Opportunistic bacterial, viral and fungal infections of the lung

Katharine M Pates
Jimstan N Periselneris
Jeremy S Brown

Katharine M Pates MB BS MBiochem MRCP is a Specialist Registrar in respiratory medicine. She is currently undertaking research in opportunistic infections in immunocompromised patients. Competing interests: none declared.

Jimstan N Periselneris BSc MB ChB MRCP PhD is a Consultant in respiratory medicine at King's College Hospital NHS Foundation Trust, London, UK. He has a specialist interest in respiratory infection in immunocompromised hosts and respiratory complications of haemato-oncological disease. Competing interests: received speaker fees from Gilead.

Jeremy S Brown MB BS PhD FRCP is a Clinician Scientist and a Professor in respiratory infection in the Centre for Inflammation and Tissue Repair, UCL Respiratory at University College London, UK. His main clinical interests are pneumonia, infections in the immunocompromised host, and bronchiectasis. Competing interests: none declared.

Abstract

Respiratory opportunistic infections are a major cause of morbidity and mortality in severely immunocompromised patients, such as those treated with biological therapies, chemotherapy and solid organ or stem cell transplants, and those with haematological malignancy, aplastic anaemia or HIV infection. 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 also 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 help identify the most likely pathogens, allowing timely appropriate therapy.

Keywords

Aspergillus; *Cryptococcus*; fungi; immunocompromised host; *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 plain chest radiographs at defining the radiological pattern of disease and hence the likely causative pathogen 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 drugs inhibiting T lymphocyte function predispose to *Pneumocystis jirovecii* pneumonia
• 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 bacterial pathogens associated with bronchiectasis)

Introduction

Opportunistic infections occur when the loss of established innate or adaptive immune responses allows an organism that is normally weakly virulent to cause infection. 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 also complicate treatment with the new biological therapies for inflammatory and neoplastic conditions. The challenge when managing respiratory infection in immunocompromised patients is the large number of potential pathogens, compounded by a range of differential diagnosis including several non-infectious problems such as idiopathic and organising pneumonias, GvHD, and alveolar haemorrhage.

The type and degree of immune defect dictate the profile of potential opportunistic pathogens (Table 1) and can be used to predict the likely potential causes of infection. Pathogens commonly encountered in otherwise healthy individuals should not be forgotten as they usually also have a higher incidence in the immunocompromised hosts. Aggressive, initially empirical, treatment is required for the optimum chance of a positive outcome.

Computed tomography (CT) is more sensitive than chest radiography for defining the predominant pattern(s) of lung involvement by opportunistic infections; when combined with knowledge of the patient's immune status (loss of T-cell- or antibody-mediated immunity, or defects in neutrophil-mediated immunity), the CT appearances often suggest the most likely causative pathogens. This review provides a concise overview of the most common opportunistic lung infections.

Bacteria

Conventional bacterial pathogens

Conventional bacterial pathogens are more prevalent in immunosuppressed individuals than immunocompetent individuals, and generally have a similar presentation with acute onset of fever, respiratory symptoms, focal consolidation and rapid rises in inflammatory markers. Bacterial lung

infections are particularly common after a respiratory virus infection. The major risk factors for bacterial infections are neutropenia, antibody deficiencies and high-dose corticosteroids. Even in well-controlled HIV there are increased rates of bacterial pneumonia with bacteraemia.

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 (e.g. *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, other enteric pathogens) organisms.

Mycobacteria

Mycobacterium tuberculosis spreads from person to person and can cause disease in immunocompetent hosts, often reactivating long after primary infection. However, reactivation of latent tuberculosis (TB) is increased in immunocompromised hosts. Particular risk factors include HIV, diabetes mellitus, chronic kidney disease, solid organ transplant, haematological malignancy, exposure to anti-tumour necrosis factor (TNF) medications, and high-dose corticosteroids or chemotherapy. Culture for *M. tuberculosis* and a polymerase chain reaction (PCR) on respiratory samples should be considered for immunocompromised patients with previous TB exposure presenting with fever and new pulmonary infiltrates.

There are also many species of environmental non-tuberculous mycobacteria that can cause pulmonary disease in patients with structural lung disease (e.g. chronic obstructive pulmonary disease, bronchiectasis) or immunodeficiency. Particular risk factors include long term corticosteroid use, anti-TNF medication, GATA2 (GATA binding protein 2) deficiency and advanced HIV, the latter associated with disseminated infection when CD4 counts are <50 cells/mm^3.

Nocardiosis

Nocardia are Gram-positive bacteria found in soil, decaying vegetable matter and stagnant water. The inhalation of *Nocardia asteroides* complex is most commonly implicated in human disease. Nocardiosis is uncommon but has a higher incidence in immunosuppressed individuals and is associated with a relatively high mortality. 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. Common radiological features are patches of dense consolidation or macronodules, and cavitation and pleural effusions are common. These appearances are often mistaken for malignancy. Local spread to the pericardium and mediastinum, and haematogenous spread to brain, joints and soft tissue, occurs 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 with specific media. PCR testing is sensitive but difficult to

interpret, particularly in respiratory tract samples, because positive results can represent colonization. Once cultured, matrix-assisted laser desorption ionization-time of flight mass spectrometry can identify the common *Nocardia* species in 95–100% patients.

Susceptibility to antibiotics varies among *Nocardia* spp. Trimethoprim–sulfamethoxazole is first-line therapy and can be used as a single agent in non-severe disease. However, treatment with two or three drugs can be necessary in immunocompromised individuals, with intravenous induction with carbapenems, amikacin and/or third-generation cephalosporins, and then continuing with tetracyclines, amoxicillin–clavulanate and linezolid. Duration of treatment is prolonged – up to 12 months in immunocompromised patients or in central nervous system (CNS) disease.[1]

Viral infections

Respiratory viruses

Lower respiratory tract infections with the respiratory viruses (respiratory syncytial virus (RSV), parainfluenza, influenza, adenovirus, metapneumovirus, coronavirus, rhinovirus) are relatively common in immunocompromised patients with defects in T-cell- and B-cell-mediated immunity. Respiratory viruses usually cause a bronchiolitis that presents with coryzal symptoms, cough, fever and dyspnoea. Auscultation of the lungs can reveal characteristic squeaks or wheeze. 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 rapidly confirmed using nasopharyngeal samples for PCR or viral antigen testing. If nasopharyngeal aspirate results are negative, immunofluorescence or PCR on bronchoalveolar lavage fluid (BALF) has higher sensitivity.

In the absence of frank consolidation, mortality from respiratory virus infection is relatively low, although infection can persist for several weeks. Antiviral treatment is recommended for some respiratory viruses in immunocompromised hosts (Table 2), potentially in combination for severe infections with intravenous immunoglobulin or monoclonal antibodies (e.g. for COVID-19). With the exception of COVID-19 pneumonitis in immune-naive subjects, adjunctive corticosteroids are not beneficial when treating respiratory viruses, and could prolong the period of active infection. Other immunomodulators, such as interleukin-6 inhibitors and Janus kinase inhibitors also improve outcomes for immune-naive patients with COVID-19 pneumonitis.

Viral infection, particularly influenza, predisposes to secondary bacterial infection, which in immunocompromised hosts usually leads to a more severe illness. Clinically, this is suspected when there is a relapse of the fever and respiratory symptoms with new radiographic evidence of infiltrates, specifically patches of consolidation and focal areas of tree-in-bud change. In immunosuppressed individuals the antibiotic treatment for secondary bacterial infection should cover the organisms most commonly encountered after influenza in immunocompetent people (e.g. *S. pneumoniae*, *S. aureus*) and also a range of Gram-negative organisms that are more common in immunosuppressed individuals such as *Enterobacterales* (*Enterobacteriaceae*) and *P. aeruginosa.*

As the last decade has shown, epidemics of novel viruses such as the coronavirus causing COVID-19, new endemic respiratory viral infections such as Middle Eastern respiratory syndrome, and

potential novel pandemic organisms present significant potential additional problems for immunosuppressed individuals. Higher mortality and weaker immune responses to infection or vaccination increase the need for immunocompromised individuals to avoid infection by self-isolation, with negative socioeconomic and psychological consequences.

Vaccination against COVID-19 is significantly less effective in immunosuppressed patients, potentially necessitating the need for post-exposure treatment with monoclonal antibodies or antivirals.[2] Pre- and post-exposure prophylaxis for influenza with the neuraminidase inhibitors oseltamivir or zanamivir is also useful for selected immunocompromised patients. Where possible, vaccination against influenza, COVID-19 and (in the future) RSV should be completed before the start of periods of immunosuppression.

Cytomegalovirus (CMV) and other herpesviruses

The herpesvirus CMV is an important cause of pneumonitis in patients with impaired T-cell-mediated immunity. CMV infection is defined as active CMV replication regardless of the symptoms or signs, and CMV disease is infection associated with evidence of organ-specific disease. CMV infection usually results from reactivation of latent CMV acquired in early life but can be a primary infection. Pneumonitis is an important complication, commonly presenting with an insidious onset of fever, malaise, cough and dyspnoea with hypoxia. Classic features on CT are bilateral peribronchovascular and alveolar infiltrates predominantly affecting the lower lobes; however, 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. CMV infection can also be identified by culture of urine, throat and BALF specimens. However, 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. In haemopoietic stem cell transplantation (HSCT) recipients high CMV DNA loads in BALF are associated with poorer outcomes.[3] CMV pneumonitis is also confirmed by finding inclusion bodies in cells obtained by BALF or lung biopsies.

First-line treatment of CMV pneumonitis is intravenous ganciclovir or oral valganciclovir. Second-line treatments include foscarnet, cidofovir and maribavir, and CMV immunoglobulin can be used as adjunct therapy. Treatment efficacy is monitored by measuring blood CMV viral load, with treatment usually continued for at least 2 weeks after resolution of viraemia. In HSCT recipients letermovir prophylaxis significantly decreases the incidence of CMV disease and improves 6-month survival.

Other herpesviruses, such as herpes simplex virus (HSV) and varicella-zoster virus (VZV) are rare causes of diffuse pneumonitis in immunocompromised hosts. HSV and VZV infections are associated with their characteristic rashes. First-line treatment of HSV and VZV is with aciclovir, but valaciclovir, famciclovir, cidofovir and foscarnet can also be used.

Fungal infections

Pneumocystis and *Aspergillus* spp. are the main fungal pathogens causing respiratory tract infections in immunocompromised individuals, although several other fungi are less common causes. The treatment options for pulmonary fungal infections are listed in Table 3.

Pneumocystis jirovecii (formerly *P. carinii*)

Pneumocystis jirovecii is a commensal of the human lung probably transmitted by aerosol droplets, and causes infections only in profoundly immunosuppressed people. *Pneumocystis jirovecii* pneumonia (PJP) is a complication of HIV infection (CD4 count <200 cells/mm^3); it is also seen in non-HIV immunocompromised patients with defects in T-cell-mediated immunity or CD4 counts <200 cells/mm^3, or who are taking prolonged high-dose systemic glucocorticoids. Additionally, there is an increased risk of PJP in individuals with CMV infection, which is thought to inhibit T cell function.

PCP classically causes slowly increasing dyspnoea, dry cough and hypoxaemia with few physical or radiological findings, but it can be fulminant, especially in non-HIV patients. Exercise-induced oxygen desaturation is a sensitive marker. The chest radiograph features are diffuse, bilateral interstitial infiltrates but radiographs can look normal. High-resolution CT usually shows extensive ground-glass opacities with a tendency for an apical distribution and peripheral sparing. Chronic infection can lead to pneumatocoeles and bizarre-looking cystic changes.

Pneumocystis jirovecii cannot be cultured, and diagnosis requires identification of the organism in induced sputum or BALF by microscopy with direct immunofluorescence or methamine silver stains. PCR increases the diagnostic yield but cannot readily distinguish infection from colonization. *Pneumocystis jirovecii* can be found in BALF for 48–72 hours after starting empirical treatment. Elevated serum concentrations of β-D-glucan (a cell wall component of many fungi including *Pneumocystis*) is a useful biomarker, with a pooled sensitivity of 95% and specificity of 85%.

First-line treatment is with high-dose trimethoprim–sulfamethoxazole for 21 days (Table 3). Adjunctive corticosteroids are given for severe hypoxaemia (partial pressure of oxygen, PaO_2 <8 kPa) because of the survival benefit seen in HIV patients; however, a meta-analysis of observational studies suggested limited survival benefit in non-HIV immunocompromised patients. Second-line therapies include clindamycin plus primaquine, atovaquone, or trimethoprim plus dapsone or pentamidine. Prophylaxis with trimethoprim–sulfamethoxazole, dapsone or nebulized pentamidine is recommended in patients with HIV infection (CD4 count <200 cells/mm^3) or other causes of prolonged CD4 lymphopenia, transplant recipients (solid organ, HSCT) and those given prolonged high-dose glucocorticoids (>20 mg/day for ≥21 days).

Invasive aspergillosis

Aspergillus species are ubiquitous saprophytes adapted to living on rotting vegetation, releasing microsopic conidia that are continuously inhaled but readily controlled by immunocompetent individuals. The most common infective species is *Aspergillus fumigatus*. Infection is usually established only when

there are major defects in phagocyte function, such as severe and prolonged neutropenia (e.g. after HSCT, aplastic anaemia), or in patients who are taking high-dose glucocorticoids or have a haematological malignancy or chronic granulomatous disease. Chronic pulmonary GVHD is also a significant risk factor. Patients with chronic lung disease and/or milder forms of immunosuppression develop semi-invasive forms of aspergillosis that present over weeks or months. Treatment with tyrosine kinase inhibitors also predisposes to invasive aspergillosis.

The respiratory tract (including sinuses) is most often affected, although blood-borne spread to the internal organs (especially the CNS) and skin can occur. The classic presenting triad in invasive pulmonary aspergillosis (IPA) is fever, chest pain and haemoptysis, but this is relatively rare, and fever alone is more common. *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 classically have a 'halo' (surrounding ground-glass infiltrates caused by haemorrhage), and in the presence of neutrophils form an 'air crescent' (cavitation around a fungal ball) sign. When the patient's immune function recovers, fungal balls can remain in a walled-off cavity created by the disease's invasive phase.

Aspergillus species also cause tracheobronchitis, with infection restricted to the tracheobronchial tree; this presents with 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.*

The European Organisation for Research and Treatment of Cancer (EORTC) has set international consensus criteria for the diagnosis of invasive fungal disease (Table 4).[4] A positive culture for *Aspergillus* in a high-risk patient is strongly indicative of IPA, but culture probably only has 50% sensitivity. Galactomannan (a relatively specific fungal cell wall component) in blood or BALF,[5] and β-D-glucan antigen in blood, are useful biomarkers of IPA. False-positive results occur, for example with concomitant treatment with β-lactam antibiotics or intravenous immunogloblins, or with haemodialysis. *Aspergillus* PCR can also aid diagnosis.

A definitive diagnosis of IPA is made by histopathological demonstration of tissue invasion, and biopsies are highly sensitive (95%), showing septated hyphae with dichotomous (45°) branching on methenamine silver or Calcofluor White staining. Hence CT-guided biopsies (or on occasion video-assisted thoracoscopic surgery biopsies) are very helpful in making the diagnosis, but can be difficult to perform because of the specific site of infection and co-existing thrombocytopenia and other co-morbidities. As a consequence, a diagnosis of IPA is frequently made on clinical grounds alone (i.e. a compatible clinical and radiological presentation in an at-risk patient).

First-line treatment can be with triazoles (voriconazole, posaconazole, isavuconazole), echinocandins (e.g. caspofungin) or AmBisome (liposomal amphotericin); therapeutic monitoring of azole drug concentrations helps ensure therapeutic dosing and improve outcome. Resistance of *A. fumigatus* to triazoles has increased worldwide, largely driven by agricultural use. In very severe

infection dual antifungals have been used. Some species of *Aspergillus*, for example *A. terreus*, are constitutively resistant to amphotericin.

Non-*Aspergillus* filamentous fungi

Other filamentous fungi, including *Fusarium*, *Scedosporium* and *Penicillium*, can cause invasive pulmonary infections in immunocompromised patients, with a clinical presentation similar to IPA. Treatment is with triazoles or AmBisome and dictated by drug sensitivity. Mucormycosis is caused by fungi from the order Murocales (e.g. *Rhizopus* and *Mucor* species) and classically causes a 'reverse halo' or 'atoll' sign on lung CT. They are often associated with upper respiratory tract or CNS involvement. Diabetes and haematological malignancy are particular risk factors.

Microbiological diagnosis is important as some species are resistant to conventional antifungal agents, and is made by culture from respiratory samples or lung biopsy. Galactomannan and β-D-glucan cell wall antigen tests are negative in mucormycosis. Isavuconazole and AmBisome can be used,but despite their use, mortality remains high.

Candidiasis

Direct pulmonary invasion by *Candida* species is rare even in immunocompromised patients, with positive sputum cultures usually reflecting colonization or oropharyngeal infection. Pulmonary infection presenting as lung nodules (often peripheral and large) occurs in neutropenic patients as haematogenous spread from other infected sites such as indwelling vascular catheters. *Candida albicans* is the most common species, but a range of non-albicans *Candida* (e.g. *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*) also cause disease. β-D-Glucan concentrations are elevated in serum; however, the sensitivity is only 75% and specificity 80%, and varies with the *Candida* species.

Cryptococcosis

Cryptococcus neoformans can cause pneumonia in immunocompromised patients and occasionally in immunocompetent individuals. It presents with dyspnoea, cough and fever. HIV/AIDS (CD4 count <200 cells/mm^3) 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 lumbar puncture and cerebrospinal fluid culture.

Diagnosis is by microscopic identification (India 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-positive results and the test can remain positive for many months after treatment. Treatment with prolonged courses of fluconazole, with or without the addition of flucytosine, is usually effective.

Endemic fungi

Several fungal pathogens are found in specific geographical areas and cause primary infection by inhalation or inoculation of contaminated material (e.g. faecal matter from bats or bamboo rats, depending on the fungus). Common endemic fungi causing pulmonary infections include *Histoplasma capsulatum*, *Coccidioides* (*C. immitis*, *C. posadasii*), *Blastomyces dermatitidis* and *Talaromyces* (formerly *Penicillium*) *marneffei*. Reactivation of latent infection occurs in immunocompromised patients, especially with defects in T-cell-mediated immunity, and can result in a disseminated infection with a high mortality. Hence a history of travel or residence in a high-risk area can be highly relevant.

The presentation varies by pathogen but often mimics TB, with cavitating pneumonias, pulmonary nodules and enlarged mediastinal and hilar lymph nodes. Systemic infection presents with a miliary pattern and multiorgan involvement. The diagnosis requires identifying the fungus in respiratory samples or biopsy material, including bone marrow aspirates. Culture can take 6 weeks. *Histoplasma capsulatum* can be rapidly detected using an antigen detection assay. For most endemic fungi serology identifies patients with previous exposure, but it is not reliable in immunocompromised patients.

Table 1. 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, sulfonamides) Leukaemia AIDS Felty syndrome Aplastic anaemia Early HSCT	Gram-positive bacilli (*Staphylococcus aureus*, streptococci) Gram-negative bacilli Fungi (*Aspergillus* spp., *Candida* spp., non-*Aspergillus* filamentous fungi)
Neutrophil chemotaxis	Diabetes mellitus Cirrhosis Sarcoidosis Drugs (glucocorticoids)	*Staphylococcus aureus* Streptococci *Candida* spp. *Mucor* spp.
Neutrophil phagocytosis	Chronic granulomatous disease Myeloproliferative disorders Inherited phagocyte defects	*Staphylococcus aureus* *Nocardia* spp. Gram-negative bacilli Fungi (*Aspergillus* spp., *Candida* spp., non-*Aspergillus* filamentous fungi)
T-cell-mediated immunity	AIDS Lymphoma HSCT Solid organ transplantation Drugs (T-cell-depleting antibodies, glucocorticoids, ciclosporin, tacrolimus)	Herpesviruses Respiratory viruses *Pneumocystis jirovecii* Endemic mycoses, e.g. *Histoplasma capsulatum*, *Cryptococcus* Parasites (*Strongyloides*, *Toxoplasma*) Mycobacteria *Nocardia* *Legionella pneumophila*
B-cell-mediated/antibody deficiency	Multiple myeloma Plasmaphaeresis Drugs (anti-B-cell therapies)	Encapsulated bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*) Herpesviruses

Immune disorder	Causes	Typical microorganisms
	HSCT Chronic lymphocytic leukaemia Lymphoma Multiple myeloma	
Other		
Complement deficiency	Congenital Acquired (systemic lupus erythematosus, anorexia nervosa)	Encapsulated bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae)* *Staphylococcus aureus*
Asplenia	Splenectomy Sickle cell disease	Encapsulated bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*) *Staphylococcus aureus*
Other immunosuppressive medication	Anti-TNF medication	Mycobacteria, endemic mycoses
	Tyrosine kinase inhibitors	Fungi (*Aspergillus* spp.), varicella-zoster virus
	JAK inhibitors	Varicella-zoster virus
CAR-T therapy		Persistent respiratory virus infection, encapsulated bacteria causing exacerbations of bronchiectasis linked to hypogammaglobulinaemia

CAR-T, chimeric antigen receptor T-cell therapy; HSCT, haemopoietic stem cell transplantation; JAK, Janus kinase; TNF, tumour necrosis factor.

Table 2. Treatment of specific respiratory viruses

Virus	Treatment
Influenza	Neuraminidase inhibitors (zanamivir, oseltamivir)[a]
	Amantadine
Parainfluenza	IVIG[b]
	Ribavarin[c]
RSV	Ribavarin[c]
	Palivizumab
Human metapneumovirus	Ribavarin[b,c]
	IVIG[b]
Adenovirus	Ribavarin[b,c]
	Cidofovir[b]
	Brincidofovir[d]
Sars-CoV-2 (coronavirus)[e]	Remdesevir[a]
	Nirmatrelvir and ritonavir[a]
	Molnupiravir[a]

[a] Effective at reducing disease severity and duration.

[b] *In vitro* activity present but lack of data means there are no currently available recommendations on treatment.

[c] Can be administered orally, intravenously or nebulized.

[d] In Phase III clinical trials.

[e] Effectiveness in other types of coronavirus unknown.

IVIG, Intravenous immunoglobulin.

Table 3. Treatment of specific fungal pathogens

Fungal pathogen	Treatment
Aspergillus species	*First line*: •Voriconazole •Lipid formulation of amphotericin *Second line*: •Posaconazole[a] •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 *Second line*: •Posaconazole •Voriconazole
Candida species	*First line*: •Fluconazole (*C. albicans*) •Caspofungin (*C. glabrata*, *C. krusei*) *Second line*: •Voriconazole •Itraconazole •Posaconazole[a] •Micafungin •Amphotericin
Non-*Aspergillus* filamentous fungi (e.g. *Fusarium*, *Mucor* spp., *Scedosporium*, *Penicillium)*	*First line*: •Liposomal amphotericin •Isavuconazole *Second line*: •Posaconazole
Endemic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*, *Talaromyces*)	*First line*:

Fungal pathogen	Treatment
	•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 4. EORTC criteria for the diagnosis of invasive fungal disease

Category	Criteria
Probable (one from A, B and C) or Possible (one from A and B, without C)	A. Host factors (neutropenia for >10 days, allogeneic stem cell transplant, haematological malignancy, solid organ transplant, prednisolone 0.3 mg/kg for ≥3 weeks, T cell or B cell immunosuppressant, inherited severe immunodeficiency), GVHD B. CT signs (nodule ± halo, air crescent sign, cavity), tracheobronchitis C. Culture in BALF or sputum, positive galactomannan in BALF or serum, positive β-D-glucan in serum, ≥2 positive *Aspergillus* PCR results in serum and/or BALF
Proven	Culture of fungus from normally sterile sites (not BALF), or PCR positive with fungus seen in tissue, or demonstration of tissue invasion on biopsy

Commented [CW1]: AQ: T cell or B cell what, please?

Commented [JP2R1]: I have removed the comma

KEY REFERENCES

1. Lynch JP, 3rd, Reid G, Clark NM. Nocardia spp.: a rare cause of pneumonia globally. *Semin Respir Crit Care Med* 2020; **41:** 538–54.
2. Galmiche S, Luong Nguyen LB, Tartour E, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect* 2022; **28:** 163–77.
3. Piñana JL, Giménez E, Gómez MD, et al. Pulmonary cytomegalovirus (CMV) DNA shedding in allogeneic hematopoietic stem cell transplant recipients: implications for the diagnosis of CMV pneumonia. *J Infect* 2019; **78:** 393–401.
4. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46:** 1813–21.
5. de Heer K, Gerritsen MG, Visser CE, Leeflang MM. Galactomannan detection in broncho-alveolar lavage fluid for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev* 2019; **5:** CD012399.

Question 1

A 38 year old Caucasian woman who has undergone a allogenic stem cell transplant 2 months previously presents with a 1 week history of cough, breathlessness on exertion and low grade fever. She is on valganciclovir for a recently diagnosed CMV viraemia. She has no travel history of note. Her chest x-ray shows bilateral reticulonbodular infiltrates. Which is the most likely organism causing her symptoms?

A) *Haemophilus influenzae*
B) *Histoplasma capsulata*
C) *Mycobacterium tuberculosis*
D) *Pneumocystis jirovecii*
E) *Treponema pallidum*

Answer D: D

Pneumocysitis jirovecii infections are associated with CMV and commonly affect patients after stem cell transplant. There is no travel history to suggest Histoplasma or Mycobacterial infection, Trepnoemal infections rarely affect the lungs. While Haemophilus is a common cause of respiratory infections, it does not typically cause widespread infiltrates.

Question 2

A 43-year-old Caucasian man with chronic granulomatous disease presents with cough, purulent sputum and weight loss over the past 6 weeks. His symptoms have not improved with sequential courses of intravenous flucloxicillin, co-amoxiclav and meropenem. A CT scan of his chest shows focal consolidation with no mediastinal lymphadenopathy, over a background of unchanged nodules, likely granuloma. Which treatment should be added next?

A) Linezolid orally
B) Prednisolone orally
C) Quadruple antituberculous therapy
D) Rituximab intravenously
E) Vorinconazole, intravenously

Answer E

Voriconazole is the current answer as patients with CGD have high rates of invasive fungal disease, such as aspergillosis. There are no common autoimmune/autoinflammatory diseases associated with CGD that would necessitate immunosuppression with prednisolone or rituximab. While pulmonary TB is possible, patients with CGD don't have a significant increase in TB risk compared to the general population.

Question 3

A 63-year-old woman, of South Asian ethnicity who spent her childhood in Kenya, with a background of Ulcerative colitis treated with infliximab and prednisolone presented with a 3 week history of fevers, weight loss and non-productive cough. There was no improvement with a course of amoxicillin. A chest x-ray showed right upper zone shadowing and a subsequent CT demonstrated right apical consolidation with cavitation and right hilar and subcarinal lymphadenopathy. What would be the next best test to perform?

A) Serum β-D-glucan
B) Sputum Calcofluor White stain

C) Serum Cryptococcal Ag
D) Serum QuantiFERON
E) TB PCR of bronchoalveolar lavage or endobronchial ultrasound aspirate of mediastinal lymph nodes

AnswerE

The most likely cause of this patient's symptoms is *Mycobacterium tuberculosis* due to the anti-TNF treatment and probable exposure The quickest way of getting a positive result is a Genexpert PCR test of a relevant microbiolgical sample. β-D-glucan is elevated in many fungal infections, Cryptococcal Ag is specific for cryptococcal infection, Calcofluor stains for fungal cell wall components. QuantiFERON is a test that shows previous exposure to TB but does not confirm active infection.