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REVIEW

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.

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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,

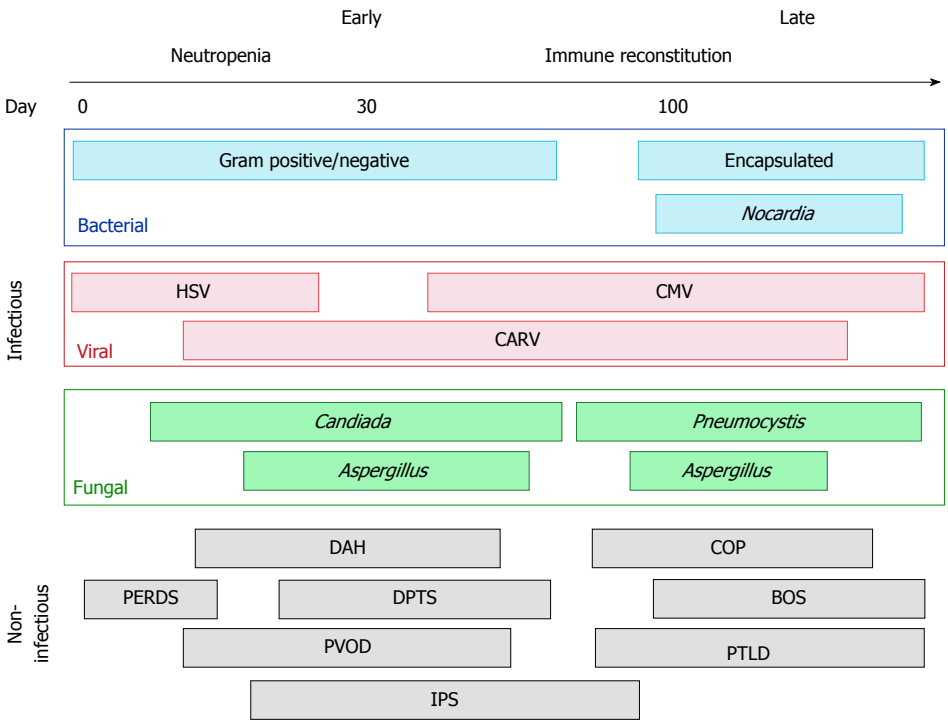

Figure 1 Time-course of pulmonary complications following hematopoietic stem cell transplantation. BOS: Bronchiolitis obliterans syndrome; CARV: Community-acquired respiratory viruses; CMV: Cytomegalovirus; COP: Cryptogenic organizing pneumonia; DAH: Diffuse alveolar hemorrhage; DPTS: Delayed pulmonary 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 nosocomial 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 uncommon 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 myelodysplastic 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 aminocaproic acid[70], a subsequent larger study failed to show benefit[75]. Further, even in the presence of thrombocytopenia, 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 benefit[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 cytokine-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 complication 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 presence 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 factors 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 pulmonary 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, prognosis 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 occurring 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 cancer[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 associated 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 extensive 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 predominant lymphocytosis[95]. Previously referred to as bronchiolitis 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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REVIEW

Vitamin C in the critically ill - indications and controversies

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Abstract

Ascorbic acid (vitamin C) elicits pleiotropic effects in the body. Among its functions, it serves as a potent anti-oxidant, a co-factor in collagen and catecholamine synthesis, and a modulator of immune cell biology. Furthermore, an increasing body of evidence suggests that high-dose vitamin C administration improves hemodynamics, end-organ function, and may improve survival in critically ill patients. This article reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with respect to its therapeutic potential.

Key words: Ascorbic acid; vitamin C; Sepsis; Shock; Critical care medicine; Vasopressors; Cardiovascular

Core tip: An increasing body of evidence suggests that high-dose vitamin C administration improves hemodynamics, end-organ function, and may improve survival in critically ill patients. This article reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with respect to its therapeutic potential.

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INTRODUCTION

Vitamin C is one of the most well-known essential nutrients and is believed by many to confer a litany of health benefits (Figure 1). The Nobel Prize Winner Linus Pauling may have been the foremost ambassador to date who suggested that vitamin C would enhance cardiovascular health, improve the body's immune function to overcome infections, and even help abate cancer[1-4]. These health claims created significant controversies that lasted for decades. While many of Pauling's "more is better" claims have not been supported by rigorous scientific

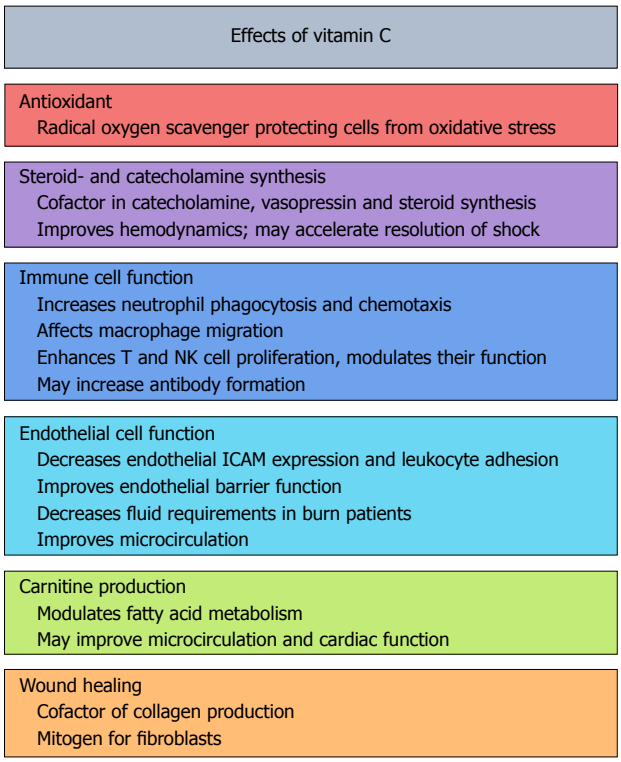

Figure 1 Biological functions of vitamin C. NK: Natural killer cells; ICAM: Intercellular adhesion molecule.

investigation, a growing number of benefits of vitamin C administration have been identified for medical treatment, including in the field of critical care. This mini-review will examine the evidence in support of vitamin C administration for critically ill patients and provide general recommendations for use by intensive care unit practitioners.

VITAMIN C LEVELS IN THE CRITICALLY ILL

Vitamin C is water-soluble and circulates in the plasma. It is freely filtered by the glomerulus and reabsorbed in the proximal tubule *via* the first sodium-dependent vitamin C transporter (SVCT1). In the setting of hypovitaminosis C, its urinary excretion is minimal[5]. While SVCT1 regulates whole-body homeostasis of vitamin C, a high-affinity, low-capacity sodium-dependent vitamin C transporter SVCT2 protects metabolically-active cells against oxidative stress, which facilitates vitamin C accumulation where it is needed[6]. The recommended daily oral dose of vitamin C is 75 mg (adult female)/90 mg (adult male), and only ten mg of daily oral vitamin C is necessary to prevent scurvy (plasma level < 0.1 mg/dL; normal range 0.8-1.6 mg/dL). Despite meeting these recommended daily intakes, many critically ill patients exhibit decreased vitamin C plasma levels. Carr *et al*[7] reported hypovitaminosis C in 44 critically ill patients receiving standard intensive care unit nutrition, of which one-third had vitamin C deficiency. The degree of vitamin C deficiency was more pronounced in the septic population as compared to the non-septic critically ill. Continuous renal replacement is commonly utilized in critically ill patients and is believed to lead to a depletion of water-soluble vitamins[8-10]. A retrospective study of critically ill patients receiving continuous renal replacement revealed that 87% (13 out of 15) had vitamin C deficiencies[9].

BIOLOGICAL EFFECTS OF VITAMIN C

Among vitamin C's pleiotropic functions that are of relevance to critical illness are its immune-enhancing effects, anti-oxidant properties, and potential anti-mutagenic effects[11,12]. Vitamin C has been shown to enhance neutrophil chemotaxis, phagocytosis, and thus microbial clearance[13,14]. In addition, vitamin C promotes T cell and natural killer cell proliferation and modulates their functions[13,15]. Studies on vitamin C's effects on B cells have revealed conflicting data with regard to proliferation and differentiation[13,15]. Vitamin C appears to induce antibody production in human lymphocytes and those of guinea pigs[16,17]. In a mouse model of abdominal sepsis induced by cecal-puncture ligation, parenteral vitamin C administration improved sepsis outcomes through reversal of regulatory T cell inhibitory function[18]. Hypovitaminosis C in a sepsis model using guinea pigs was also associated with fewer macrophages in the peritoneal cavity and impaired macrophage migration[19,20]. Interestingly, the adverse effects of vitamin C deficiency were more pronounced in elderly guinea pigs[19].

In cell culture and rodent experiments, vitamin C has been shown to decrease lipid peroxidation, prevent occludin dephosphorylation, and thus diminish the loosening of tight junctions[5,21-23]. Vitamin C also improves microcirculatory flow impairment by inhibiting tumor-necrosis-factor (TNF)-induced intercellular adhesion molecule 1 expression, thereby decreasing leukocyte adhesiveness[5,24,25]. In smokers, a single bolus administration of vitamin C (3 g Ⅳ) was found to increase coronary flow reserve, which is an integrated parameter of endothelial function and vascular smooth muscle relaxation. This effect was not seen in healthy control patients[26].

Vitamin C is a cofactor in collagen synthesis, a mitogen for fibroblasts, and is believed to positively modulate proinflammatory signaling and inflammation resolution that occur in wound beds[27,28]. Vitamin C supplementation in deficient mice promotes wound healing through enhanced matrix deposition and fibroblast proliferation[27]. In addition, topical vitamin C increases dermal collagen biosynthesis in healthy volunteers[29,30]. However, vitamin C supplementation does not consistently improve pressure ulcer healing in nursing homes and hospitalized patients, and recent systematic reviews have concluded that vitamin C (often administered in conjunction with zinc and other nutrients) is ineffective in treatment for this condition[31-35].

Vitamin C is a cofactor in carnitine synthesis, a molecule that facilitates fatty acid shuttling into mitochondria,

reduces oxidative stress, and promotes endothelial sprouting[36,37]. Its deficiency has been linked to cardiomyopathy and neurometabolic disease[38,39]. Despite carnitine's essential metabolic roles, clinical data to date have not yielded convincing evidence that supplementation in critically ill patients will improve outcomes[40-42].

Vitamin C is also a cofactor in catecholamine synthesis and adrenal steroidogenesis[43,44]. Vitamin C contributes to the conversion of dopamine to norepinephrine by dopamine beta-hydroxylase[45]. Vitamin C enhances norepinephrine synthesis both by recycling tetrahydrobiopterin, a critical cofactor in catecholamine synthesis, and increasing tyrosine hydroxylase expression[46]. Furthermore, vitamin C is a cofactor for the peptidylglycine α-amidating monooxygenase that is required for the endogenous synthesis of vasopressin[47]. One study in cardiac surgical patients has suggested that pre-operative administration of vitamin C mitigates etomidate-induced adrenal suppression[48]. Thus, there has been significant interest in utilizing vitamin C for the management of hemodynamically-unstable patients[49].

VITAMIN C IN CARDIOVASCULAR PATIENTS

While a recent review concluded that there is insufficient evidence to support the use of vitamin C to reduce cardiovascular disease risk or mortality in the general population, increasing evidence suggests that it may have a beneficial role in patients with acute coronary syndromes or undergoing cardiac surgical procedures[50]. Cardiac surgery, extracorporeal membrane oxygenation and hemodialysis produce oxidative stress, which negatively impacts morbidity and mortality[51]. Vitamin C's ability to scavenge reactive oxygen species and increase nitric oxide production through induction of endothelial nitric oxide synthase have made it a focus of interest as a cardiovascular therapy adjunct[52]. In one study of cardiac surgical patients undergoing cardiopulmonary bypass, statistically significant reductions in plasma levels of vitamin C were found intraoperatively compared to preoperative levels, even prior to initiation of cardiopulmonary bypass (Δ16.3% compared to baseline). This decrease in vitamin C plasma levels continued after cardiopulmonary bypass and lasted for at least six days[53].

Perioperative vitamin C administration has also been shown to prevent post-operative atrial fibrillation in the majority of the studies[54-59]. Its effects appear to result in reductions in the duration of hospital and intensive care unit patient stay following cardiac surgery[54-57].

Other studies examining the effects of vitamin C administration on patients with acute myocardial infarction and undergoing coronary revascularization procedures have reported improved left ventricular ejection fraction, microcirculation, and limited infarct size in patients with acute myocardial infarction[60-62]. One recent randomized multicenter clinical trial on patients with myocardial infarction undergoing percutaneous coronary angioplasty did not show a significant improvement in infarct size or ejection fraction at the time of the intervention with vitamin C administration. However, a decline in the LVEF between 7-15 d and 2-3 mo noted in the control group was not seen in the vitamin C group[63]. The authors of this study suggested that vitamin C may have ameliorated myocardial reperfusion injury[63].

In addition to potential beneficial effects on microperfusion and myocardial protection, a growing body of evidence suggests that vitamin C administration may positively affect hemodynamic parameters and hasten freedom from vasopressors in critically ill patients[64-67]. Interestingly, some evidence suggests that vitamin C's effects on hemodynamics may have a ceiling effect. A recently reported pharmacokinetic study by de Grooth *et al*[68] only found a minimal reduction in heart rate among critically ill patients randomized to receive 2 g/d *vs* 10 g/d of vitamin C. However, only the treatment group that received the 2 g/d of vitamin C, but not the 10 g/d treatment regimen, had a clinically-relevant decrease in norepinephrine requirements over 48 h[68].

VITAMIN C IN BURN-INJURED PATIENTS

Increased capillary leakage is a clinical hallmark of burn injury. It is associated with significant fluid and protein extravasation. The term "fluid creep" was coined to describe the phenomenon that burn patients often receive significantly more resuscitation fluid than anticipated based on Parkland formula calculations[69]. This excess fluid resuscitation can be associated with edema-related complications[70]. Endothelial damage leading to increased permeability in patients with burn injury may partly be mediated by reactive oxygen species-induced lipid peroxidation. As an antioxidant, vitamin C has been evaluated as a therapy to decrease fluid resuscitation requirements[71,72]. In a rodent model of burn injury, high-dose vitamin C appeared to improve microvascular barrier dysfunction, without affecting leukocyte activation[73]. In a study of guinea pigs with 70% third-degree burns given high dose vitamin C (170, 340 and 680 mg/kg per day), fluid requirements were significantly reduced while stable cardiac outputs were maintained[74]. In a study of dogs with burn injuries, vitamin C administration (14 mg/kg per hour) decreased lipid peroxidation and microvascular protein and fluid leakage[75]. A burn study in sheep provided additional evidence that high-dose vitamin C (250 mg/kg bolus plus 15 mg/kg per hour) could reduce fluid requirements and lipid peroxidation, as well as improve antioxidant status[76]. Preliminary studies in humans have also been promising. In a study of 37 patients with > 30% total body surface area burns, vitamin C administration (66 mg/kg per hour) reduced fluid requirements, wound edema, and increased the ratio of PaO2 to a fraction of inspired oxygen[66]. In a retrospective review of 40 patients with > 20% total body surface area, vitamin C (66 mg/kg per hour) was associated with increased urine output and decreased fluid requirements, but no change in outcomes or incidence of acute kidney injury[77]. In another small

study (n = 30) of patients with second degree burns, topical vitamin C accelerated formation of granulation tissue[78].

VITAMIN C IN SEPTIC PATIENTS

There has recently been a surge of interest in the use of vitamin C as an adjuvant treatment for sepsis. This interest was stimulated by the findings of a cohort study by Marik *et al*[64] that administered a cocktail of vitamin C (1.5 g Ⅳ every 6 h), hydrocortisone (50 mg Ⅳ every 6 h) and thiamine (200 mg Ⅳ every 12 h) to 47 septic patients and found a significant reduction in SOFA scores, dependence on vasopressors, and most importantly in hospital mortality to 8.5% in the treatment arm *vs* 40.4% in a historic control group. These findings were consistent with small phase Ⅰ double-blinded placebo-controlled trials suggesting the beneficial effects of vitamin C in patients with sepsis[67]. This trial, which randomized 24 septic patients with documented hypovitaminosis C to receive placebo, low-dose (50 mg/kg per day) or high-dose (200 mg/kg per day) parental vitamin C for four days, found significant reductions in SOFA scores and CRP plasma levels in the vitamin C-treated groups[67]. In another small trial of critically ill surgical patients, Zabet *et al*[65] reported a significant reduction in 28 d mortality in 14 patients with septic shock who were randomized to receive 25 mg/kg per day of ascorbic acid every 6 h for 72 h, when compared to 14 patients with septic shock who received placebo. Despite these promising findings, there are potential safety concerns worthy of consideration with vitamin C administration in the critically ill population. A recent study by De Grooth *et al*[68] evaluated four parenteral vitamin C repletion regimens (2 g/d *vs* 10 g/d; bolus *vs* continuous infusion) administered for 48 h to critically ill patients with multiple organ dysfunction. The patients receiving 10 g vitamin C per day had supraphysiologic vitamin C levels and hyperoxaluria, oxalate being a metabolite of vitamin C. These findings raise concern for an increased risk of oxalate nephropathy, as has been reported with high-dose vitamin C administration and more prolonged administration in the noncritically ill population[68,79,80]. This theoretical risk of oxalate nephropathy stands in contrast with the mostly reassuring data about the safety of short-term high-dose vitamin C administration[64,65,67].

At present, multiple ongoing randomized controlled trials, including the VICTAS, ACTS, and HYVCTTSSS trials, are aimed at confirming the beneficial effects of vitamin C and adjuncts in critically ill patients with sepsis[81-83].

VITAMIN C IN HEMORRHAGIC SHOCK

Trauma and hemorrhagic shock can lead to significant coagulopathy and inflammation, and both are associated with increased mortality and morbidity. Given its antioxidant effects, vitamin C has long been evaluated as a protective agent to mitigate effects on proinflammatory and procoagulant pathways caused by trauma and hemorrhagic shock[84-88].

In a swine model of acute hemorrhagic shock, animals were randomized to receive either intravenous normal saline, low-dose Vitamin C (50 mg/kg), or high-dose Vitamin C (200 mg/kg). The group of animals receiving normal saline (control) showed significantly greater histological end-organ damage, including elevated acute lung injury scores and increased mRNA levels of interleukin (IL)-1β, IL-8, TNF-α, plasminogen activation inhibitor-1 and tissue factor compared with the groups receiving vitamin C. Furthermore, only a modest correction of coagulopathy was observed in the vitamin C group when compared to the normal saline group[88]. Similarly, in a rat model of hemorrhagic shock, vitamin C administration (low 100 mg/kg or high 500 mg/kg) was shown to attenuate renal injury, possibly *via* a SIRT1-mediated mechanism. Levels of serum creatinine, BUN, TNF-α, and IL-1β were lower in the vitamin C group when compared to a sham group. Conversely, levels of hemeoxygenase-1 (HO-1), a stress-response protein believed to play key roles in mediating protection against oxidant-mediated lung injury, were higher in kidneys treated with vitamin C. This effect appeared to occur irrespective of the vitamin C dose administered[89]. Another study of the effects of vitamin C administration (100 mg/kg) on renal function found a decrease in expression of the induced dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin protein in the tubular epithelial cells of rat kidneys. Levels of this protein are believed to correlate with the occurrence of kidney injury. Vitamin C administration prior to resuscitation was also found to decrease proinflammatory cytokine production, which mitigated renal injury[90]. Another rat model of hemorrhagic shock found that vitamin C treatment induced HO-1 expression in a variety of tissues, including kidney, lung and liver, with decreased organ injury and proinflammatory responses[91]. Likewise, vitamin C pretreatment in the setting of hemorrhagic shock appears to protect the intestinal epithelium by decreased proinflammatory cytokine expression and neutrophil infiltration. This effect was also believed to be mediated by HO-1 and was abrogated by pharmacological HO-1 inhibition[92]. Prior studies have suggested that pretreatment of rats with vitamin C (1 mg/100 g or 5 mg/100 g) decreases gastric mucosal bleeding after induction of hemorrhagic shock and retransfusion[93]. Lastly, the combination of vitamin C administration (50 mg/kg per day for 3 d) prior to inducing hemorrhage together with intravenous infusion vitamin C (50 mg/kg) following hemorrhage improved cardiovascular parameters, such as blood pressure and LV dp/dt, and decreased free radical production in a rat model of hemorrhagic hypotension[94].

These beneficial effects of vitamin C stand in contrast with those obtained in a rat model of liver injury and hemorrhagic shock, in which vitamin C preconditioning (10 mg/kg) did not improve the recovery of animals after resuscitation[95]. Likewise, a survival study in rats with hemorrhagic shock did not show a difference when lactated Ringer's solution plus vitamin C (50 mg/kg) was administered for resuscitation, compared with lactated

Ringer's solution alone[96].

These preclinical studies point out multiple mechanisms by which vitamin C may serve as an antioxidant in hemorrhagic shock and thus could provide organ protection. However, evidence suggesting a vitamin C-mediated survival benefit is missing. To our knowledge, there is thus far no human trial data available that demonstrate a clinical benefit of vitamin C administration as an adjunct for the treatment of trauma and hemorrhagic shock.

VITAMIN C AND PAIN

Pain is a common problem in critically ill patients, either due to injuries secondary to infection, inflammation, trauma, surgery, cancer, or in the setting of the reactivation of herpes zoster. Evidence suggests that vitamin C acts as a cofactor for the biosynthesis of opioid peptides and as a potent anti-inflammatory agent[97,98].

Several case reports and a cohort study have reported clinical improvement in relief for patients with acute herpes zoster exacerbation who were administered vitamin C [99-101]. While a recent randomized controlled trial of high dose intravenous vitamin C (5 g *iv* bolus per day on day 1, 3 and 5) failed to find a reduction in acute herpes zoster pain, there was a decrease in the incidence of post-herpetic neuropathy[102]. A similarly designed study found lower plasma concentrations of vitamin C in patients with post-herpetic neuropathy than in healthy volunteers, and a reduction in spontaneous post-herpetic neuropathy pain after high-dose vitamin C treatment[103].

Several trials have found reductions in the development of complex regional pain syndrome after wrist and ankle surgery with vitamin C[104-107]. A study of patients with osteoarthritis-related hip or knee joint pain found that vitamin C that was administered enterally for 14 d provided modest pain relief, equivalent to approximately half the effect of nonsteroidal anti-inflammatory drugs[108]. In a randomized controlled trial of vitamin C in patients undergoing single-level posterior lumbar interbody fusion, there was no difference in postoperative pain intensity between the two groups, but vitamin C administration was associated with improved functional status[109].

A majority of the prospective and case studies of vitamin C administration for cancer-related pain have reported improvements in quality-of-life indicators such as pain, fatigue, insomnia, nausea and vomiting[110-115]. However, clinical trial data regarding vitamin C-related opioid-sparing effects in cancer patients have yielded mixed results[116-119].

VITAMIN C IN CANCER PATIENTS

Perhaps more widely investigated than any other vitamin C-related claim is the assertion of benefit for patients with cancer. In fact, a quick PubMed search of "ascorbic acid + cancer" yielded 4,376 items, 247 of which were clinical trials (as of May 2018).

Cancer patients have been recognized to have low vitamin C levels compared with healthy controls[120]. In a large randomized, placebo-controlled trial, daily intake of antioxidants, vitamins and minerals, a combination of vitamin C (120 mg/d), vitamin E, zinc, beta carotene and selenium lowered total cancer incidence and all-cause mortality in men but not women at 7.5 years[121]. A similar regimen of vitamin C and E supplementation with beta carotene did not, however, prevent the formation of colon adenomas in a randomized trial of 864 patients[122]. Another study of vitamin C and E supplementation for cancer prevention did not identify immediate or long-term effects on the risk of total cancers, prostate cancer, or other site-specific cancers[123].

A randomized clinical trial examining different doses of vitamin C (1, 2 or 4 g/d) failed to find a dose-response relationship or an association between serum ascorbic acid levels and mutagen sensitivity, which has been described as a risk factor for tobacco-related epithelial cancers[124]. Despite these clinical findings, basic science data suggest that vitamin C may have a beneficial role in cancer progression through several different mechanisms. Vitamin C was recently found to restore Tet methylcytosine dioxygenase 2 function, one of the most frequently mutated genes in hematopoietic malignancies. Through this mechanism, vitamin C may block aberrant self-renewal and leukemia progression[125]. Vitamin C also facilitates DNA oxidation in leukemia cells, rendering them more sensitive to poly ADP ribose polymerase inhibitors[125].

In cholangiocarcinoma, SVCT2 expression levels have been shown to correlate with susceptibility to vitamin C-induced cancer cell death *in vitro* and *in vivo*[126]. In separate experiments, Vitamin C has been shown to increase methotrexate-mediated hepatocellular carcinoma cell death[127]. Furthermore, vitamin C enhances the effectiveness of radiation therapy for glioblastoma and gemcitabine/epigallocatechin-3-gallate treatment for mesothelioma[128,129]. These findings are in contrast to data showing that vitamin C interferes with chemotherapy drugs such as doxorubicin, methotrexate, and cisplatin[128-131]. Moreover, vitamin C may enhance the growth of some cancers. For example, plasmocytoma cell growth is dependent on the presence of vitamin C[132]. Vitamin C exposure showed differential effects in an *in vitro* model of colony-forming bone marrow cell growth in patients with myelodysplastic syndrome. In this model, vitamin C responsiveness (both growth enhancement or inhibition) was associated with shorter survival when compared to patients with no response to vitamin C[133]. Adding to this complex picture is data derived from *in vitro* work that examined the response of HL-60 cells from an acute myeloid leukemia cell line to vitamin C. Vitamin C administration decreased oxidative stress and thus protected HL-60 cells from H_2O_2-induced cell death[134].

Curiously, high-dose vitamin C (0.5-5 mmol/L) has also been shown to increase the procoagulant properties of freshly isolated red blood cells *via* externalization of phophatidylserine, a mechanism known to lead to throm-

bus formation. Interestingly, this effect was more pronounced in red blood cells from cancer patients and could be confirmed in a rat model of thrombus formation[135].

In one study in terminal cancer patients, vitamin C was associated with increased quality-of-life and survival[116]. In contrast, in two double-blinded randomized controlled trials that included patients with advanced cancers (stomach, colon, pancreas, lung, breast and others), vitamin C (10 g/d) did not improve survival[136,137].

Given the complexities of cancer biology and vitamin C, the risks and benefits of initiating high-dose vitamin C therapy in critically ill oncology patients should be carefully weighed and discussed with the oncology consultant.

CONCLUSION

Vitamin C is once again a focus of intense interest with respect to its role in the treatment of critically ill patients. Evidence suggests that vitamin C administration may have a variety of beneficial effects in patients undergoing cardiac surgical procedures, during resuscitation with acute burn injury, for the treatment of sepsis, in reducing pain, and in the treatment of cancer. While many questions have yet to be answered, there is little data to suggest that short-term high-dose vitamin C would elicit major harm, except for the risk of oxalate nephropathy. In fact, evidence suggests that short-term high-dose vitamin C in selected patients may improve hemodynamic parameters, decrease fluid resuscitation requirements, reduce the incidence of perioperative atrial fibrillation, improve pain and potentially reduce sepsis-associated mortality. We eagerly await additions to the growing body of evidence that examine the role of vitamin C administration for improving outcomes for our sickest patients.

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REVIEW

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.

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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,

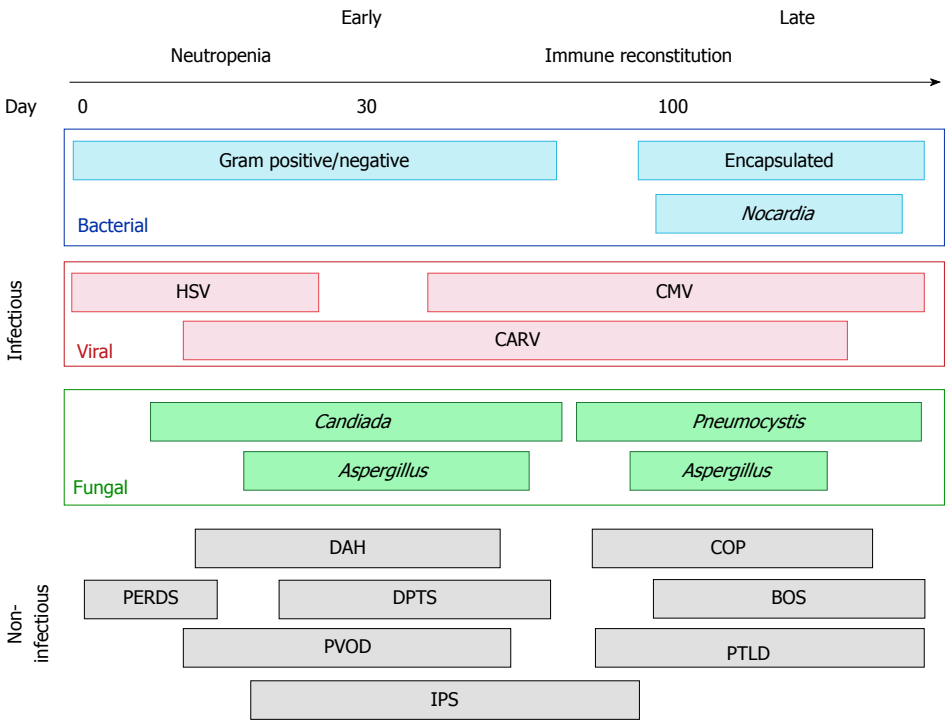

Figure 1 Time-course of pulmonary complications following hematopoietic stem cell transplantation. BOS: Bronchiolitis obliterans syndrome; CARV: Community-acquired respiratory viruses; CMV: Cytomegalovirus; COP: Cryptogenic organizing pneumonia; DAH: Diffuse alveolar hemorrhage; DPTS: Delayed pulmonary 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 nosocomial 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 uncommon 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 myelodysplastic 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 aminocaproic acid[70], a subsequent larger study failed to show benefit[75]. Further, even in the presence of thrombocytopenia, 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 benefit[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 cytokine-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 complication 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 presence 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 factors 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 pulmonary 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, prognosis 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 occurring 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 cancer[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 associated 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 extensive 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 predominant lymphocytosis[95]. Previously referred to as bronchiolitis 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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