Acute Respiratory Failure After Hematopoietic Stem Cell Transplantation

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Key Points

1. Pulmonary complications occur in up to 60% of HSCT recipients and are the leading cause of respiratory failure requiring mechanical ventilation and ICU admission.
2. Infectious complications are time dependent, with bacterial pneumonias and invasive fungal infections common during the pre-engraftment period and viral pneumonias (especially cytomegalovirus) and other opportunistic infections during the early and post-engraftment phases.
3. Unique noninfectious pulmonary complications include peri-engraftment respiratory distress syndrome, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome.
4. Risk factors for respiratory failure include older age, active malignancy, donor-recipient marrow HLA mismatch, and pretransplant abnormal pulmonary function tests.
5. HSCT recipients requiring invasive mechanical ventilation continue to have high mortality rates (80–90%).

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34.1 Introduction

Hematopoietic stem cell transplantation (HSCT) is used to treat over 50,000 patients with malignancies every year worldwide [1]. In 2014, >40,000 HSCT in 36,469 patients (15,765 allogeneic (43%), 20,704 autologous (57%)) were reported by 656 centers in 47 countries in Europe [2]. Patients may receive autologous HSCT, wherein hematopoietic stem cells are collected from the patient prior to the administration of high dose chemotherapy to treat the underlying malignancy followed by reinfusion of these cells, or allogeneic HSCT, where stem cells are harvested from the bone marrow or peripheral blood of matched or unmatched, related or unrelated donors or from umbilical cord blood. The most common indications for autologous HSCT are multiple myeloma and non-Hodgkin lymphoma and the vast majority of allogeneic transplants are performed for acute myeloid and lymphoid leukemias and myelodysplastic syndrome [2].

Improved conditioning regimens, human leukocyte antigen (HLA) typing, supportive care, and prevention and treatment of serious infections have significantly reduced transplantation-related mortality and morbidity [3]. Nevertheless, HSCT recipients can face multiple complications relating to the underlying malignancy, the conditioning received prior to transplant, as well as posttransplant infections.

Traditionally, the posttransplant course is divided into three phases reflecting the recovery of immune system: pre-engraftment phase (0–30 days), early posttransplant (days 30–100), and late posttransplant (>100 days). Pulmonary infectious and noninfectious complications are common, occurring in up to 60% of HSCT recipients and are the leading cause for ICU admission and respiratory failure requiring initiation of mechanical ventilation [4–6].

Specific infectious and noninfectious pulmonary complications occur depending on the phase of recovery (Fig. 34.1). This chapter will provide a brief overview of the causes of respiratory failure among HSCT patients, risk factors for mechanical ventilation, treatment strategies, and prognosis.

34.2 Risk Factors for Respiratory Failure and Need for Mechanical Ventilation

A recent report showed that among HSCT recipients admitted to the ICU, 42–88% of HSCT patients received mechanical ventilation for respiratory failure [7]. Risk factors for the development of respiratory failure include older age, active malignancy, and donor-recipient marrow HLA mismatch. Patients who were found to have pretransplant abnormal pulmonary function tests (e.g., restrictive physiology, total lung capacity <80%) had twice the risk for respiratory failure [8].

34.3 Infectious Causes of Respiratory Failure

Infection is more common in allogeneic than in autologous HSCT patients due to prolonged immunosuppressive therapy and graft-versus-host disease (GVHD). Although the timing of infections may suggest a diagnosis, some presentations are

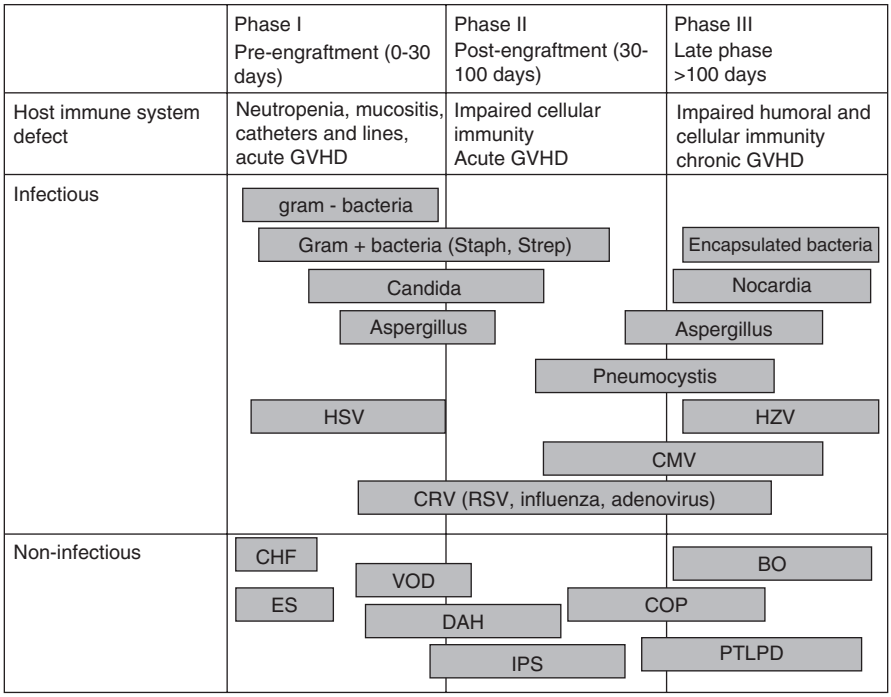

Fig. 34.1 The timeline of pulmonary complications following hematopoietic stem cell transplantation (HSCT). *BO* bronchiolitis obliterans, *CHF* congestive heart failure, *CMV* cytomegalovirus, *COP* cryptogenic-organizing pneumonia, *DAH* diffuse alveolar hemorrhage. Amy K. Chi, Ayman O. Soubani, Alexander C. White, Kenneth B. Miller. An Update on Pulmonary Complications of Hematopoietic Stem Cell Transplantation. Chest, Volume 144, Issue 6, 2013, 1913–1922

atypical. Fiberoptic bronchoscopy can be valuable especially if performed early, yielding a diagnostic pathogen in 55% of patients [4]. However, because bronchoscopy may cause respiratory deterioration with less than half of them revealing definitive diagnoses, other modalities should be considered for diagnosis of pulmonary infection in HSCT patients. These include noninvasive strategies such as nasopharyngeal washings or swabs sent for immunofluorescence antibody or multiplex polymerase chain reaction (PCR) testing for respiratory viruses and culture, blood cultures, sputum studies, and imaging studies (chest radiography and computed tomography (CT)).

During the pre-engraftment phase (0–30 days post-HSCT), the transplant recipient develops defects in mucocutaneous barriers as well as neutropenia, which predisposes to bacterial and fungal (especially Candida) infections. In a study of 427 consecutive allogeneic HSCT recipients, bacterial pneumonia developed in the first post-HCT month in 4%, fungal pneumonia in 9%, and viral pneumonia in 2%; 4% percent of patients who had suspected pneumonia had no specific organism identified [9]. The most common bacterial organisms causing pneumonia were *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.

Community acquired respiratory viruses including respiratory syncytial virus (RSV), influenza, and parainfluenza may also cause pulmonary infections, with RSV the most common. Untreated RSV pneumonia is associated with a high mortality (up to 80%). Treatment consists of aerosolized ribavirin and IV immunoglobulin. More recently, influenza A subtype H1N1 infection in HSCT patients was associated with a 28-day mortality rate of 7 and 19% at 4 months post diagnosis [10].

Among the fungal infections, invasive pulmonary aspergillosis is the most common with a reported incidence of 5–30% in allogeneic and 1–5% in autologous HSCT [4]. Prophylaxis with voriconazole or posaconazole is recommended for HSCT patients who remain neutropenic for >14 days and those on immunosuppressive treatment for GVHD. Screening measures in high risk patients include pretransplant ferritin level >1000 ng/mL, Aspergillus galactomannan, serum beta-D-glucan, or serum Aspergillus PCR testing. Imaging with high resolution chest CT is recommended with radiographic findings such as halo sign (nodule surrounded by ground-glass attenuation), hypodense sign (low density within nodules), and cavitation in late stages suggestive for aspergillosis. Treatment of choice is voriconazole, although there is increased risk of secondary infection with mucormycosis. Failure with voriconazole alone may require treatment with liposomal amphotericin B, combination therapy (echinocandins with voriconazole), or surgical intervention. Despite therapy, survival at 1 year is 20%. Other fungal species such as Zygomycetes (Mucor, Rhizopus), Fusarium, and Scedosporium require surgical resection of localized lesions. The diagnosis and treatment of *Pneumocystis jiroveci* pneumonia is identical to nontransplant patients.

In the early post-engraftment phase (30–100 days), impaired cellular and humoral immunity are the main factors contributing to pulmonary infection with cytomegalovirus (CMV) pneumonitis being a major concern. Older patients, positive CMV serology, allogeneic grafts, and GVHD are risk factors. Although ganciclovir has been used for CMV prophylaxis, it causes myelosuppression. Recent studies have shown comparable viral clearance with valganciclovir [4]. The gold standard for diagnosis of CMV pneumonitis is by lung tissue biopsy demonstrating viral inclusion bodies. However, CMV may be diagnosed presumptively by PCR testing of blood or bronchoalveolar fluid, clinical symptoms (fever, nonproductive cough, dyspnea, and hypoxemia), and CT imaging demonstrating ground glass attenuation, parenchymal opacification, or innumerable small (<5 mm) nodules. Treatment requires ganciclovir and CMV immunoglobulin. Treatment failure is associated with high mortality (>90%) particularly for those patients who progress to respiratory failure.

34.4 Noninfectious Causes of Respiratory Failure

The noninfectious causes of respiratory failure in HSCT patients include pulmonary edema of cardiogenic or noncardiogenic etiology and lung parenchymal damage secondary to the preparative conditioning regimen and/or radiation. Although

capillary leak syndrome may be the culprit, pulmonary edema in HSCT recipients is most commonly secondary to the volume of blood and blood products given during the pre-engraftment phase and immediate posttransplant period. Plasma B-type natriuretic peptide is usually elevated and the echocardiogram reveals left ventricular dysfunction.

There are unique acute pulmonary syndromes that are described following HSCT. These include peri-engraftment respiratory distress syndrome (PERDS), diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome.

34.4.1 Peri-engraftment Respiratory Distress Syndrome (PERDS)

Engraftment syndrome is more common in autologous HSCT patients, with an incidence of up to 11% [4]. Clinical characteristics include fever, non-drug induced erythematous rash, noncardiogenic pulmonary edema, and hypoxemia occurring within 96 h of engraftment. PERDS is attributed to the release of proinflammatory cytokines, such as interleukin (IL)-2, tumor necrosis factor-α, interferon-γ, IL-8 and IL-6, macrophage colony-stimulating factor, and erythropoietin that precedes neutrophil engraftment. Use of granulocyte colony-stimulating factor (G-CSF) has been identified as a risk factor. Major criteria for diagnosis include fever without infectious etiology, rash involving more than 25% total body surface area and pulmonary edema. Minor criteria include hepatic dysfunction, renal insufficiency, weight gain of 2.5% of baseline body weight, and transient encephalopathy. Three major criteria or two major criteria and one minor criterion are typically required for diagnosis. Discontinuation of G-CSF is recommended as well as corticosteroids (methylprednisolone 1–1.5 mg/kg/day) for severe cases. Up to one-third of patients require ICU admission and mechanical ventilation [4, 7].

34.4.2 Diffuse Alveolar Hemorrhage (DAH)

Diffuse alveolar hemorrhage may occur in the pre-engraftment or early post-engraftment phases. It occurs equally in autologous and allogeneic recipients, with an overall incidence of 4%. Patients at greatest risk include those over 40 years old, those that underwent total body irradiation, presence of fever, severe mucositis, acute GVHD, renal insufficiency, and HSCT for solid tumors. Neither platelet level nor type of conditioning appears to play a role in the development of DAH. It is hypothesized that DAH is induced by neutrophil infiltration of the lung accentuating alveolar hemorrhage induced by chemotherapy/radiation or occult infection. The diagnosis of DAH is suggested by dyspnea, nonproductive cough, fever, diffuse interstitial infiltrates of the middle and lower lung zones, and confirmed by progressively bloody BAL fluid samples from three separate lung subsegments [4]. Treatment with corticosteroids is recommended given the high mortality associated with this syndrome. Platelet transfusion is of limited value. Mortality is commonly due to superimposed multiorgan system failure or sepsis.

34.4.3 Idiopathic Pneumonia Syndrome (IPS)

Idiopathic pneumonia syndrome represents a pattern of diffuse lung injury for which no pathogens are identified and is considered to be the result of intensive chemotherapy and radiation. It usually occurs in the early post-engraftment phase. It has been hypothesized that TNF-α and donor T cell effectors play a role in lung injury. Risk factors include old age, low performance status, transplantation for solid tumors, high intensity conditioning, total body irradiation, GVHD, and positive donor CMV serology. IPS is less common in autologous than in allogeneic recipients (5.7% vs. 7.6%, respectively). Diagnosis is made by radiologic evidence of diffuse alveolar injury, negative infectious workup including BAL, lung biopsy (if performed) demonstrating alveolar damage or interstitial pneumonitis, and the absence of iatrogenic volume overload or cardiac or renal dysfunction. Chest radiograph may show non-lobar infiltrates. Small studies have shown improvement with etanercept (TNF-α binding protein) as well as etanercept and corticosteroids [4]. High dose steroids alone do not appear to be effective. Progression of disease is rapid with nearly two-thirds of patients requiring mechanical ventilation. Mortality rates with IPS ranges from 60 to 86% with 1 year survival rate less than 15%.

34.4.4 Late Noninfectious Complications

Noninfectious pulmonary complications in the late posttransplant phase include bronchiolitis obliterans (BO) and cryptogenic organizing pneumonia (COP) especially in those patients with chronic GVHD [4]. Bronchiolitis obliterans occurs mainly in allogeneic transplant recipients, with an average incidence of 8%. Risk factors for BO include progressive chronic GVHD, age >20 years, prior evidence of airflow obstruction, respiratory infections, unrelated donor, total body irradiation >12 Gy, low pretransplant serum surfactant D protein level, and NOD2/CARD15 genetic polymorphism. Several pathogenetic mechanisms have been suggested including lung injury caused by conditioning regimens, injury secondary to infectious etiology, recurrent aspirations-microaspirations or due to esophagitis-associated GVHD, or donor T cells targeting epithelial cells of bronchioles, leading to inflammation and damage. The majority of patients report dry cough and wheezing. Up to 25% experience upper respiratory tract symptoms; conversely, 20% of patients are initially asymptomatic. Diagnosis is made based on clinical characteristics, chest CT findings (air trapping, hyperinflation, ground-glass opacities), pulmonary function tests (PFTs) demonstrating new onset airflow obstruction, and no evidence of infection (including negative BAL). Biopsy is generally discouraged as the disease is patchy and peripheral, and samples may not show pathology. Patients may experience slow progression with occasional exacerbations. Some patients may develop recurrent respiratory infections and colonization with Pseudomonas, Staphylococcus aureus, and Aspergillus, while others may progress rapidly to respiratory failure within a few months. Treatment is aimed at slowing and stabilizing the disease with recommendations based on small trials and expert opinions. Generally,

high dose corticosteroids are given; adjunctive therapies include augmentation of immunosuppressive therapy with cyclosporine A or tacrolimus, and potentially macrolides. Promising new directions include use of inhaled corticosteroids, extracorporeal photodynamic therapy, and anti-TNF-α monoclonal antibodies. Lung transplantation has been successful in a minority of patients. Mortality is 18% at 10 years, whereas attributable mortality in those with GVHD is 40% at 10 years. Age over 60 years, progressive chronic GVHD, disease relapse, respiratory viral infections, and rapid deterioration of PFTs are associated with higher mortality [5, 6].

Cryptogenic organizing pneumonia (formerly known as bronchiolitis obliterans organizing pneumonia) occurs in the early posttransplant period and is more common in allogeneic recipients with an incidence of 2%. It usually occurs within the first 100 days. Patients at risk for COP include those with leukemia, radiation exposure, and presence of GVHD. Clinical presentation includes fever, nonproductive cough, and dyspnea. Diagnosis is made by clinical characteristics, radiography showing patchy peripheral consolidations/ground glass opacities, PFTs with restrictive pattern with no airflow obstruction, decreased diffusing capacity, and negative infectious workup including negative BAL. Biopsy is required for definitive diagnosis. Patients generally respond well to systemic corticosteroids with up to 78% resolving or remaining stable. Case fatality rate approaches 20% [4, 5, 7].

34.5 Ventilatory Support and Supportive Care Measures

Despite advances in the treatment of infectious and noninfectious causes of respiratory insufficiency in HSCT patients, HSCT recipients who end up requiring intubation and invasive mechanical ventilation have extremely high mortality (80–90%) [7]. Noninvasive positive pressure ventilation (NIPPV) has been shown to reduce endotracheal intubation rates in HSCT patients. Thus, early application of NIPPV in HSCT patients with reversible causes of respiratory failure should be strongly considered.

In general, ventilator management strategies for HSCT patients with respiratory failure are similar to non-HSCT patients. The use of lower tidal volumes and conservative fluid management for patients with ARDS, early and appropriate antibiotics and fluid and vasopressor therapy for sepsis, and use of corticosteroids for DAH and PERDS are integral to the management of the critically ill HSCT recipient.

34.6 Prognosis and Outcomes

Mortality for HSCT patients requiring mechanical ventilation in the 1990s approached 100%. With advances in ventilation strategies, supportive therapies, early diagnosis, and prophylaxis for varying opportunistic infections, it would seem that mortality rates would decrease. However, mortality for the intubated HSCT patient remains high ranging from 80 to 90% and is 94–100% with the onset of multiorgan failure [7]. Risk factors for poor prognosis include advanced age,

coexisting comorbidities, lower functional status, allogeneic transplant, progression of underlying disease, and high dose conditioning. Although there are multiple scoring systems to calculate mortality on intensive care unit (ICU) admission (e.g., Acute Physiology and Chronic Health Evaluation II, III, IV, Mortality Probability Model II, III), there is limited data evaluating these models in HSCT patients.

Despite the high mortality of HSCT patients requiring intubation, there are no validated criteria for admission to the ICU for these patients. Because the HSCT physicians are extremely familiar with the patient's entire course, their input is needed when deciding to institute a trial of ICU care in clinically deteriorating HSCT patients. In the event an unfavorable outcome is expected, transition to palliative care measures should be discussed with these patients and their families early in the ICU course. These discussions should be held in conjunction with the transplant teams to ensure that the most appropriate goals of care and therapeutic interventions are provided to this high-risk patient population.

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