Pulmonary complications of bone marrow transplantation

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Shareable abstract (@ERSpublications)
Respiratory complications are common in haemopoietic stem cell transplantation. The timeline of the first 100 days post-transplant is a useful way of categorising the probability of occurrence of both infectious and non-infectious complications. https://bit.ly/4bRJREU

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Abstract

Bone marrow transplantation, now often known as haematopoietic stem cell transplantation (HSCT), is a complex choreographed procedure used to treat both acquired and inherited disorders of the bone marrow. It has proven invaluable as therapy for haematological and immunological disorders, and more recently in the treatment of metabolic and enzyme disorders. As the number of performed transplants grows annually, and with patients enjoying improved survival, a knowledge of both early and late complications of HSCT is essential for respiratory trainees and physicians in practice. This article highlights the spectrum of respiratory complications, both infectious and non-infectious, the timeline of their likely occurrence, and the approaches used for diagnosis and treatment, keeping in mind that more than one entity may occur simultaneously. As respiratory issues are often a leading cause of short- and long-term morbidity, consideration of a combined haematology/respiratory clinic may prove useful in this patient population.

Introduction

Modern bone marrow transplantation, now often known as haematopoietic stem cell transplantation (HSCT), could be said to have started in 1977 when Thomas *et al*. [1] reported long-term survival in patients with acute leukaemia allografted after conditioning with chemotherapy and radiotherapy. The subsequent decades of the 1980s and 1990s saw a proliferation of transplant centres around the world, with a dramatic increase in the annual number of both autologous and allogeneic bone marrow transplants [2]. The most recent European Society for Blood and Marrow Transplantation (EBMT) activity survey reported almost 48 000 transplants performed in 2021 (42% allogeneic and 58% autologous) across ∼700 centres, with a noted drop during the coronavirus disease 2019 (COVID-19) pandemic [3]. In the USA, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported just over 23 000 transplants in 2018, of which 60% were autologous and 40% allogeneic [4]. The indications for bone marrow transplant continue to expand but primarily include haematological malignancies, marrow failure syndromes, haemoglobinopathies and immune deficiency states (table 1) [5, 6].

Two forms of HSCT exist: autologous and allogeneic. In an autologous stem cell transplant, the patient's own cells are harvested, cryopreserved and used to re-establish bone marrow viability following ablation with high-dose chemotherapy. In an allogeneic bone marrow transplant, haematopoietic stem cells are obtained from a human leukocyte antigen (HLA)-matched or partially mismatched family member, unrelated volunteer, or umbilical cord blood donation. Donor-derived immunity can mount a graft-*versus*-tumour effect, reducing the risk of relapse. However, this comes with the attendant risk of immunologically mediated organ damage due to graft-*versus*-host disease (GvHD). It is important to keep in mind, as we progress through this review, that we are discussing these two distinct types of HSCT.

GvHD is a multiorgan complication seen almost exclusively in allogeneic HSCT, although it has been described in about 5% of autologous HSCT cases [7]. It is caused by donor immune cells recognising the host tissue as "foreign" and mounting an immune response against it. GvHD can present as both an acute

TABLE 1 Indications for haematopoietic stem cell transplantation

	Haematological malignancies	Solid malignancies	Non-malignant
Autologous	Main indications: Myeloma Non-Hodgkin lymphoma Hodgkin lymphoma Amyloidosis	Neuroblastoma Medulloblastoma Ewing sarcoma Germ cell tumour Wilms tumour Osteosarcoma Experimental indication: Soft tissue sarcoma	Multiple sclerosis Systemic sclerosis Experimental indications: Crohn's disease Myasthenia gravis Systemic lupus erythematosis Rheumatoid arthritis
Allogeneic	Main indications: Acute myeloid leukaemia Acute lymphoblastic leukaemia Myelodysplastic syndrome Chronic myeloid leukaemia Myeloproliferative neoplasm Chronic myelomonocytic leukaemia Non-Hodgkin lymphoma Hodgkin lymphoma Myeloma Chronic lymphocytic leukaemia	Experimental indications: Neuroblastoma Ewing sarcoma Germ cell tumour Soft tissue sarcoma Metastatic breast cancer Metastatic renal cancer	Main indications: Aplastic anaemia Paroxysmal nocturnal haemoglobinuria Other indications: Fanconi anaemia Diamond–Blackfan anaemia Dyskeratosis congenita Sickle cell disease Thalassaemia major Severe combined immune deficiency Wiskott–Aldrich syndrome Chronic granulomatous disease Haemophagocytic lymphohistiocytosis GATA2 deficiency Activated phosphoinositide 3-kinase delta syndrome Inborn errors of metabolism: mucopolysaccharidosis, sphingolipidoses, glycoproteinoses Osteopetrosis

form (aGvHD) and a chronic form (cGvHD) and a GvHD overlap syndrome. aGvHD typically presents within the first 100 days post-transplant and is characterised by a maculo-papular skin rash, nausea, emesis, diarrhoea, abdominal crampy pain and elevated serum bilirubin levels. The median time of onset has increased in recent decades and the frequency of disease has declined from close to 50% to 16% of current allogeneic HSCTs [8]. cGvHD manifests itself after 100 days with a frequency of 60–70% of allogeneic HSCTs [9] and can affect any organ, although it typically manifests with involvement of the skin, oral mucosa, gastrointestinal tract, liver and lungs. Pathologically, one finds fibroproliferation leading to end organ damage and dysfunction. In overlap GvHD syndrome, features of cGvHD are present along with simultaneous manifestations of aGvHD. This entity is associated with an overall reduction in survival and non-relapse-related mortality [10].

A detailed discussion of the various pre-HSCT regimes is beyond the scope of this article. However, two main categories of pre-HSCT conditioning regimes are used. The first, a more intense myeloablative regime, has the benefit of a reduced rate of disease relapse at the expense of increased treatment-related mortality and non-relapse mortality, primarily due to complications related to acute and chronic GvHD and risk of infection. The second, a reduced intensity regime, has a lower treatment-related mortality due to less GvHD and infections, but has a higher risk of disease relapse. An additional benefit is that it can be used in older adults, in patients with comorbid illness and in those with non-malignant conditions who may benefit from HSCT but would not tolerate more aggressive myeloablative regimes [11].

Factors predisposing patients to develop post-transplant complications include older age, pre-existing underlying lung disease, stem cell source, choice of chemotherapeutic conditioning regimen, and allogeneic transplant. For example, a diffusing capacity of the lung for carbon monoxide (D_{LCO}) corrected for haemoglobin of <60% predicted was associated with reduced overall survival in autologous HSCT patients treated with BEAM (carmustine, etoposide, cytarabine, melphalan) and in allogeneic HSCT patients treated with FBN (fludarabine, carmustine, melphalan). Additionally, pre-existing lung disease such as COPD, pulmonary embolism and sleep apnoea were associated with an increased risk of non-relapse-related mortality [12]. The timing of onset of the clinical syndrome may help differentiate the underlying aetiology and guide treatment approaches.

In this review, we discuss the major pulmonary complications from HSCT, divided into two major areas: 1) non-infectious and 2) infectious complications of HSCT. Pulmonary complications in general are

common after HSCT, occurring in up to 50% of recipients, and are also a major cause of morbidity and mortality, both acutely and in the years after transplant [7]. As HSCT techniques have matured and knowledge of anti-microbial prophylaxis and treatment has improved, there has been an overall reduction in post-transplant infections, while the non-infectious complications remain problematic [8]. The co-existence of both infectious and non-infectious complications remains a major challenge to physicians managing these patients. Additionally, although there is a probability timeline of pulmonary complications, which evolves as the patient's recovery progresses, this is variable and many complications, both infectious and non-infectious, may have overlapping time frames (figure 1). Several factors have been identified that increase the risk of post-transplant respiratory problems, including older age, cigarette smoking, impaired pre-transplant lung function, and GvHD in other organs [9].

Non-infectious pulmonary complications

Non-infectious pulmonary complications of HSCT contribute significantly to morbidity and mortality in the early and late post-transplant periods. They can largely be divided into three main groups depending on the time of onset post-transplant: 1) those seen in the immediate pre- and peri-engraftment period (0–30 days), 2) those in the early post-engraftment stage (30–100 days), and 3) those that develop in the late post-transplant period (>100 days).

With improved treatment and prophylaxis regimens for common infectious complications of HSCT, non-infectious pulmonary complications have become an increasingly important cause of morbidity. Improved survival rates and longevity post-transplant mean the burden of long-term and late-developing complications needs to be considered.

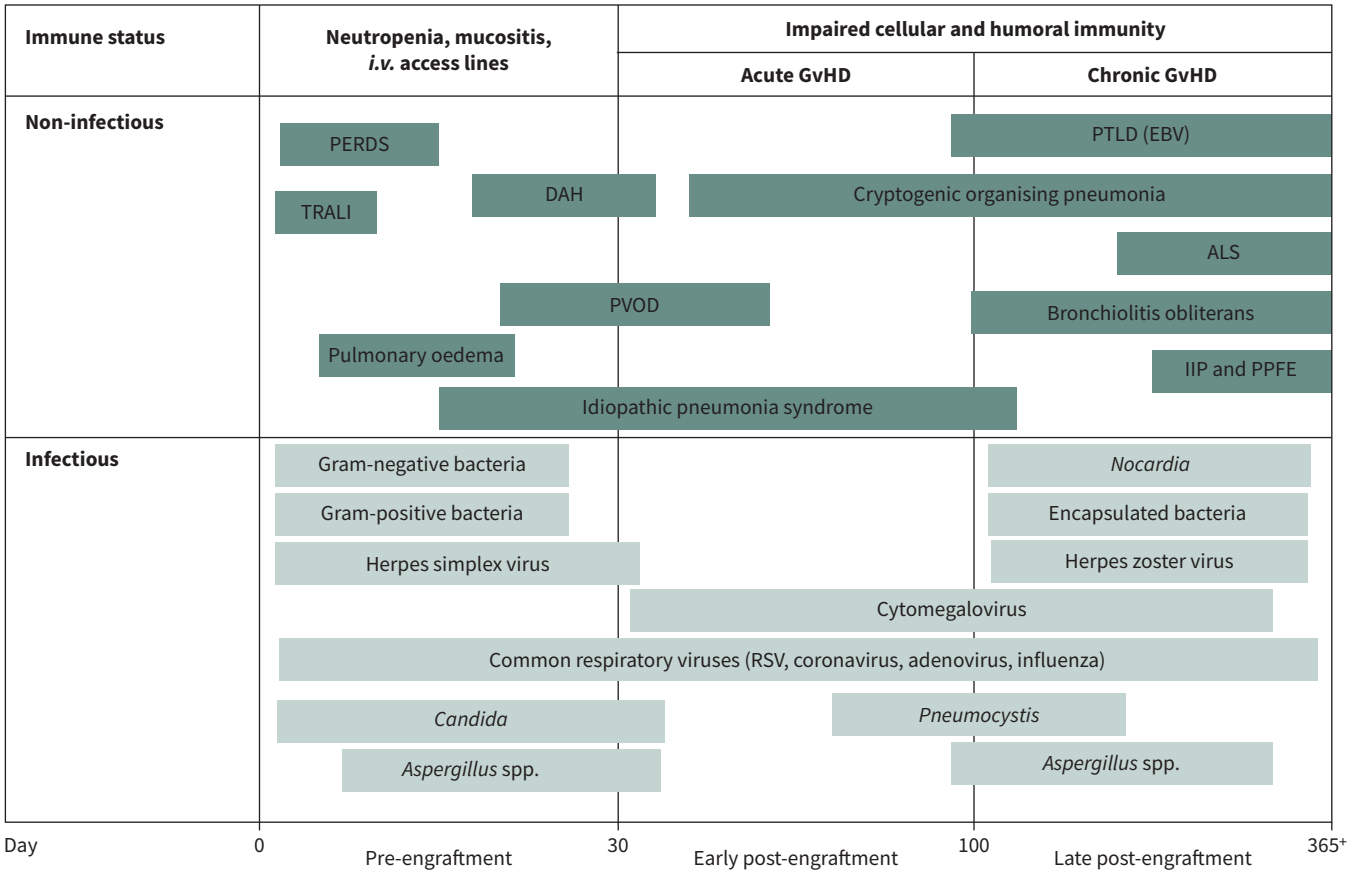

FIGURE 1 Timeline of pulmonary complications following haematopoietic stem cell transplantation. GvHD: graft-*versus*-host disease; PERDS: peri-engraftment respiratory distress syndrome; TRALI: transfusion-related acute lung injury; DAH: diffuse alveolar haemorrhage; PTLD: post-transplant lymphoproliferative disorder; EBV: Epstein–Barr virus; ALS: air leak syndrome; PVOD: pulmonary veno-occlusive disease; IIP: idiopathic interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis; RSV: respiratory syncytial virus. Adapted from [13].

Pre-/peri-engraftment stage (0–30 days)

Engraftment typically occurs within the first 30 days post-HSCT and is characterised by recovery of peripheral blood counts. Neutrophil engraftment is defined as the first three consecutive days where peripheral blood neutrophil count is $>0.5\times10^9$ cells·L^{-1}.

Engraftment syndrome

Engraftment syndrome is a multiorgan systems disorder, usually seen within 7 days of HSCT. It is a well-defined non-infectious clinical entity seen both in allogeneic and autologous HSCT, with reported frequency of 13–20% following allogeneic HSCT [14] and 5–25% for autologous HSCT [15]. It is characterised by systemic symptoms of fever, skin rash, diarrhoea, weight gain (fluid), abnormal renal and liver function tests, pulmonary infiltrates, and pulmonary oedema thought to be caused by diffuse capillary injury. Whether engraftment syndrome in allogeneic HSCT can be truly differentiated from aGvHD of the lungs is an area of debate. The treatment in both instances is high-dose steroids (1–1.5 mg·kg^{-1}·day^{-1} for 3 days followed by oral prednisolone 40–50 mg·day^{-1} for an additional 3 days). This is in addition to the standard use of T-cell suppressing drugs such as tacrolimus, mycophenolate mofetil and methotrexate [16].

Peri-engraftment respiratory distress syndrome (PERDS) is the pulmonary manifestation of engraftment syndrome, defined as a syndrome of hypoxaemia, alveolar infiltrates, and other clinical features seen with engraftment syndrome. It is one of the earliest non-infectious post-transplant complications, usually occurring within 11 days of transplant, in about 5% of HSCT cases, and is associated with neutrophil recovery. Autologous HSCT, female sex, rapid rate of engraftment, HSCT for POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin abnormalities) and higher rates of platelet transfusion in the peri-engraftment period are all recognised non-modifiable risk factors associated with the development of PERDS [17]. The release of proinflammatory cytokines due to an influx of neutrophils into the lungs during the engraftment period is thought to play a major role in the development of PERDS.

Features of PERDS often overlap with other acute pulmonary complications of HSCT, with associated systemic features often proving helpful in differentiating PERDS from other causes of respiratory failure in the peri-engraftment stage. Bilateral pulmonary infiltrates, ground-glass opacities, and inter- and intra-lobular septal thickening are classic radiographic features in PERDS, with radiographic features preceding the engraftment period by several days [7]. Awareness of this may allow for more rapid recognition of the clinical condition, resulting in earlier intervention. Other investigations including bronchoscopy, sputum and blood cultures are usually required to out rule other possible diagnoses.

Intravenous corticosteroids are the mainstay of treatment, which usually results in rapid clinical improvement, unlike other lung HSCT disorders. Supportive therapy, including mechanical ventilation, may be required during this period. Outcomes are usually good with prompt recognition and treatment, with mortality of about 5% after 100 days post-HSCT *versus* 1.8% in patients with no PERDS [17].

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a clinical syndrome described as respiratory distress and non-cardiac pulmonary oedema, with onset typically occurring within the first 6 h (but up to 72 h) following transfusion of a blood product [18]. Patients undergoing HSCT often require a high burden of blood product transfusions in the pre-engraftment stage and are at a higher risk of developing TRALI in this window. However, it can occur at any time with any blood product. TRALI is characterised by neutrophil activation leading to endothelial damage, capillary leak and, subsequently, non-cardiac pulmonary oedema [19]. Pathologically, it is similar to early acute respiratory distress syndrome (ARDS), with interstitial and alveolar oedema and disruption of type 1 alveolar cell membranes. Clinical hallmarks include acute onset of hypoxia (within 6 h of transfusion), a ratio of arterial oxygen tension to inspiratory oxygen fraction <300 or oxygen saturation <90% on room air, bilateral pulmonary oedema on chest radiography or computed tomography (CT) scan, no relationship with other risks for ARDS and no evidence of circulatory overload.

Supportive measures, which may include non-invasive or invasive mechanical ventilation, are usually sufficient for management, with immediate suspension of the transfusion if a reaction occurs. The development of conservative transfusion protocols helps reduce the frequency of transfusions, thus minimising risk.

Diffuse alveolar haemorrhage

The entity diffuse alveolar haemorrhage (DAH) was first described in 1989 [20] and occurs in the immediate post-transplant phase, with an incidence of ~5% in autologous HSCT [21] and 10% in allogeneic HSCT, with a median onset time of 30 days [22]. The clinical presentation is characterised by

profound hypoxaemia and alveolar infiltrates, with haemoptysis occurring in up to 50% of patients. As a subtype of idiopathic pneumonia syndrome (IPS), the presentation of DAH can be similar to PERDS, with rapidly progressive hypoxaemia and bilateral ground-glass opacities seen on radiographic imaging. However, with DAH there are characteristic bronchoscopic findings of increasing blood on serial bronchoalveolar lavage (BAL) aliquots, or a BAL with >20% haemosiderin-laden macrophages in the absence of an infectious aetiology.

The pathophysiology of DAH remains poorly understood; delayed platelet engraftment, graft failure, GvHD, infection, allogeneic HSCT, and toxicity related to the conditioning regimens are all felt to contribute [22]. Although not very effective, high-dose *i.v.* steroids are given as first-line treatment, with empirical anti-microbial cover due to the high risk of opportunistic infection associated with high doses of immunosuppression. Many patients require an intensive care unit stay and mechanical ventilation due to progressive hypoxaemic respiratory failure. The mortality rate of patients with DAH is reported as anywhere in the region of 60–90% [23].

Early post-transplant period (30–100 days)

Idiopathic pneumonia syndrome

IPS is defined by the American Thoracic Society (ATS) as an acute pulmonary dysfunction with multilobe infiltrates on imaging (figure 2), symptoms and signs of pneumonia, and an impaired alveolar to arterial oxygen gradient, where an infectious aetiology has been excluded and no other causes of fluid overload (cardiac disease, renal disease, iatrogenic causes) are evident [24]. It is seen in 3–5% of HSCT cases, with a higher incidence observed with the use of total body irradiation [25]. BAL should be performed to rule out haemorrhage or an underlying infectious aetiology. The median time to onset is 112 days [25].

High-intensity pre-transplant conditioning, total body irritation, aGvHD, age >40 years, and an underlying diagnosis of acute leukaemia or myelodysplastic syndrome are considered major risk factors for the development of IPS [26].

Categorising IPS by presumed anatomic site of injury may prove useful, with acute interstitial pneumonitis, ARDS and delayed pulmonary toxicity syndrome believed to reflect lung parenchymal injury, while PERDS and DAH indicate a vascular aetiology and cryptogenic organising pneumonia (COP) is a manifestation of parenchymal and airway epithelial injury.

The ATS proposed IPS as an umbrella term describing acute lung injury that encompasses other causes of acute lung injury including PERDS and DAH [24]. While clinical features are similar to those of PERDS and DAH, IPS typically occurs later in the post-transplant course and has been documented to occur up to 120 days post-transplant, although some studies report a median time of onset of 20–40 days [25]. Also, they behave differently clinically and require different treatment approaches: IPS, unlike PERDs, responds very poorly to high-dose *i.v.* corticosteroids. Morbidity rates are high, with many patients requiring mechanical ventilation, and the mortality rates for autologous and allogeneic transplants approach 50% and 80%, respectively [27]. As IPS is believed to result from various lung insults, one being the release of inflammatory cytokines, the finding of elevated levels of tumour necrosis factor (TNF)-α in BAL samples led to the use of etanercept (anti-TNF-α) along with high-dose corticosteroids, with variable success [27].

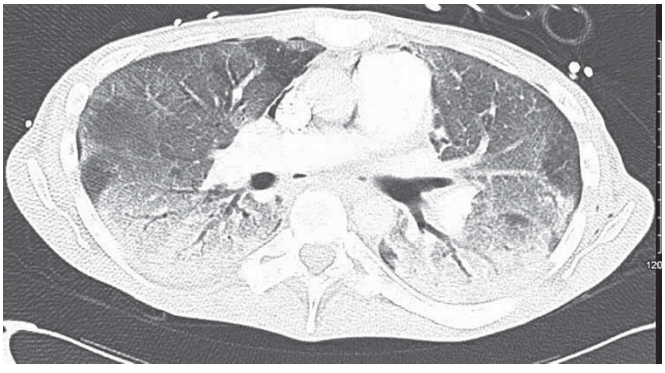

FIGURE 2 Idiopathic pneumonia syndrome developing 80 days post-allogeneic haematopoietic stem cell transplantation, characterised by diffuse bilateral pulmonary infiltrates.

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication of allogeneic HSCT, characterised by uncontrolled lymphoid proliferation in the setting of immunosuppression. Fortunately, it is relatively rare, seen in 0.2% of cases with no risk factors but up to 8% in patients with multiple risk factors. Epstein–Barr virus (EBV) is a ubiquitous virus in humans and weakened T-cell immunity in the early post-transplant period results in uncontrolled proliferation of donor-derived EBV-infected B-cells. Reactivation of latent recipient EBV infection is also seen. As such, donor EBV serological status and donor/recipient mismatch are some of the most important risk factors to consider for the development of PTLD. Other risk factors include the source of stem cell transplant, such as use of cord blood, reduced-intensity conditioning regimens, T-cell depletion of the donor marrow, HLA mismatch, male donor, younger donor, older age of transplant recipient, the presence of acute or chronic GvHD, and total body irradiation [28]. In relation to survival from PTLD, use of a bone marrow graft (*versus* peripheral blood stem cells) and presence of GvHD were associated with an increased mortality [29].

The onset of PTLD typically occurs within the first 6 months post-HSCT, when T-cell immunity is most profoundly suppressed. Late-onset PTLD is rare in HSCT and is usually EBV-negative, typically seen in the setting of prolonged immunosuppression for the management of GvHD [30].

PTLD usually presents with fevers and lymphadenopathy, and although it may occur anywhere in the body, the lungs are habitually involved. Thoracic lymph node involvement is common, but intra-parenchymal nodules and pleural effusions may also be seen [31]. Position emission tomography imaging can help in the diagnosis of PTLD and identify targets for tissue samples to confirm the diagnosis.

Treatment approaches generally focus on the reduction of immunosuppressive agents, which may be difficult to achieve, particularly in the setting of GvHD. In HSCT-related PTLD, anti-$CD20^{+}$ therapies such as rituximab are increasingly used as first-line management in conjunction with reduction of immunosuppression [30]. In refractory cases, lymphoma-directed chemotherapy or administration of allogeneic EBV-specific cytotoxic T-lymphocytes are salvage options.

Late post-transplant period (>100 days)

Organising pneumonia

Organising pneumonia (OP) is a clinical syndrome mimicking infection, characterised by fever, dyspnoea and cough, coupled with patchy pulmonary infiltrates (figure 3). OP is more likely to occur in allogeneic transplant recipients and affects about 1–10% of such patients [32]. Pathologically, one sees buds of granulation tissue proliferating in alveoli and terminal bronchioles. The median time of onset is ~286 days [33].

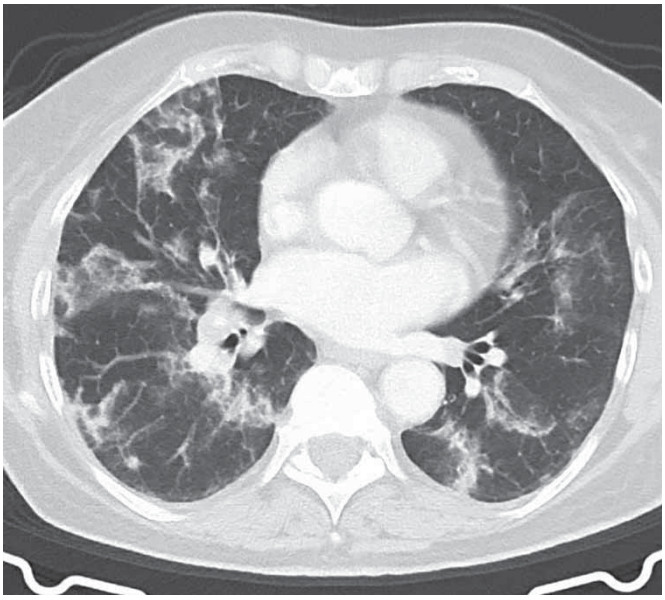

FIGURE 3 Cryptogenic organising pneumonia in a patient 112 days post-allogeneic haematopoietic stem cell transplantation, with patchy bilateral consolidation.

Risk factors for the development of OP include peripheral stem cell transplant, female-to-male transplant, and the presence of cGvHD [34]. Certain pre-conditioning regimens, such as fludarabine-based reduced-intensity conditioning, have been associated with lower risk. Pulmonary function testing (PFT) demonstrates a restrictive deficit with globally reduced forced vital capacity (FVC) and total lung capacity (TLC). CT scans feature ground-glass infiltrates, consolidation, linear opacities and traction bronchiectasis [35]. Bronchoscopy is necessary to rule out any infectious cause and transbronchial biopsies usually can confirm the clinical diagnosis. BAL typically shows a predominant lymphocytosis and a reduced CD4/CD8 lymphocyte count, which may help support the diagnosis [36].

Treatment is similar to that needed for COP in non-HSCT recipients, with the use of high-dose steroids (starting doses recommended at 0.75–1.5 $mg \cdot kg^{-1}$) with a prolonged tapering course over months. The risk of OP relapse as the steroid dose is reduced is high, with patients often requiring re-treatment with higher steroid doses. Other agents such as rituximab and ruxolitinib have also been used in relapsing cases, or as steroid-sparing agents [33].

Bronchiolitis obliterans syndrome

Bronchiolitis obliterans syndrome (BOS) is a progressive obstructive ventilatory defect that develops as a late complication of HSCT. BOS is a pulmonary manifestation of cGvHD and as such is almost exclusively seen in patients with allogeneic bone marrow transplantation. Onset is typically within 2 years of transplant, with some studies estimating an overall incidence of ∼5% and reaching 10% in patients who develop cGvHD, with a median time of onset of ∼300 days [37]. However, it can occur years later and patients can have slowly progressive airflow obstruction over decades.

The onset of BOS can be insidious, with patients typically reporting progressive exertional dyspnoea or cough. On occasion, it can develop over weeks. Some patients are asymptomatic at the time of diagnosis, with ventilatory deficits identified on routine PFT. Current recommendations suggest routine interval PFT in the post-transplant period to identify new or worsening obstructive deficits early in the clinical course.

Risk factors identified for the development of BOS include GvHD at another site, use of peripheral stem cell grafts, impaired pre-transplant lung function, prior interstitial pneumonitis and significant respiratory infection in the early post-transplant period [36].

BOS is clinically defined as a progressive, fixed obstructive deficit on spirometry. This is characterised by a forced expiratory volume in 1 s (FEV_1)/FVC ratio of <0.7, and FEV_1 of <75% predicted with no significant bronchodilator response. Additional evidence of small airways disease is also required (one out of the two following parameters): CT of the thorax demonstrating evidence of air trapping, small airways thickening or bronchiectasis (figure 4); or a residual volume (RV) >120% predicted, or elevated RV and TLC. Absence of evidence of respiratory infection is also required (by culture, radiology or microbiology) [37]. The use of change in forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) may be more useful than the change in FEV_1, for monitoring BOS [38].

Although the gold standard for diagnosis is a surgical lung biopsy demonstrating typical histological features of BOS (constrictive bronchiolitis obliterans with chronic inflammation and fibrotic scarring of bronchioles resulting in bronchial narrowing), this is rarely performed, as a suggestive clinical picture with supporting imaging features and negative culture results is usually sufficient.

The rate of progression of BOS is difficult to predict. Serial PFT measurements are useful in identifying those who are progressing and require intervention. The initial first line in the management of BOS is to address any possible contributing comorbidities and optimise immunosuppressive treatment. Protracted courses of corticosteroids have previously been used for the management of GvHD-BOS, but this is no longer recommended unless required for extrapulmonary complications of cGvHD. Inhaled fluticasone, azithromycin and montelukast have all been studied with varied results. A study looking at the prophylactic use of azithromycin 250 mg three times a week prior to transplant found that this treatment was not beneficial [39]. Inhaled corticosteroids and formoterol were shown in one study to have benefit in established BOS [40], but corroborating evidence is sparce. Montelukast was also shown to be of benefit in one small single-centre trial [41], while the use of the FAM regime (inhaled fluticasone, azithromycin and montelukast) has been included in the recent European Respiratory Society (ERS)/EBMT guidelines, albeit recognising the limited evidence base for this and other therapies in general [42]. More recently, drugs that have shown a benefit in cGVHD, such as ruxolitinib and ibrutinib, have been employed [43]. Ruxolitinib may be useful in cases where extrapulmonary GvHD is present, given its efficacy in that area.

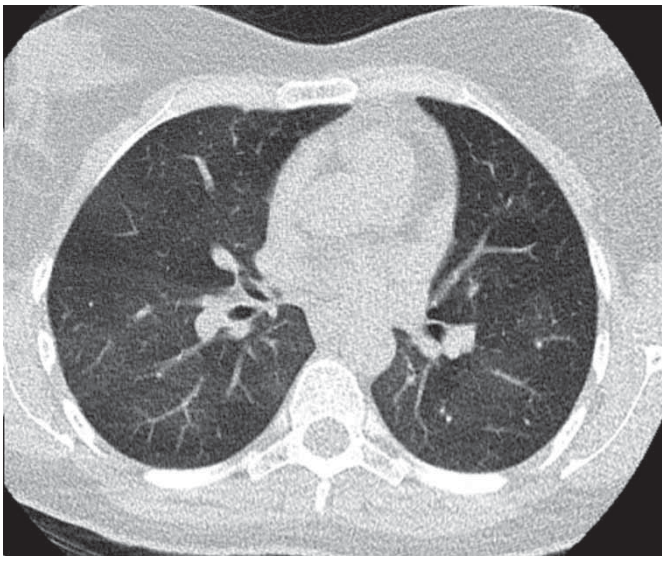

FIGURE 4 Bronchiolitis obliterans in a 31-year-old female with progressive dyspnoea over 8 weeks, 14 months after allogeneic haematopoietic stem cell transplantation. Small airway narrowing leads to mosaic perfusion on computed tomography of the thorax.

Supportive measures with oxygen and medications for symptom control are also important, due to the progressive nature of BOS. Additionally, extracorporeal photophoresis has been studied in cGvHD, with 40–70% showing beneficial results for various organs such as skin, liver, mucosa, eyes and gastrointestinal tract, although its effect on the lungs is less impressive [44]. It is believed its favourable effects are related to enhanced regulatory T-cell function.

Whether identifying BOS at an earlier phase of progression can result in improved outcomes remains to be determined, but sequential monitoring of lung function every 3 months for the first 2 years after HSCT is recommended. The prognosis of BOS is poor, with an overall 5-year survival of 45% in the post-FAM regime era. Consideration for lung transplantation is appropriate in certain cases for those who are otherwise healthy.

Interstitial lung disease

Interstitial lung disease is an uncommon manifestation of cGvHD of the lung, seen in about 2.4% of cases, although it has been recognised by the National Institutes of Health (NIH) working group of clinical trials for cGVHD. Generally, patients present with progressive dyspnoea and cough with restrictive pulmonary function studies. Radiologically, there can be patterns of ground-glass infiltrates, consolidation, fibrosis, reticulation, septal lines and traction bronchiectasis. The 5-year survival rate of interstitial lung disease has been reported as 70%, with many patients dying of respiratory failure [45], although one study reported a 2-year survival of 61%. One pattern rarely seen is pleuroparenchymal fibroelastosis with a particularly foreshortened survival (figure 5).

Pulmonary air leak syndrome

Pulmonary air leak syndrome is generally seen in patients suffering from BOS as part of cGvHD. It is a relatively rare presentation in 2–6% of cases, occurring late in the post-HSCT period with a median time to onset of 253 days. This condition usually presents as either acute onset of dyspnoea, chest pain, or both, as well as occasionally being asymptomatic but picked up on chest radiography or CT of the thorax. It may manifest as subcutaneous emphysema of the chest and neck, with hoarseness or a crunching sound synchronous with systole on heart auscultation. It is thought to be caused by rupture at an alveolar level due to underlying lung disease. It is typically managed conservatively or with chest tube insertion, but its presence portends a very poor prognosis [46].

Pulmonary vascular disease

Pulmonary vascular disease can manifest as either pulmonary hypertension or pulmonary veno-occlusive disease. Most reported cases are children and, rarely, young teenagers. The incidence of pulmonary hypertension is unknown but it is rare and presages a reduced survival. It may present with dyspnoea,

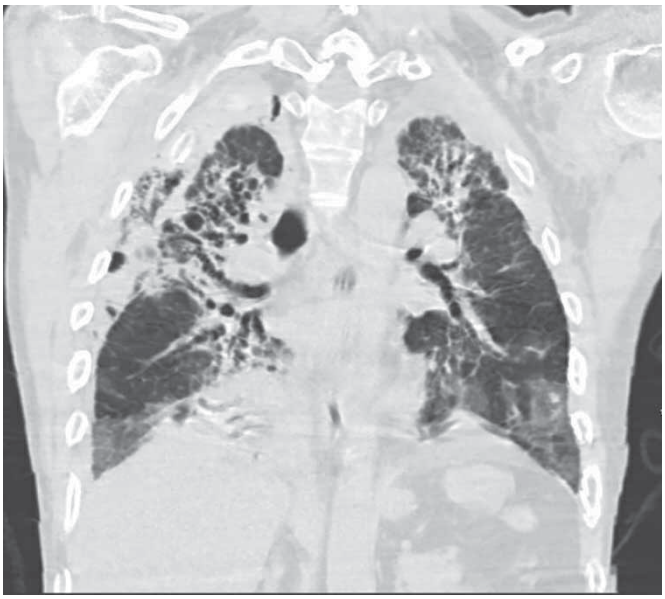

FIGURE 5 Pleuroparenchymal fibroelastosis (biopsy confirmed) in a 55-year-old male with chronic graft-*versus*-host disease. This is characterised by the development of apical pleural thickening, subpleural fibrosis, traction bronchiectasis, hilar retraction and, frequently, pneumothorax.

fatigue, hypoxia and dizziness. The diagnosis may be suspected on a plain chest radiograph or seen more accurately with dilated pulmonary arteries on CT of the thorax. Echocardiography is useful and is often performed before right heart catheterisation. Treatment is directed at correcting any underlying hypoxia and left ventricular dysfunction, with the use of calcium channel blockers, prostanoids, endothelium receptor antagonists and phosphodiesterase-5 inhibitors [47].

Pulmonary veno-occlusive disease is also a rare complication of HSCT, with the presumed cause being infections or conditioning regimen drug toxicity. The endothelium shows narrowing and occlusion in the small venules and veins of the pulmonary circulation. Progressive dyspnoea and reduced energy are seen, typically 2–6 months post-transplant. CT imaging shows a classic triad of dilated pulmonary arteries, interlobular septal thickening and centrilobular ground-glass infiltrates. Definitive diagnosis requires a biopsy, which is not always performed if the characteristic radiological features are accompanied by typical findings on right heart catheterisation. Treatment is generally supportive with oxygen and management of right heart failure. The reported 1-year mortality approaches 70% [48].

Infectious pulmonary complications

Factors affecting the risk of infection

Infections are a major source of morbidity and mortality in HSCT, and pulmonary infections make up a considerable proportion of these. Appropriate design and maintenance of the bone marrow transplantation unit to the highest standards, along with strict nursing guidelines and protocols, are necessary to support patient health and an effective therapeutic environment [49]. One salient feature contributing to infection risk is the type of HSCT performed. Due to a variety of factors, the risk of any infection in general is higher in allogeneic compared with autologous HSCT. Allogeneic HSCT is associated with a longer pre-engraftment phase (15–30 days *versus* 10–14 days for autologous HSCT) [50]. As a result, allogeneic recipients have a greater risk of infection due to neutropenia and the typical mucosal injury associated with the pre-engraftment phase.

Allogeneic HSCT also has a higher risk of infection in the post-engraftment phases [7]. To minimise the risk of both graft rejection and GvHD, immunosuppressive therapy is continued following engraftment in allogeneic HSCT for some months, which is not necessary for autologous HSCT. As a result of pharmacological immunosuppression, cell-mediated immunity is slower to reconstitute in allogeneic HSCT, enhancing the risk of infection. Independent of other factors, the development of GvHD is invariably associated with opportunistic infections, as the prolonged immunosuppression therapy needed to treat GvHD delays the recovery of cell-mediated and humoral immunity beyond the early post-transplant period [51].

A variety of other graft factors affect the risk of infection in allogeneic HSCT. Grafts from an unrelated or HLA-mismatched donor are associated with higher rates of GvHD and slower T-cell and B-cell reconstitution, increasing infection risk in the post-engraftment phases. Peripheral blood transplants lead to a shorter engraftment period compared with transplants derived from marrow or cord blood, with an ensuing lower period of neutropenia and fewer pulmonary infections [52]. However, the trade-off is more frequent GvHD with peripheral blood transplants, which, as mentioned, itself augments the risk of infection in the post-engraftment phases. *Ex vivo* or *in vivo* graft manipulation, performed pre-transplant to deplete T-cells, will also affect the risk of infection. A lower graft T-cell count will generally reduce the risk of GvHD and its associated infections in the post-engraftment phases but will also lead to slower T-cell reconstitution after transplant, leading to more prolonged immunosuppression.

Other pre-transplant patient-specific factors affecting the risk of pulmonary infection include patient age, comorbidities, the underlying disease requiring HSCT, and prolonged neutropenia and mucosal injury [53]. Finally, contemporaneous non-infectious complications lead to added infection risk *via* structural damage, effects on membrane integrity, compromised physiological function, and the need to introduce immunosuppression for their treatment.

Patterns of specific pulmonary infections

Pulmonary infections can be categorised by type of pathogen (bacterial, fungal or viral) and the phase of the HSCT process at which they tend to occur (pre-engraftment, early post-engraftment or late post-engraftment). The pre-engraftment phase (~10–30 days) is defined by neutropenia in the context of non-functioning bone marrow. Pulmonary infections during this period are typically the result of neutropenia, mucosal breakdown and *i.v.* access lines [50]. Engraftment marks the beginning of immune recovery (~30–100 days) and has been defined as the first three consecutive days in which the patient has an absolute neutrophil count $>0.5\times10^{9}$ cells·L^{-1} [54]. Cell-mediated immunity begins to reconstitute in the early post-engraftment phase; however, other infectious risks emerge (viral, *Pneumocystis jirovecii* pneumonia (PJP) and fungal), complicated by the presence of GvHD and the immunosuppression needed to treat it. The period beyond 3 months is known as the late post-engraftment phase. At this point, both cellular and humoral immunity return towards normal (usually regarded as normal in allogeneic transplants after 1 year in the absence of GvHD) [50]. However, the risk of infection persists in those with cGvHD, due both to its direct dysregulation on the immune system and the need for treatment with further immunosuppressives.

Bacterial infections

In allogeneic HSCT, bacterial infections make up about 90% of the total infections seen in the pre-engraftment phase (0–30 days), similar to what is seen in non-HSCT neutropenic patients, with a majority of these being Gram-positive organisms. Bacterial infection appears to be the leading cause of pneumonia following HSCT, making up 44% of cases of pneumonia in one study, compared with 29% fungal and 19% viral. In the post-engraftment phase (~30–100 days), bacterial infections continue at a less frequent rate, and often occur without a definitive source being identified, although line infections cause up to 30% of cases [55].

In the late post-engraftment phase (>100 days), if there is no GvHD, no requirement for immunosuppression, adequate CD4 cell numbers and normal immunoglobulin levels, opportunistic infections are rare. However, if immunosuppression is needed for GvHD, patients have impaired humoral and cellular immunity and are at risk of encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus* spp. [56]. In some studies, invasive pneumococcal disease is up to 30 times higher following allogeneic HSCT than in the general population, with a reported mortality of 14% in a recent study [57].

Rarely, *Nocardia* spp. infections are described in the late post-engraftment phase [58]. This typically manifests as pneumonia not responding to conventional antibiotics, with a macronodular appearance on CT in 75% of cases [59]. Treatment is full-dose trimethoprim/sulfamethoxazole (TMP/SMX) but may require meropenem and/or linezolid for resistant cases and brain abscess. It typically affects patients requiring immunosuppression and can occur even in those receiving prophylactic TMP/SMX [60].

Mycobacterium tuberculosis infection is a comparatively rare complication of HSCT. The infection rate inevitably depends on the prevalence of tuberculosis in the country where the HSCT is occurring, ranging from 0.0014% (USA) to 16% (Pakistan) of HSCT recipients [61]. The particulars of treatment are beyond the scope of this article but are reviewed by Bergeron *et al.* [62].

Pulmonary nontuberculous mycobacterial infection is more common in allogeneic HSCT recipients (with a reported incidence of 2%) than in the general population. Those with cGvHD are more at risk. Species

isolated include *Mycobacterium avium* complex, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium intracellulare* and *Mycobacterium fortuitum* [63].

Fungal infections

Fungal infections are a major cause of morbidity and mortality post-HSCT. With current management strategies and preventative measures, the incidence is between 2% and 5% [64]. However, fungal infection post-allogeneic HSCT still has a significant mortality of around 10%. Fungal infections can present in all three engraftment periods, especially if acute or chronic GvHD is present. *Candida* infections are most common in the pre-engraftment phase due to neutropenia and mucosal injury. However, the incidence of invasive *Candida* infection has become less frequent with the widespread use of azole prophylaxis [7].

PJP, which was historically a significant cause of morbidity in the early and late post-engraftment phases, is now rare due to the near-universal use of TMP/SMX prophylaxis. In one large observational study involving over 450 transplant centres, the incidence of PJP was found to be <1% of allogeneic HSCT patients [65].

The most common fungal infection affecting HSCT patients is invasive aspergillosis [51]. This can affect patients in all three phases post-HSCT, with patients at risk early due to neutropenia and in later phases due to immunosuppression and cGvHD. Invasive aspergillosis may present as a macronodular pattern on chest CT with the "halo sign" (nodules surrounded by ground-glass opacities) particularly characteristic of angioinvasion, or as centrilobular micronodules (figure 6) [66]. Treatment is usually with *i.v.* voriconazole or isavuconazole. Despite this, mortality rates remain high [67, 68].

Other mould species may also cause pulmonary infections in the post-engraftment period, with Zygomycetes (Mucorales and Entomophthorales) being the second most common, making up 10–20% of cases of mould pneumonia and classically causing a "bird's nest" sign on CT. Zygomycetes infections have an extremely high mortality rate despite treatment (usually with *i.v.* liposomal amphotericin B) [68]. Endemic fungi such as *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis* are rarely encountered.

Viral infections

Viral illnesses can occur at any time during the transplant process, with herpes simplex virus (HSV) tending to be one of the earlier viruses encountered, typically in the pre-engraftment phase. Without antiviral prophylaxis, reactivation of seropositive patients occurs in about 70–80% of individuals during this period, with pneumonia typically caused by direct spread from the oropharynx. In addition to pneumonia, HSV may also cause tracheobronchitis, with haemoptysis in severe cases. Acyclovir prophylaxis is now recommended in seropositive patients to reduce the risk of reactivation, which effectively decreases reactivation rates to about 16% [69].

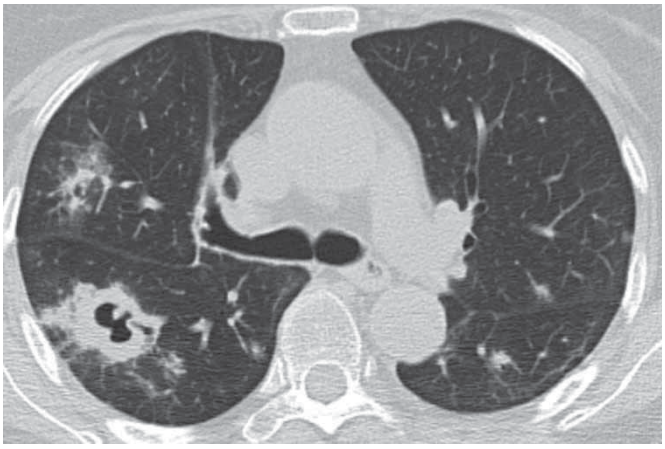

FIGURE 6 Invasive pulmonary aspergillosis. A cavitary pulmonary nodule, an area of consolidation with a "halo" sign and small peripheral peribronchial nodular infiltrates.

Herpes zoster virus (HZV) can also cause complications, usually in the late phase post-HSCT, with disseminated HZV having a mortality rate of about 34%. Valacyclovir prophylaxis is effective in preventing most cases [70], while more recently the use of a recombinant HZV vaccine has shown vaccine efficacy of 68% [71].

Cytomegalovirus (CMV) is traditionally considered a major infection risk of HSCT, with significant potential pulmonary complications. Typically, it manifests in the post-engraftment stages (early and late), having a strong association with GvHD [72]. CMV disease has been found to affect up to 16% of allogeneic HSCT patients, with a higher rate in seropositive HSCT patients, as well as seronegative patients receiving transplants from seropositive donors. For those at risk serologically, current recommendations are to administer pharmaco-prophylaxis with letermovir until 100 days post-transplant to reduce the risk of reactivation and end-organ damage. Where this is not possible, regular monitoring for viraemia is recommended to enable pre-emptive treatment with either oral valganciclovir or *i.v.* ganciclovir [73]. In refractory or resistant cases, cidofovir, foscarnet or the novel agent maribavir are salvage options [74].

Common respiratory viruses including influenza A and B, parainfluenza, human metapneumovirus, adenovirus and respiratory syncytial virus pose a significant hazard following HSCT, with chronic lung disease, GvHD, immunosuppressive use and lack of routine vaccination all enhancing the risk [75].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; causing COVID-19) is now an endemic respiratory virus in the community and healthcare setting and poses challenges to HSCT patients. A multicentre retrospective study of HSCT patients with COVID-19 between February 2020 and March 2022 showed an overall mortality rate of 21%, with COVID-19 being the main or a secondary cause of death in 16% [76]. The median time from HSCT to the diagnosis of COVID-19 illness was 268 days. Prolonged viral shedding is common, affecting the duration of isolation requirements. Recommendations include prompt treatment with ritonavir-boosted nirmatrelvir (Paxlovid), although drug–drug interactions with common chemotherapeutic agents are an important consideration. Intravenous remdesivir is an alternative. Although a decreased humoral response to vaccination may occur in HSCT patients before full immune reconstitution, up-to-date vaccination of HSCT recipients and caregivers is recommended [77].

Conclusion

The complications arising from HSCT often require input from respiratory physicians and their trainees. Categorising the disorders and their timelines of appearance improves the recognition, diagnosis and treatment of these diverse and often overlapping disorders. Additionally, specialised combined haematology/respiratory clinics for those with respiratory illnesses help streamline the overall management and outcome of this complex group of patients.

Key points

- Respiratory complications are common in HSCT.
- Autologous and allogeneic HSCT have different spectra of complications, due to the occurrence of GvHD in allogeneic HSCT and the immunosuppression necessary to control it.
- The timeline of the first 100 days post-transplant is a useful way of categorising the probability of occurrence of both infectious and non-infectious complications, although there is significant overlap in time frames, and more than one condition may be present simultaneously.

Self-evaluation questions

1. A 34-year-old nonsmoker underwent a matched unrelated allogeneic HSCT 9 months ago. Apart from an initial period of skin, mucosal and liver GvHD, he had made an uneventful recovery. He was being weaned off tacrolimus and was maintained on valacyclovir, fluconazole and TMP/SMX prophylaxis. 3 weeks following a mild viral illness, he noticed dyspnoea walking up inclines. Pre-HSCT, PFT was normal. CT of the thorax was reported to be normal. Routine full blood count, C-reactive protein, renal, liver and thyroid function tests, D-dimer and brain natriuretic peptide were normal. An echocardiogram showed normal valve function and normal left ventricular function. PFT showed a normal D_{LCO} corrected for haemoglobin, normal TLC, FEV_1 of 69% predicted, FVC of 81% predicted and $FEF_{25–75\%}$ of 54% predicted. What is the most likely cause of the patient's symptoms?
    a) Cryptogenic organising pneumonia
    b) Idiopathic pneumonia syndrome
    c) Pulmonary veno-occlusive disease
    d) Bronchiolitis obliterans
    e) *Pneumocystis jirovecii* pneumonia

2. A 52-year-old female developed a cough, fever and progressive dyspnoea 2 weeks after autologous HSCT. Her vitals showed tachycardia, a respiratory rate of 24 breaths·min^{-1} and a temperature of 38.5°C. Her absolute neutrophil count is 200×10^6 cells·L^{-1}. C-reactive protein is elevated at 201 mg·L^{-1}. A chest radiograph demonstrates patchy bilateral infiltrates. There is no rash, diarrhoea or weight gain, and renal and liver function tests are normal. BAL returns a clear fluid that is sent for culture and viral studies, which are pending. What is the most likely explanation for this patient's deterioration?
    a) *Pneumocystis jirovecii* pneumonia
    b) Peri-engraftment respiratory distress syndrome
    c) Cytomegalovirus infection
    d) Idiopathic pneumonia syndrome
    e) Gram-positive bacterial infection
3. Which one of the following radiological findings is not believed to be a manifestation of chronic GvHD of the lung?
    a) Bronchiectasis
    b) Cryptogenic organising pneumonia
    c) Emphysema
    d) Tree-in-bud appearance
    e) Idiopathic interstitial pneumonia
    f) Pleuroparenchymal fibroelastosis
    g) Air leak syndrome

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Suggested answers

1. d. All other conditions would be expected to reduce the D_{LCO} or demonstrate some evidence of inflammation. Bronchiolitis obliterans, on the other hand, can present solely with progressive dyspnoea, with normal imaging unless one performs inspiratory and expiratory CT phases which demonstrates air trapping. Characteristically, there is a progressive relentless decline in the $FEF_{25–75\%}$ that is poorly responsive to treatment.
2. e. In the pre-engraftment phase post-HSCT, bacterial infections are the most frequent cause of pneumonia, exceeding cases caused by viral or fungal infections. PJP is typically seen later in the post-HSCT period and is now rare due to the universal use of prophylaxis. IPS is a diagnosis of exclusion and is typically seen in the early post-engraftment phase and beyond. Additionally, it is defined as an entity where infection has been excluded and in this scenario the results are still pending, so one cannot have a diagnosis of IPS at this juncture.
3. c. Emphysema. All the other conditions are identifiable complications of HSCT and, on occasion, more than one entity may occur simultaneously. For example, it is not uncommon for a patient to have both bronchiolitis obliterans and bronchiectasis on the same CT image.