Investigation and Management of Invasive Fungal Infection (IFI) in Haematology Patients

Cardiff and Vale University Health Board

Document Control Sheet

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High Risk Patients:

- AML/ MDS undergoing remission-induction therapy
- Aplastic Anaemia (requires MDT discussion)
- Lymphoblastic leukaemia including CLL (during treatment with Alemtuzumab and for 6 months after)
- Lymphoma patients if heavily pre-treated (Brentuximab and Ibrutinib), or Burkitts lymphoma
- Autologous and Allogeneic SCT

Prophylaxis:

Fluconazole prophylaxis: 400mg od

- All high risk patients as defined above except patient with Acute Lymphoblastic Leukaemia (ALL) undergoing Phase 1 induction
- Stem Cell Transplant (SCT) recipients without GvHD*

AmBisome® (liposomal amphotericin) prophylaxis: 1mg/kg three times a week (or 7mg/kg once a week)

- ALL patients undergoing phase I induction
- Any high risk patient not suitable for other antifungals

Mould active agent (posaconazole):

- SCT with active GVHD (antifungal therapy continues until patient is weaned off immunosuppressive therapy)

** Patients who are unable to tolerate Fluconazole, should be considered for an alternative agent (eg. Voriconazole, posaconazole, caspofungin or liposomal amphotericin)*

Screening:

- Weekly fungal PCR / ELISA* for high risk patients on Fluconazole prophylaxis
- Patients on mould-active prophylaxis (voriconazole, liposomal amphotericin or posaconazole) do **NOT** require aspergillosis PCR / ELISA screening
- All other patients should only have fungal PCR / ELISA if there is a clinical suspicion of IFI
- Patients with a repeat positive PCR and/or ELISA may be considered for additional testing with β-D-Glucan to aid diagnostic evaluation. While β-D-Glucan is not recommended as a front-line screening test it may be beneficial as a confirmatory follow-up test as part of the enhanced diagnostic work-up, particularly when PCR and ELISA provide conflicting results.

Screening should be discontinued:

- In general haematology patients when chemotherapy treatment is complete and blood counts have recovered
- When BMT patients have stopped all immunosuppression and have no evidence of active GvHD

*(*see appendix 3.2 for interpretation)*

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Suspicious clinical features *(see appendix 4)*

Investigation of suspected IFI

- Aspergillus PCR/ ELISA (if not undertaken) preferably on a sample from the focus of infection (e.g. BAL)
- Blood cultures
- HRCT as clinically indicated
- PCP PCR on BAL or respiratory swab
- β-D-Glucan should be performed if Pneumocystis Pneumonia (PCP) or Invasive Candida (IC) is suspected, or to assist in interpretation of conflicting Aspergillus PCR / ELISA

If localising signs:

- CT sinuses if suspected sinus infection and ENT review
- Serum serology for Aspergillus galactomannan antigen and beta D-glucan antigen
- Lumbar puncture
- CT chest / MRI head
- Sputum / BAL **if positive, CT scan should be gained to confirm presence of fungal infection**

Define IFI (proven, probable, possible) using EORTC/MSG criteria *(see appendix 6)*

Treatment indicated in cases of proven and probable IFI

- Initiate with approval of consultant haematologist
- If empirical treatment is considered, liaise with microbiology *(see appendix 6.1)*

First line:

- Voriconazole: Body weight >40kg: initially 400mg every 12 hours for 2 doses then 200mg every 12 hours (half dose in patients <40kg)
- If significant liver impairment or clinical suspicion of mucor: AmBisome® 3mg/kg OD IV

STOP screening fungal PCR/ ELISA whilst on active treatment

Stopping treatment

If CT normal or non-specific:

- Send ELISA after 12-14 days. Stop treatment if negative and resume screening

If CT suggestive of IFD:

- Send ELISA after 14 days and weekly thereafter. Stop after 2 consecutive negatives. Discuss at MDT regarding need for ongoing secondary prophylaxis or resume screening

Mould active secondary prophylaxis

Indicated for:

- Patients with previous proven/probable disease after discussion at MDT

Treatment should be discontinued :

- In general haematology patients when chemotherapy treatment is complete and blood counts have recovered and
- When BMT patients have stopped all immunosuppression and have no evidence of GvHD

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Investigation and Management of Invasive Fungal Infections in Haematology Patients Protocol

1. Introduction

Invasive fungal infections (IFI) present a unique group of opportunistic organisms in immunocompromised patients accounting for significant mortality and morbidity. There is a wide variation in the risk associated with patient groups and the treatment they receive. Candidaemia associated mortality is approximately 24% (Viscoli et al 1999) and invasive proven aspergillosis mortality at 3 months for matched unrelated donor allografts 84.6% (Morgan et al 2005). In addition, there is a huge financial burden in both the investigation and treatment of such patients hence a rational and targeted approach is imperative. Therefore, the diagnosis of IFI should be confirmed wherever possible (BCSH 2008).

2. Risk factors

High Risk Patients (Herbrecht et al 2012)			
Underlying condition	Incidence of invasive aspergillosis (%)	Identified specific patient and treatment-related risk factors	
Allogeneic haematopoietic stem cells	2.7–23	Delayed neutrophil engraftment Secondary neutropenia Lymphocytopenia, monocytopenia Cord blood T cell-depleted or CD34-selected stem cell products Unrelated or mismatched donor graft Acute or chronic graft versus host disease, corticosteroids, CMV disease	Respiratory virus infections Renal failure Reduced-intensity conditioning regimen Purine analogues or monoclonal antibodies History of invasive aspergillosis Iron overload Advanced age Donor toll-like receptor polymorphism
Acute myeloid leukemia chemotherapy	5–24	Neutropenia Monocytopenia Purine analogues Monoclonal antibodies	Advanced age Iron overload Influenza H1N1 virus Lack of response to induction
Acute lymphoblastic leukaemia	3.8	Lymphopenia Corticosteroids Advanced age	

Intermediate Risk/ Low risk (Herbrecht et al 2012)			
Underlying condition	Incidence of invasive aspergillosis (%)	Identified specific patient and treatment-related risk factors	
Autologous haematopoietic stem cells	0.5–6	Neutropenia Purine analogues or monoclonal antibodies	Lymphoproliferative malignancy as indication for transplantation
Multiple myeloma	2–3	Neutropenia Corticosteroids	Advanced age
Non-Hodgkin lymphoma	0.8	Corticosteroid Purine analogues or monoclonal antibodies	Advanced age
Hodgkin lymphoma	0.4	None identified	

3. Prophylaxis

In the context of allogeneic transplant patients, there is no difference in overall survival with fluconazole and voriconazole in the prevention of IFI (Wingard et al 2010).

The use of itraconazole is not well tolerated and it is difficult to control levels. In a previous audit of its use in the local haematology population there was break-through IFI in 17.5% of cases, even when levels were therapeutic in patients receiving this prophylaxis (Barnes et al 2013).

Patients at high risk of IFI should receive fluconazole 400mg OD PO. These include:

1. AML/ MDS patients undergoing remission-induction therapy
2. CLL (during treatment with Alemtuzumab and for 6 months after)
3. Lymphoma patients if heavily pre-treated, Burkitts or lymphoblastic leukaemia
4. Allogeneic stem cell transplant patients from conditioning and receiving GVHD prophylaxis or treatment

Acute Lymphoblastic Leukaemia (ALL) patients undergoing induction chemotherapy should receive weekly AmBisome® (1mg/kg three times a week) prophylaxis in light of the interaction of azoles and vincristine. Thereafter, fluconazole 400mg OD PO should be used.

In SCT patients, switch to IV fluconazole 400 mg daily in the presence of significant mucositis or if patient is unable to tolerate PO.

Patients with severe aplastic anaemia should be discussed at MDT and may be treated as high risk and screened or may receive mould active prophylaxis.

Other patients should NOT receive prophylaxis unless there is a history of IFI although general risk factors should be taken into account in making this decision.

3.1 Screening for invasive aspergillosis

The following groups of patients should have weekly aspergillus PCR/ ELISA screening:

1. AML/ MDS patients undergoing remission-induction therapy
2. Allogeneic transplant patients from conditioning and receiving GVHD prophylaxis or treatment

If a patient is positive by either or both tests, a follow-up specimen should be taken ASAP.

In patients with a repeat positive PCR or ELISA, β-D-Glucan antigen testing should be performed on the repeat sample as part of the diagnostic work-up into potential fungal disease and may be particularly useful if positive when PCR and ELISA results are conflicting. β-D-Glucan testing is not recommended as a front-line screening test.

Patients receiving mould active prophylaxis (voriconazole, AmBisome® or posaconazole) or treatment should not undergo screening. Patients with suspected breakthrough infection should be investigated (see section 4 below).

All other patients should only have fungal PCR/ ELISA testing if there is a neutropenic fever or clinical suspicion of IFI (see section 4 below).

All biomarker tests requested from the haematology department in UHW will be reviewed on a weekly basis with input from microbiology and haematology teams (general and transplant). This occurs fortnightly on a Tuesday morning in the haematology day centre.

For tests sent from other hospitals, discussion with the local microbiology department or the Mycology Regional Reference Unit (029 2074 4515) to aid interpretation and decision making is advised.

It is the responsibility of the person requesting the test to ensure that it is appropriate.

3.2 Interpretation of screening

PCR and ELISA negative:	If there is suspicion of fungal infection other than aspergillosis, consider β-D-glucan testing. Invasive aspergillosis extremely unlikely pre-emptive anti-fungal treatment **not** indicated. If empirical therapy has been started then this should be stopped in light of these results, unless other clinical evidence is available (e.g. HRCT).
Single positive ELISA Index >0.7:	Request a repeat specimen.
Single positive PCR:	Request a repeat specimen.
Confirmatory β-D-Glucan positive:	Consider further investigations. Discuss at MDT.
Both ELISA and PCR positive:	Request a repeat specimen. Consider further investigations. Discuss at MDT.

Single positive PCR, or a single positive GM index of ≥0.7 or two consecutive GM indices of 0.5-0.6 may indicate false positivity.
It is not an indication for commencement of anti-fungal therapy in patients without clinical signs but should prompt repeat specimens and may lead to further investigation.

Repeat PCR or ELISA positive:	Consider further investigations, (including β-D-glucan testing/CT/BAL) and anti-fungal treatment. Discuss at MDT.

If patient has multiple PCR and ELISA positive results β-D-glucan testing is not warranted.

4. Investigation of suspected IFI

There should be a high index of suspicion of IFI when patients' pyrexia fails to respond to broad-spectrum antibacterials in the context of prolonged neutropenia and/or immunosuppression.

Clinical features suggestive of IFI (BSCH 2008)

- Any new fever during prolonged, severe neutropenia or immunosuppression
- Fever resistant to broad spectrum antibacterial therapy while neutropenic
- Symptoms and signs of new, resistant or progressive lower respiratory tract infection, e.g. pleuritic pain, pleural rub
- Prolonged, severe lymphopenia in chronic graft versus host disease (GVHD) and immunosuppression
- Symptoms and signs of progressive upper respiratory tract infection
- Periorbital swelling
- Maxillary swelling and tenderness
- Palatal necrosis or perforation
- Focal neurological or meningeal irritation symptoms and signs with fever
- Unexplained mental changes with fever
- Papular or nodular skin lesions
- Intra-ocular signs of systemic fungal infection

5. Diagnosis

Clinical features suggestive of invasive fungal infection (IFI) warrant early and thorough investigation to yield microbiological data and early use of systemic antifungal therapy. The 2nd revision of the EORTC/MSG consensus group guidelines (to be published in 2018) should be used in defining IFI.

Proven	
Identification of fungal elements via • Microscopic examination of sterile material, or • Culture of sterile material or blood, or • Serological analysis of CSF i.e. Cryptococcal antigen	
Probable (all 3 factors present)	
Host factor	1. Neutropenia 2. Allogeneic stem cell transplant recipient 3. Prolonged corticosteroid use 4. Treatment with T cell immunosuppressants (e.g. ciclosporin, alemtuzumab) 5. Low CD4 count 6. Acute GVHD grade III/IV, or GvHD of GIT, liver and/or lungs that is refractory to treatment with steroids
Clinical criteria	1. Lower respiratory tract infection (positive HRCT findings) ▪ Dense, well circumscribed lesion(s) with or without halo sign ▪ Air-crescent sign ▪ Cavity ▪ Wedge-shaped and segmental or lobar consolidation ▪ Reverse halo sign (Possible sign of Mucorales infection, occasionally associated with IA) 2. Sinonasal infection (positive imaging, acute localised pain, extension from paranasal sinus across bony barriers), 3. CNS infection (focal lesions/ meningeal enhancement on imaging) 4. Disseminated candidiasis (Bull's eye lesions in liver/ spleen, progressive retinal exudates on ophthalmic examination)
Mycological criteria	1. Positive fungal PCR 2. Positive galactomannan antigen (plasma, serum, BAL, CSF) 3. Positive β-D-glucan 4. Evidence of mould from respiratory specimen (Sputum, BAL, NBL or sinus aspirate: ▪ Microscopic evidence of fungal elements in keeping with mould ▪ Recovery of mould by culture
Possible (only host factors and clinical criterion met)	

In patients with suspected IFI, the following should be requested:

- Aspergillus PCR/ ELISA
- Blood cultures
- Urine cultures
- HRCT
- β-D-glucan
- Respiratory throat swap for PCP PCR

If localising signs:

- CT sinuses if suspected sinus infection and ENT review
- Lumbar puncture
- CT/ MRI head
- Sputum/ BAL

When performing confirmatory biomarker testing for IFI the testing of specimens from the focus of infection will improve performance, particularly in patients where screening has not been performed. In these patients performing PCR/ELISA testing of blood on a one-off occasion should not be used to exclude IFI.

Diagnosis of PCP

If the β-D-glucan test is positive, consider investigating for a diagnosis of PCP.

For the diagnosis of PCP the following algorithm should be followed with the exception of immuno-fluorescent microscopy that is not required (Alanio et al 2016):

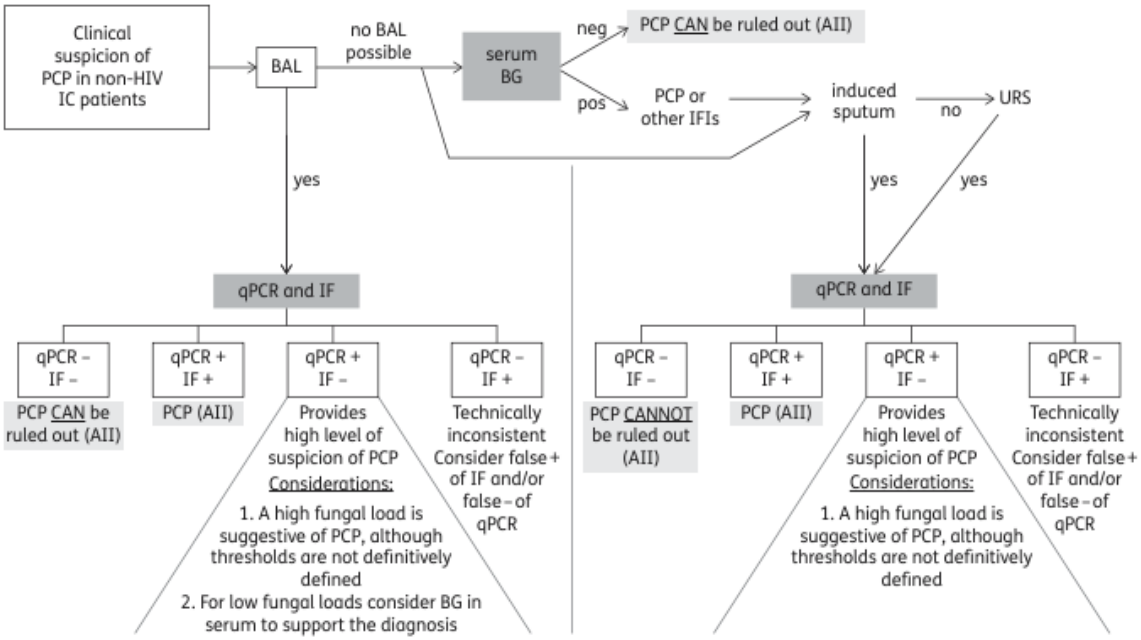

Figure 1. Flow chart for the diagnosis of *Pneumocystis* pneumonia in non-HIV immunocompromised (IC) patients. Biological tests are highlighted in dark grey and recommendations in light grey. BG, β-D-glucan; A-II, level of recommendation; IFI, invasive fungal infection.

6. Treatment issues in IFI

Treatment should be initiated after discussion with the microbiology team and haematology consultant.
Cases of 'proven' and 'probable' IFD warrant treatment.
Pre-emptive therapy based on screening results or targeted treatment based on positive results during fever or on the basis of clinical signs may be initiated after discussion of risk

6.1 Empirical treatment

Empirical treatment is generally not recommended (BCSH 2008). However, in cases where no investigations (biomarkers/CT/BAL etc.) have been performed, treatment may be warranted after 96 hours of refractory fever while investigations (HRCT/Bronchoscopy and biomarkers) are pending.

For patients with clinical symptoms and a high level of clinical concern, send enhanced diagnostics and consider empirical treatment after biomarker testing has been performed whilst waiting for results.

6.2 First line therapy

In the absence of specific fungal elements:

First line: Voriconazole: Body weight >40kg: initially 400mg every 12 hours for 2 doses then 200mg every 12 hours (half dose in patients <40kg). If cannot tolerate PO then 6mg/kg IV for 2 doses then 4mg/kg thereafter.

Where there is significant liver dysfunction (i.e. bilirubin > 50 μmol/L or Child-Pugh class C) or clinical suspicion of mucor use AmBisome® 3mg/kg OD IV. Give test dose if no previous exposure and monitor for signs of anaphylaxis.

Liaise with microbiology if proven IFD for definitive treatment.

6.3. Stopping treatment

Where patients have completed a defined treatment course for IFI, the decision to recommence non-active mould prophylaxis (e.g. fluconazole prophylaxis) should be made after consideration of individual risk factors.

The decision to stop treatment in patients should be taken in the setting of an MDT approach with the microbiology, haematology and transplant teams. Radiological findings should determine the next course of action.

If CT normal or non-specific of IFD
Send ELISA after 12-14 days therapy. Stop treatment if negative and resume screening. Total therapy would amount to 12 days.

If CT suggestive of IFD
Send ELISA after 14 days therapy and weekly thereafter. Stop after 2 consecutive negatives. Hence a minimum of 21 days of treatment. Discuss at MDT regarding need for ongoing secondary prophylaxis or resume screening.

The duration of empirical antifungal therapy depends on the results of investigations and final likelihood of fungal infection, as well as neutrophil recovery. Treatment should be reviewed after 5-7 days of therapy.

6.4. Secondary prophylaxis

Secondary prophylaxis should be considered for patients with previous proven/probable IFD and who require ongoing intensive chemotherapy and / or are proceeding to or recently received an allogeneic stem cell transplant

Screening of fungal PCR/ ELISA is not indicated for these patients.

Voriconazole may be used as secondary prophylaxis. An ECG should be undertaken on initiation, as voriconazole can prolong the QTc interval.

The decision to start secondary mould active prophylaxis together with the choice of agent should be taken in the setting of an MDT approach with microbiology, haematology and transplant teams present. Drugs such as Isavuconazole may be considered.

SCT patients with prior proven or probable invasive fungal infection should receive secondary prophylaxis with a mould active agent with granulocyte infusions during neutropenia. Antifungal drug choice depends on patient's characteristics and type of previous mould fungal infection.

Treatment should be discontinued:
- In general haematology patients when chemotherapy treatment is complete and blood counts have recovered and
- When BMT patients have stopped all immunosuppression and have no evidence of active GvHD

If secondary prophylaxis is stopped then biomarker screening should be resumed if patient is on continuing therapy or immunosuppression.

6.5 Primary prophylaxis in SCT recipients with GvHD

SCT recipients with active GvHD should be considered for primary prophylaxis with posoconazole.

Antifungal prophylaxis is continued until the patient is off all immunosuppression with no active GvHD.

6.6 Proven fungal infections

Patients diagnosed with proven fungal infection should have their antifungal therapy directed against the specific type of fungal spp. infection and according to sensitivity results if available. For invasive aspergillosis voriconazole remains the drug of choice. Alternatives include liposomal amphotericin, caspofungin or posaconazole. Treatment of candidiasis depends on clinical setting/organ involved, type of spp., sensitivity results and presence or absence of neutropenia.

7.0 Additional Drug Information

Patients on azole type of antifungal prophylaxis should have any potential significant drug interactions reviewed regularly with the clinical pharmacist (see table below for Voriconazole interactions). In this context ciclosporin / tacrolimus levels should be monitored closely.

Azoles should be avoided *during* induction chemotherapy conditioning which contain vincristine to avoid drug interactions. Azole prophylaxis can commence 5 days post chemotherapy. If the patient has commenced azoles, suspend 48 hours before and 5 days after Vincristine dose.

Amphotericin preparations are potentially nephrotoxic. SCT patients who receive amphotericin (including liposomal preparations) should have their renal function closely monitored. Patients with rising creatinine level should be switched to an appropriate alternative antifungal agent, to avoid the risk of affecting ciclosporin GVHD prophylaxis.

VORICONAZOLE

Additional precautions
The patient must be counselled on initiation of treatment. This should include information regarding:

- The risks of phototoxicity, squamous cell carcinoma of the skin and the need for regular dermatological evaluation (if phototoxicity occurs)
- The need to avoid sunlight and sun exposure, including use of protective clothing and sufficient sunscreen with high sun protective factor SPF 30+ during treatment with voriconazole
- The signs and symptoms of phototoxicity that warrant contacting the doctor immediately
- The risk of liver toxicity with voriconazole and the need for periodic monitoring of liver function

The following measures should be considered when commencing voriconazole:

- Record the start date of voriconazole on a patient alert card
- At least weekly LFTs during 1st month required
- The maximum duration of treatment should be 6 months as per spc
- Voriconazole should be discontinued if photosensitivity or keratitis develops on treatment
- Consider monthly therapeutic drug monitoring of voriconazole levels (discuss with microbiology)
- Refer to dermatology for 3-6 monthly surveillance if patient experiences photosensitivity

Voriconazole levels

Levels should be considered in patients who are suspected of being sub-therapeutic due to treatment failure/refractory infection or suspected of having toxicity.

TDM Sampling:
Both IV and Oral Voriconazole – Pre-dose after 3-5 days therapy

Expected ranges 1.0-5.5mg/L

If drug levels fall out of therapeutic range discuss with microbiology

Exclusions of use include:

1. Patent undergoing photopheresis
2. CLL patients
3. Patients already on posaconazole for secondary prophylaxis
4. Patients with severe skin GvHD requiring phototherapy

Caution should be given to prescribing in patients > 65 years of age due to the increased risk of skin cancer with age

Interactions

Voriconazole is metabolized by, and inhibits the activity of the cytochrome P450 enzymes. Inhibitors or inducers of these enzymes my affect voriconazole plasma concentrations, and there is a potential for voriconazole to increase the plasma concentrations of substances metabolized by these enzymes.

Always check for interactions in the spc

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