Systemic fungal infections

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Abstract

Systemic fungal infections have increased in incidence and are associated with significant mortality. The challenges they pose are further compounded by difficulties with early diagnosis and the high cost of the newer antifungal drugs. These include voriconazole, a broad-spectrum triazole. In treatment of invasive aspergillosis, voriconazole was associated with improved survival compared with amphotericin. Posaconazole is similar but with a slightly different spectrum of activity and side effect profile. Caspofungin was the first of a new class of intravenous antifungals, the echinocandins, which have largely superseded amphotericin in treatment of invasive candidiasis.

The management of candidiasis and aspergillosis is discussed in the light of these new agents and advances in susceptibility testing for *Candida* sp. and of diagnostic tests for aspergillosis. Cryptococcal meningitis remains a leading cause of death in HIV-infected patients in Africa and Asia. Initial treatment is with amphotericin plus flucytosine. Patients with high cerebrospinal fluid opening pressure may need serial therapeutic lumbar punctures. Rhinocerebral mucormycosis is a rare but devastating infection in diabetic and neutropenic patients, presenting with orbital swelling, fever and facial pain. The endemic dimorphic fungal infections include histoplasmosis, which is widespread but most common in the Ohio and Mississippi valleys, and penicilliosis in South-East Asia.

Keywords amphotericin; aspergillosis; candidaemia; candidiasis; caspofungin; cryptococcal meningitis; cryptococcosis; fluconazole; histoplasmosis; mucormycosis; posaconazole; voriconazole

What's new?

- Echinocandins have largely replaced amphotericin formulations for the initial treatment of serious *Candida* infections
- For febrile neutropenic and other very immunosuppressed patients, there has been a move away from empirical antifungal therapy towards pre-emptive or very early treatment based on abnormal CT scans and/or molecular diagnostic investigations
- For induction therapy, adding an echinocandin to voriconazole may benefit some patients with invasive aspergillosis

The incidence of systemic fungal infections has increased over the last decades as a consequence of immunosuppression by chemotherapy, transplantation and HIV infection, and the prolonged survival of critically ill patients as a result of advances in intensive care medicine. Most systemic fungal infections are associated with significant mortality. The challenges they pose are further compounded by difficulties with early diagnosis and the high cost of the newer antifungal drugs.

Unlike other common fungal pathogens, *Candida* spp. are part of the normal human flora and are commonly found on the skin and throughout the gastrointestinal tract. *Aspergillus, Cryptococcus* and the agents of mucormycosis are essentially environmental saprophytes that are accidental pathogens, having evolved factors that allow them to cause human infection. The endemic dimorphic fungi grow as saprophytic moulds in the environment, but transform at 37°C into parasitic yeast forms well adapted for survival in mammalian hosts. *Candida* invades through the gastrointestinal tract and skin, but the other fungal pathogens are thought to be acquired by inhalation. Defective neutrophil numbers or function predispose to invasive candidiasis, aspergillosis and mucormycosis, whereas defects in cell-mediated immunity are more important risk factors for cryptococcosis and endemic dimorphic fungi. *Pneumocystis carinii* infection is discussed in 'HIV and the lung' (*MEDICINE* 2013; **41**(8): 435–441).

Newer antifungal classes

***Extended spectrum triazoles*:** voriconazole is a broad-spectrum triazole available in intravenous and oral preparations. In a trial of treatment for invasive aspergillosis, voriconazole was compared to starting therapy with amphotericin deoxycholate (1 mg/kg/day for a mean 10 days, usually followed by itraconazole or lipid formulation amphotericin). The voriconazole arm was associated with higher survival at 12 weeks (71% vs 58 %), and fewer drug-related adverse events.[1] Voriconazole is associated with visual disturbance in about 30% of patients. However, this is transient and resolves without intervention in all cases. Other adverse effects include photosensitivity, rash and liver function abnormalities. Wide inter-patient pharmacokinetic variability means therapeutic drug monitoring is recommended. Posaconazole is a similar broad-spectrum triazole with a slightly different adverse effect profile and fewer drug–drug interactions than voriconazole. The current preparation requires a high-fat meal for adequate absorption. Posaconazole is used mainly for prophylaxis in patients with haematological malignancy, with monitoring of serum concentrations.[2]

***Echinocandins*:** caspofungin was the first of a new class of intravenous antifungals, the echinocandins, that target glucan synthesis in the fungal cell wall. It is active against *Candida* and *Aspergillus*. In a trial comparing caspofungin with amphotericin in candidaemia and invasive candidiasis, caspofungin was as effective (similar relapse and mortality rates) and associated with

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fewer adverse events than amphotericin.[3] Anidulafungin and micafungin are similar.

Candidiasis

In addition to neutropenia, risk factors for candidaemia and disseminated candidiasis include prolonged administration of antibiotics, central venous lines, parenteral nutrition, surgery of the gastrointestinal tract, and colonization by *Candida* of sites such as skin, sputum and urine. Disseminated disease is unlikely in the absence of such colonization. Candidaemia is often associated with high fever and a sepsis-like syndrome. The attributable mortality is probably in the range of 30–40%.

Management

If possible, in addition to antifungal therapy, all existing central lines should be removed. Catheter-related infections in immunocompetent patients may resolve rapidly. Immunosuppressed

Suggested antifungal therapy for selected systemic fungal infections

Candidaemia and acute disseminated candidosis	Echinocandin[a] *or* Fluconazole, 800 mg loading then 400–800 mg/day *plus* Remove existing central lines • Lipid formulation AmB[c] or AmB 0.7 mg/kg/day[d] are alternatives to echinocandins if intolerant	• Factors favouring initial echinocandin – patient unstable, neutropenic, previous azole therapy, unknown *Candida* species • Factors favouring initial fluconazole – patient stable, no previous azoles, known *C. parapsilosis*, or *C. albicans*, *C. tropicalis* • *C. krusei* – echinocandin • *C. glabrata* – echinocandin preferred	• Minimum 2 weeks after last positive blood culture and resolution of symptoms and signs • End-organ involvement requires longer courses • Switch to oral fluconazole if possible, based on speciation and local epidemiology, and susceptibility, when available. If fluconazole resistant, use echinocandin or voriconazole[b]. • Use AmB only pending speciation and susceptibility, to avoid nephrotoxicity
Invasive aspergillosis	Voriconazole[b]	• Watch for drug interactions, monitor liver function; 20% Oriental patients are poor metabolizers – check serum concentration	• Overall response rate at 12 weeks with voriconazole still only 53% • Combination of azole and echinocandin supported by animal models, cohort, and some controlled trial data
	or Initial combination voriconazole and echinocandin *or*	• With step down to voriconazole alone	
	Lipid formulation AmB[c]	• Given dose and duration required, conventional AmB best avoided	• Adjuvant surgery sometimes indicated in patients with focal disease or lesions impinging on great vessels or major airways
	alternative caspofungin[a]	• Data only in second-line treatment	
Cryptococcal meningitis	AmB, 0.7–1 mg/kg/day[d], plus flucytosine, 25 mg/kg 6-hrly, for 2 weeks, then fluconazole, 400 mg/day for 8 weeks, then 200 mg/day thereafter until immune restoration (CD4 count>100 cells/μL) In non HIV-associated infection, continue fluconazole for 6–12 months depending on immune status		• Serial lumbar puncture to reduce intracranial pressure is recommended when opening pressure high (>25–30 cm)

[a] Caspofungin, dose is 70 mg IV on day 1, 50 mg IV daily thereafter (70 mg/day if > 80 kg). Avoid if severe hepatic insufficiency. Moderate hepatic insufficiency maintenance dose is 35 mg/day; or anidulafungin 200 mg loading, then 100 mg/day; or micafungin 100 mg/day.
[b] Voriconazole IV dose is 6 mg/kg 12-hourly on day 1, 4 mg/kg 12-hourly thereafter. Oral bioavailability is 96% so switch to oral as soon as possible. Avoid IV formulation if creatinine clearance <50 ml/minute due to accumulation of IV vehicle. Oral dose: 400 mg 12-hourly on day 1 (if not previously loaded), 200 mg 12-hourly thereafter, at least 1 hour before or after food. Halve maintenance dose in mild/moderate hepatic cirrhosis. Check serum concentration after 4–7 days of therapy.
[c] i.e. Liposomal amphotericin, 3–5 mg/kg/day. Optimal doses for lipid formulations are not defined.
[d] AmB – amphotericin. There are no firm data supporting the need for dose escalation or a test dose. Commence with full dose but start initial infusion slowly. Amphotericin nephrotoxicity may be reduced by administration of potassium chloride (0.15%) and sodium chloride (0.9%) IV infusion, 1 litre/day over 2–4 hours, before amphotericin. Oral potassium and magnesium supplements are recommended with monitoring of serum concentrations. Acute toxicities may be reduced by longer duration of infusion. Can switch to lipid formulation if nephrotoxicity occurs.

Table 1