Management and prevention of invasive fungal infection (IFI) in adult haemato-oncology

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Contents

1. Background

Invasive fungal infections (IFI) including invasive candidiasis, aspergillus and mucormycosis can cause significant morbidity and mortality among patients with haematological malignancies and are associated with increased healthcare costs.

It is important to highlight that invasive fungal infection must be considered in patients with persistent neutropenic fever, despite broad spectrum antibiotic treatment. The diagnostic and treatment strategy in these patients should be discussed with the Infectious Diseases (ID) or Microbiology team.

This guidance incorporates information on treatment of IFI as well as prophylaxis against IFI. Please ensure you have reviewed the dosing indication when using this document.

1.1 Definition of IFI

Infections are classified as “possible,” “probable,” and “proven” (as per EORTC/MSG consensus) using a range of host factors, clinical features and mycologic evidence.

Whilst these criteria have proven their value for clinical research, in clinical practice treatment is often initiated for possible/probable infections.

2. Risk stratification

In the following tables ‘high dose steroid’ is defined as more than 20mg per day of prednisolone, or an equivalent dose of another corticosteroid.

Prolonged neutropenia is defined as an absolute neutrophil count (ANC) less than 1 x 10^9/L for 2 weeks or more.

Table 1 – General host risk factors influencing IFI risk

1.	**Prolonged neutropenia**
2.	**Receipt of haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOC)**
3.	**High-dose steroid > 2-week duration**
4.	**Treatment with other T-cell immunosuppressants** (such as calcineurin inhibitors (CNIs) e.g. ciclosporin), anti-human thymocyte immunoglobulin (ATG)), **tumor necrosis factor-α blockers** (TNFα inhibitors e.g. etanercept), **lymphocyte-specific monoclonal antibodies** (e.g. rituximab, alemtuzumab) or **immunosuppressive nucleoside analogues** (e.g. fludarabine, nelarabine) during the past 90 days.
5.	**Inherited severe immunodeficiency**
6.	**Steroid-refractory acute graft-versus-host disease (aGvHD)**
7.	**Iron overload**
8.	**Other comorbidities;** CMV disease and respiratory viral infections, diabetes, respiratory disease (COPD, pulmonary fibrosis etc.), malnutrition.

In addition to host risk factors, environmental factors such as construction work, gardening or a lack of laminar air flow are known to increase risk of fungal infection in the immunosuppressed haematological population.

2.1 High risk patients

Primary prophylaxis with mould-active anti-fungals is recommended for these patients.

CAR-T cell therapy is not classified as a part of this current guidance. There are separate guidelines available under the Advanced Cellular Therapy (ACT) haematology folders which advocates treating all patients as high-risk of IFI.

Upcoming ECIL10 guidelines may challenge this stance with further scrutiny of CAR-T indication and resultant risk profile, we expect a future edition of this guidance to include a full review of anti-fungal prescribing within CAR-T indications.

Table 2 – Circumstances classifying a haematological patient as 'high risk' of IFI

1.	**History of prior IFI + receipt of intense immunosuppression.**
2.	**Induction therapy in AML, APML, MDS and ALL***
3.	**Severe aplastic anaemia with prolonged neutropenia** and/or receiving anti-human thymocyte immunoglobulin (ATG) therapy
4.	**Allogeneic stem cell transplant (alloSCT)**, until neutrophil recovery and engraftment
5.	**Acute or chronic GvHD steroid dependent/refractory, or grade 3 or 4**
6.	**Autologous stem cell transplant (autoSCT) with prolonged neutropenia** prior to or following transplant.

*Acute Myeloid Leukaemia (AML), Acute Promyelocytic Leukaemia (APML), Myelodysplastic Syndrome (MDS) and Acute Lymphoblastic Leukaemia (ALL)

2.2 Low risk patients

Primary prophylaxis with low intensity therapy is recommended. For example, low dose fluconazole or intermittent dosing of amphotericin B liposomal (Tilomed/Gilead/AmBisome®).

Table 3 – Circumstances classifying a haematological patient as 'low risk' of IFI

1.	**Myeloid malignancy with neutropenia (<1 x 10^9/L)** – excludes induction, see above
2.	**Lymphoma patients + intensive/dose escalated therapy.**
3.	**Autologous stem cell transplant recipients** (without prolonged neutropenia)
4.	**Fludarabine / alemtuzumab in treatment-refractory CLL** or lymphoma**
5.	**ALL** intensification/consolidation**
6.	**Myeloma patients**

**Chronic Lymphocytic Leukaemia (CLL), Acute Lymphoblastic Leukaemia (ALL)

2.3 Very low risk

Primary prophylaxis is **not recommended** for these patients.

Table 4 – Circumstances classifying a haematological patient as 'very low risk' of IFI

1.	**Lymphoma patients on standard therapy (e.g. RCHOP)**
2.	**Chronic Myeloid Leukaemia (CML)**
3.	**Chronic lymphocytic leukaemia (CLL)**

4. Aplastic anaemia (non-severe)
5. Other myeloproliferative malignancy
6. ALL* patients undergoing maintenance therapy**

***Acute Lymphoblastic Leukaemia (ALL)

3. Anti-fungal prophylaxis

All prophylactic treatment should be prescribed throughout the period of anticipated neutropenia.

There should be discontinuation of treatment when there is consistent neutrophil recovery over 2 or 3 days (ANC >1 x 10^9/L). ANC should be unsupported by granulocyte colony stimulating factor (GCSF).

3.1 High risk prophylaxis

High risk patients should receive mould active 'azole' prophylaxis with either posaconazole (OUH first line) or voriconazole dependent on local preferences.

3.1.1 Alternatives to '-azole' prescribing

Where azole prophylaxis is unsuitable for a patient, treatment with an echinocandin anti-fungal such as caspofungin (or 2nd line micafungin / local Trust preferred agent) should be considered.

3.2 Low risk prophylaxis

Patients in the low-risk group should receive prophylactic low-dose oral fluconazole 50mg OD.

3.3 Prophylaxis in ALL regimens / vinca alkaloid intense regimens

Administration of vinca alkaloids (e.g. vincristine, vinblastine) in combination with strong CYP3A4 inhibitors (e.g. posaconazole, voriconazole) can increase the risk of toxicity, particularly neurotoxicity.

The ALL-induction scheme involves administration of weekly vincristine which heightens the potential for this interaction to be problematic. It is recommended to avoid use of posaconazole or voriconazole for prophylaxis.

Prescribe prophylaxis with amphotericin B liposomal (Tilomed/Gilead/AmBisome®) 7mg/kg at a reduced **ONCE weekly** frequency - modified doses are recommended where there are renal concerns.

4. Diagnosis of IFI

In neutropenic patients, with fever persisting at 96 hours despite broad spectrum antibiotic treatment:

1. Obtain CT thorax (and sinuses where clinically indicated). Further scanning as clinically indicated.
2. ***If radiological features are suggestive of IFI:***
   - B-D-glucan on serum
   - Early bronchoscopy with BAL and commence empirical antifungal therapy. Samples should be sent for microscopy and culture, respiratory virus PCR, fungal microscopy and culture, PCP PCR, aspergillus antigen and fungi. Biopsies (lung, other tissue) should be sent for microscopy (incl Calcofluor) and culture, fungal microscopy and culture, and histology. Additional antigen and molecular studies

(galactomannan, beta-D glucan and fungal PCR) should be discussed with the ID/micro team.
- Anti-fungal drug levels (where indicated)
- Early discussion with chest medicine, ENT, radiology and infectious diseases/ microbiology as appropriate.

3. ***In the absence of IFI radiological features:***
   - Empirical antifungal therapy is not required.
   - Alternative causes for persisting fever should be sought. Consider repeat imaging after one week.
4. ***Where candidiasis is suspected***
   - Repeat blood cultures and beta-D glucan (3 sets of cultures are required to confirm the diagnosis).
   - Refer to further information in Section 5.2.

5. Treatment of suspected / confirmed IFI

Treatment approaches may be empirically driven (i.e., initiated prior to identifying/confirming the infective organism), or pre-emptively driven (diagnostically supported).

There may be combination of both approaches depending on the availability of diagnostic tools.

5.1 Aspergillosis

Treatment of proven or probable aspergillosis should continue until there is clear clinical improvement, accompanied by radiological response and improvement in immune status with an expectation that treatment will continue for a **minimum of 6 weeks.**

Longer treatment durations may be appropriate and should be considered on an individual basis.

5.1.1 First line treatment

Patients who are not on mould-active prophylaxis, should receive treatment with posaconazole (OUH first line), or voriconazole (if local Trust preference) except where:

- There is concern about mucormycosis (see below).
- Severe chronic liver disease (Child Pugh score C) – consider amphotericin B liposomal (Tilomed/Gilead/AmBisome®).

Consider initiating therapy intravenously if there are concerns about adequate absorption (e.g. severe mucositis).

Patients already on mould-active prophylaxis should move to second line therapy if clinically unwell.

5.1.2 Second line treatment

Amphotericin B liposomal (Tilomed/Gilead/AmBisome®) can be used second line.

5.1.3 Third line treatment

Discuss with ID/microbiology. Treatment options at this stage are dependent on individual circumstances, for example, the pathogen detected & susceptibility, prior

exposure to antifungal agents, possibility of fungal co-infection or presence of multi-site disease.

Immune reconstitution should be ruled out. This is associated with the onset of clinical or radiological deterioration consistent with worsening of aspergillosis and temporally related to neutrophil recovery, despite no change to antifungal therapy and an apparent treatment response prior to this time.

A clear anti-fungal dosing timeline, serum drug levels where indicated and documented reasons behind previous switch between anti-fungal agents is crucial in helping to determine the best path forward.

ID/Micro may make further management recommendations including isavuconazole (ID/micro advice only), posaconazole/voriconazole (dependent on prior exposure) or use of echinocandins (caspofungin - OUH first line, or micafungin/anidulafungin).

These agents may also be suggested either alone or in combination. Combination treatment will always mix 2 separate classes of anti-fungal (e.g. triazole antifungal + echinocandin) and should only ever be initiated in consultation with ID/micro.

5.1.4 Mucormycosis (clinical emergency)

Suspected and confirmed mucormycosis is a medical emergency. Initiate rapid treatment with surgical debridement (where indicated) and effective systemic antifungal therapy.

Prescribe amphotericin B liposomal (Tilomed/Gilead/AmBisome®) – discuss dose with ID/microbiology, higher doses of 5 - 10mg/kg per day are usually required.

Isavuconazole (ID/microbiology recommendation only) is an alternative option where liposomal amphotericin is contraindicated (e.g. renal impairment).

Treatment duration should be guided by microbiology and clinical course of infection.

5.2 Invasive candidaemia

Source control (e.g. removal of contaminated lines and drainage of infected collections e.g. peritoneal, pleural fluid and/or abscess material) and early initiation of treatment with early, effective systemic antifungal therapy are essential to the successful management of invasive candidiasis.

5.2.1 Management recommendations:

- Three sets of blood cultures should be sent to make the initial diagnosis
- Daily blood culture sets.
- Ophthalmic review is advised where vision cannot be tested
- Remove central venous catheter (CVC)
- Treatment should continue for 14 days following first negative cultures, and resolution of symptoms attributable to candidemia.

5.2.2 First line treatment

If the patient is not unwell and there is no prior azole exposure: Fluconazole can be initiated for fluconazole-sensitive candida.

For unwell / azole exposed patients: An echinocandin anti-fungal (e.g. caspofungin (OUH first line) or micafungin) is recommended as initial therapy for candidaemia.

5.2.3 Second line treatment

Amphotericin B liposomal (Tilomed/Gilead/AmBisome®) can be used second line.

5.2.4 Step-down treatment

In stable patients with a fluconazole-sensitive strain, switch to PO fluconazole can be considered within 5 to 7 days (i.e. from caspofungin, or amphotericin B liposomal).

Step-down in fluconazole-resistant isolates should be discussed with ID/microbiology.

6. Ongoing management

6.1 Stopping antifungal therapy

The diagnosis of invasive fungal infection is unlikely in the absence of radiological infiltrates or positive culture results.

Antifungal therapy can be stopped in patients with fever resolution, recovering neutrophils and no subsequent evidence of invasive fungal infection.

6.2 Continuing anti-fungal therapy

Any on-going administration of antifungal therapy should be subject to regular review.

Patients with evidence supporting a diagnosis of invasive fungal infection (imaging, histological, culture) should continue treatment. Modification to treatment may be made on the basis of culture, identification and sensitivities.

The duration of treatment for invasive mould infections is difficult to precisely define. Treatment should continue until there is clear clinical improvement, accompanied by radiological response and improvement in immune status with an expectation that treatment will continue for a minimum of 6 weeks.

Longer treatment durations may be appropriate and should be considered on an individual basis.

6.3 Future prophylaxis

Patients who have undergone treatment for IFI are candidates for **secondary prophylaxis** if undergoing further therapy which results in prolonged neutropenia or immunosuppression.

7. Dosing recommendations

7.1 Posaconazole

Therapeutic drug monitoring (TDM) is recommended – See Appendix 1

Posaconazole treatment / prophylaxis	
Tablets	**Loading dose:** 300mg (3 x 100mg tablets) every 12 hours for 2 doses **Continuous dose**: 300mg (3 x 100mg tablets) OD **Caution - tablets and suspension are not dose equivalent.**
Intravenous **Caution in renal impairment**	**Loading dose:** 300mg every 12 hours for 2 doses **Continuous dose**: 300mg OD **Administer as IV infusion over 90 minutes via CVC. Dilute the vial contents in sodium chloride 0.9% using 150 – 283mL volume*. Peripheral administration is also possible, see Medusa.** *Withdraw 217 - 350 mL from a 500mL fluid bag before dilution of the vial.
Oral suspension	**Erratic / variable absorption – avoid where possible.** **Prophylactic dose**: No loading dose. 200mg (5 mL) **TDS.** **Treatment of IFI:** Not recommended – consider IV administration. **Administer during/immediately after a meal, or a nutritional supplement**

Where oral route unavailable, or impaired absorption (e.g. severe mucositis):
Temporary switch to the **intravenous formulation** is recommended for most inpatients to maintain optimal therapeutic drug levels.

Oral suspension has limited absorption in healthy patients and should be avoided if possible. Therapeutic drug monitoring (TDM) is strongly recommended when unavoidable.

Interactions

Strong CYP3A4 inhibitor	Metabolite in UDP glucuronidation	P-gp substrate	QTc prolongation

It is recommended a pharmacist is involved in multi-drug interaction checking. Interactions can be extensive. Otherwise please reference the summary medicinal product characteristics (SmPC) sheet at medicines.org.uk.

Online antifungal interaction checkers exist; **however**, their recommendations may not meet with local practice and the resource has not been clinically validated. Online resources may not always be fully up to date.

- **Posaconazole strongly inhibits CYP3A4**, altering the metabolism of many drugs processed via this liver enzyme. The onset of CYP3A4 inhibition is rapid (within 2-3 days). Concurrent drugs such as ciclosporin, tacrolimus and venetoclax all require dose adjustments or close monitoring - see relevant NSSG protocols for advice. Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and

atorvastatin is contra-indicated due to increased risk of rhabdomyolysis, patients can be switched to rosuvastatin which has a reduced risk (as CYP2C9 substrate only).

- **Posaconazole is metabolized via UDP glucuronidation and is a substrate for p-glycoprotein (P-gp),** drugs affecting these pathways may alter posaconazole plasma concentrations.
- **Posaconazole affects the QT-interval**. Whereas alone this may not be problematic, in patients taking multiple QT-affecting drugs or with clinical circumstances that affect QT prolongation (e.g. electrolyte derangement) ECG monitoring and drug rationalisation may be necessary.

Renal impairment: No dose adjustment is required.

- **Intravenous formulation (CrCl <50 ml/min)**: Accumulation of the drug vehicle (SBECD) can cause nephrotoxicity. Monitor for changes in renal function closely, consider switch to oral tablets if possible.

Hepatic impairment: Limited data – potential for higher plasma concentrations however upfront dose adjustment is not necessary. TDM would be helpful in this scenario.

Side-effects: Posaconazole is generally better tolerated by patients than voriconazole. Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Allergic reaction, rash, pruritis, pyrexia (fever), asthenia, fatigue, electrolyte imbalance (hypokalaemia, hypomagnesaemia), anorexia, decreased appetite, paraesthesia, dizziness, somnolence, headache, dysgeusia, hypertension, nausea and/or vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort, LFT derangements
- **Visual disturbances, including hallucinations:** These are more commonly associated with high posaconazole levels. TDM is recommended in this case to exclude toxicity (appendix 1). Uncommonly and rarely side-effects include blurred vision, photophobia, reduced visual acuity and neurological signs/symptoms including hallucinations. Retinal haemorrhage should be excluded.
- **Photosensitivity:** Posaconazole has been associated with phototoxicity reactions.
- **Severe dermatologic reaction:** Stevens-Johnson syndrome has been reported with use of triazole antifungals.

7.2 Voriconazole

Therapeutic drug monitoring (TDM) is recommended – See Appendix 1

Voriconazole treatment / prophylaxis		
Tablets / Oral suspension*	**Weight > 40 kg**	**Loading dose:** 400mg every 12 hours for 2 doses **Continuous dose**: 200mg every 12 hours **Administer on empty stomach, one hour before / two hours after a meal**
	Weight ≤ 40 kg	**Loading dose:** 200mg every 12 hours for 2 doses **Continuous dose**: 100mg every 12 hours **Administer on empty stomach, one hour before / two hours after a meal**
Intravenous **Caution in renal impairment**	**Loading dose:** 6 mg/kg every 12 hours for 2 doses **Continuous dose**: 4 mg/kg every 12 hours, if not tolerated reduce to 3mg/kg every 12 hours **Administer as IV infusion over 60 – 180 minutes via CVC/peripheral line (max rate 3 mg/kg/hour). Reconstitute as per manufacturer instructions and dilute in sodium chloride 0.9% to 0.5 – 5 in 1mL concentration. See Medusa.**	

***** Tablets are available in 200mg and 50mg strengths. 100mg is available but not all hospitals will stock this strength. Oral suspension is available as 200mg/5mL (70mL bottles).

Long term use

Long term exposure to voriconazole greater than 6 months requires careful assessment of the benefit-risk balance. Squamous cell carcinoma (SCC) of the skin and non-infectious periostitis (with elevated fluoride and ALP levels has) have been reported.

Interactions

Strong CYP3A4 inhibitor	Metabolism by CYP2C19*, CYP2C9, and CYP3A4	P-gp substrate	QTc prolongation

*Known CYP 2C19 polymorphism (ultra-rapid, rapid and slow metabolisers).

It is recommended a pharmacist is involved in multi-drug interaction checking. Interactions can be extensive. Otherwise please reference the summary medicinal product characteristics (SmPC) sheet at medicines.org.uk.

Online antifungal interaction checkers exist; **however**, their recommendations may not meet with local practice and the resource has not been clinically validated. Online resources may not always be fully up to date.

- **Voriconazole strongly inhibits CYP3A4**, altering the metabolism of many drugs processed via this liver enzyme. The onset of CYP3A4 inhibition is rapid (within 2-3 days). Use of drugs such as phenytoin, carbamazepine or rifampicin are contraindicated. Concurrent drugs such as ciclosporin, tacrolimus and venetoclax all require dose adjustments or close monitoring - see relevant NSSG protocols for advice. Other

substrates of CYP3A4 can be affected such as opiates (possibility of increased exposure and therefore toxicity).

- **Voriconazole is a substrate for CYP2C9 / 2C19, CYP3A4 and P-gp** - Voriconazole levels may be reduced in patients taking letermovir (a CYP2C19 inducer). Other substrates of CYP2C9 / C19, 3A4 and P-gp may be affected e.g. courmarins (warfarin) need close INR monitoring in combination.
- **Voriconazole affects the QT-interval.** Whereas alone this may not be problematic, in patients taking multiple QT-affecting drugs or with clinical circumstances that affect QT prolongation (e.g. electrolyte derangement) ECG monitoring and drug rationalisation may be necessary.

Renal impairment: No dose adjustment is required.

- **Intravenous formulation (CrCl <50 ml/min)**: Accumulation of the drug vehicle (SBECD) can cause nephrotoxicity. Monitor for changes in renal function closely, consider switch to oral tablets if possible.

Hepatic impairment: Use caution, see below.

- **Moderate liver impairment (Child Pugh B):** Consider reducing the maintenance dose of voriconazole by 50%. TDM is helpful in this scenario.
- **Severe chronic liver disease (Child Pugh C):** Consider alternative therapy.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, deranged liver function tests, respiratory distress and abdominal pain.
- **Visual disturbances, including hallucinations:** (up to 30% patients) These are transient and become less pronounced with repeated dosing. Drug withdrawal is not necessary. Retinal haemorrhage should be excluded.
- **Photosensitivity:** Voriconazole has been associated with phototoxicity reactions.
- **Squamous cell carcinoma (SCC) of the skin** has also been reported in patients receiving voriconazole, some of whom have reported prior phototoxic reactions. All patients should be educated about avoiding exposure to direct sunlight during voriconazole treatment and using measures such as protective clothing and sufficient sunscreen with high sun protection factor (SPF).
- **Severe dermatologic reaction:** Stevens-Johnson syndrome has been reported with use of triazole antifungals.

7.3 Caspofungin

Caspofungin treatment / prophylaxis
Weight > 80 kg: 70 mg IV on day 1, then **70 mg** IV OD **Weight < 80 kg**: 70 mg IV on day 1, then **50 mg** IV OD

Administration: IV Infusion over 1 hour

Interactions: Modification of dose is recommended in combination with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine) particularly where treatment duration is more than 1 – 2 weeks, see SPC for information (https://www.medicines.org.uk/). Avoidance of other hepatotoxic drugs is recommended where possible.

Renal impairment: No dose adjustment is required.

Hepatic impairment: Use caution, see below.

- **Moderate liver impairment (Child Pugh B):** Consider reducing the maintenance dose by 50%.
- **Severe chronic liver disease (Child Pugh C):** Consider alternative therapy.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Arthralgia; diarrhoea; dyspnoea; electrolyte imbalance; fever; headache; hyperhidrosis; nausea; skin reactions; vomiting

7.4 Micafungin

Micafungin treatment
Weight > 40 kg: **100 mg** IV OD – may increase to 200 mg daily if inadequate response. Higher doses of 150mg to 300mg daily can also be used. **Weight < 40 kg**: **2 mg/kg** IV OD – may increase to 4 mg/kg daily if inadequate response.
Micafungin prophylaxis
Weight > 40kg: 50 mg fixed dose IV OD **Weight ≤ 40kg: 1 mg/kg** IV OD

Administration: IV Infusion over 1 hour. Reconstitute as per manufacturer directions and dilute in sodium chloride 0.9% or glucose 5%.

Administering micafungin more rapidly than 1 hour can increase the risk of allergic reaction and is not recommended.

Interactions: Limited interaction potential.

Renal impairment: No dose adjustment is required.

Hepatic impairment: Use caution, see below.

- **Moderate liver impairment (Child Pugh B):** Consider reducing the maintenance dose by 50%.
- **Severe chronic liver disease (Child Pugh C):** Consider alternative therapy.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Nausea and/or vomiting; abdominal pain; LFT derangements; rash; phlebitis; headache

7.5 Amphotericin B liposomal (Tilomed/Gilead/AmBisome®)

Amphotericin B liposomal treatment
3 mg/kg once DAILY (max 5mg/kg*) *Doses more than 5mg/kg/day should be discussed with ID/microbiology and consultant haematologist, intravenous infusion over a 2-hour period is recommended
Amphotericin B liposomal prophylaxis (e.g. in ALL indications)
7 mg/kg once WEEKLY If concern about renal impairment dose modification is necessary (see advice below)

Administration: IV infusion over a 60-minute period and the patient closely observed. For doses of, or greater than 5mg/kg/day, intravenous infusion over a 2-hour period is recommended. Slower infusion rates reduce the risk of infusion-related reaction.

Administration of a 1mg test dose prior to infusion is no longer recommended.

Monitoring & electrolyte derangement: **Do not administer treatment in the presence of profound electrolyte derangement – consult medical team.**

- **Daily administration** - Monitor daily renal function with U&Es – including magnesium.
- **Prophylactic (once weekly) administration** – Monitor renal function with U&Es – including magnesium, twice weekly in the first week, reducing to once weekly testing thereafter. Monitoring should be **increased to twice a week** where deteriorating renal function, or frequent electrolyte derangement.
- Hypokalaemia, alongside hypomagnesaemia are common adverse effects and may require supplementation throughout treatment. Administration of higher doses (more than 3 mg/kg) greatly increases the risk of renal failure and electrolyte derangement.
- For persistent hypokalaemia, consider commencing amiloride PO 5 mg OD.

Renal impairment: To reduce the risk of nephrotoxicity, ensure that patient is well hydrated and consider stopping other nephrotoxic drugs. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation.

> **Dose reduction in prophylaxis**: 3 mg/kg three times a week OR 1mg/kg once daily may be considered with close monitoring of renal function.

Important safety: Always check the correct **Amphotericin B liposomal** (Tilomed/Gilead/AmBisome®) product has been prescribed and selected on the ward/day unit prior to administration.

Non-liposomal products are available which are **not interchangeable** and are associated with increased toxicity. Confusion between amphotericin products has caused serious harm and fatal overdose.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Hypo and hyperkalaemia, hyponatraemia, hypomagnesaemia, hypocalcaemia, hyperglycaemia, headache, tachycardia, hypotension, flushing, dyspnoea, nausea and/or vomiting, diarrhoea, abdominal pain, LFT derangements, back pain, chest pain, raised creatinine/urea, infusion-related reactions: fever, chills/rigors.

7.6 Fluconazole

Fluconazole treatment
Loading dose: 800mg IV/PO once only on day 1. **Continuous dose**: 400mg IV/PO once daily from day 2 onwards.
Fluconazole prophylaxis
50mg PO once daily

IV administration: Administer as an IV infusion, no further dilution necessary. Maximum infusion rate 10mL/min (20 mg/min).

Interactions:

Moderate CYP3A4 and CYP2C9 inhibitor	Strong inhibitor of CYP2C19*	P-gp substrate	QTc prolongation

*Known CYP2C19 polymorphism (ultra-rapid, rapid and slow metabolisers).

The risk of a clinically relevant interaction increases with higher doses (> 100mg daily). The enzyme inhibiting effect of fluconazole persists 4- 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

It is recommended a pharmacist is involved in multi-drug interaction checking. Otherwise please reference the summary medicinal product characteristics (SmPC) sheet at medicines.org.uk.

Online antifungal interaction checkers exist; **however**, their recommendations may not meet with local practice and the resource has not been clinically validated. Online resources may not always be fully up to date.

- **Fluconazole moderately inhibits CYP3A4**, altering the metabolism of many drugs processed via this liver enzyme. The onset of CYP3A4 inhibition is rapid (within 2-3 days). Use of drugs such as phenytoin, carbamazepine or rifampicin are contraindicated. Concurrent drugs such as ciclosporin, tacrolimus and venetoclax all require dose adjustments or close monitoring - see relevant NSSG protocols for advice. Other substrates of CYP3A4 can be affected such as opiates (possibility of increased exposure and therefore toxicity).
- **Fluconazole is a strong inhibitor of CYP2C19 / moderate inhibitor of 2C19**, altering the metabolism of many drugs processed via this liver enzymes. For example, clopidogrel efficacy may be significantly decreased or toxicity associated with anti-epileptic use could be increased.
- **Fluconazole is a substrate for P-gp,** drugs affecting or competing for these pathways may alter fluconazole plasma concentrations.
- **Fluconazole affects the QT-interval.** Whereas alone this may not be problematic, in patients taking multiple QT-affecting drugs or with clinical circumstances that affect QT prolongation (e.g. electrolyte derangement) ECG monitoring and drug rationalisation may be necessary.

Renal impairment: Fluconazole is cleared primarily by renal excretion as unchanged drug. No dose adjustment is required for loading dose; however, the maintenance dose may require adjustment as per recommendations* below:

Maintenance dosing, renal adjustments:

eGFR (mL /min /1.73m^2)	**Dose (IV and oral)**
More than 10	50-100% of normal dose
Less than 10	50% of normal dose
Haemodialysis (HD) / HDF (Haemodiafiltration) /High Flux	50% of normal dose daily, or 100% of normal dose 3 times a week. Dialysed; give after dialysis
Peritoneal dialysis (PD)	Dose as in eGFR less than 10ml/min/1.73m^2. Dialysed; give after dialysis.

***Recommendations as per OUH Eolas antimicrobial guide – fluconazole monograph, Dec 2024.

Hepatic impairment: Use with caution in patients with hepatic impairment and/or when used with other hepatotoxic drugs - monitor LFTs.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Headache, abdominal pain, diarrhoea, nausea and/or vomiting, LFT derangements (usually reversible on drug withdrawal) and rash.
- **Severe dermatologic reaction:** Drug reaction with eosinophilia and systemic symptoms (DRESS), also Stevens-Johnson syndrome and toxic epidermal necrolysis have been rarely associated with treatment.

7.7 Isavuconazole (ID/microbiology recommendation)

Isavuconazole should only be initiated following discussion, and recommendation from ID/Microbiology.

Isavuconazole treatment	
Oral capsule	**Loading dose:** 200mg (2 x 100mg capsule) PO TDS for 48 hours (6 doses) **Continuous dose**: 200mg (2 x 100mg capsule) PO OD **Capsules contain gellin gum which is a plant-based alternative to gelatin and suitable for those adverse to animal or pork products**
Intravenous	**Loading dose:** 200mg IV TDS for 48 hours (6 doses) **Continuous dose**: 200mg IV OD

IV administration: IV Infusion over 1 hour via CVC using a 0.2-micron filter. Reconstitute as per manufacturer directions and dilute in sodium chloride 0.9% or glucose 5%.

Therapeutic drug monitoring (TDM): Discuss with ID/microbiology, not routinely recommended but may be appropriate in some clinical circumstances.

Interactions:

Mild P-gp inhibitor	BCRP, OCT2 and UGT inhibitor	CYP3A4 and CYP3A5 substrate	QTc shortening

It is recommended a pharmacist is involved in multi-drug interaction checking. Otherwise please reference the summary medicinal product characteristics (SmPC) sheet at medicines.org.uk.

Online antifungal interaction checkers exist; **however**, their recommendations may not meet with local practice and the resource has not been clinically validated. Online resources may not always be fully up to date.

- **Isavuconazole mildly inhibits P-gp**, avoid use with drugs that have a narrow therapeutic index and are a P-gp substrate as serum levels can be increased (e.g. dabigatran, digoxin).
- **Isavuconazole is an inhibitor of BCRP, OCT2 and UGT**, concomitant use of drugs affected by these pathways may result in increased levels of the substrate drug. For example, metformin, mycophenolate and other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, methotrexate) – monitor for increased toxicities.
- **Isavuconazole is a substrate for CYP3A4 and CYP3A5,** drugs affecting or competing for these pathways may alter isavuconazole plasma concentrations. For example, CYP3A inducers such as carbamazepine, phenytoin and rifampicin will reduce isavuconazole efficacy and should be avoided. CYP3A inhibitors such as clarithromycin will increase isavuconazole drug concentrations and therefore close toxicity monitoring would be recommended. For most concomitant CYP3A substrates (e.g. sirolimus,

ciclosporin, tacrolimus), no dose adjustment is necessary but monitoring for increased toxicity of either drug is sensible.

- **Isavuconazole shortens the QT-interval,** unusually and in contrast to other triazole antifungals. Caution is needed if administered alongside other drugs that shorten the QT interval (e.g. rufinamide). Contraindicated in patients with familial short QT syndrome.

Renal impairment: No dose adjustment is necessary.

Hepatic impairment:

- **Moderate liver impairment (Child Pugh B):** No dose adjustment necessary
- **Severe chronic liver disease (Child Pugh C):** Consider alternative therapy.

Side-effects: Please refer to the SPC for full information https://www.medicines.org.uk/.

- **Most common:** Headache, nausea & vomiting, GI disturbances, hypokalaemia, anorexia, confusion/delirium/hallucinations, stomach/chest pain, shortness of breath, fatigue, rash, pruritus, deranged LFTs,
- **Severe dermatologic reaction:** Stevens-Johnson syndrome has been reported with use of triazole antifungals.

8. Audit

1. Annual audit of all patients with positive fungal cultures.
2. Antifungal usage drug reports available from the pharmacy department.

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10. Review

Name	Revision	Date	Vers	Review
Dr Jean O'Driscoll, Microbiology Consultant & Dr Monique Andersson, Infection Consultant, Thames Valley Microbiology Professional Development Group Claire Brandish, Lead Anti-infectives Pharmacist & Kate Russell-Hobbs, Infectious Diseases Pharmacist, Buckinghamshire Trust Dr Rob Danby, Consultant Haematologist. Oxford University Hospital NHS Foundation Trust (OUHFT) Nadjoua Maouche, Lead Haematology Pharmacist, OUHFT	New document. We would like to thank the Department of Clinical Haematology at University Hospitals Birmingham for sharing their guideline during the development stage of version 3.0.	Mar 2021	3.0	Mar 2023
Donna Constantine, Advanced Cancer Pharmacist, OUHFT	Remove isavuconazole Blueteq requirement following NHSE update.	Nov 2022	3.1	Mar 2023

Donna Constantine, Advanced Cancer Pharmacist, OUHFT Dr Monique Andersson, Infection Consultant, OUHFT	Removal of appendix 1 (EORTC definitions). Removal of interaction table, incorporation into drug monograph information. Content streamlining / reorganisation. Formatting. Recommendations for posaconazole dose adjustment. New TDM table. TDM recommended for posa/vori. Amphotericin B liposomal, removal of test dose.	Dec 2024	4.0	Jan 2027

11. Appendix 1 – Therapeutic drug monitoring (TDM) in adults

The table below summarises basic principles of therapeutic drug monitoring for antifungal agents. Certain cases may require different monitoring regime when advised by micro/ID team.

All reference ranges are taken from the Bristol Mycology Reference Lab. If a patient sample is sent to another laboratory, these ranges may not be applicable. Discuss with Microbiology/Infectious Diseases. Turnaround time for results is around 3 – 5 working days.

There is no evidence for TDM with echinocandins (caspofungin and micafungin) or Amphotericin B liposomal (Tilomed/Gilead/AmBisome®).

Antifungal agent	TDM recommended	Initial sample	Target range	Repeat levels
Fluconazole (PO / IV)	**Not routinely**	Target levels not yet established. May be indicated in rare cases.		
Isavuconazole (PO / IV)	**Not routinely**	First level after 5 - 7 days. **IV/PO**: Pre-dose level (1 hour before administration of next dose)	**Pre-dose level: 2 - 4 mg/L**	Weekly level until therapeutic, once in therapeutic range, check level 2-weekly for 8 weeks total, then three monthly if stable. Repeat level 2 weeks after any dose change, new drug interaction, suspected poor compliance or absorption issues.
Posaconazole (PO / IV)	**Prophylaxis: Not routinely*** **Treatment: Yes**	First level after 7 days. **IV/PO:** Pre-dose level (taken immediately before administration)	**Prophylaxis: 0.7 - 3.75mg/L** **Treatment: 1 - 3.75 mg/L** Aim to keep below 3.75 mg/L to reduce risk of toxicity.	Monthly for the first three months then three monthly Repeat level 1 to 2 weeks following dose change, new drug interaction, suspected poor compliance or absorption issues
Voriconazole (PO / IV)	**Prophylaxis: Not routinely*** **Treatment: Yes**	First level after 5 - 7 days. **IV/PO:** Pre-dose level (taken immediately before administration)	**Prophylaxis and therapy: 1.0 – 5.5 mg/L** **Bulky or disseminated infections: 2.0 – 5.5 mg/L** Aim to keep levels below 5.5 mg/L to reduce risk of toxicity.	Weekly level until therapeutic, once in therapeutic range, check level 2-weekly for 8 weeks total, then three monthly if stable. Recommend repeat TDM 5 days after IV to PO switch. Repeat level two weeks after any dose change, new drug interaction, suspected poor compliance or absorption issues

***TDM recommendation for prophylactic posaconazole or voriconazole in the following cases:**

- Obesity (BMI over 30kg/m^2)
- Liquid posaconazole
- GI absorption concerns, especially if prolonged diarrhoea
- Initiation or stopping of interacting drugs that affect azole metabolism (See BNF or Summary of Product Characteristics for information)
- Toxicity concerns
- Suspected poor compliance
- Dose adjustment

Posaconazole dose adjustments

- **Level < 0.7 or 1 mg/L (low):**
  - **Tablet / IV formulation:** Increase dose by 100mg increment, split dose twice daily (e.g. 400mg daily would be given as 200mg BD).
  - **Liquid formulation:** Increase dose by 200mg increment. Ensure the patient is taking the drug alongside a meal or liquid feed, discontinue/reduce acid suppressive agents – **it is strongly recommended to switch to IV or tablet formulation if possible**.
- **Level > 5.5 mg/L (high):** Consider withholding dosing and recommencement at lower dose

Voriconazole dose adjustments

- **Level < 1 or 2 mg/L (indication dependent, low):** Increase dose by 1mg/kg 12 hourly rounded to tablet size (50mg or 100mg). Make sure the patient is taking the drug on an empty stomach.
- **Level > 5.5 mg/L (high):** Consider withholding dosing and recommence at lower dose