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Opportunistic bacterial, viral 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 biological therapies, patients with haematological malignancy, aplastic anaemia or HIV infection, and recipients of solid-organ or stem cell transplants. The type and degree of the immune defect dictate the profile of potential opportunistic pathogens; T-cell-mediated defects increase the risk of viral (cytomegalovirus, 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. Importantly, conventional non-opportunistic pathogens are frequently encountered in immunocompromised hosts and should not be overlooked. The radiological pattern of disease (best assessed by computed tomography) and speed of onset help to identify the likely pathogen(s); radiological imaging can subsequently be supported by targeted investigation including the early use of bronchoscopy in selected patients. Rapid and expert clinical assessment can identify the most likely pathogens, which can then be treated aggressively, providing the best opportunity for a positive clinical outcome.

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

Key points

- Knowledge of the immune defect helps to narrow down the potential pathogens
- Computed tomography of the chest is better than radiographs at defining the radiological pattern of disease in immunocompromised hosts
- In selected patients, early bronchoscopy increases the yield of microbiological identification of a potential pathogen
- Prolonged high-dose glucocorticoids (>20 mg/day for >21 days) predispose to *Pneumocystis jirovecii* pneumonia (PJP)
- Biological agents are associated with specific immune defects that 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)
- Due to the increase in azole resistance of *Aspergillus fumigatus*, combination of an azole with an echinocandin antifungal agent is recommended in immunocompromised hosts with severe invasive pulmonary aspergillosis
- A travel history is important to identify infections caused by endemic fungi

Introduction

Opportunistic infections occur when a loss of established innate or adaptive immune responses allows an organism that is normally weakly virulent to cause infection. The type and degree of immune defect dictate which potential opportunistic pathogens are likely (Table 1). 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 can complicate treatment with the new biological therapies for inflammatory conditions. Immunocompromised patients also have an increased risk of infections caused by more conventional pathogens, which should be considered in the differential diagnosis. Expert clinical assessment with early diagnosis and aggressive treatment are required for a positive outcome. Computed tomography (CT) is more sensitive than plain chest radiography for defining the predominant pattern(s) of lung involvement. Combined with knowledge of the patient's immune status (loss of T-cell or antibody-mediated immunity, or defects in neutrophil-mediated immunity), this can often identify the most likely pathogens. This article provides a concise overview of the most common opportunistic lung infections.

Bacteria

Conventional bacterial pathogens

Although the risk of opportunistic infection is high in immunocompromised patients, most pneumonias are related to the more

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Type of immune defect according to disease/treatment and range of commonly associated pathogens

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* spp., *Candida* spp., non-*Aspergillus* filamentous fungi)
	Felty's syndrome	
	Aplastic anaemia	
	Early HSCT	
Neutrophil chemotaxis	Diabetes mellitus	*Staph. aureus*
	Cirrhosis	Streptococci
	Sarcoidosis	*Candida* spp.
	Drugs (glucocorticoids, amphotericin B)	Zygomycosis
Neutrophil phagocytosis	Chronic granulomatous disease	*Staph. aureus*
	Myeloproliferative disorders	*Nocardia* spp.
	Inherited phagocyte defects	Gram-negative bacilli
		Fungi (*Aspergillus* spp., *Candida* spp., 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*, *Haem. influenzae*)
	Acquired (systemic lupus erythematosus, anorexia nervosa)	*Staph. aureus*
Asplenia	Splenectomy	Encapsulated bacteria (e.g. *Strep. pneumoniae*, *Haem. influenzae*)
	Sickle cell disease	*Staph. aureus*

HSCT, haemopoietic stem cell transplantation.

Table 1

conventional bacterial pathogens. These are particularly common after a viral illness. They usually present similarly to pneumonia in immunocompetent individuals[1] 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 are more likely to be resistant to first-line antibiotics. They include both Gram-positive (*Streptococcus pneumoniae*, *Staphylococcus aureus*) and Gram-negative (e.g. *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, other enteric pathogens) organisms.

Mycobacteria

Reactivation of latent tuberculosis occurs in patients with T-cell immune defects. *Mycobacterium tuberculosis* cultures and

polymerase chain reaction (PCR) should be carried out on respiratory samples from immunocompromised individuals with pulmonary infiltrates who were born or live in countries with a high prevalence of tuberculosis. Non-tuberculous mycobacterial infections can present similarly. Mycobacterial infections are usually readily diagnosed by microscopy and culture or by biopsy of affected lung tissue.

Nocardiosis

Nocardiosis is an uncommon Gram-positive bacterial infection with a high mortality when disseminated. There are over 80 *Nocardia* species, but human disease is usually caused by the *Nocardia asteroides* complex. *Nocardia* is found in soil, decaying vegetable matter and stagnant water. Inhalation is the most common route of entry so pneumonia is the most common infection.

The main risk factors are defects in T-cell-mediated immunity (e.g. after 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. Cavitation and pleural effusions are common. These appearances can be mistaken for metastases, mycobacterial infection or invasive aspergillosis. Local spread to the pericardium and mediastinum, and haematogenous spread to brain, joints and soft tissue, occur in about half of patients. A rapid diagnosis can be made by identifying the characteristic beaded, branching Gram-positive and weakly acid-fast filaments on microscopy of tissue or respiratory samples.

Blood and sputum cultures can be positive but require prolonged aerobic culture. Susceptibility to antibiotics varies among the *Nocardia* species, and treatment with two or three intravenous antibiotics may initially be necessary in immunocompromised individuals. Trimethoprim–sulphamethoxazole is first-line therapy, with carbapenems, amikacin, third-generation cephalosporins, tetracyclines or amoxicillin–clavulanate as alternatives. The duration of treatment is prolonged (up to 12 months) in immunocompromised patients and with central nervous system (CNS) disease.

Viral infections

Respiratory viruses

Lower respiratory tract infections with the respiratory viruses (respiratory syncytial virus, parainfluenza, influenza, adenovirus, metapneumovirus, coronavirus, rhinovirus) are relatively common in immunocompromised patients with defects in T-cell-mediated immunity. Respiratory viruses usually cause bronchiolitis that presents with coryzal symptoms, cough, fever and dyspnoea. In a minority of patients, auscultation of the lungs reveals characteristic squeaks or wheeze.

The chest radiograph is often normal or non-specific. CT classically demonstrates 'tree-in-bud' changes suggestive of small airways inflammation or diffuse ground-glass opacities. The diagnosis is confirmed rapidly using nasopharyngeal aspirate samples for viral antigen immunofluorescence or PCR for viral nucleic acids, the latter being favoured in immunocompromised hosts. If nasopharyngeal aspirate findings are negative, immunofluorescence or PCR of bronchoalveolar lavage fluid (BALF) has a higher sensitivity.

In the absence of pneumonia, mortality from respiratory virus infection is relatively low, although infection can persist for several weeks. Treatment is supportive, but in immunocompromised hosts specific antiviral treatment is recommended (Table 2). In cases of severe infection, combination with intravenous immunoglobulin should be considered. Viral infection, particularly influenza (including H1N1) has effects on lung host defences and predisposes to secondary bacterial infection,[1, 2] which in immunocompromised hosts (particularly after chronic glucocorticoid use, chemotherapy for cancer and haemopoietic stem cell transplantation (HSCT)) can lead to more severe illness. Clinically, this is suspected when there is relapse of fever, increased oxygen requirements and C-reactive protein concentration, and radiographic evidence of more dense consolidation or infiltrates. Antibiotic treatment for secondary bacterial infection should cover the organisms most commonly encountered after influenza, including *Strep. pneumoniae*, *Staph. aureus* and *Haemophilus influenzae*. Novel viruses that have recently emerged, such as Middle East respiratory syndrome coronavirus and avian influenza A strain H7N9, are potential rare causes of severe pneumonias in immunocompromised patients.[1]

Cytomegalovirus (CMV) and other herpesviruses

The herpesvirus 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 irrespective of symptoms or signs, while CMV disease is infection associated with evidence of organ-specific disease. CMV infection in immunocompromised patients is usually caused by 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 an insidious onset of fever, malaise, cough and dyspnoea with hypoxia. Classic features on CT are symmetrical peribronchovascular and alveolar infiltrates predominantly affecting the lower lobes, but asymmetrical changes, consolidation and effusions are not uncommon.

In suspected CMV infection/disease, CMV replication can easily be identified and the viral load determined by PCR or CMV pp65 antigen testing of blood or BALF. CMV infection is also identified by culture of urine, throat and BALF specimens. Evidence of CMV reactivation does not always mean that concurrent lung disease is caused by CMV, and conversely CMV viraemia can occasionally 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 oral valganciclovir (unlicensed indication). Second-line treatments include foscarnet (unlicensed indication), cidofovir (unlicensed indication) and maribavir. CMV

Antiviral treatments for respiratory viruses

Virus	Known and recommended treatment	Potential therapies
Influenza	Neuraminidase inhibitors (zanamivir or oseltamivir)[a] Amantadine	
Parainfluenza		Ribavirin[b,c] IVIG[b]
Respiratory syncytial virus	Palivizumab Ribavirin[c]	
Human metapneumovirus		Ribavirin[b,c] IVIG[b]
Adenovirus		Ribavirin[b,c] Cidofovir[b] Brincidofovir[d]

IVIG, intravenous immunoglobulin.
[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.
[c] Can be administered orally, intravenously or in nebulized form.
[d] In Phase III clinical trials.

Table 2

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 virus (HSV), varicella zoster (VZV) (both associated with the characteristic rash) and human herpesvirus (HHV) 6, are rare causes of diffuse pneumonitis similar to CMV in the immunocompromised host. First-line treatment of HSV and VZV is with aciclovir, but valaciclovir, famciclovir (licensed for HZV, unlicensed for HSV), cidofovir (licensed for HSV) and foscarnet (licensed for HSV, unlicensed indication for HZV) can also be used. No drug has been specifically approved for the treatment of HHV-6, but ganciclovir and foscarnet are recommended by experts for the treatment of severe HHV-6 infection.[3]

Fungal infections

Treatment options for fungal pneumonias are listed in Table 3.

Pneumocystis jirovecii (formerly *P. carinii*)

Pneumocystis 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 with slowly increasing dyspnoea, dry cough and hypoxaemia, with few physical or radiological findings, but can be more rapidly progressive fulminant disease. Exercise-induced oxygen desaturation is a sensitive clinical marker.

Chest radiographs may show diffuse, bilateral, interstitial infiltrates but can be normal, whereas high-resolution CT 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. *P. jirovecii* cannot be cultured, and diagnosis requires identification of the organism in induced sputum or BALF by microscopy with Giemsa and Grocott staining. Immunofluorescence and PCR techniques increase the diagnostic yield, but false-positive PCR can occur because of lung colonization by *P. jirovecii*. *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/mm^3), transplant recipients (solid-organ and HSCT) and patients receiving prolonged high-dose glucocorticoids (>20 mg/day for 21 days or longer). Mortality is approximately 10%.

Invasive aspergillosis

Aspergillus species are ubiquitous and are continuously inhaled 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 with haematological malignancy or chronic granulomatous disease. Chronic GVHD is also a significant risk factor and, rarely, patients with chronic lung disease or milder forms of immunosuppression develop semi-invasive forms of aspergillosis. The most common infective species is *Aspergillus fumigatus*. 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

Antifungal treatment choices

Fungal pathogen	Treatment
Aspergillus species	*First-line:*
	Voriconazole ± caspofungin
	Lipid formulation of amphotericin
	Second-line:
	Posaconazole[a]
	Itraconazole
	Isavuconazole
	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 (*Can. albicans*)
	Caspofungin (*Can. glabrata*, *Can. krusei*)
	Second line:
	Voriconazole
	Itraconazole
	Posaconazole[a]
	Micafungin
	Amphotericin
Non-*Aspergillus* filamentous fungi (e.g. *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

[a] Intravenous formulation not approved in the UK.

Table 3

fatal massive haemorrhage. Chest radiographs show patchy infiltrates or nodules that can cavitate. CT features include macronodules (single or multiple, with or without cavitation) or patchy consolidation. Nodules can show the 'halo' (surrounding ground-glass infiltrates caused by haemorrhage) or 'air-crescent' (cavitation around a fungal ball) signs. When the patient's immune function recovers, fungal balls can 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 may show focal bronchial wall thickening and 'tree-in-bud' changes. Bronchoscopy is diagnostic, identifying highly inflamed mucosa with necrotic white slough that is positive for *Aspergillus* on culture and histology.
- Chronic necrotizing pulmonary aspergillosis (CNPA) or chronic cavitary 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. There is also a slowly progressive patch of consolidation with or without cavitation (CNPA) or an expanding dry upper lobe cavity with a thickened wall (CCPA).

Diagnosis of IPA is suggested by detection of galactomannan (a relatively specific cell wall component) or β-D-glucan (a cell wall component of many fungi including *Aspergillus* and *Pneumocystis*) antigen in blood or BALF. False-positives galactomannan antigen results occur with concomitant treatment with β-lactam antibiotics. Definitive diagnosis of IPA is made by positive culture for *Aspergillus* and histopathological demonstration of tissue invasion on CT-guided or VATS biopsy specimens. Histology is highly sensitive, showing dichotomous (45°) branching of septated hyphae 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, with or without a positive galactomannan test). *Aspergillus* antibodies have no role in the diagnosis of IPA but are positive in CCPA and sometimes in CNPA. There has been a worldwide increase in *A. fumigatus* resistance to azoles,[4] and treatment with a combination of an azole and an echinocandin antifungal agent may be necessary in immunocompromised hosts with severe IPA.

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* 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. *Candida albicans* is most commonly identified, but a range of non-albicans *Candida* (e.g. *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*) can cause disease. A novel culture-independent test allows for the rapid detection of *Candida* in blood, with a particularly high negative predictive value – positive results require confirmation by culture.[5] Infected indwelling lines should be removed.

Cryptococcosis

Cryptococcus neoformans pneumonia almost always affects only immunocompromised patients and can present with dyspnoea, cough and fever. HIV/AIDS (CD4 count <200 cells/mm^3) is the most common risk factor but cryptococcal pneumonia also occurs in other defects of T-cell-mediated immunity (especially after solid organ transplantation). 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* (*Candida immitis*, *Candida posadasii*), *Blastomyces dermatitidis* and *Sporothrix schenckii*. Presentation varies by 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 can take 6 weeks. *Hist. capsulatum* can be rapidly detected with an antigen detection assay but this can cross-react with other endemic fungi. Serology identifies patients with previous exposure for most fungi but is not reliable in immunocompromised patients. Mortality is high without timely appropriate treatment. ◆

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