Respiratory failure in the hematopoietic stem cell transplant recipient

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Abstract

The number of patients receiving hematopoietic stem cell transplantation (HSCT) is rapidly rising worldwide. Despite substantial improvements in peri-transplant care, pulmonary complications resulting in respiratory failure remain a major contributor to morbidity and mortality in the post-transplant period, and represent a major barrier to the overall success of HSCT. Infectious complications include pneumonia due to bacteria, viruses, and fungi, and most commonly occur during neutropenia in the early post-transplant period. Non-infectious complications include idiopathic pneumonia syndrome, peri-engraftment respiratory distress syndrome, diffuse alveolar hemorrhage, pulmonary veno-occlusive disease, delayed pulmonary toxicity syndrome, cryptogenic organizing pneumonia, bronchiolitis obliterans syndrome, and post-transplant lymphoproliferative disorder. These complications have distinct clinical features and risk factors, occur at differing times following transplant, and contribute to morbidity and mortality.

Key words: Respiratory failure; Pulmonary complications; Hematopoietic stem cell transplantation; Stem cell transplant; Immunocompromised host

Core tip: Respiratory failure in the hematopoietic stem cell transplant recipient is common and is a major contributor of morbidity, mortality, and healthcare utilization. Etiology may be infectious or non-infectious in nature, and in some cases these may coexist. While identification remains challenging, infectious and non-infectious syndromes have distinct clinical features and risks.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is increasingly utilized worldwide for definitive treatment of hematologic malignancy and other conditions, with over 50000 transplants performed annually[1]. During HSCT, patients undergo high dose conditioning chemotherapy and/or radiation therapy with a view to eradicate their immune system along with any residual malignant cells. Stem cells are collected beforehand and are administered after conditioning is complete to reconstitute the immune system. HSCT may be autologous (where the donor stem cells are the patient's own) or allogeneic (where the donor stem cells are from an appropriately matched donor).

The post-transplantation period is temporally separated into three phases and represents a dynamic, individualized spectrum of risk (Figure 1). The first phase is the pancytopenic phase immediately following transplantation, typically lasting 10-21 d following HSCT. Autologous transplant recipients typically engraft before allogeneic, and several peri-transplant factors such as peripheral stem cell harvest and the use of granulocyte stimulating factors in the post-transplant period promote earlier marrow recovery. The second phase occurs after neutrophil engraftment, once the absolute neutrophil count consistently exceeds 500 cells per mm^3. The second phase typically lasts for the first 100 or so days following transplantation. The third phase can be considered "late" complications of transplantation, occurring more often in allogeneic transplantation where graft-versus-host effects have pulmonary manifestations. Pulmonary complications and respiratory failure are common, occurring in up to two-thirds of HSCT recipients, and are associated with significant morbidity and mortality[2-4]. These pulmonary complications can be characterized by the phase of the post-transplant period when they are most likely to occur (Figure 1). The purpose of this mini-review is to highlight the infectious and non-infectious sources of respiratory failure in the HSCT recipient.

INITIAL APPROACH IN THE ACUTELY ILL PATIENT

Respiratory failure following HSCT presents on a spectrum of severity. Several aspects of the clinical presentation provide clues about possible etiologies: acute versus subacute, early post-HSCT or late post-HSCT, diffuse versus focal. A substantial number of patients on the more severe end of this spectrum present with acute hypoxemic respiratory failure and diffuse pulmonary infiltrates, meeting criteria for the acute respiratory distress syndrome (ARDS)[2]. While the underlying etiology is often not known at the time of presentation, the principles of ARDS management and prevention are equally valid in this population. Specifically, this includes lung-protective mechanical ventilation with low tidal volume strategies, appropriate recruitment, and use of neuromuscular blockade where appropriate[5-7]. In addition, there should be a focus on preventing iatrogenic "second-hits" through judicious fluid and blood product administration, aspiration precautions, and early focus on mobilization and ventilator liberation[7-10]. These lung injury prevention guidelines have been conceptualized into the Checklist for Lung Injury Prevention, which was recently implemented as part of an ARDS prevention clinical trial[7,11]. Patients with pre-existing pulmonary disease are more susceptible to pulmonary complications, particularly those receiving high dose radiation to the lungs as part of their conditioning program[12,13]. Concurrently, patients should be evaluated for possible etiologies for their presentation. These can be divided broadly into infectious and non-infectious causes.

INFECTIOUS RESPIRATORY FAILURE

Infectious pulmonary complications are most common in the immediate post-transplant period during neutropenia. Recipients of allogeneic HSCT are typically more prone to infectious pulmonary complications due to a longer period of neutropenia and the need for immunosuppressant medication administration to prevent graft-versus-host disease[14]. Routine infectious prophylaxis during neutropenia has dramatically reduced the burden of infectious complications. However, breakthrough infections can occur from a variety of causative organisms and vary dependent on patient and transplant characteristics, and time elapsed following transplant (Figure 1)[3].

Bacterial

Bacterial pneumonias most commonly occur in the early transplant period[15]. Risk for bacterial pneumonias in allotransplants is greater if myeloablative (as opposed to non-myeloablative or reduced intensity) conditioning is used, the patient has graft-versus-host disease, there is delayed engraftment and a prolonged period of neutropenia, or if there are indwelling devices[16-18]. In the early post-transplant period, gram-negative organisms such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* should be suspected, whereas encapsulated organisms are a concern late after HSCT[19]. When patients develop hypoxemic respiratory failure and new pulmonary infiltrates following HSCT, infection is typically presumed. This approach is reasonable given the substantial mortality associated with delayed antimicrobial therapy in immunocompromised patients. Ideally, microbiological sampling from bronchoalveolar lavage (BAL) is preferred,
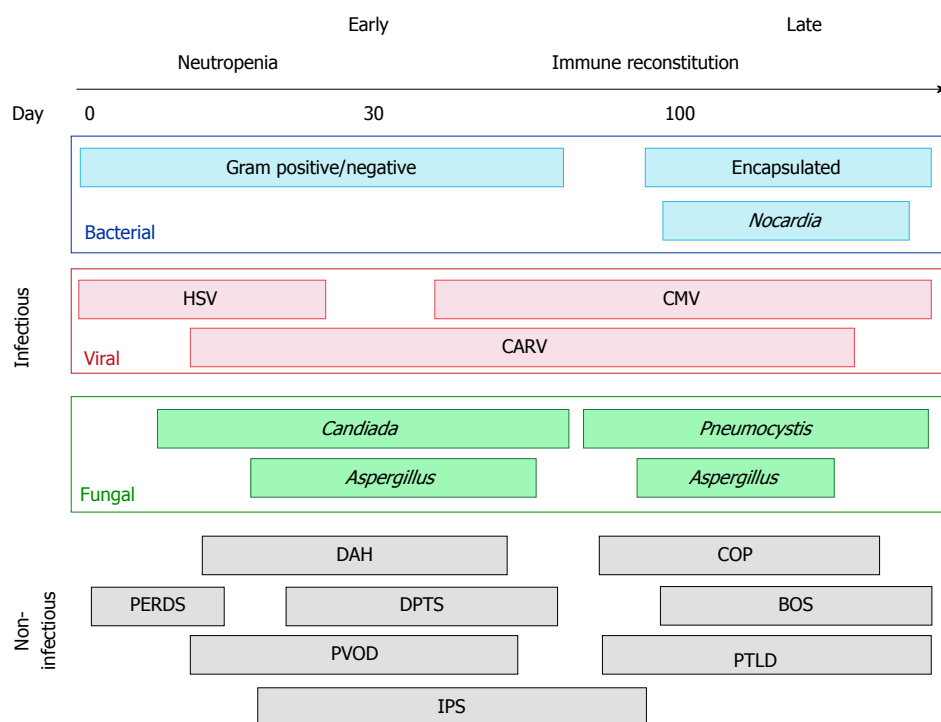
Figure 1 Time-course of pulmonary complications following hematopoietic stem cell transplantation. BOS: Bronchiolitis obliterans syndrome; CARV: Community-acquired respiratory viruses; CMV: Cytomegalovirus; COP: Cryptogenic organizing pneumonia; DAH: Diffuse alveolar hemorrhage; DPTS: Delayed pulmonary toxicity syndrome; HSV: Herpes simplex virus; IPS: Idiopathic pneumonia syndrome; PERDS: Peri-engraftment respiratory distress syndrome; PTLD: Post-transplant lymphoproliferative disorder; PVOD: Pulmonary veno-occlusive disease.

although the risk and benefits of invasive sampling need to be individually assessed. If patients are on antibacterial infectious prophylaxis when pneumonia is suspected, antibacterial agents should be broadened to cover noso-comial pathogens[20,21].

Certain infectious syndromes are worthy of additional discussion. Encapsulated bacteria, particularly *Streptococcus pneumoniae*, should be suspected later following HSCT, most commonly after 6 mo[22]. Invasive pneumococcal disease has been reported to be 30 times more prevalent in HSCT recipients compared to the general population[15], and up to 88% of cases have bacteremia[23]. Nocardia pneumonia can occur in the late post-transplant period, usually after 6 mo[24]. While nocardial infection is uncommon after HSCT, it should be suspected in non-responders to initial antimicrobial therapy. Sulfamethoxazole-trimethoprim is the treatment of choice and response to therapy is typically robust[24,25]. Routine use of sulfamethoxazole-trimethoprim for *Pneumocystis* prophylaxis does not adequately protect against nocardiosis. Mycobacterial pneumonia is rare, but can occur in the late post-transplant period, and typically presents one year after HSCT[26,27]. Incidence of *Mycobacteria tuberculosis* among HSCT recipients is higher in endemic areas and those receiving allogeneic grafts[27]. Presentation and management of these infections and non-tuberculous *Mycobacteria* are similar to that of the general population[27,28].

Viral
Herpes simplex virus (HSV) infection is relatively uncom-

mon following HSCT due to routine infectious prophylaxis with acyclovir[29]. HSV pneumonia typically occurs in the early post-transplant period and is a result of latent reactivation (Figure 1). Allotransplants receiving grafts from seropositive donors and those with graft-versus-host disease are at increased risk of HSV[29,30]. Diagnosis of HSV pneumonia can be challenging since low-grade HSV reactivation and viral shedding is not uncommon in critical illness, and qualitative polymerase chain reaction (PCR) on BAL samples is exquisitely sensitive.

Cytomegalovirus (CMV) pneumonia occurs in up to 30% of allotransplants and typically presents after engraftment until around 4 mo (Figure 1)[31,32]. It occurs most commonly when a seropositive allograft recipient receives a seronegative transplant. Pulmonary imaging findings are nonspecific, typically bilateral and diffuse, with both alveolar and nodular opacities[33]. BAL fluid should be analyzed to confirm the presence of CMV by PCR (most common), shell assay, or viral culture. Again, low grade CMV shedding is not uncommon in critical illness and doesn't necessarily indicate pneumonitis. Definitive diagnosis requires demonstration of tissue involvement on lung biopsy[34], but this is rarely performed. In the presence of CMV in BAL and a compatible clinical/radiographic picture, supportive evidence of widespread CMV reactivation is usually needed before initiation of treatment. Elevated and escalating quantitative serum PCR, or evidence of CMV involvement in other organs (*e.g.* gut, CNS) all support systemic CMV infection. Ganciclovir is the treatment of choice for invasive CMV disease, though treatment can be limited by leukopenia,

particularly problematic among the HSCT population[35]. The epidemiology of post-HSCT CMV pneumonitis may change if novel CMV prophylactic agents are routinely administered[36].

The community-acquired respiratory viruses (CARV) including influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, rhinovirus, enterovirus, and coronavirus, can occur during the entire post-transplant period (Figure 1)[37]. Diagnosis occurs most commonly by nasal PCR-amplification assays, or with BAL. RSV is the most commonly isolated CARV, and is estimated to be recovered in up to a third of patients undergoing HSCT in the first three years[37-39]. In addition to hypoxia, patients typically present with fever, productive cough, and dyspnea[37,40]. Chest imaging findings include diffuse patchy alveolar opacities[40]. RSV in the HSCT population is highly morbid and has mortality rates reported up to 80%. Beyond supportive care no specific therapy has shown consistent benefit. Given the high mortality rates in HSCT recipients, high RSV titer immune globulin or aerosolized ribavirin may be considered[41].

Fungal
Pulmonary aspergillosis effects up to two-thirds of HSCT recipients, although incidence is declining with routine anti-*Aspergillus* prophylaxis during neutropenia and more effective treatment of graft-versus-host disease[42-44]. Pulmonary aspergillosis has been reported in upwards of 30% of HSCT recipients[3,42]. Risk factors include allogeneic transplant, unrelated donors, prolonged neutropenia, immunosuppressant use for graft-versus-host disease, and CMV infection[45-47]. Most common findings radiologically include pulmonary nodules with or without halo sign, ground glass opacities, and an air crescent sign from necrotic tissue in advanced cases[47-49]. Hemoptysis can be present and is typically associated with poor prognosis[50-52]. Diagnosis is confirmed by *Aspergillus*-specific PCR or *Aspergillus* sp. antigen in BAL[53,54]. Monotherapy with isavuconazole or voriconazole is the preferred first-line treatment and therapeutic drug monitoring should be utilized to ensure adequacy of dosing[55]. Severe cases refractory to medical therapy or recurrent hemoptysis may be considered for surgical evaluation, though lung resection is highly morbid and associated with significant mortality in this population[56].

Incidence of *Pneumocystis jirovecii* pneumonia (PCP) has marginally declined in recent years as the use of prophylaxis has increased[57,58]. However, there is limited guidance and no consensus on which patients outside of HIV-positive individuals should receive prophylaxis, and therefore PCP remains highly relevant in HSCT recipients. Our institution routinely implements prophylaxis from engraftment until the first 100 d (or longer if patients are immunosuppressed for graft-versus host disease). PCP occurs late after HSCT and presents with acute onset severe respiratory failure[58-60]. Diagnosis is confirmed by the identification of *Pneumocystis* organisms in respiratory samples by PCR or fungal smear[58,61]. Sulfamethoxazole-trimethoprim is the treatment of choice and is highly effective in killing *Pneumocystis* sp[58]. Patients with PCP typically die due to refractory hypoxemia from severe respiratory failure, and corticosteroids have failed to demonstrate benefit outside of the HIV population[62,63]. Nonetheless, adjunctive corticosteroids are typically administered in individuals with HSCT who develop PCP.

NON-INFECTIOUS RESPIRATORY FAILURE
Noninfectious respiratory failure syndromes are common throughout the entire post-HSCT period, and our understanding of them remains incomplete. The risks of these syndromes vary based on transplant type, and a variety of modifiable and non-modifiable transplant and patient characteristics. In addition to key distinguishing clinical criteria, non-infectious complications are categorized by when they occur temporally following HSCT (Figure 1). Often infection cannot be ruled out at the time of initial presentation and should be concurrently treated given the substantial mortality associated with delayed antimicrobial administration.

Peri-engraftment respiratory distress syndrome
The peri-engraftment respiratory distress syndrome (PERDS) is a pulmonary subset of the engraftment syndrome, a systemic capillary leak disorder that develops around the time of immune system reconstitution early after autologous HSCT (Figure 1)[64]. PERDS is defined as hypoxemic respiratory failure and bilateral pulmonary infiltrates that occur in the 5 d surrounding neutrophil engraftment, not fully explained by cardiac dysfunction or infection.

Focused studies of PERDS patients found an incidence of nearly 5% in autotransplants[65,66]. Case-fatality rates in excess of 20% nearly two decades ago have substantially reduced to 6% in the current era[65,66]. Risk factors include female gender, blood product administration, rapid engraftment, and HSCT for the POEMS syndrome. We recently found radiographic changes consistent with lung injury precede neutrophil engraftment and may aid in early identification of the syndrome[66]. Treatment consists of short courses of high dose corticosteroids, most commonly 1 to 2 mg/kg methylprednisolone twice daily for 3 d, followed by a rapid taper[65,67]. Response is typically prompt with improvements in oxygenation in most within 24 h of steroid initiation.

Diffuse alveolar hemorrhage
Diffuse alveolar hemorrhage (DAH) is a syndrome characterized by diffuse, bilateral pulmonary infiltrates, progressively bloody return during BAL, and presence of > 20% hemosiderin-laden macrophages in alveolar lavage fluid[64]. While hemoptysis can be seen, it is often absent[68]. DAH mainly occurs during the early post-transplant period (Figure 1).

DAH occurs in 5%-12% of HSCT recipients and is highly morbid with reported mortality rates as high as

60% to 100%[68-72]. Risk factors include age over 40 years, higher intensity conditioning therapies, total body irradiation, and HSCT for acute leukemia and myelo-dysplastic syndrome[69,70,73]. Our understanding of DAH following HSCT is limited. While some cases of alveolar hemorrhage occur during the thrombocytopenic period following transplant, many cases occur after platelet counts are adequate. Also, while DAH may occur in the setting of ARDS or pneumonia, some DAH cases occur in the absence of both.

Treatment of DAH consists of high-dose corticosteroids, most commonly 500 to 1000 mg methylprednisolone per day for 5 d[70,72,74-76]. While one study showed improved survival in 8 patients treated with anti-fibrinolytic amino-caproic acid[70], a subsequent larger study failed to show benefit[75]. Further, even in the presence of thrombo-cytopenia, platelet transfusion did not affect morbidity or mortality in DAH[68].

Idiopathic pneumonia syndrome
Idiopathic pneumonia syndrome (IPS) is an umbrella term for widespread alveolar injury occurring in the absence of cardiac or renal dysfunction, iatrogenic-induced circulatory overload, and infection[64]. Symptoms are consistent with ARDS and pulmonary imaging typically reveals diffuse, bilateral pulmonary infiltrates. There are many similarities and overlap in the clinical presentation of IPS and other non-infectious complications discussed in this review. Those conditions have key distinguishing features and are therefore discussed separately.

IPS effects up to 10% of HSCT recipients, more so allotransplants, and typically occurs during the early post-transplant period (Figure 1)[64]. Mortality is as high as 80% and even greater in those requiring respiratory support with the mechanical ventilator[45,64]. Risk factors include higher intensity conditioning therapies, radiation administration, allogeneic transplant, age, and the presence of graft-versus-host disease.

Treatment of IPS is controversial, and no therapy has shown favorable outcome. Corticosteroids may be administered, though while some studies have shown be-nefit[45,77], others have not[78,79]. When given, higher doses (4 mg/kg per day, prednisolone equivalent) have been shown to be no better than lower doses (2 mg/kg per day or less, prednisolone equivalent), but have the potential to carry greater risk of adverse effects[45]. There has been an ongoing interest in tumor necrosis factor (TNF)-α inhibition due to the observation that patients with IPS have cyto-kine-rich BAL fluid[64]. Preliminary retrospective studies have shown promise with increased response rates and improved overall survival when TNF-α inhibitor, etanercept, was added to corticosteroid therapy[80,81], though these findings were not replicated when a randomized controlled trial design as applied[82]. Further studies are needed to better phenotype what IPS truly represents, and whether any therapies can be effective.

Pulmonary veno-occlusive disease
Pulmonary veno-occlusive disease (PVOD) is a rare com-plication of HSCT with high associated mortality, typically occurring late after HSCT (Figure 1)[83-85]. PVOD should be suspected in those who are progressively dyspneic, have evidence of pulmonary hypertension in the absence of left heart failure, and imaging suggestive of pulmonary edema[64,83,85]. PVOD may occur in the absence of these and therefore, diagnosis must be confirmed by the pre-sence of fibrous intimal proliferation of the pulmonary venules on open surgical lung biopsy[64,86].

Due to the low incidence of PVOD following HSCT and inability to study large numbers of cases, risk fac-tors are extrapolated from the non-HSCT population. These include viral infections, genetic predisposition, autoimmune disorders, and toxic insult to endothelia[86]. In the context of HSCT, these insults include conditioning chemotherapies bleomycin, mitomycin, and carmustine, and irradiation[86-89]. Despite their use in primary pul-monary hypertension, pulmonary vasodilators may be detrimental in PVOD and should be avoided. Dilating the pulmonary arterial vasculature in the setting of fixed venous resistance may precipitate pulmonary edema and worsen respiratory status[86]. Corticosteroids may be administered, though data is sparse[83,86]. Overall, prog-nosis is poor and patients may consider evaluation for lung transplantation if eligible.

Delayed pulmonary toxicity syndrome
The delayed pulmonary toxicity syndrome (DPTS) is a constellation of interstitial pneumonitis and fibrosis occur-ring in the late transplant period, and can present years after HSCT[64]. Characteristically, DPTS appears to be confined to patients receiving high-dose chemotherapy followed by autologous stem cell rescue for breast can-cer[90-93]. Accordingly, the incidence of DPTS in this specific population is reported to be as high as 72%[91]. Symptoms are non-specific and include dyspnea, fevers, and non-productive cough[64]. Similarly, chest imaging reveals bilateral interstitial infiltrates and ground glass opacities. DPTS occurs late following HSCT and can present several years following transplant (Figure 1)[90-93]. The syndrome is highly responsive to corticosteroids and typically asso-ciated with favorable outcomes[91,92].

Cryptogenic organizing pneumonia
Cryptogenic organizing pneumonia (COP) is an interstitial and airspace disease with symptoms mimicking classic pneumonia. Imaging findings include nodular lesions, ground glass attenuation, and patchy peribronchovascular, peripheral, band-like consolidative distributions[64,94]. Biopsy reveals chronic alveolar inflammation and exten-sive granulation of the alveolar ducts and small airways[94]. Bronchoscopy is useful to distinguish COP from infectious pneumonia, and analysis of lavage fluid reveals a predo-minant lymphocytosis[95]. Previously referred to as bron-chiolitis obliterans-organizing pneumonia, COP is a distinct entity from the bronchiolitis obliterans syndrome (BOS), which is discussed separately and should not be confused.

COP occurs in up to 10% of HSCT recipients and typically presents late following transplant (Figure 1)[94,96].

Risk factors include cyclophosphamide conditioning, total body irradiation, male allotransplants with a female cell donor, presence of graft-versus-host disease, and HSCT for leukemia[94,95,97]. Generally, COP is responsive to corticosteroid therapy and typical regimens include 1 mg/kg prednisone daily with an extended taper up to 6 mo[94]. Case fatality rates are reported up to 20%, and are usually due to respiratory failure in the setting of relapsed, steroid-refractory disease[97,98].

BOS

BOS is a slow progression of small airway obstruction believed to be a consequence of graft-versus-host disease[99]. While BOS classically manifests over months to years, abrupt decompensation and severe respiratory failure is not uncommon[100-102]. Histology will reveal intraluminal fibrosis, however yield on transbronchial biopsy is highly dependent on disease presence in the area sampled and open surgical biopsy is very high risk in this population[64,103]. Therefore in the acute setting, diagnosis is established on the basis of reduced expiratory flow with obstructive airflow and radiologic findings include hyperinflation, air trapping, and a mosaic pattern of attenuation[64,95,103].

The incidence of BOS is estimated to be up to 20% and more likely associated with the presence of chronic graft-versus-host disease[99,104,105]. Other risk factors include elder age, reduced expiratory capacity pre-transplantation, unrelated graft donor, irradiation, and viral infection post-HSCT[99,105,106]. High-dose corticosteroids administered for weeks to months are the mainstay of treatment, though response rates are poor as BOS is irreversible, and mortality rates can be as high as 40%[4,95,99,103]. Despite extensive extrapolated use from solid organ transplant patients, macrolides have shown to worsen airflow decline-free survival in HSCT recipients[107]. Other therapies with inconclusive utility include inhaled corticosteroids, intravenous immune globulin, TNF-α inhibitors, cyclosporine, and tacrolimus[4]. Extracorporeal photophoresis is a promising therapy with increasing evidence suggesting its potential benefit[108,109]. Lung transplantation for advanced BOS has been reported[110-113].

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a rare form of malignancy secondary to Epstein Barr virus (EBV)-infected B lymphocytes occurring in the first six months following allotransplant (Figure 1)[64,114,115]. Risk factors include T-cell depleted donors, HLA donor mismatch, T-cell depleting therapies including antithymocyte globulin and anti-CD3 antibodies, and CMV antigens[114,115]. In addition to hypoxia, symptoms are consistent with viral illness, and chest imaging reveals diffuse basal and subpleural infiltrates[64,114]. Definitive diagnosis is established when EBV-associated lymphoid proliferation is demonstrated on biopsy[64,116]. Treatment includes modulation of T-cell depleting immunosuppression and administration of rituximab, an anti-B cell antibody[117,118].

Preliminary reports demonstrate promise of infusion of EBV-specific T-cells as a therapeutic for PTLD, though others have demonstrated resistance to such therapy[119].

CONCLUSION

Respiratory failure due to infectious and non-infectious complications is common following HSCT and is associated with significant mortality, especially in those necessitating mechanical ventilation. Pulmonary complications are differentiated by key distinguishing features and their time-course following transplantation. In acutely ill patients meeting ARDS criteria, routine use of best-practice lung-protective strategies is recommended even once the underlying explanation for the respiratory failure is identified.

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