Non-infectious respiratory disease in non-HIV immunocompromised patients

This review summarizes current knowledge regarding frequently encountered non-infectious respiratory complications in adult immunocompromised hosts (excluding those with human immunodeficiency virus (HIV) infection). In particular it will discuss complications of transplantation and of primary immunodeficiencies.

This review summarizes current knowledge regarding frequently encountered non-infectious respiratory complications in adult immunocompromised hosts (excluding those with human immunodeficiency virus (HIV) infection). The plethora of immunocompromised patients may be the result of more frequent use of chemotherapeutic agents and transplantation as well as the advent of new therapies for various inflammatory and neoplastic diseases such as biological therapies (e.g. anti-tumour necrosis factor (TNF) and anti-CD20 drugs). These therapies often improve the outcomes of the primary disease, but may cause significant immunosuppression and toxicity as a consequence of their mechanism of action. Rarer causes of immunodeficiency associated with lung disease are a wide range of primary immune deficiencies involving components of the innate and adaptive immune system, most of which have an onset before adulthood.

Infections related to immunodeficiency are a notorious cause of pulmonary disease in immunocompromised patients (José and Brown, 2012), but non-infectious complications may often cause respiratory symptoms or pulmonary infiltrates and must be considered during the clinical evaluation. These non-infectious respiratory conditions are mainly evidence of therapeutic toxicity, although they can also be related to the underlying disease or the effects of immunosuppression. They may be the sole cause of a respiratory presentation or may co-exist with infection, thus explaining a poor response to empirical antimicrobial therapy (*Table 1*).

Respiratory complications post-stem cell and solid organ transplantation

Pulmonary oedema

Cardiogenic pulmonary oedema is common post-transplantation as a result of underlying comorbidities (e.g. pre-existing cardiac disease, renal impairment), the development of drug-induced cardiac toxicity (e.g. anthracyclines and cyclophosphamide), and the infusion of large volumes of intravenous fluids for hydration (renal protection) and medications. The onset of breathlessness may be acute or sub-acute, and is often accompanied with orthopnoea. Furthermore, the severity of dyspnoea and oxygen saturations may fluctuate, together with the individual's overall fluid status, peripheral oedema and weight. Chest radiographs (*Figure 1*) commonly demonstrate bilateral symmetric alveolar shadowing (peri-hilar infiltrates), upper lobe vascular diversion and bilateral pleural effusions. These findings may be amplified on computed tomography chest scans, and the images may raise the concern of infection or precipitate a diagnostic procedure (e.g. bronchoalveolar lavage and thoracentesis). Echocardiography is useful to confirm left ventricular systolic or diastolic dysfunction and a raised level of plasma brain natriuretic peptide also supports the diagnosis.

Table 1. Non-infectious pulmonary complications post-stem cell transplantation

<100 days	Pulmonary oedema (fluid overload)
	Pleural effusions
	Diffuse alveolar haemorrhage
	Idiopathic pneumonia syndrome
	Engraftment syndrome
	Pulmonary veno-occlusive disease
	Organizing pneumonia
	Drug toxicity
	Bronchiolitis obliterans (rare)
>100 days	Pulmonary oedema (fluid overload)
	Bronchiolitis obliterans
	Lymphocytic interstitial pneumonitis
	Organizing pneumonia
	Drug and radiation toxicity

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,* **Dr Saadia A Faiz** *is Associate Professor and* **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)

Non-cardiogenic pulmonary oedema caused by increased capillary permeability may also occur with infection, engraftment syndrome, hyperacute graft *vs* host disease or primary graft dysfunction (e.g. in the first 72 hours post-lung transplantation), and it may progress into acute lung injury or acute respiratory distress syndrome (e.g. perfusion-reperfusion of the allograft)(*Figure 2*). Acute respiratory distress syndrome is associated with high mortality despite improvements in supportive care. The presentation is similar to that of hydrostatic pulmonary oedema without evidence of cardiac dysfunction on echocardiography and with a pulmonary capillary wedge pressure <18 mmHg (The ARDS Definition Task Force, 2012).

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome results in acute pulmonary dysfunction associated with widespread alveolar injury post-haematopoietic stem cell transplantation and is associated with high mortality (>60%) (Panoskaltsis-Mortari et al, 2011). It presents with signs and symptoms of pneumonia (dyspnoea, cough and fever) in absence of infection, cardiac dysfunction, renal failure or fluid overload (Panoskaltsis-Mortari et al, 2011). Although the aetiology is not known, it is thought that alveolar injury is caused by toxic effects of chemoradiotherapy, occult infection and immune cell-mediated injury with the release of pro-inflammatory cytokines (Panoskaltsis-Mortari et al, 2011). The differential diagnosis overlaps a spectrum of disorders (*Figure 3*), which are discussed below.

Figure 1. Pulmonary oedema. Chest radiograph demonstrating bilateral peri-hilar shadowing with upper lobe diversion. These features may also be suggestive of* Pneumocystis jirovecii *infection especially in the absence of pleural effusions, which are commonly present in patients with fluid overload and pulmonary oedema and a rare finding in* P. jirovecii *pneumonia.

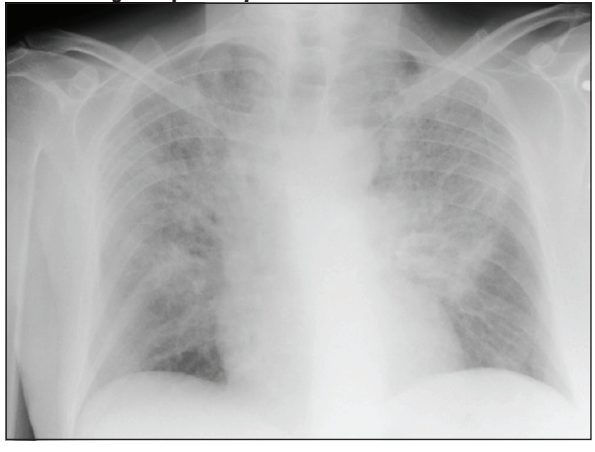
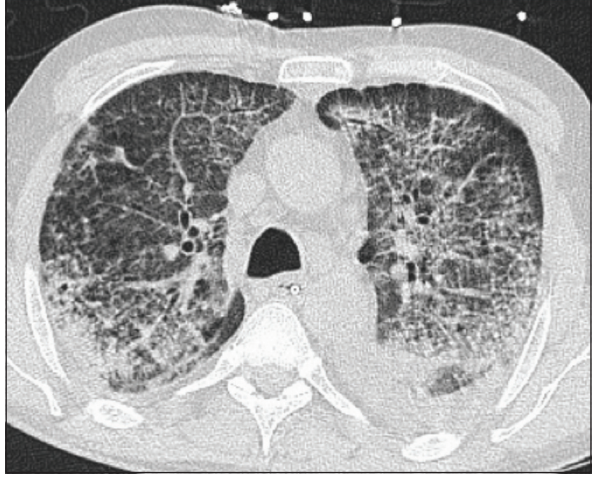


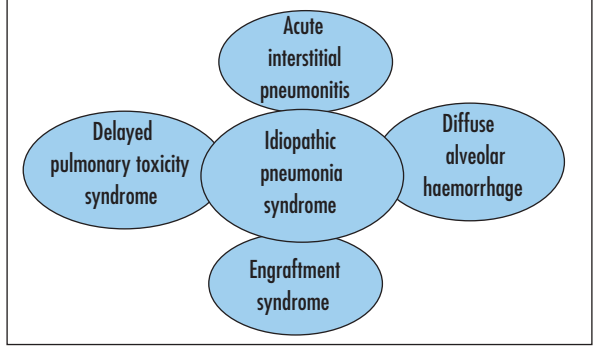
Figure 2. Acute respiratory distress syndrome. Computed tomography of the chest demonstrating bilateral patchy consolidation and pleural effusions.



Bronchoalveolar lavage needs to be performed to exclude respiratory infection. Occasionally transbronchial or surgical lung biopsies are performed if clinically tolerated and haematological parameters permit, however, these are not very helpful as the histology is often non-specific, usually demonstrating acute interstitial pneumonitis or diffuse alveolar damage. Hence the diagnosis is difficult to confirm with certainty. Treatment of idiopathic pneumonia syndrome consists of high dose glucocorticoid therapy (methylprednisolone 0.5–1 g daily for several days followed by tapering of oral prednisolone over 2–4 weeks), but as occult infection is the main differential diagnosis and may co-exist, broad spectrum antibiotics are usually administered concomitantly.

Diffuse alveolar haemorrhage is a relatively rare cause of bilateral infiltrates seen in both post-haematopoietic stem cell transplantation and solid organ transplantation. The pathogenesis of diffuse alveolar haemorrhage is similar to that of idiopathic pneumonia syndrome and is not related to derangements in coagulation or thrombocytopaenia. It is thought to be caused by inflammation and injury to the alveolar endothelium that results in damage and associated thrombosis with the deposition of fibrin in the alveoli and interstitium (Majhail et al, 2006; Nadir and Brenner, 2012); however, diffuse alveolar haemorrhage is seen in many patients who are thrombocytopaenic (e.g. leukaemic patients). Although it is not an infective complication, infectious pathogens are isolated from the lungs of 50–60% of haematopoietic stem cell transplantation patients with diffuse alveolar haemorrhage and increases the mortality two-fold (Majhail et al,

Figure 3. Disease spectrum of idiopathic pneumonia syndrome.



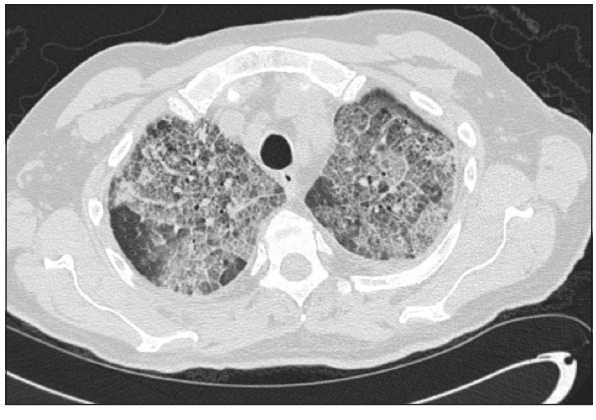
2006). Drug toxicity is another common cause (Rossi et al, 2000). Patients present with breathlessness, hypoxia and may have haemoptysis associated with falling haemoglobin levels. Computed tomography of the chest demonstrates bilateral patches of alveolar consolidation or ground glass infiltration (*Figure 4*). On bronchoscopy macroscopic fresh bleeding can be seen on occasion; the diagnosis is confirmed by a progressive bloodier return from alveolar lavage, or >20% haemosiderin-laden macrophages on cytological evaluation of the lavage fluid. Lung function tests can be a sensitive test for the diagnosis of diffuse alveolar haemorrhage showing an increase in the diffusing capacity of carbon monoxide, but most patients are often not stable enough to perform the test.

Engraftment syndrome (peri-engraftment respiratory disease syndrome)

Engraftment syndrome occurs commonly post-haematopoietic stem cell transplantation (most often post-autologous haematopoietic stem cell transplantation), during the neutrophil recovery phase (usually in the first 2 weeks post-transplantation) and within 5 days of neutrophil engraftment (>500/mm^3 for three consecutive days) (Capizzi et al, 2001).

The pathogenesis is thought to be the result of disruption of the alveolar capillary barrier caused by the increase in pro-inflammatory cytokines associated with neutrophil recovery. The increased capillary permeability leads to the development of widespread pulmonary infiltrates on the chest X-ray and hypoxaemia (Spitzer, 2001). Fever, erythematous rash and diarrhoea are common associated features and in severe cases multiple organ failure may be observed. The diagnosis of engraftment syndrome is largely clinical (new pulmonary infiltrates coinciding with rapid increase in neutrophil numbers and associated with fever and/or rash) and bronchoalveolar lavage is often performed to exclude infection and assess for diffuse alveolar haemorrhage. Most patients respond to high-dose steroid therapy, unlike with those with idiopathic pneumonia syndrome (Spitzer, 2001).

Figure 4. Diffuse alveolar haemorrhage. Computed tomography scan of the chest demonstrating bilateral patches of ground-glass change and septal thickening.



Drug-induced lung injury

Pulmonary drug toxicity as a result of chemotherapeutic and immunosuppressive agents (e.g. for the treatment of cancer or graft *vs* host disease) is relatively rare, but needs to be considered in the differential diagnosis of immunocompromised patients presenting with dyspnoea and pulmonary infiltrates. Some drugs, e.g. calcineurin inhibitors, have a high incidence of pulmonary toxicity, with 10 patients in a case series of 22 patients on temsirolimus reporting the development of pulmonary radiographic abnormalities (Duran et al, 2006). The onset of symptoms may occur months after initiation of therapy or even after cessation of treatment, which makes associating a specific drug with new lung disease more difficult.

Early detection allows cessation of the drug and commencement of high dose glucocorticoid therapy, which may lead to reversal of the injury or stop disease progression. A complete list of drugs that have been reported to cause pulmonary toxicity is available at www.pneumotox.com; the list continues to evolve with the use of new agents. *Table 2* summarizes common drugs used in immunocompromised patients and associated pulmonary manifestation.

Affected patients present with dyspnoea and cough. The radiological and lung function presentations of drug-related lung injury are variable (Rossi et al, 2000); common patterns are bilateral subacute interstitial pneumonitis or organizing pneumonia (*Figure 5*). However, other patterns can occur (e.g. bronchiolitis obliterans, diffuse alveolar damage or acute respiratory distress syndrome), and these more unusual presentations may become more common with the increasing use of biological and other targeted therapies. The main differential diagnosis is infection (e.g. pneumocystis pneumonia for a patient presenting with a subacute pneumonitis pattern) or idiopathic pneumonia syndrome. Hence bronchoscopy is necessary to exclude infective causes, but unfortunately histological findings from transbronchial and even open lung biopsies are not specific and the diagnosis is often clinical only.

Organizing pneumonia

Organizing pneumonia was previously known as bronchiolitis obliterans organizing pneumonia, and is termed cryptogenic organizing pneumonia when the aetiology is unknown. It is a rare but serious complication in patients post-allogeneic stem cell tranplantation, post-lung transplantation and in those with cytomegalovirus pneumonitis but may also occur secondary to numerous drugs (Afessa et al, 2001; Epler, 2001). Patients may be asymptomatic but usually present with cough, dyspnoea and fever. Chest radiographs or computed tomography demonstrate patches of ground-glass opacities or consolidation in the peripheries of the lungs; these often occur subpleurally in a non-lobar distribution and can be migratory or recurrent. Inflammatory markers such as white cell count, C-reactive protein level and erythrocyte sedimentation rate are frequently raised and infection needs to be excluded. Lung function tests generally demonstrate a restrictive

Table 2. Common drugs associated with pulmonary complications

Drugs		Respiratory complication
Epidermal growth factor receptor inhibitors	Erlotinib	Interstitial pneumonitis (usual or non-specific), diffuse alveolar damage, cryptogenic organizing pneumonia, non-cardiogenic pulmonary oedema
	Gefitinib	Interstitial pneumonitis (non-specific), diffuse alveolar damage, non-cardiogenic pulmonary oedema
VEGF inhibitors	Bevacizumab and sunitinib	Diffuse alveolar damage, cardiogenic pulmonary oedema
Antipodophyllotoxin	Etoposide	Interstitial pneumonitis (non-specific), diffuse alveolar damage, hypersensitivity pneumonitis
Bcr-Abl tyrosine kinase inhibitors	Imatinib	Interstitial pneumonitis (non-specific), hypersensitivity pneumonitis, pulmonary alveolar proteinosis, diffuse alveolar damage, cardiogenic pulmonary oedema, pleural effusion
	Dasatinib	Interstitial pneumonitis (non-specific), cardiogenic pulmonary oedema, pleural effusion
	Crizotinib	Interstitial pneumonitis (non-specific), diffuse alveolar damage
Mammalian target of rapamycin (mTOR) inhibitors	Temsirolimus and sirolimus	Interstitial pneumonitis (non-specific), diffuse alveolar damage, cryptogenic organizing pneumonia
	Everolimus	Interstitial pneumonitis (non-specific), non-cardiogenic pulmonary oedema
	Tacrolimus	Interstitial pneumonitis (non-specific), cryptogenic organizing pneumonia
Taxanes	Paclitaxel	Hypersensitivity pneumonitis, diffuse alveolar damage, non-cardiogenic pulmonary oedema
	Docetaxel	Hypersensitivity pneumonitis, diffuse alveolar damage, pleural effusion, non-cardiogenic pulmonary oedema
Alkylating agents	Busulfan	Interstitial pneumonitis (usual or non-specific), pleural effusion
	Melphalan	Interstitial pneumonitis (usual or non-specific)
	Cyclophosphamide	Interstitial pneumonitis (non-specific), diffuse alveolar damage, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, pleural effusion
Anti-metabolites	Methotrexate	Interstitial pneumonitis (non-specific or usual), hypersensitivity pneumonitis, cryptogenic organizing pneumonia, diffuse alveolar damage, pleural effusion, non-cardiogenic pulmonary oedema
	Azathioprine	Interstitial pneumonitis (non-specific), diffuse alveolar damage, cryptogenic organizing pneumonia
	Fludarabine	Interstitial pneumonitis (non-specific), diffuse alveolar damage, hypersensitivity pneumonitis
Cytotoxic antibiotics	Mitomycin C	Diffuse alveolar damage, pleural effusion, non-cardiogenic pulmonary oedema
	Bleomycin	Interstitial pneumonitis (usual), diffuse alveolar damage, hypersensitivity pneumonitis, cryptogenic organizing pneumonia, pleural effusion
Other	Rituximab	Interstitial pneumonitis (non-specific), cryptogenic organizing pneumonia, non-cardiogenic pulmonary oedema

VEGF = vascular endothelial growth factor. Diffuse alveolar damage is a histological feature of acute respiratory distress syndrome and diffuse alveolar haemorrhage.

defect with a reduction in the transfer factor. If the diagnosis is in doubt or there is severe impairment in lung function, open lung biopsies are obtained, which may demonstrate granulomas within the distal airspaces. This needs to be differentiated from sarcoidosis, hypersensitivity pneumonitis or fungal infections.

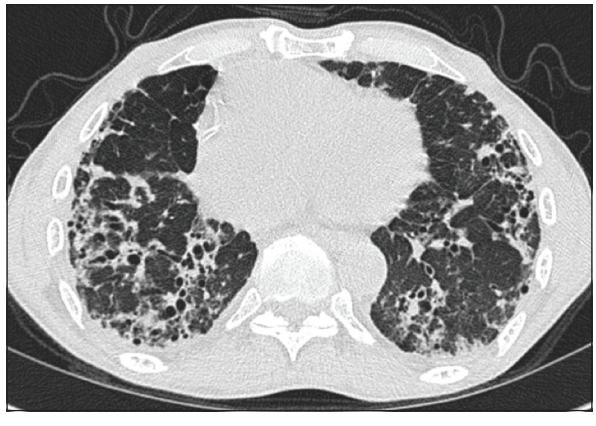
Treatment is with oral glucocorticoids (e.g. 0.75–1.0 mg/kg ideal body weight (max 100 mg) for 1–2 months followed by weaning over 3–4 months)(Bradley et al, 2008) and the response is usually rapid with reduction in radiographical abnormalities within 2 or 3 weeks. Relapse can occur when corticosteroids are stopped but is unusual. In cases that do not respond to steroids, cyclophosphamide or macrolides (e.g. azithromycin) may be used as alternatives (Purcell et al, 1997; Stover and Mangino, 2005; Vaz et al, 2011).

Graft *vs* host disease

Graft *vs* host disease is a relatively common complication of allograft haematopoietic stem cell transplantation that can result in significant lung-related morbidity and mortality. Graft *vs* host disease occurs when donor lymphocytes attack the recipient's tissue resulting in multisystem organ dysfunction (commonly skin, gut, liver and bone marrow, less commonly the lung) (Hamilton and Pearson, 1986). Graft *vs* host disease is divided into acute (within the first 100 days) or chronic (after 100 days) graft *vs* host disease. Patients with classical acute graft *vs* host disease present with a rash, diarrhoea or abdominal cramps and rising serum bilirubin levels, but usually without pulmonary involvement. However, acute graft *vs* host disease predisposes patients to the development of non-cardiogenic pulmonary oedema, diffuse alveolar haemorrhage and infections (related to the immunosuppressive medication).

Chronic graft *vs* host disease also commonly affects the skin, buccal mucosa, gut and liver, but in contrast to acute graft *vs* host disease only 5–10% of patients post-allograft haematopoietic stem cell transplantation have lung involve-

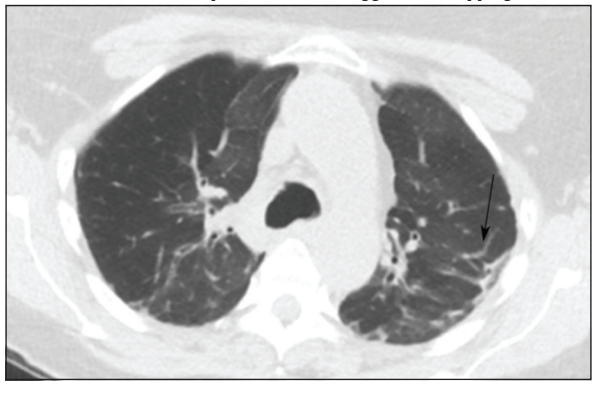
Figure 5. Interstitial lung disease (pulmonary fibrosis) post-chemotherapy with lenalidomide. Computed tomography scan of the chest showing bilateral pulmonary fibrosis with traction bronchiectasis.



ment (Bacigalupo et al, 2012). Lung graft *vs* host disease usually causes bronchiolitis obliterans, characterized by airflow limitation caused by concentric narrowing of the bronchioles as a result of inflammation and fibrosis. Bronchiolitis obliterans usually presents with progressive dyspnoea over weeks or months, cough and wheeze associated with new onset of obstructive lung function impairment. A very similar condition occurs after lung transplantation as a result of host *vs* graft disease. Despite significant breathlessness and lung function impairment, chest radiographs are usually normal or demonstrate hyperinflation only. Computed tomography scans may demonstrate air trapping (mosaic attenuation), thickened small vessel airways, and sometimes diffuse mild bronchiectasis (*Figure 6*).

The diagnosis is made by demonstrating new obstructive lung function defects (i.e. a forced expiratory volume in 1 s < 75% predicted and forced expiratory volume in 1 s/forced vital capacity ratio <0.7 after allograft haematopoietic stem cell transplantation) with no other potential explanation (e.g. respiratory virus infection) (Filipovich et al, 2005) (*Figure 7*). Histological confirmation is often not required but when there is doubt in the diagnosis, lung biopsies can confirm the presence of a constrictive bronchiolitis. Furthermore, other forms of lung graft *vs* host disease can occur (e.g. pleuropericarditis and lymphocytic interstitial pneumonia) but are rare (Alousi et al, 2011).

Figure 6. Bronchiolitis obliterans. Computed tomography scan of the chest demonstrating thickening and dilatation of the small airways (arrow) and the mosaic pattern, which suggest air trapping.

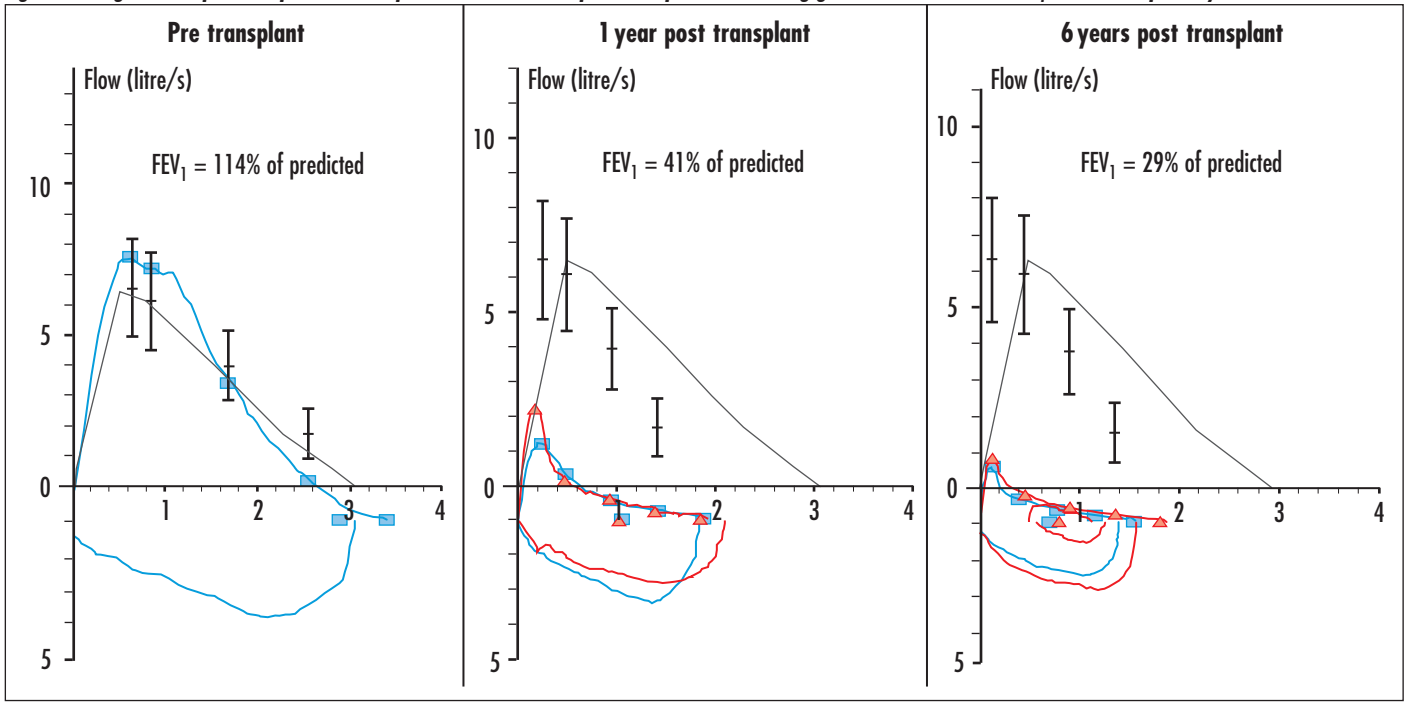


Treatment of lung graft *vs* host disease aims to preserve lung function and consists of increasing immunosuppression with glucocorticoids or other immunosuppressive therapy (e.g. ciclosporin, tacrolimus or mycophenolate). High-dose inhaled steroids may be sufficient in some patients with bronchiolitis obliterans post-haematopoietic stem cell transplantation (Bashoura et al, 2008) but are not effective in host *vs* graft disease post-lung transplantation (Whitford et al, 2002). Other therapies may include long-term low-dose azithromycin, extracorporeal photopheresis or plasmapheresis. However, severe bronchiolitis obliterans caused by lung graft *vs* host disease is often resistant to treatment and leads to substantial permanent loss of lung function, progressing to respiratory failure and death in a substantial proportion of patients. In selected patients with respiratory failure lung transplantation is an option (Soubani et al, 2014).

Post-transplant lymphoproliferative disease and development of solid organ malignancy

Post-transplant lymphoproliferative disease occurs as a consequence of immunosuppression in stem cell or solid organ transplantation (bowel > lung > heart > liver > kidney). In almost all cases it is associated with Epstein–Barr

Figure 7. Lung function pre- and post-haematopoietic stem cell transplant in a patient with lung graft vs host disease. FEV_1 = forced expiratory volume in 1 second.



virus (Ibrahim and Naresh, 2012), which causes a monoclonal or polyclonal lymphoproliferation, usually of B-cells. The risk of developing post-transplant lymphoproliferative disease is greatest in the first year post-transplantation and patients with pulmonary involvement often present with lung nodules, lymphadenopathy and occasionally with pleural effusions. Although the radiological features often suggest post-transplant lymphoproliferative disease, the differential diagnosis includes recurrence of primary disease (e.g. lymphoma) and infections (e.g. fungal, mycobacterial or nocardia infections), and the diagnosis requires obtaining tissue for histology.

Initial treatment involves reducing the intensity of immunosuppression to allow reconstitution of the host T-cell response against Epstein–Barr virus but this increases the risk of graft *vs* host disease or rejection of the transplanted organ. Rituximab (anti-CD20 monoclonal antibody) induces remission in a high proportion of patients with CD20-positive post-transplant lymphoproliferative disease (75% of cases) (Zimmermann and Trappe, 2013). Those with CD20-negative post-transplant lymphoproliferative disease or not responding to rituximab may be treated with a combination of standard chemotherapy, radiotherapy and adoptive immunotherapy with Epstein–Barr virus-specific cytotoxic T cells (Zimmermann and Trappe, 2013).

In addition to post-transplant lymphoproliferative disease, post-haematopoietic stem cell transplantation patients are at increased risk of developing solid organ malignancy as a result of the use of total body irradiation and high dose chemotherapy conditioning regimens. Primary lung cancer is not common post-haematopoietic stem cell transplantation but the more frequently encountered malignancies (melanoma and thyroid) may present with pulmonary metastasis (Curtis et al, 1997; Rizzo et al, 2009).

Respiratory disease associated with primary immunodeficiency

Airway disease

Recurrent respiratory infections associated with any primary immune deficiency lead to airway damage that may result in bronchiectasis and obstructive airway disease with air trapping. Bronchiectasis is the abnormal dilatation and thickening of the bronchioles that results in impaired mucociliary clearance, leading to a vicious circle of infection and inflammation with frequent exacerbations (José and Brown, 2014). It is common in patients with IgG deficiency (e.g. X-linked agammaglobulinaemia and common variable immunodeficiency), but also occurs in patients with deficiency of signal transducer and activator of transcription (STAT)-3 (hyper IgE syndrome).

Patients present with chronic or recurrent production of infected sputum, and the diagnosis is confirmed by identifying dilated bronchi on computed tomography of the chest, usually in a cylindrical, diffuse and predominantly lower lobe pattern (Bierry et al, 2009). Bronchiolitis obliterans causes chronic dyspnoea and is identified by lung function testing showing irreversible or partially reversible airways obstruction. Identification and treatment of the primary immune deficiencies, if possible (e.g. intravenous IgG replacement therapy), together with early treatment of pulmonary infections is essential to prevent deterioration of lung function. Regular airway clearance is also very beneficial in preventing recurrent infective exacerbations. Bronchodilators (β_2 agonists and anti-muscarinic) can provide symptomatic relief of airways obstruction.

Interstitial lung disease

Interstitial lung disease describes a broad spectrum of parenchymal lung disease with several histological and radiological patterns including non-specific interstitial pneumonitis, organizing pneumonia, lymphocytic interstitial pneumonia and granulomatous interstitial lung disease, all of which can be found in patients with primary immune deficiencies. In particular there is a high prevalence in patients with common variable immunodeficiency of lymphocytic interstitial pneumonia and/or granulomatous interstitial lung disease, which is known as granulomatous lymphocytic interstitial lung disease (Bates et al, 2004).

As the interstitial lung diseases may initially be asymptomatic it is important to screen patients with primary immune deficiencies for interstitial lung disease with chest radiographs and lung function tests; the latter will demonstrate a restrictive pattern with a reduction in transfer factor in patients with lymphocytic interstitial pneumonia or granulomatous lymphocytic interstitial lung disease. Both lymphocytic interstitial pneumonia and granulomatous lymphocytic interstitial lung disease cause parenchymal infiltrates (e.g. ground glass nodules with thickened interlobular septa and lymphadenopathy for granulomatous lymphocytic interstitial lung disease) that are best detected using computed tomography. Treatment of the interstitial lung diseases associated with primary immune deficiencies includes correction of the underlying immune disorder if possible and, paradoxically, systemic immunosuppression (e.g. oral glucocorticoids). Long-term lymphocytic interstitial pneumonia and granulomatous lymphocytic interstitial lung disease can result in irreversible lung damage, poor lung function and potentially respiratory failure.

Malignancy

Primary immune deficiencies such as common variable immunodeficiency, severe combined immunodeficiency, ataxia-telangiectasia syndrome, auto-immune lymphoproliferative syndrome (Canale–Smith syndrome) and eczema-thrombocytopaenia-immunodeficiency syndrome (Wiskott–Aldrich syndrome) are associated with an increased risk of malignancy and may present with thoracic (mediastinal) adenopathy or metastatic lesions in the lungs (e.g. from primary stomach, breast, bladder or cervical cancer) (Salavoura et al, 2008). However, mediastinal adenopathy in this cohort is not always the result of

malignancy and may be caused by granulomatous inflammation (e.g. granulomatous lymphocytic interstitial lung disease) or secondary to infection. Additionally, autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome and common variable immunodeficiency may also present with generalized non-malignant adenopathy. Patients with common variable immunodeficiency also have an increased risk of developing lymphoma (Cunningham-Rundles et al, 1991). As a result, careful follow up and early biopsy may be necessary for primary immune deficiencies patients in whom computed tomography scanning has shown pulmonary nodules or mediastinal lymphadenopathy. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Non-infectious respiratory disease is common in immunocompromised patients and may mimic infection; detection requires a high index of suspicion.
- Owing to the overlap in the clinical presentation between different non-infectious and infectious pulmonary conditions, diagnosis is often clinical as histology is frequently unreliable.
- Non-infectious respiratory disease post-transplantation is associated with high morbidity and mortality.
- In primary immune deficiencies early detection of respiratory disease is necessary to improve outcomes and prevent lung function decline.
- Early coordinated specialist input is required (e.g. respiratory physician, haematologist, immunologist).