Invasive fungal infections
causes and diagnosis

By James Hatcher, MBChB, MRCP, and Mark Gilchrist, MSc, MRPharmS

Over recent years, the NHS has seen many initiatives focused on effective infection control procedures. These include prudent anti-infective prescribing and multidisciplinary anti-infective stewardship programmes. These have been important in the fight against antimicrobial resistance and trying to reduce healthcare associated infections, but fungal disease and antifungal therapy have been largely neglected within these initiatives.

Undoubtedly, the number of people affected by bacterial infections is higher than those with fungal disease; however, with an ageing population, increasing numbers of organ transplants and a greater choice of immunosuppressive therapies, the number of invasive fungal infections is increasing. Therefore, it could be argued that healthcare professionals should know as much about the prevention and treatment of fungal infections as about bacterial infections.

Moulds and yeasts
Moulds are multicellular organisms with branching filamentous hyphae that reproduce either asexually or sexually by spore formation. They derive nutrition from organic matter and are responsible for fluffy growths such as those seen on bread and cheese.

Yeasts are unicellular organisms that reproduce like dividing bacteria by budding or binary fission. They also derive nutrition from organic matter and can ferment carbohydrates — a characteristic exploited in the making of bread and alcoholic beverages.

Dimorphic fungi can exist in either yeast or mould form depending on environmental factors such as temperature. An example is Histoplasma spp, which grow as yeast at 37°C but as mould at less than 30°C.

Epidemiology
The incidence of invasive fungal infections is increasing because of a rising number of patients who are at risk (see below). Data from the US showed that invasive fungal disease was ranked as the 10th most fatal infection in 1980 rising to seventh in 1997. Candida spp followed by Cryptococcus spp are the yeasts most commonly isolated. Aspergillus spp are the most commonly isolated moulds, but Fusarium spp, Penicillium spp, and zygomycetes are becoming increasingly common.

Risk factors
The risk of invasive fungal disease depends on both human and fungal factors.

Breakdown of external barriers, for example in patients with burns, allows fungi to enter the body. Neutrophils, monocytes and macrophages are fundamental parts of the human defence mechanism against fungal infection, and
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Dysfunction of these cells decreases the ability of the immune system to clear fungal pathogens.

Other risk factors for invasive fungal disease include:

- Immunosuppression — for example patients who have had a solid organ or bone marrow transplant and patients with HIV/AIDS or graft-versus-host disease (see Box 1)
- Systemic corticosteroids — patients receiving systemic corticosteroids for autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis
- Malignancy — patients with a solid tumour or haematological malignancy
- Severe debilitation — for example, patients in intensive care or those with multi-organ failure, severe trauma or burns
- Invasive devices — such as central venous catheters (CVCs) or pacemakers
- Extremes of age — neonates and the elderly are more susceptible to invasive fungal infections
- Endocrine disorders such as diabetic ketoacidosis increase the risk of invasive fungal infections
- Use of broad-spectrum antibiotics

Various features of fungi make them more likely to cause disease. Spores of *Aspergillus* spp and zygomycetes have a low settling rate, which means they stay airborne and are therefore easily inhaled.

Virulence factors are molecules that are expressed or secreted that allow a pathogen to have a survival advantage within a host. *Candida* spp and *Cryptococcus* spp both secrete hydrolytic enzymes, causing tissue damage and facilitating dissemination throughout a host. *Cryptococcus* spp have a protective polysaccharide capsule and also produce melanin, both of which prevent antibody-mediated phagocytosis. *Candida* spp produce adhesins allowing binding to host cells and entry into tissue.

### Box 1: Risk of invasive fungal disease

Predicting the risk of an immunocompromised patient developing an invasive fungal infection is based on incidence and mortality data, with patients classed as low, intermediate or high risk depending on the cause of the immunosuppression.

**Low risk:**
- Autologous stem cell transplant
- Hodgkin’s lymphoma
- Chronic myeloproliferative disorders
- Solid cancer
- Myeloma
- Kidney transplantation
- Chronic immunological disease
- Systemic lupus erythematosus

**Intermediate risk:**
- Acute lymphoblastic leukaemia
- Chronic lymphocytic leukaemia
- Lymphoma
- Chronic obstructive pulmonary disease
- HIV/AIDS
- Myelodysplastic syndromes

**High risk:**
- Acute myeloid leukaemia
- Allogenic stem cell transplant
- Heart, liver, lung transplantation

### Organisms and disease

**Candida** spp

*Candida* spp are yeasts that normally colonise human skin and the gastrointestinal and genitourinary systems without causing infection. *Candida albicans* is the most commonly isolated fungus in clinical specimens, but other species are becoming increasingly common (eg, *Candida glabrata*). This is important since these other species can be resistant to the antifungal medicines that are traditionally used for treatment.

Infections caused by *Candida* spp are particularly common on intensive care wards because patients often have invasive devices inserted (eg, CVCs). In addition, exposure to broad-spectrum antibiotics can change patients’ normal skin flora, making colonisation with *Candida* spp common, which can lead to vascular invasion via such invasive devices. Once the organism has gained entry into the bloodstream (candidaemia) it can cause endorgan disease such as endophthalmitis (inflammatory condition of the intraocular cavities) or endocarditis. Endocarditis caused by *Candida* spp has a poor prognosis if untreated and invariably results in heart valve replacement.

**Cryptococcus** spp

*Cryptococcus neoformans* is the most common species of *Cryptococcus* — it is ubiquitous in the environment and is commonly found in bird droppings, especially from pigeons. A pulmonary syndrome of fever, cough and pulmonary infiltrates can affect individuals who are immunocompetent or immunocompromised.
**Presentation:** QUTENZA™ 179 mg cutaneous patch. Each 280 cm² cutaneous patch contains a total of 179 mg of capsaicin or 0.640 micrograms of capsaicin per cm² of patch (8% w/w). Excipient: Each 50g tube of cleansing gel for QUTENZA contains 0.2mg/g butyrylloxyanisole (E320). Indications: QUTENZA is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

**Posology and administration:** QUTENZA should be applied to the most painful skin areas (i.e. a maximum of 4 patches). The painful area should be determined by the physician and marked on the skin. QUTENZA must be applied to intact (unbroken), non-eroded, dry skin, and allowed to remain in place for 30 minutes for the feet (e.g. HIV-associated neuropathy) and 60 minutes for other locations (e.g. postherpetic neuralgia). QUTENZA treatments may be repeated every 90 days, as warranted by the persistence of or return of pain. The QUTENZA cutaneous patch should be applied by a physician or a healthcare professional under a physician's supervision. Patients with renal and/or hepatic impairment: No dose adjustment is required for patients with renal or hepatic impairment.

**Paediatric population:** QUTENZA is not recommended for use in children and adolescents due to lack of data on safety and efficacy. Consult SmPC for full prescribing information.

**Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Warnings and precautions: Health care professionals should wear nitrile gloves when handling patches and cleansing treatment areas. QUTENZA should be used only on dry, intact skin and not on the face, above the hairline of the scalp, and/or in proximity to mucous membranes. Care must be taken to avoid unintentional contact with the patches or other materials that have come in contact with the treated areas.

**Undesirable effects:** Common (n ≥ 1/10) application site: pruritus, papules, vesicles, oedema, swelling, erythema. Common (n ≥ 1/100 and n < 1/10) Application site: pruritus, papules, vesicles, urticaria, swelling, dryness. Uncommon (n ≥ 1/1,000 and n < 1/100) Application site: urticaria, dysgeusia, irritations, inflammation, irritation, itching, pruritus, burning sensation, herpes zoster. Consult SmPC for complete information.


**For full prescribing information : Refer to the summary of product characteristics.**

**Adverse events should be reported.** Reporting forms and information can be found at www.yellowcard.gov.uk

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Although cryptococcosis can affect immunocompetent hosts, the incidence is markedly higher among patients with HIV. For these immunocompromised hosts, the most common clinical manifestation is meningitis. The mortality of untreated cryptococcal meningitis is close to 100% and the disease is a major healthcare burden in developing countries.

*Aspergillus* spp. *Aspergillus* spp are moulds and the most commonly isolated species is *Aspergillus fumigatus.* Invasive aspergillosis is a particular problem for patients with haematological malignancies undergoing allogeneic bone marrow transplantation — up to 13% of patients have been reported to be affected. Similarly, patients who have had a solid-organ transplant are at risk of invasive aspergillosis, although the risk is highest for patients who have had a lung transplant. *Aspergillus* spp enter the body via the respiratory system. Invasion occurs directly into the lungs or sinuses and can then disseminate throughout the body via the blood. Pulmonary aspergillosis is the most common form and it should be suspected in haematology patients with pulmonary symptoms and signs consistent with infection that are not responding to broad-spectrum antibiotics.

*z Zygomycetes* *Zygomycetes* is an umbrella term for a class of fungi that cause a disease called zygomycosis. *Zygomycetes* are characterised by the production of sporangiospores (spores that are produced in a fungal structure called the sporangium), which distribute easily in the air and can then be inhaled; this is the reason that the most common clinical manifestation of zygomycosis is rhinocerebral and pulmonary disease. Zygomycosis is the most acute and fulminant fungal infection known. Once the pathogen has settled in the sinuses, it can spread locally into the orbit causing pain and visual disturbance. Neutrophil dysfunction and neutropenia, especially prolonged neutropenia, is a significant risk factor for developing zygomycosis. Invading *zygomycetes* spread via arteries, causing embolisation and necrosis of surrounding tissue. Rapid diagnosis is essential because invasion of the central nervous system is associated with a high mortality despite aggressive treatment.

**Dimorphic fungi** Although invasive diseases can be caused by dimorphic fungi, such diseases are rare in the UK. Therefore, it is important to know the travel history of any patients suspected of having a fungal disease (see Box 2, p175).

**Diagnosis** The diagnosis of invasive fungal disease can be difficult. The most useful diagnostic method depends on the fungal pathogen causing the disease. The ubiquitous nature of fungi means that, when a fungus is isolated in a...
In the microbiology laboratory, the question of whether or not that particular fungus is the causative organism remains (it could, for example, be caused by environmental contamination or normal flora).

Isolating fungus from the site of disease is the gold standard for diagnosis. Direct microscopy will show that fungus is present but will not give a definitive species. Fungus can be cultured on specialised media and this will aid further identification. Culture of a fungus from normally sterile tissue or fluid, such as cerebrospinal fluid, bone or blood, is diagnostic of fungal disease but laboratory contamination is possible. Blood cultures are the diagnostic test for candidaemia.

Serology can be used to test for fungal antigens in body fluids and is particularly useful for detecting cryptococcosis. Difficulties arise when using serology results because of the poor specificity and sensitivity of tests, particularly in immunocompromised patients. Polymerase chain reaction (PCR) has been studied for diagnosis of invasive aspergillosis but the test results have not been standardised and there has been wide variation in PCR study results.12

Galactomannan is a cell wall component of *Aspergillus* spp and *Penicillium* spp. Detection of galactomannan is possible via immunoassays and can help diagnosis, especially in patients with haematological malignancies.

### Box 2: Dimorphic fungal diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CAUSATIVE ORGANISM</th>
<th>GLOBAL DISTRIBUTION</th>
<th>COMMON CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em>;</td>
<td>Worldwide except Europe</td>
<td>95% of patients are symptomatic or have pulmonary or cutaneous disease</td>
</tr>
<tr>
<td></td>
<td><em>Histoplasma duboisi</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td><em>Coccidioides immitis</em></td>
<td>Semi-desert areas in the Americas</td>
<td>Disseminated disease in patients with HIV</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Predominantly north America</td>
<td>Chronic granulomatous and suppurrative with lung disease</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td><em>Paracoccidioides brasiliensis</em></td>
<td>South and central America</td>
<td>Pulmonary or mucocutaneous disease; uncommon in patients with HIV</td>
</tr>
<tr>
<td>Penicilliosis marneffei</td>
<td><em>Penicillium marneffei</em></td>
<td>Endemic in south-east Asia</td>
<td>High incidence of disseminated disease in patients with HIV</td>
</tr>
</tbody>
</table>
However, problems include a lack of standardisation of test results, issues with statistical test cut-offs and false positives. Despite these problems, galactomannan detection can be used in conjunction with imaging to guide empirical antifungal therapy for adult patients with haematological malignancies.

Radiological imaging can be used to detect invasive fungal disease. High-resolution computed tomography scanning and magnetic resonance imaging are particularly useful for detecting mould infections and will show pulmonary and extra-pulmonary lesions. Other findings include wedge-shaped nodules, consolidation, cavitation or air-crescent signs. These are non-specific findings since other infections or malignancies can cause such appearances. These findings are associated with a poor prognosis because they indicate a large burden of disease.

The European Organisation for Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group have published standard definitions for invasive fungal infections, which were developed to improve the diagnosis of invasive fungal infections in clinical research. The definitions use a combination of clinical information, radiological findings and histological and microbiological data to assign three levels of diagnostic probability (proven, probable and possible) based on set criteria. Further resources can be found in Box 3.

Ultimately, in many cases of fungal infection, it may be difficult or impossible to isolate the causative organism. Even when a fungus is identified expertise is necessary to establish the clinical significance of the organism.

References

Box 3: Resources

The following are useful resources for pharmacists with an interest in fungal infections:

- www.mycology.adelaide.edu.au
- www.doctorfungus.org
- www.idsociety.org