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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 given chemotherapy or biological therapies, and those with haematological malignancy, aplastic anaemia or HIV infection, or recipients of solid organ or stem cell transplants. The type and degree of immune defect dictates 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 identify the likely pathogen(s); this 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, allowing timely appropriate therapy.

Keywords Aspergillus; Cryptococcus; fungi; immunocompromised host; MRCP; Nocardia; opportunistic infections; pneumonia; viruses

Key points
- Knowledge of the immune defect helps to narrow down the potential pathogens causing infection
- CT scans of the chest are better than radiographs at defining the radiological pattern of disease in immunocompromised hosts
- In selected patients, early bronchoscopy is helpful and increases the yield of microbiological identification of a potential pathogen
- Prolonged high-dose glucocorticoids (>20 mg/day for >21 days) and calcineurin inhibitors 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)

Introduction
Opportunistic infections occur when 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 the profile of potential opportunistic pathogens (Table 1). Infections commonly encountered in otherwise healthy individuals should not be forgotten as they can cause infection in immunocompromised hosts. Opportunistic lung infections are a major cause of morbidity and mortality for patients immunocompromised by HIV infection, haematological malignancy, aplastic anaemia or chemotherapy treatment, or who are recipients of solid organ or stem cell transplants; opportunistic infections can also complicate treatment with the new biological therapies for inflammatory conditions. Expert clinical assessment with early diagnosis and aggressive treatment is required for a positive outcome. Computed tomography (CT) is more sensitive than chest radiography for defining the predominant pattern(s) of lung involvement; when combined with knowledge of the patient’s immune status (loss of T-cell- or antibody-mediated immunity, or defects in neutrophil-mediated immunity), it often identifies the most likely pathogens. This review provides a concise overview of the most common opportunistic lung infections.

Bacteria
Conventional bacterial pathogens
Despite the high risk of opportunistic infection pneumonias related to the more conventional bacterial pathogens are still more prevalent in immunocompetent individuals, with fever, respiratory symptoms, focal consolidation and rapid rises in inflammatory markers. These are particularly common post-viral
illness. The major risk factors are neutropenia, antibody deficiencies and high-dose corticosteroids. The organisms involved are more diverse than in conventional pneumonia and more likely to be resistant to first-line antibiotics. These include both Gram-positive (Streptococcus pneumoniae, Staphylococcus aureus) and Gram-negative bacilli, fungi (Aspergillus spp., Candida spp., non-Aspergillus filamentous fungi).

Reactivation of latent tuberculosis also occurs; Mycobacterium tuberculosis cultures and polymerase chain reaction (PCR) must therefore be performed on respiratory samples from immunocompromised individuals with pulmonary infiltrates, particularly in high-prevalence areas.

**Nocardiosis**

Nocardiosis is an uncommon Gram-positive bacterial infection with a high mortality in disseminated disease. There are >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 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 metastasis. Local spread to the periocardium 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. PCR testing is sensitive but difficult to interpret, particularly in respiratory tract samples, because positive results can represent colonization.

Susceptibility to antibiotics varies among Nocardia spp., and treatment with two or three intravenous antibiotics may initially be necessary in immunocompromised individuals. 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.

**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 a bronchitis that presents with coryzal symptoms, cough, fever and dyspnoea. In a minority of patients auscultation of the lungs reveals characteristic squawks or wheeze. The chest radiograph is often normal or non-specific. CT classically demonstrates diffuse ‘tree-in-bud’ changes suggestive of small airways inflammation, but can also show ground-glass infiltrates. The diagnosis can be rapidly confirmed using nasopharyngeal aspirate samples for viral antigen immunofluorescence or PCR for viral nucleic acids, the latter favoured in immunocompromised hosts. If nasopharyngeal aspirate results are negative, immunofluorescence or PCR on bronchoalveolar lavage fluid (BALF) has 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 specific antiviral treatment is recommended in immunocompromised hosts (Table 2), and combination with intravenous immunoglobulin for severe infection.

Viral infection, particularly influenza (including H1N1), has effects on lung host defences and predisposes to secondary bacterial infection, which in immunocompromised hosts (particularly with chronic glucocorticoid use, chemotherapy for cancer and haemopoietic stem cell transplant (HSCT) recipients) can lead to more severe illness. Clinically, this is suspected when there is relapse of fever and respiratory symptoms with new radiographic evidence of infiltrates, but it is important to note that fever may not be present in immunocompromised individuals. 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 have emerged including the Middle Eastern respiratory syndrome coronavirus and avian influenza A strain H7N9. The latter has a low rate of transmission but a high associated mortality. Treatment of these infections is generally supportive. However, most international guidelines suggest treating adenovirus infections after allogeneic HSCT, first-line treatment generally being cidofovir until a defined reduction in viral load is reached; however, treatment success is estimated at approximately 70%. There are also case-series detailing the efficacy of brincidofovir, an orally bioavailable conjugate of cidofovir, in cidofovir-resistant cases but this is not yet licensed in the UK.

**Cytomegalovirus (CMV) and other herpesviruses**

The herpesvirus CMV is an important cause of lung infection in patients with impaired T-cell-mediated immunity, for example transplant recipients. CMV infection is defined as active CMV replication regardless of symptoms or signs, and CMV disease is infection associated with evidence of organ-specific disease. CMV infection in immunocompromised patients usually results from reactivation of latent CMV acquired in early life; however, it can also be primary infection in previously uninfected individuals, in whom it is often more severe. Pneumonitis is an important complication, commonly presenting with insidious onset of fever, malaise, cough and dyspnoea with hypoxia. Classic features on CT are symmetrical peribronchovascular and

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**Antiviral treatments for respiratory viruses**

| Virus                          | Treatment                  |
|-------------------------------|----------------------------|
| Influenza                     | Neuraminidase inhibitors   |
|                               | (zanamivir, oseltamivir)   |
|                               | Amantadine                 |
| Parainfluenza                 | Ribavirin                  |
|                               | IVIG                       |
| Respiratory syncytial virus   | Ribavirin                  |
|                               | Palivizumab                |
| Human metapneumovirus         | Ribavirin                  |
|                               | IVIG                       |
| Adenovirus                    | Ribavirin                  |
|                               | Cidofovir                  |
|                               | Brincidofovir              |

IVIG, Intravenous immunoglobulin.

a Effective at reducing disease severity and duration.
b In vitro activity present but no recommendations on treatment are currently available owing to lack of data.
c Can be administered orally, intravenously or nebulized.
d In Phase III clinical trials.

Table 2
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 can also be 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 is occasionally absent in patients with CMV pneumonitis. CMV pneumonitis is more likely with high-level viraemia, especially if the viral load increased rapidly. Furthermore, high CMV DNA loads (>500 IU/ml) in BALF from HSCT recipients are associated with poor outcome. CMV pneumonitis can also 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. Second-line treatments include foscarnet, cidofovir and maribavir. Letemovir, used to prevent CMV reactivation and disease in allogeneic HSCT, has been successfully used off-licence for difficult-to-treat CMV infection and disease. 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. Recent National Institute for Health and Care Excellence endorsement of letemovir for prophylaxis in allogeneic HSCT CMV-seropositive recipients should reduce the incidence of CMV disease in this cohort, but could have unrecognized impacts on diagnosing and treating breakthrough disease. Other herpesviruses, such as herpes simplex virus (HSV), varicella-zoster (VZV) and human herpesvirus 6 (HHV-6), are rare causes of diffuse pneumonitis similar to CMV in immunocompromised hosts and can be associated with the characteristic rash. First-line treatment of HSV and VZV is with aciclovir, but valaciclovir, famciclovir, cidofovir and foscarnet can also be used. No drug has been specifically been approved for the treatment of HHV-6, but ganciclovir and foscarnet are recommend by experts to treat severe HHV-6 infection.

Fungal infections

Treatment options for pulmonary fungal infections 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/mm³). It is also important in non-HIV immunocompromised patients who have defects in T-cell-mediated immunity or are taking prolonged high-dose systemic glucocorticoids or calcineurin inhibitors. In non-HIV immunocompromised hosts, a CD4 count <200 cells/mm³ is present in most patients who develop PJP and can be used as a biomarker to identify at-risk individuals. Additionally, there is increased risk of PJP in individuals with CMV infection caused by inhibition of T cell function.

Clinical presentation is classically insidious with slowly increasing dyspnoea, dry cough and hypoxaemia with few

### Table 3

| Fungal pathogen | Treatment |
|-----------------|-----------|
| **Aspergillus species** | **First-line:**  
| | • Voriconazole ± caspofungin  
| | • Lipid formulation of amphotericin  
| | **Second-line:**  
| | • Posaconazole  
| | • Itraconazole  
| | • Isavuconazole  
| | • Caspofungin  
| | • Anidulafungin  
| **Pneumocystis jirovecii** | **First-line:**  
| | • Trimethoprim—sulfamethoxazole  
| | **Second-line:**  
| | • Clindamycin + primaquine  
| | • Atovaquone  
| | • Pentamidine  
| | • Trimethoprim + dapsone  
| **Cryptococcus neoformans** | **Induction therapy:**  
| | • Liposomal amphotericin + flucytosine  
| | **Consolidation and maintenance therapy:**  
| | • Fluconazole  
| | • Posaconazole  
| | • Voriconazole  
| **Candida species** | **First-line:**  
| | • Fluconazole (C. albicans)  
| | • Caspofungin (C. glabrata and C. krusei)  
| | **Second-line:**  
| | • Voriconazole  
| | • Itraconazole  
| | • Posaconazole  
| | • Micafungin  
| | • Amphotericin  
| **Non-Aspergillus filamentous fungi (e.g. Fusarium, Zygomycetes, Scedosporium, Penicillium)** | Consider surgical debridement  
| | **First-line:**  
| | • Liposomal amphotericin  
| | • Isavuconazole  
| | **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.*
physical or radiological findings, but it can be fulminant. Exercise-induced oxygen desaturation is a sensitive marker. The chest radiograph features are diffuse, bilateral interstitial infiltrates but X-rays can be normal. High-resolution CT is much more sensitive and often shows extensive ground-glass opacities with an apical distribution and peripheral sparing. Pneumatoceles 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 stains. Immunofluorescence and PCR techniques increase the diagnostic yield, but false-positive PCR can result from PJP lung colonization. P. jirovecii can be found in BALF for 48–72 hours after starting empirical treatment. Elevated serum levels of b-D-glucan (a cell wall component of many fungi and Pneumocystis) can be useful in patients too sick to provide bronchoscopic samples, with pooled sensitivity of 95% and specificity of 85%.

First-line treatment is high-dose trimethoprim–sulfamethoxazole for 21 days (Table 3). Adjunctive corticosteroids are given for severe hypoxaemia (PO2 < 8 kPa) because of the survival benefit seen in HIV patients; however, a meta-analysis of observational studies suggested that there might be no survival benefit in non-HIV immunocompromised hosts. Second-line therapies include clindamycin plus primaquine, pentamidine, atovaquone, or trimethoprim plus dapsone. Prophylaxis with trimethoprim–sulfamethoxazole or nebulized pentamidine is recommended in patients with HIV infection (CD4 count < 200 cells/mm³), transplant recipients (solid organ and HSCT) and those given prolonged high-dose glucocorticoids (> 20 mg/day for ≥ 21 days).

Invasive aspergillosis

Aspergillus species are ubiquitous and continuously inhaled by all humans. Infection is usually established only when there are major defects in phagocyte function, such as severe and prolonged neutropenia (e.g. after HSCT or aplastic anaemia), or in patients who are taking high-dose glucocorticoids or have 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. Recently, treatment with tyrosine kinase inhibitors has been recognized to predispose to invasive aspergillosis. The most common infective species is Aspergillus fumigatus.

The respiratory tract (including 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 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 disease’s invasive phase. 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 can show focal bronchial wall thickening and ‘tree-in-bud’ changes. Bronchoscopy is diagnostic, identifying highly inflamed mucosa with necrotic white slough that is positive on culture and histology for Aspergillus.
- Subacute IPA, previously known as chronic necrotizing pulmonary aspergillosis (CNPA) or chronic cavitatory pulmonary aspergillosis (CCPA), more indolent forms of invasive aspergillosis associated with mild immunosuppression or chronic lung disease. These present with a long history of cough and, frequently, 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).

| Category            | Criteria                                                                 |
|---------------------|--------------------------------------------------------------------------|
| Possible            | A. Risk factors (neutropenia for > 10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥ 3 weeks, T cell immunosuppressant, inherited severe immunodeficiency) |
|                     | B. CT signs (nodule ± halo, air crescent sign, cavity)                   |
| Probable (one from A, B and C) | A. Risk factors (neutropenia for > 10 days, allogeneic stem cell transplant, prednisolone 0.3 mg/kg for ≥ 3 weeks, T cell immunosuppressant, inherited severe immunodeficiency) |
|                     | B. CT signs (nodule ± halo, air crescent sign, cavity)                   |
|                     | C. Culture in BALF or sputum, positive galactomannan in BALF or serum, or positive b-D-glucan in serum |
| Definite            | Culture of fungus from normally sterile sites (not BALF), or demonstration of tissue invasion on biopsy |

Table 4

EORTC criteria for the diagnosis of invasive fungal disease
The European Organisation for Research and Treatment of Cancer (EORTC) has set out international consensus criteria for invasive fungal disease (Table 4). Detection of galactomannan (a relatively specific cell wall component) or β-d-glucan antigen in blood or BALF is useful for detecting IPA. However, it is important to note that false-positives can occur, for example with concomitant treatment with β-lactam antibiotics or ingestion of flavoured frozen desserts containing sodium gluconate; false-negatives can occur with concomitant use of antifungals. A BALF galactomannan optical density index (ODI) >1.5 is, however, a strong indicator of invasive aspergillosis, whereas with an ODI cut-off of 0.5, approximately 17% of cases are incorrectly diagnosed with IPA. 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, septated hyphae showing dichotomous (45°) branching on Gomori methenamine silver or periodic acid–Schiff staining. Histology specimens are, however, 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 CNPA.

It is important to note that, worldwide, there has been an increase in azole resistance of A. fumigatus. Therefore combination of an azole with an echinocandin antifungal agent is recommended in immunocompromised hosts with severe IPA. Monitoring of therapeutic azole drug levels in blood should be undertaken to help ensure therapeutic doses and improve outcome.

**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. Isavuconazole and liposomal amphotericin B may be used off-licence as treatment despite their use, mortality is high.

**Candidiasis**

Direct pulmonary invasion by Candida species is rare even in immunocompromised patients, despite frequently being isolated 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 the species most commonly identified, but a range of non-albicans Candida (e.g. Candida parapsilosis, Candida tropicalis, Candida glabrata, Candida krusei) also cause disease. β-d-glucan levels are elevated in serum; however, as the sensitivity is 75% and specificity 80%, and these can vary by Candida species, this test is not necessarily useful in isolation. An interesting novel culture-independent test based on miniaturized magnetic resonance detection of pathogen nucleic acid allows rapid detection of Candida in blood; this has a particularly high negative predictive value, although positive results can still require confirmation by culture.

**Cryptococcosis**

Cryptococcus neoformans pneumonia almost always affects only immunocompromised patients and can present with dyspnoea, cough and fever. HIV/AIDS (CD4 < 200 cells/mm³) is the most common risk factor, but cryptococcal pneumonia also occurs with 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. The lung is the port of entry for disseminated infection (usually to the CNS), and neurological symptoms should prompt a lumbar puncture and cerebrospinal fluid culture. Diagnosis is by microscopic identification (Indian ink stain) or culture from respiratory tract samples. Identification of cryptococcal antigens using a lateral flow assay is sensitive for detecting the presence of Cryptococcus, but up to 34% of results showing low positive titres are actually false-positives.

**Endemic fungi**

These 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, Coccioidioides (Candida immittis, 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. H. 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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