Systemic fungal infections

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Abstract

Most systemic fungal infections are caused by opportunistic fungal pathogens in immunocompromised hosts. However, invasive disease can occur in immunocompetent individuals if the exposure dose is high or with primary (dimorphic) fungal pathogens (causes of endemic mycoses include *Blastomyces*, *Coccidioides*, *Histoplasma*, *Paracoccidioides* and *Talaromyces* spp.). Systemic fungal infections usually originate either in the lungs (*Aspergillus*, *Cryptococcus*, *Mucorales* spp., as a result of inhalation) or from endogenous flora (*Candida* spp. as a result of infected lines or leakage from the gastrointestinal tract), and may spread to many other organs. Systemic fungal infections are medical emergencies and have high mortality rates, especially if appropriate therapy is delayed. At the same time, fungal infections are a diagnostic challenge, and a combination of investigations is often required to confirm the diagnosis. Therefore, antifungal treatment is often initiated when infection is suspected clinically, and diagnostic tests should be used as part of antifungal stewardship to guide the cessation of unnecessary therapy. Antifungal resistance is an emerging problem, and all isolates should be identified and tested for their sensitivity profile.

Keywords Aspergillosis; candidosis (candidiasis); cryptococcosis; dimorphic fungi; MRCP; mucormycosis; *Pneumocystis* pneumonia

Key points

- Most systemic fungal infections are caused by opportunistic fungal pathogens in immunocompromised hosts
- In immunocompetent individuals, invasive disease can occur if exposure is high or infection is caused by primary (endemic) pathogens
- Systemic fungal infections usually originate either in the lungs as a result of inhalation or from endogenous flora (*Candida* spp. as a result of infected lines or leakage from the gastrointestinal tract), and can spread to many other organs
- Systemic fungal infections are medical emergencies and have a high mortality, especially if appropriate therapy is delayed
- Systemic fungal infections are a diagnostic challenge, and a combination of investigations is required to confirm the diagnosis. Antifungal treatment is often initiated when infection is suspected clinically, and diagnostic tests should be used to stop unnecessary therapy

Introduction

Fungal infections in humans can be broadly divided into superficial infections of the skin and mucosae, and deep, systemic or disseminated infections such as candidaemia and invasive aspergillosis.[1,2] Superficial infections do not necessarily require systemic predisposing factors, whereas deep and systemic infections are more commonly seen in immunocompromised hosts.

Systemic fungal infections usually originate in the lungs (aspergillosis and other mould infections as a result of inhalation) or from endogenous flora (candidaemia as a result of infected lines or leakage from the gastrointestinal tract), and can spread to many other organs. Systemic fungal infections are medical emergencies and have high mortality rates, especially if appropriate therapy is delayed. In immunocompromised hosts, antifungal therapy is only partially successful, and immunotherapeutic adjunctive therapies such as colony-stimulating factors are needed to improve outcomes.[3] Antifungal resistance is an emerging problem, and azole resistance among *Candida* and *Aspergillus* species is one of the greatest challenges to clinical success, followed by echinocandin and multidrug resistance among some *Candida* species, especially *Candida glabrata* and *Candida auris*.[4]

The organisms that cause systemic fungal infection can be divided into two distinct groups: the opportunists, for example *Aspergillus* and *Candida* spp., and the true pathogenic (dimorphic) fungi that are able to invade and develop in the tissues of a normal host with no recognizable predisposition.[5]

Compared with dimorphic fungi, opportunistic fungi consist of less virulent and less well-adapted organisms that are only able to invade the tissues of an immunocompromised host. Although new species of fungi are regularly being identified as causes of disease in immunocompromised patients, five diseases still account for most reported invasive infections: aspergillosis, candidosis (candidiasis), cryptococcosis, mucormycosis and pneumocystosis.

Opportunistic fungal infections occur in individuals who are immunosuppressed as a result of an underlying illness or their treatment. In most cases, infection results in significant disease. Resolution of the infection does not confer protection, and reinfection or reactivation can occur if host resistance becomes impaired. Many opportunistic fungi are ubiquitous worldwide, being found in soil, on decomposing organic matter and in the air. These infections are associated with high mortality rates, but estimates of their incidence are thought to be conservative in comparison with their true magnitude, because many cases go undiagnosed or unreported.

In contrast, true pathogenic fungi have a restricted geographical distribution. In many instances, infections caused

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by these fungi are asymptomatic or mild, and of short duration. Individuals who recover from these infections can enjoy marked and lasting resistance to reinfection, while the few patients with chronic or residual disease often have serious underlying illness. The principal diseases are blastomycosis, coccidioidomycosis, histoplasmosis and paracoccidioidomycosis.

Candidosis

Yeasts belonging to the genus *Candida* can cause acute or chronic deep-seated infection. Infections are seen in surgical, debilitated or immunocompromised patients and can be confined to one organ or become systemic. In the intensive care setting, candidaemia can be associated with infected central venous catheters. Intravenous drug users are also at a higher risk of candidaemia. The predominant species are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis and C. krusei*. *Candida auris* is a globally emerging pathogen, primarily in the critical care setting.

Acute disseminated candidosis: disseminated infection occurs more frequently than single-organ infection. Infection should be suspected in patients with one or more predisposing factors who develop a fever unresponsive to broad-spectrum antibiotics. Fundoscopy should be performed in non-neutropenic patients with candidaemia to exclude endophthalmitis and chorioretinitis. Characteristic macronodular skin lesions occur in up to 10% of patients. The disease can involve any organ, and infection typically extends to three or four organs, most commonly the kidneys (80%), heart, gastrointestinal tract and central nervous system (CNS). In this setting, removal of intravenous devices, along with specific antifungal therapy, is essential for cure.

Chronic disseminated candidosis: previously known as hepatosplenic candidosis, this frequently involves the liver and spleen. It is seen in leukaemic patients whose neutrophil counts have recovered. Infection is often by translocation from the gastrointestinal tract.

Other *Candida* infections: *Candida* infections of the renal tract can follow disseminated candidosis or can complicate instrumentation of the urinary tract. Rarely, fungal balls can form within the renal pelvis, leading to obstructive uropathy. Meningitis and brain abscesses can occur after candidaemia, and are sometimes associated with neurosurgical procedures. *Candida* can also affect the heart, presenting as endocarditis, often with large vegetations. Myocarditis and pericarditis are also described. Bone and joint infections occurs and can mimic bacterial disease.

Investigations

Microscopy and culture of normally sterile body fluids reveals yeast cells with or without hyphal production, and growth of yeast colonies after 24–48 hours. Isolates should be identified to species level, and antifungal susceptibility testing is advisable. Histopathology provides definitive evidence of infection.

Candidaemia is a diagnostic challenge. The concentration of *Candida* in the blood during candidaemia is low, and up to 65% of positive blood cultures have <1 colony-forming unit per millilitre. In addition, *Candida* rapidly forms biofilms and is released into the bloodstream only intermittently and transiently. The mean sensitivity of blood culture is <40% (autopsy-proven cases), and 60 ml (three sets of 2 × 10 ml samples) of blood must be collected within a 30-minute period to achieve sensitivity of 50–75%. The low concentration and intermittent presence of *Candida* is also a major challenge for the polymerase chain reaction (PCR).

Serology is useful in immunocompetent individuals. High or rising antibody titres (1:8 or greater) are considered indicative of active infection, and a raised antibody titre is the single most consistent finding in *Candida* endocarditis. Quantitative determination of anti-*Candida* mannan immunoglobulin G (Bio-Rad Platelia™ *Candida* antibody) is useful in various manifestations. Detection of mannoprotein antigen (Bio-Rad Platelia™ *Candida* antigen) by enzyme-linked immunosorbent assay (ELISA) is useful in some cases of invasive disease. Detection of β-1,3-D-glucan in serum or sterile body fluids is a sensitive but non-specific indicator of fungal infection. Failure to detect β-1,3-D-glucan has a high negative predictive value and can be used in antifungal stewardship to guide cessation of therapy.

Treatment

Initiation of therapy for systemic fungal infections is empirical and should be based on local epidemiology. Targeted therapy should be guided by the species of yeast isolated and, where available, antifungal susceptibility test results.

Candidaemia: documented candidaemia should always be treated, and lines should be removed or replaced where possible. In neutropenic patients with severe disease, an echinocandin or a lipid formulation of amphotericin B is recommended. For less severely ill patients, and for candidaemia in non-neutropenic patients who have not had prior azole exposure, fluconazole (800 mg loading dose followed by 400 mg daily) is often effective. Treatment should be continued for 14 days after the first negative blood culture. If lines cannot be removed, an echinocandin or liposomal amphotericin B is recommended.

Urinary tract infections: urinary colonization with *Candida* is common and does not normally require antifungal therapy. When ascending infection is suspected, fluconazole is the treatment of choice as it excreted unchanged in the urine (200–400 mg/day, for 2 weeks). For fluconazole-resistant species, flucytosine alone for 2 weeks or amphotericin B with or without flucytosine is recommended. Fungal balls should be removed surgically, with antifungal treatment as above.

***Candida* endophthalmitis:** fluconazole reaches high concentrations in the vitreous humour so is useful in *Candida* endophthalmitis (800 mg loading dose followed by 400 mg daily).

Voriconazole (400 mg/twice a day for 24 hours as a loading dose, followed by 200 mg twice daily) or flucytosine (25 mg/kg four times daily) can be used for fluconazole-resistant organisms. For treatment failure, severe endophthalmitis or infections with azole-resistant species, liposomal amphotericin B (3–5 mg/kg per day) plus flucytosine (25 mg/kg four times a day) is recommended. Treatment should be for at least 4–6 weeks, until clinical resolution.

***Candida* CNS infections:** treatment is with liposomal amphotericin B with or without flucytosine. Voriconazole and

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