Invasive Fungal Disease in Adults; Prophylaxis, Investigation, and Treatment - Microbiology Full Clinical Guideline

Reference number: CG-T/2023/216

Introduction

- The human body and the environment harbour microorganisms including fungi. For example, the skin and mucosae can be colonised with *Candida* species; and *Cryptococcus* species, *Aspergillus* species, and Mucorales reside in soil and vegetation.
- The fungi capable of colonisation - or resident in environmental niches - are also, periodically, causes of infection.
- The risks for infectious disease include hosts with immunodeficiencies - e.g. haematology patients or human immunodeficiency virus (HIV) - and immunosuppression - e.g. haematopoietic stem cell transplant (HSCT) and oncology patients undergoing chemotherapy.
- The invasion of cells, tissues, organs, and systems by *Candida* species, *Cryptococcus* species, *Aspergillus* species, and Mucorales - in combination with symptoms, signs, and pathological stigmata - constitutes invasive fungal disease (IFD).
- With the immunocompromised nature of haematology and oncology pathologies, and associated therapies, fungi have the potential to disseminate from one body system to others, i.e. disseminated IFD.
- *Candida* species are the commonest cause of yeast IFD. Reservoirs include the skin and mucosa of the upper respiratory tract, urethra, gastrointestinal tract, and vagina. In haematology and oncology patients, cytotoxic chemotherapy may mediate injury to the mucosa; enabling localised invasion. *Candida* IFD manifests most commonly as candidaemia.
- *Cryptococcus* species can be another cause of yeast IFD. Inhalation from soil/bird droppings into the respiratory tract may enable initial nidus formation with dissemination to the central nervous system latterly. Cryptococcal IFD manifests most commonly as meningoencephalitis.
- *Aspergillus* species are the commonest cause of mould IFD. Its environmental reservoirs are transmissible via inhalation into the respiratory tract and sinuses. *Aspergillus* IFD manifests most commonly as pneumonia.
- Mucorales can be another cause of mould IFD. Inhalation from soil and vegetation into the sinuses and respiratory tract may manifest in rhino-orbital and pulmonary IFD, respectively.
- NB Please note, this guidance relates especially to *Candida* species, *Cryptococcus* species, *Aspergillus* species, and Mucorales.
    - If the differential diagnosis includes pneumocystosis, please note *Pneumocystis jirovecii* hospital guidelines.

Primary prophylaxis

Yeast (*Candida* species)

- The combination of:
    - *Candida* species colonising the skin and mucosa; and
    - The immunocompromise of haematology and oncology patients; and
    - Cytotoxic chemotherapy induced mucositis

  can cause invasive *Candida* disease.
- Antifungal prophylaxis is recommended when the incidence of *Candida* IFD is ≥ 6 %. In specific populations of haematology and oncology patients (please note the

primary prophylaxis table), antifungal prophylaxis against *Candida* species is recommended:

- First line: fluconazole 100 mg per oral 24 hourly.
- Second line: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
  - Therapeutic drug monitoring (TDM) recommended.
- Third line: Ambisome® 1 mg/kg intravenously Mondays, Wednesdays, and Fridays.

Yeast (*Candida* species) and mould (*Aspergillus* species)

- The combination of:
  - Environmental niches; and
  - The immunocompromise of haematology and oncology patients; and
  - Transmission via inhalation

  can cause invasive *Aspergillus* disease.
- Antifungal prophylaxis is recommended when the incidence of *Aspergillus* IFD is ≥ 6 %. In specific populations of haematology and oncology patients (please note the primary prophylaxis table), antifungal prophylaxis against *Candida* and *Aspergillus* species is recommended:
  - First line: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
    - TDM recommended.
  - Second line: Ambisome® 1 mg/kg intravenously Mondays, Wednesdays, and Fridays.

Primary prophylaxis table (with neutropenia [< 0.5 x 10^9 neutrophils/l])

Diagnoses and therapies	**Prophylaxis**	**Duration**
Chronic lymphocytic leukaemia (CLL)	No prophylaxis	
CLL + geriatric or advanced and unresponsive disease or neutropenia > 6 months	± Prophylaxis	
Chronic myeloid leukaemia (CML). Tyrosine kinase inhibitor	No prophylaxis	
Lymphoma. No intensive chemotherapy	No prophylaxis	
Myelodysplastic syndrome. No intensive chemotherapy	No prophylaxis	
Myeloma	No prophylaxis	
Autologous HSCT with mucositis anticipated preengraftment	Fluconazole	From initiation to 7 days after resolution of neutropenia
Lymphoma. Intensive chemotherapy	Fluconazole	From initiation to 7 days after resolution of neutropenia
Solid tumour + mucositis anticipated for ≥ 7 days + neutropenia	Fluconazole	From initiation to 7 days after resolution of neutropenia
Acute myeloid leukaemia. Intensive chemotherapy	Posaconazole	From initiation to 7 days after resolution of neutropenia
Allogeneic HSCT	Posaconazole	Engraftment, or post HSCT day 75
Aplastic anaemia, severe	Posaconazole	From initiation to 7 days after resolution of neutropenia
Autologous HSCT; neutropenia > 14 days or slow engraftment anticipated or failure of engraftment	Posaconazole	Engraftment, or post HSCT day 75
CML. Intensive chemotherapy	Posaconazole	From initiation to 7 days after resolution of neutropenia
Graft versus host disease + prednisolone (or equivalent) ≥ 1 mg/kg per day for > 1 week + neutrophils < 1 x 10^9 /l for > 1 week	Posaconazole	Graft versus host disease resolved, or prednisolone (or equivalent) < 10 mg/day
Graft versus host disease + prednisolone (or equivalent) ≥ 2 mg/kg per day for > 2 weeks	Posaconazole	Graft versus host disease resolved, or prednisolone (or equivalent) < 10 mg/day
Myelodysplastic syndrome. Intensive chemotherapy	Posaconazole	From initiation to 7 days after resolution of neutropenia
Acute lymphocytic leukaemia. Intensive chemotherapy	Ambisome®	From initiation to 7 days after resolution of neutropenia

Investigation

Please note, the IFD focus of this microbiology clinical guideline is candidiasis, cryptococcosis, aspergillosis, and mucormycosis.

If the differential diagnosis includes pneumocystosis, please note *Pneumocystis jirovecii* guidance.

Microbiology

- 8-10 ml of blood into a blood culture aerobic bottle and 8-10 ml of blood into a blood culture anaerobic bottle:
    - If positive, for microscopy, culture, and susceptibilities (MC&S).
- Serum (≥ 1.5 ml) into a Vacutainer®:
    - For beta glucan ± galactomannan.
- If the differential diagnosis includes cryptococcosis:
    - Serum (1-2 ml) into a Vacutainer®:
        - For cryptococcal antigen.
- If the differential diagnosis includes cryptococcosis with central nervous system infection:
    - Cerebrospinal fluid (0.1-0.2 ml) into a universal container:
        - For cryptococcal antigen.
- If the differential diagnosis includes respiratory tract IFD:
    - Sputum (≥ 5 ml) x 3 into universal containers:
        - For culture and susceptibilities.
- If the differential diagnosis includes rhino-orbital/pulmonary IFD, and if for invasive management/investigation:
    - Sinus aspirate (≥ 2 ml) and/or bronchoalveolar lavage (BAL; ≥ 20 ml) into universal containers:
        - For MC&S.
        - BAL also for galactomannan ± *Aspergillus* species polymerase chain reaction (PCR).

  NB Regarding the BAL:
    - Via switchboard, contact the respiratory consultant on call.
    - Provision of respiratory and cardiovascular status (respiratory rate, saturation, fraction of inspired oxygen, supplementation, ventilation; blood pressure, heart rate, haemoglobin, platelets, and coagulation) and past medical history (especially respiratory and cardiac) enable clinical assessment regarding proceeding with the BAL.
- If the differential diagnosis includes aspergillosis; and
    - If the serum and BAL are beta glucan and galactomannan negative:
        - Plasma, serum, or whole blood:
            - Into a Vacutainer®:
                - For *Aspergillus* species PCR.
- If for invasive management/investigation:
    - Aspirate/Biopsy:
        - Into sterile water, in a universal container:
            - For MC&S.
            - ± PCR and sequencing of fungal DNA.

NB The duty microbiologist will communicate microbiology results raising the differential diagnosis of IFD to the physicians and provide management advice.

Radiology

- Chest x-ray (CXR) is required initially.
- After CXR investigation, further imaging of the respiratory tract can be considered with high resolution computed tomography (HRCT):
    - Indications for HRCT chest include:

        - Neutropenic sepsis with respiratory tract symptoms and signs, and with normal CXR.
        - Neutropenic sepsis with respiratory tract stigmata, and with CXR abnormalities raising the differential diagnosis of atypical infection.
        - Neutropenic sepsis, on broad spectrum antimicrobial chemotherapy for 4-5 days, with persistent pyrexia.

- If the differential diagnosis includes sinusitis and/or mucormycosis, imaging of the sinuses/head/neck can be considered with CT and/or magnetic resonance imaging (MRI):
    - Indications for CT and/or MRI sinus include:
        - Acute localised pain (re sinusitis).
        - Nasal ulcer with black eschar.

- If the differential diagnosis includes brain abscess, meningitis, and/or cryptococcosis, imaging of the central nervous system can be considered with gadolinium enhanced MRI:
    - Indications for gadolinium enhanced MRI include:
        - Acute, focal neurological deficits potentially reflecting parietal, occipital, temporal, frontal, cerebellar, and/or cranial nerve lesions.

NB The responsibility for chasing radiology and disseminating reports to the relevant physician(s) remains that of the requesting team.

Histology

- If for invasive management/investigation:
    - Aspirate/Biopsy for histopathology:
        - Histology may enable detection of fungi in tissue and characterisation of fungal morphology (yeasts or hyphae).

NB If the histological features raise the possibility of IFD, the histopathologists will collaborate with the duty microbiologist responsible for sterile site investigations. Histology-microbiology joint discussions may culminate in referral of the histopathology to the mycology reference laboratory for further characterisation. The duty microbiologist will communicate histological features raising the differential diagnosis of IFD to the physicians and provide management advice.

Criteria for diagnosis of IFD

The European Organisation for Research and Treatment of Cancer divides IFD into proven, probable, or possible.

Proven

- Proven IFD centres on the detection of fungal elements in diseased tissue:

Specialty	Sample	Method	Criteria for proven IFD
Histology and/or microbiology	Sterile site (needle aspirate or biopsy)	Microscopy	Yeast cells, or hyphae of moulds with tissue damage
Histology + microbiology	Tissue (formalin-fixed paraffin-embedded)	Microscopy + molecular technique	Yeast cells or mould + detection and sequencing of fungal DNA
Microbiology + medicine/radiology	Sterile site (sterile procedure)	Culture	Culture of yeast or mould + symptoms, signs, or radiological features of IFD
Microbiology	Cerebrospinal fluid	Molecular technique	Detection of cryptococcal antigen
Microbiology	Blood	Culture	Culture of yeast or mould

Probable

- Probable IFD requires ≥ 1 host factor, ≥ 1 clinical criteria, and ≥ 1 mycology criteria:

Host factors: yeast (candidiasis) and moulds
Inherited severe immunodeficiency
Haematologic malignancy
Allogeneic stem cell transplant
Solid organ transplant
Corticosteroids at a mean minimum dose of ≥ 0.3 mg/kg per day of prednisone equivalent for ≥ 3 weeks in the past 60 days
T cell immunosuppressant treatment during the past 90 days
Neutropenia (< 0.5 x 10^9 neutrophils/l) for > 10 days
Host factors: yeast (cryptococcosis)
Haematologic malignancy
Idiopathic CD4 lymphocytopenia
Antibody deficiency
Stem cell transplant
HIV
End stage kidney disease
End stage liver disease
Solid organ transplant
Immunosuppressant treatment

Clinical criteria
Medical/radiological evidence of sinusitis + ≥ 1 of 3 of acute localised pain, nasal ulcer with black eschar, or extension from the paranasal sinus across bony barriers
Tracheobronchitis with tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar on bronchoscopy
Radiological evidence of lower respiratory tract IFD with 1 of 5 on CT of: (i) air-crescent sign; (ii) cavity; (iii) dense, well-circumscribed lesion(s) with or without a halo sign; (iv) reverse halo sign; (v) wedge-shaped, segmental, or lobar consolidation
Central nervous system infection with 1 of 2 on CT/MRI of meningeal enhancement/ inflammation or focal lesion
Candidaemia, within 2 weeks, with ≥ 1 of 2 of: (i) progressive retinal exudates or vitreal opacities on ophthalmic examination; (ii) meningeal enhancement, or target-like, small abscesses (bull's eye lesions) in the brain, spleen, or liver
Radiological lesion consistent with cryptococcosis

Mycology criteria
Microscopic detection of mould fungal elements - or culture of mould - from non-sterile site sinus aspirate, sputum, BAL, or bronchial brush samples
Culture of *Cryptococcus* species from non-sterile site sample(s)
Detection of beta glucan in serial (≥ 2) serum samples
Detection of galactomannan in CSF, BAL, plasma, or serum
Detection of *Aspergillus* nucleic acid in: (i) serial (≥ 2) BAL samples; (ii) BAL + plasma/serum/whole blood samples; (iii) serial (≥ 2) plasma/serum/whole blood samples

Possible

- The criteria for possible IFD are ≥ 1 host factor and ≥ 1 clinical criteria, without mycology criteria.

Treatment of IFD

Empiric intravenous antifungals

- First line:
    - Ambisome®: 3 mg/kg intravenously 24 hourly.
- Second line options:
    - Posaconazole: 300 mg intravenously 12 hourly for the first 24 hours, and 300 mg intravenously 24 hourly thereafter.
        - TDM recommended.

      NB Posaconazole's empiric antifungal spectrum of activity includes *Candida* species, *Cryptococcus* species, *Aspergillus* species, and Mucorales.
    - Caspofungin:
        - If ≥ 81 kg, 70 mg intravenously 24 hourly.
        - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.

      NB Caspofungin's empiric antifungal spectrum of activity includes *Candida* species and *Aspergillus* species; however, there is no anti-cryptococcal activity, and anti-Mucorales activity is limited to a putative, synergistic role in dual therapy with Ambisome®.

Management of *Candida* IFD: candidaemia

Investigation

- *Candida* IFD manifests itself most commonly as candidaemia:
    - Repeat blood cultures are recommended for evidence of clearance.
- Associated complications/infectious diseases include fungal endophthalmitis and infective endocarditis. Therefore:
    - Ophthalmology review is recommended; and
    - Echocardiogram is also recommended.

Treatment

- *Candida* species awaiting speciation and susceptibilities:
    - First line: caspofungin:
        - If ≥ 81 kg, 70 mg intravenously 24 hourly.
        - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.
    - Second line, if contraindications/interactions/side-effects with caspofungin: Ambisome® 3 mg/kg intravenously 24 hourly.
- *Candida albicans*:
    - If clinically for antifungals intravenously:
        - First line: fluconazole 800 mg intravenously for the first 24 hours, and 400 mg intravenously 24 hourly thereafter.
        - Second line, if contraindications/interactions/side-effects with fluconazole: caspofungin:
            - If ≥ 81 kg, 70 mg intravenously 24 hourly.
            - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.
        - Third line, if contraindications/interactions/side-effects with fluconazole and caspofungin: Ambisome® 3 mg/kg intravenously 24 hourly.
    - If clinically for antifungals per oral (e.g. reconstitution of immune function, no evidence of fungal endophthalmitis, no evidence of infective endocarditis, etc.):
        - First line: fluconazole 400 mg orally 24 hourly.

        - Second line, if contraindications/interactions/side-effects with fluconazole: voriconazole 400 mg orally 12 hourly for the first 24 hours, and 200 mg orally 12 hourly thereafter.
            - TDM recommended.
        - Third line, if contraindications/interactions/side-effects with fluconazole and voriconazole: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
            - TDM recommended.
- *Candida glabrata*, according to susceptibilities:
    - If clinically for antifungals intravenously:
        - First line: fluconazole 800 mg intravenously 24 hourly.
        - Second line, if contraindications/interactions/side-effects with fluconazole: caspofungin:
            - If ≥ 81 kg, 70 mg intravenously 24 hourly.
            - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.
        - Third line, if contraindications/interactions/side-effects with fluconazole and caspofungin: Ambisome® 3 mg/kg intravenously 24 hourly.
    - If clinically for antifungals per oral (e.g. reconstitution of immune function, no evidence of fungal endophthalmitis, no evidence of infective endocarditis, etc.):
        - First line: fluconazole 800 mg orally 24 hourly.
        - Second line, if contraindications/interactions/side-effects with fluconazole: voriconazole 400 mg orally 12 hourly for the first 24 hours, and 200 mg orally 12 hourly thereafter.
            - TDM recommended.
        - Third line, if contraindications/interactions/side-effects with fluconazole and voriconazole: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
            - TDM recommended.
- Other *Candida* species: collaborate with the microbiologist.
- Duration:
    - If there is no evidence of fungal endophthalmitis/infective endocarditis:
        - Antifungals ≥ 2 weeks:
            - From reconstitution of immune function; and
            - From the first negative, repeat blood cultures.

Management of *Cryptococcus* IFD: cryptococcal meningitis

Treatment: medicine[1]

- If the drug history includes immunosuppressants, reduce the immunosuppressive chemotherapy in collaboration with the medical (e.g. haematology, oncology) senior/consultant.

Treatment: medicine[2]

- Phase 1, 'induction':
    - First line:
        - Ambisome® 5 mg/kg intravenously 24 hourly ≥ 2 weeks; **and**
        - **If available**, flucytosine 25 mg/kg per oral 6 hourly ≥ 2 weeks.
    - Second line, if contraindications/interactions/side-effects with flucytosine, or if flucytosine is unavailable:
        - Ambisome® 5 mg/kg intravenously 24 hourly ≥ 2 weeks; **and**
        - Fluconazole 800-1200 mg intravenously/per oral ≥ 2 weeks.

        - Third line, if contraindications/interactions/side-effects with flucytosine and fluconazole, or if flucytosine is unavailable:
            - Ambisome® 5 mg/kg intravenously 24 hourly 4-6 weeks.
        - Fourth line, if contraindications/interactions/side-effects with Ambisome®:
            - Fluconazole 800-1200 mg intravenously 4-6 weeks; **and**
            - **If available**, flucytosine 25 mg/kg per oral 6 hourly 4-6 weeks.
        - Fifth line, if contraindications/interactions/side-effects with Ambisome® and flucytosine, or if flucytosine is unavailable:
            - Fluconazole 1200-2000 mg per oral 24 hourly 10-12 weeks.
- Phase 2, 'consolidation':
    - First line: fluconazole 400-800 mg per oral 24 hourly 8 weeks.
    - Second line, if contraindications/interactions/side-effects with fluconazole: itraconazole 200 mg per oral 12 hourly 8 weeks.
        - TDM recommended.
- Phase 3, 'maintenance':
    - First line: fluconazole 200 mg per oral 24 hourly 6-12 months.
    - Second line, if contraindications/interactions/side-effects with fluconazole: itraconazole.
        - TDM recommended.
- Duration:
    - In general, months-year from reconstitution of immune function.
        - Reflecting the rarity of invasive *Cryptococcus* disease, there remains no definitive recommendations on duration of therapy.
        - The duty microbiologist will collaborate with the mycology reference laboratory and communicate management advice to the physicians re duration of antifungals.

Management of *Aspergillus* IFD: respiratory tract aspergillosis

Treatment

- If clinically for antifungals intravenously:
    - If there is: (i) no drug history of antifungal prophylaxis; or (ii) drug history of posaconazole prophylaxis without therapeutic levels; or (iii) drug history of Ambisome® prophylaxis:
        - First line: voriconazole 6 mg/kg intravenously 12 hourly for the first 24 hours, and 4 mg/kg intravenously 12 hourly thereafter.
            - TDM recommended.
        - Second line, if contraindications/interactions/side-effects with voriconazole: posaconazole 300 mg intravenously 12 hourly for the first 24 hours, and 300 mg intravenously 24 hourly thereafter.
            - TDM recommended.
        - Third line, if contraindications/interactions/side-effects with voriconazole or posaconazole: in collaboration with the duty microbiologist, isavuconazole 200 mg intravenously 8 hourly for the first 48 hours, and 200 mg intravenously 24 hourly thereafter.
            - TDM recommended.
    - If there is drug history of posaconazole prophylaxis with therapeutic levels:
        - Ambisome® 3 mg/kg intravenously 24 hourly.
    - If there are contraindications/interaction/side-effects with voriconazole, posaconazole, isavuconazole, and/or Ambisome®:
        - Caspofungin:
            - If ≥ 81 kg, 70 mg intravenously 24 hourly.

        - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.
- If clinically for antifungals per oral (e.g. reconstitution of immune function, resolution of symptoms/signs, microbiological evidence [for example, galactomannan] of resolving *Aspergillus* IFD):
    - First line: voriconazole 200 mg per oral 12 hourly.
        - TDM recommended.
    - Second line: posaconazole 300 mg 24 hourly.
        - TDM recommended.
    - Third line: isavuconazole 200 mg 24 hourly.
        - TDM recommended.
- Duration:
    - Antifungals 6 weeks:
        - From reconstitution of immune function.

Management of Mucorales IFD: rhino-orbital and respiratory tract mucormycosis

- Mucormycosis is life threatening; mortality rates range from 24-49%.
- Reflecting the nature of invasive Mucorales disease, both medical and surgical interventions are recommended.

Treatment: surgical intervention

- In general:
    - Exploration and debridement of diseased tissue to non-infected/'clean' margins.

Treatment: medicine[1]

- If the drug history includes immunosuppressants, reduce the immunosuppressive chemotherapy in collaboration with the medical (e.g. haematology, oncology) senior/consultant.

Treatment: medicine[2]

- Intravenous monotherapy:
    - First line: Ambisome® 5 mg/kg intravenously 24 hourly.
    - Second line, if contraindications/interaction/side-effects with Ambisome®: posaconazole 300 mg intravenously 12 hourly for the first 24 hours, and 300 mg intravenously 24 hourly thereafter.
        - TDM recommended.
    - Third line, if contraindications/interaction/side-effects with Ambisome® and posaconazole: in collaboration with the duty microbiologist, isavuconazole 200 mg intravenously 8 hourly for the first 48 hours, and 200 mg intravenously 24 hourly thereafter.
        - TDM recommended.
- ± Intravenous dual therapy:
    - Contraindications to surgery and refractory disease are both scenarios wherein dual therapy* can be contemplated:
        - First line:
            - Ambisome® 5-10 mg/kg intravenously 24 hourly; **and**
            - Posaconazole 300 mg intravenously 12 hourly for the first 24 hours, and 300 mg intravenously 24 hourly thereafter.
                - Posaconazole TDM recommended.
        - Second line:
            - Ambisome® 5-10 mg/kg intravenously 24 hourly; **and**

                - If contraindications/interaction/side-effects with posaconazole: in collaboration with the duty microbiologist, isavuconazole 200 mg intravenously 8 hourly for the first 48 hours, and 200 mg intravenously 24 hourly thereafter.
                    - Isavuconazole TDM recommended.
            - Third line:
                - Ambisome® 5-10 mg/kg intravenously 24 hourly; **and**
                - If contraindications/interaction/side-effects with posaconazole and isavuconazole: caspofungin:
                    - If ≥ 81 kg, 70 mg intravenously 24 hourly.
                    - If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter.
- If clinically for antifungals per oral (resection of diseased tissue to non-infected/'clean' margins, reconstitution of immune function, resolution of symptoms/signs, no histopathology evidence of ongoing IFD, and no microbiology evidence of ongoing IFD):
    - First line: posaconazole 300 mg 24 hourly.
        - TDM recommended.
    - Second line: isavuconazole 200 mg per oral 24 hourly.
        - TDM recommended.
- Duration:
    - In general, months from reconstitution of immune function.
        - Reflecting the rarity of invasive Mucorales disease, there remains no definitive recommendations on duration of therapy.
        - The duty microbiologist will collaborate with the mycology reference laboratory and communicate management advice to the physicians re duration of antifungals.

***** No compelling evidence base re efficacy of dual therapy.

Management of IFD: summary

Symptoms, signs, background of immunocompromise, or pathology (e.g. neutropenia > 10 days) concerning for IFD

Investigate

Microbiology
- Blood cultures
- Beta glucan and galactomannan
- ± Sputum x 3, ± sinus aspirate, ± BAL
- ± Needle aspirate or biopsy

Radiology
- CXR
- ± HRCT chest
- ± CT sinuses
- ± CT and/or MRI head

Histology
- ± Needle aspirate or biopsy

Treat

Empiric intravenous antifungals
- First line: Ambisome® 3 mg/kg intravenously 24 hourly
- Second line options:
  - Posaconazole 300 mg intravenously 12 hourly for the first 24 hours, and 300 mg intravenously 24 hourly thereafter
    NB Posaconazole's empiric antifungal spectrum includes *Candida* species, *Cryptococcus* species, *Aspergillus* species, and Mucorales
  - Caspofungin. If ≥ 81 kg, 70 mg intravenously 24 hourly**.** If < 81 kg, 70 mg intravenously for the first 24 hours, and 50 mg intravenously 24 hourly thereafter
    NB Caspofungin's empiric antifungal spectrum includes *Candida* species and *Aspergillus* species; however, there is no anti-cryptococcal activity, and anti-Mucorales activity is limited to a putative, synergistic role in dual therapy with Ambisome®

Review microbiology, radiology, and/or histology criteria re proven, probable, and/or possible IFD

POSITIVE
- Candidiasis/cryptococcosis/aspergillosis/mucormycosis management, including directed antifungals

NEGATIVE
- Consider ceasing empiric antifungal treatment in collaboration with the medical senior/consultant

NB Please note, this guidance relates especially to *Candida* species, *Cryptococcus* species, *Aspergillus* species, and Mucorales. If the differential diagnosis includes pneumocystosis, please note *Pneumocystis jirovecii* hospital guidelines

Secondary prophylaxis

In haematology and oncology patients with a history of IFD, *Candida* or *Aspergillus* infectious disease may recur. Antifungal prophylaxis can reduce the risk of recurrent IFD episodes.

Candida IFD

- In patients with a history of invasive *Candida* disease:
    - Receiving myelosuppressive chemotherapy with neutropenia anticipated for ≥ 2 weeks; **or**
    - With a prolonged period of neutropenia prior to HSCT; **or**
    - Undergoing autologous HSCT; **or**
    - Undergoing allogeneic HSCT

  Antifungal prophylaxis is recommended:
    - First line: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
        - TDM recommended.
    - Second line: Ambisome® 1 mg/kg intravenously Mondays, Wednesdays, and Fridays.

  NB Ensure the isolate was susceptible to the selected prophylactic.
- The antifungal prophylaxis is continued to the point of myeloid reconstitution in patients undergoing chemotherapy, and to discontinuation of immunosuppressive therapy in patients undergoing HSCT.

Aspergillus IFD

- In patients with a history of invasive *Aspergillus* disease:
    - Receiving myelosuppressive chemotherapy with neutropenia anticipated for ≥ 2 weeks; **or**
    - With a prolonged period of neutropenia prior to HSCT; **or**
    - Undergoing autologous HSCT; **or**
    - Undergoing allogeneic HSCT

  Antifungal prophylaxis is recommended:
    - First line: posaconazole 300 mg tablet 12 hourly for the first 24 hours, and 300 mg tablet 24 hourly thereafter.
        - TDM recommended.
    - Second line: Ambisome® 1 mg/kg intravenously Mondays, Wednesdays, and Fridays.

  NB1 Ensure the isolate was susceptible to the selected prophylactic.
- The antifungal prophylaxis is continued to the point of myeloid reconstitution in patients undergoing chemotherapy, and to discontinuation of immunosuppressive therapy in patients undergoing HSCT.
- NB2 Fungal markers (beta glucan and galactomannan) are recommended 2-4 weeks after completion of prophylaxis, to safety net regarding recurrence/reactivation of *Aspergillus* IFD.

Appendix: antifungal chemotherapy

	Fluconazole	Isavuconazole
Prophylactic dose • Intravenous • Per oral	 100 mg 24 hourly 100 mg 24 hourly	 - -
Treatment doses (in general) • IV • PO	 400-800 mg 24 hourly 400-800 mg 24 hourly	 200 mg 8 hourly for 48 hours; 200 mg 24 hourly thereafter 200 mg 8 hourly for 48 hours; 200 mg 24 hourly thereafter
Contraindications	Acute porphyrias	Acute porphyrias; short QT syndrome
Interactions	Please review the British National Formulary (BNF) for up-to-date interactions	Please review the BNF for up-to-date interactions
Common or very common side-effects (please review BNF for uncommon and rare or very rare)	Diarrhoea, gastrointestinal discomfort, headache, nausea, skin reactions, and vomiting	Appetite decreased, asthenia, chest pain, confusion, delirium, diarrhoea, drowsiness, dyspnoea, electrolyte imbalance, gastrointestinal discomfort, headache, hepatic disorders, hyperbilirubinaemia, nausea, renal failure, respiratory disorders, skin reactions, thrombophlebitis, vomiting
Renal impairment • GFR 20-50 ml/min • GFR 10-20 ml/min • GFR < 10 ml/min	 50-100% of normal dose 50-100% of normal dose 50% of normal dose	 Dose as in normal renal function Dose as in normal renal function Dose as in normal renal function
Hepatic impairment	Manufacturer advises caution - limited information available	Manufacturer advises caution in severe impairment (no information available) - monitor for drug toxicity
Therapeutic drug monitoring • Recommended • Sample • Repeat • Expected level	 ± In renal failure (collaborate with duty microbiologist) 1-2 ml serum, pre and post (2 hours) dose If required, 4-8 days Area under the curve (AUC): minimum inhibitory concentration (MIC) ratio > 100	 Yes, if renal impairment 1-2 ml serum, pre dose 4-8 days 2-4 mg/l

	Posaconazole
Prophylactic dose • Intravenous • Per oral[1] • Per oral[2]	300 mg 12 hourly for 24 hours; 300 mg 24 hourly thereafter 300 mg TABLET 12 hourly for 24 hours; 300 mg TABLET 24 hourly thereafter 200 mg SUSPENSION PO 8 hourly*,**
Treatment doses • Intravenous • Per oral[1] • Per oral[2]	300 mg 12 hourly for 24 hours; 300 mg 24 hourly thereafter 300 mg TABLET 12 hourly for 24 hours; 300 mg TABLET 24 hourly thereafter If tolerant of food, 400 mg SUSPENSION 12 hourly; if intolerant of food, 200 mg SUSPENSION 6 hourly*,**
Contraindications	Acute porphyrias
Interactions	Please review the BNF for up-to-date interactions
Common or very common side-effects (please review BNF for uncommon and rare or very rare)	Appetite decreased, asthenia, constipation, diarrhoea, dizziness, drowsiness, dry mouth, electrolyte imbalance, gastrointestinal discomfort, gastrointestinal disorders, headache, hypertension, nausea, neutropenia, sensation abnormal, skin reactions, taste altered, vomiting
Renal impairment • GFR 20-50 ml/min • GFR 10-20 ml/min • GFR < 10 ml/min	Per oral, dose as in normal renal function. Intravenous, discuss with pharmacy***/microbiology*** Per oral, dose as in normal renal function. Intravenous, discuss with pharmacy***/microbiology*** Per oral, dose as in normal renal function. Intravenous, discuss with pharmacy***/microbiology***
Hepatic impairment	Manufacturer advises caution (risk of increased exposure, limited information available)
Therapeutic drug monitoring • Recommended • Sample • Repeat • Prophylactic level • Therapeutic level	Yes, within 3-8 days of starting therapy 1-2 ml serum, pre dose 4-8 days 0.7-3.75 mg/l 1.0-3.75 mg/l

* Posaconazole oral suspension is **not** interchangeable with tablets on a milligram-for-milligram basis

** Posaconazole oral suspension should be taken with food (preferably a high fat meal) or nutritional supplement to ensure adequate exposure for systemic effects. Where possible, tablets should be used in preference to suspension because tablets have a higher bioavailability

*** Manufacturer advises caution if creatinine clearance less than 50 ml/minute - intravenous vehicle may accumulate

	Voriconazole
Prophylactic dose • Intravenous • Per oral	 - -
Treatment doses • IV • PO	 6 mg/kg 12 hourly for 24 hours; 4 mg/kg 12 hourly thereafter ≥ 40 kg: 400 mg 12 hourly for 24 hours; 200 mg 12 hourly thereafter < 40 kg: 200 mg 12 hourly for 24 hours; 100 mg 12 hourly thereafter
Contraindications	Acute porphyrias
Interactions	Please review the BNF for up-to-date interactions
Common or very common side-effects (please review BNF for uncommon and rare or very rare)	Acute kidney injury, agranulocytosis, alopecia, anaemia, anxiety, arrhythmias, asthenia, bone marrow disorders, chest pain, chills, confusion, constipation, depression, diarrhoea, dizziness, drowsiness, dyspnoea, electrolyte imbalance, eye disorders, eye inflammation, fever, gastrointestinal discomfort, haemorrhage, hallucination, headache, hepatic disorders, hypoglycaemia, hypotension, increased risk of infection, insomnia, leucopenia, muscle tone increased, nausea, neutropenia, oedema, oral disorders, pain, pulmonary oedema, respiratory disorders, seizure, sensation abnormal, skin reactions, syncope, tetany, thrombocytopenia, tremor, vision disorders, vomiting
Renal impairment	Intravenous vehicle may accumulate if creatinine clearance less than 50 ml/minute - use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required)
Hepatic impairment	Manufacturer advises use usual initial loading dose then halve maintenance dose in mild to moderate cirrhosis. Manufacturer advises caution, particularly in severe impairment (no information available)
Therapeutic drug monitoring • Recommended • Sample • Repeat • Prophylactic level • Therapeutic level	 Yes, within 5 days of starting therapy 1-2 ml serum, pre dose 4-8 days 1.0-5.5 mg/l 1.0-5.5 mg/l (2.0-5.5 mg/l for “bulky or disseminated infection”)

	Caspofungin	Ambisome®*, **
Prophylactic dose • Intravenous • Per oral	- -	1 mg/kg (round up to the nearest 50 mg) Mondays, Wednesdays, and Fridays* -
Treatment doses • IV • PO	≥ 81 kg: 70 mg 24 hourly < 81 kg: 70 mg for 24 hours; 50 mg 24 hourly thereafter -	Non-mucor: 3 mg/kg 24 hourly* Mucor: 5-10 mg/kg 24 hourly* -
Contraindications	-	-
Interactions	Please review the BNF for up-to-date interactions	Please review the BNF for up-to-date interactions
Common or very common side-effects (please review BNF for uncommon and rare or very rare)	Arthralgia, diarrhoea, dyspnoea, electrolyte imbalance, fever, headache, hyperhidrosis, nausea, skin reactions, vomiting	Anaemia, appetite decreased, azotaemia, chills, diarrhoea, dyspnoea, electrolyte imbalance, fever, headache, hepatic function abnormal (discontinue), hyposthenuria, hypotension, nausea, nephrocalcinosis, renal impairment, renal tubular acidosis, skin reactions, vomiting
Renal impairment • GFR 20-50 ml/min • GFR 10-20 ml/min • GFR < 10 ml/min	 Dose as in normal renal function Dose as in normal renal function Dose as in normal renal function	 Dose as in normal renal function Dose as in normal renal function Dose as in normal renal function
Hepatic impairment	70 mg on first day then 35 mg once daily in moderate impairment. No information available for severe impairment	-
Therapeutic drug monitoring • Recommended • Sample • Repeat • Expected level	 No - - -	 No - - -

* Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg or 5-10 mg/kg 24 hourly

** Please note that Ambisome® contains amphotericin, and that there are other registered medicines (Abelcet® and Fungizone®) containing amphotericin. The dosages and side-effects vary from one preparation to another. This hospital guideline relates to the Ambisome® preparation. Clinical certainty regarding the administration of the correct formulation is essential to safeguard patients and prevent complications, including fatalities. If there is clinical uncertainty (1) STOP, and (2) collaborate with the nursing senior, or discuss with the ward pharmacist, or escalate to the on call pharmacist to clarify.

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Document control

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