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Non-infectious pulmonary complications of hematopoietic stem cell transplantation

Courtney Rowan[a], Orkun Baloglu[b] and Jennifer McArthur[b,*]
[a]*Department of Pediatrics, Section of Critical Care, Indiana University School of Medicine, Indianapolis, IN, USA*
[b]*Department of Pediatrics, Division of Critical Care Medicine, Medical College of Wisconsin, Milwaukee, WI, USA*

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Abstract. Noninfectious pulmonary complications of hematopoietic stem cell transplant are currently more prevalent than infectious complications. Unfortunately, the pathophysiology basis is not completely understood. However, there is a string association with graft-versus-host disease for many of them. Therefore, an important component of their pathophysiology is likely an allo-immune response. There is much research that needs to be conducted to improve the less than optimal outcomes for these disorders.

Keywords: Hematopoietic cell transplant, pulmonary complications, graft versus host disease

1. Introduction

Non-infectious pulmonary complications of hematopoietic stem cell transplant (HSCT) are poorly understood. The names and classifications of these disorders have evolved over time in the literature, making them sometimes difficult to grasp. This article aims to help bring clarity to the more common of these disorders, with the exception of idiopathic pneumonia syndrome (IPS), which will be discussed in a separate article.

Pulmonary complications of HSCT are common, affecting 5–25% of patients and are an important cause of non-relapse mortality [1–5]. They remain an elusive challenge for the transplant, pulmonary and critical care communities. Outcomes for HSCT patients who develop respiratory failure are much worse than those of the general pediatric population as well as those of non-transplant oncology patients. However, outcomes have demonstrated improvement over the last two decades with the most recent studies reporting survival rates to pediatric intensive care unit discharge as high as 40–58% [6–9] compared to an 88% mortality rate reported in 1995 [10]. It is unclear if these improvements are related to advancements in critical care management, selection of more suitable candidates for intensive care unit care or advancements in transplant medicine, or some combination [11, 12]. An important aspect is the shift from infectious complications being the most prominent pulmonary complication (prior to the 1990s) to the current decade in which non-infectious complications have become more frequent [13, 14].

Non-infectious pulmonary complications are often classified as early and late onset. The timing of their occurrence can help develop the differential diagnosis (Fig. 1). Complications more typically observed in the first 100 days after transplant include diffuse alveolar hemorrhage (DAH), peri-engraftment respiratory distress syndrome (PERDS), also known as engraftment syndrome, and pulmonary cytolytic thrombi (PCT) [15]. Bronchiolitis obliterans or bronchiolitis obliterans syndrome (BOS), bronchiolitis

*Corresponding author: Dr. Jennifer McArthur, Medical College of Wisconsin, Department of Pediatrics, Division of Critical Care Medicine MS #681, 9000 West Wisconsin St., Milwaukee, WI 53226, USA. Tel.: +1 414 266 3360; Fax: +1 414 266 3563; E-mail: jmcarthu@mcw.edu.

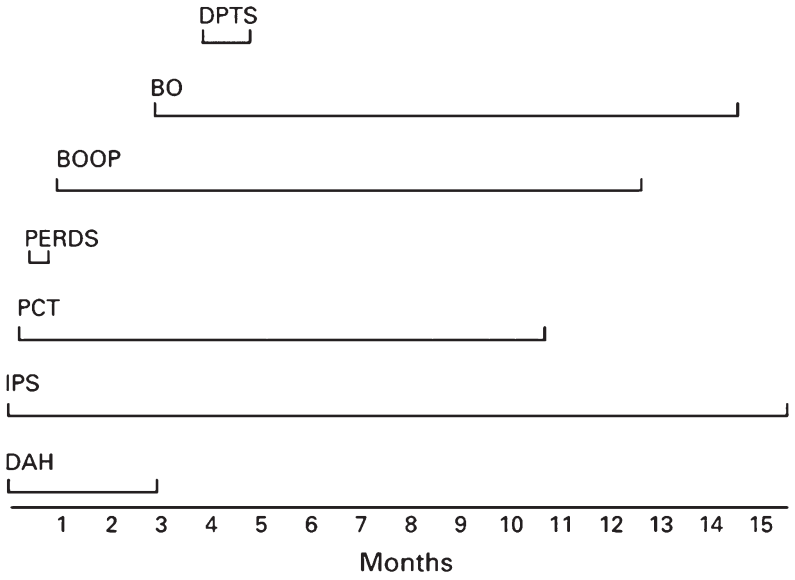

Fig. 1. Approximate time of onset of non-infectious pulmonary complications following hematopoietic stem cell transplant. BO = Bronchiolitis obliterans; BOOP = Bronchiolitis obliterans organizing pneumonia; DAH = Diffuse alveolar hemorrhage; DPTS = Delayed pulmonary toxicity syndrome; IPS = Idiopathic pneumonia syndrome; PERDS = Peri-engraftment respiratory distress syndrome; PCT = Pulmonary cytolytic thrombi (taken from ref. 2).

obliterans organizing pneumonia (BOOP), also known as cryptogenic organizing pneumonia and pulmonary veno-occlusive disease (PVOD) [3, 4, 15, 16], are considered late complications. Less frequently, BOOP may be seen in the first 100 days after transplant. As survival of pediatric cancer has been extended for several decades, we are beginning to gain more insight into the late effects of treatment that may occur. HSCT survivors can develop both obstructive and restrictive lung diseases up to several years after their initial treatment [17].

The classification of IPS can be varied. A recent consensus committee of the American Thoracic Society defined IPS as having evidence of widespread alveolar damage, which is not due to infection, cardiac disease, renal failure or fluid overload [16]. Using this definition, many non-infectious pulmonary complications from HSCT could fulfill the criteria. IPS can be seen both early and late in the transplant course [15]. The term IPS is often used interchangeably with interstitial pneumonia or interstitial pneumonitis [18], it is increasingly thought of as a spectrum disorder that encompasses a myriad of disorders such as interstitial pneumonitis, BOS, BOOP, DAH, PERDS, delayed pulmonary toxicity syndrome and non-cardiogenic capillary leak syndrome [18, 19]. At other times, only a few disorders are lumped under its umbrella such as DAH and PERDS [16] and early in the literature it is often discussed as though it is a single entity.

Another source of controversy in the classification of transplant associated lung disease involves the concept of graft versus host disease (GVHD). In the early 2000s, whether or not the lung could be affected by GVHD was debated in the literature [20]. However, this concept is more widely accepted in the recent literature [21–23]. In fact, BOS, BOOP, DAH, lymphocytic interstitial pneumonia, lymphocytic bronchitis, eosinophilic interstitial pneumonia and non-specific interstitial pneumonia are all considered to be manifestations of GVHD of the lung by some authors [24].

2. Early non-infectious pulmonary complications

2.1. DAH

Alveolar hemorrhage can be a result of pulmonary infections in HSCT patients; however the term DAH is used to describe a non-infectious pulmonary complication in HSCT patients. Alveolar hemorrhage may occur in patients other than HSCT recipients as a result of various disease processes (i.e. rheumatological diseases such as systemic vasculitides), pharmacological agents

(i.e. amiodarone) and infectious agents. However, no clear pathophysiological mechanism has been suggested to explain DAH in HSCT patients. Pulmonary vascular injury, thrombotic microangiopathy formation [25] and inflammatory damage [26] have been suggested as potential causes for DAH. Currently used diagnostic criteria for DAH are 1) the presence of radiological or clinical evidence of widespread alveolar damage, for example multilobar, bilateral, interstitial or alveolar infiltrates that are usually located centrally in middle and lower zones of lung in chest radiographs [27] or hypoxia with increased alveolar-arterial oxygen gradient, 2) the absence of infectious causes for alveolar hemorrhage, 3) progressively increasing bloody return of bronchoalveolar lavage fluid from three separate subsegmental bronchi, the presence of 20% or more hemosiderin-laden macrophages or the presence of blood in at least 30% of the alveolar surface [28, 29].

DAH usually develops within 30 days post-HSCT [28] and coincides with the engraftment of stem cells. Signs of respiratory distress and fever are common clinical findings whereas hemoptysis is an uncommon symptom of DAH in HSCT patients. The incidence of DAH is reported to be about 5% in pediatric HSCT patients [30] and significantly higher in pediatric HSCT patients with an underlying diagnosis of mucopolysaccharide storage disorders [31, 32]. Although initially DAH was thought to be more common in allogeneic HSCT patients than autologous, Afessa et al. [28] did not find any difference in DAH incidence between allogeneic and autologous HSCT patients when they combined all previously reported DAH cases.

Surprisingly, neither low platelet count nor prolonged prothrombin time were associated with DAH and correcting low platelet counts did not seem to improve DAH in one report [29]. Mortality due to DAH in pediatric HSCT patients remains high ranging from 57% [30] to 83% [33]. High dose corticosteroids have been reported to decrease mortality and the need for mechanical ventilation [34]. Despite a lack of concrete evidence for their efficacy, corticosteroids are considered standard of care for DAH within the transplant community. However, more recent studies have not confirmed those findings [35]. Recombinant human factor VIIa has been used in DAH treatment to control bleeding [36], but was not found to improve survival [37]. Similarly, the addition of aminocaproic acid, an antifibrinolytic agent, to a high dose methylprednisolone regimen was reported to be promising in a retrospective study among adult HSCT patients [38]. There is also a reported case of successful use of extracorporeal membrane oxygenation in a pediatric HSCT patient with DAH [39].

2.2. *PERDS*

PERDS is defined as a constellation of symptoms including; fever, diffuse erythematous skin rash, weight gain, non-cardiac pulmonary edema, and pulmonary infiltrates on radiographs, hypoxia, hepatic dysfunction, renal insufficiency and transient encephalopathy [40]. However, there is no consensus about clear diagnostic criteria of PERDS [41, 42]. The incidence of PERDS is reported to range from 17% to 48% [42–45]; however, investigators have used different criteria for PERDS rendering it difficult to ascertain the true incidence. As its name suggests, PERDS occurs around the time of neutrophil engraftment. In one study, PERDS occurred at median of 14 days (range 8–27 days) post-HSCT with a median time to neutrophil recovery >500/mm^3 being 16 days (range 13–26 days) [45]. PERDS is believed to be due to capillary leak resulting from complex interactions between the host's existing immune system and transplanted stem cells. This results in the release of pro-inflammatory cytokines during engraftment and an influx of neutrophils into the lungs and other organs. PERDS can be found in both autologous and allogeneic HSCT patients, but appears to occur more commonly in autologous HSCT patients [45]. Supportive care with supplemental oxygen, mechanical ventilation, close attention to maintaining a stable fluid balance and prophylactic antibiotics are commonly used. PERDS has been found to respond to corticosteroids within 3 days of administration [42, 46]. Survival from PERDS is relatively good, being >90% in recent reports [45]. Overall survival rates after HSCT did not seem to be different in HSCT patients with or without occurrence of PERDS [42, 45].

2.3. *PCT*

PCT is an uncommon and recently recognized noninfectious pulmonary complication. It was first described in 2000 [47] in a small case series with 13 HSCT recipients. Twelve of those patients were younger than 18 yr of age with a median age of 11.9 yr. Nine of those 13 patients survived in this case series [47]. All patients had fever at a median of 72 days

(range, 8–343 days) post-HSCT along with cough in two patients. Pulmonary nodules were described on chest computerized tomography (CT). Pathological examination of those nodules revealed a unique pattern of necrotic, basophilic thromboemboli with amorphous material suggestive of cellular breakdown products. Immunohistochemical staining revealed entrapped leukocytes and disrupted endothelium. Those leukocytes were later identified as monocytes [48].

Infarcted lung parenchyma adjacent to PCTs is frequently noted in biopsies likely secondary to entrapped debris in blood vessels. Chest CT usually reveals bilateral small nodules (few millimeters to 1.2 cm) typically in the peripheral, subpleural and basilar regions. Final diagnosis and differentiation of PCT from other pulmonary nodules in HSCT patients requires pathological examination. Acute and chronic GVHD is more commonly observed in patients who developed PCT as compared to those without PCT [49]. Interestingly, leukemia patients who receive an HSCT and develop PCT are at lower risk of relapse [49]. PCT is reported to be responsive to intravenous methylprednisolone and cyclosporine within 1-2 wk with clinical improvement and near complete radiological resolution of pulmonary nodules [47, 50].

3. Non-infectious pulmonary complications after 100 days

3.1. BOS and chronic GVHD of the lung

The occurrence of chronic GVHD of the lung has been a debatable entity [18]. It is now believed to exist, although it is still not well understood. In 2005, an NIH consensus paper defined criteria for the diagnosis of chronic GVHD of the lung. Chronic GVHD of the lung was defined as either 1) biopsy proven BOS or 2) BOS diagnosed by typical pulmonary function test (PFT) and radiologic findings associated with chronic GVHD at another site. Typical PFT findings include forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC) ratio <0.7 and an FEV1 <75% predicted. CT findings include air trapping and small airway thickening or bronchiectasis. High-resolution CT findings with inspiratory and expiratory cuts demonstrate a residual volume >120% predicted [21].

Despite the consensus statement from the NIH, there is discussion in the literature regarding chronic GVHD of the lung being manifest as entities other than just BOS. In a study by Xu et al. [23], lung biopsies in patients with respiratory symptoms and chronic GVHD had significant variation in histology. The appearance of biopsy specimens included acute lung injury, organizing pneumonia and chronic interstitial pneumonia. BOS developed in the group whose biopsy specimen revealed chronic interstitial pneumonia [23]. Other late-onset pulmonary complications hypothesized to be possible alternative manifestations of chronic GVHD include BOOP, IPS, DAH, lymphocytic bronchitis, eosinophilic pneumonia and non-specific interstitial pneumonia [3, 24]. Despite the discussion in the literature, chronic GVHD of the lung being manifested as anything other than BOS is not widely accepted within the transplant community.

Table 1
Risk factors for bronchiolitis obliterans syndrome

Risk factors	References
Probable	
Older age of donor	70, 75, 77
Obstructive lung disease prior to hematopoietic stem cell transplant	70, 75
Viral infection, particularly within the first 100 days following transplant	70, 75
Possible	
Busulfan-based conditioning regimen	72, 74
Human leukocyte antigen matching	92
Hypogammaglobulinemia	76, 92
Methotrexate prophylaxis against graft versus host disease	92
Chronic myeloid leukemia	72
Female donor to male donor	60
Interval from leukemia diagnosis to hematopoietic stem cell transplant of greater than 14 mo	60

BOS is a fibrotic disorder of the terminal and respiratory bronchioles that leads to progressive airflow obstruction with a notable absence of parenchymal infiltrates on chest radiograph and poor response to therapy [51–54]. It was first described in 1978 [55] when lymphocytic bronchitis was reported in 10% of HSCT lung biopsies. While it has been reported to be the most common, late pulmonary complication of HSCT [56], the incidence in the literature varies ranging from 2–26% likely due to the lack of a consistent definition [56–59]. In one review of 2152 allogeneic HSCT recipients, BOS was reported to occur in 8.3% of the cohort [15]. Another investigation of 1131 allogeneic HSCT patients noted a general incidence of BOS of 26% with this number increasing to 32%

in the presence of chronic GVHD [56]. In contrast, a review of the International Bone Marrow Transplantation Registry noted an incidence of only 1.7% at 2 yr after transplantation in matched sibling transplants [60].

Risk factors for the development of chronic GVHD of the lung include peripheral blood stem cell source [61], busulfan use during conditioning, hypogammaglobulinemia, an unrelated donor source, and the use of methotrexate for GVHD prophylaxis. Alam et al. [61] reported that the risk of developing chronic GVHD of the lung was 40% at 2 yr for patients who received matched unrelated donor transplants with peripheral blood as the stem cell source. In comparison, patients who received matched related donor transplants with bone marrow as the stem cell source only had an 11.9% risk of developing chronic GVHD of the lung.

Chronic GVHD at any site has been described as a significant risk factor for the development of late-onset pulmonary complications in several studies. Eikenberry et al. [1] reviewed charts from 363 children who received an allogeneic stem cell transplant over a 5 yr period. Ninety (25%) of these children developed pulmonary complications. He found that patients with grade III-IV GVHD had two times the risk of developing pulmonary complication [1]. Nishio et al. [3] found an association between chronic GVHD and development of late onset non-infectious pulmonary complications in a cohort of 97 allogeneic pediatric stem cell transplant patients. Several others have reported similar findings [4, 63, 64].

Numerous risk factors for BOS have been explored (Table 1). One consistent risk factor is allogeneic transplant; it typically does not develop post autologous transplant with only a few cases reported [65–67]. It is exceedingly rare post umbilical cord blood transplant with only a few biopsy proven case reports [68, 69]. The most important risk factor identified for BOS is GVHD at any site, especially if it is chronic and progressing [70–75]. One study found the prevalence of BOS to be 6% in allogeneic transplants with chronic GVHD [76]. In another report, 81% of all BOS patients were found to have GVHD at another site [77].

The pathophysiology of BOS is not completely elucidated, but there is accumulating evidence that suggests a T-cell mediated recognition of alloantigens in lung tissue is responsible for the underlying process. One piece of evidence supporting this theory is a decreased frequency of BOS in patients who receive T-cell depleted grafts [78]. The lung epithelium is likely the site of immune mediated-injury induced by donor cytotoxic T cells in GVHD [76]. The lymphocytes infiltrate the blood vessels and small airways leading to epithelial cell necrosis. This necrosis releases inflammatory mediators causing migration of fibroblasts, smooth muscle proliferation, and finally collagen and fibrous deposition in the lumen of the airways [79].

There are several proposed mechanisms for the development of BOS. The most important mechanisms is likely the alloreactive immune process described above where the donor T cell lymphocytes target the epithelial cells of the bronchioles leading to the inflammatory reaction observed in BOS. As a result, some suggest that BOS is simply a continuum of GVHD [80]. A number of potential precipitants of the lung injury observed in BOS have been identified. The conditioning regimen has been suggested due to the higher incidence of BOS in those treated with busulfan-based conditioning regimens [72, 74] and the lower incidence in those receiving a non-myeloablative HSCT [81]. There is also evidence that the development of BOS is related to infections with risk factors of hypogammaglobulinemia, associated viral infection, and impaired mucocilliary clearance noted in chronic GVHD leading to recurrent bronchial infections [82]. Another association with GVHD is the related esophagitis that may result in recurrent aspiration causing lung irritation and inflammation. This association has been linked with BOS following lung transplantation [83–85]. Additionally, BOS may be the end result following acute lung injury in the HSCT recipient [86]. In sum, it is likely that BOS is the result of a multitude of factors, perhaps in combination, including chemotherapy, infection, and an alloreactive immune reaction.

In an effort to establish a formal definition for BOS, the NIH released a consensus statement in 2005 with a proposed amendment in 2009 (Table 2). As BOS is traditionally a clinical diagnosis, there have been suggested diagnostic criteria including: allogeneic HSCT, chronic GVHD, insidious onset of respiratory symptoms (dyspnea, cough, wheezing) greater than 100 days following transplant, exclusion of an infectious process, PFTs demonstrating new airflow obstruction, a normal chest radiograph, and a high resolution chest CT with areas of air trapping, hyperinflation, and/or bronchial dilation with no parenchymal involvement [87].

Clinically, the majority (80%) of patients with BOS present between 6 and 12 mo following HSCT [76, 88,

Table 2
Consensus definition of bronchiolitis obliterans syndrome

National Institutes of Health consensus definition 2005 [44]	Proposed National Institutes of Health amended 2009 [126]
No active infection	Same
Another chronic graft versus host disease manifestation	Same
Forced expiratory volume in 1 sec <75% predicted	Forced expiratory volume in 1 sec <75% predicted or decline >10%
Forced expiratory volume in 1 sec/forced expiratory vital capacity <0.70	Forced expiratory volume in 1 sec/forced expiratory vital capacity <0.7 or residual volume or residual volume/total lung capacity >120% and computerized tomography findings of air trapping or bronchiectasis
Residual volume >120%	
Computerized tomography findings of air trapping or bronchiectasis	

89]. Initial symptoms may include a dry cough, wheezing, sinusitis, and dyspnea, particularly on exertion [19, 90]. On physical exam, the patient may exhibit signs of hyperinflation, decreased breath sounds and evidence of GVHD. While patients are typically afebrile without evidence of active infection, patients may have a history of recurrent respiratory tract infections and airway colonization with pseudomonas, staphylococcus and aspergillus. Several diagnostic studies, including radiologic, tissue biopsy and PFT can be used to support the diagnosis of BOS (Table 3). For example, the findings of fibrin deposition obliterating the lumen of the bronchioles on lung biopsy can aid in the diagnosis. Further lung biopsy discoveries and additional study findings are summarized in Table 3.

Serial PFTs may be used to aid in making an earlier diagnosis of obstructive lung disease. Chien et al. [91] found that abnormalities seen on pre transplant PFTs were associated with an increased risk of developing pulmonary complications after transplant. Their group recommends that all patients undergo PFTs prior to HSCT both as a screening tool for future pulmonary complications as well as to have baseline PFTs in the event the patients develop respiratory symptoms after transplant. Patients who have abnormalities seen on pre-transplant PFTs would be followed with serial PFTs even if they are asymptomatic. This has become standard practice at many pediatric transplant centers.

Treatment for BOS is based on small, uncontrolled trials and expert opinion. Many of the therapies used are similar to GVHD. First line therapy has remained systemic corticosteroids with an initial burst and a prolonged taper over 6–12 mo [15, 77, 92–94]. Inhaled corticosteroids have exhibited only minor success [9]. Immunosuppressive therapy has also been traditionally accomplished with cyclosporine or tacrolimus [15, 73, 77], but azathioprine has been used successfully [73, 77, 92]. Second line treatments such as azithromycin [71] and tumor necrosis factor-alpha inhibitors [95, 96] have had some success in small studies. There have been small studies that suggest the combined use of fluticasone, azithromycin and montelukast, known as

Table 3
Summary of diagnostic study findings in bronchiolitis obliterans syndrome

Studies	Findings
Chest radiograph	Initially normal, but then can progress to bronchiectasis, with dilated thickened bronchi
Chest computerized tomography	Hyperinflation, air trapping, bronchiectasis, areas of hypoattenuation with obstruction, ground glass appearance of patent airways
Bronchoscopy	Little value in the diagnosis except to exclude infection. Bronchial alveolar lavage may demonstrate higher levels of tumor necrosis factor-alpha [126]
Pulmonary function tests	Airflow obstruction with decreased forced expiratory volume in 1 sec and forced expiratory volume in 1 sec/forced expiratory vital capacity, a 20% decrease from baseline in forced expiratory volume in 1 sec, a lack of improvement in forced expiratory volume in 1 sec with a bronchodilator [54, 88, 92]
Lung biopsy	Bronchiolitis of the small airways, fibrin deposition obliterating the lumen of the bronchioles; polymophonuclear leukocytes and mononuclear cells are present early. As the bronchiolitis obliterans syndrome progresses, there is variable degree of intraluminal and peribronchiolar fibrosis [127, 128]. This fibrosis leads to scaring creating new and worsening airflow obstruction

FAM, can be used to minimize corticosteroid exposure without compromising lung function based on PFT results [97]. Extracorporeal photopheresis has demonstrated mixed results [98, 99], while intravenous immunoglobulin has been found to not be effective [100].

The reported mortality rate is highly variable ranging from 14–100% with a median of 65% [19, 65, 73, 76, 88, 89, 101, 102]. It is well demonstrated to be a progressive disease with irreversible airflow obstruction. At this time, stabilization of the process and prevention of further deterioration in the FEV1 is the best outcome described. The 2 yr survival rate is reported to be approximately 44% while the 5 yr survival rate drops to 13% [56, 70, 77, 88, 92]. Concerning prognostic signs include rapid deterioration of FEV1, underlying active disease at the time of transplant, disease relapse, viral infections, the early development of BOS and a lack of response to the initial treatment for BOS [56, 70, 77, 92].

3.2. BOOP

BOOP, also known as cryptogenic organizing pneumonia, was first described in 1985 [103]. It is a non-infectious disorder that involves the bronchioles, alveolar ducts, and the alveoli. The lumens of the bronchioles and the distal air spaces become filled with granulation tissue consisting of both fibroblasts and connective tissue. There is inflammation, but no fibrosis of the bronchiolar walls [104]. The incidence is reported to be between 1% and 2% [105, 106]. Risk factors for BOOP are similar to BOS in that the majority of cases occur post-allogeneic transplant and in patients with GVHD [105, 106]. A decreased incidence of BOOP following T-cell depleted HSCT has also been noted [78]. Human leukocyte antigen disparity and female gender have been suggested to be associated with an increased incidence of BOOP [59].

The pathophysiology of BOOP is poorly understood. There is some consideration that its development is secondary to an alloimmunologic reaction. Animal studies suggest that there is a role for T-cell and Th1-derived cytokines such as tumor necrosis factor-alpha leading to the inflammatory process observed [107]. Though rare, BOOP has been described in children after autologous HSCT. Therefore, an alloimmunologic reaction may not be the only mechanism involved [108]. Regardless of the precipitating insult, it appears that BOOP is secondary to alveolar epithelial injury [109, 110]. This injury leads to leaking of plasma proteins into the alveolar lumen causing fibroblast recruitment and fibrin formation.

Clinically, patients present acutely with fever, cough, and dyspnea within the first 2–6 mo post-HSCT [111, 112]. The median day of occurrence, while variable, has been found to be 108 days post-transplant [105]. On exam, rales and crackles may be detected. Most patients have bilateral airspace disease with consolidated infiltrates on chest CT. Laboratory work may reveal a moderate leukocytosis with neutrophilia and an elevated C-reactive protein level. Biopsy is usually required to establish the diagnosis. Additional diagnostic studies may aid in the diagnosis of BOOP (Table 4). Also, important to recognize that BOS and BOOP are two very different clinical entities (Table 5). The mainstay of treatment for BOOP remains systemic corticosteroids. Generally, patients are placed on higher treatment doses for several months followed by a prolonged gradual taper, which may take up to a year. However, this prolonged steroid taper has not been found to create a significant difference in outcome or survival [105].

The outcome with BOOP from all causes is generally good particularly if there is a quick response to the steroid therapy. Survival rates have been reported to be between 50–70% [105, 106]. However, BOOP that follows HSCT is not as well defined and likely has a higher mortality than idiopathic BOOP [113, 114]. In one report of BOOP following HSCT, 57% of cases resolved, 21% remained stable, and 22% progressed [105].

3.3. PVOD and pulmonary hypertension

PVOD is a rare complication of HSCT and is a form of pulmonary hypertension. Pulmonary hypertension is defined as an increase in pulmonary vascular resistance with a resulting increase in right ventricular pressure >50% of systemic pressures or >25 mmHg [115, 116].

Pulmonary hypertension has been described in both oncology and HSCT patients, but is incompletely understood. Some cases of pulmonary hypertension reported in the literature have been attributed to PVOD [117], a type of pulmonary arterial hypertension, while others were likely due to chronic lung disease [14]. The incidence of pulmonary hypertension in the HSCT population is unknown given the lack of prospective studies screening for the disorder. However, from avail-

Table 4
Summary of study findings in bronchiolitis obliterans organizing pneumonia

Studies	Findings
Chest imaging	Peripheral airspace consolidation with ground-glass and nodular opacities [111, 112]; consolidation is predominantly subpleural with peribronchovascular distribution in 60% of patients [129]. Bronchiolitis obliterans organizing pneumonia following hematopoietic stem cell transplantation has more ground glass appearance, less areas of consolidation and more frequent pulmonary nodules than immunocompetent patients [129]
Bronchoscopy	Bronchial alveolar lavage demonstrates a lymphocytosis and a decreased CD4/CD8 ratio
Pulmonary function tests	There is no airflow obstruction noted. A restriction defect can be found with forced expiratory vital capacity <80% and/or forced expiratory volume in 1 sec/forced expiratory vital capacity ≥80%
Lung biopsy	Biopsy is usually required to establish the diagnosis [130]. Granulation tissue filling distal airways, alveolar ducts and sacs, foamy macrophages in the alveoli, chronic interstitial inflammation, and widening of the alveolar septa due to infiltration of mononuclear cells [131]

Table 5
Summary comparison of bronchiolitis obliterans syndrome and bronchiolitis obliterans organizing pneumonia

Characteristics	Bronchiolitis obliterans syndrome	Bronchiolitis obliterans organizing pneumonia
Incidence	Highly variable; ranging from 2–10%	1-2%
Pathophysiology	Lymphocyte infiltration of blood vessels and small airways leads to epithelial cell necrosis releasing inflammatory mediators causing migration of fibroblasts, smooth muscle proliferation and finally collagen and fibrous deposition in the lumen of the airways	Secondary to alveolar epithelial injury leading to leaking of plasma proteins into the alveolar lumen causing fibroblast recruitment and fibrin formation
Major risk factors	Allogeneic hematopoietic stem cell transplant, chronic graft versus host disease	Allogeneic hematopoietic stem cell transplant, graft versus host disease
Timing of onset	Later; 6–12 mo post-hematopoietic stem cell transplant	Earlier; 2–6 mo post- hematopoietic stem cell transplant
Clinical findings	Insidious; cough, dyspnea on exertion, afebrile	Acute; cough, dyspnea, fever, rales, crackles
Radiographic findings	Hyperinflation, bronchiectasis, air trapping; ground glass appearance in patent airways	Airspace consolidation with ground glass and pulmonary nodules
Bronchoscopy findings	Not useful	Lymphocytosis, decreased CD4/CD8 ratio
Pulmonary function tests	Obstructive findings	Restrictive findings
Biopsy	Bronchiolitis of small airways; fibrin deposition obliterating the lumen of the bronchioles	Granulation tissue filling distal airways, alveolar ducts and sacs, alveoli with foamy macrophages, chronic interstitial inflammation
Therapy	Systemic corticosteroids and immunosuppressants	Systemic corticosteroids
Outcomes	Poor prognosis; progressive disease	Better prognosis; potentially reversible

able retrospective reports, the incidence varies from 2.4% to 28% [118]. This variability likely reflects differences in the screening and diagnosis of pulmonary hypertension, in the underlying disorder being treated with HSCT, in the conditioning regimens and in the subsequent complications from HSCT. The incidence of PVOD in the general population is estimated at 0.1–0.2 cases per million [119]. The incidence of PVOD as the cause of pulmonary hypertension in the HSCT population is speculative given the limited available data [117].

Pulmonary hypertension has been described in various types of hemolytic anemias [118]. Therefore, it is not surprising that it has been described in HSCT patients with transplant associated - thrombotic microangiopathy [115, 120], a microangiopathic hemolytic anemia [90]. Pulmonary hypertension has also been described in malignant infantile osteopetrosis patients undergoing HSCT [121]. In this case series, five of 12 osteopetrosis patients developed significant pulmonary hypertension, which was fatal in four of the five cases. Fatal pulmonary hypertension has also been described in pediatric patients undergoing HSCT for hemophagocytic lymphohistiocytosis and idiopathic myelofibrosis [122, 123]. Whether or not any of these case reports represent PVOD is unclear, as differentiating PVOD from other causes of pulmonary arterial hypertension is difficult.

The pathophysiology of PVOD in HSCT patients is speculated to involve endothelial cell damage [117,

118]. Histologically, there are similarities between PVOD and hepatic VOD. Therefore, important pathophysiologic mechanisms in hepatic VOD such as nitric oxide dysregulation and plasminogen activator inhibitor-1 up regulation may play a similar important role in PVOD. There is likely a role for a genetic predisposition to PVOD as abnormalities in the bone morphogenetic protein receptor type II have been described in pulmonary hypertension [118] as well as in PVOD [119].

The clinical presentation of PVOD and other forms of pulmonary hypertension is nearly indistinguishable. In the early stages, patients may be asymptomatic. As the disease progresses, patients develop progressive dyspnea, hypoxemia and signs of right heart failure [116–119]. On physical exam, the patients may have peripheral edema, hepatomegaly, jugular venous distention, a loud second heart sound and a holosystolic murmur from tricuspid regurgitation [117, 118]. Clubbing and pleural effusions are more frequent in PVOD than other forms of pulmonary hypertension. Chest radiographic findings in PVOD may demonstrate perihilar pulmonary congestion and enlarged hilar vessels. High-resolution CT may illustrate dilation of the pulmonary arteries, interstitial pulmonary edema, diffuse ground glass opacities, interlobular septal thickening and mediastinal lymphadenopathy [117, 118].

Echocardiogram is most frequently used to evaluate for pulmonary hypertension due to its safety profile. Echocardiographic findings may be normal in early stages of pulmonary hypertension. Therefore, if suspicion remains, serial echocardiograms may need to be performed. Echocardiogram findings of pulmonary hypertension include flattening of the ventricular septum, right atrial dilatation and dilated pulmonary arteries [118]. The echocardiogram cannot differentiate between PVOD and other forms of pulmonary hypertension. Other diagnostic modalities to diagnose pulmonary hypertension include cardiac magnetic resonance imaging, which may demonstrate similar findings as the echocardiogram, but with better definition [118].

Right heart catheterization is the gold standard for diagnosing pulmonary hypertension. Pulmonary artery pressures and cardiac output can be measured and pulmonary vascular resistance can be calculated [118]. If pulmonary hypertension is detected, further testing may be performed to determine whether or not it is responsive to vasodilator therapy. Right heart catheterization requires sedation and carries more risk than echocardiography. Therefore, it is reserved for patients in whom the diagnosis has been challenging or for those who are not responding as expected to therapy [118].

In order to differentiate PVOD from other types of pulmonary hypertension, lung biopsy was previously believed to be essential. However, it has recently been suggested that putting together the clinical picture with diagnostic testing may be sufficient [116, 124]. PFT would be characterized by a normal forced expiratory volume, functional vital capacity, and total lung capacity, but reduced diffusing capacity (carbon monoxide diffusing capacity) <50% predicted [124]. Bronchoalveolar lavage may contain evidence of occult hemorrhage with increased numbers of hemosiderin-laden macrophages [125]. CT will demonstrate patchy ground glass opacities in 83% of cases and thickening of interlobular septal lines in 50% [116]. Mineo et al. [124] demonstrated that the presence of two of three CT findings (i.e. ground glass appearance, septal thickening and mediastinal lymphadenopathy) identified PVOD with 95.5% sensitivity and 89% specificity. Lung biopsy in these patients carries a significant risk. If histology testing is done, the typical appearance of PVOD is that of patchy fibrous intimal proliferation involving the pulmonary venules and small veins with a gradual reduction in the vascular lumen to the eventual complete occlusion of the vessel [124]. Treatment of PVOD is primarily supportive care. Oxygen, anticoagulation, diuretics, avoidance of tobacco and physiologic stress, and immunizations to prevent lung infections are important aspects of treatment [119]. Pulmonary vasodilators used in other types of pulmonary hypertension may be poorly tolerated in PVOD. The increased blood flow caused by the vasodilating agent may cause an increase in transcapillary hydrostatic pressure leading to the development of pulmonary edema. While vasodilators have been beneficial in some patients, fatal pulmonary edema associated with pulmonary vasodilator therapy has been described [117, 119]. If these medications are implemented, patients should be observed closely for signs and symptoms of worsening respiratory distress as an inpatient.

Corticosteroids have been used to combat any inflammatory component of the disease, but without consistent results [117]. Other immunosuppressive agents such as azathioprine and cyclophosphamide have been tried with limited success [116, 119]. Lung transplantation is currently the only curative option [117, 119]. However, the time to transplant may be

prohibitive with patients dying while awaiting transplant [117]. Defibrotide and N-acetylcysteine, both promising treatments for hepatic VOD, may be useful in PVOD. However, given the small numbers of PVOD patients, evaluation will be difficult [117].

In conclusion, pulmonary complications after HSCT often present insidiously with similar presentations such as increasing work of breathing and a new oxygen requirement. In the early stages, they are often difficult to differentiate. Typically, when these patients arrive in the pediatric intensive care unit, it is difficult to diagnose the specific etiology of respiratory failure. However, increasing clinician's knowledge and awareness of the specific pulmonary complications of HSCT could lead to earlier intervention and improve outcomes for these fragile patients. Improving definitions of these pulmonary complications will aid in our ability to conduct well designed research trials for improving diagnostic capabilities or studying novel therapies.

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