

# Fungal infections

## — causes and diagnosis

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The incidence of fungal infections seen in hospital and in the community is rising, due to increased numbers of susceptible patients and increasing resistance to antifungal drugs. This article gives an overview of the most common fungal infections and the organisms that cause them



Onychomycosis (nail plate infection) is caused by the *Candida* species

**F**ungal infections of the skin, hair and nails are commonly encountered in general practice. However, community-acquired infections are increasingly being seen in the hospital environment, and hospital-acquired infections are becoming more common. This upward trend is concerning, considering the limited number of antifungal drugs available, because prophylaxis with antifungals may lead to the emergence of resistant strains.

### About fungi

Fungi are plant-like organisms that lack chlorophyll. They are saprophytic (ie, they mainly live off decaying matter), but can also utilise living matter. There are more than a million species of fungi, of which only a minority cause infection in humans.

Fungi are ubiquitous, living in soil and decaying matter. Spores are usually present in the air, enabling them to be inhaled. Usually, host defence mechanisms clear these spores but, in susceptible individuals (ie, the immunocompromised), spores may germinate within the lungs or another site within

the body and cause infection. Spores can also enter the body via direct inoculation, to cause superficial infection.

Most mycotic infections are not transmissible between humans and do not require special precautions (such as barrier nursing). However, some fungi can be highly infectious if inhaled and may grow on fomites such as bandages. For example, special precautions need to be taken with *Coccidioides immitis*, a highly infectious agent that, when inhaled, can cause severe pulmonary infection.

Fungi are generally classed as either yeasts or moulds, although there are also dimorphic fungi, which exist as yeasts within the host but take the form of mould at room temperature *in vitro* (see Panel 1, p318). Yeasts are single, rounded organisms that reproduce via budding or fusion, resulting in more rounded forms. Moulds are composed of long tubular filaments called hyphae; these grow by branching and longitudinal extension both over the surface of and inside living and dead matter. When the hyphae have formed a cottony mass that is visible to the naked eye, this is called a mycelium. Decay is caused by the growth of moulds over living matter. Moulds reproduce by sporulation (the production of spores). Spores act like seeds, germinating and producing a new mould colony whenever they

land in a suitable place, either in the environment or within the body. Different moulds produce different types of spores, which enables identification of the mould.

Fungal infections in humans are known as mycoses, and they can be divided into two main groups: those causing superficial infections, and those causing deeper, or systemic infections. This article gives an overview of the most common fungal infections encountered in the hospital and in general practice. Due to the association with immunocompromised patients, the highly infectious dimorphic fungi are also mentioned, although they do not commonly cause infection in the UK.

### Superficial infections

**The dermatophytes** Superficial fungal infections usually involve the skin, hair and nails. The group of fungi most commonly responsible for causing infection of these sites are known as the dermatophytes, and include the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. The infection they cause is commonly known as tinea or ringworm, with the full name relating to the site of infection. For example, tinea capitis is infection of the scalp, tinea corporis is infection of the body, and tinea unguium is infection of the nails. These organisms need

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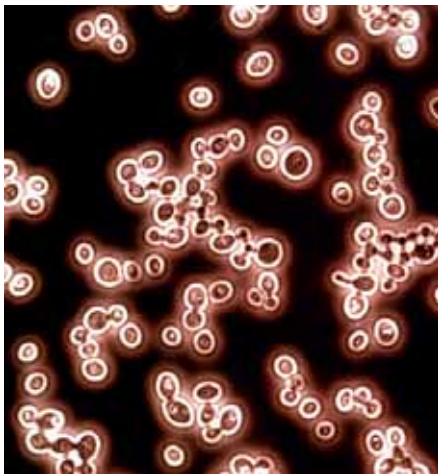


Figure 1: *Candida albicans*

to spread from host to host in order to survive, and may be zoophilic (living on an animal host) or anthrophilic (living on a human host). Geophilic organisms prefer to live in the soil.

The classical skin lesion of dermatophytosis is an annular scaling patch with a raised margin. There tends to be more inflammation at the edge of the lesion than in the centre. The inflammatory response of the host, the site of infection and the infecting fungal species all contribute to the clinical appearance of the lesion. Patients with altered T-cell immunity may have less inflammatory lesions. Zoophilic fungi often cause inflammatory lesions, but may also cause pustular lesions (called kerion). Anthrophilic fungi usually cause chronic and/or less inflammatory lesions.

Some dermatophytes can cause infection of the hair. The principal conditions are:

- **White piedra** — a rare, superficial infection of the hair shafts, caused by yeasts of the *Trichosporon* genus. It is characterised by small nodules.
- **Black piedra** — another, rare infection of the hair shafts, which is usually only seen in the tropics. It is caused by the yeast *Piedraia hortae* and is characterised by black nodules.

**Candida species** Superficial skin infections can also commonly be caused by *Candida* species, which are yeasts. The most common *Candida* species causing infection is *Candida albicans* (Figure 1). Superficial infections caused by *Candida* spp include candida vulvovaginitis, balanitis (penile thrush), intertrigo (skin fold infections), napkin dermatitis (nappy rash), chronic paronychia (nail fold infection) and onychomycosis (nail plate infection). Chronic mucocutaneous candidiasis is a widespread, persistent infection, which usually presents in childhood. *Candida* spp are part of the normal oral flora in 25–50 per cent of healthy individuals.<sup>1</sup> When these organisms cause infection, oropharyngeal candidiasis (oral thrush)

occurs (Figure 2). Populations most at risk of oropharyngeal candidiasis include neonates, the elderly, patients with diabetes, the immunosuppressed (including HIV-positive patients) and malnourished patients. Therapy predisposing to candidiasis includes oral and inhaled steroids, broad-spectrum antibiotics, and immunosuppressive therapy. *Candida* spp may also cause invasive disease, particularly in the immunocompromised.

Candidiasis or thrush is characterised by creamy white, curd-like patches or discharge on mucosal surfaces such as the tongue, oropharynx, oesophagus and vagina. Other parts of the gastrointestinal tract can also be affected, especially in those patients with underlying malignancy. With vulvovaginitis, the vulva is usually oedematous and itchy, and extension of infection onto the perineum may occur. The patches or discharge seen are actually a pseudomembrane consisting of candida, desquamated epithelial cells, bacteria, keratin, and necrotic debris. Oral patches also contain leucocytes.

Both *Candida* spp and the dermatophytes can cause onychomycosis, and adjacent fungal skin infection is usually seen in these patients. The nail is usually thickened and discoloured (white, yellow or brown). In some cases white crumble plaques may form on the top of the nail.

Other less common superficial infections include: skin and/or nail infections due to *Scytalidium dimidiatum*, and onychomycosis due to infection by *Scopulariopsis brevicularis*, *Acremonium* spp, or *Fusarium* spp.

**Pityriasis versicolor** Pityriasis versicolor is a superficial infection caused by the yeasts of *Malassezia* species. These are lipophilic yeasts, and only cause infection of the trunk and proximal limbs, never the hair or nail plates. Infections are more common in the tropics and sun exposure can be a trigger factor. Lesions are usually non-itchy, hyper- or hypo-pigmented macules that coalesce to form scaling plaques. *Malassezia furfur* is the species usually responsible for causing this infection. *Malassezia* yeasts can also cause folliculitis and seborrheic dermatitis.

**Ear infections** Otitis externa and media may be caused by infections due to *Candida* spp and *Aspergillus* spp (especially *Aspergillus terreus*).

## Systemic infections

Over recent years, the population of patients susceptible to systemic fungal infections (eg, the critically ill and the immunocompromised) has increased due to improved therapies for these patients. Diagnosis of a fungal infection in these patients is often difficult because symptoms may be minimal and are often non-specific. Since fungi are ubiquitous, it stands to reason that they can easily contaminate cultures. They can also



Figure 2: Oropharyngeal candidiasis (oral thrush)

colonise the upper airways, perineum and urinary catheters. Therefore, diagnosis rests on the isolation of fungus from an appropriate specimen, for example, bronchoalveolar lavage for respiratory infections rather than a sputum sample. However, it may be difficult to obtain an appropriate specimen from a critically ill patient.

Radiographic changes such as in the lungs may suggest a fungal infection but cannot confirm a diagnosis. Treatment may be started in the absence of a positive culture, in which case susceptibility to an antifungal drug cannot be tested. Inappropriate treatment given to an already critically ill patient may contribute to the mortality and morbidity associated with the fungal disease.

## Systemic candidiasis

*Candida* spp can infect almost any organ of the body, and the incidence of deeper infections has increased over the last decade.

**Candidaemia** Over recent years, there has been a significant increase in the incidence of candidaemia. It is reported to be the fourth most common form of bloodstream infection in the US.<sup>3</sup> This increase in incidence is thought to be due in part to an increase in the number of immunocompromised individuals, plus a significant increase in the number of intravascular devices such as tunnelled catheters. Other risk factors include admission to the intensive care unit, total parenteral nutrition, multiple antibiotics, corticosteroid use, chemotherapy and neutropenia (especially with haematological malignancy) and renal transplantation. Both arterial and venous circulations can be affected. The urinary and gastrointestinal tracts can also act as sources of infection. It has been postulated that damage to the endothelium predisposes the patient to haematogenous infection with candida.

In patients with candidaemia, *Candida albicans* is the most frequently isolated species, although *Candida glabrata*<sup>4-6</sup> and *Candida tropicalis* are increasingly being isolated.

Complications of candidaemia include: endocarditis, superior vena cava obstruction and infective pulmonary venous thrombosis.

With disseminated candidiasis, candida can affect multiple organs, especially the brain, myocardium, kidneys and eyes. Classically, an acute suppurative and granulomatous reaction with diffuse microabscess and macroabscess formation is seen in these organs.

Patients with candidaemia may appear to be quite well with minimal symptoms. However, the extent of the underlying disease may be quite extensive and the associated mortality rate has been reported to be between 35 and 55 per cent. Treatment failure and clinical relapse are common so removal of any focus of infection such as infected prosthetic material should always be considered. In up to 50 per cent of cases of disseminated candidiasis, blood cultures are negative<sup>1</sup> and diagnosis may be difficult.

**Ocular candidiasis** Fungal eye infection can occur via haematogenous spread (in approximately 50 per cent of cases) or direct inoculation (from trauma or surgery). Any part of the eye may be involved. Endophthalmitis (inflammation of the interior of the eye) is difficult to treat and permanent damage often ensues. Symptoms include blurred vision, bulbar pain and floating scotomas (areas of blindness). *Candida albicans* is the species most frequently isolated from fungal eye infections. Diagnostic techniques include funduscopy (examination of the back part of the eyeball) and surgical removal of the vitreous humour (this can be both diagnostic and therapeutic because intravitreal antifungal therapy can be given). As with most fungal infections involving the eye, ocular candidiasis is a serious condition and permanent blindness may occur.

#### **Central nervous system candidiasis**

Both the brain parenchyma and meninges can be affected by candidiasis. Approximately 50 per cent of patients with candida meningitis have disseminated disease. Involvement of the brain parenchyma is associated with both micro- and macroabscesses. Clinical features are similar to those seen with bacterial CNS infections (eg, meningism) and if meningitis is present, cerebrospinal fluid examination typically reveals a pleocytosis (the presence of more cells than normal) with a lymphocyte predominance. CNS candidiasis may also occur as a complication of neurosurgery or ventricular shunt implantation. AIDS is also a predisposing factor.

**Candida pneumonia** *Candida pneumonia* usually manifests as either a diffuse bronchopneumonia or as a diffuse nodular infiltrate. Features are non-specific and can be similar to congestive heart failure.

Because yeasts can commonly colonise the respiratory tract, culture of *Candida* spp from sputum samples is not diagnostic, and biopsies of lung tissue showing fungal invasion are required for definitive diagnosis.

**Other candida infections** *Candida* spp is the most common fungal organism that causes endocarditis. This condition is associated with: pre-existing bacterial endocarditis (superimposed infection), underlying cardiac valvular disease and prosthetic valves, intravenous catheters, chemotherapy and neutropenia, and intravenous heroin use. Infection post-cardiac surgery accounts for approximately 50 per cent of cases. The aortic and mitral valves are most commonly affected by the fungi. Clinical signs are similar to those seen with bacterial endocarditis, and in most cases *Candida* is isolated from blood cultures. Combined surgical and medical therapy has seen the mortality rate for endocarditis caused by candida fall from over 90 per cent to 45 per cent.

*Candida* can also cause urinary tract infections (most commonly as a complication of an indwelling urinary catheter) and less commonly, arthritis, osteomyelitis, and myositis. Following surgery or trauma, the peritoneum and abdominal organs may become seeded with candida. It may also cause infection in patients on peritoneal dialysis.

### — Aspergillus infections

Systemic infection caused by *Aspergillus* spp usually only occurs in the immunocompromised host. However, this mould can also cause infection in immunocompetent people where there has been recent tissue damage (eg, endophthalmitis, keratitis, infection of burn wounds), allergic aspergillosis (allergic bronchopulmonary aspergillosis, allergic aspergillus sinusitis), and the superficial infections described earlier.

**Aspergilloma** *Aspergillus* can colonise existing cavities within the lung or sinuses (eg, following infection with tuberculosis). A ball of fungus develops within the cavity. In sinus infection, there may be no mucosal involvement, and surgical removal of the fungal ball is usually curative. Lung infection may be asymptomatic, but most patients have persistent productive cough, weight loss, haemoptysis, wheeze and finger clubbing. Chest radiographs or computerised tomography (CT) scans show masses of hyphae within the cavity, with a surrounding rim of air (known as the "halo" or "crescent" sign).

**Invasive aspergillosis** Invasive aspergillosis is a condition that mainly affects immunocompromised patients.<sup>8,9</sup> It is most commonly seen in neutropenic patients, often when their neutrophil counts start to

recover. The lungs are affected in 80–90 per cent of cases. Symptoms of invasive pulmonary aspergillosis (IPA) vary, and up to 33 per cent of patients may not have any initial symptoms. The disease can progress rapidly in profoundly immunocompromised patients, although initially there are few symptoms. A more indolent, chronic picture is seen in, for example, AIDS patients, in whom there is a relatively lower degree of immunocompromise. Other conditions associated with chronic IPA include chronic granulomatous disease, alcoholism and diabetes mellitus. Symptoms include dry cough, fever, pleuritic chest pain and dyspnoea. Hypoxia is common in extensive disease.

**Aspergillus tracheobronchitis** Patients with AIDS and lung transplant recipients are more at risk of developing aspergillus tracheobronchitis than other patients. However, in 25 per cent of cases, there is no apparent immunocompromise. Symptoms of cough, fever, dyspnoea, chest pain, haemoptysis or wheeze will occur in 80 per cent of patients with the condition. Initially, patients may have mild tracheobronchitis, but this can progress to ulcerative or even pseudomembranous tracheobronchitis. This can result in occlusion of the airways, followed by death due to respiratory insufficiency. Chest radiographs usually appear normal in the early stages of the disease, but consolidation may occur later.

**Aspergillus sinusitis** Acute or chronic invasive aspergillus sinusitis is the presenting feature in approximately 10 per cent cases of invasive aspergillosis in neutropenic patients, and in those who have recently had a bone marrow transplant. The condition is rare in patients who have had a solid organ transplant. Local extension of the infection may occur and it can rapidly spread to the brain. CT and magnetic resonance imaging scans may show fluids in the sinuses, suggestive of infection there. Aspergillosis can affect the sinuses and the lungs at the same time.

**Cerebral aspergillosis** Cerebral involvement occurs in 10–20 per cent of patients with invasive aspergillosis. It is usually only seen in immunocompromised patients, especially in allogeneic bone marrow recipients (this accounts for 25–50 per cent of cases). Symptoms include seizures, altered mental state and headache, and there may be focal neurological signs. CT scans of the brain usually show ring enhancing lesions (ring-like lesions which glow when the patient is given IV contrast before the scan) or cerebral infarctions.

**Cutaneous aspergillosis** As with most other types of aspergillosis, cutaneous aspergillosis is more commonly seen in immunocompromised patients, although

infection can occur in immunocompetent persons. Infection may be primary (ie, at the site of injury, including at or near intravenous catheter access sites, where there has been traumatic inoculation, and sites associated with recent surgery, burns and wounds) or secondary (due to either haematogenous spread or contiguous spread from underlying infected structures). Lesions can vary in appearance.

## — Mucormycosis

Mucormycosis is a term that covers a number of different diseases caused by fungi of the order Mucorales, of which the Zygomycetes (including *Mucor circinelloides*, *Absidia* spp, *Rhizomucor pusillus* and *Rhizopus* spp) are most commonly encountered in human disease. These fungi commonly enter the body via the respiratory tract, but can also be inoculated directly into the skin to cause primary cutaneous mucormycosis. Although these fungi are ubiquitous in decaying matter and soil, disease is usually limited to those with severe underlying immunocompromise, diabetes mellitus (especially with ketoacidosis), trauma or solid organ transplants.<sup>7</sup> The fungi are characterised by rapid growth and abundant spore production, thus disease spread can be rapid and is often fatal.

The most frequently encountered manifestation of the disease is rhinocerebral mucormycosis. Symptoms begin with a headache, fever and orbital cellulitis, and rapidly progress to involve the deeper tissues of the orbit (the bony cavity in which the eye is held). Angioinvasion and involvement of the cranial nerves may occur; this represents a poor prognostic sign, and coma and death usually follow.

Pulmonary mucormycosis is a condition mainly seen in neutropenic patients, often as

a cause of nosocomial pneumonia. Patients with diabetes may develop a more indolent, subacute form of pulmonary mucormycosis. Symptoms are minimal and may be no more than fever and dyspnoea. Chest X-rays reveal consolidation or cavitation in 66 per cent and 40 per cent of cases, respectively. Other organs may also be involved, and dissemination can occur with disease progression.

Cutaneous mucormycosis may present as a chronic, non-healing ulcer with central necrosis. It may follow a fungaemia, or more commonly, inoculation after an insect bite or gardening injury.

Mucormycosis can also less commonly affect any part of the gastrointestinal tract, heart, bones, kidneys and bladder.

## — Cryptococcosis

The yeast *Cryptococcus neoformans* grows well in nitrogen-enriched soil with an alkaline pH. Thus, optimum conditions for growth are soil mixed with bird excreta. People who are exposed to dirt containing bird droppings, such as poultry farm workers, and groundskeepers of parks, are at risk of inhaling the yeast. Cave explorers are also at risk, because bats also carry *C neoformans*. Cryptococcosis can cause pneumonia and cutaneous infections, but the most serious presentation is cryptococcal meningitis. This condition can occur in immunocompetent persons (caused by *C neoformans* var *gatti*), where the picture is more insidious and chronic. The acute presentation with rapid onset of confusion, headache and/or reduced levels of consciousness is more commonly seen in AIDS patients (where *C neoformans* var *neoformans* tends to cause disseminated disease) or in those with haematological malignancies.<sup>11</sup> Other non-specific symptoms can also occur.

## — *Pneumocystis jiroveci*

*Pneumocystis jiroveci* was previously classified as *Pneumocystis carinii* and thought to be a protozoan. However, biochemical and nucleic acid analysis has revealed that it is a fungus. It is found throughout the world, most children have been exposed by the age of four years. *Pneumocystis jiroveci* causes pneumonia in the immunocompromised, especially those with (a CD4 count <200) such as AIDS patients and patients with idiopathic CD4 deficiency.

Respiratory symptoms alone are non-diagnostic and include fever, dyspnoea and dry cough. The classical chest X-ray findings are of a bilateral interstitial infiltrate in a “bat wing” distribution. However, almost any X-ray changes can occur, and disease can also be present with an apparently normal X-ray. Hypoxia may be profound and if the infection remains untreated, death may ensue. Disseminated infection is rare.

## — Other fungal infections

Phaeoophomycosis is the term given to all cutaneous, subcutaneous and systemic infections caused by dark-walled fungi such as *Fusarium* spp and *Scedosporium* spp. Common conditions caused by these agents include keratitis in contact lens wearers, onychomycosis and eumycotic mycetoma (subcutaneous infection with discharging sinus tracts, usually involving the feet [Madura foot] and hands).

## — Diagnosis

Because of the risk of environmental contamination, care must be taken when taking specimens for culture. Wherever possible, sterile cultures are preferred. Nail clippings may need to be pre-softened before culture. Direct microscopic examination of the nail scrapings (to look for fungal elements) can be undertaken.

The fluorescent stain Calcofluor White, with or without potassium hydroxide, is often used for detection of fungi in specimens.<sup>13</sup> The India ink stain can be used to look for the capsule surrounding *Cryptococcus neoformans*. Specialised culture medium (eg, Sabouraud dextrose agar) is used for fungal culture. It is important to select the appropriate media, as the properties of the media vary, and some may be selective for one type of fungus only. Some media are used to identify morphological characteristics of the fungus, and others identify characteristics of spores. Antibacterial and antifungal agents may be added to the medium to eliminate contamination from bacteria and environmental fungi. The optimal temperature for growth of most clinically relevant fungi is 30C. Cultures should be incubated for two to three weeks to allow for the growth of slow-growing

### Panel 1: Dimorphic fungi

Dimorphic fungi exist in the mould form *in vitro* and at 25–30C, but take on the yeast form of the fungus within the host and/or at 35–37C. The dimorphic fungi, with their geographic distribution are:

- *Coccidioides immitis* (Southwestern US, parts of Central and South America)
- *Histoplasma capsulatum* (global, mainly Central US, Central and South America, Africa)
- *Blastomycosis dermatitidis* (South Central US, South East US, Central and South America, Africa)
- *Paracoccidioides brasiliensis* (South and Central America)
- *Penicillium marneffei* (South East Asia)
- *Sporothrix schenckii* (global)<sup>12</sup>

They are all highly infectious in the mould form and can cause infection in laboratory workers handling live cultures. Infection can occur in any susceptible individual but is more severe in the immunocompromised. The dimorphic fungi commonly cause pulmonary or cutaneous infections, but disseminated infections occur more commonly in the immunocompromised. Such infections should be considered in anyone who has come from an endemic area.

fungi. They are usually kept taped closed for safety and to prevent moisture loss.

Once a fungus has grown in culture, identification is presumptively made using morphological characteristics and microscopic appearances. Special stains can be used to visualise characteristic fungal elements.<sup>14</sup> Commercial test kits are also available which use a combination of biochemical, morphological and microscopic characteristics to make a definitive identification.<sup>15</sup>

Where fungus identification by culture is not possible, either due to difficulty in obtaining a suitable specimen or because of negative cultures, serological tests can be used to aid in the diagnosis. These include the galactomanan antigen test for *Aspergillus* spp and the cryptococcal antigen test, although it should be remembered that both false positives and false negatives can occur. Polymerase chain reaction testing could also be a useful tool in the future.

## Conclusion

The current increase in cases of severe fungal infections is of concern, given the limited antifungal agents available and the potential difficulty in making an accurate diagnosis. Knowledge of the nature and epidemiology of fungal infections is an important aid to their diagnosis. Molecular tests (eg, polymerase

chain reaction) have potential, but culture remains the gold standard. As medical treatment of immunocompromised patients continues to improve, the surviving population will be at risk for fungal infections. The use of antifungal drugs for prophylaxis means that culture will remain essential for the determination of drug-resistant antifungal strains.

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