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Royal Cornwall Hospitals NHS Trust

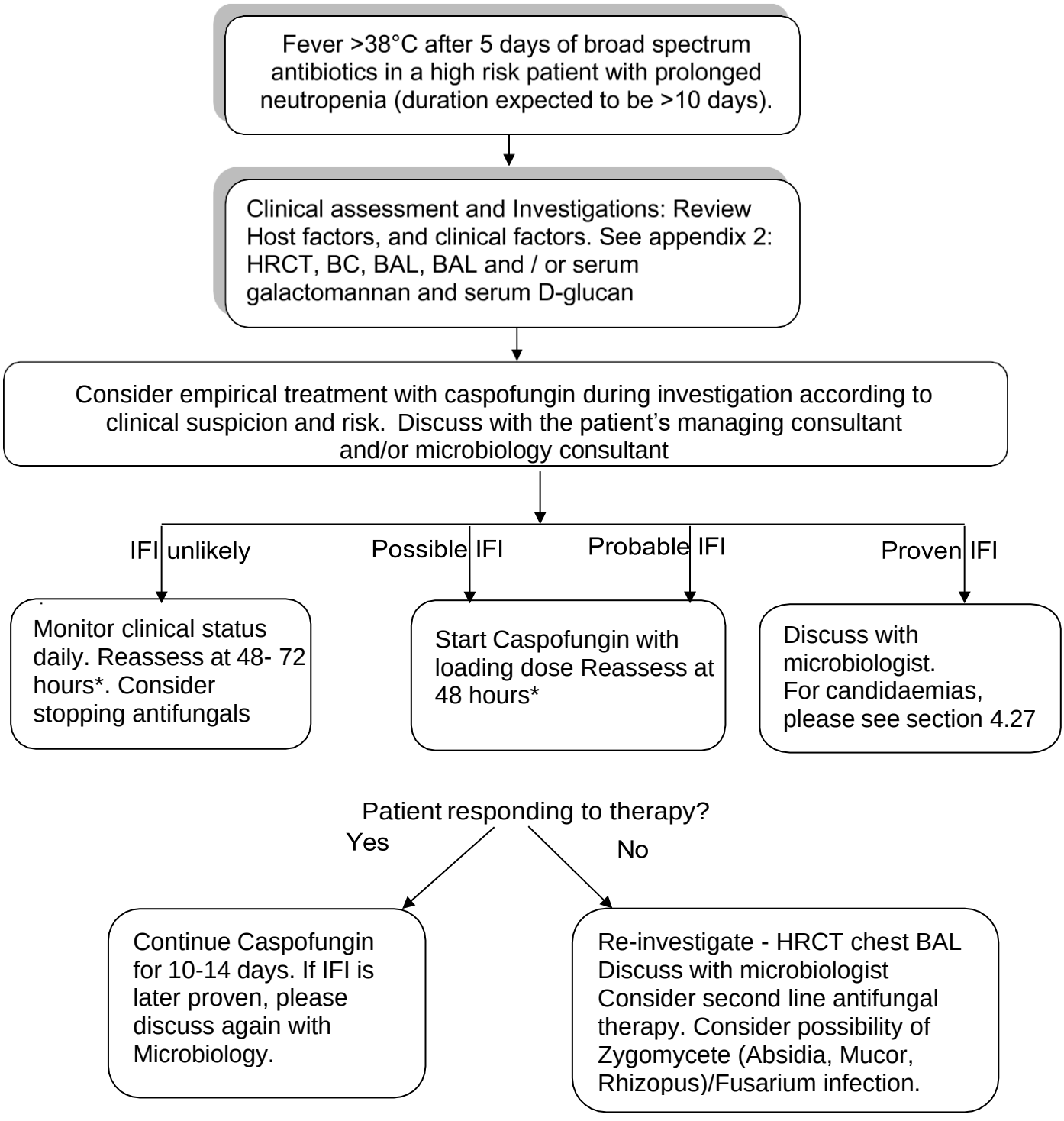
Invasive Fungal Infection in Adult Haematology and Oncology Patients Clinical Guideline

V3.0

June 2023

Summary

Flow chart for the Management of patients with suspected IFI (Invasive Fungal Infection)



*If fungi have been isolated, susceptibilities should be obtained where possible in order to guide antifungal therapy.

1. Aim/Purpose of this Guideline

1.1. This guideline applies to all clinical staff involved in the care of adult patients at the Royal Cornwall Hospital Trust.

1.2. The purpose of this guidance is:

- To ensure early consideration and appropriate management of fungal infection in refractory febrile neutropenia.
- To promote avoidance of empirical treatment of low-risk patients.

1.3. This version supersedes any previous versions of this document.

Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation

The Trust has a duty under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

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Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1. Protecting patients from exposure

Hospitalised allogenic HSCT recipients should be placed in a protected environment to reduce mold exposure and where possible also other highly immunocompromised patients at increased risk for invasive aspergillosis. Where a protected environment is not available then admit to a side room not connected to a construction site and away from cut flowers.

2.2. General Information

2.2.1. Invasive fungal infection (IFI) has been redefined as invasive fungal disease (IFD) by the EORTC/MSG Consensus Group (2008). For the purpose of this guidance the two terms are synonymous for the same disease and will be referred to as IFI to avoid confusion with the current guidance from the British Committee for Standards in Haematology (2008). IFI is defined into three different categories; possible, probable and proven based on a combination of host factors, clinical criteria and mycological criteria (see Appendix 4).

2.2.2. A neutrophil count below 0.5 x109 /L for more than ten days is considered to confer significant risk of fungal infection. Milder neutropenia. However, in combination with other immunosuppressant factors, particularly the prolonged use of steroids, may also represent significant risk. It is also worthy of note that some patients with myelodysplasia may have normal neutrophil numbers but functional deficiency ("functional neutropenia").

2.2.3. There must be a high level of clinical suspicion to allow early consideration of IFI in high-risk patients. In those neutropenic patients with fever refractory to second line antibacterial agents IFI should always be considered. Risk factors for invasive fungal infection (IFI):

- Neutropenia (Neutrophil <0.5x109/L; risk increases with duration).
- Steroids.
- GVHD: (Graft Versus Host Disease) or post allograft patient who has not yet recovered lymphocyte count.
- Bacterial infection.
- Mucosal colonisation of candida.
- Indwelling central IV line (increased risk of Candida infection).
- Antibacterial's (increased risk of Candida infection).
- CMV infection (increased risk of Aspergillus infection).
- Building works (increased risk of Aspergillus infection).

2.2.4. Persistent fever has poor specificity for diagnosis of IFI and therefore further investigations are necessary to rule in or rule out IFI in order to prevent unnecessary exposure to antifungal agents. For persistently febrile neutropenic patients who may be receiving anti- aspergillus prophylaxis, the cause of fever is less likely to be of a fungal origin. Careful evaluation for non-fungal causes as well as the possibility of breakthrough IFI resistant to the prophylaxis regimen should be considered.

2.2.5. Neither clinical examination nor any single available test for IFI (radiological or microbiological) is sufficiently sensitive and specific. A positive culture from a non-sterile site does not necessarily imply infection; this may be due to colonisation or environmental contamination. It is therefore important that these results are interpreted in the context of the patient's individual risk factors and clinical features by an appropriately experienced clinician.

2.2.6. BAL remains the cornerstone for microbiological identification in diffuse interstitial or alveolar lung infiltrates in immunocompromised patients. BAL galactomannan is an accurate biomarker for the diagnosis of invasive aspergillus in haematological malignancy and HSCT. BAL increases the likelihood of a diagnosis of a mold and therefore a BAL sample should be sent for routine culture and cytology as well as galactomannan.

2.2.7. Serum galactomannan is not recommended for blood screening in patients receiving mold-active antifungal therapy or prophylaxis but can be used in BAL from these patients.

2.2.8. Galactomannan is not recommended for solid organ transplant or chronic granulomatous disease.

2.2.9. Serum 1-3 Beta-D–glucan is recommended for diagnosing invasive aspergillus in high-risk patients (haematological malignancy and HSCT). But is not specific for aspergillus. Biomarker-driven strategies (B D-glucan) are associated with less unnecessary antifungal use without a compromise in overall survival because of its high negative predictive valve regardless of whether the patient is receiving prophylaxis antifungal therapy.

2.2.10. The treatments for IFI are both toxic and prolonged and therefore accurate risk assessment is necessary. The diagnosis may also affect other management decisions such as the decision to transplant and long-term prophylaxis. It is therefore important to pursue tissue culture and histology, when possible, to guide management.

2.2.11. CT findings such as halo sign and cavitation are extremely useful in diagnosing IFI. Pulmonary nodules are less specific. In the event of a normal CT scan, the table below shows how this does not exclude IFI, particularly in the 7-15 days after onset of illness/fever; it is therefore imperative to consider repeating the scan within 7 days.

Appearance of radiological signs in IFI	Early (<10 days)	Intermediate (7-15 days)	Late (>10days)
Halo sign	73-100%	0%	23%
Cavitation	0	25%	23-100%

2.2.12. According to clinical symptoms – paranasal, CNS as well as abdominal CT may also be required.

2.2.13. Samples should be sent for both microscopy and culture. Demonstrating tissue invasion by hyphae through microscopic examination of biopsy provides a diagnosis of proven invasive fungal infection. Sensitivity of microscopy for invasive aspergillus is 50% at best.

2.3. **Prophylaxis**

2.3.1. The choice of antifungal used in prophylaxis varies depending on the chemotherapy regimen used (azoles interact with vinca alkaloids) or individual patient factors e,g, previous drug reactions or previous colonisation/infection. Prophylaxis is commenced and discontinued according to the period of risk. In Acute Leukaemia this is from initiation of intensive chemotherapy until resolution of the ensuing neutropenia. In cases of prior proven fungal infection, a decision may be made to continue secondary prophylaxis between cycles. The following haematology patients should be routinely taking anti-fungal prophylaxis unless specified.

2.3.2. **Acute Myeloid Leukaemia undergoing intensive chemotherapy:**

First line: Posaconazole tablets 300mg bd on day 1 then 300mg once daily. NB dose of posaconazole liquid 200mg tds (tablets used preferentially).

Second line: Caspofungin daily or Liposomal amphotericin (Ambisome®) intravenous 3mg/kg three days per week (rounded to the nearest 50mg vial).

2.3.3. **Acute Lymphoblastic Leukaemia following UKALL protocol chemotherapy:**

If the patient is on vincristine, liposomal amphotericin (Ambisome®) intravenous 3mg/kg given three times a week on Mondays, Wednesdays and Fridays. Azole may be used safely after phase 1 of induction and this can be posaconazole 300mg od.

2.3.4. **Lymphoma:**

Patients undergoing outpatient and non-intensive chemotherapy regimens do not require fungal prophylaxis as these involve only a short period of neutropenia and therefore low risk for fungal infection. Refer to specific chemotherapy protocol for inpatient regimens e.g. CODOXM/IVAC as these have a much higher risk of IFI.

2.3.5. **Myeloma**

The risk of IFD in multiple myeloma including autologous HSCT is <1%. Based on this low risk, primary antifungal prophylaxis is not recommended.

2.3.6. **Bone Marrow Transplant patients:**

Autologous transplant: do not require fungal prophylaxis unless previous history of fungal infection.

Allogeneic transplant: regarded as a high-risk population and should be considered for antifungal prophylaxis - refer to patient specific advice from transplant centre.

2.4. Diagnosing IFI

2.4.1. Investigation of suspected invasive fungal infection

- Clinical assessment. See appendix 3.
- FBC, U and E, LFT, Calcium, C-reactive protein, Group and Save.
- Blood cultures - peripheral and central (each lumen) – three sets of 20 ml to yield a total of 60mls is necessary to optimise sensitivity of blood culture.
- CXR.
- Urgent HRCT Thorax regardless of chest radiograph results + contrast if nodule or mass is close to a large vessel. Consider follow up CT to assess response to treatment after a minimum of 2 weeks treatment. More frequent monitoring may be required if the nodule is close to a large vessel and earlier if patient clinically deteriorates.
- BAL (+ trans bronchial biopsy for peripheral nodular lesions) for routine culture and cytology as well as non-culture-based methods (e.g. galactomannan).
- The following tests should be considered where appropriate.
  - CT sinuses.
  - Biopsy of skin or mucosa.
- BAL Galactomannan, and serum β-D-glucan (and serum galactomannan if not had mold active prophylaxis).
- Consider alternative diagnosis.
- Serology for atypical respiratory organisms.
  - Urine for culture and legionella antigen.
  - Other investigations as part of a septic screen.
- DISCUSS WITH MICROBIOLOGIST.
- NB: If the initial HRCT is inconclusive, consider repeat scan within 7 days (for explanation see ‘Timing of CT changes’ on page 2).
- Reducing doses of, or eliminating altogether, immunosuppressive agents, when feasible recommended.

2.5. Interpretation of diagnostics results

2.5.1. Blood cultures - a negative BC does not rule out IFI.

2.5.2. Serum B-D-glucan is a fungal cell wall carbohydrate moiety present in Aspergillus spp, Candida spp and P. Jirovecii (but not Cryptococcus spp or Mucorales). B D-Glucan has a high negative predictive value but a positive result does not rule in IFI in and warrants further investigation. The presence or absence of antifungal drug therapy does not affect B-D Glucan assay sensitivity.(i.e. B D Glucan test is not affected by prophylaxis antifungal therapy).

2.5.3. Serum galactomannan (aspergillus antigen) detection in body fluid is more sensitive than culture for diagnosis of invasive aspergillus. In neutropenic patients with a 0.5 cut off, sensitivity is 78% and specificity 81%. Serum galactomannan is less sensitive if patient is on mold prophylaxis.

2.5.4. BAL galactomannan is the most sensitive diagnostic test for pulmonary aspergillus and remains sensitive even if patient on mold prophylaxis.

2.6. **Possible / Probable IFI** (See Appendix 4 for these definitions of IFI.)

First line: Caspofungin for 10 to 14 days. If unresponsive, other antifungals may be considered with advice from microbiology. Second line antifungals such as voriconazole and Ambisome® may be considered

2.7. **Proven IFI.**

2.7.1. This requires discussion with microbiology in conjunction with the regional reference mycology centre regarding likely species and sensitivities.

2.7.2. See appendix 5 regarding likely organism sensitivities.

2.8. **Proven or probable aspergillosis**

2.8.1. Commence intravenous voriconazole.

2.8.2. Continue intravenous voriconazole for 7 days after which switch to oral voriconazole if the oral route of administration is suitable. Patients may be switched to oral earlier than 7 days if a prompt and satisfactory response is observed with initial intravenous therapy. Total course 6-12 weeks dependent on the degree and duration of immunosuppression, site of disease and evidence of disease improvement.

2.8.3. If aspergillosis is unresponsive or progressing, please discuss with microbiology and the regional reference mycology centre.

2.8.4. Consider therapeutic drug level monitoring 7 days after initiation of therapy for those on long-term therapy. Discuss with microbiology and the reference laboratory.

2.8.5. Alternative therapies include liposomal Amphotericin B, isuvaconazole.

2.8.6. For refractory or progressive aspergillosis (salvage therapy) an individualized approach is recommended that considers the rapidity, severity and extent of infection, patient co-morbidities, and to exclude the emergence of a new pathogen. General strategies to include (1) changing antifungal class (2) tapering or reversal of underlying immunosuppression when feasible, and (3) surgical resection of necrotic lesions in selected cases.

2.8.7. An additional antifungal agent may be added to the current therapy.

2.8.8. Salvage therapy agents include lipid formulations of Amphotericin B, micafungin, caspofungin, posaconazole, or itraconazole. If using a triazole take in to account prior antifungal therapy, host factors, pharmacokinetic considerations and possible antifungal resistance.

2.8.9. Treatment duration depends on clinical response and on immune reconstitution or recovery of GvHD. Good partial or complete remission requires no persistent clinical, including imaging (scarring allowed), or microbiological evidence of disease. The range of treatment duration is 3 to>50 weeks.

2.9. Therapeutic drug monitoring (TDM)

2.9.1. Patients with invasive aspergillus often have multiple conditions that may affect the absorption, distribution, metabolism and clearance of antifungal medications. Standard dosing regimens for prevention and treatment may not achieve effective or safe drug exposures in all patients.

2.9.2. TDM is recommended once steady state has been reached for patients receiving triazole-based therapy (itraconazole, voriconazole, posaconazole and possibly isavuconazole) for invasive aspergillus, prolonged azole prophylaxis, or where drug interactions are anticipated in order to identify patients at risk of treatment failure or toxicity.

2.10. Suspected mucormycosis (zygomycosis) or Fusarium infection

2.10.1. The term mucormycosis (zygomycosis) is used to refer to infections caused by moulds belonging to the Order Mucorales of the Class Zygomycetes. These include the genera of Absidia, Mucor, Rhizomucor, and Rhizopus. Mucormycosis is an uncommon, but often lethal infection in immunocompromised patients. Those at greatest risk include persons with acute leukaemia in relapse, and allogeneic transplant with severe GVHD. There are five major clinical forms of mucormycosis; rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. The clinical manifestations of pulmonary mucormycosis cannot be distinguished from Gram-negative bacterial pneumonia, or aspergillosis.

2.10.2. Fusarium can cause a broad spectrum of human diseases. In the neutropenic patient it can present as a persistent fever (greater than 38°C) that is unresponsive to antibacterial and antifungal treatment. Pleurisy, non- productive cough and haemoptysis are other presenting signs. Radiological findings range from non-specific infiltrates to nodular or cavitating lesions.

2.10.3. Please discuss with microbiology in conjunction with the regional reference mycology centre if treatment for these conditions is being contemplated.

2.11. **Special Cases**

All special cases require discussion with microbiology in conjunction with the regional mycology centre.

2.12. **Suspected hepatosplenic candidiasis**

- Unless aspergillus is excluded use Ambisome® as first line and consider early switch to caspofungin if poor response.
- If hepatosplenic candidiasis is proven, discuss with microbiologist for sensitivities.

2.13. **Proven systemic candidiasis**

2.13.1. Blood cultures are usually positive in these cases and treatment should be guided by sensitivities:

- **First line if azole naive:** Fluconazole IV 800 mg loading dose followed by 400mg daily.
- **If previous azole prophylaxis, known azole resistance or suspected non-albicans candidiasis:** Caspofungin or liposomal amphotericin (Ambisome®)intravenous 3 – 5mg/kg once daily - discuss with microbiologist.

2.13.2. Blood cultures should be repeated 48 to 72 hours after commencement of antifungal treatment.

2.13.3. The recommended duration of therapy for candidaemia without persistent fungaemia or metastatic complications is for 2 weeks after documented clearance of Candida from the bloodstream, resolution of symptoms attributable to candidaemia, and resolution of neutropenia.

2.13.4. All patients should have an ophthalmological review.

2.13.5. Intravascular catheter removal is recommended for catheter related bloodstream infections due to Candida spp., instead of treatment with antifungal lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site).

2.14. **Aspergilloma/fungal ball**

Consider surgical referral as some patients may benefit from resection.

2.15. **Sinus involvement**

ENT referral is essential for endoscopy and possible biopsy or Debridement.

2.16. **CNS involvement**

Joint management with neurosurgery +/- implanted reservoir.

- **First line:** Voriconazole IV.
- **Second line:** Ambisome®.

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Appropriate use of antifungal agents in accordance with these guidelines.
Lead	Haematology Lead Clinician.
Tool	Audit and review tool using patient documentation.
Frequency	Yearly and reported through departmental governance meeting.
Reporting arrangements	Report sent to the Haematology Governance Committee and Antimicrobial stewardship management committee.
Acting on recommendations and Lead(s)	Haematology clinical lead to act on any recommendations from the report.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned within one month. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Invasive Fungal Infection in Adult Haematology and Oncology Patients Clinical Guideline V3.0
This document replaces (exact title of previous version):	Invasive Fungal Infection in Adult Haematology and Oncology Patients Clinical Guideline V2.0
Date Issued/Approved:	27 April 2023
Date Valid From:	May 2023
Date Valid To:	May 2026
Directorate / Department responsible (author/owner):	Michelle Furtado, Consultant Haematologist.
Contact details:	01872 252524
Brief summary of contents:	Clinical guideline for the treatment of invasive fungal infections.
Suggested Keywords:	Antifungal, invasive, fungal infection.
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** No
Executive Director responsible for Policy:	Chief Medical Officer.
Approval route for consultation and ratification:	Haematology Governance Meeting.
General Manager confirming approval processes:	Ian McGowan.
Name of Governance Lead confirming approval by specialty and care group management meetings:	Suzanne Atkinson.
Links to key external standards:	None required.
Related Documents:	RCHT Management of Neutropenic Sepsis in Cancer patients - Clinical Guideline.

Information Category	Detailed Information
Training Need Identified?	No.
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet.
Document Library Folder/Sub Folder:	Clinical / Haematology.

Version Control Table

Date	Version No	Summary of Changes	Changes Made by (Name and Job Title)
Mar 2016	V1.0	Initial Issue.	Neil Powell, Antibiotic Pharmacist.
December 2019	V2.0	Removed HIV and critical care from this version.	Neil Powell, Antibiotic Pharmacist.
April 2023	V3.0	Small content changes and updated to new trust template.	Michelle Furtado, Consultant Haematologist.

All or part of this document can be released under the Freedom of Information Act 2000.

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document.

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Initial Equality Impact Assessment Form

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity, and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Invasive Fungal Infection in Adult Haematology and Oncology Patients Clinical Guideline V3.0
Directorate and service area:	General Surgery and Cancer Services, Haematology.
Is this a new or existing Policy?	Existing.
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Michella Furtado, Consultant Haematologist.
Contact details:	01872 252524

Information Category	Detailed Information
Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	Provide guidance on the effective treatment of invasive fungal infections.
Policy Objectives	Effective treatment of invasive fungal infections.
Policy Intended Outcomes	Effective treatment of invasive fungal infections.

Information Category	Detailed Information
How will you measure each outcome?	Audit appropriate use of antifungal agents in accordance with these guidelines.
Who is intended to benefit from the policy?	Haematology and oncology patients.
Who did you consult with? (Please select Yes or No for each category)	Workforce: Yes Patients/ visitors: No Local groups/ system partners: No External organisations: No Other: No
Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/ groups:** Specialty Governance for Haematology and Oncology.
What was the outcome of the consultation?	Agreed.
Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff, or patient surveys:** No.

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	

Protected Characteristic	(Yes or No)	Rationale
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment:

Michelle Furtado, Consultant Haematologist.

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis

Appendix 3. Clinical signs suggestive of Invasive fungal infection- BCSH guideline 2008:

- Any new fever during prolonged, severe neutropenia or immunosuppression.
- Fever resistant to broad spectrum antibacterials while neutropenic.
- Symptoms and signs of new, resistant or progressive lower respiratory tract infection; e.g. pleuritic pain, pleural rub.
- Prolonged, severe lymphocytopenia in chronic 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 SFI (systemic fungal infection).

Appendix 4. Revised EORTC/MSG Definitions of Invasive Fungal Infection/disease except for endemic mycoses (CID 2008: 46; 1813-21)

Possible: 1 host factor + clinical criterion.

Probable: 1 host factor + clinical criterion + mycological criterion.

Proven: Positive microscopic analysis (by histopathologic, cytopathogenic or direct microscopic examination) of a specimen from a sterile site or positive culture from a sterile specimen/blood or positive cryptococcal antigen in the CSF.

Host factors

- Recent history of neutropenia (<0.5 x 109 neutrophils/L [<500 neutrophils/mm3] for >10 days) temporally related to the onset of fungal disease.
- Receipt of an allogeneic stem cell transplant.
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks.
- Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-a blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days.
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

Clinical criteria.

Lower respiratory tract fungal disease.

The presence of 1 of the following 3 signs on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign.
- Air-crescent sign.
- Cavity.

Tracheobronchitis.
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis.

Sinonasal infection.

Imaging showing sinusitis plus at least 1 of the following 3 signs:

- Acute localized pain (including pain radiating to the eye).
- Nasal ulcer with black eschar.
- Extension from the paranasal sinus across bony barriers, including into the orbit.

CNS infection.

1 of the following 2 signs:

- Focal lesions on imaging.
- Meningeal enhancement on MRI or CT.

Disseminated candidiasis.

At least 1 of the following 2 entities after an episode of candidaemia within the previous 2 weeks:

- Small, target-like abscesses (bull's-eye lesions) in liver or spleen.
- Progressive retinal exudates on ophthalmologic examination.

Mycological criteria.

Direct test (cytology, direct microscopy, or culture).

Mould in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:

- Presence of fungal elements indicating a mould.
- Recovery by culture of a mold (e.g., Aspergillus, Fusarium, Zygomycetes, or Scedosporium spp.).

Indirect tests (detection of antigen or cell-wall constituents).

Aspergillosis.

- Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF.

Invasive fungal disease other than cryptococcosis and zygomycoses.

- β-D-glucan detected in serum.

Appendix 5. Organism sensitivities: Spectrum of activity of selected antifungal agents (Sanford Guide to Antimicrobial Therapy 2011).

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Ambisome	Caspofungin
Candida albicans	Yes	Yes	Yes	Yes	Yes	Yes
Non albicans Candida	Variable	Variable	Yes	Yes	Variable	Yes
Aspergillus Spp.	No	Yes	Yes	Yes	Yes	Yes
Zygomycete (Absidia, Mucor, Rhizopus)	No	No	No	Yes	Yes	No
Fusarium	No	No	Yes	Yes	Yes	No
Cryptococcus	Yes	Yes	Yes	Yes	Yes	No

Appendix 6. Checklist for all patients commenced on voriconazole.

There is a checklist for all patients commenced on voriconazole at www.mhra.go.uk. Summary of that checklist below.

VFEND® (voriconazole) Healthcare Professional Checklist.

Please complete this Checklist at each visit with your patient being treated with VFEND® (voriconazole).

Each of the three sections includes important risk information followed by a series of check boxes to help in the management of your patient for whom you prescribed VFEND.

- VFEND has been associated with phototoxicity and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sufficient sunscreen with high sun protection factor (SPF).

- The frequency of phototoxicity reactions is higher in the paediatric population. As an evolution towards SCC has been reported, stringent measures for the photoprotection are warranted in this population of patients. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

- Squamous cell carcinoma (SCC) of the skin has been reported in patients taking VFEND, some of whom have reported prior phototoxic reactions.

- If phototoxic reactions occur, multidisciplinary advice (e.g., a consultation with a dermatologist) should be sought for the patient. VFEND discontinuation and use of alternative antifungal agents should be considered.

- Dermatologic evaluation should be performed on a regular basis whenever VFEND is continued, despite occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions.

- VFEND should be discontinued if premalignant skin lesions or skin SCC are identified.

- SCC has been reported in relation with long-term VFEND treatment. Treatment duration should be as short as possible. Long- term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit risk balance and physicians should therefore consider the need to limit the exposure to VFEND.

- For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered. Refer to the Summary of Product Characteristics for full prescribing information.