Abstract

Both autologous and allogeneic hematopoietic stem cell transplants are important therapeutic options for several benign and malignant disorders. Pulmonary complications, although they have become less frequent, remain a significant cause of morbidity and mortality after hematopoietic stem cell transplant. These complications range from bacterial, fungal, and viral pulmonary infections to noninfectious conditions such as diffuse alveolar hemorrhage and idiopathic pneumonia syndrome. Bronchiolitis obliterans syndrome is the primary chronic pulmonary complication, and treatment of this condition remains challenging. This report highlights the advances in the diagnosis and management of the major pulmonary complications after hematopoietic stem cell transplant. It also underscores the need for prospective and multicenter research to have a better understanding of the mechanisms behind these complications and to obtain more effective diagnostic tool and therapeutic options.

Key words: Adverse effects, Lung diseases/etiology, Lung diseases/diagnosis, Respiratory tract infections/etiology, Graft versus host disease

Introduction

Hematopoietic stem cell transplant (HSCT) is increasingly being used for treatment of a wide range of benign and malignant diseases. About 50,000 to 60,000 HSCTs are done annually. Hematopoietic stem cell transplant can be classified as autologous when the stem cells are harvested from the same patient and infused after high-dose chemotherapy, whereas, in allogeneic HSCT, the stem cells are donated by another person. Allogeneic HSCT can be related or unrelated and matched or mismatched. The hematopoietic stem cells might be derived from the bone marrow, umbilical cord, or peripheral blood.

Hematopoietic stem cell transplant can be a life-saving treatment of a wide range of neoplastic and nonneoplastic diseases; however, it is still limited by the development of serious complications. Advances in the preparative regimen using a nonmyeloablative preparative regimen, reduced-intensity conditioning transplants, and posttransplant supportive care have contributed to improved overall survival. Despite these advances, pulmonary complications still occur in about 37% of patients after HSCT and are associated with significant morbidity and mortality. In 1 study, the hazard ratio for death due to pulmonary complications was 30. However, there is evidence that the overall mortality and pulmonary complications after HSCT are improving. A recent review of allogeneic HSCT patients in a large transplant center from 1993 to 2007 showed that the risk of nonrelapse mortality decreased by 60% and overall mortality decreased by 41%. In addition, the risk of acute respiratory failure dropped by 36%, with risk of gram-negative bacterial and invasive mold infections decreasing by 39% and 51%. In this study, we provide an update of the main pulmonary complications (both infectious and noninfectious) after HSCT, including an overview of the diagnostic approach and treatment of these complications.

Noninfectious complications after hematopoietic stem cell transplant

Advances in the prophylactic regimen against infections after HSCT, as well as the diagnosis and treatment of the infectious complications after HSCT,
have led to their decreased incidence. However, the incidence of noninfectious complications has not changed, which increases the significance of these conditions. Noninfectious pulmonary complications after HSCT range from acute to subacute causes of acute respiratory failure, such as diffuse alveolar hemorrhage and idiopathic pneumonia syndrome, to chronic progressive small airway disease like bronchiolitis obliterans syndrome (BOS), and include vascular complications like pulmonary veno-occlusive disease and cytolysis thrombi. Table 1 provides a comparison of the primary noninfectious causes of acute respiratory failure after HSCT. Although some of these entities, such as pulmonary alveolar proteinosis, are reversible, others are obstinate and associated with poor prognosis.

**Periengraftment respiratory distress syndrome**

Previously referred to as engraftment syndrome, periengraftment respiratory distress syndrome is characterized by the development of fever with no identifiable infectious cause, erythematous rash not attributable to medications, and noncardiogenic pulmonary edema. Other features might include hepatic dysfunction, renal insufficiency, weight gain, and transient encephalopathy. It is more common in autologous HSCT recipients and usually occurs within 96 hours of engraftment, coinciding with neutrophil recovery. The median onset time is 11 days, with an incidence of 7% to 11%.

The incidence and severity of this syndrome have increased as a result of use of granulocyte colony-stimulating factor, which regulates the production of cytokines (tumor necrosis factor α, interleukin 1B, and interleukin 8). These mediators in turn increase neutrophil influx into the lungs and alveolar permeability and are likely implicated in acute lung injury.

Patients with periengraftment respiratory distress syndrome have a favorable prognosis, and outcomes of most patients improve with supportive therapy. Consideration should be given to stopping granulocyte colony-stimulating factor. Patients with more severe cases associated with acute respiratory failure respond dramatically to systemic corticosteroids.

**Diffuse alveolar hemorrhage**

Diffuse alveolar hemorrhage (DAH) is an important cause of acute respiratory failure that occurs in 2% to 14% of recipients, with similar incidence in both autologous and allogeneic HSCT recipients. Diffuse alveolar hemorrhage is most commonly observed within the first month after HSCT (a median of 23 days), often during the pre-engraftment phase; however, later onset is encountered in up to 42% of cases. Risk factors for DAH after HSCT include age > 40 years, total body irradiation, high-dose cyclophosphamide, HSCT for solid tumors, the presence of high fevers, severe mucositis, leukocyte recovery, and renal insufficiency. There is no relation between DAH and type of preparatory regimen, whether it is reduced intensity or myeloablative. Postmortem studies have shown that most patients with DAH had a pattern of diffuse alveolar damage. The hallmark of diagnosis of DAH is a finding of progressively bloodier return from bronchoalveolar lavage (BAL) from at least 3 separate subsegments (or 20% hemosiderin-laden macrophage) in the absence of an identifiable respiratory tract infection. The following diagnostic criteria for DAH have been suggested: (1) evidence of widespread alveolar injury manifested

| Table 1. Comparison of the Characteristics of the Main Noninfectious Causes of Acute Lung Injury After Hematopoietic Stem Cell Transplant

<table>
<thead>
<tr>
<th>Feature</th>
<th>Periengraftment Respiratory Distress Syndrome</th>
<th>Diffuse Alveolar Hemorrhage</th>
<th>Idiopathic Pneumonia Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Autologous &gt; allogeneic</td>
<td>Autologous = allogeneic</td>
<td>Allogeneic &gt; autologous</td>
</tr>
<tr>
<td>Onset</td>
<td>Early/acute</td>
<td>Early/acute</td>
<td>Late/subacute</td>
</tr>
<tr>
<td>Relation to stem cell engraftment</td>
<td>Within 96 h of engraftment</td>
<td>Relation to engraftment is less definite</td>
<td>No relation</td>
</tr>
<tr>
<td>Characteristic clinical feature</td>
<td>Systemic manifestations</td>
<td>Bloody bronchoalveolar lavage</td>
<td>Progressive respiratory failure</td>
</tr>
<tr>
<td>Pathology</td>
<td>Diffuse alveolar damage; granulocyte-colony-stimulating factor plays a role</td>
<td>Diffuse alveolar damage with release of several cytokines</td>
<td>Diffuse alveolar damage; tumor necrosis factor α plays a role</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Excellent response</td>
<td>Moderate response</td>
<td>Poor response die with respiratory failure</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable prognosis</td>
<td>Less favorable prognosis; usually die with multiorgan failure and sepsis</td>
<td></td>
</tr>
</tbody>
</table>

*Data adapted from Soubani and associates.*

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by multilobar pulmonary infiltrates, symptoms, and signs of pneumonia and abnormal physiology with hypoxemia and widened alveolar-arterial gradient; (2) BAL showing progressively bloodier return from at least 3 separate subsegmental bronchi or > 20% hemosiderin-laden macrophages on examination of the BAL fluid or, if a surgical lung biopsy is performed, > 30% of the alveolar surface of the examined lung tissue is covered by blood; and (3) absence of infection compatible with the diagnosis.8

There are no prospective randomized trials that have addressed the treatment of DAH. Retrospective studies and case reports have suggested that early diagnosis of DAH and high-dose treatment with corticosteroids (500-1000 mg/d of methylprednisolone for 3-4 d followed by tapered dosage over 2-4 wk) may improve survival rate.6 In addition, aminocaproic acid and recombinant factor VIIa have been tried in some studies with variable results.11 However, a recent report showed no difference in outcome with methylprednisolone at low doses (≤ 250 mg/d), medium doses (250-1000 mg/d), or high doses (≥ 1000 mg/d) with or without the addition of aminocaproic acid.12 Mortality rates in patients with DAH range from 74% to 100%.8,9 However, mortality as low as 38% has been reported.13 Mortality is usually due to superimposed multiorgan failure or sepsis. Autologous HSCT, onset within the first 30 days of transplant, and lack of mechanical ventilation are associated with favorable outcome.6

**Idiopathic pneumonia syndrome**

Idiopathic pneumonia syndrome (IPS) is another subacute cause of acute respiratory failure after HSCT. The definition of IPS has been recently updated by the American Thoracic Society. It is diagnosed when there is (1) evidence of widespread alveolar injury (with multilobar infiltrates on chest imaging, symptoms and signs of pneumonia, and evidence of abnormal pulmonary physiology such as hypoxemia with high alveolar-arterial gradient or new or increased restrictive pulmonary function test abnormality); (2) absence of active lower respiratory tract infection, such as bacteria, Legionella, viruses, and Fungi by performing bronchoscopy with BAL and negative appropriate serologic studies for viruses and fungi; and (3) absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as cause of pulmonary dysfunction.14 The recent American Thoracic Society definition of IPS suggested that this condition includes a variety of noninfectious pulmonary complications after HSCT such as acute respiratory distress syndrome, delayed pulmonary toxicity syndrome, perengraftment respiratory distress syndrome, DAH, and cryptogenic organizing pneumonia.14

The incidence rate of IPS ranges from 2% to 17%. It usually occurs in the first 120 days after HSCT, and the median time of onset is 21 to 49 days after transplant.5 Idiopathic pneumonia syndrome is more common after allogeneic HSCT. Risk factors for developing IPS after HSCT include older age, lower pretransplant performance status, transplant for a malignancy other than leukemia, high-intensity conditioning regimens, total body irradiation, high-grade acute graft-versus-host disease (GVHD), prior HSCT, and methotrexate-based GVHD prophylaxis.15-17

The clinical course of IPS is typically rapid, with most patients progressing to respiratory failure requiring mechanical ventilation. Mortality rate is around 74% and is primarily related to progressive respiratory failure. Poor prognostic factors include the need for mechanical ventilation and higher serum creatinine levels at the onset of IPS.15 Beyond supportive therapy, there is no proven therapy for IPS. High-dose corticosteroid therapy appears to be of minimal benefit. The administration of etanercept, a soluble tumor necrosis factor α binding protein, was promising in a few studies.18,19 However, in a recent randomized placebo controlled trial, 34 patients with IPS after allogeneic HSCT were randomized to 2 mg/kg/day of methylprednisolone with etanercept (0.4 mg/kg twice weekly for 4 wk). The 28-day mortality rate was not different between the 2 groups, and there were no differences in other outcomes. However, in this trial, the overall survival rate exceeded 60%, which is better than historic results.19 Etanercept may be considered in patients with severe refractory IPS.

**Bronchiolitis obliterans syndrome**

Bronchiolitis obliterans syndrome is the primary late noninfectious pulmonary complication after allogeneic HSCT. It is reported to be more common after peripheral blood HSCT.5 It is also more frequent after conventional myeloablative than after nonmyeloablative HSCT and with busulfan-based preparative regimens.5 It usually presents after the first 100 days after HSCT.20 It is considered the
primary pulmonary manifestation of chronic GVHD. Risk factors for BOS include the presence of chronic GVHD, older age of the recipient (>20 y), the presence of airflow obstruction (forced expiratory volume in 1 s/forced vital capacity < 0.7) before HSCT, and respiratory viral infections in the first 100 days after HSCT. In a review of 1145 allogeneic HSCT recipients, 5.5% developed BOS. The prevalence was 14% in patients with chronic GVHD. The median time between HSCT and diagnosis of BOS was 439 days (range, 274-1690 d). Factors that were significantly associated with BOS on multivariate analysis were baseline forced expiratory volume in 1 second-to-forced vital capacity ratio, nonwhite race, chronic GVHD, and immunoglobulin G level. Patients with BOS had a 1.62-fold increase in mortality after diagnosis. In another recent review of 1854 allogeneic HSCT recipients, BOS was diagnosed in 4.8% of patients, with 97% of these having chronic GVHD. Patients with BOS were compared with 2 matched groups of patients with chronic GVHD and no BOS and another with no GVHD and no BOS. A busulfan-based regimen even in the setting of reduced intensity conditioning, use of an unrelated donor or female donor, pretransplant lung disease, acute GVHD, Cytomegalovirus (CMV)-positive status, and high-risk transplant were associated with increased risk of BOS. On the other hand, antithymocyte globulin (ATG) was protective against GVHD and BOS. The study highlights the importance of busulfan as a risk factor for chronic GVHD and BOS. This could be due to direct pulmonary toxicity by the medication leading to exposure of antigens and donor alloreactivity contributing to the development of BOS. Table 2 provides a summary of the risk factors that could lead to BOS after HSCT.

The presentation of BOS is usually insidious and may be preceded by upper respiratory tract symptoms. The main symptoms are dry cough, dyspnea, wheezing, and sinusitis. Approximately 20% of patients are asymptomatic, and the diagnosis is suspected based on pulmonary function test findings showing new-onset airflow obstruction. Most patients have a slow progressive airflow obstruction, with episodes of acute exacerbations. In the minority of patients, the airflow obstruction progresses rapidly into respiratory failure within a few months. In the advanced stages of BOS, patients are physically limited due to severe obstructive airway disease and may require home oxygen therapy. Some patients may develop features of bronchiectasis with recurrent respiratory tract infections. The most common radiologic sign of BOS on high-resolution computed tomography of the chest is the presence of air trapping during the expiratory phase of imaging. These views show areas of hypoattenuation that correspond to obstructed airways interspaced with areas of “ground-glass” appearance corresponding to the pulmonary lobules with patent airways giving a “mosaic” appearance. High-resolution computed tomography of the chest is recommended in the work-up of these patients to evaluate for the above features but also to rule out other pulmonary complications, such as infectious causes and cryptogenic organizing pneumonia or IPS, which are usually associated with pulmonary infiltrates. Spirometry is the main test used to diagnose and follow-up patients with BOS after HSCT. It usually shows evidence of new airflow obstruction with reduction in forced expiratory volume in the first second and the forced expiratory volume in 1 second-to-forced vital capacity ratio.

<table>
<thead>
<tr>
<th>Table 2. Risk Factors for Bronchiolitis Obliterans After Hematopoietic Stem Cell Transplant</th>
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<tbody>
<tr>
<td><strong>Consistent</strong></td>
</tr>
<tr>
<td>1. Allogeneic HSCT</td>
</tr>
<tr>
<td>2. Progressive chronic GVHD</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>1. De novo or quiescent chronic GVHD</td>
</tr>
<tr>
<td>2. Airflow obstruction before HSCT</td>
</tr>
<tr>
<td>3. Early respiratory viral infection</td>
</tr>
<tr>
<td>4. Older age of recipient</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
</tr>
<tr>
<td>1. Acute GVHD</td>
</tr>
<tr>
<td>2. Busulfan-based conditioning regimen</td>
</tr>
<tr>
<td>3. Total body irradiation</td>
</tr>
<tr>
<td>4. Methotrexate-based GVHD prophylaxis</td>
</tr>
<tr>
<td>5. Gastroesophageal reflex disease</td>
</tr>
<tr>
<td>6. Cytomegalovirus infection</td>
</tr>
<tr>
<td>7. Hypogammaglobulinemia</td>
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<tr>
<td>8. Older age of donor</td>
</tr>
<tr>
<td>9. Underlying diseases (such as chronic myelogenous leukemia)</td>
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<tr>
<td>10. Lower levels of pulmonary surfactant protein D</td>
</tr>
<tr>
<td>11. Single nucleotide polymorphisms of certain genes (such as NOD2/CARD15)</td>
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</table>

The following criteria were recently established by a special National Institutes of Health workshop for the diagnosis of BOS after HSCT: (1) forced expiratory volume in 1 second-to-forced vital capacity ratio < 0.7 and forced expiratory volume in 1 second < 75% of predicted; (2) evidence of air trapping or small airway thickening or bronchiectasis on high-
resolution chest computed tomography (with inspiratory and expiratory cuts), residual volume > 120%, or pathologic confirmation of constrictive bronchiolitis; and (3) absence of infection in the respiratory tract, documented by investigations targeting clinical symptoms, such as radiologic studies (radiographs or computed tomographic scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or BAL).

Pathologic confirmation of bronchiolitis obliterans can be achieved by surgical lung biopsy and occasionally by transbronchial biopsy. However, these are rarely necessary in clinical practice. A recent study confirmed that pathologic bronchiolitis obliterans diagnosis was not superior to BOS criteria in predicting decreased pulmonary function beyond the time of biopsy.26

Treatment of BOS is based primarily on expert opinion and aims at stabilization of the pulmonary function. Clinical evidence is limited to small and uncontrolled trials. Generally, treatment includes high-dose corticosteroids (usually prednisone at 1-1.5 mg/kg/d) to be tapered gradually over 6 to 12 months, reinstitution or augmentation of immunosuppressive agents such as tacrolimus and cyclosporine, macrolides such as low doses of azithromycin or clarithromycin, inhaled corticosteroids or bronchodilators, and montelukast.27-29 Treatment with budesonide/formoterol improved forced expiratory volume in 1 second compared with placebo in a small prospective study of patients with mild to severe BOS after HSCT.30 Patients should receive antireflux measures and prophylactic therapy against Pneumocystis jiroveci, Fungi, and CMV. Lung transplant has been successful in selected patients.30 Other treatments for BOS have been reported in small series or are currently under investigation, including leukotriene receptor antagonists, extracorporeal photodynamic therapy, antitumor necrosis factor α monoclonal antibodies (such as infliximab), imatinib mesylate, alefacept, daclizumab, and rituximab.31-34 In advanced cases, patients may benefit from supplemental oxygen therapy and pulmonary rehabilitation referral.35

The response to therapy is variable, and the best results of treatment are to maintain lung function and prevent further deterioration. Factors that have been shown to correlate with better outcomes include lymphocytic bronchiolitis versus constrictive bronchiolitis on surgical lung biopsy.36 In addition, in 1 study, the presence of high concentrations of neutrophils and interleukin 8 in BAL predicted better response to azithromycin.37

Cryptogenic organizing pneumonia

Cryptogenic organizing pneumonia has been previously called bronchiolitis obliterans-organizing pneumonia and is frequently confused with BOS, although they are separate entities. Cryptogenic organizing pneumonia complicates both autologous and allogeneic HSCT but is more common in the latter, with an incidence of 0.9% to 10.3%. Onset time ranges from 5 to 2800 days with a median of 108 days.6 In a recent review of 9550 allogeneic HSCT recipients,38 cryptogenic organizing pneumonia was diagnosed in 2% of patients. HLA disparity, female-to-male HSCT, and peripheral blood stem cell transplant were significantly associated with an increased risk of cryptogenic organizing pneumonia. On the other hand, busulfan-based myeloablative conditioning or fludarabine-based reduced-intensity conditioning in comparison with a total body irradiation-based regimen and in vivo T-cell depletion were associated with a lower risk. The 3-year nonrelapse mortality rate and overall survival rate in the cryptogenic organizing pneumonia group were 29.0% (95% confidence interval, 20.2%-38.3%) and 60.5% (95% confidence interval, 49.9%-69.5%).38 The clinical presentation is usually acute or subacute with 2 weeks of fever, nonproductive cough, and dyspnea. Radiologically, findings include patchy (multifocal, diffuse, or focal) consolidations that tend to be peripheral and/or peribronchovascular, ground glass opacities, or nodular lesions. In contrast to BOS, pulmonary function tests typically show mild to moderate restrictive pattern and characteristically low diffusing capacity and usually no airflow obstruction. Bronchoscopy is useful in these patients to exclude other conditions such as infections. Bronchoalveolar lavage fluid reveals lymphocytosis with low CD4-to-CD8 ratio.39 Histologic confirmation is usually necessary and can be made by transbronchial biopsies; however, many patients require surgical lung biopsy by video-assisted thoracoscopy. Pathologically, cryptogenic organizing pneumonia is characterized by patchy distribution of plugs of granulation tissue that fill the lumens of the distal airways extending to the alveolar ducts and spaces associated with chronic interstitial inflam-
Contrary to BOS, patients with cryptogenic organizing pneumonia after HSCT have more favorable response to systemic corticosteroid therapy tapered over 3 to 6 months. Most patients achieve resolution or stability of the disease.40

**Infectious complications after hematopoietic stem cell transplant**

Despite the advances in prophylaxis and treatment of respiratory infections, infections after HSCT remain a cause of death in more than 40% of HSCT recipients.4,5 Infectious complications are more common in patients with allogeneic HSCT because of the prolonged immune-suppressive therapy and GVHD.

**Bacterial pneumonia**

Hematopoietic stem cell transplant recipients are at highest risk for bacterial pneumonia within the first 30 days after transplant, with incidence rates reported to be 20% to 50%.4 Bacterial pneumonia is more common in allogeneic transplants with the risk significantly increased depending on the presence of previous GVHD, the degree and duration of neutropenia, the type of conditioning regimen (being more common with administration of myeloablative regimen), and the presence of indwelling catheters.5,41,42

Gram-negative organisms such as *Pseudomonas* are the usual causatives during the pre-engraftment phase and are associated with a higher risk of septic shock and acute respiratory distress syndrome. During this phase, patients may present with neutropenic fever. Chest radiographs may be negative in about half of the cases. High-resolution computed tomography of the chest is usually recommended in febrile neutropenic patients due to their higher sensitivity in detecting pneumonic infiltrates.5

Bacterial pneumonia is less common in the postengraftment period, and the incidence of bacterial pneumonia is much lower after 100 days of HSCT except in patients with chronic GVHD where it is usually due to encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.5,41

The most recent guidelines from the Infectious Diseases Society of America recommend prophylaxis with a fluoroquinolone in high-risk patients with expected durations of prolonged and profound neutropenia (absolute neutrophil count < 100 cells/mm³ for > 7 d).41 although it might increase the risk of fluoroquinolone resistance.43 Patients should receive pneumococcal vaccine at 12 and 24 months after HSCT and the *Haemophilus influenzae* type b vaccine at 12, 14, and 24 months. Prophylaxis with intravenous immunoglobulin may be considered for HSCT recipients with unrelated HSCT with profound hypogammaglobulinemia (immunoglobulin level < 400 mg/dL) in the first 100 days after transplant.44

**Nocardia pneumonia**

Nocardia pneumonia is uncommon but should be considered in patients not responding to initial antibiotic therapy. The median time of onset is 210 days after HSCT. Risk factors include use of pentamidine instead of trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis and chronic GVHD. The usual radiologic presentation is pulmonary nodules with or without infiltrates. The first-line treatment is with trimethoprim-sulfamethoxazole, usually requiring prolonged duration of therapy and has a good prognosis.5,45

**Mycobacterial diseases**

The incidence of *Mycobacterium tuberculosis* infection is low, 0.1% to 5.5% in nonendemic areas, but is of more concern in endemic areas or in patients from endemic areas.46 The incidence increases by 3-fold in patients who have received allogeneic HSCT compared with those who have had autologous transplant, for which the incidence is similar to the general population.5 The infection usually occurs more than 90 days after HSCT, with median time being 324 days after transplant. The clinical presentation and treatment are similar to the general population with consideration given to drug interactions. According to a recent report, the diagnosis of *M tuberculosis* is made by cultures of respiratory samples (55% of cases), acid fast bacilli stain (25% of cases), and histology (20% of cases).47 It should be noted that HSCT recipients should be treated for latent *M tuberculosis* if they have more than 5-mm induration on tuberculin skin test or have *M tuberculosis* contact even with a negative tuberculin skin test.5,46,47

Nontuberculous mycobacterial infections (such as *Mycobacterium avium* complex, *Mycobacterium kansasii*, and *Mycobacterium chelonae*) are rare in HSCT recipients and are more common in patients with chronic GVHD involving the lungs. Clinical presentation and treatment are similar to the general population.48
Invasive fungal infections

Invasive fungal infections are serious problem after HSCT, especially with allogeneic transplant. In a recent multicenter study involving 16 200 HSCT transplant patients, invasive Aspergillosis was the most common fungal infection (43%), followed by invasive Candidiasis (28%) and Mucormycosis (8%).

Risk factors for fungal pneumonia include prolonged neutropenia, immunosuppressive therapies to prevent or treat GVHD, the widespread use of broad-spectrum antibiotics, and a high ferritin level of > 1550 ng/mL.

Invasive pulmonary Aspergillosis (IPA) is more common after allogeneic HSCT, especially in those with chronic GVHD, with reported incidence of 5% to 30% in allogeneic and 1% to 5% in autologous HSCT. Invasive pulmonary Aspergillosis becomes increasingly more significant during the late postengraftment phase during treatment of chronic GVHD. The incidence of IPA in the neutropenic phase is now decreased due to the routine use of stem cells instead of bone marrow for transplant, the use of nonmyeloablative regimens, the use of colony-stimulating factors during neutropenia, and the widespread use of antifungal agents for prophylaxis.

In a recent multicenter study, the median time for IPA infection was 99 days after HSCT. Risk factors include unrelated allogeneic HSCT, the use of high-dose corticosteroids, cyclosporine, antitumor necrosis factor α agents, and concurrent CMV infection. Radiologic features on high-resolution computed tomography of the chest include ill-defined consolidations and ground glass opacities, nodules with halo sign and air-crescent sign, and pleural effusions. A negative sputum sample does not rule out the infection, and usually a bronchoscopy with BAL is needed. Elevated BAL galactomannan with cut-off > 0.5 has 73% sensitivity and about 85% specificity in diagnosing IPA in patients with HSCT. In a study of 67 patients with hematologic malignancies (45% were HSCT recipients), the sensitivity and specificity of BAL galactomannan were 73% and 89%, with positive and negative predictive values of 73% and 83%. Bronchoalveolar lavage galactomannan performed better than BAL cytology (0%), BAL culture (27%), transbronchial biopsies (40%), and serum galactomannan (67%). Bronchoalveolar lavage galactomannan was positive in all patients who had invasive fungal infection and were on active antifungal therapy for < 3 days. Serum galactomannan can be falsely elevated in patients with gastrointestinal GVHD and those receiving beta lactams such as piperacillin-tazobactam. Elevated serum 1,3-beta-D-glucan assay levels may be useful in the diagnosis but is not well defined in patients with IPA. The treatment of choice for IPA is voriconazole, which is a triazole. Echinocandins either alone or in combination with posaconazole are used as a second-line treatment in patients who no longer respond to voriconazole. Surgical resection is reserved to selected patients, such as those with massive hemoptysis.

Prophylaxis against IPA is important and can be achieved with voriconazole, posaconazole, or itraconazole. Recent guidelines recommend that allogeneic HSCT recipients receive prophylaxis through the neutropenic period and for at least 75 days after transplant or until cessation of immunosuppressive therapy.

The incidence of invasive Candidiasis has decreased due to the widespread use of prophylactic antifungal therapy after HSCT; however, there is a shift in the Candida species from Candida albicans to more resistant species such as Candida glabrata and Candida krusei.

Mucormycosis infections, including those involving Mucor species and Rhizopus species, are rare, with the most recent data indicating the incidence might be rising with the use of voriconazole prophylaxis. Treatment includes amphotericin B and surgical resection.

The incidence of Pneumocystis jiroveci infection is almost negligible in the era of prophylaxis with trimethoprim-sulfamethoxazole and usually occurs in patients who are on other types of prophylaxis, such as atovaquone or pentamidine. Infection usually happens in month 2 to 6 after HSCT.

Viral pneumonia

The incidence of CMV pneumonia has decreased significantly after the use of prophylactic and preemptive antiviral therapy in high-risk patients. Currently, in allogeneic HSCT recipients, the incidence of CMV pneumonia is 10% to 30%, whereas, in autologous recipients; it is extremely rare (1%-9%). The onset of CMV pneumonia in allogeneic HSCT is now delayed to after the first 100 days (median of 169 d). Diagnosis depends on the presence of clinical and radiologic features in combination with detection of CMV in blood and BAL through CMV DNA quantitative polymerase chain reaction, shell assay, and viral cultures. Patients
present clinically with rapid onset of fever, nonproductive cough, dyspnea, and hypoxemia, with progression to acute respiratory failure within 2 weeks. Radiologically, the most common findings are an interstitial pattern with tiny pulmonary nodules and patchy areas of consolidation. The definitive diagnosis is made histologically with presence of intracytoplasmic inclusion bodies seen on lung biopsies. The treatment of choice is ganciclovir with or without CMV immunoglobulins. Although ganciclovir is effective for CMV prophylaxis, the myelosuppressive toxicity has limited its use as routine prophylaxis. Preemptive treatment of CMV with ganciclovir or valganciclovir is an alternative approach and is usually based on plasma pp65 antigen or polymerase chain reaction testing.

Community respiratory viruses also include respiratory syncytial virus, parainfluenza, influenza, and adenovirus. The incidence is close to 30% in patients with HSCT, with more common incidence after allogeneic transplant. Respiratory syncytial virus pneumonia is the most common. Mortality from untreated respiratory syncytial virus pneumonia is high. In a recent retrospective cohort of 82 patients with respiratory syncytial virus pneumonia, the 30-day and 100-day mortality rates were 32% and 43%. The increased mortality was associated with bone marrow as a source of HSCT and baseline need for oxygen supplementation (> 2 L/min). Aerosolized ribavirin and respiratory syncytial virus-specific immunoglobulins might be beneficial.

Parainfluenza and influenza viruses have a similar incidence in both autologous and allogeneic transplant recipients. The mortality is much lower than for respiratory syncytial virus. Treatment is supportive. The use of oseltamivir within 48 hours of onset of symptoms reduces progression to pneumonia. In addition to higher risk of lower respiratory tract infection by these viruses, there is an increased risk of coinfection or superinfection with bacteria and fungi.

Approach to the diagnosis of pulmonary complications after hematopoietic stem cell transplant

There are no standard guidelines for the evaluation of pulmonary complications after HSCT. Most studies in the literature are based on retrospective analysis of single center studies. There are general considerations when approaching HSCT patients with pulmonary symptoms and/or infiltrates. These include the immune status, such as presence and duration of neutropenia, immunosuppressive therapy, the dose and duration of corticosteroid therapy, and immunoglobulin deficiency, all important in predicting the cause of the respiratory infection. Recently, tobacco smoking has been identified as a potential risk factor for respiratory infections after HSCT. The type of HSCT (allogeneic vs autologous) and the presence of GVHD are also significant considerations in the spectrum of respiratory problems. Another consideration is that pulmonary complications after HSCT tend to follow a predictable timeline, as illustrated in Figure 1. Therefore, it is prudent to consider the timing of the respiratory event during the approach to diagnosis and management. In addition, the type of prophylactic antimicrobial agent is also useful in excluding certain infections such as trimethoprim-sulfamethoxazole in cases of P jiroveci. Prior hospitalizations for respiratory problems and previous infections, such as CMV, may shed some light on the cause of pulmonary infiltrates. Respiratory infections may lack the classic signs and symptoms, and presentation may be subtle or nonspecific. These observations could be related to presence of neutropenia or medications that may affect the inflammatory response such as...
corticosteroids. Not all pulmonary infiltrates are due to infections. Commonly, pulmonary complications after HSCT are due to noninfectious complications such as pulmonary edema, engraftment syndrome, DAH, IPS, cryptogenic organizing pneumonia, or sometimes secondary malignancy. Radiologic findings are helpful but not specific. A classic example is the presence of the halo sign in patients with IPA. It appears primarily in neutropenic patients and early in the course of infection. The absence of this radiologic sign does not exclude IPA, whereas its presence does not always mean IPA. *Pseudomonas aeruginosa*, *Nocardia species*, and *Mucormycosis* also may cause halo infiltrate.62,63 In determining whether to proceed with an invasive procedure such as bronchoscopy or surgical lung biopsy, it is important to decide whether such an intervention is likely to change the care or outcome of the patient, as will be discussed further below. The best outcome of the diagnostic approach to pulmonary infiltrates is when it is carried out expeditiously by a multidisciplinary team that includes specialists from pulmonary, bone marrow transplant, infectious diseases, and radiology departments and, when indicated, from thoracic surgery.

Although sputum cultures have several limitations with low sensitivities and false positive results, they may be helpful in certain circumstances, such as Mycobacterial infection, *P jiroveci*, *Legionella*, *Nocardia*, and fungal infections. The detection of *Aspergillus* spp. may be difficult to interpret because it may colonize the upper respiratory tract, especially in patients with chronic lung disease. However, in an HSCT patient, it should not be ignored, and further studies are generally indicated to exclude IPA.

The use of chest radiography may be helpful; however, most patients with respiratory symptoms after HSCT require chest computed tomography with high-resolution images to evaluate for infectious and noninfectious causes that may have distinctive features. Radiologic signs that are better detected by chest computed tomography include pulmonary nodules, the halo and air crescent signs, “ground-glass” infiltrates, changes that are suggestive of BOS and cryptogenic organizing pneumonia, and mediastinal lymphadenopathy. Furthermore, chest computed tomography assists in better yield if invasive procedures are indicated. There is evidence that early use of chest computed tomography for evaluation of pulmonary disease was associated with earlier diagnosis of serious infections such as IPA and better outcomes of patients.63

Serologic studies have recently emerged as useful tools in the evaluation of infectious pulmonary complications after HSCT. Serum and BAL galactomannan antigens are very useful, in the appropriate setting, for diagnosis of IPA as outlined above. In addition, serum 1,3-beta-D-glucan analysis is another supportive test that could show the presence of fungal infection. Bronchoalveolar lavage 1,3-beta-D-glucan has not been studied yet, and polymerase chain reaction assay for Aspergillus DNA in BAL is currently under evaluation.64 Serum CMV polymerase chain reaction is helpful in diagnosis and monitoring of patients with CMV infection.

Fiberoptic bronchoscopy and BAL are the major investigative and least invasive tools for obtaining lower respiratory tract specimens. The overall diagnostic yield of bronchoscopy with BAL in HSCT patients ranges between 42% and 65%.65 The highest yield is in allogeneic HSCT patients, when there is presence of focal versus diffuse infiltrates, and when the procedure is done within 24 hours of presentation or before start of antimicrobial therapy. It is worth noting that BAL is still useful within 3 days of initiation of therapy.66,67 The lowest diagnostic yield of BAL is in critically ill patients with acute respiratory failure and in the presence of acute GVHD and neutropenia.68,69 Changes in the management in HSCT following bronchoscopy with BAL vary in the literature from 20% to 70%.65 Changes in the outcome based on the procedure are even more variable and inconsistent.

Transbronchial biopsies are commonly restricted by severe thrombocytopenia and critical respiratory status. The additional diagnostic yield is around 10%.70,71 Transbronchial biopsies are more useful in the diagnosis of noninfectious pulmonary complications after HSCT such as cryptogenic organizing pneumonia.

Surgical lung biopsy, preferably by video-assisted thoracoscopic surgery, is the diagnostic criterion standard in the evaluation of pulmonary infiltrates after HSCT. The outcome of patients is improved when a specific diagnosis is made. However, commonly, this procedure is limited by the relatively high surgical morbidity and mortality rates in this patient population.72 Chellapandian and associates recently compared the diagnostic yield of BAL with that of lung biopsy.73 Although yield was similar for
both procedures, BAL diagnosed more infectious causes, whereas lung biopsies led to more noninfectious ones. Not surprisingly, complications and procedure-related mortality were higher in patients who underwent lung biopsies.

Figure 2 provides a suggested approach to evaluation of pulmonary infiltrates in HSCT recipients.

Figure 2. Suggested Algorithm for the Approach to the Diagnosis and Management of Respiratory Complications After Hematopoietic Stem Cell Transplant

Conclusions

Hematopoietic stem cell transplant is a therapeutic option for a variety of diseases, and indications for this procedure and other types of stem cell transplant are likely to expand in the future. There have been significant advances in the conditioning regimens and supportive measures. However, pulmonary complications remain a major problem after HSCT. The available evidence for risk factors, diagnostic approach, and treatment options is primarily based on retrospective, single center studies. Prospective, observational, and interventional multicenter trials are needed to better diagnose and treat these complications.

References


