENTS

Patients who are pyrexial (temperature > 38ºC) despite being on antibacterials for 48 hours and have had gastric/duodenal/pancreatic/hepatic/complex abdominal surgery - consider antifungals. Septic screen crucial.

1st line:	**Fluconazole** 400mg IV OD (initial loading dose: 800mg stat).	Review treatment after 5 to 7 days against culture and sensitivity results. Discuss with Microbiology
2nd line:	**Anidulafungin** 200mg IV on first day then 100mg IV OD.	

2. HAEMATOLOGY / ONCOLOGY

2.1 EMPIRICAL THERAPY

Febrile neutropenic patients (<1.0 x 10_9/L) unresponsive to broad-spectrum antibacterials for 96 hours:

1st line:	**Ambisome** 3mg/kg IV OD (initial test dose: 1mg over 10 minutes). Max. period of treatment 42 days.	Continue until afebrile for 72 hours. If high resolution CT scan of chest, CT scan of upper abdomen and X-ray of sinuses are normal and no other clinical suspicion of invasive fungal infection, discontinue antifungal therapy.
2nd line:	**Voriconazole** 6 mg/kg IV every 12 hours for 2 doses then 4mg/kg IV every 12 hours.	

2.2 PROBABLE OR PROVEN INFECTION

1st line:	Treat according to tissue cultures and biopsies, supplemented by radiological findings. Discuss with Microbiology.

2.3 PRIMARY PROPHYLAXIS

(Adapted from NHS England Antifungal Stewardship Implementation Pack - Antifungal Fungal Risk Stratification, v 0.1, August 2018)

Fungal Risk Stratification	Patient group	Choice of Prophylaxis	Duration
High	• Allogenic haematopoietic stem cell transplantation (Allo-HSCT) ‡ • Intensive treatment for acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) • Significant graft-versus-host disease (GvHD) • Chronic myeloid leukaemia (CML) intensive chemotherapy • Severe aplastic anaemia	*1st line:* **Itraconazole** 200mg PO BD *2nd line:* **Voriconazole** 400mg PO every 12 hours for 2 doses then 200mg PO BD (half both the loading and maintenance dose if body-weight under 40kg) *If receiving vinca alkaloids (i.e. vinblastine or vincristine) containing regimen:** **Ambisome** 2mg/kg IV three times a week (i.e. Mon/Wed/Fri)	*Allografts* Until Day 75 to 100. *GvHD* 16 weeks or until prednisolone < 10mg/day *Others* Until unsupported neutrophil count > 1 x 10^9/L
Low	• Autologous stem-cell transplantation (Auto-SCT) – if mucositis or recent excessive chemotherapy • Myeloma • Lymphoma – intensive or dose-escalation therapy • Solid tumours – if profound neutropenia and mucositis expected to last for ≥ 7 days in environments with > 10% risk of invasive Candida infection	*1st line:* **Fluconazole**	*Auto-SCT* Until neutrophil resolved *Others* Until patients is no longer at risk.
Very low	• Myelodysplastic syndromes (MDS) – not undergoing intensive chemotherapy • Chronic myeloid leukaemia (CML) – treated with tyrosine kinase inhibitor (TKI) or conventional treatment • Lymphoma – on standard chemotherapy • Chronic lymphocytic leukaemia (CLL) – except if prolonged neutropenia (> 6 months), elderly, or advanced and unresponsive disease • Other myeloproliferative neoplasms	**No prophylaxis**	Nil

‡ If conditioning contains cyclophosphamide, itraconazole should start 48 hours AFTER the end of chemotherapy.

* Avoid using itraconazole, posaconazole and voriconazole with vinca alkaloid containing regimen i.e. vinblastine or vincristine due to increased risk of neurotoxicity.

2.4 SECONDARY PROPHYLAXIS

Patients presenting with neutropenia or graft-versus-host disease, who have had previous probable or proven invasive fungal infection but is currently regarded as inactive:

<table>
<tr><td>1st line:</td><td>Itraconazole 200mg PO BD</td><td rowspan="5">Continue until unsupported neutrophil count > 1 x 10_9/L.

Allograft patients will continue longer in presence of GvHD or therapy with corticosteroids.</td></tr>
<tr><td colspan="2">If previous infection broke through itraconazole prophylaxis or unresponsive to itraconazole:</td></tr>
<tr><td>2nd line:</td><td>Voriconazole 400mg PO every 12 hourly for 2 doses then 200mg PO BD (half both the loading and maintenance dose if body-weight under 40kg)</td></tr>
<tr><td colspan="2">If patient receiving vinca alkaloid*:</td></tr>
<tr><td>3rd line:</td><td>Ambisome 2mg/kg IV Mon/Wed/Fri</td></tr>
</table>

* Avoid using itraconazole, posaconazole and voriconazole with vinca alkaloid containing regimen i.e. vinblastine or vincristine due to increased risk of neurotoxicity.

- **Targeted antifungal therapy**

CANDIDIASIS:

Candida is a commensal in the oropharynx and the bowel. *Candida albicans* is the commonest species, but others include *C. glabrata, C. tropicalis, C. krusei*, *C. parasilosis*. Following are the groups likely to need treatment for candidosis:

- High risk ITU patients:
  Long term central venous catheters, diabetes, abdominal surgery, exposure to broad spectrum antibacterials (>7 days), steroid use, immunosuppression, PN, renal failure, prolonged ITU stay (>15 days), candida colonisation (≥ 3 sites) or mechanical ventilation. Evidence shows increase in the number of non-albicans candida in ITU.
- High risk Haematopoietic Stem Cell Transplantation (HSCT) patients:
  First 3 weeks of Intensive conditioning for HSCT, AML induction, high dose cytarabine, severe mucositis or colonisation by yeasts at > 1 site during neutropenia.
- HIV patients
- Intravenous drug users

Definition of candidaemia: presence of positive blood cultures with *candida sp..*

TREATMENT FOR CANDIDAEMIA / CANDIDIASIS

Non-neutropenic patients and ITU patients

1st line:	**Fluconazole** 400mg IV OD (initial loading dose: 800mg stat).	Treat for 14 days after first negative blood culture. Remove all intravascular devices if possible. Opthalmological examination and ECHO recommended.
If previous azole exposure, severe infection (hemodynamic instability) or if organism confirmed to be C. glabrata or C. krusei :		
2nd line:	**Anidulafungin** 200mg IV on first day then 100mg IV OD	

Neutropenic patients

NB: Regimens may need to be altered according to further microbiological identification and sensitivities.

1st line:	**Anidulafungin** 200mg IV on first day then 100mg IV OD	Treat for 14 days after first negative blood culture AND neutropenia resolved.
2nd line:	**Ambisome** 3mg/kg IV OD (initial test dose: 1mg over 10 minutes)	
3rd line:	**Voriconazole** 400mg PO every 12 hours for 2 doses then 200mg PO every 12 hours (half both the loading and maintenance dose if body-weight < 40kg)	

Candida osteomyelitis/septic arthritis/endocarditis/endophthalmitis/central nervous infection

1st line:	Discuss all suspected cases with microbiology Team

PROPHYLAXIS IN HIGH RISK GROUPS FOR CANDIDAEMIA / CANDIDIASIS

Repeated gastrointestinal perforations and anastomotic leaks, liver and pancreatic transplant:

1st line:	**Fluconazole** 400mg IV OD (initial loading dose: 800mg stat).	Review treatment after 5 – 7 days against culture and sensitivity results. Discuss with Microbiology.

ASPERGILLOSIS:

Risk factors for Invasive Aspergillosis:

- Allogenic haematopoietic stem cell transplantation (Allo-HSCT) with steroid dependent GVHD or graft failure.
- Intensive chemotherapy for AML, and ALL or advanced myelodysplastic syndrome (MDS)
- Prolonged neutropenia (> 21 days).
- Previous mould infection during previous neutropenia
- Exposure to high levels of environmental spores during neutropenia.

TREATMENT OF ACUTE INVASIVE ASPERGILLOSIS

Surgical interventions crucial in management of sinonasal, paranasal granuloma, osteomyelitis, cerebral and endocarditis.

1st line:	**Voriconazole** 6 mg/kg IV every 12 hours for 2 doses then 4mg/kg IV every 12 hours (reduce to 3mg/kg IV BD if not tolerated). Max: 6 months.	Minimum 2 week treatment
2nd line:	**Ambisome** 3 – 5 mg/kg IV OD (initial test dose: 1mg over 10 minutes)	

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

Refer to MicroGuide under "Bronchiectasis – Allergic Bronchopulmonary Aspergillosis (ABPA)".

CRYPTOCOCCOSIS

1. Cryptococcal meningitis in HIV positive patients:

1st line:	**Ambisome** 3 mg/kg IV OD (initial test dose: 1mg over 10 minutes) for 2 weeks *PLUS* **Flucytosine** 25 mg/kg IV/PO QDS for 2 weeks *FOLLOWED BY* **Fluconazole** 400mg PO OD for 8 weeks *MAINTAINENCE THERAPY:* **Fluconazole** 200mg PO OD long term for at least 12 months and until HIV controlled by antiretroviral therapy (i.e. undetectable HIV viral load and CD4 > 100 cells/µL on two occasions 6 months apart).

If bone marrow suppression with Flucytosine:

Alternative:	**Ambisome** 3 mg/kg IV OD (initial test dose: 1mg over 10 minutes) for 2 weeks *PLUS* **Fluconazole** 800 mg PO OD for 2 weeks *FOLLOWED BY* **Fluconazole** 400 mg PO OD for 8 weeks *MAINTAINENCE THERAPY:* **Fluconazole** 200mg PO OD long term for at least 12 months and until HIV controlled by antiretroviral therapy (i.e. undetectable HIV viral load and CD4 > 100 cells/µL on two occasions 6 months apart).

If Ambisome contraindicated / not appropriate:

Alternative:	**Fluconazole** 800 mg PO OD for 6 weeks *PLUS* **Flucytosine** 25 mg/kg IV/PO QDS for 6 weeks *MAINTAINENCE THERAPY:* **Fluconazole** 200mg PO OD long term for at least 12 months and until HIV controlled by antiretroviral therapy (i.e. undetectable HIV viral load and CD4 > 100 cells/µL on two occasions 6 months apart).

2. Cryptococcal meningitis in non–HIV positive patients:

1st line:	**Ambisome** 3 mg/kg IV OD (initial test dose: 1mg over 10 minutes) for 2 weeks *PLUS* **Flucytosine** 25mg/kg IV QDS for 2 weeks (NB: Consider a longer course of induction therapy of 4 – 6 weeks in those with high risk therapeutic failure e.g. uncontrolled underlying disease, inadequate clinical response to initial 2-week induction therapy or neurological complications) *FOLLOWED BY* **Fluconazole** 400mg PO OD for 8 weeks *MAINTAINENCE THERAPY:* **Fluconazole** 200mg PO OD long term for at 6 – 12 months.

If bone marrow suppression with Flucytosine:

Alternative:	**Ambisome** 3 mg/kg IV OD for 6 – 10 weeks.

PNEUMOCYSTIS JIROVECI (CARINII) PNEUMONIA:

Refer to MicroGuide under “Opportunistic infections”.

OTHER MOULD INFECTIONS

Contact Microbiology for advice.

3. Antifungal Agents

	FLUCONAZOLE	ITRACONAZOLE	AMBISOME (LIPOSOMAL AMPHOTHERICIN B)	VORICONAZOLE	ANIDULAFUNGIN	FLUCYTOSINE
Formulary status	General use	Restricted antifungal - Microbiology approval required	Restricted antifungal - Microbiology approval required	Restricted antifungal - Microbiology approval required	Restricted antifungal - Microbiology approval required	Restricted antifungal - Microbiology approval required
Preparation	IV / **PO**	IV / **PO**	IV	IV / **PO**	IV	IV
Oral bioavailability	> 90%	55% (capsule) 80% (oral solution)	N/A	> 90%	N/A	N/A
Activity	Fungistatic	Fungistatic	Fungicidal	Fungicidal against *Aspergillus* spp. Fungistatic against *Candida* spp.	Fungicidal against *Candida* spp. Fungistatic against *Aspergillus fumigatus*	Fungicidal
CSF penetration	**Good** (~ 80%)	Poor (< 10%)	Poor (< 2.5%)	**Good** (40 – 60%)	Poor (< 10%)	**Good** (71 – 85%)
Ocular penetration	**Good** (70 – 79%)	Not detectable (if inflamed, aqueous levels can reach 45%)	Not detectable (if inflamed, aqueous levels can reach 40%)	**Good** (38 – 53% or if inflamed up to 90%)	Not detectable	**Good** (20%)
Urinary concentration (% of unchanged active drug)	**High** (66 – 76%)	Low (< 2%)	Better urinary drug level attainment with non-liposomal **Fungizone**® (~20.6%)	Low (< 1.5%)	Low (< 1%)	**High** (80%)
Pregnancy	Avoid. Multiple congenital abnormalities reported	Only in life-threatening cases (toxicity at high doses in animal study)	Only if benefit outweighs risk - but not known to be harmful.	Avoid unless benefit outweigh s risk. Toxicity in animal studies.	Avoid unless benefit outweigh s risk. Toxicity in animal studies.	Only in life-threatening cases (toxicity in animal study)
Breast feeding	Not recommended. Concentration in milk 85% of plasma level.	Avoid. Small amount excreted in milk-may accumulate	Avoid. No safety information.	Avoid. No safety information.	Avoid unless benefit outweigh s risk. Present in milk in animal studies.	Avoid. No safety information.
Dosing in Obesity	Higher end of dosing	Corrected body weight*	Actual body weight*	Corrected body weight	No dose change	Ideal body weight

* Limited evidence

	FLUCONAZOLE	ITRACONAZOLE	AMBISOME (LIPOSOMAL AMPHOTHERICIN B)	VORICONAZOLE	ANIDULAFUNGIN	FLUCYTOSINE
Monitoring requirements	• WEEKLY bloods for first month then MONTHLY thereafter: ○ LFT ○ Renal function ○ U&E ○ FBC ○ CRP	• **TDM – see below** • WEEKLY bloods for first month then MONTHLY thereafter: ○ LFT ○ Renal function ○ U&E ○ FBC ○ CRP	• WEEKLY bloods: ○ LFT ○ Renal function ○ U&E ○ FBC ○ CRP	• **TDM – see below** • WEEKLY bloods for first month then MONHTLY thereafter: ○ LFT ○ Renal function ○ U&E ○ FBC ○ CRP	• WEEKLY bloods for first month then MONTHLY thereafter: ○ LFT ○ U&E ○ FBC ○ CRP	• **TDM – see below** • WEEKLY bloods: ○ LFT ○ Renal function ○ U&E ○ FBC ○ CRP
Therapeutic Drug Monitoring (TDM)	Nil	Aim **trough** level: > 0.5 but < 1 mg/L • Initial trough level 5 -7 days of starting treatment, dosage / formulation changes, drug interactions or compliance issues. • Re-assay MONTHLY for acute treatment, or every 3-MONTHLY for prophylaxis. • IMPORANT: Oral solutions have 30% higher bioavailability than capsules, which will affect drug levels. • Steady state =15 days (or 2 days with loading dose) • Saturable clearance. Non-linear pK.	Nil	Aim **trough** level: > 1 but < 4 mg/L • Initial trough level 2-5 days of starting treatment or dosage/formulation changes. • Always take a second sample one week later as patient may be progressively accumulating. • Re-assay MONTHLY for acute treatment, or every 3-MONTHLY for prophylaxis. • Saturable clearance. Non-linear pK.	Nil	Aim **trough** level: > 20 – 40 mg/L AND Aim **peak** level (30 mins after a dose): 50 – 100 mg/L • Initial levels within 72 hours of starting treatment or dosage change. • Short half-life hence serum concentration can change rapidly. • Re-assay WEEKLY.

3. Antifungal Agents

	FLUCONAZOLE	ITRACONAZOLE	AMBISOME (LIPOSOMAL AMPHOTHERICIN B)	VORICONAZOLE	ANIDULAFUNGIN	FLUCYTOSINE
Elimination route	Renal	Hepatic	Unknown	Hepatic	Hepatic	Renal
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	No	Yes
Hepatic dose adjustment	No	Yes (based on trough levels)	No	Yes (half maintenance dose)	No	No
Adverse drug reaction	GI Hepatotoxicity Skin reactions Alopecia CNS side effects	GI Hepatotoxicity Congestive heart failure CNS side effects Hypokalaemia Alopecia	Infusion-related reactions (e.g.chest pain, dyspnoea, abdomen/flank/ leg pain, flushing and urticaria) Nephrotoxicity Hypokalaemia Hypomagnesaemia Hepatotoxicity	Visual disturbances Hepatotoxicity Acute kidney injury Phototpxicity Hallucinations Alopecia Periostitis	GI Rash (histamine release) Hypokalaemia Elevated liver enzymes	Bone marrow suppression GI (including ulcerating enterocolitis) Rash Hepatotoxicity
Potential drug interaction	++ CYP2C9, CYP3A4 and CYP2C19 inhibitor	+++ Potent CYP2C9 & CYP3A4 inhibitor	+	++ CYP2C9, CYP3A4 and CYP2C19 inhibitor	-	-
Comments	Nil	**Capsule** bioavailability increased with food and gastric acidity (carbonated drink). **Oral solution** bioavailability increased at fasting state and not pH dependent. Palatability issue. Effective contraception during and after therapy	Initial test dose - before every new course of treatment. Observe over 30 minutes for anaphylactic or anaphylactoid reaction. If non-anaphylactic infusion-related reactions occur (see above), infuse slower over 2 hours.	**For oral**, reassess need every 6 months due to increases risk of phototoxicity and squamous cell carcinoma. **For IV**, maximum duration of 6 months. Avoid intense or prolonged sun exposure and avoid sunbeds.	Slow infusion <1.1mg/min - to avoid histamine release (i.e. rash, urticaria, flushing, hypotension, dyspnoea and bronchospasm).	Genotoxic and potential human teratogen. Effective contraception during treatment and for one month (female) or three months (male and their female partners) post treatment.

➢ Appendix 2

This table is a guide to clinical susceptibility of fungi and should be used to guide empirical treatment of suspected fungal infections in the absence of laboratory confirmation. It is not intended to substitute specialist advice or laboratory data.

Organism	Azoles			Echinocandins	Polyenes	Others
	Fluconazole	Itraconazole	Voriconazole	Anidulafungin	Ambisome	Flucytosine
Yeasts						
Candida albicans	S	S	S	S	S	S
Candida glabrata				S		S
Candida krusei			S	S		
Candida lusitaniae	S	S	S	S		S
Candida parapsilosis	S	S	S		S	S
Candida tropicalis	S	S	S	S	S	S
Cryptococcus neoformans			S		S	S
Dimorphic fungi						
Histoplasma capsulatum		S	S		S	
Moulds						
Aspergillus spp.			S	S	S	
Scedosporium apiospermum			S			
Fusarium spp.						
Zygomycetes						
Absidia, Apophysomyces					S	
Mucor					S	
Rhizomucor, Rhizopus					S	

S	Susceptible
	Susceptibility dependent on achieving the maximal blood concentration of antifungal agent
	Variable susceptibility
	Resistant
	No data available

➢ Contacts (inside and outside the Trust including out-of-hours contacts)

During working hours (Monday to Friday, 09:00 – 17:00)

ST Doctor in Microbiology	ext. 5085 or bleep 3069
Dr Michael Kelsey (Consultant Microbiologist)	ext. 5082
Dr Julie Andrews (Consultant Microbiologist)	ext. 3894
Lead Pharmacist, Antimicrobials	ext. 3732 or bleep 3138
Medicines Information	ext. 5021

Out of hours

On-call SpR in Microbiology	aircall via Whittington switchboard
On-call pharmacist	aircall Via Whittington switchboard

➢ References

1. BRITISH COMMITTEE FOR STANDARDS IN HAEMATOLOGY (2008) Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1365-2141.2007.06906.x
2. ULLMANN, A. J., AQUADO, J. M., ARIKAN-AKDAGLI, S. (2018) Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. Vol 24 (Suppl 1) pp e1 – e 38 https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(18)30051-X/pdf
3. AIDSinfo. Guidelines for Prevention and Treatment of Opportunistic

   Infections in HIV-Infected Adults and Adolescents. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf
4. PAPPAS, P. G., KAUFFMAN, C. A., ANDES, D.R . et al (2016) Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* Vol 62 (40) pp e1 – e50 https://academic.oup.com/cid/article/62/4/e1/2462830
5. PATTERSON, T. F., THOMPSON, G. R., DENNING, D. W. et al (2016) Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* Vol 63 (4) pp e1 – e60 https://academic.oup.com/cid/article/63/4/e1/2595039
6. PERFECT, J. R., DISMUKES, W. E., DROMER, F. et al (2010) Clinical practice guidelines for the management of Cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* Vol 50 (3) pp 291 – 322 https://academic.oup.com/cid/article/50/3/291/392360
7. Patterson, T. F., Thompson, G. R., Denning, D. W., Fishman, J. A., Hadley, S., Herbercht, R., Kontoyiannis, D. P., Marr, K. A., Morrison, V. A., Nguyen, M. H. et al (2016) Practice guideline for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. Vol 63 (4): e1 – e60.
8. Pappas, P. G., Kauffman, C. A., Andes, D. R., Clancy, C. J., Marr, K. A., Ostrosky-Zeichner, L., Reboli, A. C., Schuster, M. G., Vazquez, J. A., Walsh, T. J., Zoutis, T. E.

and Sobel, J. D. (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. Vol 62 (4): e1 - e50

9. PERFECT, J. R., DISMUKES, W. E. et al (2010) Clinical practice guideline for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, vol 50 (3) pp 291 – 322. Available at: http://cid.oxfordjournals.org/content/50/3/291.full.pdf+html

10. British HIV Association (2011) British HIV Association and British Infection Association Guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Medicine*, vol 12 (Suppl. 2) pp1 – 5. Available at: http://www.bhiva.org/documents/guidelines/oi/hiv_v12_is2_iss2press_text.pdf

11. FLÜCKIGER, U., MARCHETTI, O., BILLE, J. et al (2006) Treatment options of invasive fungal infections in adults. *Swiss Medical* Weekly, vol 136 (26) pp 447 – 463.

12. A joint collaboration between the Royal Free Hospital, University College Hospital and the North London Cancer Network (2005) Antifungal Strategy for Patients with Haematological Malignancies. *NLCN*

13. Schelenz S, Barnes RA, Barton RC, Cleverley JR, Lucas SB, Kibbler CC, et al. (2015) British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. *The Lancet Infectious Diseases*, vol 15 (4) pp 461–74.

14. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K et al. (2018) Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*, vol 24 (Suppl 1) e1-e38.

15. World Health Organisation (2018) Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/ (Accessed 10th June 2019)

16. Schelenz, S., Barnes, R. A., Barton, R. C., Cheverlye, J. R., Lucas, S. B. and Kibbler, C. C. (2015) British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal disease. *Lancet Infect Dis*. Vol 15 (4) pp 461 – 474. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/03/PSS1-Meds-Optimisation-trigger-5-BSMM-Guidelines-Fungal-Diagnosis.pdf

17. Kucers' the Use of Antibiotics. Available online. Accessed on 01/010/2019.

18. Felton, T., Troke, P. F. and Hope, W. W. (2014) Tissue penetration of antifungal agents. *Clin Microbiol Rev.* Vol 27 (1) pp 68 – 88.

19. Bellmann, R. and Smuszkiewicz, P. (2017) Pharmacokinetics of antifungals: practical implications for optimized treatment of patients. Infection. Vol 45 (6) pp 737 – 779

20. Polso, A. K., Lassiter, J. L. and Nagel, J. L. (2014) Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. *J Clin Pharm Ther.* Vol 39 (6) pp 584 – 608. Available from: https://deepblue.lib.umich.edu/bitstream/handle/2027.42/109281/jcpt12200.pdf?sequence=1&isAllowed=y

21. Pea, F. and Lewis, R. E. Overview of antifungal dosing in invasive candidiasis. *J Antimicrob Chemother.*Vol 73 (suppl 1) pp i33 – i43. Available from: https://academic.oup.com/jac/article/73/suppl_1/i33/4769702/

➢ Compliance with this guideline

Tool to Develop Monitoring Arrangements for Policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/Assess/inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Compliance with antifungal treatment guideline. Appropriate dosing and duration of treatment of antifungal agents.	Respective speciality team supported by the Microbiology & Pharmacy Department.	In-house audit tool	Ad hoc as issues arises.	Respective departmental meeting.

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		

	Title of document being reviewed:	Yes/No	Comments
	Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?	Yes	
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			