Review

Pulmonary Hypertension after Hematopoietic Stem Cell Transplantation

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ABSTRACT
Pulmonary hypertension (PH) is a potentially fatal complication of hematopoietic stem cell transplantation (HSCT). Given its nonspecific clinical presentation, it is likely that this clinical entity is underdiagnosed after HSCT. Data describing the incidence, risk factors, and etiology of PH in HSCT recipients are minimal. Physicians caring for HSCT recipients should be aware of this severe post-transplant complication because timely diagnosis and treatment may allow improved clinical outcomes. We summarize the pathophysiology, clinical presentation, diagnosis, and management of PH in HSCT recipients.

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INTRODUCTION
Pulmonary hypertension (PH) is an uncommon and potentially fatal condition associated with increased pulmonary vascular resistance and elevated right ventricular pressure. Elevated pulmonary arterial pressures can lead to permanent changes in the pulmonary vasculature, right ventricular failure, and death. The incidence of PH in hematopoietic stem cell transplantation (HSCT) recipients is unknown. The initial symptoms of PH are nonspecific, and diagnosis can be challenging in this complex population. The most commonly reported types of PH in HSCT recipients are pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD), depending on the location of vascular injury. There are no uniform clinical management strategies given the paucity of data describing PH in HSCT recipients. In this review, we summarize the pathophysiology, clinical presentation, available diagnostic tools, and clinical interventions for HSCT recipients with PH.

PH AND HSCT
The first account of PH as a complication of HSCT was published in 1984 by Troussard et al. [1], who reported autopsy findings consistent with PH in a 12-year-old boy who underwent HSCT for acute lymphoblastic leukemia. Including the report from Troussard et al., PH in HSCT recipients has been described in 40 patients and reported in 16 single patient case reports and 7 case series of 2 to 8 patients [1-23]. This paucity of data provides little insight into the etiology, incidence, and risk factors for PH after HSCT but offers opportunity for further investigation and development of screening strategies and treatment approaches.

In reported cases, 55% of patients had underlying diagnosis of malignancy, 15% immunodeficiencies, and 30% genetic disorders or marrow failure syndromes. PH is described as occurring after myeloablative regimens (73%) as well as reduced-intensity regimens. PH has been reported in both children and adults, with a median age at transplant of 12.6 years (range, 1 month to 51 years), although most reports describe children [1-23]. This may indicate reporting bias, because PH is very infrequent in children, perhaps making authors more likely to report the finding.

All patients who developed PH presented with new-onset respiratory symptoms such as tachypnea, hypoxia, and respiratory distress, and these symptoms occurred a median of 70 days after transplant (range, 0 to 365). In the 40 patients reported in the literature, overall mortality was 55% (22 of 40), with 86% (19/22) of deaths attributed to PH and 14% (3 of 22) to relapse of the primary malignancy [1-23]. Patients had variable pulmonary vasculature involvement. Most patients (28 of 40, 70%) were diagnosed with PAH involving the pulmonary arterioles only, with documented pulmonary arteriolar injury on the tissue specimens and/or increased arterial vascular resistance measured by cardiac catheterization [3,7,10,11,13,14,17,18,21-23]. Nine patients (23%) were reported to have PVOD, with pulmonary venule involvement and vascular congestion only [1,2,4,5,8,12,16,19,20]. Two patients (5%) were diagnosed as having mixed arteriolar-venous pathology, and, finally, 1 patient had no documentation of the vascular component involved [2,6].

Underlying endothelial injury can clearly occur both on the pre- and postpulmonary capillary vasculature. However, further investigation is required to understand the mechanism of endothelial damage. Patients received a variety of therapies for PH, including steroids, anticoagulants, prostacyclines,
inhaled nitric oxide (iNO), phosphodiesterase-5 inhibitors (sildenafil), limiting any conclusions about the effectiveness of clinical interventions [1-23]. Data indicate that both pediatric and adult patients undergoing HSCT are at risk of developing PH, and PH should be considered in patients who develop cardiorespiratory symptoms after transplantation.

Seven case series describing PH after HSCT are summarized in Table 1. The exact incidence of PH in HSCT population remains unknown due to a lack of prospective studies; however, the prevalence of PH was reported in a few retrospective reports. Schechter et al. [23] performed a retrospective analysis of all pediatric patients who underwent serial autologous transplantation for central nervous system tumors between 2001 and 2010. They found PH in 3 of 20 patients (15%), with 2 dying from progressive respiratory disease. Steward et al. [11] described PH occurring in 8 of 29 pediatric patients (28%) with malignant infantile osteopetrosis over a 6-year period of time, suggesting a possible particular susceptibility in children with that diagnosis. Five of the 8 children (62%) with osteopetrosis died from respiratory disease. In a recent pediatric series, Jodele et al. [22] reported a prevalence of PH of 2.4% (5 of 209), with 80% PH-associated mortality. In this report, all patients who developed PH were also diagnosed with transplant-associated thrombotic microangiopathy (TA-TMA), suggesting that endothelial damage due to TA-TMA may play a role in the pathogenesis of PH.

Pulmonary complications after HSCT are common and caused by various etiologies, so PH can be overlooked [24]. PH should be considered in patients who develop respiratory symptoms after HSCT. Prospective studies are needed to determine the incidence of PH as well as associated risk factors and to allow for targeted screening of high-risk cases. Further research to determine the underlying cause and mechanism of endothelial injury in PH will help identify future therapies and prevention strategies.

HEMODYNAMICS OF PH

The main function of the right ventricle is to deliver venous blood to the pulmonary vasculature for oxygen exchange. The right ventricle is sensitive to increased afterload, mainly determined by pulmonary vascular resistance. Excessive and prolonged increase of afterload due to PH impairs right ventricular filling and contractility [25]. Over time, continued pressure overload cannot be sustained by the right ventricle, which leads to decreased elasticity and impaired contractility. Patients may experience repeated acute right-sided heart decompensation and eventually global cardiac dysfunction and death [26].

A mean pulmonary artery pressure of 8 to 20 mm Hg is considered normal, and PH is defined as a mean pulmonary artery pressure >25 mm Hg at rest [27]. Elevation of pulmonary artery pressure can be caused by primary PAH, left-sided heart disease, lung disease, and thromboembolic disease [28]. Table 2 reviews the various hemodynamic definitions of PH that can assist in the diagnosis and underlying etiology.

CLASSIFICATION

In 2008, the 4th World Symposium of Pulmonary Hypertension created consensus general guidelines and a classification of PH, dividing PH into 5 large subtypes [29,30]: PAH, PH from left-sided heart disease, PH due to lung disease, chronic thromboembolic PH, and PH with unclear multifactorial mechanisms (Table 3). The reported cases of PH after HSCT have been classified as PAH, PVOD, and PVOD with pulmonary arterial involvement. In general, PH after HSCT that is not a consequence of heart disease falls into the first category of this classification. The underlying diagnoses for which transplant is performed, for example, myeloproliferative disorders, as well as potential complications from HSCT, such as heart disease and thromboembolism, can give rise to PH of various classifications. In general, PH occurring in older persons as a consequence of these known etiologies is not reported in the HSCT literature, weighting the literature toward younger persons with direct vascular injury specific to HSCT, which is the major focus of this review.

Pulmonary Arterial Hypertension

PAH is defined by a progressive increase of pulmonary arterial vascular resistance leading to right ventricular failure and premature death. Histopathologically, PAH is characterized by vascular proliferation and remodeling of all 3 levels of the vessel wall, with proliferative and obstructive changes including endothelial, smooth muscle cells, and fibroblasts [31]. Pulmonary vasoconstriction is a significant early component in PAH. Early in the disease, PAH might be asymptomatic or may present with very nonspecific symptoms such as exertional dyspnea and fatigue, making early diagnosis in HSCT patients very challenging. If untreated, PAH results in a progressive increase in mean pulmonary artery pressure and pulmonary vascular resistance, leading to right ventricular failure and death [32].

PAH evolves after a trigger, causing pulmonary arteriolar intimal damage later and resulting in hypertrophy through smooth muscle proliferation and fibroblast infiltration. The trigger may also result from an increase in intravascular wall stress and presumed intimal damage [33].

PAH has been reported in nearly all forms of inherited and acquired hemolytic anemias as well as in patients with TA-TMA [4,15,22,34]. In sickle cell and paroxysmal nocturnal hemoglobinuria, the NO pathway is shown to be involved in PH, as decreased synthesis or consumption of NO may lead to increased vasoconstriction [32,35]. PH has also been shown to develop in patients with HSCT-associated-TMA. TA-TMA occurs when endothelial injury, in the context of HSCT, causes microangiopathic hemolytic anemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation and end-organ injury [36,37]. The kidney is most commonly affected, but untreated TA-TMA may evolve into multivisceral disease that also affects the lungs, with associated PAH.

Pulmonary Veno-Occlusive Disease

PVOD is an uncommon entity, with an incidence of .1 to .2 cases per million and was first termed in 1966 as an obliterative disease of the pulmonary veins [38]. PVOD affects the pulmonary venules, with some reports mentioning arteriolar involvement. In the general consensus guidelines, PVOD is listed as a distinct category under PAH [29]. The clinical presentation of PAH and PVOD are the same, and genetic abnormalities in the bone morphogenetic protein receptor type II (BMPR2) defect has been found in both types of PH [39]. Simonneau et al. [40] proposed that both PVOD and PAH may be a different aspect of the same disease and noted that it is not possible to differentiate PVOD from PAH by clinical symptoms alone nor by cardiac catheterization. Ultimately, the diagnosis of PVOD or PH can only be made by lung biopsy to determine the exact vascular compartment.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age at Transplantation</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Conditioning Regimen</th>
<th>HSCT Type</th>
<th>PH Classification</th>
<th>Diagnosis of PH</th>
<th>Symptoms</th>
<th>Diagnosis Modality</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackman et al. [2]</td>
<td>4 yr</td>
<td>F</td>
<td>ALL</td>
<td>MA</td>
<td>MRD × 2</td>
<td>PVOD, arterial involvement</td>
<td>Day +46 of second SCT</td>
<td>Dyspnea</td>
<td>Biopsy</td>
<td>Methylprednisolone</td>
<td>Died from relapsed disease</td>
</tr>
<tr>
<td>Steward et al. [11]</td>
<td>3.5 mo</td>
<td>M</td>
<td>MIO</td>
<td>MA</td>
<td>MRD</td>
<td>PAH</td>
<td>Day +60</td>
<td>Dyspnea</td>
<td>ECHO, Cath</td>
<td>Methylprednisolone, Defibrotide</td>
<td>Died of PH</td>
</tr>
<tr>
<td>1 mo</td>
<td>M</td>
<td>MIO</td>
<td>MA</td>
<td>MMRD</td>
<td>PAH</td>
<td>Day +20</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO</td>
<td>iNO, epoprostenol, nicardipine</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>1.5 mo</td>
<td>F</td>
<td>MIO</td>
<td>MA</td>
<td>MMRD</td>
<td>PAH</td>
<td>Day +49</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO</td>
<td>iNO, surfactant, epoprostenol</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>F</td>
<td>MIO</td>
<td>MA</td>
<td>MUD</td>
<td>PAH</td>
<td>Day +53</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO</td>
<td>iNO, epoprostenol</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>F</td>
<td>MIO</td>
<td>MA</td>
<td>MMRD</td>
<td>PAH</td>
<td>Day +65</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO</td>
<td>iNO</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>8 mo</td>
<td>M</td>
<td>MIO</td>
<td>MA</td>
<td>MMRD</td>
<td>PAH</td>
<td>Day +60</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO, Cath</td>
<td>Deferonitide, epoprostenol</td>
<td>Alive 3 mo later</td>
<td></td>
</tr>
<tr>
<td>8 mo</td>
<td>M</td>
<td>MIO</td>
<td>MA</td>
<td>MMRD</td>
<td>PAH</td>
<td>Day +96</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO, autopsy</td>
<td>Methylprednisolone</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>Limsuwan et al. [14]</td>
<td>15 yr</td>
<td>M</td>
<td>ALL</td>
<td>MA</td>
<td>MRD</td>
<td>PAH</td>
<td>8 mo</td>
<td>Dyspnea, hypoxia, syncope</td>
<td>CT, ECHO, Cath, biopsy</td>
<td>Iloprost, sildenafil, beraprost</td>
<td>Died of PH</td>
</tr>
<tr>
<td>Limsuwan et al. [18]</td>
<td>16 yr</td>
<td>F</td>
<td>CML</td>
<td>MA</td>
<td>MUD</td>
<td>PAH</td>
<td>4 mo</td>
<td>Dyspnea, edema</td>
<td>CT scan, CXR, ECHO, Cath</td>
<td>Beraprost, sildenafil</td>
<td>Died of PH</td>
</tr>
<tr>
<td>20 yr</td>
<td>F</td>
<td>CML</td>
<td>MA</td>
<td>MUD</td>
<td>PAH</td>
<td>8 mo</td>
<td>Syncope, desaturations</td>
<td>ECHO, Cath, biopsy</td>
<td>Beraprost, sildenafil</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>7 mo</td>
<td>F</td>
<td>HLH</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>4 mo</td>
<td>Dyspnea, edema</td>
<td>CT, ECHO, Cath</td>
<td>Iloprost, sildenafil, beraprost</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>F</td>
<td>HLH</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>9 mo</td>
<td>Respiratory distress, respiratory failure</td>
<td>CT, autopsy</td>
<td>None</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>Zeilhofer et al. [21]</td>
<td>4 mo</td>
<td>F</td>
<td>HLH</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>4 mo</td>
<td>Respiratory distress, hypoxia</td>
<td>ECHO, autopsy</td>
<td>iNO</td>
<td>Died of PH</td>
</tr>
<tr>
<td>1.8 yr</td>
<td>M</td>
<td>XLP</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>Day +169</td>
<td>Respiratory distress, respiratory failure</td>
<td>ECHO, autopsy</td>
<td>iNO</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>Jodele et al. [22]</td>
<td>5.8 yr</td>
<td>F</td>
<td>FA</td>
<td>MA</td>
<td>MUD</td>
<td>PAH</td>
<td>Day +79</td>
<td>Hypoxia, respiratory failure</td>
<td>ECHO, Cath</td>
<td>iNO, atrial septostomy</td>
<td>Died of PH</td>
</tr>
<tr>
<td>6 mo</td>
<td>M</td>
<td>HLH</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>Day +208</td>
<td>Hypoxia, respiratory failure</td>
<td>ECHO, autopsy</td>
<td>iNO</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>1.8 yr</td>
<td>M</td>
<td>XLP</td>
<td>RIC</td>
<td>MMUD</td>
<td>PAH</td>
<td>Day +71</td>
<td>Hypoxia, respiratory failure</td>
<td>Autospy</td>
<td>iNO</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>10.4 yr</td>
<td>F</td>
<td>CML</td>
<td>MA</td>
<td>MUD</td>
<td>PAH</td>
<td>Day +250</td>
<td>Hypoxia, respiratory failure</td>
<td>ECHO, biopsy</td>
<td>Sildenafil</td>
<td>Died of PH</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>M</td>
<td>ATRT</td>
<td>MA</td>
<td>SAT</td>
<td>PAH</td>
<td>Day +7 of second SCT</td>
<td>Tachypnea, hypoxia</td>
<td>ECHO, biopsy</td>
<td>None</td>
<td>Died of disease progression</td>
<td></td>
</tr>
<tr>
<td>Schechter et al. [23]</td>
<td>4 mo</td>
<td>F</td>
<td>ATRT</td>
<td>MA</td>
<td>SAT</td>
<td>PAH</td>
<td>Day +5 of 3rd SCT</td>
<td>Respiratory failure</td>
<td>ECHO, biopsy</td>
<td>iNO, steroids</td>
<td>Died of PH</td>
</tr>
<tr>
<td>32 mo</td>
<td>M</td>
<td>Medullo</td>
<td>MA</td>
<td>SAT</td>
<td>PAH</td>
<td>Day 0 of 3rd SCT</td>
<td>Hypoxia, respiratory distress</td>
<td>ECHO, biopsy</td>
<td>iNO</td>
<td>Died of PH</td>
<td></td>
</tr>
</tbody>
</table>

ALL indicates acute lymphoblastic leukemia; ATRT, atypical teratoid rhabdoid tumor; Cath, cardiac catheterization; CML, chronic myeloid leukemia; CXR, chest x-ray; ECHO, echocardiography; HLH, hemophagocytic lymphohistiocytosis; MA, myeloablative regimen; Medullo, medulloblastoma; MIO, malignant infantile osteosarcoma; MMRD, mismatched related donor; MRD, matched related donor; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; NR, not reported; RIC, reduced-intensity conditioning; SAT, sequential autologous transplant; XLP, X-linked lymphoproliferative disorder.
PH is defined as a mean pulmonary artery pressure >25 mm Hg. PH secondary to left-sided heart disease will have increased capillary wedge pressure in comparison with all other clinical groups of PH. Adapted from Bossone et al. [28].

Injured. Clinically, differentiation of the 2 entities (PAH and PVOD) is likely not key, because treatment is similar. One-year mortality reported in the literature in patients with PVOD is as high as 70% [41].

**PH from Left-Sided Heart Disease**

PH caused by left-sided heart disease may occur in some patients, especially those with left-sided heart dysfunction before transplantation [42]. Congestive heart failure may develop from any or a combination of cardiotoxic medications, mitral or aortic stenosis, coronary artery disease, or infectious myocarditis [29]. This type of PH occurs because of an increase in left atrial pressure with pulmonary venous congestion, which creates a passive increase in pulmonary arterial pressure. It is important that patients with suspected PH have a comprehensive cardiac assessment.

**PH Due to Hypoxia and Interstitial Lung Disease**

Patients undergoing HSCT are at risk of developing interstitial pneumonitis, bronchiolitis obliterans, bronchiolitis obliterans with organizing pneumonia, diffuse alveolar damage, and lymphocytic interstitial pneumonia, among others [43]. Development of PH has been associated with bronchiolitis obliterans in lung transplant patients [44]. Long-term hypoxemia can lead to vascular remodeling and angiogenesis, which in turn leads to increased vessel wall proliferation and increased vascular resistance [45].

**PH Due to Miscellaneous Causes**

Type 5 PH encompasses disorders with multifactorial mechanisms, each of which alone are rare but significant, because these patients may present for HSCT and may have PH before the transplantation starts. Patients with myeloproliferative disorders and those who have undergone splenectomy have a higher incidence of PH, although a mechanism for this has not been reported [46,47]. Patients with systemic disorders such as Langerhans cell histiocytosis and sarcoidosis are at high risk of developing PH secondary to chronic inflammation and destruction of the vascular bed [48,49]. Patients with underlying metabolic disorders such as Gaucher disease are at risk of developing PH secondary to glycolipid-laden macrophages infiltrating pulmonary capillaries and causing intimal fibrosis [50].

Steward et al. [11] described PH in 29% of pediatric patients (8 of 28) who underwent HSCT for malignant infantile osteopetrosis. Their report identified 6 patients (75%) who required assisted ventilation and 5 patients (62%) who died from respiratory complications. The underlying etiology of PH in patients with osteopetrosis is not known, but PH should be strongly considered in the differential diagnosis of respiratory distress in children with osteopetrosis after HSCT.

**PATHOLOGICAL FINDINGS IN PH AFTER HSCT**

PH after HSCT has been described as affecting both pulmonary arterioles and venules [6,13,22,51,52]. Histopathological changes found in PAH affect all vascular layers of arterioles, including proliferation of the smooth muscle cells, intimal proliferation, medial hypertrophy, fibrotic changes, adventitial thickening, and perivascular inflammatory infiltrates (Figure 1A) [29,53,54]. Plexogenic lesions can form in patients with chronic PAH (Figure 1B). In patients with TAPVR and PAH, the vascular lesions may show endothelial injury and vascular wall hypertrophy of different age and

### Table 2
**Hemodynamic Definitions of PH**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical Groups of PH</th>
</tr>
</thead>
</table>
| Precapillary PH | Mean pulmonary artery pressure >25 mm Hg and decreased capillary wedge pressure | • PAH  
• PM to lung disease  
• Chronic thromboembolic PH  
• PH with unclear and multifactorial mechanisms |
| Postcapillary PH | Mean pulmonary artery pressure >25 mm Hg and increased capillary wedge pressure | • Left-sided heart disease PH |

### Table 3
**Updated Clinical Classification of PH**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Etiology</th>
</tr>
</thead>
</table>
| 1. PAH | • Due to remodeling of pulmonary arteries and arterioles  
• Increased pulmonary vascular resistance |
| 2. PH due to left-sided heart disease | • Increased pulmonary artery pressure due to left-sided heart disease  
• No increase in pulmonary vascular resistance |
| 3. PH due to lung diseases and/or hypoxia | • PH due to chronic lung disease |
| 4. Chronic thromboembolic PH | • PH due to thromboemboli  
• Unclear etiology |
| 5. PH with unclear multifactorial mechanisms | • Hematological disorders: myeloproliferative disorders, splenectomy  
• Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, vasculitis  
• Metabolic disorders: glycogen storage disease, Gaucher disease |

Consensus general classifications taken from the 4th World Symposium of Pulmonary Hypertension with brief description of etiology [29,30].
severity, often causing vascular microthrombi and interstitial hemorrhages.

Histologically, PVOD is characterized by extensive occlusion of the pulmonary venules with fibrous tissue that evolves into sclerotic occlusion without thrombosis (Figure 1C). Anti-α-actin staining may show involvement of the smooth muscle cells as well as myofibroblasts within the venules [39,54,55].

DIAGNOSIS OF PH
Medical and Family History

Early identification and diagnosis of PH is critical so that timely treatment may be initiated before right-sided heart failure and irreversible cardiac compromise. In HSCT patients, family history might be unrevealing because most risk factors are associated with HSCT therapy or complication in these patients. Questions should be directed to identify relatives with PH or early cardiac disease and detailed thrombophilia history to identify events of deep vein thrombosis or pulmonary emboli.

Differential Diagnosis of Respiratory Symptoms after Transplantation

The most common pulmonary complications after transplantation include infectious pneumonia, acute respiratory distress syndrome, pulmonary edema, diffuse alveolar hemorrhage, heart failure, interstitial pneumonitis, idiopathic pneumonia syndrome, bronchiolitis obliterans, and organizing pneumonia [24,56]. PH is rarely included in the differential diagnosis of respiratory distress post-transplantation and can be easily overlooked. The most common respiratory symptoms reported in patients with PH in the literature are acute hypoxemia (72%), dyspnea (33%), and acute respiratory failure (37%) with no clear underlying cause [3-25]. It is not uncommon that hypoxemia and acute respiratory failure occur after additional stressors such as anesthesia or a septic event, likely inducing acute collapse of already injured pulmonary vessels [3]. It is important to consider PH among other common diagnoses after HSCT in patients with unexplained hypoxemia or respiratory distress, especially in those requiring intensive care, so appropriate diagnostic studies can be initiated [57].

Clinical Symptoms of PH

The initial symptoms of PH, including shortness of breath, fatigue, dizziness, weakness, and hypoxemia, can be vague and difficult to differentiate in the post-transplantation patient. Edema and ascites may develop in later stages from increased venous congestion [29,58]. Patients with advanced disease develop progressive tachypnea and hypoxemia preceding respiratory failure. Unrecognized and untreated PH in HSCT patients is nearly always lethal.

Findings on Physical Examination

Initial findings on physical examination in patients with PH may be subtle. However, with more advanced PH, physical signs become more obvious. Peripheral signs of elevated central venous pressure such as jugular venous distension are well recognized in adult clinical practice but may be overlooked in children. Peripheral, flank, or periorbital edema may be present [32]. Hepatomegaly or ascites are further indications of elevated central venous pressure but may be difficult to differentiate from other causes in patients after HSCT. A parasternal lift and palpable second heart sound component in the second left intercostal space are surface manifestations of an exaggerated second heart sound. These are borne out on auscultation when an exaggerated pulmonic component of the second heart sound may be heard. A holosystolic murmur may be audible in the tricuspid area if tricuspid regurgitation is present, and an
early diastolic decrescendo murmur in the pulmonic area, representative of pulmonary insufficiency, is also occasionally heard. In the face of deteriorating ventricular function, third and fourth sound gallops may also become evident [58]. These findings are representative of both failing systolic function and deteriorating ventricular compliance, when more active atrial contraction becomes necessary to fill the right ventricle and maintain adequate output.

**Chest Radiography**

Up to 90% of patients with advanced PH have abnormal findings on chest x-ray. These findings can include prominence of the pulmonary artery, enlarged hilar vessels, and decreased peripheral vessels. In the early stages of PH, radiological studies may not show any lung abnormalities and vascular changes might be difficult to appreciate [22]. PH should be considered in the differential diagnosis of any HSCT patient with “unexplained” hypoxemia or respiratory distress without obvious radiological lung abnormalities or documented infections [58].

**Electrocardiography**

Electrocardiograms of patients with PH may show evidence of right atrial enlargement or right ventricular hypertrophy with peaked P waves, right axis deviation, excessive electrical forces in the anterior leads, and right bundle branch block pattern. Electrocardiography is sensitive as a tool for diagnosing right ventricular hypertrophy but is not sufficiently specific as a screening tool to rule out PH [59].

**High-Resolution Chest Computed Tomography and Magnetic Resonance Imaging**

Computed tomography (CT) is a useful modality in identifying patients with PH, and high-resolution CT scanners allow for improved resolution, shorter scanning times, and shorter breath holds. Dilation of the pulmonary artery is an important finding in patients with PH and, when detected on CT scan, has a 77.4% sensitivity and 89.6% specificity of detecting PH [60]. High-resolution CT is helpful in identifying patients with pulmonary PVOD and can show interstitial lung edema, diffuse ground-glass opacities with a centrilobular distribution, adenopathy, and septal lines [61]. CT scans can give insight to underlying etiologies of PH such as pulmonary emboli.

Cardiac magnetic resonance imaging (MRI) is the gold standard for functional and structural assessment of right-sided cardiopulmonary circulation [60]. Cardiac MRI can provide an excellent anatomical and functional evaluation without radiation exposure, and it enables the radiologist to evaluate for right atrial dilation, right ventricle hypertrophy, and septal flattening [62]. Finally, MRI can provide information on right ventricular global dysfunction [26]. CT and MRI may not be options for critically ill HSCT patients and are not suitable for longitudinal monitoring and will likely only identify symptoms of advanced disease.

**Echocardiography**

Transthoracic echocardiography is an excellent noninvasive screening tool for PH [29,63]. Dedicated echocardiography specifically targeting signs of PH should be requested and should be interpreted by a cardiologist or PH specialist. It is important to note that in most institutions, routine echocardiography requested to evaluate cardiac function will not include a comprehensive right-sided heart evaluation and will not be sufficient to rule out PH. For this reason, specific echocardiographic protocols have been developed for this purpose. An example of such an echocardiographic protocol for evaluation of PH is shown in Appendix 1.

Using echocardiography, right ventricular pressure can be estimated with interrogation of the Doppler regurgitant jet velocity across the tricuspid valve if tricuspid regurgitation is present. In the absence of tricuspid regurgitation, dedicated echocardiography to specifically evaluate PH may reveal subtle findings otherwise overlooked. These less direct signs of PH may include evidence of right-sided heart chamber dilation, right ventricular hypertrophy, systolic septal flattening, or dilated pulmonary arteries. These signs may not always be found in patients with mild PH, and some of these may be late findings [22]. Given these limitations in screening patients with mild or early PH, the HSCT physician should be aware that echocardiography might need to be repeated over time.

Echocardiography is also an excellent noninvasive means to assess the response to treatment if significant PH is found on the initial screening study and therapy was initiated. The intervals at which echocardiography should be repeated depend on the severity of the diagnosed PH, extent of treatment, and the clinical setting. Echocardiographic guidelines for diagnosis of PH are listed in Table 4.

**Cardiac Catheterization**

Cardiac catheterization remains the gold standard in the diagnosis of PH and should be considered in the HSCT patient suspected of PH after proper risk and benefit assessment. During cardiac catheterization, cardiac output is directly measured, the impact of intracardiac shunts is evaluated, pulmonary artery pressures are measured, and pulmonary resistance can be calculated [30]. If significant PH or elevation of pulmonary resistance is present, it is recommended that all patients undergo acute vasodilator testing. Currently, iNO, intravenous epoprostanol, or adenosine are recommended, with iNO the drug of choice for acute vasodilator testing [64,65]. The information derived from vasodilator testing is essential for the best PH therapy selection.

In general, given the potential risks of cardiac catheterization in a population with other significant comorbidities, such as those after HSCT, invasive testing is reserved for those in whom a clear diagnosis cannot be achieved with noninvasive means. In addition, any patient with apparent hemodynamically compromising PH (at any stage of treatment) should undergo cardiac catheterization, as well as those who do not appear to be responding appropriately to first-line PH therapy (see Treatment of PH, below).

**BIOMARKERS**

Novel biomarkers for PH diagnosis and monitoring after HSCT would be valuable but are not currently available.

**Table 4**

<table>
<thead>
<tr>
<th>Echocardiographic Evaluation</th>
<th>Likelihood of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRV &lt; 2.8 m/s and SPAP &lt; 36 mm Hg with no secondary characteristics of PH</td>
<td>Unlikely</td>
</tr>
<tr>
<td>TRV of 2.9–3.4 m/s and SPAP of 37–50 mm Hg or secondary characteristics of PH</td>
<td>Possible</td>
</tr>
<tr>
<td>TRV &gt; 3.4 m/s and SPAP &gt; 50 mm Hg with or without secondary signs of PH</td>
<td>Likely</td>
</tr>
</tbody>
</table>

Echocardiographic evaluation of the tricuspid regurgitant velocity (TRV) is needed to calculate the systolic pulmonary artery pressure (SPAP). These values help determine the likelihood of a diagnosis of PH. Guidelines adopted from the European Society of Cardiology Guidelines [29,30].
Several biomarkers of PH have been studied in other clinical settings and are listed in Table 5.

### Table 5

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human pentraxin 3 (PTX3)</td>
<td>Acute-phase reactant, a specific biomarker for PH reflecting pulmonary vascular degeneration</td>
</tr>
<tr>
<td>N-terminal of brain natriuretic peptide (NT-ProBNP)</td>
<td>An inactive amino-terminal fragment of brain natriuretic peptide predicts long-term outcome in severe PH; highly specific/sensitive in PH</td>
</tr>
<tr>
<td>Endothelin-1 (ET-1)</td>
<td>Vasoconstrictor, involved in vascular remodeling; increased in PH; bosentan is an ET-1 receptor antagonist and a potential target for therapy</td>
</tr>
<tr>
<td>Angiopoietin-2 (Ang-2)</td>
<td>Angiogenic factor essential for vascular development and maturation; correlates with disease severity in PH</td>
</tr>
<tr>
<td>Bone morphogenic protein-9 (BMP-9)</td>
<td>Circulating peptide; affects endothelial function and associated with ET-1 in PH</td>
</tr>
<tr>
<td>Endoglin (Eng)</td>
<td>Membrane glycoprotein involved in vascular remodeling; increased in patients with PH in systemic sclerosis</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Signal protein involved in vasculogenesis; potent mediator of vascular regulation in angiogenesis; increased in PH</td>
</tr>
<tr>
<td>Transforming growth factor β (active TGF-β)</td>
<td>Multifunctional peptide secreted by cells that control epithelial cell differentiation, proliferation, and function; found downstream of therapeutic agent losartan</td>
</tr>
<tr>
<td>Soluble vascular cell adhesion molecule-1 (sVCAM-1)</td>
<td>Endothelial adhesion molecule that correlates with PH in sickle cell disease; normally suppressed by NO; potential treatment with ET-1 receptor antagonist bosentan</td>
</tr>
<tr>
<td>Asymmetrical dimethylarginine (ADMA)</td>
<td>NO synthase inhibitor; increased in PH in sickle cell disease and contributes to decreased NO production</td>
</tr>
</tbody>
</table>

* Biomarkers used in PH for diagnostic, prognostic, or therapeutic purposes.

### TREATMENT OF PH

PH therapy can be disease specific or supportive. Ideally, a cardiologist or PH specialist should prescribe targeted PH therapy after thorough patient evaluation. Figure 2 shows a suggested treatment algorithm for PH after HSCT [29,32].

### Supportive Therapy

The initial focus of therapy should be aimed at optimizing cardiac function, especially if PH has resulted in right ventricular compromise. Pharmacological agents useful for this purpose are described.

### Diuretics

Right-sided heart failure can lead to fluid retention with resulting hepatic congestion, pulmonary edema, ascites, and peripheral edema. Diuretics may be indicated to prevent worsening fluid retention, including hepatic congestion. Excessive rapid diuresis may lead to decreased cardiac output, however, so caution is required [29].

### Afterload-reducing agents

Afterload-reducing agents reduce systemic vascular resistance, improving cardiac mechanics. Although afterload-reducing agents do not work specifically on the pulmonary vasculature, they play an important role in improving left ventricular efficiency when right ventricular hypertension adversely affects the left ventricular morphology.

### Intravenous inotropes

Bipyridine inotropes (eg, milrinone) selectively inhibit the cyclic adenosine monophosphate phosphodiesterase isoenzyme found in both cardiac and vascular smooth muscle. Inhibition leads to increased intracellular ionized calcium in heart muscle cells, increased contractility, and peripheral edema.
vasodilation. These drugs are used as first-line agents in the face of hemodynamically compromising PH [29].

**Pulmonary Vasodilator Therapy**

Various drugs with differing mechanisms of action are now available that specifically target the pulmonary vasculature. Although often used in combination, adverse event profiles and the means of administration should be taken into account before commencing these therapies. Therapy is frequently commenced on the basis of clinical diagnosis and echocardiographic findings. Any patient with an estimated right ventricular pressure greater than 50% of systemic pressure should be started on treatment, even in the absence of invasive testing (cardiac catheterization). Typical first-line therapies are supplemental oxygen (if evidence of hypoxia) and phosphodiesterase-5 inhibitors. Nonresponse to initial therapy or evidence of deterioration of PH with serial follow-up screening is an indication for cardiac catheterization and therapeutic testing, before escalation to other treatment options (Figure 2).

**Oxygen therapy**

Oxygen is a potent pulmonary vasodilator and is used in most patients with PH. In patients with PH but without hypoxemia, oxygen therapy has been shown to improve pulmonary vasodilation and perfusion [66]. In PH associated with hypoxemia, oxygen therapy should be administered to maintain oxygen saturations >90%. It is vitally important that HSCT patients diagnosed with PH have immediate access to supplemental oxygen. This is particularly relevant in patients with PH in outpatient settings where symptoms may be exacerbated by viral illness or other stressors.

**Inhaled nitric oxide**

NO is an endogenous vasodilator produced from L-arginine, oxygen, and NADPH by various NO synthase enzymes. It is used as a signaling molecule in vascular endothelial cells to signal triggering smooth muscle cells relaxation. Inadequate or defective production of endogenous NO is a key mechanism in the development of PH. NO can be administered as a continuous inhalation (iNO) through a facemask, nasal cannula, or endotracheal tube in intubated patients. NO diffuses rapidly throughout the pulmonary vasculature, decreasing vascular tone and relaxing pulmonary arteries. Excess iNO is rapidly converted to nitrate and methemoglobin after binding to hemoglobin and therefore causes few systemic side effects [67]. iNO is often used in intensive care settings for acute management of PH due to the ease of administration and the favorable side-effect profile.

**Calcium channel blockers**

Only a small number of patients with PH (those who respond to pulmonary vasodilator testing) benefit from calcium channel blocker therapy. The most commonly used calcium channel blockers in this setting are amiodipine, nifedipine, and diltiazem. These agents are used less frequently because of the availability of an increasing array of newer pulmonary vasodilator drugs. Calcium channel blockers are negative inotropic agents, often precluding their use in the face of compromised hemodynamics [68].

**Phosphodiesterase-5 inhibitors**

Phosphodiesterase-5 inhibitors increase the effects of NO by inhibiting breakdown. Increased NO results in vasodilation and decreased smooth muscle proliferation. Sildenafil, tadalafil, and other phosphodiesterase inhibitors have been shown to improve symptoms and length of distance during 6-minute walk tests as well as hemodynamic parameters [69]. These drugs are generally administered orally, with some available as intravenous formulations. The side-effect profile of these drugs is generally benign (headaches, hypertension, and priapism), but the US Food and Drug Administration has recently limited the use of sildenafil in patients with heritable or idiopathic PH due to an increase in mortality when used at higher doses in those specific populations.

**Endothelin receptor antagonists**

Endothelin is a potent vasoconstrictor implicated in the pathogenesis of PAH. Endothelin has been found to cause pulmonary arteriole smooth muscle vasoconstriction and proliferation, fibroblast proliferation, and endothelium proliferation. Nonselective endothelin receptor antagonists (eg, bosentan and ambrisentan) have become a part of the standard of care in patients with chronic PAH [70]. These drugs are administered orally and have a side-effect profile that includes hepatotoxicity, idiosyncratic anemia, and peripheral edema. Monthly liver enzyme and complete blood counts are mandatory for any patients treated with these drugs.

**Prostanoids**

Patients with PAH have reduced prostacyclin synthase, resulting in decreased production of prostacyclin I2, a potent vasodilator. Prostanoids, such as epoprostenol and treprostinil, are potent vasodilators, acting directly on pulmonary and systemic vascular beds to cause vasodilation [71]. They have been shown to improve functional class and exercise tolerance as well as survival in PAH [72,73]. These drugs do have significant side effects, including nausea and vomiting with initial commencement in a dose-dependent manner, diarrhea, jaw pain, and headache. Many different modes of administration have been developed, although the most common means of delivery when used chronically is by continuous intravenous infusion through tunneled central lines. Treprostinil is stable at room temperature (compared with epoprostenol, which requires continuous cooling) and has a substantially longer half-life. Treprostinil can be administered subcutaneously, and an inhaled form is now available in the United States. Orally administered prostanoids are not yet available in the United States.

**Other Therapies for PH**

**Oral anticoagulation**

Patients with PH secondary to thromboembolic disease and those with extensive late disease from any etiology are at risk of developing worsening disease from intrapulmonary microthrombi [65]. Oral anticoagulation with a target International Normalized Ratio of 2.0 is generally recommended [29]. The risk-to-benefit ratio of anticoagulation in patients with PH after HSCT should be carefully weighed because of the high risk of bleeding complications.

**Atrial septostomy**

Invasive therapeutic measures might be required in HSCT patients with acute right-sided heart failure attributed to PH. Under these circumstances, right ventricular output is diminished, resulting in decreased left atrial return, impaired left ventricular preload, and a low cardiac output state. An atrial septostomy allows right to left shunting at the atrial level and provides adequate left atrial filling. Cardiac output is enhanced at the expense of lower systemic arterial saturations. The
improved cardiac output compensates for the decrease in hemoglobin oxygenation due to the shunt, and tissue oxygen delivery is typically enhanced [29].

CONCLUSIONS

The lack of prospective studies evaluating PH after HSCT limits insight into the etiology, incidence, and risk factors for PH. PH should be considered in any HSCT patient with hypoxemia, respiratory failure, or symptoms of TMA, intravascular hemolysis, or thrombosis, especially those who are critically ill (Figure 3). Recognition of PH in this population requires a high degree of awareness followed by targeted evaluation and clinical intervention, guided by an experienced cardiologist. Noninvasive diagnostic methods such as echocardiography are readily available and should be used for PH evaluation, recognizing that early signs of PH might be missed, requiring diagnostic follow-up if respiratory or cardiac symptoms persist. HSCT physicians should seek prompt consultation with an experienced cardiologist when PH is suspected. It is also important to properly communicate the PH diagnosis to the anesthesia team in any HSCT patient scheduled for procedures requiring sedatives because PH may be exacerbated by such interventions, placing patients at risk for acute respiratory decompensation.

Our incomplete understanding of the etiology of PH in HSCT patients limits targeted noninvasive diagnostic and therapeutic options, especially in children undergoing transplantation. Children and young persons with PH post-HSCT likely have a different mechanism of disease from older persons with typical PH associated with long-standing heart disease or multiple emboli. Reports of an association with TA-TMA support the hypothesis that PH post-HSCT is due to endothelial injury as a consequence of complement activation [37]. Careful prospective studies, including state-of-the-art diagnostics and biomarker studies, will help elucidate mechanisms of disease and optimal therapy.

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SUPPLEMENTARY DATA

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