Infectious respiratory disease in non-HIV immunocompromised patients

This review summarizes current knowledge regarding frequently encountered infectious respiratory complications in adult immunocompromised hosts (excluding those with human immunodeficiency virus (HIV) infection). It discusses the clinical approach to these patients, the usual patterns of disease and the most important pathogens.

Respiratory disease is often seen in immunocompromised patients but both diagnosis and management can be complex and challenging, especially as atypical presentations and the co-existence of infection (sometimes with more than one pathogen) and non-infectious disease are common. However, although non-infective causes of lung disease are common in this population, the patient presenting with new respiratory symptoms, pulmonary infiltrates and fever should be considered as having a lung infection until proven otherwise. The infection may be caused by pathogens that normally cause infection in healthy individuals, but is frequently caused by opportunistic pathogens that are usually weakly virulent but can cause severe infections in the immunodeficient host.

The immunodeficiency may involve the innate and/or adaptive immune function, and is most commonly the result of an acquired rather than a congenital cause. In adults this is usually as a result of medication (cytotoxic chemotherapy, prolonged use of glucocorticosteroids (>30 mg/day for 21 days or longer), use of biological compounds such as anti-TNF and anti-CD20 drugs), post-transplantation (haematopoeitic stem cell transplantation or solid-organ transplantation), haematological malignancy, aplastic anaemia and AIDS (Yale and Limper, 1996; Kim et al, 1998; Alvarez et al, 2011; José and Brown, 2012).

Clinical assessment

Immunocompromised patients may develop infection as a result of a range of pathogens and targeting all of these with empirical therapy is not practical because of the potential toxicity of some of these agents. Fortunately, targeted empirical therapy can be started at the time of presentation, using the clinical features to narrow down the differential diagnosis to the most likely pathogens. This involves knowing the underlying immune defect(s) as these predispose to specific pathogens (*Table 1*), timing post-transplantation (*Table 2*), as well as the clinical presentation, particularly the rate of disease onset and the radiological features on computed tomography scan of the thorax. Other factors that need to be considered are:

- Current prophylactic regimen – those receiving prophylactic doses of co-trimoxazole, aciclovir or an antifungal agent (e.g. voriconazole) are less likely to develop infection with *Pneumocystis jirovecii*, herpes viruses or *Aspergillus* spp. respectively. Furthermore, although fluconazole prophylaxis reduces the incidence of *Candida albicans* infection, it predisposes to non-albicans *Candida* infection
- Location of exposure – as in healthy individuals, respiratory infections acquired in the community are more likely to be caused by viruses (e.g. respiratory syncytial virus) or gram-positive bacteria (e.g. *Streptococcus pneumoniae*) and less likely to be infected with potential antibiotic-resistant pathogens (e.g. *Pseudomonas aeruginosa*, meticillin-resistant *Staphylococcus aureus*)
- Previous microbiological results – patients with a previous history of *Aspergillus* infection or cytomegalovirus viraemia may have recurrences during periods of immunosuppression
- Ethnicity and travel – patients from certain ethnic backgrounds and geographical locations such as sub-Saharan Africa have an increased risk of developing tuberculosis as a result of re-activation of latent infection. Furthermore, travel to areas of with a high incidence of endemic fungi (e.g. *Histoplasma capsulatum* in the mid-west of the USA) may lead to exposure, latent infection and future re-activation when the individual is immunosuppressed
- Pre-existing lung disease – bronchiectasis is common in immunocompromised patients and predisposes individuals to infection with *P. aeruginosa* or *S. aureus.* Cavitatory disease (e.g. from previous tuberculosis) may predispose to aspergillomas and *Aspergillus* infection (José and Brown, 2014)
- Presence of indwelling vascular catheters – septic emboli can occur from infected catheters (e.g. *C. albicans*).

Dr Ricardo J José *is Wellcome Trust Clinical Research Fellow in the Centre for Inflammation and Tissue Repair, University College London and Honorary Specialist Registrar, Department of Thoracic Medicine, University College London Hospital, London WC1E 6JF,* **Professor Burton F Dickey** *is Professor and Chair in the Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Centre, Houston, and* **Professor Jeremy S Brown** *is Professor of Respiratory Infection, Centre for Inflammation and Tissue Repair, University College London and Consultant Respiratory Physician, Department of Thoracic Medicine, University College London Hospital, London*

Correspondence to: Dr RJ José (r.jose@ucl.ac.uk)

Investigations

Radiology

Radiological features help with the differential diagnosis of potential pathogens (*Table 3*) and although chest radiographs are useful for monitoring progress, they are generally unable to adequately characterize the distribution and nature of pulmonary infiltrates to help identify potential causative pathogens. Therefore, computed tomography of the thorax is recommended for most patients presenting with fever and lung infiltrates on the chest radiograph to help define whether they represent consolidation, ground glass shadowing, nodules or 'tree-in-bud' appearances (*Figures 1a–d*). The main exception is lobar consolidation that can usually be identified using chest radiographs alone. Computed tomography scans can also identify new changes that are not always visible on a chest radiograph (e.g. in a patient with fever and no localizing symptoms), and help direct diagnostic procedures (e.g. bronchoalveolar lavage or biopsy).

Routine blood tests

Blood tests that should be done include:

- Full blood count (including white cell differential) for the identification of neutropaenia or neutrophilia
- Acute phase reactants may be useful to help differentiate between bacterial, viral and fungal infection. For example, high levels of C-reactive protein (>250 mg/litre) and high levels of procalcitonin (>0.5 µg/litre) suggest bacterial infection (Ip et al, 2007), while C-reactive protein levels between 100–300 mg/litre

Table 1. Nature of immune defect, cause and probable pathogens

Immune disorder		Causes	Typical microorganisms
Neutrophil disorders	Neutropenia	Drugs (cytotoxic chemotherapy, azathioprine, methotrexate, carbimazole, sulphonamides), leukaemia, acquired immune deficiency syndrome, Felty's syndrome, aplastic anaemia, early haematopoetic stem cell transplantation	Gram-positive (e.g. *Staphylococcus aureus, Streptococcus* spp.), gram-negative bacilli (e.g. *Pseudomonas aeruginosa, Moraxella catarrhalis, Legionella pneumophila*), Fungi (*Aspergillus* spp., *Candida* spp., non-*Aspergillus* filamentous fungi)
	Neutrophil chemotaxis	Diabetes mellitus, cirrhosis, drugs (glucocorticoids, amphotericin B)	*Staphylococcus aureus, Streptococcus* spp., *Candida* spp., Zygomycosis
	Neutrophil phagocytosis	Chronic granulomatous disease, myeloproliferative disorders, inherited phagocyte defects (Kostman syndrome, leukocyte adhesion deficiency, hyper-immunoglobulin E (IgE) syndrome, myeloperoxidase deficiency)	*Staphylococcus aureus*, Nocardia spp., gram-negative bacilli (e.g. *Pseudomonas aeruginosa, Moraxella catarrhalis, Legionella pneumophila*), fungi (*Aspergillus* spp., *Candida* spp., non-*Aspergillus* filamentous fungi)
T-cell-mediated immunity		Acquired immune deficiency syndrome, lymphoma, haematopoetic stem cell transplantation, 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		Plasmapheresis, drugs (anti-B cell therapies, e.g. anti-CD20), haematopoetic stem cell transplantation, chronic lymphocytic leukaemia, lymphoma, multiple myeloma, congenital (common variable immune deficiency, x-linked agammaglobulinaemia, hyper IgM syndrome, selective IgG subclass deficiency)	Encapsulated bacteria (e.g. *Streptococcus pneumoniae, Haemophilus influenzae), Staphylococcus aureus, Mycoplasma pneumoniae*, herpesviruses
Other	Complement deficiency	Congenital (C1-C9 deficiency, mannose-binding lectin deficiency), acquired (systemic lupus erythromatosus, 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, Neisseria meningitides*), *Staphylococcus aureus*

Adapted from José and Brown (2012)

Table 2. Differential diagnosis based on duration post-transplantation

	Immediate	Early	Late
Stem cell transplantation	<30 days	<100 days	>100 days
	Bacterial pneumonia (gram-negative, hospital-acquired), invasive aspergillosis	Respiratory viruses, Cytomegalovirus pneumonitis, *Pneumocystis jirovecii*	Similar infections as in healthy individuals unless graft *vs* host disease is present and the patient is on immunosuppressive medication
Solid organ transplantation	<1 month	<6 months	>6 months
	Bacterial pneumonia (gram-negative, hospital-acquired)	Cytomegalovirus pneumonitis, *Pneumocysitis jirovecii*, invasive aspergillosis, Nocardiosis, Mycobacteria	Similar infections as in healthy individuals unless rejection is present and patient is on immunosuppressive medication

Table 3. Differential diagnosis based on onset of clinical presentation and pattern of radiological features

	Speed of onset		
Radiological pattern	Acute (<24 h)	Sub-acute (days)	Chronic (weeks)
Consolidation	Bacterial pneumonia	Bacterial pneumonia, Mycobacteria*, invasive filamentous fungi, Aspergillosis, *Nocardia* spp., *Legionella pneumophila*	Mycobacteria*, *Nocardia* spp., bacterial pneumonia, invasive filamentous fungi
Diffuse ground glass	Respiratory viruses, viral pneumonitis	Respiratory viruses, Cytomegalovirus pneumonitis, *Pneumocystis jirovecii*	
Nodules	Metastatic infection (e.g. septic emboli from central venous catheter), invasive filamentous fungi	Metastatic infection, invasive filamentous fungi, Nocardia spp., Mycobacteria*	Mycobacteria*, *Nocardia* spp., invasive filamentous fungi
Tree-in-bud appearance	Respiratory viruses, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*	Respiratory viruses (diffuse), *Chlamydia pneumoniae* (diffuse), *Mycoplasma pneumoniae* (diffuse), Mycobacteria (focal), Aspergillus tracheobronchitis (focal)	Mycobacteria (focal), Aspergillus tracheobronchitis (focal)

*Tuberculous and non-tuberculous mycobacteria. Adapted from Quint and Brown (2013)

associated with low procalcitonin levels (<0.5 µg/litre) suggest fungal infection (Marková et al, 2013). A combination of low C-reactive protein (<20 mg/litre) and low procalcitonin (<0.1 µg/litre) indicate a viral aetiology (Ruuskanen et al, 2011)

- Renal function tests are useful because antibiotic dosing needs to be adjusted in the presence of renal impairment
- Liver function tests may identify the liver or bone as other sites of infection (e.g. disseminated nocardiosis), and if abnormal may affect the choice of antimicrobial agent.

Microbiological investigations

All patients should have blood and sputum cultures. Those with consolidation on chest radiograph or computed tomography should also have *Legionella* and pneumococcal urinary antigen tests. Those with ground glass or tree-in-bud changes on computed tomography should have a nasopharyngeal aspirate for respiratory virus culture, polymerase chain reaction or immunofluorescence (depending on what tests are available within the hospital), serology for *M. pneumoniae* and *C. pneumoniae*, and assessment of cytomegalovirus status. Patients presenting with macronodules, consolidation or focal tree-in-bud changes should be tested for serum fungal antigens (β-D-glucan and galactomannan). Mycobacterial cultures may be necessary if the patient was born in a country with a high incidence of tuberculosis, and if non-tuberculous mycobacterial infection is suspected.

Bronchoscopy and other invasive investigations

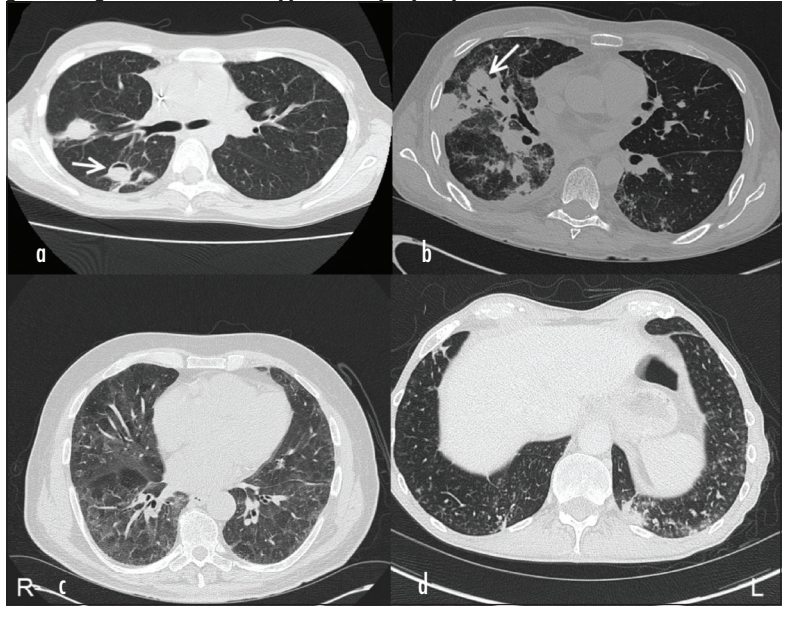
More invasive diagnostic tests are required in some patients, particularly if not responding to empirical therapy within 48 hours. If the patient is clinically stable, bronchoscopy and bronchoalveolar lavage is a useful test, with sensitivity for detecting clinically relevant pathogens reported between 31–80%. However, yields are better if the procedure is performed early after clinical presentation (< 4 days), with the highest yields in bronchoscopies performed within 24 hours (Shannon et al, 2010). Computed tomography-guided biopsies of macronodules are a very effective way of confirming invasive aspergillosis or other fungal pathogens, as well as *Nocardia* or mycobacterial infection. Additionally, when the diagnosis remains unclear and a poor response to empirical therapy remains, video-assisted thoracoscopic surgery biopsy may be required.

Non-opportunistic infections

Bacterial pneumonia

Although immunocompromised patients are prone to infection with opportunistic pathogens, the most common cause of infection is still bacterial pneumonia. This is the result of neutropenia, prolonged use of high dose

Figure 1. Radiological features seen on computed tomography scans of the thorax. a. Macronodules (arrow – air crescent sign). b. Peri-bronchial consolidation. c. Ground-glass change. d. 'Tree-in-bud' appearance (periphery of the left lower lobe).



steroids, use of cytotoxic medications, antibody deficiencies and increased risk of aspiration as a result of oral mucositis. Additionally, prolonged hospital admissions predispose to nosocomial infections that are usually the result of gram-negative bacteria with a high frequency of antimicrobial resistance (e.g. *P. aeruginosa*, *Escherichia coli*, *Enterobacter*). However, infections with gram-positive bacteria such as *S. pneumoniae* and *S. aureus* are also common. Presentation is usually with fever, cough, dyspnoea and focal lobar consolidation on chest radiographs associated with rapid rises in inflammatory markers. First-line empiric antibiotic therapy varies according to local hospital guidelines but usually includes an extended spectrum β-lactam ± aminoglycoside for 10–21 days. Importantly, if patients are not responding within 48–72 hours of starting antibiotics, bronchoscopy and antibiotic switch to second-line agents (e.g. carbapenems, and/or teicoplanin if meticillin-resistant *S. aureus* infection is suspected) and bronchoalveolar lavage should be considered. Anaerobic bacterial pathogens are usually effectively treated by the empirical therapies used in immunocompromised patients.

Respiratory viruses

The respiratory viruses, respiratory syncytial virus, parainfluenza, influenza, adenovirus, human metapneumovirus, coronavirus and rhinovirus are relatively common causes of bronchiolitis and pneumonia in patients with defects in T-cell mediated immunity and lead to significant morbidity and mortality (Shah et al, 2012). Symptoms include characteristic coryzal symptoms but the clinical examination and chest radiograph findings are often unremarkable.

Unlike the immunocompetent host, in the immunocompromised patient these infections can persist for weeks and frequently cause significant lower respiratory tract infection. Computed tomography scans can show characteristic diffuse tree-in-bud changes, or less specific ground glass infiltrates. The diagnosis is confirmed by identification of the virus in nasopharyngeal aspirate or bronchoalveolar lavage fluid samples by either immunofluorescence for viral antigens or polymerase chain reaction for viral ribonucleic acids; the sensitivity is higher in bronchoalveolar lavage fluid samples (Ruuskanen et al, 2011).

Treatment is mainly supportive but specific therapy with neuraminidase inhibitors or amantadine may be used to reduce duration and severity of influenza infection, and ribavirin or pavlizumab may be used for the treatment of severe respiratory syncytial virus infection. Ribavirin and intravenous immunoglobulins have in-vitro activity against parainfluenza virus and human metapneumovirus but recommendations for clinical use have not yet been made. Secondary bacterial infections are common and patients will often require concurrent antibiotics. Respiratory virus infections can exacerbate lung graft *vs* host disease in allograft haematopoietic stem cell transplant recipients.

Specific opportunistic infections

Herpesviruses

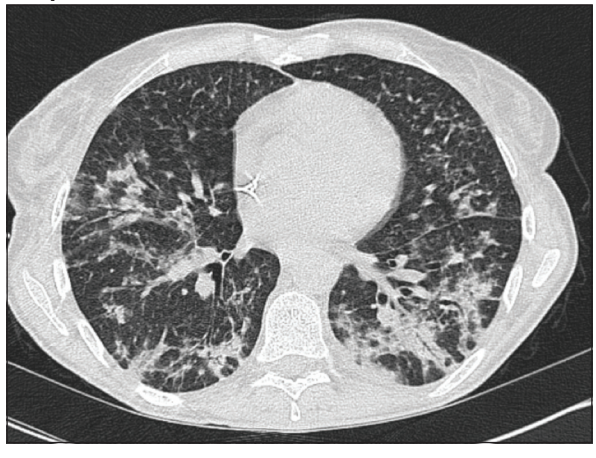
Cytomegalovirus pneumonitis commonly affects patients with deficiencies in cell-mediated immunity, particularly after solid organ transplant recipients or haematopoeitic stem cell transplantation. It is associated with high mortality and usually presents with insidious onset of fever, cough and progressive breathlessness with hypoxia, and diffuse ground glass change or peri-bronchial consolidation on computed tomography, commonly affecting the lower lobes (*Figure 2*).

The diagnosis can be difficult to establish and requires demonstration of cytomegalovirus infection (active cytomegalovirus replication) by measuring pp65 antigen or cytomegalovirus DNA levels by polymerase chain reaction in blood or bronchoalveolar lavage, and evidence of organ-specific involvement. However, in cytomegalovirus pneumonitis, viraemia is not always detectable, and when it is detectable it is not proof that the pulmonary infiltrates are caused by cytomegalovirus. Cytomegalovirus is a more likely cause of pneumonia in the presence of a very high or rapidly increasing viral load. Additionally, cytomegalovirus identification in the respiratory tract is required by culture or polymerase chain reaction methods on bronchoalveolar lavage or biopsy samples.

First-line treatment consists of intravenous ganciclovir or oral valganciclovir for at least 2 weeks and until cytomegalovirus is no longer detected. Additionally, in the immunocompromised patient, cytomegalovirus immunoglobulin or hyperimmune intravenous immunoglobulin can be given (National Comprehensive Cancer Network, 2014). Second-line therapies include foscarnet and cidovir.

Other herpesviruses such as herpes simplex virus, varicella zoster virus and human herpes virus-6 are rare causes of pneumonia. Presentation is similar to cytomegalovirus pneumonitis but these may be associated with a rash, which allows isolation of the virus from skin lesions in addition to bronchoalveolar lavage fluid. First-line treat-

Figure 2. Peri-bronchial organizing pneumonia in response to cytomegalovirus infection post-haematopoietic stem cell transplantation.



ment of herpes simplex virus and varicella zoster virus is with aciclovir but valaciclovir, famciclovir, cidovir and foscarnet can also be used. No drug has specifically been approved for the treatment of human herpes virus-6 but ganciclovir and foscarnet are recommended by experts for the treatment of severe human herpes virus-6 infection (National Comprehensive Cancer Network, 2014).

Nocardiosis

Nocardia spp. are gram-positive bacteria that are found in soil and stagnant water and are an uncommon late complication in patients post-stem cell transplantation, particularly in those with graft *vs* host disease, on prolonged glucocorticosteroid therapy, and associated with concomitant cytomegalovirus infection. Infection with these organisms, typically with *N. asteroids* complex, occurs through inhalation, causing focal consolidation and nodular infiltrates. The pneumonia usually develops over weeks with cough, haemoptysis, fever, night sweats and weight loss.

Classically, the computed tomography scan demonstrates patches of dense consolidation or large pleural-based nodules that frequently cavitate (*Figure 3*). In half of patients the infection can spread haematogenously to the brain, joints and soft tissue, carrying a high mortality, particularly with CNS involvement. The diagnosis is made by identifying characteristic beaded branching gram-positive bacteria with weakly positive acid-fast filaments on microscopy or by prolonged (up to 3 weeks) aerobic culture of blood and sputum (Martínez et al, 2008). Initial treatment in immunocompromised patients involves the use of two or three antibiotics and is prolonged, lasting up to 12 months. First-line therapy includes co-trimoxazole, and most strains are also sensitive to carbapenems, amikacin, third generation cephalosporins or tetracyclines.

Pneumocystis jirovecii pneumonia

P. jirovecii pneumonia usually affects patients with impaired T-cell immunity or those on prolonged therapy with high dose glucocorticoids. The clinical presentation is typically that of a dry cough and progressive breathlessness over days to weeks (but may be fulminant), associated with hypoxaemia which is particularly marked during exercise. Often there is paucity of clinical findings on examination and there is not much fever or a particularly raised C-reactive protein level. Computed tomography scans classically demonstrate ground glass changes in the upper lobes, which spare the peripheries (*Figure 4*).

The diagnosis is confirmed by identifying *Pneumocystis* cysts in bronchoalveolar lavage fluid or induced sputum with Giesma or Grocott stains. Polymerase chain reaction increases the diagnostic yield but is associated with false positives as a result of colonization in the absence of disease. First line treatment consists of high dose trimethoprim-sulphamethoxazole. Alternative agents include clindamycin plus primaquine, atovaquone, pentamidine or trimethoprim plus dapsone. Glucocorticosteroids should also be given to patients with severe hypoxaemia (PaO_2 <8 kPa).

Pulmonary aspergillosis

Aspergillus spp. are ubiquitous in the environment and are continually inhaled by humans, but they usually are only able to cause infection when there are defects in neutrophil- or macrophage-mediated immunity such as prolonged neutropaenia (>10 days), chronic granulomatous disease and the prolonged use of high-dose steroids. There is also an association with lung graft *vs* host disease. As they enter the body via the respiratory tract, the sinuses and lungs are the most common sites of infection but haematogenous spread to the CNS, bone and skin may also occur. The clinical presentation of patients with invasive pulmonary aspergillosis classically consists of fever, chest pain and haemoptysis, although many patients will present only with fever. Computed tomography scan features include patchy consolidation or large nodules. The nodules may be surrounded by ground glass infiltrates caused by haemorrhage ('halo' sign) or they may cavitate as immune function is restored ('air-crescent' sign). Furthermore, fungal balls may form within the cavities, forming aspergillomas. Aspergillosis can cause life-threatening haemoptysis as a result of invasion of the pulmonary arteries.

Aspergillus spp. can be identified by microscopy with the Gomori methenamine silver stain as septated hyaline hyphae with dichotomous acute angle branching. A con-

Figure 3. Multiple pulmonary nodules in a patient with* Nocardia *infection post-haematopoietic stem cell transplantation.

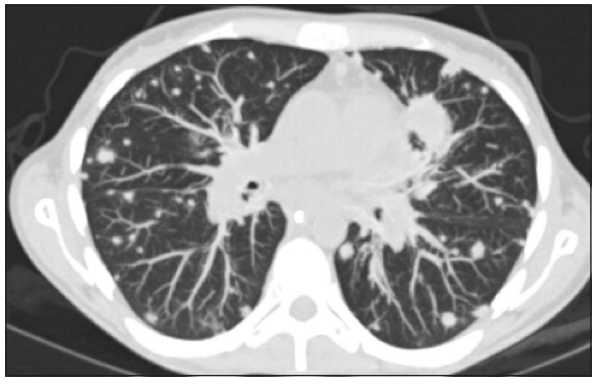
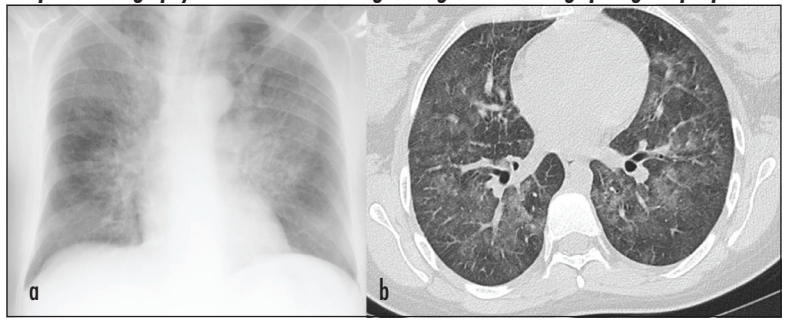


Figure 4. Chest radiograph and computed tomography scan of the chest in a patient with* Pneumocystis jirovecii *infection post-haematopoetic stem cell transplantation. a. Chest radiograph demonstrates bilateral peri-hilar shadowing (bat-wing appearance) and (b) computed tomography scan shows bilateral ground-glass shadowing sparing the peripheries.



firmed diagnosis requires culturing *Aspergillus* spp. from sputum or bronchoalveolar lavage fluid and demonstrating tissue invasion by histological evaluation of biopsies. However, because of the difficulty in obtaining histological samples the diagnosis is usually established based on the clinical scenario and computed tomography appearances supported by culture and/or detection of galactomannan antigen (a cell wall component of *Aspergillus* spp. and other fungi) in bronchoalveolar lavage fluid or blood. However, false-positive galactomannan results may occur with concomitant use of tazobactam-piperacillin or the intravenous formulation of amoxicillin clavulanate, and in post-stem cell transplant patients with gastrointestinal graft *vs* host disease or mucositis.

Less commonly, patients may develop *Aspergillus* tracheobronchitis which presents with a relentless cough, perhaps fever, tracheal and bronchial wall thickening on computed tomography. The diagnosis is confirmed by bronchoscopy which will show macroscopically inflamed and necrotic bronchial mucosa, biopsies and washings of which will contain *Aspergillus*. Patients with milder immunosuppression may develop chronic necrotizing pulmonary aspergillosis or chronic cavitatory pulmonary aspergillosis. These are more indolent forms of invasive aspergillosis that present with a history of chronic cough, malaise and weight loss, and a slowly progressive patch of consolidation (with or without cavitation) or an expanding upper lobe cavity with a thickened wall respectively. Treatment of invasive aspergillosis usually involves a 12-week course of voriconazole but the lipid formulation of amphotericin B, posaconazole, itraconazole, caspofungin or anidulafungin can be used as alternatives. Therapeutic drug monitoring of voriconazole, posaconazole and itraconazole is recommended to ensure adequate therapeutic plasma levels are achieved (National Comprehensive Cancer Network, 2014).

Cryptococcal pneumonia

The clinical presentation and radiological features of pneumonia with *Cryptococcus neoformans* are non-specific; patients can be asymptomatic despite obvious chest radiograph changes. Therefore a high index of suspicion is required, particularly in patients with impaired T-cell mediated immunity (CD4 <200 cells/mm^3). The fungi can be identified by microscopy using Indian ink staining or cultures from sputum or bronchoalveolar lavage fluid. Additionally, a positive cryptococcal antigen test is diagnostic and suggests disseminated disease with bacteraemia or CNS involvement. Treatment consists of at least 2 weeks of liposomal amphotericin B plus flucytosine followed by 8 weeks of fluconazole or alternatively, posaconazole or voriconazole. **BJHM**

KEY POINTS

- Knowledge of the immune defect combined with the clinical presentation and computed tomography radiological features helps narrow down the potential pathogens causing infection.
- Not all infections in immunocompromised individuals are caused by opportunistic pathogens.
- Prolonged use of moderate dose corticosteroids (20–30 mg/day for >21 days) is an often-overlooked risk factor for opportunistic infections.
- In selected patients early bronchoscopy (within 48 hours) is helpful and increases the yield of microbiological identification of a potential pathogen.

Table 1 *is adapted from José and Brown (2012) by kind permission of Elsevier.*

Conflict of interest: none.

Alvarez B, Arcos J, Fernández-Guerrero ML (2011) Pulmonary infectious diseases in patients with primary immunodeficiency and those treated with biologic immunomodulating agents. *Curr Opin Pulm Med* **17**(3): 172–9 (doi: 10.1097/MCP.0b013e3283455c0b)

Ip M, Rainer TH, Lee N et al (2007) Value of serum procalcitonin, neopterin, and C-reactive protein in differentiating bacterial from viral etiologies in patients presenting with lower respiratory tract infections. *Diagn Microbiol Infect Dis* **59**(2): 131–6 (doi: 10.1016/j.diagmicrobio.2007.04.019)

José RJ, Brown JS (2012) Opportunistic and fungal infections of the lung. *Medicine* **40**(6): 335–9 (doi: 10.1016/j.mpmed.2012.03.013)

José RJ, Brown JS (2014) Bronchiectasis. *Br J Hosp Med (Lond)* **75** (Suppl 10): C146–51 (doi: 10.12968/hmed.2014.75.Sup10.C146)

Kim HA, Yoo CD, Baek HJ et al (1998) *Mycobacterium tuberculosis* infection in a corticosteroid-treated rheumatic disease patient population. *Clin Exp Rheumatol* **16**(1): 9–13

Marková M, Brodská H, Malíčková K, Válková V, Cetkovský P, Kolář M, Haluzík M (2013) Substantially elevated C-reactive protein (CRP), together with low levels of procalcitonin (PCT), contributes to diagnosis of fungal infection in immunocompromised patients. *Support Care Cancer* **21**(10): 2733–42 (doi: 10.1007/s00520-013-1844-1)

Martínez R, Reyes S, Menéndez R (2008) Pulmonary nocardiosis: risk factors, clinical features, diagnosis and prognosis. *Curr Opin Pulm Med* **14**(3): 219–27 (doi: 10.1097/MCP.0b013e3282f85dd3)

National Comprehensive Cancer Network (2014) Prevention and Treatment of Cancer-Related infections. www.nccn.org/professionals/physician_gls/pdf/infections.pdf (accessed 29 June 2014)

Quint J, Brown JS (2013) Pneumonia in the non-HIV immunocompromised patient. In: Spiro S, Silvestri G, Agusti A, eds. *Clinical Respiratory Medicine*. Elsevier, Philadelphia, PA, USA: 330–45

Ruuskanen O, Lahti E, Jennings LC, Murdoch DR (2011) Viral pneumonia. *Lancet* **377**(9773): 1264–75 (doi: 10.1016/S0140-6736(10)61459-6)

Shah DP, Ghantoji SS, Mulanovich VE, Ariza-Heredia EJ, Chemaly RF (2012) Management of respiratory viral infections in hematopoietic cell transplant recipients. *Am J Blood Res* **2**(4): 203–18

Shannon VR, Andersson BS, Lei X, Champlin RE, Kontoyiannis DP (2010) Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transpl* **45**(4): 647–55 (doi: 10.1038/bmt.2009.203)

Yale SH, Limper AH (1996) *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* **71**(1): 5–13

Further reading

National Comprehensive Cancer Network (2014) Prevention and Treatment of Cancer-Related infections. www.nccn.org/professionals/physician_gls/pdf/infections.pdf (accessed 29 June 2014)

Quint J, Brown JS (2013) Pneumonia in the non-HIV immunocompromised patient. In: Spiro S, Silvestri G, Agusti A, eds. *Clinical Respiratory Medicine*. Elsevier, Philadelphia, PA, USA: 330–45

Shannon VR, Eapen GA, Jimenez CA et al (2010) Respiratory complications. In: Hong WK, Bast RC, Hait WN et al, eds. *Holland-Frei Cancer Medicine*. 8th edn. People's Medical Publishing House, Shelton, Connecticut: 1849–70