Opportunistic fungal lung infections

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Abstract

Fungi are ubiquitous in the environment. Differentiating between invasive disease and harmless colonization is frequently difficult, but almost all endemic fungi causing significant lung disease occur in immunocompromised hosts. The particular fungal species involved, and the clinical manifestations that result, are dictated by the nature and degree of the immunocompromised state. Some non-endemic fungi cause significant disease in the immunocompetent host or reactivate in patients that become immunocompromised after many years of asymptomatic latent infection.

Keywords aspergillosis; blastomycosis; candidiasis; coccidioidomycosis; cryptococcosis; fungal lung infections; histoplasmosis; paracoccidioidomycosis; pneumocystis; zygomycosis

Moulds and yeasts are commonly isolated from soil, plant and vegetable matter and the general environment, including hospitals. Human disease is caused by inhalation of airborne spores and can result in life-threatening illness, particularly in immunosupressed individuals. The incidence of many fungal lung infections has increased over the past few decades due to widespread use of immunosupressive chemotherapy and the increasing incidence of HIV infection. Table 1 summarizes the most common fungi causing pulmonary disease in humans.

Aspergillosis

Allergic broncho-pulmonary aspergillosis

This non-invasive form of disease is essentially an hypersensitivity reaction against the presence of spores of the fungus colonising the respiratory tract. It can occur in all patients but is found more frequently in those with cystic fibrosis, asthma and bronchiectasis. ABPA presents with dyspnoea and wheeze and pulmonary infiltrates are noted on chest X-ray. Patients may have eosinophilia, raised IgE and presence of serum Aspergillus-specific antibodies. Oral steroids are the usual treatment (inhaled steroids have no effect). Itraconazole may reduce recurrences.

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Invasive aspergillosis

This is the most common form and can be subdivided into three forms.

Angio-invasive

Risk factors for angio-invasive pulmonary aspergillosis include:

- neutropenia (e.g. < 0.5 cells/cm^3 for > 10 days)
- solid organ and blood/bone marrow transplantation
- prolonged/high dose corticosteroid therapy (e.g. 0.5–1.0mg/kg/day for 10 days or more)
- haematological malignancy
- cytotoxic chemotherapy
- advanced HIV infection
- chronic granulomatous disease (CGD).

Early diagnosis is difficult since there are no characteristic clinical features and fever may be absent, particularly if the patient is receiving steroids. The diagnosis should be considered in any neutropenic patient with risk factors who has upper or lower respiratory tract symptoms and/or a febrile illness, unresponsive to broad spectrum antibiotics.

Diagnosis of invasive aspergillosis is difficult. Culture of broncho-alveolar lavage (BAL) has an approximate sensitivity of 50% and definitive diagnosis requires biopsy (e.g. transthoracic), which demonstrates histological evidence of fungal invasion into tissue, or recovery of mould on culture (Figure 1). The chest CT is a key investigation. Multiple infiltrates or discrete nodules may be a feature of early disease. A hazy zone of ground glass shadowing may develop around nodules (the 'halo sign'), particularly in the neutropenic patient. If untreated, these lesions may progress with cavitation (the 'air crescent sign'), especially as neutropenia recovers. However, the administration of empirical treatment means that these classic radiological features are relatively rare nowadays. Detection and serial monitoring of galactomannan (a polysaccharide cell wall component) is sometimes used to aid diagnosis and assess response to treatment, but its precise role is uncertain, particularly in non-neutropenic patients. There are also a number of polymerase chain reaction (PCR)-based molecular tests available, but they are largely unstandardized and interpretation is also difficult.

Acute invasive aspergillosis is rapidly fatal and treatment must be commenced promptly. In practice, antifungal therapy is often started empirically in neutropenic patients that remain unresponsive to broad spectrum antibiotics. Treatment with three different classes of antifungals is effective: the polyenes (e.g. amphotericin B), azoles (e.g. itraconazole and voriconazole) and the echinocandins (e.g. caspofungin and anidulafungin). Improvement in neutropenia and reduction of immunosuppression increases the success rate of treatment.

Airway-invasive

This comprises 10–34% of cases of invasive pulmonary aspergillosis and more frequently occurs in those with HIV or who have undergone organ transplant (however 25% of cases occur in the immunocompetent). It is characterized radiologically by bronchocentric lesions representing haemorrhage/consolidation. Histology shows aspergillus organisms and a neutrophil infiltrate. Accumulation of necrotic and inflammatory material can result in airway obstruction.

The most common fungi which cause pulmonary disease in humans

	Disease (organism)	Risk factors	Treatment
Endemic	Aspergillosis (*Aspergillus fumigatus* and others)	Prolonged neutropenia (<0.5 cells/cm^3 for >10 days) Solid organ transplantation Haematopoetic stem cell transplantation Prolonged corticosteroid therapy Cytotoxic chemotherapy HIV/AIDS (CD4 count <200 cells/mm^3) Chronic granulomatous disease (CGD)	Amphotericin B Voriconazole Caspofungin Itraconazole Posaconazole
	Pneumocystis pneumonia (*Pneumocystis jiroveci)*	HIV/AIDS (CD4 count <200 cells/mm^3) Organ transplantation Haematological maligancies Cytotoxic chemotherapy Prolonged steroid therapy	Trimethoprim – Sulphamethoxazole Clindamycin/Primaquine Atovaquone Pentamidine Primary and secondary prophylaxis for HIV positive patients with CD4 <200cells/mm^3
	Cryptococcosis *(Crytococcus neoformans)*		Fluconazole Amphotericin B Caspofungin Anidulafungin
	Candidiasis (*Candida albicans* and others)	Neutropenia (<0.5 cells/cm^3 for >10 days) Central venous catheters Parenteral nutrition Major GI surgery Severe burns Broad spectrum antibiotic exposure	Fluconazole/Voriconazole Amphotericin B Echinocandins
	Zygomycosis (*Absidia* spp., *Rhizopus* spp., *Rhizomucor* spp.)	Severe burns Diabetes mellitus Haematological malignancies HIV/AIDS	Surgical debridement Amphotericin B
Non-endemic	Histoplasmosis *(Histoplasma capsulatum)*	Relevant travel or residence in endemic area Occupational or recreational risk HIV/AIDS (with CD4 count <200cells/mm^3) Lymphoma Solid organ transplantation	Mild disease: no treatment or itraconazole Moderate disease: itraconazole Severe or disseminated disease: amphotericin B
	Coccidioidomycosis *(Coccidioides immitis)*		Mild-to-moderate disease: itraconazole, fluconazole Severe or disseminated disease: amphotericin B followed by itraconazole
	Blastomycosis *(Blastomyces dermatitidis)*		Itraconazole Amphotericin B
	Paracoccidioidomycosis *(Paracoccidioides brasiliensis)*		Itraconazole Ketoconazole

Table 1

Chronic necrotizing aspergillosis

This semi-invasive form usually occurs in those with milder forms of immunosuppression, including alcoholism, diabetes mellitus, corticosteroid therapy, CGD and underlying lung disease (e.g. chronic obstructive pulmonary disease). Symptoms include fever and productive cough with haemoptysis for weeks or months. The chest X-ray shows cavitating lesions with surrounding consolidation and differentiation from malignancy