Opportunistic and fungal infections of the lung

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Abstract

Opportunistic infections are a major cause of morbidity and mortality in severely immunocompromised patients, such as those receiving chemotherapy or with haematological malignancy, aplastic anaemia or HIV infection, or recipients of solid-organ or stem cell transplants. In addition, the increasing use of biological therapies will result in more patients at risk of opportunistic infections, albeit to a lesser degree than classic causes of immunocompromise. The type and degree of immune defect dictates the profile of potential opportunistic pathogens; T-cell mediated defects increase the risk of viral (cytomegalovirus and respiratory viruses) and *Pneumocystis jirovecii* infections, whereas neutrophil defects are associated with bacterial pneumonia and invasive aspergillosis. However, patients often have combinations of immune defects and a wide range of other opportunistic infections can cause pneumonia. The radiological pattern of disease (best assessed by CT scan) and speed of onset also help identify the likely pathogen(s), which can then be supported by targeted investigation including early use of bronchoscopy in selected patients. Rapid and expert clinical assessment can identify the most likely pathogens, which can then be treated aggressively and so provide the best opportunity for a positive outcome.

Keywords *Aspergillus*; fungi; immunocompromised host; opportunistic infections; pneumonia; viruses

Introduction

Opportunistic infections occur when loss of established innate or adaptive immune responses allow an organism that is normally weakly virulent to cause infection. The type and degree of immune defect dictate the profile of potential opportunistic pathogens (Table 1). Infections commonly encountered in healthy individuals should not be forgotten as they can also cause infection in

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What's new?

- Recognition that prolonged high-dose glucocorticoids (>20 mg/day for more than 21 days) predispose to *Pneumocystis jirovecii* pneumonia (PJP)
- Increasing use of biological agents is associated with specific immune defects that will increase the risk of opportunistic lung infections (e.g. tumour necrosis factor α inhibitors and risk of mycobacterial disease, endemic fungi and *Legionella pneumophila*; anti-CD20 drugs and mycobacterial disease, cytomegalovirus pneumonitis and PJP)
- Early detection of *Aspergillus* using non-culture-based techniques
- Considerable advances in treatments for invasive fungal disease with newer antifungal agents (echinocandins, such as caspofungin, micafungin and anidulafungin, and azoles such as voriconazole and posaconazole)

immunocompromised hosts. Opportunistic lung infections are a major cause of morbidity and mortality for patients immunocompromised because of HIV infection, haematological malignancy, aplastic anaemia or chemotherapy treatment, or who are recipients of solid-organ or stem cell transplants, and also may complicate treatment with the new biological therapies for inflammatory conditions.[1] Expert clinical assessment with early diagnosis and aggressive treatment are required for a positive outcome. The CT scan is more sensitive than the chest radiograph at defining the predominant pattern(s) of lung involvement, and when combined with knowledge of the patient's immune status (loss of T-cell or antibody-mediated immunity, or defects in neutrophil-mediated immunity) can often identify the most likely pathogens. This review provides a concise overview of the most common opportunistic lung infections.

Viral infections

Cytomegalovirus and other herpesviruses

The herpesvirus cytomegalovirus (CMV) is an important cause of lung infection in patients with impaired T-cell-mediated immunity such as transplant recipients. CMV infection is defined as active CMV replication regardless of symptoms or signs, whilst CMV disease is infection associated with evidence of organ-specific disease. CMV infection in immunocompromised patients is usually due to reactivation of latent CMV acquired in early life, but can also be primary infection in previously uninfected individuals, in whom it is often more severe. Pneumonitis is an important complication, and commonly presents with insidious onset of fever, malaise, cough and dyspnoea with hypoxia. Classic features on CT scan are symmetrical peribronchovascular and alveolar infiltrates predominantly affecting the lower lobes, but asymmetric changes, consolidation and effusions are not uncommon.

In suspected CMV infection/disease CMV replication can easily be identified and the viral load determined by polymerase chain reaction (PCR) or CMV pp65 antigen testing of blood or bronchoalveolar lavage fluid (BALF).[2] Evidence of CMV reactivation does not always mean that concurrent lung disease is caused by CMV, and conversely CMV viraemia can occasionally

Type of immune defect according to disease/treatment and range of pathogens commonly associated with infections in patients with this type of immune defect

Immune disorder	Causes	Typical microorganisms
Neutrophil disorders		
Neutropenia	Drugs (chemotherapy, azathioprine, methotrexate, carbimazole, sulphonamides)	Gram-positive bacilli (*Staphylococcus aureus*, streptococci)
	Leukaemia	Gram-negative bacilli
	AIDS	Fungi (*Aspergillus* sp. *Candida* sp., non-*Aspergillus* filamentous fungi)
	Felty's syndrome	
	Aplastic anaemia	
	Early haematopoietic stem cell transplantation (HSCT)	
Neutrophil chemotaxis	Diabetes mellitus	*Staph. aureus*
	Cirrhosis	Streptococci
	Sarcoidosis	*Candida* sp.
	Drugs (glucocorticoids, amphotericin B)	Zygomycosis
Neutrophil phagocytosis	Chronic granulomatous disease	*Staph. aureus*
	Myeloproliferative disorders	*Nocardia* sp.
	Inherited phagocyte defects	Gram-negative bacilli
		Fungi (*Aspergillus* sp. *Candida* sp., non-*Aspergillus* filamentous fungi)
T-cell mediated immunity	AIDS	Herpesviruses,
	Lymphoma	Respiratory viruses
	HSCT	*Pneumocystis jirovecii*
	Solid organ transplantation	Endemic mycoses e.g. *Histoplasma capsulatum*, *Cryptococcus*
	Drugs (T-cell depleting antibodies, glucocorticoids, ciclosporin, tacrolimus)	Parasites (*Strongyloides*, *Toxoplasma*)
		Mycobacteria
		Nocardia
		Legionella pneumophila
B-cell mediated/antibody deficiency	Multiple myeloma	Encapsulated bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*)
	Plasmapheresis	Herpesviruses
	Drugs (anti-B cell therapies)	
	HSCT	
	Chronic lymphocytic leukaemia	
	Lymphoma	
	Multiple myeloma	
Other		
Complement deficiency	Congenital	Encapsulated bacteria (e.g. *Strep. pneumoniae*, *H. influenzae*)
	Acquired (systemic lupus erythematosus, anorexia nervosa)	*Staph. aureus*
Asplenia	Splenectomy	Encapsulated bacteria (e.g. *Strep. pneumoniae*, *H. influenzae*)
	Sickle cell disease	*Staph. aureus*

Table 1

be absent in patients with CMV pneumonitis. CMV pneumonitis is more likely with high-level viraemia, especially if the viral load increased rapidly. CMV pneumonitis can be confirmed by finding inclusion bodies in BALF cells or transbronchial or video-assisted thoracic surgery (VATS) biopsy samples.

First-line treatment of CMV pneumonitis is intravenous ganciclovir or valganciclovir. Second-line treatments include foscarnet and cidovir. CMV immunoglobulin can be used as an adjunct to therapy in immunocompromised individuals. Treatment efficacy is monitored by measuring blood CMV viral load, with treatment usually continued for at least 2 weeks after resolution of viraemia. Other herpesviruses such as herpes simplex, varicella zoster (VZV) and human herpesvirus 6 are rare causes of diffuse pneumonitis similar to CMV in the immunocompromised

336

host.[3] VZV pneumonitis may be associated with the characteristic rash. Ebstein—Barr virus infection can cause lymphoproliferative disorders after solid organ or stem cell transplantation, which present as focal lesions within the lungs.

Respiratory viruses

Lower respiratory tract infections with the respiratory viruses (respiratory syncytial virus, parainfluenza, influenza, adenovirus, metapneumovirus, coronavirus and rhinovirus) are relatively common in immunocompromised patients with defects in T-cell mediated immunity.[4] Respiratory viruses usually cause a bronchiolitis that presents with coryzal symptoms, cough, fever and dyspnoea. In a minority of patients auscultation of the lungs reveals characteristic squeaks. The chest radiograph is often normal or non-specific. CT scans classically demonstrate diffuse 'tree in bud' changes suggestive of small airways inflammation, but can also show ground glass infiltrates. The diagnosis can be confirmed rapidly using nasopharyngeal aspirate (NPA) samples for viral antigen immunofluorescence or PCR for viral nucleic acids.[5] If NPA is negative, immunofluorescence or PCR on bronchoalveolar lavage fluid (BALF) has a higher sensitivity.[5] In the absence of pneumonia, the mortality from respiratory virus infection is relatively low although infection can persist for several weeks. Secondary bacterial infections are common and patients will often require concurrent antibiotics. Specific anti-viral treatment options are listed in Table 2.

Bacteria

Conventional bacterial pathogens

Although the risk of opportunistic infection is high in immuno-compromised patients, the majority of pneumonias are related to the more conventional bacterial pathogens that present similarly to pneumonia in immunocompetent individuals, with fever, respiratory symptoms, focal consolidation and rapid rises in inflammatory markers. The major risk factors are neutropenia, antibody deficiencies and high-dose corticosteroids. The organisms involved are more diverse than those seen in conventional pneumonia and include both Gram-positive (*Streptococcus pneumoniae*, *Staphylococcus aureus*) and Gram-negative (e.g. *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli* and other enteric pathogens) organisms, which require treatment with antibiotics that are effective against a large range of bacteria, including *P. aeruginosa*.

Nocardiosis

Nocardiosis is an uncommon Gram-positive bacterial infection with a high mortality, up to 64% in disseminated disease.[6] There are over 80 *Nocardia* species but those usually involved in human disease are the *Nocardia asteroides* complex. *Nocardia* are found in soil, decaying vegetable matter and stagnant water. Inhalation is the commonest route of entry so pneumonia is the commonest infection. The main risk factors are defects in T-cell mediated immunity (e.g. post-transplantation), prolonged glucocorticoid therapy, malignancy, graft versus host disease (GVHD), diabetes mellitus, chronic granulomatous disease and alveolar proteinosis. *Nocardia* pneumonia usually develops over weeks with cough, haemoptysis, weight loss, fever and night sweats but can be more acute. Common radiological features are patches of dense consolidation or macronodules, frequently pleurally based.

Anti-viral treatments for respiratory viruses

Virus	Treatment
Influenza	Neuraminidase inhibitors (zanamivir or oseltamivir)[a]
	Amantadine
Parainfluenza	Ribavarin[b]
	Intravenous immunoglobulin (IVIG)[b]
Respiratory syncytial virus	Ribavarin
	Palivizumab
Human metapneumovirus	Ribavarin[b]
	IVIG[b]
Adenovirus	Ribavarin[b]
	Cidofovir[b]

[a] Effective at reducing disease severity and duration.
[b] *In vitro* activity present but no recommendations on treatment are currently available due to lack of data.

Table 2

Cavitation and pleural effusions are common. These appearances can be mistaken for metastasis. Local spread to the pericardium and mediastinum, and haematogenous spread to brain, joints and soft tissue occur in about half of patients. The diagnosis can be made rapidly through identification of characteristic beaded, branching Gram-positive and weakly acid-fast filaments on microscopy. Blood and sputum cultures can be positive but require prolonged aerobic culture. Susceptibility to antibiotics varies among the *Nocardia* sp. and treatment with two or three intravenous antibiotics may be necessary initially in immunocompromised individuals.[6] Trimethoprim—sulfamethoxazole is first-line therapy, with carbapenems, amikacin, third-generation cephalosporins, tetracyclines or amoxicillin—clavulanate as alternatives. Duration of treatment is prolonged — up to 12 months in immunocompromised patients and central nervous system (CNS) disease.

Fungal infections

Treatment options for fungal pneumonias are listed in Table 3.

Pneumocystis jirovecii (formerly *P. carinii*)

P. jirovecii pneumonia (PJP) is the most common AIDS-defining illness (CD4 counts <200 cells/mm^3) but is also important in non-HIV immunocompromised patients with defects in T-cell mediated immunity or who are taking prolonged high-dose systemic glucocorticoids. Clinical presentation is classically insidious with slowly increasing dyspnoea, dry cough and hypoxaemia with few physical or radiologic findings, but can be fulminant.[7] Exercise-induced oxygen desaturation is a sensitive marker. The chest radiograph features are diffuse, bilateral, interstitial infiltrates but can be normal, whereas high-resolution CT scan is much more sensitive and often shows extensive ground glass opacities with an apical distribution and peripheral sparing. Pneumatocoeles are not uncommon, and chronic infection can lead to bizarre-looking cystic changes. PJP cannot be cultured and diagnosis requires identification of the organism in induced sputum or BALF by microscopy with Giemsa and Grocott stains. Immunofluorescence and PCR

Anti-fungal treatment choices

Fungal pathogen	Treatment
Aspergillus species	*First-line:* Voriconazole Lipid formulation of amphotericin *Second-line:* Posaconazole Itraconazole Caspofungin Anidulafungin
Pneumocystis jirovecii	*First line:* Trimethoprim−sulphamethoxazole *Second-line:* Clindamycin plus primaquine Atovaquone Pentamidine Trimethoprim plus dapsone
Cryptococcus neoformans	*Induction therapy:* Liposomal amphotericin plus flucytosine *Consolidation and maintenance therapy:* Fluconazole *Second line:* Posaconazole Voriconazole
Candida species	*First line:* Fluconazole (*C. albicans*) Caspofungin (*C. glabrata* and *C. krusei*) *Second line:* Voriconazole Itraconazole Micafungin Amphotericin
Non-*Aspergillus* filamentous fungi (eg. *Fusarium*, *Zygomycetes*, *Scedosporium*, *Penicillium*)	Consider surgical debridement *First line:* Liposomal amphotericin *Second line:* Posaconazole
Endemic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*, *Sporothrix*)	*First line:* Mild disease immunocompetent: no treatment (*Histoplasma*), itraconazole (others) Moderate disease: itraconazole Severe disease: amphotericin *Second line:* Posaconazole Voriconazole Fluconazole

Table 3

techniques increase the diagnostic yield but false-positive PCR can occur due to PJP lung colonization. *P. jirovecii* can be found in BALF for 48−72 hours after starting empirical treatment. First-line treatment is high-dose trimethoprim−sulphamethoxazole for 21 days, with adjunctive corticosteroids for severe hypoxaemia ($pO_2 < 8$ kPa) (Table 3). Second-line therapies include clindamycin plus primaquine, pentamidine, atovaquone, or trimethoprim plus dapsone. Prophylaxis with trimethoprim−sulphamethoxazole or nebulized pentamidine is recommended in patients with HIV infection (CD4 count <200 cells/mm³), transplant recipients (solid organ and haematopoietic stem cell transplantation (HSCT)) and those receiving prolonged high-dose glucocorticoids (>20 mg/day for 21 days or longer).[1] Mortality is about 10%.[8]

Invasive aspergillosis

Aspergillus species are ubiquitous and continuously inhaled by all humans but usually establish infection only when there are major defects in phagocyte function, such as severe and prolonged neutropenia (e.g. after HSCT or aplastic anaemia), in patients taking high-dose glucocorticoids, or in those with haematological malignancy or chronic granulomatous disease. Chronic graft versus host disease (GVHD) is also a significant risk factor and, rarely, patients with chronic lung disease or milder forms of immunosuppression can develop semi-invasive forms of aspergillosis. The most common infective species is *Aspergillus fumigatus*.[9] The respiratory tract (including the sinuses) is most often affected, although blood-borne spread to internal organs (especially the CNS) and skin can occur. The classic presenting triad in invasive pulmonary aspergillosis (IPA) is fever, chest pain and haemoptysis, although fever alone or various respiratory symptoms can occur. *Aspergillus* has a predilection for growing into blood vessels, potentially causing fatal massive haemorrhage. Chest radiographs show patchy infiltrates or nodules that can cavitate. CT scan features include macronodules (single or multiple, with or without cavitation), or patchy consolidation. Nodules may show the 'halo' (surrounding ground glass infiltrates due to haemorrhage) or 'air-crescent' (cavitation around a fungal ball) signs. When the patient's immune function recovers, fungal balls may form in a walled-off cavity created by the invasive phase of the disease. Other manifestations of invasive aspergillus infections affecting the lung include:

- *Aspergillus* tracheobronchitis, in which infection is restricted to the tracheobronchial tree causing a relentless cough. CT scans may show focal bronchial wall thickening and 'tree and bud' changes. Bronchoscopy is diagnostic, identifying highly inflamed mucosa with necrotic white slough that is positive on culture and histology for *Aspergillus*.
- Chronic necrotizing pulmonary aspergillosis (CNPA) or chronic cavitatory pulmonary aspergillosis (CCPA), which are more indolent forms of invasive aspergillosis associated with mild immunosuppression or chronic lung disease. These present with a long history of cough and frequently with marked systemic symptoms, and a slowly progressive patch of consolidation with or without cavitation (CNPA), or an expanding dry upper lobe cavity with a thickened wall (CCPA).[10]

Diagnosis of IPA is suggested by detection of galactomannan (a relatively specific cell wall component) or β-D-glucan (cell wall component of many fungi and *Pneumocystis*) antigen in blood or

BALF.[11] False-positives of the galactomannan antigen test occur with concomitant treatment with β-lactam antibiotics.[9] Definitive diagnosis of IPA is made by positive culture for *Aspergillus* and histopathologic demonstration of tissue invasion on CT-guided or VATS biopsy specimens. Histology is highly sensitive, septated hyphae showing dichotomous (45°) branching on Gomori methenamine silver or periodic acid-Schiff staining. However histology specimens are often unavailable, and culture is relatively insensitive, so diagnosis is frequently made on clinical grounds (suggestive CT appearances, high-risk patient, positive galactomannan test). *Aspergillus* antibodies have no role in the diagnosis of IPA but are positive in CCPA and sometimes in CNPA.

Non-*Aspergillus* filamentous fungi

Filamentous fungi, including *Fusarium*, *Zygomycetes*, *Scedosporium* and *Penicillium*, can cause invasive pulmonary infections in immunocompromised patients with a clinical presentation similar to IPA. Diagnosis is made by culture from respiratory samples or lung biopsy, and is important as some species are resistant to conventional antifungal agents. Galactomannan and β-D-glucan cell wall antigen tests are negative in *Zygomycetes*[12] infections. Mortality is high.

Candidiasis

Direct pulmonary invasion by *Candida* species is rare even in immunocompromised patients, despite frequent isolation from sputum. Pulmonary infection usually occurs in neutropenic patients as haematogenous spread from infected indwelling vascular catheters or infections related to transplant surgery. Lung nodules are often peripheral and sometimes very large. Blood cultures should be positive. *Candida albicans* is the most common species identified but a range of non-albicans *Candida* also can cause disease (e.g. *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata*, and *Candida krusei*). Infected indwelling lines should be removed.

Cryptoccosis

Cryptococcus neoformans pneumonia almost always affects only immunocompromised patients and can present with dyspnoea, cough and fever.[13] HIV/AIDS (CD4 <200 cells/mm^3) is the most common risk factor but cryptococcal pneumonia also occurs in other defects of T-cell-mediated immunity (especially post-solid organ transplantation).[14] Radiological features include diffuse interstitial infiltrates, focal consolidation, discrete nodules, and hilar lymphadenopathy. Diagnosis is by microscopic identification (Indian ink stain) or culture from respiratory tract samples. The lung is the port of entry for disseminated infection (usually CNS), and neurological symptoms should prompt a lumbar puncture and cerebrospinal fluid culture.

Endemic fungi

Endemic fungi are found in specific geographical areas and cause primary infection by inhalation or inoculation of contaminated material (e.g. bat faeces). Reactivation of latent infection can occur in immunocompromised patients, especially with defects in T-cell-mediated immunity, so a history of travel or residence in a high-risk area can be relevant. Common endemic fungi causing pulmonary infections include *Histoplasma capsulatum*, *Coccidioides* (*Coccidioides immitis* and *Coccidioides posadasii*), *Blastomyces dermatitidis* and *Sporothrix schenckii*.[15] Presentation varies with pathogen but tends to mimic tuberculosis with cavitating pneumonias, pulmonary nodules, enlarged mediastinal and hilar lymph nodes, or a miliary pattern. Systemic dissemination is not uncommon in immunocompromised patients. Diagnosis requires identification of the fungus in respiratory samples or biopsy material, including bone marrow aspirates. Culture may take 6 weeks. *H. capsulatum* can be rapidly detected with an antigen detection assay but this may cross-react with other endemic fungi.[16] Serology will identify patients with previous exposure for most fungi, but is not reliable in immunocompromised patients. Mortality is high without timely appropriate treatment. ◆

REFERENCES

1 Alvarez B, Arcos J, Fernández-Guerrero ML. Pulmonary infectious diseases in patients with primary immunodeficiency and those treated with biologic immunomodulating agents. *Curr Opin Pulm Med* 2011 May; **17:** 172–9.

2 Bek B, Boeckh M, Lepenies J, et al. High-level sensitivity of quantitative pp65 cytomegalovirus (CMV) antigenemia assay for diagnosis of CMV disease in AIDS patients and follow-up. *J Clin Microbiol* 1996 Feb; **34:** 457–9.

3 Zamora MR. DNA viruses (CMV, EBV, and the herpesviruses). *Semin Respir Crit Care Med* 2011 Aug; **32:** 454–70.

4 Pavia AT. Viral infections of the lower respiratory tract: old viruses, new viruses, and the role of diagnosis. *Clin Infect Dis* 2011 May; **52**(suppl 4): S284–9.

5 Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet* 2011 Apr. 9; **377:** 1264–75.

6 Martínez R, Reyes S, Menéndez R. Pulmonary nocardiosis: risk factors, clinical features, diagnosis and prognosis. *Curr Opin Pulm Med* 2008 May; **14:** 219–27.

7 Huang L, Cattamanchi A, Davis JL, et al. HIV-associated *Pneumocystis pneumonia*. *Proc Am Thorac Soc* 2011 Jun; **8:** 294–300.

8 Kelley CF, Checkley W, Mannino DM, Franco-Paredes C, Del Rio C, Holguin F. Trends in hospitalizations for AIDS-associated *Pneumocystis jirovecii* pneumonia in the United States (1986 to 2005). *Chest* 2009 Jul; **136:** 190–7.

9 Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev* 2011 Sep 1; **20:** 156–74.

10 Denning DW, Hope WW. Therapy for fungal diseases: opportunities and priorities. *Trends Microbiol* 2010 May; **18:** 195–204.

11 Hage CA, Knox KS, Davis TE, Wheat LJ. Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. *Curr Opin Pulm Med* 2011 May; **17:** 167–71.

12 Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1–>3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis* 2005 Sep 1; **41:** 654–9.

13 Li SS, Mody CH. Cryptococcus. *Proc Am Thorac Soc* 2010 May; **7:** 186–96.

14 Vilchez RA, Irish W, Lacomis J, Costello P, Fung J, Kusne S. The clinical epidemiology of pulmonary cryptococcosis in non-AIDS patients at a tertiary care medical center. *Medicine (Baltimore)* 2001 Sep; **80:** 308–12.

15 Hsu LY, Ng ES-T, Koh LP. Common and emerging fungal pulmonary infections. *Infect Dis Clin North Am* 2010 Sep; **24:** 557–77.

16 Wheat LJ. Approach to the diagnosis of the endemic mycoses. *Clin Chest Med* 2009 Jun; **30:** 379–89. viii.