Fungal Lung Infections

See also separate Systemic Mycoses article.

Fungi may cause lung disease through direct infection of pulmonary tissue, through infection of pulmonary air spaces/lung cavities, or through their ability to trigger an immunological reaction when fungal material is inhaled. The latter mechanism is involved in cases of allergic bronchopulmonary aspergillosis, aspergillus-induced asthma and extrinsic allergic alveolitis due to fungi (eg, maltworker's lung, farmer's lung). This article will concentrate on those diseases caused by direct fungal infection of the lung (fungal pneumonias).

With the exception of aspergillosis, these infections are usually not present to any significant degree in immunocompetent residents of the UK. They are more likely to affect those who have travelled abroad to areas where they are endemic, or arise as opportunistic infections in patients who are immunocompromised as a result of oncological treatment, due to immunomodulation following solid organ transplantation, or HIV infection. Pulmonary infection occurs after inhalation of spores/conidia, or by the reactivation of latent infection. Haematogenous dissemination of fungal infection leading to a systemic mycosis tends to occur chiefly in immunocompromised patients.

Endemic fungal pneumonia pathogens

- *Histoplasma capsulatum* causing histoplasmosis.
- *Coccidioides immitis* causing coccidioidomycosis.
- *Blastomyces dermatitidis* causing blastomycosis.
- *Paracoccidioides brasiliensis* causing paracoccidioidomycosis.

Opportunistic fungal pneumonia pathogens

- *Candida* spp. causing candidiasis.
- *Aspergillus* spp. causing aspergillosis.
- *Mucor* spp. causing mucormycosis.
- *Cryptococcus neoformans* causing cryptococcosis.

Epidemiology and distribution

In the UK the endemic fungi are exceedingly rare and occur only in returning travellers. The endemic fungi are distributed in the Americas in the valleys of the Mississippi and Ohio rivers (histoplasmosis and blastomycosis), the Southwestern United States and Northern Mexico (coccidioidomycosis) and Central and South America (paracoccidioidomycosis). In Africa histoplasmosis is found in the equatorial regions.

The opportunistic pathogens are ubiquitously distributed and may cause disease in those with immunosuppression. There are few figures for their incidence in the population at large in the UK. One review estimated that 15-18.3% of HIV-infected patients admitted to hospital will suffer a nosocomial pulmonary infection. Of these, a small but significant proportion (around 5-10%) will be due to opportunistic fungal pneumonias.

Risk factors

- Travel to an area where fungal pneumonia pathogens are endemic (see above).
- Regular exposure to bird, bat or rodent droppings in endemic areas.
- Any cause of immunocompromise, for opportunistic infections.
- Endemic fungal infections seem to be more common in men than in women, as oestrogen is thought to exert an inhibitory effect on the growth cycle of fungi.

Presentation

Symptoms

- Fever - persistent fever in the immunocompromised should always raise the suspicion of opportunistic pulmonary or systemic fungal infection.
- Cough which is usually dry.
- Chest discomfort (dull and poorly localised or focal and pleuritic).
- Progressive dyspnoea, particularly on exertion.
- Haemoptysis is a relatively common symptom of invasive aspergillosis/mucormycosis.
- Endemic mycoses may cause lymphadenopathy and obstruction of large airways through pressure effects.
- Endemic mycoses have a predilection for causing symptoms of 'rheumatological' syndromes - eg, arthritis/arthralgia, erythema multiforme, erythema nodosum, pericarditis.
- Enigmatic mycoses may also cause symptoms by haematogenous dissemination to skin, brain/meninges, bone and joints and full-blown sepsis.
Infections with Aspergillus and Candida spp. and other opportunistic fungi may cause symptoms of hypersensitivity reactions - eg, allergic asthma, allergic bronchopulmonary aspergillosis, extrinsic allergic alveolitis.

Symptoms due to other sites of extrapulmonary involvement (particularly in the immunocompromised) - eg, meningoencephalitis/brain abscess, skin lesions, kidneys, liver, muscles, endophthalmitis, nasal passages and sinuses, systemic sepsis affecting blood and bone marrow.

**Signs**
- Fever.
- Tachycardia.
- Tachypnoea.
- Wheeze.
- Signs of focal pulmonary consolidation - eg, reduced expansion, dullness to percussion and bronchial breathing.
- Signs of bronchial obstruction if thoracic lymphadenopathy is significant.
- Signs of pleural effusion.
- Seek signs of extrapulmonary involvement - eg, skin lesions, signs of meningism, joint pain or swelling, retinal lesions on ophthalmoscopy.

**Differential diagnosis**
- Bacterial, atypical or viral pneumonia.
- Aspiration pneumonia.
- Pneumocystis jirovecii pneumonia.
- Eosinophilic pneumonia.
- Hypersensitivity reaction caused by fungal antigen - eg, allergic asthma, allergic bronchopulmonary aspergillosis, extrinsic allergic alveolitis.
- Chemical pneumonitides - eg, chemical worker's lung.
- Löfffer's disease (marked eosinophilia and benign, transient, migratory or recurrent pulmonary infiltrates with minimal constitutional upset).
- Adult respiratory distress syndrome.
- Causes of pulmonary fibrosis.
- Tuberculosis (TB).
- Pulmonary oedema.
- Helminthic infections.
The diagnosis of invasive pulmonary aspergillosis, histoplasmosis and blastomycosis, has improved with the use of easily performed antigen detection systems in serum and bronchoalveolar lavage fluid.

- **FBC:**
  - Raised WCC in immunocompetent patients.
  - Eosinophilia may predominate.
  - Progressive neutropenia or leukopenia in an unwell immunocompromised host suggests systemic candidiasis/aspergillosis.

- **CXR:**
  - May show patchy infiltration, nodules, consolidation, cavitation or pleural effusion.
  - Pronounced mediastinal lymphadenopathy - some endemic fungal pneumonias.
  - Miliary-pattern pulmonary infiltration in extensive disease.

- **Blood cultures** (may require specific fungal culture bottles).
- **Urine/sputum/invasive catheter cultures** (potassium hydroxide staining can be used for sputum but may detect colonising rather than invasive species).

- **CT/MRI scanning of thorax:**
  - Early chest CT scan in immunocompromised patients suspected of having invasive fungal pneumonia can help identify and treat disease early, leading to an improved outcome. \[4\]
  - Halo sign: ground-glass opacity surrounding a pulmonary nodule or mass. Most commonly associated with invasive pulmonary aspergillosis. \[5\]
  - Reversed halo sign: focal rounded area of ground-glass opacity surrounded by a crescent or complete ring of consolidation. Most often associated with pulmonary mucormycosis. \[5\]

- **Bronchoscopy** - to obtain bronchoalveolar lavage/transbronchial biopsy specimens for fungal staining and culture.
- **Transthoracic fine-needle biopsy** - usually radiologically guided to biopsy nodules for staining/histology/culture.
- **Open lung biopsy** - used occasionally.
- **Lumbar puncture** in cases of suspected meningeal involvement.
- **Bone marrow aspiration/biopsy** in immunocompromised patients with suspected disseminated disease.
- **Biopsy of any skin lesions.**
- **Joint aspiration** if joint effusion.
- There are specific antigen-detection tests, PCR techniques and ELISA assays and serial serology available to detect specific pathogens - seek microbiological advice on the most appropriate test in the clinical context.

It is also important to think of why the patient might be immunosuppressed. There are other illnesses that may explain the reason for immunosuppression - eg, previously unknown TB, diabetes and HIV. Thus history, examination and investigations also need to be tailored to try to determine the cause of immunosuppression. TB should be particularly sought after, as it is an important differential diagnosis.

**Management** \[6\]

- In immunocompromised patients, factors that are contributing to the illness, such as chemotherapy, steroids, indwelling venous catheters, etc, need to be addressed where possible.
- Immunocompromised patients may benefit from the use of colony-stimulating factors to boost immune cell production.
- The new azoles (eg, voriconazole) are most often used. Amphotericin is now used less often, and when used is often given as lipid formulation to decrease toxicity. \[3\]

**British National Formulary recommendations:** \[7\]

- Amphotericin or caspofungin is used for the empirical treatment of serious fungal infections.
- Aspergillosis: voriconazole is the treatment of choice; liposomal amphotericin is an alternative first-line treatment when voriconazole cannot be used. Caspofungin, itraconazole or posaconazole can be used in patients who are refractory to, or intolerant of, voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis.
- Invasive or disseminated candidiasis: an echinocandin (eg, anidulafungin, caspofungin and micafungin) can be used. Fluconazole is an alternative for clinically stable patients. Amphotericin is an alternative when an echinocandin or fluconazole cannot be used. In refractory cases, flucytosine can be used with intravenous amphotericin.
- Cryptococcosis is usually treated with amphotericin and flucytosine, followed by fluconazole for eight weeks or until cultures are negative.
- Histoplasmosis: itraconazole can be used for immunocompetent patients. Amphotericin is preferred for patients with fulminant or severe infections. Following successful treatment, itraconazole can be used for prophylaxis against relapse until immunity recovers.

- Cardiothoracic surgery may be needed to resect infiltrated/necrotic pulmonary tissue as an adjunct to antifungal therapy, or to treat some complications such as massive haemoptysis and pulmonary abscesses.

**Complications**
Dissemination of fungal infection to other sites such as the brain, meninges, skin, liver, kidneys, adrenal glands, heart, eyes, spleen.
- Progressive respiratory failure.
- Systemic fungaemia and septic shock.
- Blood vessel invasion causing massive haemoptysis, pulmonary infarction, myocardial infarction, cerebral infarction/embolism.
- Associated rheumatological complex/pericarditis with endemic fungal pneumonias.
- Lung cavitation.
- Development of mycetoma in a lung cavity.
- Local pulmonary damage causing bronchopleural or tracheo-oesophageal fistulas, mediastinal fibrosis, calcification in pulmonary tree, chronic pulmonary symptoms.
- Immunological reaction to fungal antigens.
- Fungal endocarditis.

**Prognosis**

- This is highly variable in cases of opportunistic infection, depending on the cause and degree of immunocompromise, comorbidities and speed of recognition of pulmonary fungal infection.
- Overall mortality is relatively high (probably >50% in immunocompromised patients).
- Mortality for untreated disseminated histoplasmosis is ~80%, reduced to ~25% with treatment.[8]
- Aspergillosis and mucormycosis have mortality rates of 50-85% in transplant recipients, especially after bone marrow transplantation.[9]
- Coccidioidomycosis has a mortality rate as high as 70% in patients with AIDS.[1]

**Prevention**

- HIV patients are routinely treated with prophylactic antifungal drugs to try to avoid infection with opportunistic fungal pathogens, particularly Cryptococcus neoformans.
- Transplant patients may also benefit from prophylactic antifungal agents.[10]
- Fluconazole has shown some benefits as prophylaxis against invasive fungal infections in transplant patients.[10]
- Patients likely to have prolonged neutropenia should avoid activities that increase exposure to environmental fungal spores, such as gardening or working with potted plants and fresh flowers, cleaning, building work and handling uncooked vegetables.
Further reading & references

- British National Formulary (BNF); NICE Evidence Services (UK access only)

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