review

The spectrum of noninfectious pulmonary complications following hematopoietic stem cell transplantation

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Hematopoietic stem cell transplantation (HSCT) is an established treatment for a variety of malignant and nonmalignant conditions. Pulmonary complications, infectious and noninfectious, are a major cause of morbidity and mortality in these patients. The recent advances in prophylaxis and treatment of infectious complications increased the significance of noninfectious pulmonary conditions. Acute lung injury due to diffuse alveolar hemorrhage or idiopathic pneumonia syndrome are the main acute complications, while bronchiolitis obliterans remains the most challenging pulmonary complications facing clinicians who are taking care of HSCT recipients. There are other noninfectious pulmonary complications following HSCT that are less frequent. This report provides a clinical update of the incidence, risk factors, pathogenesis, clinical characteristics and management of the main noninfectious pulmonary complications following HSCT.

Hematopoietic stem cell transplantation (HSCT) is a treatment option for several malignant and nonmalignant disorders. In autologous HSCT, the stem cells are collected from the patient then infused back after high dose chemotherapy. In allogeneic HSCT, the stem cells are donated from another individual (who may be related or unrelated and matched or unmatched). The hematopoietic stem cells may be obtained from bone marrow or peripheral blood, or harvested from umbilical cord blood. Allogeneic HSCT is further classified according to the intensity of the conditioning regimen. Myeloablative regimen is when supralethal doses of chemotherapy with or without irradiation are given, leading to significant toxicity and immunosuppression. More recently, nonmyeloablative regimens have been used to extend transplant to older patients and those with co-morbidities. This approach may also be associated with less graft versus host disease (GVHD) and more potent graft versus malignancy effect.

Pulmonary complications, both infectious and noninfectious, occur in 25%-50% of HSCT recipients, and are associated with significant morbidity and mortality[1-3] (Figure 1). The advances in the diagnosis and management of infectious pulmonary complications following HSCT have increased the significance of noninfectious conditions. This review provides a clinical update of the main non-infectious pulmonary complications following HSCT, describing the incidence, risk factors, pathogenesis, diagnosis, management and outcome of these conditions.

Engraftment syndrome

Engraftment syndrome describes a clinical entity characterized in its full expression by a combination of fever, erythrodermatous rash, and noncardiogenic pulmonary edema coinciding with neutrophil recovery.[4] It usually develops within 96 hrs of engraftment.[4] The syndrome has been described as occurring more frequently after autologous HSCT, with an incidence of 7–11% when stringent diagnostic criteria are utilized.[5] A similar presentation after allogeneic transplantation has been described, but must be distinguished from acute GVHD. The etiology of this syndrome is poorly understood. Release of proinflammatory cytokines during engraftment is postulated to play a principal role. The use of granulocyte colony-stimulating factor (G-CSF) may increase the incidence and severity of the engraftment syndrome. G-CSF up regulates the production of cytokines (TNF-α, IL-1B, and IL-8), which increase alveo-

	Phase I pre-engraftment (0-30 days)	Phase II post-engraftment (0-30 days)	Phase III late phase >100 days
Host immune system defect	Neutropenia, mucositis, catheters and lines, acute GVHD	Impaired cellular immunity Acute GVHD	Impaired humoral and cellular immunity chronic GVHD
Infectious	Gram - bacteria		
	Gram + bacteria (staph, strep)		Encapsulated bacteria
	Candida		Nocardia
	Aspergillus		Aspergillus
		Pneumocystis	
	HSV		HZV
		CMV	
	CRV (PIF, RSV, influenza, adenovirus)		
Non-infectious	CHF		BO
	VOD		
	ES	BOOP	
	DAH		
	IPS	PTLPD	

Figure 1. The time line of the main pulmonary complications following HSCT. HSV: herpes simplex virus, HZV: herpes zoster virus, CMV: cytomegalovirus, RSV: respiratory syncytial virus, CHF: congestive heart failure, BO: bronchiolitis obliterans, VOD: veno-occlusive disease, ES: engraftment syndrome, DAH: diffuse alveolar hemorrhage, BOOP: bronchiolitis obliterans organizing pneumonia, IPS: idiopathic pneumonia syndrome, PTLPD: post transplant lymphoproliferative disorder

lar permeability and neutrophil influx.[6]

Specific criteria have been suggested for the diagnosis of engraftment syndrome following HSCT. These include major criteria: temperature ≥38.3°C with no identifiable infectious etiology, erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication, and noncardiogenic pulmonary edema manifested by diffuse pulmonary infiltrates consistent with the diagnosis and hypoxia. Minor criteria include: hepatic dysfunction, renal insufficiency, weight gain ≥2.5% of baseline body weight, and transient encephalopathy unexplainable by other causes. Three major or two major and one or more minor criteria are needed for the diagnosis of engraftment syndrome following HSCT.[7]

The prognosis of engraftment syndrome is generally favorable. Mild cases are managed by supportive measures. Strong consideration should be given to discontinue G-CSF. More severe cases, especially those with pulmonary involvement have dramatic response to systemic corticosteroids with improvement within one day of treatment. Patients who require mechanical ventilation have worse prognosis.[4,7-9]

Diffuse alveolar hemorrhage

The development of diffuse alveolar hemorrhage (DAH) as a noninfectious complication after HSCT was first brought to light by Robbins and colleagues

who, in a retrospective review of 141 consecutive autologous transplant recipients identified 29 patients (21%) with this disorder.[10] The hallmark of the syndrome was the finding of progressively bloodier return from bronchoalveolar lavage (BAL) in the absence of an identifiable respiratory tract infection. Since the initial description, DAH has been reported by multiple other groups, albeit with a significantly lower incidence ranging between 2% and 14% with a mean of 5% of HSCT recipients.[11] The incidence among autologous and allogeneic recipients appears to be equivalent.[11] In a study of 48 patients with DAH, the incidence was 4% of all HSCT recipients. 52% of the patients had autologous HSCT and 48% were allogeneic HSCT recipients. The stem cells were from peripheral blood in 67% of the patients.[12] Risk factors for DAH following HSCT include age greater than 40 years, total body irradiation, transplantation for solid tumors, and the presence of high fevers, severe mucositis, leukocyte recovery, and renal insufficiency. Although thrombocytopenia is common, platelet counts are not lower than those found in patients without DAH and aggressive platelet transfusion does not result in improvement in respiratory status.[10] There is also no relation between DAH and type of preparatory regimen, whether it is reduced intensity or myeloablative.[13]

The pathogenesis of DAH in HSCT recipients remains obscure. Postmortem investigations have shown that the majority of patients with DAH have evidence of diffuse alveolar damage.[10,11,14] It is possible that DAH is part of a spectrum of acute lung injury induced by conditioning chemotherapy, radiation, or occult infection. The fact that many cases occur at the time of engraftment suggests that neutrophil influx into the lung may accentuate the injury and in some way precipitate alveolar hemorrhage.

DAH is most commonly observed within the first month after HSCT (a median of 23 days) often during the periengraftment phase, but later onset is encountered in up to 42% of cases.[11] Patients present with dyspnea, nonproductive cough, fever, and diffuse pulmonary infiltrates, but hemoptysis is notably rare. Intensive care unit admission and mechanical ventilation are required by the majority of patients. Radiological findings are usually diffuse interstitial, alveolar or ground glass changes that are more prominent in the perihilar areas and lower lobes (Figure 2). The radiological findings may appear up to 3 days prior to clinical diagnosis of DAH. The diagnosis is usually made by BAL that reveals progressively bloodier lavage fluid return from at least three separate subsegmental bronchi. However, it is possible to have DAH with nonbloody BAL fluid,

especially if the procedure is done few days after the onset of symptoms.[14] The presence of greater than 20% hemosiderin-laden macrophages in BAL fluid is an alternative diagnostic criterion, but because it may take 48-72 hours for this finding to appear.[11,12]

The following diagnostic criteria have been suggested to diagnose DAH following HSCT: 1) evidence of widespread alveolar injury manifested by multilobar pulmonary infiltrates, symptoms and signs of pneumonia, and abnormal physiology with widened A-a gradient, 2) BAL showing progressively bloodier return from three separate subsegmental bronchi, or more than 20% hemosidren-laden macrophages on examination of the BAL fluid, or if a surgical lung biopsy is performed, more than 30% of the alveolar surface of the examined lung tissue is covered by blood, and 3) absence of infection compatible with the diagnosis.[11]

There are no prospective randomized trials to address the management of DAH following HSCT. Retrospective case series and anecdotal reports suggest that high-dose corticosteroids (500-1000 mg per day of methylprednisolone for 3-4 days followed by taper over 2-4 weeks) may improve the survival rate.[15-17] One study suggested that the addition of an antifibrinolytic agent such as aminocaproic acid was associated with lower mortality and no side effects.[18] With supportive therapy alone, mortality rates in patients with DAH of 74-100% have been reported.[10, 11,15] A series from the Mayo Clinic suggested that the mortality associated with DAH is lower than previously reported (48%) and that autologous HSCT, onset within the first 30 days of transplantation and lack of mechanical ventilation were associated with favorable outcome.[12] The cause of death in patients with DAH following HSCT is usually a result of superimposed multi organ failure or sepsis rather than respiratory failure from refractory alveolar hemorrhage.[11] Long term survivors of DAH following HSCT have normal lung function.[17]

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) is another important cause of non-infectious diffuse lung injury following HSCT. A National Institutes of Health workshop defined IPS as "diffuse lung injury occurring after marrow transplant for which an infectious etiology is not identified".[19] This workshop put forward the following diagnostic criteria for IPS: 1) evidence of widespread alveolar injury as manifested by multilobar infiltrates, symptoms and signs of pneumonia, and increased A-a gradient and/or restrictive lung disease based of pulmonary function tests. 2) absence of lower respiratory tract infection after appropriate evaluation that includes
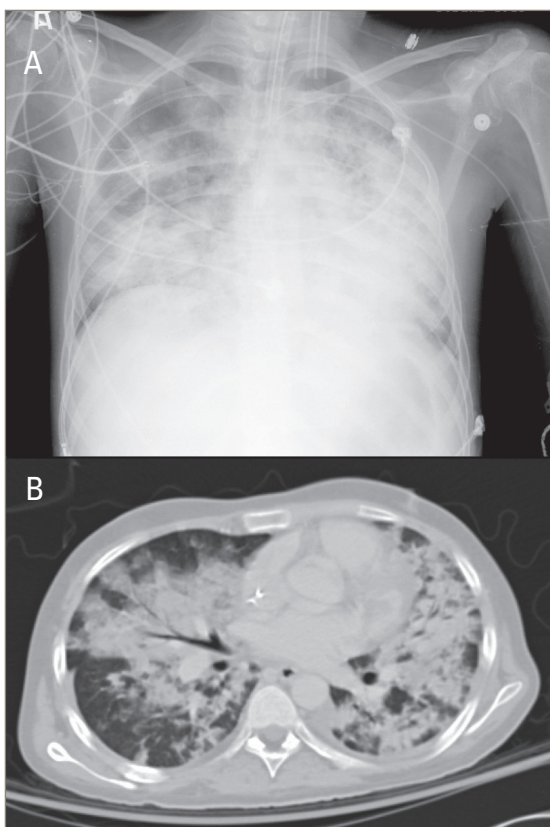

Figure 2A,B. Chest radiograph and chest CT scan image showing bilateral diffuse alveolar infiltrates in a patient with DAH following allogeneic HSCT.

BAL that is negative for bacterial and non-bacterial pathogens, lack of improvement with broad spectrum antibiotics, and a second confirmatory test within 2-14 days. 3) If lung biopsy is performed it usually reveals one of two patterns: diffuse alveolar damage or interstitial pneumonitis.[19] Applying these criteria to a retrospective review of 1165 consecutive patients at the Fred Hutchinson Cancer Research Center, Kantrow and colleagues found that the incidence of IPS in the first 120 days was 7.6% after allogeneic HSCT and 5.7% after autologous procedures.[20] In a review of 12 studies (4496 HSCT recipients) the incidence of IPS was a mean of 10% (range 2-17%). The condition was more common following allogeneic HSCT (10.6%) as compared to autologous HSCT (5.8%).[21]

Risk factors for developing IPS following HSCT include older age, lower pre-transplantation performance status, transplantation for a malignancy other than leukemia, high-intensity conditioning regimens, total body irradiation, high-grade acute GVHD, and methotrexate based GVHD prophylaxis.[21-23] A study focusing exclusively on allogeneic HSCT recipients

found that the incidence of IPS was significantly lower after nonmyeloablative versus conventional high-dose conditioning regimens (2.2% vs 8.4%), suggesting that IPS may be the result of toxicity from intensive chemotherapy and radiation.[22] The occurrence of IPS after both allogeneic and autologous HSC transplantation provides further evidence that conditioning-related toxicities are principally involved. On the other hand, the association of IPS with acute GVHD after allogeneic transplantation suggests that alloreactive T cell injury may be a contributing factor in this setting. It is also possible that some cases of "idiopathic" pneumonia actually represent acute lung injury secondary to an occult infection. Murine models of IPS following allogeneic HSCT suggest that there are two pathways for immune mediated lung injury: one involving soluble inflammatory effectors such as TNF-α, and the other driven by antigen specific, donor T-cell effectors. Both pathways are associated with increased BAL concentrations of inflammatory mediators such as TNF-α, TNFRI, TNFRII, IL-6, IL-8, s-CD14, and MCP-1. These, in turn, trigger the acute lung injury associated with IPS.[24,25] Patients with IPS usually present with dyspnea, fever, nonproductive cough, increasing oxygen requirements, and diffuse radiographic infiltrates. In the study from Seattle, the median time to onset of IPS was 21 days after transplantation. Other studies have reported a more delayed median onset, between 42 and 49 days following HSCT.[19,20] The clinical course of IPS is typically rapid, with up to two-thirds of patients progressing within several days to respiratory failure requiring mechanical ventilation.[20] Collective mortality in six of the larger clinical series was 74% (range

60-86%).[21] Mortality in patients with IPS is primarily related to progressive respiratory failure. Factors that predict mortality include the need for mechanical ventilation and higher serum creatinine level at the onset of IPS.[21,22]

Beyond supportive care, there is no proven treatment for IPS. High-dose corticosteroid therapy does not appear to be of benefit.[20,22] The administration of etanercept, a soluble TNF-α–binding protein, was well tolerated by three pediatric allogeneic HSC transplant recipients with IPS and was associated with significant improvement in pulmonary function within the first week of therapy.[26] In another recent report,[15] HSCT recipients with IPS were treated with combination of etanercept at a dose of 0.4 mg/kg (maximum dose 25mg), twice weekly for maximum total of 8 doses, combined with corticosteroids (2 mg/kg per day) for 7 days then tapered as clinically indicated. This treatment was well tolerated. Two third of the patients had complete response a median of 7 days after initiation of therapy.[24] These clinical reports are encouraging and should prompt clinical trials to prove the efficacy of this therapy. In the meantime, etanercept may be considered in patients with IPS following allogeneic HSCT.

Table 1 summarizes the similarities and differences between the 3 main noninfectious causes (engraftment syndrome, DAH, and IPS) of diffuse lung injury following HSCT.

Delayed pulmonary toxicity syndrome

The term "delayed pulmonary toxicity syndrome" describes a form of mild-to-moderate pulmonary injury observed after high-dose chemotherapy and autologous

Table 1. Comparison of the characteristics of the main non-infectious causes of acute lung injury following HSCT.

Feature	Engraftment syndrome	DAH	IPS
Incidence	Autologous > allogeneic	Autologous = allogeneic	Allogeneic > autologous
Onset	Early/acute	Early/acute	Late/subacute
Relation to stem cell engraftment	Within 96 hr of engraftment	Relation to engraftment is less definite	No relation
Characteristic clinical feature	Systemic manifestations	Bloody BAL	Progressive respiratory failure
Pathology	Diffuse alveolar damage. G-CSF plays a role	Diffuse alveolar damage with release of several cytokines	Diffuse alveolar damage. TNF-α plays a role.
Response to corticosteroids	Excellent response	Moderate response	Poor response
Prognosis	Favorable prognosis	Less favorable prognosis. Usually die with multi-organ failure and sepsis	Poor prognosis usually die with respiratory failure

HSCT for breast cancer.[27] In contrast to IPS, this syndrome presents at a later time point, is generally responsive to corticosteroid therapy, and has a better prognosis. In a study of 45 consecutive women who received high-dose chemotherapy with cyclophosphamide, cisplatin, and bischloroethylnitrosourea (BCNU) followed by autologous HSCT, 26 patients (58%) developed symptomatic pulmonary toxicity with a mean onset of 10 weeks after transplantation.[28] Symptoms are nonspecific and include dyspnea on exertion, nonproductive cough, and fever. Pulmonary function testing reveals a marked reduction in the diffusing capacity associated with a mild to moderate restrictive pattern. Ground glass opacities are the most common radiographic findings demonstrated on CT scan imaging, but these abnormalities may be absent or delayed in up to one-third of patients.

Delayed pulmonary toxicity syndrome likely represents a manifestation of chemotherapy-induced lung injury. In support of this therapy, lung pathology specimens in 10 patients with this syndrome demonstrated findings consistent with pulmonary drug toxicity, including alveolar septal thickening, interstitial fibrosis, and type II pneumocyte hyperplasia.[27] Moreover, in a study that randomized patients to high-dose versus standard chemotherapy before autologous HSCT, the incidence of delayed pulmonary toxicity syndrome was 72% in the high-dose group and only 4% in the group receiving standard therapy.[29] Two of the chemotherapeutic agents used in the conditioning regimen administered to patients with this syndrome–BCNU and cyclophosphamide–have been associated with lung toxicity. Although the high-dose chemotherapy regimens associated with delayed pulmonary toxicity syndrome utilized doses of BCNU below the threshold typically associated with pulmonary toxicity, it is likely that the risk of toxicity is enhanced by synergism with concurrently administered cyclophosphamide. The nitric oxide pathway may also play a role in the pathogenesis of this syndrome. A study of 20 patients with breast cancer who developed delayed pulmonary toxicity syndrome following high dose chemotherapy and autologous HSCT showed that there is increase in the concentration of exhaled nitric oxide following transplant as compared to pre-transplant values and this findings correlated very well with reduction in diffusing capacity.[30]

Patients with delayed pulmonary toxicity syndrome respond well to systemic corticosteroid therapy with improvement in their symptoms, radiological and physiological findings. Typically, the dose of corticosteroids is equivalent to prednisone 60mg daily that is tapered over two months.[28]

Bronchiolitis obliterans

Bronchiolitis obliterans (BO) is the most important late non-infectious pulmonary complication following HSCT. This condition is characterized by the new onset of air flow obstruction (AFO) following HSCT. Due to the lack of a standardized definition, the incidence of BO varies widely in the literature. The reported incidence ranges from 0 to 48%. In a review of 2152 allogeneic HSCT recipients reported in nine studies, the average incidence of BO was 8.3%.[21] In a report from Seattle, the incidence of BO in 1131 allogeneic HSCT recipients was 26%; however, in patients with chronic GVHD, the incidence of BO was 32%.[31] The International Bone Marrow Transplantation Registry (IBMTR) has reported that the incidence of BO was 1.7% in the two years following matched sibling HSCT of 6275 patients.[32] One report specifically commented on the incidence of BO following peripheral blood stem cell transplantation and showed that there was three-fold increase in the risk of BO compared with bone marrow transplantation (hazard ratio 3.35; 95% confidence interval (CI) 1.79–6.27; $P<.0002$).[32] Yoshihara et al[33] reported that the incidence of BO following non-myeloablative HSCT was 2.3% compared with 17% following conventional myeloablative HSCT. The difference between these two groups was statistically significant, but the clinical course and outcome of BO were similar. In general, BO does not develop following autologous HSCT. There are only a few cases reported in the literature of BO developing following autologous HSCT with fatal outcome.[34,35] Furthermore, there are very few reports of BO proven by lung biopsy developing in patients who received umbilical cord blood stem cell transplantation.[36,37]

Several risk factors have been suggested as predisposing to BO following HSCT. The presence of chronic GVHD is the most important association with BO. Earlier studies suggest that BO does not develop in patients without evidence of chronic GVHD.[38,39] However, more recent studies from large HSCT centers report that BO may develop in a small percentage of patients who do not have manifestations of GVHD.[32,40] The risk of BO appears to be higher in those with progressive chronic GVHD (which evolves without hiatus from active acute GVHD) as compared to those with quiescent chronic GVHD (that develops after an interval of response to treatment of acute GVHD) or de novo chronic GVHD (in patients who never had acute GVHD). In the study by Chien et al[40] the adjusted relative risk (95% CI; P value) for GVHD types associated with AFO was: 1.3 (0.8-2.0; 0.3) with acute GVHD; 1.5 (0.8-2.0; .04) with de novo chronic GVHD; 1.6

(1.3-2.4; <.001) with quiescent chronic GVHD; and 1.9 (1.4-2.4; <.001) with progressive chronic GVHD. In the majority of reports, acute GVHD alone does not appear to significantly increase the risk of BO.[31,40-42]

Other frequently observed risk factors for BO include: an older age of the recipient (>20 yrs); the presence of AFO (forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <0.7) prior to HSCT; and respiratory viral infections, such as influenza, parainfluenza and respiratory syncytial virus, in the first 100 days following HSCT.[31,40] Recent reports also suggest that biochemical (such as low pre-transplant serum surfactant D protein level) and genetic factors (such as NOD2/CARD15 polymorphism) may predispose HSCT recipients to BO, and detection of these factors may lead to earlier recognition of these patients.[43,44]

The pathogenesis of BO following HSCT is not well defined. Several theories have been suggested, although none of them have satisfactorily explained the pathogenesis of BO. One of these theories explains BO as a result of a lung injury precipitated by the conditioning regimen. This is based on the higher incidence of BO in busulfan-based conditioning regimen[45,46] and the apparent lower incidence of BO in non-myeloablative HSCT compared with conventional regimen.[33] Another proposed mechanism focuses on the development of BO due to infectious etiology. This is supported by various observations including the association of BO with low serum immunoglobulins secondary to slow reconstitution of B cells following transplantation.[41,47,48] This deficiency may be associated with abnormal local defense mechanisms in the lung, predisposing them to infections that lead to BO. This is also supported by the observation that allogeneic HSCT recipients who develop parainfluenza and respiratory viral infections early in the course following transplantation are at an increased risk of developing BO.[40] Although, infection may still be an important mechanism in the pathogenesis of BO, there is lack of exclusive evidence to prove this theory. Recurrent microaspirations have been suggested as one of the mechanisms of BO following lung transplantation.[49-51] Recurrent aspiration due to esophagitis associated with chronic GVHD may promote chronic inflammation and recurrent infections in the lower airways that may lead to BO.

The most important mechanism contributing to BO is probably an alloreactive immune process in which the donors T-lymphocytes target the epithelial cells of the bronchioles, leading to the inflammatory reaction seen in BO. This mechanism is evident from the exclusive occurrence of BO following allogeneic HSCT, and the strong association between BO and chronic GVHD. Indeed, some authors suggest that BO is a manifestation of chronic GVHD.[52] Also, the reported stabilization of BO in some HSCT recipients by systemic corticosteroids and intensification of immunosuppressive therapy supports the theory that suppression of T-cells may decrease the manifestation of BO following HSCT. It also suggests that depletion of T lymphocytes may decrease the incidence of BO in these patients.[53] A well-characterized mouse model studied BO caused by low dose allogeneic T cell infusion in bone marrow transplant setting. Examination of the lungs after 2 months showed histological evidence of BO with extensive perivascular and peribronchiolar inflammation consistent with donor CD4+ and CD8+ T cells, B cells, macrophages, neutrophils and fibroblasts. At the same time, features of GVHD in the skin, liver and colon were mild to moderate.[54] These immune mechanisms are thought to trigger inflammatory reactions that lead to BO. These inflammatory reactions are characterized by an increase in cytokines, such as IL-1, IL-6, IL-8, IL-18 and TNF-α.[55,56]

BO is a late complication of allogeneic HSCT and usually presents after the first 100 days following transplantation.[38,41,57-61] Although there are reports of BO as early as 30 days following HSCT, 80% of cases present between 6 and 12 months post-transplantation.[47,62] The presentation of BO is usually insidious. In total, 23% of patients describe antecedent upper respiratory tract symptoms.[58] The main symptoms associated with BO are dry cough (60-100%) and dyspnea (50-70%).[39, 47,58,63] Wheezing and sinusitis are other frequent symptoms. Fever is rare unless there is a concomitant infectious process. Approximately 20% of patients are asymptomatic and the diagnosis is suspected based on pulmonary function test findings.[58] In the advanced stages of BO, the 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 and colonization of the airways by *Pseudomonas* spp., *Staphylococcus aureus* and, occasionally, *Aspergillus* species.

The clinical course of BO is variable. The majority of patients have a slow progressive AFO, with episodes of acute exacerbation of AFO. In the minority of patients, the AFO progresses rapidly and patients develop respiratory failure within a few months. However, some patients may have stabilization or even improvement in the AFO.[64,65]

In the early stages of BO, the chest radiograph is normal. The presence of parenchymal changes suggests

an infection or an unrelated process. As BO becomes more advanced, there are signs of hyperinflation on the chest radiograph and, later, there are changes consistent with bronchiectasis with dilated and thickened bronchi and areas of scarring. Pneumothorax, pneumomediastinum, and pneumopericardium may develop in advanced cases, and are usually associated with significant morbidity and mortality.[38,66,67] High-resolution computed tomography (HRCT) of the chest is much more sensitive in detecting signs of BO and is the radiological procedure of choice in evaluating these patients.[68,69] While the study may still be normal in the early stages of BO, it usually shows signs of hyperinflation with areas of decreased attenuation. Bronchiectasis is seen in advanced cases. However, the most common radiological sign of BO on HRCT 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. This "mosaic" appearance is highly suggestive of BO, and has sensitivity and specificity in the diagnosis of BO with ranges between 74-91% and 67-94%, respectively.[70,71] (Figure 3) In addition, HRCT of the chest is helpful in excluding co-existing conditions such as infections, bronchiolitis obliterans organizing pneumonia (BOOP), or idiopathic pneumonia syndrome that are usually associated with parenchymal infiltrates.[65] In summary, it is recommended that a HRCT of the chest with inspiratory and expiratory views be performed on all patients under evaluation for BO following HSCT.

Spirometry is the main study used to diagnose and follow-up patients with BO following HSCT. Spirometry usually shows evidence of new AFO with reduction in forced expiratory volume in the first second (FEV1) and FEV1 to forced vital capacity (FVC) ratio (FEV1/FVC). However, there has been a lack of consensus on the spirometric criteria for the diagnosis of BO following HSCT. Recently, the National Institutes of Health (NIH) sponsored a consensus development project for clinical trials on chronic GVHD.[72] The workshop considered BO as the only diagnostic manifestation of chronic GVHD in the lung, and suggested that the diagnosis of BO is made when: 1) there is evidence of AFO with FEV1/FVC <0.7 and FEV1 <75% of predicted; 2) there is evidence of air trapping or small airway thickening or bronchiectasis on HRCT of the chest with inspiratory and expiratory cuts, residual volume on PFT >120% of predicted or pathological confirmation of constrictive bronchiolitis; and 3) absence of infection in the respiratory tract documented by clinical
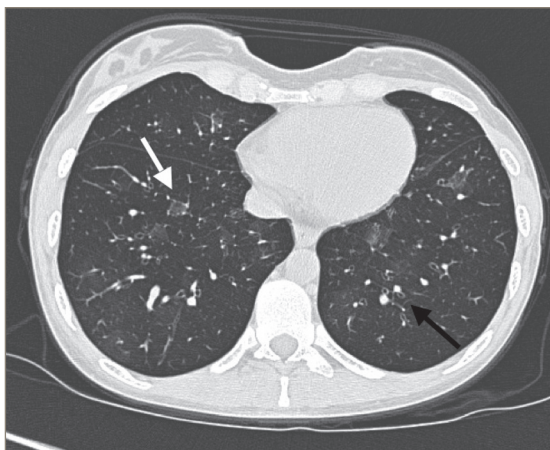

Figure 3. High resolution chest CT image showing hyperinflation with patchy ground glass areas (white arrow) and mild bronchiestasis (black arrow) consistent with bronchiolitis obliterans.

symptoms, radiological studies or microbiological cultures, obtained by sinus aspirate, upper respiratory tract viral screen, sputum culture or BAL.[72] Table 2 proposes diagnostic criteria of BO following HSCT that are based on clinical features, radiological and spirometric studies, and absence of infectious processes.[73]

Bronchoscopy has a limited role in the diagnosis of BO following HSCT. BAL is mainly carried out to rule out an infectious process in HSCT recipients who present with respiratory symptoms suggestive of BO. This is especially the case when there are infiltrates on chest radiograph or HRCT of the chest, or in the presence of fever. The main infections to be considered in this setting, and in which BAL may be useful, are viral infections such as cytomegalovirus (CMV), respiratory syncytial virus, influenza, parainfluenza, or herpes simplex virus. In addition, fungal infections and *Pneumocystis jiroveci* need to be considered if the patient is on systemic corticosteroids and/or immunosuppressive therapy.[74] BAL has also been studied to evaluate the cellular and chemical profile in patients with BO following HSCT.

Transbronchial biopsy is generally not recommended for the diagnosis of BO following HSCT. This is due to the fact that the disease is patchy and peripheral, and the biopsy samples obtained by this procedure are usually too small to show bronchiolar pathology. If histological confirmation of BO is necessary, then the best approach is a surgical lung biopsy obtained by video-assisted thoracoscopy. However, this procedure is rarely indicated for the diagnosis of BO following HSCT in clinical practice. Yousem[52] reviewed the histological findings of lung biopsies in 17 HSCT patients with GVHD-related pulmonary disease. Five patients had

Table 2. Suggested diagnostic criteria of BO following HSCT.

1.	Allogeneic HSCT
2.	Chronic GVHD
3.	Insidious onset of dyspnea, cough and wheezing usually after 100 days following transplantation
4.	Normal chest radiograph
5.	HRCT of the chest (with inspiratory and expiratory views) showing areas of air trapping on expiratory views (mosaic pattern), hyperinflation, micronodular changes, or bronchial dilatation, with no parenchymal involvement.
6.	PFT showing new onset of airflow obstruction (FEV1/FVC <0.7 and FEV1 <75% of predicted), not responsive to bronchodilators
7.	Exclusion of an infectious process by appropriate radiological, serological and microbiological studies (obtained by sinus aspirate, upper respiratory tract viral screen, sputum culture or BAL).

Table 3. Suggested approach to the management of BO following HSCT.

1.	Confirm the diagnosis of BO- (see Table 2)
2.	Systemic corticosteroids (Prednisone 1-1.5 mg/kg/day). Taper gradually over 6-12 months
3.	Immunosuppressive therapy (such as cyclosporine A or tacrolimus)
4.	Maintenance macrolide treatment
5.	Inhaled bronchodilators
6.	Prophylactic therapy against P jiroveci, fungi and CMV
7.	Anti-reflux measures
8.	Consider inhaled corticosteroids
9.	Consider extracorporeal photodynamic therapy
10.	Consider intravenous immunoglobulins
11.	In advanced cases: - long term oxygen therapy - outpatient pulmonary rehabilitation - consider lung transplantation

BO, and the biopsies showed cicatricial BO, in which the lumens of airways were obliterated by dense fibrous scar tissue. Some of these airways displayed eccentric subepithelial fibrous plagues. The epithelial cells were flattened at some locations, while other sites displayed metaplasia or hyperplasia. There was peribronchiolar mononuclear cellular inflammation, but no alveolar or interstitial involvement. The author's theory on the sequence of events leading to BO in these patients is that infiltration of the submucosa of the smaller airways by lymphocytes occurs. These cells migrate through the basement membrane of respiratory epithelium lead-

ing to epithelial cell necrosis and areas of ulceration. Myofibroblasts then grow through these denuded areas and deposit young collagen, creating intraluminal granulation tissue and scarring.

In general, the management of BO is difficult as the pathogenesis is incompletely understood and "treatment" does not result in reversible improvement of lung function. Goals of therapy may be directed towards stabilization at best. The treatment approaches are based on small uncontrolled trials and expert opinions. However, in general, the management of BO is similar to that of chronic GVHD and consists of high dose systemic corticosteroids and reinstitution or augmentation of immunosuppressive therapy. Systemic corticosteroids are suggested in the form of prednisone at 1-1.5 mg/ kg daily (up to 100 mg/day) for 2-6 weeks. If there is clinical and physiological stabilization, the dose is tapered every 2 weeks over 3-12 months. This regimen is based on expert opinions and small case series rather than controlled trials.[39,57,58,60,75-78] The immunosuppressive agents used are similar to those used in the treatment of chronic GVHD, namely cyclosporine A or tacrolimus.[39,60,61,65,75] It is possible that early treatment may prevent the progression of AFO.[31] Conversely, it was observed that the rapid taper of cyclosporine A (for prophylaxis against GVHD) was associated with increased late noninfectious pulmonary complications, including BO.[79] This treatment regimen is recommended for 3-12 months; however, some studies suggest that further improvement is unlikely after 9 months of treatment.[75] Also, intravenous immunoglobulins have been given to patients with BO, with no proven benefit.[80] Based on the experience using macrolides in the treatment of diffuse panbronchiolitis, cystic fibrosis and treatment of BO following lung transplantation, this class of medications is increasingly considered in the management of BO following HSCT.[81-84] Macrolides apparently downregulate pro-inflammatory cytokines, such as TNF-α, so they may decrease the inflammatory reaction that leads to BO.[85] In a report of eight patients with BO, azithromycin was added at a dose of 250 mg three times a week for 12 weeks, and the authors reported an average of 281 mL (20.5%) improvement in FEV1.[86] However, the value and long-term risk of adding such agents to the treatment regimen of patients with BO following HSCT is still not known, and it appears that the response to this treatment is variable.

There are reports on the addition of inhaled corticosteroids to the standard immunosuppressive regimen in the management of BO following lung transplantation.[87,88] This led some investigators to use high-dose inhaled corticosteroids in the management of patients with

BO following HSCT. A recent retrospective analysis by Bashoura et al[89] described a series of 17 adult patients to evaluate the efficacy of high-dose inhaled corticosteroids in the treatment of BO following HSCT. All patients received inhaled fluticasone propionate 500-940 mcg two times daily. Symptoms of airway obstruction improved and FEV1 stabilized 3-6 months after treatment. The authors concluded that high-dose inhaled corticosteroids may be effective in the treatment of BO. A prospective evaluation of this therapy is warranted. There are also limited studies on the combination of inhaled corticosteroids and long-acting B2 agonist in patients with BO following HSCT. Patients should be treated with short-acting bronchodilators if they are symptomatic and during acute exacerbations of respiratory symptoms; however, most of the studies show that the reversibility in AFO with these agents is negligible.[57,58,62]

Extracorporeal photodynamic (ECP) therapy is another immunotherapeutic modality that has been used in the treatment of chronic GVHD and BO. This therapy is commonly used in the management of cutaneous T-cell lymphoma, scleroderma and other autoimmune disorders. It involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen, by exposure to ultraviolet A light, followed by re-infusion of the treated cells.[90] It is believed that the photoactivated 8-methoxypsoralen binds to DNA, leading to initiation of apoptosis, and that it has a selective effect on autoreactive T cells.[91] These observations led to the use of ECP in the management of refractory acute and chronic GVHD. Several studies reported improvement in skin, mucus membrane, liver and pulmonary GVHD, resulting in fewer symptoms and tapering or discontinuation of immunosuppressive therapy.[92] The role of ECP in the management of BO following HSCT has not been well studied. The benefits are limited to case reports or small numbers of cases in small trials.[93,94]

There are a few reports that suggest treating BO using anti-TNF-α monoclonal antibodies (such as infliximab);[95] however, there are no adequate data on the effectiveness of this therapy. A recent case report highlighted the use of Imatinib mesylate 400 mg/day in a patient with CML who developed BO following HSCT. The authors reported improvement in pulmonary symptoms during the first 1 to 2 months of imatinib treatment, with gradual elimination of the need for oxygen, a return to normal ambulation, and considerable improvement in exercise tolerance.[96] Other agents that are used for treatment of skin and intestinal manifestations of chronic GVHD such as alefacept, dacluzimab, or rituximab may play a role in stabilizing BO

following HSCT, although these agents have not been specifically investigated for this purpose.[97,98]

Supportive treatment is essential in the management of patients with BO following HSCT. Infectious processes should be excluded prior to starting immunosuppressive therapy. Once treatment is started, patients should be maintained on appropriate prophylactic measures against *P jiroveci*. Prophylaxis against fungi and CMV should be considered in high-risk patients. In addition, appropriate vaccinations including against influenza and pneumococcus are recommended. Prompt treatment of pulmonary infections is essential, since these tend to worsen the course and outcome of BO. Patients with advanced BO may require long-term oxygen therapy and may benefit from outpatient pulmonary rehabilitation. There are a few reports of lung transplantation in patients with advanced BO with encouraging results.[99] Table 3 summarizes a management approach to patients with BO following HSCT.[73]

BO following HSCT is a progressive disease that leads, in the majority of patients, to irreversible AFO. The decline in lung function is usually slow over several months to years. During this course there may be exacerbations that are associated with temporary worsening of the lung function. Some patients may have a rapidly progressive AFO that leads to respiratory failure. Aggressive therapy results in improvement of lung function in only 8-20% of patients.[33,46,75,100] The best expectations in the management of patients with BO are to stabilize and prevent further drops in FEV1. The attributable mortality of BO following HSCT was, in one large study, 9% at 3 years, 12% at 5 years, and 18% at 10 years.[40] While the attributable mortality, in those with associated chronic GVHD was 22% at 3 years, 27% at 5 years, and 40% at 10 years.[40] Patients with advanced BO usually die from pneumonia.[60,75,76] Factors that are associated with increased mortality related to BO following HSCT include rapid deterioration of FEV1 (more than 10% annually), age >60years, progressive chronic GVHD, underlying disease relapse, and history of respiratory viral infection.[32,40,47] In addition, the prognosis of BO is worse if the patients do not respond to the primary treatment regimen.[21] The prognosis of BO appears not to be influenced by the presence of AFO prior to transplantation, the source of stem cells, degree of matching, CMV serologic status, or type of GVHD prophylaxis.[40]

Bronchiolitis obliterans organizing pneumonia

Bronchiolitis obliterans organizing pneumonia is a specific inflammatory condition that develops following HSCT. The term bronchiolitis obliterans organiz-

ing pneumonia (BOOP) following HSCT is commonly confused with bronchiolitis obliterans (BO). However these are two different entities with characteristic clinical, radiological and pathological findings. Table 4 summarizes the characteristics of BO and BOOP following HSCT.[101] BOOP has been described following autologous and allogeneic HSCT, although more frequently following the later. The incidence following allogeneic HSCT ranges between 0.9-10.3%.[79,102] In the largest series of histologically proven BOOP, the incidence following allogeneic HSCT was 0.9%.[102] Predictors of the development of BOOP were primary diagnosis of leukemia, radiation containing preparative regimens and the presence of acute and chronic GVHD. The strong association between BOOP and acute and chronic GVHD suggests that the donor T-cell mediated immune response against the recipient lung tissue may play a role in the pathogenesis of BOOP in these patients. Strategies to deplete T- cells may prevent BOOP in allogeneic HSCT recipients.[53] BOOP following autologous HSCT is rare and may be related to infections or medications.

BOOP usually develops earlier than BO following HSCT. The onset of BOOP ranged from 5-2800 days, with a median of 108 days in one study.[102] The clinical presentation is usually acute or subacute with 2 weeks of fever, nonproductive cough, and dyspnea. There are rales and occasionally inspiratory squeak on physical examination. Radiologically, there are patchy (multifocal, diffuse or focal) consolidations that tend to be peripheral and/or peribronchovascular. In addi-

tion, there may be ground glass opacities or nodular lesions.[102] Pulmonary function tests typically show mild to moderate restrictive pattern and characteristically low diffusing capacity. Usually there is no airflow obstruction. Bronchoscopy is very useful in patients with BOOP to exclude other conditions such as infections. BAL fluid reveals lymphocytosis with low CD4/CD8 ratio.[103] Histological confirmation is usually necessary, and can be made by transbronchial biopsies, however most patients require surgical lung biopsy by video-assisted thoracoscopy. Pathologically, BOOP 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 and are associated with chronic interstitial inflammation. Contrary to BO, patients with BOOP following HSCT have more favorable response to systemic corticosteroid therapy with initial dose of prednisone 1mg/kg daily then tapered over 3-6 months.[102] In 78% of patients, BOOP either resolves or remains stable. Patients who progress on corticosteroids therapy usually die of respiratory failure.[102] The case fatality of BOOP following HSCT has been reported to be 19%.[104]

Other non-infectious pulmonary complications

Pulmonary veno-occlusive disease
Pulmonary veno-occlusive disease is a rare complication after both autologous and allogeneic HSCT.[105,106] This process is characterized by intimal proliferation and fi-

Table 4. Comparison between bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia.

Features	Bronchiolitis obliterans	BOOP
Incidence	0-48%	<2%
HSCT	Allogeneic	Allogeneic and autologous
Onset following HSCT	Late (around 1 year)	Usually in the first 100 days
Clinical presentation	Insidious; dyspnea, cough, wheezing	Acute; dyspnea, cough, fever
Radiological findings	Normal; hyperinflation, air trapping, bronchiectasis	Patchy consolidation (usually peripheral), ground glass attenuation, nodular opacities
Pulmonary function test	Obstructive; normal diffusing capacity	Restrictive; reduction in diffusing capacity
BAL	Predominantly neutrophils	Predominantly lymphocytes
Diagnosis	Clinical, radiological and physiological criteria	Usually requires tissue, best by surgical lung biopsy
Histolopathology	Granular plugs obliterating the bronchiols with inflammation and scarring; sparing of the alveoli and alveolar ducts	Granular plugs of bronchiols, extending to alveoli; interstitial inflammation and fibrosis
Treatment	Corticosteroids and immunosuppressive therapy	Corticosteroids
Outcome	Poor response to therapy; progressive disease with high mortality	Good response to therapy; potentially reversible

brosis of the pulmonary venules and small veins, leading to progressive vascular obstruction and increased pulmonary capillary and arterial pressures. Patients typically present several months after transplantation with progressive dyspnea on exertion and fatigue. The triad of pulmonary arterial hypertension, radiographic signs of pulmonary edema, and a normal pulmonary artery occlusion pressure strongly suggests the diagnosis, but it may not be present concurrently in all patients.[107] Surgical lung biopsy is the only way to confirm the diagnosis of pulmonary veno-occlusive disease.[107] Because pulmonary veno-occlusive disease has been reported in non-transplant patients who have received radiation and chemotherapy and in patients with viral infections, it has been hypothesized that its occurrence after HSCT is a result of an infectious or toxic injury to the endothelium. Chemotherapeutic agents such as BCNU, mitomycin C, and bleomycin have been associated with this process.[108]

Arterial vasodilatation in the setting of fixed pulmonary venous resistance can markedly increase transcapillary hydrostatic pressure and precipitate or worsen pulmonary edema. Treatment of pulmonary veno-occlusive disease with vasodilators is therefore potentially dangerous and must be initiated under close observation. Response to high-dose corticosteroid therapy has been anecdotally reported.[106] The prognosis of patients with pulmonary veno-occlusive disease is generally poor.

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder is an infrequent but serious complication following allogeneic HSCT. It represents an uncontrolled expansion of donor-derived, EBV-infected B lymphocytes as the result of weakened cytotoxic T cell immunity. Major risk factors for development of post-transplant lymphoproliferative disorder include the use of unrelated or HLA-mismatched related donors, T cell-depleted donor stem cells, and anti-thymocyte globulin or monoclonal anti-T cell antibodies for the prevention or treatment of GVHD.[109] Although the overall incidence of post-transplant lymphoproliferative disorder is only 1%, the incidence increases to 8% for those with two risk factors and to 22% for those with three risk factors.[109] The onset of post-transplant lymphoproliferative disorder is typically within the first 6 months and is most often characterized by involvement of lymph nodes, liver, and spleen. Pulmonary involvement occurs in about 20% of cases.[110] Definitive diagnosis requires biopsy but quantitative EBV DNA monitoring by PCR techniques is emerging as a noninvasive diagnostic technique.[111]

Treatment includes the administration of anti-B cell monoclonal antibodies combined with a reduction in the dose of immunosuppressive agents.[110,112] The potential benefits of the infusion of in vitro–generated EBV-specific cytotoxic T cells are under investigation.[112] Survival among HSCT recipients with post-transplant lymphoproliferative disorder is considerably lower than that of solid organ transplant recipients and is particularly poor for those who had received HSCT for hematologic malignancies.[110]

Pulmonary cytolytic thrombi

This is a rare noninfectious pulmonary complication following HSCT. Pulmonary cytolytic thrombi represent pulmonary thrombi associated with infiltration by monocytes from donor and recipient origin in the small and medium pulmonary vessels. This disorder is reported exclusively following allogeneic HSCT in patients with other features of acute or chronic GVHD.[113] The pathogenesis of pulmonary cytolytic thrombi is not known, but it may be a manifestation of GVHD. This condition has been primarily reported in pediatric population, with onset between 8 and 343 days (median 72 days) following HSCT.[114,115] The patients present with fever, cough, chest pain and dyspnea. Chest CT scan reveals multiple peripheral opacities consistent with pulmonary infarcts. Invasive pulmonary fungal infection is a major consideration with these findings; however this infection was never detected in the reported cases. The patients usually respond to intensification of immunosuppressive therapy with clinical improvement in 1-2 weeks and radiological resolution over weeks or months.[116]

Sarcoidosis

There are few reports that have described noncaseating granulomas suggestive of sarcoidosis following HSCT. Some of these reports suggest the possible transmission of sarcoidosis from the donor stem cells to the allogeneic HSCT recipients.[117-119] Another report described 4 patients with sarcoidosis following HSCT (3 autologous and 1 allogeneic HSCT) with no known history of sarcoidosis in the donor.[119] Sarcoidosis in these reports developed following stem cell engraftment a mean of 25 months (range 3-120 months) post HSCT.[117-119] This reaction may be due to an abnormal immunological host response to common antigenic triggers. It is postulated that post HSCT lung environment may promote the development of non-caseating graunlomas by high levels of chemokines such as MCP-1, CCRI, CCR2 and IL-8.[119] The reports of possible increased incidence of sarcoidosis following HSCT underscore the

importance of diagnostic biopsies in HSCT recipients who develop mediastinal lymphadenopathy or pulmonary infiltrates. Symptomatic patients with sarcoidosis following HSCT respond well to corticosteroids and prognosis of these patients is good.[119]

Pulmonary fibrosis

There are patients who develop nonspecific pulmonary fibrosis that does not fit into any of the other non-infectious pulmonary complications following HSCT. Based on the authors' observations, these patients are primarily long term survivors following allogeneic HSCT. They usually have dyspnea on exertion with cough, and develop frequent exacerbations consistent with acute bronchitis or pneumonia. The patients commonly have evidence of chronic GVHD, however it is usually quiescent. Pulmonary function tests usually reveal restrictive pattern with reduction in diffusing capacity. Radiologically, there are fibrotic changes that tend to be in the lower lobes associated with areas of bronchiectasis. The exact etiology of this presentation is not clear, however it could be due to one or more of several factors. It is possible that this syndrome is a late manifestation of pulmonary drug toxicity, or due to chronic GVHD with scleroderma like changes, or due to recurrent aspiration associated with esophageal involvement by GVHD. Other possibilities include late stage of BOOP or IPS, or due to recurrent infections. These patients are usually managed by supportive measure, and may require oxygen therapy and antibiotics when there are acute exacerbations.

Asthma

Asthma and other allergic conditions such as allergic rhinitis may develop in allogeneic HSCT recipients from donors with atopy. This suggests the transfer of marrow-derived immune cells from allergic donors. In one report of HSCT from atopic donors to 5 non-atopic recipients, asthma developed in 4 of these patients following HSCT.[120] New onset of asthma following HSCT should be differentiated from BO, which is much more common in this patient population.

Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis is pulmonary disease characterized by the accumulation of periodic acid-Schiff stain-positive amorphous material in the pulmonary alveolar space. Decreased clearance of the surfactant proteins is considered one of the major causes of pulmonary alveolar proteinosis. Recent evidence suggests that GM-CSF plays a role in the development of pulmonary alveolar proteinosis.[121] There are few reports of acquired pulmonary alveolar proteinosis following HSCT.[122,123] These cases were reported during the period of leukopenia after myeloablative conditioning for HSCT. The patients developed acute respiratory failure with diffuse alveolar pulmonary infiltrates. Prognosis of pulmonary alveolar proteinosis following HSCT is generally poor.[123] The role of interventions such as frequent BAL and administration of aerosolized recombinant GM-CSF to reverse the pulmonary disease in these patients is not known.

In conclusion, pulmonary complications remain an important problem following HSCT. The improved transplant techniques and effective diagnosis and management of infectious complications have increased the significance of non-infectious pulmonary conditions following HSCT. Future efforts should be directed to understanding the mechanisms leading to these complications and developing anti-inflammatory and immunomodulatory therapies that target these pathways.

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