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An Update on Pulmonary Complications of Hematopoietic Stem Cell Transplantation

Amy K. Chi, MD; Ayman O. Soubani, MD, FCCP; Alexander C. White, MD, FCCP; and Kenneth B. Miller, MD

The indications for hematopoietic stem cell transplantation (HSCT) continue to expand. However, the risk for pulmonary complications post-HSCT continues to be high. Early recognition and treatment of pulmonary complications may improve outcomes. This is an overview of diagnosis, manifestations, and treatment of the most common infectious and noninfectious pulmonary complications post-HSCT. Knowing the patient's timeframe post-HSCT (preengraftment, postengraftment, late), type of HSCT (allogeneic vs autologous), radiographic findings, and clinical presentation can help to differentiate between the many pulmonary complications. This article will also address pretransplantation evaluation and infectious and noninfectious complications in the patient post-HSCT. While mortality post-HSCT continues to improve, respiratory failure continues to be the leading cause of ICU admissions for patients who have undergone HSCT. Mechanical ventilation is a predictor of poor outcomes in these patients, and further research is needed regarding their critical care management, treatment options for noninfectious pulmonary complications, and mortality prediction models posttransplantation. ***CHEST 2013; 144(6):1913–1922***

Abbreviations: BO = bronchiolitis obliterans; CMV = cytomegalovirus; COP = cryptogenic-organizing pneumonia; DAH = diffuse alveolar hemorrhage; GVHD = graft-vs-host disease; HRCT = high-resolution CT; HSCT = hematopoietic stem cell transplantation; IPS = idiopathic pneumonia syndrome; PCR = polymerase chain reaction; PERDS = periengraftment respiratory distress syndrome; RIT = reduced-intensity conditioning transplant; RSV = respiratory syncytial virus; TMP-SMX = trimethoprim-sulfamethoxazole

More than 50,000 hematopoietic stem cell transplantations (HSCTs) are performed annually worldwide.[1] HSCT is a form of therapy that involves taking stem cells from a donor or from cord blood and infusing them intravenously into the recipient. Advances in human leukocyte antigen matching, conditioning regimens, and posttransplant supportive care have contributed to improved survival following HSCT.[2] The use of less-intensive conditioning regimens has dramatically changed the clinical course posttransplantation and permits transplants in older patients with multiple comorbidities and preexisting pulmonary conditions. Reduced-intensity conditioning transplants (RITs) receive less toxic preparative regimens and have shortened periods of neutropenia, reduced transplant-related toxicities, and low transplant-related mortality.

Despite the advances in HSCT, including the use of RIT, pulmonary complications occur in over one-third of patients post-HSCT and are associated with significant morbidity and mortality.[3,4] Pulmonary complications can be classified as either infectious or noninfectious and vary depending on the time course post-HSCT. The usual time course is divided into the preengraftment phase (< 30 days), immediate postengraftment (30 days to 100 days), or late postengraftment (after 100 days) (Fig 1). This time course may vary for patients undergoing RIT.

Pretransplant Pulmonary Evaluation

Evaluating the patient who has undergone HSCT for pulmonary complications begins prior to bone

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Affiliations: From Tufts Medical Center (Drs Chi and White), Boston, MA; School of Medicine (Dr Soubani), Wayne State University, Detroit, MI; New England Sinai Hospital (Dr White), Steward Health Care, Stoughton, MA; and School of Medicine (Dr Miller), Tufts University, Boston, MA.
Correspondence to: Amy Chi, MD, 800 Washington St, #369, Boston, MA 02111; e-mail: achi@tuftsmedicalcenter.org

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marrow transplantation. A recent study in the autologous HSCT population showed that the strongest predictors of pulmonary complications were low Karnofsky scores and underlying malignancy.[3]

The choice of preparatory regimen, dose of total body irradiation, and source of HSCT can also influence early pulmonary complications. For example, patients undergoing myeloablative regimens, in contrast to RIT regimens, have a higher risk of bacterial infections early post-HSCT.[5] Additionally, lower irradiation dose has been shown to reduce pulmonary complications among patients with reduced FEV_1.[6] Moreover, the type of HSCT (autologous vs allogeneic) and the stem cell source may impact the incidence, type, and timing of the pulmonary complications.[7]

The implications for pretransplant pulmonary function testing are controversial. An earlier study by Crawford and Fisher[8] (N = 1,297) showed that pretransplant pulmonary function testing did not predict mortality risk within the first year. However, more recent studies have shown that pretransplant pulmonary function abnormalities are associated with early respiratory failure and mortality.[9] For example, Ramirez-Sarmiento et al[10] demonstrated that patients with restrictive lung physiology (or total lung capacity < 80%) had a twofold higher risk of early respiratory failure and nonrelapse mortality postallogenic HSCT (n = 2,545). The restrictive physiology may be due to underlying respiratory muscle weakness.[11]

Given the benefits of HSCT, abnormal pretransplant pulmonary function testing alone should not preclude patients from HSCT. Rather it should be used to provide baseline lung function and alert the physician of possible increased risk for future pulmonary complications post-HSCT.

Infectious Complications in HSCT

Despite prophylactic strategies and advances in diagnosis and treatment of pulmonary infections, pneumonia remains an important cause of nonrelapse mortality after HSCT.[12] Infectious complications are more common in patients undergoing allogeneic transplants due to prolonged immunosuppressive therapy and graft vs host disease (GVHD) (complication in which the newly transplanted donor hematopoietic bone marrow attacks the recipient's body). Additionally, chemotherapeutic agents such as rituxan and purine analogs impair B-cell function and T-cell responses

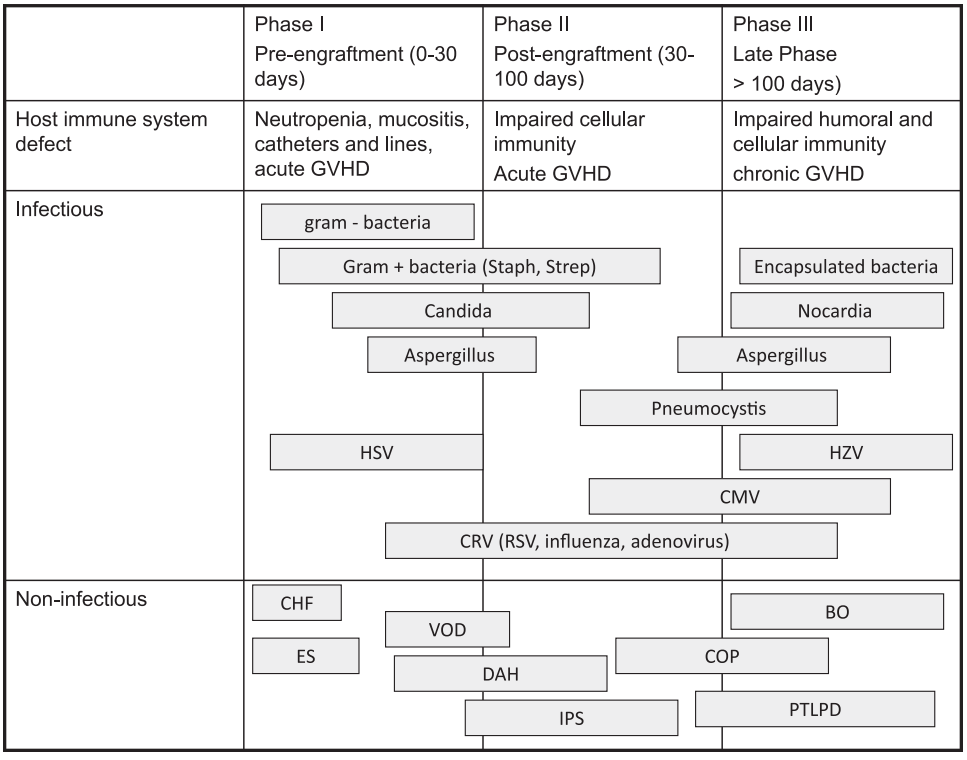

Figure 1. The timeline of pulmonary complications following hematopoietic stem cell transplantation (HSCT). BO = bronchiolitis obliterans; CHF = congestive heart failure; CMV = cytomegalovirus; COP = cryptogenic-organizing pneumonia; DAH = diffuse alveolar hemorrhage; ES = engraftment syndrome; GVHD = graft-vs-host disease; HSV = herpes simplex virus; HZV = herpes zoster virus; IPS = idiopathic pneumonia syndrome; PTLPD = posttransplant lymphoproliferative disorder; RSV = respiratory syncytial virus; VOD = venoocclusive disease.

predisposing patients who have undergone HSCT to opportunistic infections.

Bacterial pneumonia commonly occurs during the neutropenic phase with a reported incidence between 20% and 50%.[13] Empirical broad-spectrum antibiotics should be instituted in febrile neutropenic patients with suspected bacterial pneumonia. Guidelines by the Infectious Diseases Society of America recommend prophylaxis with fluoroquinolones in patients with neutropenia lasting > 7 days.[14] Experience from the Mayo Clinic showed that after initiating fluoroquinolone prophylaxis, gram-positive infections decreased relative to gram-negative infections, and fluoroquinolone resistance increased.[15]

Nocardia pneumonia is rarely reported (annual incidence of 1.75%) but should be considered in patients not improving with β-lactam or fluoroquinolone antibiotics. Incidence was only marginally increased among patients using pentamidine instead of trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis* prophylaxis.[16] Prolonged treatment with TMP-SMX (a sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole used in the treatment of bacterial infections) remains the first line of therapy.

Mycobacterium tuberculosis following HSCT is rare in nonendemic areas (0.1%-0.25%) but more prevalent in endemic areas (16%).[17] Treatment is generally similar to nontransplant patients; however, care should be given to interactions between antituberculous drugs with other medications.

Additionally, nontuberculous *Mycobacterium* including *Mycobacterium avium-intracellulare*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae* are rare (prevalence, 0.26%-0.6%), but can lead to significant morbidity and mortality.[18]

Viral Infections

The occurrence of cytomegalovirus (CMV) pneumonia infection has decreased with CMV monitoring and prophylaxis.[19] While ganciclovir for CMV prophylaxis has benefits, the myelosuppressive toxicity has limited its use as routine prophylaxis. Instead, many institutions opt for preemptive treatment of CMV based on plasma pp65 antigen or quantitative polymerase chain reaction (PCR) testing.[20]

In a recent small prospective trial, use of valganciclovir as preemptive therapy demonstrated equivalent viral clearance as compared with ganciclovir for preemptive therapy.[21] Larger trials to assess the impact on survival and efficacy of preemptive valganciclovir therapy are needed.

The diagnosis of CMV pneumonitis is confirmed by lung tissue biopsy demonstrating viral inclusion bodies in lung tissue. A presumptive diagnosis can be made for patients with compatible clinical and radiographic features of CMV pneumonitis and presence of CMV in blood or bronchoalveolar fluid via either CMV DNA PCR shell assay or positive viral cultures.

The standard of care for the treatment of CMV pneumonia is ganciclovir and CMV immunoglobulin. Resistance to ganciclovir can be considered in patients having frequent relapses, breakthrough viremia, or not improving after 2 weeks of therapy. Genotypic resistance testing can be performed to identify ganciclovir resistance.

Progression to respiratory failure has significant mortality despite the use of combination therapy. Moreover, the complications of CMV infection may be related to the host immune response to the virus and the increased incidence of GVHD associated with CMV reactivation.[22]

Community acquired respiratory viral pathogens (respiratory syncytial virus [RSV], influenza A and B, and parainfluenza) account for the majority of non-CMV viral respiratory infections in the HSCT population. Nearly one-third of patients who underwent HSCT admitted with acute respiratory symptoms have one of these pathogens isolated. RSV, an RNA-containing virus that causes respiratory infections in adults and bronchitis and bronchopneumonia in children, is the most commonly isolated viral pathogen.[23]

Previous reports have suggested that mortality from untreated RSV pneumonia can be as high as 80%. Controlled studies have shown that aerosolized ribavirin and IV immunoglobulin may decrease mortality if treatment is initiated at the earliest stages of upper respiratory symptoms.[24]

Mortality with parainfluenza and influenza pneumonia are considerably lower. A published study showed that treating with oseltamivir within 48 h of symptoms reduced progression to pneumonia.[25]

More recently, data on the morbidity and mortality associated with influenza A subtype H1N1 in HSCT have been reported. Overall mortality was 7% at 28 days and 19% at 4 months postdiagnosis of H1N1. This is higher than immunocompetent patients but similar to other critically ill hospitalized cohorts.[26]

Fungal Infections

Invasive pulmonary aspergillosis is the most common invasive fungal infection among HSCT recipients with reported incidence of 5% to 30% in allogeneic and 1% to 5% in autologous HSCT.[27] Incidence of aspergillosis continues to decrease with the increased use of *Aspergillus* prophylaxis. While a number of randomized controlled trials have shown that prophylaxis for *Aspergillus* infection is correlated with reduced all-cause mortality, long-term mortality (> 36 months) is unchanged.[28]

Prophylaxis with the newer azoles including voriconazole or posaconazole is recommended for HSCT recipients who are neutropenic for >2 weeks and those on immunosuppressive treatment of GVHD.[29] The administration of the newer azoles is associated with a decreased risk of invasive aspergillosis but with an unclear impact on overall survival.

Other centers have adopted preemptive screening for invasive aspergillosis in high-risk patients. The pretransplant ferritin level ($>1{,}000$ ng/mL) may identify a high-risk population ($r = 0.413$, $P < .001$) for the development of fungal pulmonary infections and may be a predictor of patients requiring screening for pulmonary fungal infection.[30]

Screening measures include serum *Aspergillus* galactomannan, serum β-D-glucan, or serum *Aspergillus* PCR testing.[31] False-positive serum galactomannan has been reported in patients receiving β-lactam antibiotics, particularly piperacillin-tazobactam. The effects may last up to 5 days after discontinuing antibiotics.[32] BAL testing for galactomannan can be performed and has been shown to have a higher sensitivity for invasive pulmonary aspergillosis than serum *Aspergillus* galactomannan.[33] Additionally, characteristic findings such as a perinodular halo or a crescent sign on high-resolution chest CT (HRCT) scan is suggestive for aspergillosis and may allow for earlier diagnosis[34] (Fig 2). HRCT scanning is a medical diagnostic test used for diagnosis and assessment of lung disease; it involves the use of special scanning techniques to assess the lung parenchyma.

Voriconazole is the initial antifungal agent of choice for possible invasive aspergillosis. However, voriconazole has no activity against mucormycosis, and outbreaks of mucormycosis in patients receiving voriconazole prophylaxis have been reported.[35]

For patients who are intolerant of voriconazole or for whom the diagnosis of invasive aspergillosis is not confirmed, liposomal amphotericin B may be considered. For patients who fail voriconazole, an echinocandin alone or in combination with voriconazole or posaconazole can be used as salvage therapy.[36]

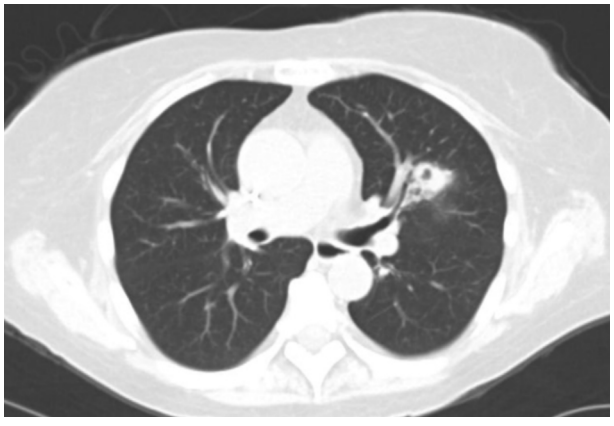

FIGURE 2. Chest CT image showing a left upper lobe cavitary lesion in a patient with invasive pulmonary aspergillosis following allogeneic HSCT. See Figure 1 legend for expansion of abbreviation.

In selected cases, surgical intervention can be successful either as treatment or prevention of relapse in patients requiring further chemotherapy or HSCT.[37] More recent studies support that secondary prophylaxis with newer azoles may be safe and effective in reducing relapse rates.[38]

Zygomycetes, including mucor and rhizopus, have a reported prevalence of 1.9% in the allogeneic patient who has undergone HSCT. Data suggest that the incidence is rising with more frequent use of voriconazole prophylaxis.[39] Treatment of zygomycetes include amphotericin B and possibly surgical resection.

Fusarium and *Scedosporium* species can also cause pulmonary infections. Incidence of *Fusarium* among allogenic patients who underwent HSCT ranges from 0.5% to 2%. Overall survival is 13% with persistent neutropenia as the strongest predictor of mortality.[40]

Scedosporium species is a virulent pathogen resembling aspergillosis. Treatment can be challenging given resistance to antifungals. Surgical resection of localized lesions is advised when feasible.

Pneumocystis jiroveci pneumonia is a fungal infection that occurs late following HSCT. The routine use of TMP-SMX prophylaxis has decreased the incidence of *Pneumocystis* pneumonia. However, *P jiroveci* pneumonia should be considered in patients who are on immunosuppressive therapy for GVHD and not receiving adequate prophylaxis. The diagnosis and treatment are similar to nontransplant patients.

Noninfectious Pulmonary Complications

While the overall incidence of infectious pulmonary complications has decreased, the morbidity and mortality with noninfectious pulmonary complications remain relatively unchanged.[41] A number of distinct acute lung injury syndromes have been described following HSCT: periengraftment respiratory distress syndrome, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome (Table 1).

Periengraftment respiratory distress syndrome (PERDS), previously referred to as engraftment syndrome, is a clinical entity characterized by fever, erythrodermatous rash, noncardiogenic pulmonary edema, and hypoxemia coinciding with neutrophil recovery. The median time to development of PERDS is 11 days post-stem cell infusion (range from 4 to 25 days). PERDS is more frequently seen in autologous patients who underwent HSCT, with an incidence of 7% to 11%.[42] It is postulated that the release of proinflammatory cytokines and the influx of neutrophils into the lungs during engraftment play a primary role.[27,43]

Table 1—*Comparison and Characteristics of Acute Lung Injury Syndromes in HSCT*

Feature	PERDS	DAH	IPS
Incidence	Autologous > allogenic	Autologous = allogenic	Allogenic > autologous
Onset	Early/acute within 96 h of engraftment	Early/acute	Late/subacute
Clinical characteristics	Temperature > 38.3°C Erythrodermatous rash over 25% of body surface area Diffuse pulmonary infiltrates Hepatic dysfunction Renal insufficiency Transient encephalopathy	Progressive bloodier lavage from > 3 subsegmental lobes > 20% hemosiderin-laden macrophage Absence of infection	Progressive respiratory failure Absence of infection confirmed by BAL confirmed by second test 2-14 d later Lung biopsy showing diffuse alveolar damage or interstitial pneumonitis
Response to corticosteroids	Excellent response	Moderate response	Poor response
Prognosis	Favorable prognosis	Poor. Usually die of multiorgan failure and sepsis	Poor. Usually die of respiratory failure

DAH = diffuse alveolar hemorrhage; HSCT = hematopoietic stem cell transplantation; IPS = idiopathic pneumonia syndrome; PERDS = periengraftment respiratory distress syndrome.

More frequent use of granulocyte colony stimulating factors and rapid engraftment postautologous HSCT may explain the higher incidence of PERDS in this population.

The prognosis of PERDS is generally favorable, with the treatment of mild cases being supportive care. Strong consideration should be given to discontinuing granulocyte colony stimulating factor in the setting of PERDS. In symptomatic patients, high-dose corticosteroids may be beneficial if instituted early. Patients who progress to respiratory failure requiring mechanical ventilation or those who develop a secondary infection have a worse prognosis.[44]

Diffuse alveolar hemorrhage (DAH) is a serious complication diagnosed by BAL demonstrating progressively bloodier lavage from three separate subsegments (or 20% hemosiderin-laden macrophage) in the absence of respiratory tract infection (Fig 3). DAH is a pulmonary syndrome characterized by bleeding into the alveolar spaces due to injury or inflammation of the arterioles, venules, or alveolar septal (alveolar wall or interstitial) capillaries. More recent studies in the population with HSCT have shown that patients with infection-associated alveolar hemorrhage are clinically indistinguishable from patients with DAH. These findings suggest that these two entities are on a spectrum of a similar disease process. The use of high-dose steroids in the setting of infection-associated alveolar hemorrhage had similar 60-day mortality rates as compared with DAH (25% vs 26%, $P = .28$).[45] Thrombocytopenia is not an independent risk factor and platelet transfusion did not improve respiratory status.[46]

There are no prospective trials to address the management of DAH. Retrospective studies and case reports suggest that early diagnosis of DAH and high-dose corticosteroids may improve survival.[47]

While earlier reports of DAH have reported mortality rates between 75% and 100%, more recent studies have shown improved survival rates approximating 38%.[48] Death is usually due to superimposed multiorgan failure, ARDS, superinfection, or sepsis, reflecting that DAH may be a symptom of multiple etiologies. The onset of DAH within the first 30 days post-HSCT and lack of mechanical ventilation have been associated with a more favorable prognosis.[49]

The most recent definition of idiopathic pneumonia syndrome (IPS) by the American Thoracic Society is "an idiopathic syndrome of pneumopathy after HSCT, with evidence of widespread alveolar injury and in which an infectious etiology and cardiac dysfunction, acute renal failure or iatrogenic fluid overload have been excluded."[50]

The mean estimated incidence of this syndrome is 1% to 10% and is less common in the patient undergoing autologous HSCT (5.8%).[51] Nearly two-thirds of patients progress to respiratory failure requiring mechanical ventilation within several days of presenting. Collective mortality from six larger clinical series was 74%.[52]

Currently, no proven treatments for IPS exist and overall mortality is high. The efficacy of corticosteroids

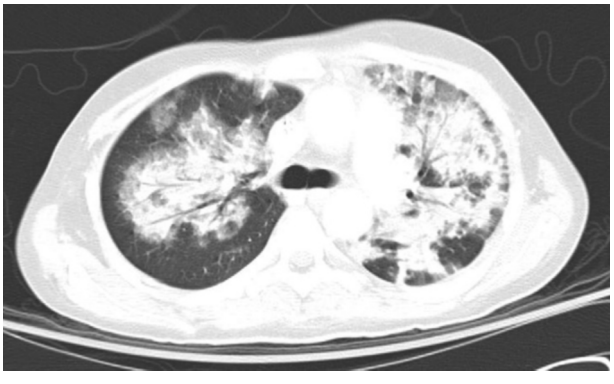

FIGURE 3. Chest CT image showing bilateral areas of consolidation in a patient with DAH. See Figure 1 legend for expansion of abbreviation.

in IPS is unclear. Clinical reports have suggested that etanercept, a soluble TNF-α-binding protein, may improve pulmonary function within the first week of therapy.[53] Improvement in infiltrates seen on high-resolution CT scan is associated with improved outcomes.[54]

Late Pulmonary Complications Post-HSCT

Late pulmonary complications (> 100 days post-transplant) occur most frequently in patients with chronic GVHD. The development of late-onset pulmonary complications is associated with reduced overall survival.[55] Moreover, with the increasing use of RIT in older patients, there is a higher incidence of late pulmonary complications.[4]

These patients are often immunosuppressed and at risk for pulmonary infections such as fungal, viral, and encapsulated bacterial organisms. Additionally, patients with GVHD are at risk for noninfectious pulmonary complications including bronchiolitis obliterans (BO), cryptogenic-organizing pneumonia (COP), posttransplant lymphoproliferative disorder, and pulmonary venoocclusive disease.

BO has an insidious presentation including dry cough and dyspnea[56] (Table 2[57]). Recent guidelines by the American Society for Blood and Marrow Transplantation recommend pulmonary function testing at 6 months and then yearly post-HSCT.[58]

The clinical course is variable, and most patients develop a slowly progressive airway obstruction with episodes of exacerbation. A few patients develop a rapid deterioration in lung function leading to respiratory failure within a few months while others stabilize or even improve lung function with treatment.[59] Similar to the lung transplant population, where BO is thought to equal chronic allograft rejection, BO in the patient who has undergone HSCT may represent a continuum of chronic GVHD with acute GVHD being an important risk factor.[59] Overall estimated mortality is 12% at 5 years and 18% at 10 years. Prognosis is worse for patients with rapidly deteriorating FEV_1 (> 10% annually), older than 60 years of age, and with progressive GVHD.[60]

Bronchoscopy has a limited role in the diagnosis of BO and is mainly performed to rule out an infectious process. Transbronchial biopsy is not recommended due to the patchy and peripheral nature of the disease. While surgical lung biopsy can be helpful to establish the diagnosis, perioperative complications are high.

The National Institutes of Health 2007 consensus criteria for the diagnosis of chronic GVHD include revised criteria for the diagnosis of lung GVHD. The diagnosis is typically made on symptoms, pulmonary function tests, and HRCT scanning (Figs 4, 5, Table 2).

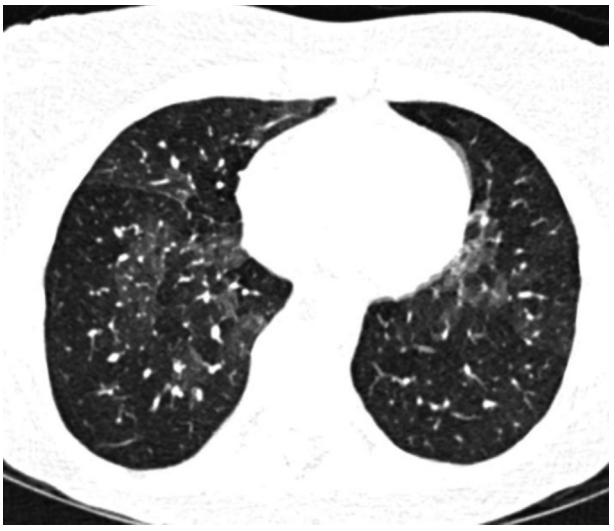

Figure 4. High-resolution CT image showing mosaic pattern in a patient with BO. See Figure 1 legend for expansion of abbreviation.

Table 2—*Suggested Diagnostic Criteria for BO*

Suggested Criteria
1. Allogeneic HSCT
2. Chronic GVHD
3. Evidence of airflow obstruction with $FEV_1/FVC < 0.7$ and $FEV_1 < 75\%$ predicted
4. Air trapping or small airway thickening or bronchiectasis on HRCT of the chest with inspiratory and expiratory cuts, residual volume of PFT > 120% predicted
5. Absence of infection based on clinical symptoms, radiographs, microbiologic cultures, sputum culture, or BAL
6. Pathologic confirmation of constrictive bronchiolitis (biopsy not required for clinical diagnosis if all above criteria met)

BO = bronchiolitis obliterans; GVHD = graft-vs-host disease; HRCT = high-resolution CT scan; PFT = pulmonary function test. See Table 1 legend for expansion of other abbreviations. (Adapted with permission from Soubani and Pandya.[57])

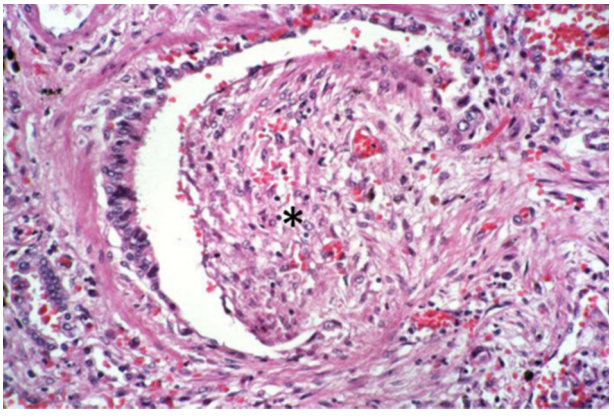

Figure 5. BO pathology showing intraluminal polypoid plug of granulation tissue found within the terminal and respiratory bronchioles (*) (hematoxylin and eosin (HE) stain; magnification × 200). See Figure 1 legend for expansion of abbreviation.

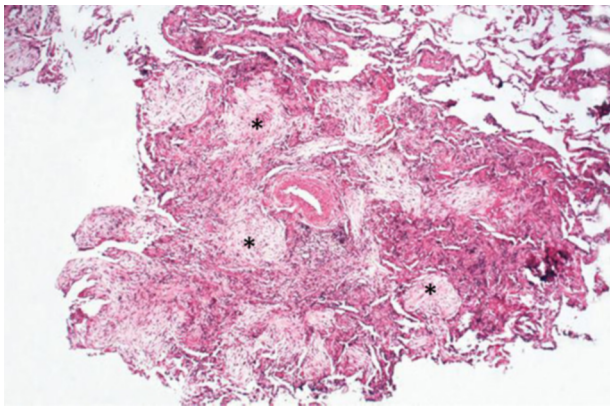

FIGURE 6. COP pathology showing intraluminal buds of granulation tissue in small airways and alveolar ducts (*) with associated chronic inflammation in the surrounding alveoli (hematoxylin and eosin (HE) stain; magnification × 100). See Figure 1 and 5 legends for expansion of abbreviations.

The risk factors for BO include older age, nonrelated donor, total body irradiation used in the preparative regimen (> 12 Gy), and acute GVHD.[7]

The management of BO remains a challenge. The goals of care should be aimed at stabilization. Treatment is based on small uncontrolled trials and expert opinions. Generally, the management of BO includes high-dose corticosteroids and reinstitution or augmentation of immunosuppressive agents.[61] Macrolides, low doses of clarithromycin or azithromycin, may have an immunomodulatory effect and may improve pulmonary function.[62]

Additionally, a retrospective case series demonstrated a steroid-sparing effect in patients who received inhaled corticosteroids, azithromycin, and montelukast.[63] Alternate therapies with unclear benefit include anti-TNF-α monoclonal antibodies and extracorporeal photodynamic therapy.[64] Lung transplantation has been successfully performed in selected patients with severe BO following HSCT.[65,66]

Future advances for treatment and diagnosis of BO will require improved understanding of the heterogeneity of the disease, earlier detection with reliable biomarkers, and better earlier therapeutic interventions.

COP, previously known as BO-organizing pneumonia, is a distinct entity and should not be confused with BO (Fig 6, Table 3). As noted in the pathology, BO is primarily an airway isolated process with normal interstitial tissue as compared with COP which has both small airway fibrosis and accompanying interstitial and alveolar inflammation. Additionally, COP can occur in both autologous and allogeneic patients who underwent HSCT as opposed to BO which occurs primarily in allogeneic patients who underwent HSCT. COP is an idiopathic form of organizing pneumonia, with characteristic histopathology findings that include excessive proliferation of granulation tissue within small airways (proliferative bronchiolitis) and alveolar ducts, associated with chronic inflammation in the surrounding alveoli.

The clinical presentation of COP may be similar to BO. However, pulmonary function testing usually shows a restrictive pattern with low diffusion capacity and minimal obstructive airflow.[67]

Unlike BO, patients with COP have a more favorable prognosis and are responsive to systemic corticosteroids. In 78% of patients, COP remains stable or resolves. COP typically occurs earlier than BO with a median onset of 108 days.[67]

Other Pulmonary Complications

Pulmonary venoocclusive disease is rare but fatal in the patient who has undergone HSCT if not recognized. The typical triad includes dyspnea, pulmonary arterial hypertension with normal pulmonary artery occlusion pressure, and radiographic imaging suggestive of pulmonary edema.[68] Treatment with high-dose steroids and heparin have been anecdotally beneficial.[56] Pulmonary venoocclusive disease rarely responds to therapy and lung transplantation should be considered for these patients.

Table 3—*Comparison Between BO and BO-Organizing Pneumonia*[57]

Features	BO	COP
Incidence	0%-48%	< 2%
HSCT	Allogenic	Allogenic and autologous
Onset	Late (1 y)	Usually in first 100 d
Clinical presentation	Cough, dyspnea, wheeze	Dyspnea, cough, fever
Radiologic findings	Normal; hyperinflated, air trapping, bronchiectasis	Pathcy consolidation, ground glass opacities, nodular opacities
Pulmonary function test	Obstructive; normal diffusion capacity	Restrictive; reduction in diffusing capacity
Diagnosis	Clinical, radiographic, physiologic	Tissue biopsy
Histopathology	Fibrotic plugs obliterating bronchioles with inflammation and scarring; spare alveoli and alveolar ducts	Granular plugs of bronchioles, extending into alveoli; interstitial inflammation and fibrosis
Treatment	Corticosteroids and immunosuppressives	Corticosteroids
Outcomes	Poor response to therapy; progressive disease with high mortality	Good response to therapy; potentially reversible

See Table 1 and 2 legends for expansion of abbreviations.

Posttransplant lymphoproliferative disorder is an uncommon but serious complication in the patient who has undergone HSCT, usually characterized by the overproliferation of Epstein-Barr virus-infected lymphocytes. Patients typically present within 6 months of HSCT with enlarged lymph nodes, liver, and/or spleen.[69] Treatment includes reduction of immunosuppressive agents and administering anti-B-cell monoclonal antibody therapy.[70]

Evaluating Suspected Pulmonary Complications

Evaluating the patient who has undergone HSCT with a suspected pulmonary complication can be challenging. Determining the time course, type of HSCT, and course of illness is the first step in narrowing the differential of potential pulmonary complications.

HRCT scanning can provide information to narrow the differential of pulmonary complications and localize an area for biopsy or sampling.[71] Characteristic findings for late HSCT pulmonary complications include mosaic lung attenuation as seen in BO or a perivascular multilobar patchy consolidation as seen with COP.[72]

BAL can be useful in the early stages of diagnosis. One study in the HSCT population demonstrated that BAL yielded a diagnostic pathogen 55% of the time. Yield was higher if bronchoscopy was performed within the first 24 h (75%).[73,74] However, a randomized controlled study suggests that use of noninvasive measures (ie, serologic studies, sputum culture) is comparable to using BAL.[73]

In one series of patients with a prior hematologic malignancy, CT imaging-guided biopsy of a new lung lesion yielded a diagnosis 60% of the time. Lesions >1 cm, cavitary lesions, and lung masses were more likely to yield a diagnosis.[71] The diagnostic yield of transbronchial biopsy in addition to BAL is low and includes an increased risk of complications.[75] Surgical lung biopsy is the diagnostic standard in evaluating pulmonary infiltrates in the patient who has undergone HSCT. However, surgical biopsies are associated with surgical complications.[76]

In conclusion, the indications and use of HSCT as a therapeutic modality continues to increase. The use of RIT and nonmyeloablative stem cell transplantation regimens have allowed older patients with more comorbidities to undergo HSCT. While progress has been made in the treatment and preemptive diagnosis of infectious pulmonary complications, noninfectious pulmonary complications remain a major cause of morbidity and mortality with limited treatment options. The rapidly evolving role and application of HSCT requires close cooperation of the pulmonologist and transplant team.

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