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Pulmonary Complications After Pediatric Stem Cell Transplant

Taylor Fitch[1]*, *Kasiani C. Myers*[1], *Maya Dewan*[2], *Christopher Towe*[3] *and Christopher Dandoy*[1]

[1] Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center (CCHMC), University of Cincinnati School of Medicine, Cincinnati, OH, United States, [2] Division of Critical Care, Cincinnati Children's Hospital Medical Center (CCHMC), University of Cincinnati School of Medicine, Cincinnati, OH, United States, [3] Division of Pulmonology, Cincinnati Children's Hospital Medical Center (CCHMC), University of Cincinnati School of Medicine, Cincinnati, OH, United States

The number of disorders that benefit from hematopoietic stem cell transplantation (HSCT) has increased, causing the overall number of HSCT to increase accordingly. Disorders treated by HSCT include malignancy, benign hematologic disorders, bone marrow failure syndromes, and certain genetic diagnoses. Thus, understanding the complications, diagnostic workup of complications, and subsequent treatments has become increasingly important. One such category of complications includes the pulmonary system. While the overall incidence of pulmonary complications has decreased, the morbidity and mortality of these complications remain high. Therefore, having a clear differential diagnosis and diagnostic workup is imperative. Pulmonary complications can be subdivided by time of onset and whether the complication is infectious or non-infectious. While most infectious complications have clear diagnostic criteria and treatment courses, the non-infectious complications are more varied and not always well understood. This review article discusses pulmonary complications of HSCT recipients and outlines current knowledge, gaps in knowledge, and current treatment of each complication. This article includes some adult studies, as there is a significant paucity of pediatric data.

Keywords: pulmonary complications, hematopoietic stem cell transplant, pediatric, non-infectious complications, infectious complications

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Rainer Gedeit, Children's Hospital of Wisconsin, United States

***Correspondence:**
Taylor Fitch
taylor.fitch@cchmc.org

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INTRODUCTION

Each year, approximately 2,500 children in the United States undergo hematopoietic stem cell transplantation (HSCT) for malignant and non-malignant conditions (1, 2). Over the past few years, improvements in supportive care have improved outcomes; however, pulmonary complications continue to be a major cause of morbidity and mortality in children undergoing autologous and allogeneic HSCT (3, 4). This article will review the causes of pulmonary complications post-HSCT, evaluate the workup and diagnosis of patients with respiratory symptoms, discuss the management of pulmonary complications, and outline the future direction of our understanding of these complications.

Incidence of Pulmonary Complications

Pulmonary complications occur in approximately 25% and 27% of pediatric and adult HSCT recipients, respectively, and are a leading cause of transplant-related mortality (5). Overall, about 9% of HSCT recipients require invasive ventilation and 10% require non-invasive ventilation (4–11). However, it is likely that pulmonary complications are underreported in both adult and

pediatric patients. Roychowdhury et al. (12) reviewed autopsies and bronchoalveolar lavage (BAL) slides of patients who died after HSCT and determined that pulmonary complications occurred in 40 (80%) of the 50 cases and were a major contributor of transplant-related mortality in 74% (37 of 50). Furthermore, Inaba et al. (13) evaluated the incidence of abnormal pulmonary function tests in 89 transplant survivors and demonstrated that abnormal pulmonary function testing was seen in 40.4% of baseline testing and 64% of post-HSCT testing.

Timing of Pulmonary Complications After Hematopoietic Stem Cell Transplantation

Time of onset from cell infusion is helpful when evaluating causes of pulmonary complications: pre-engraftment (0–30 days), post-engraftment (30–100 days), and late phase (over 100 days) (14). The pre-engraftment period is marked by neutropenia, mucositis, indwelling lines, and acute graft-versus-host disease (GVHD) (14–17). Post-engraftment phase is marked by impaired cellular immunity and acute GVHD. The late phase is marked by impaired humoral/cellular immunity and chronic GVHD (14, 17, 18). In all phases, severe GVHD (II–III), acute or chronic, increases relative risk of pulmonary complications. One study notes an increase in relative risk of 2 with a 95% CI of 1.1–3.7 (4, 19).

Further Classification

Pulmonary complications after HSCT can be subclassified as infectious vs. non-infectious (**Table 1**), related to the way impairment of immune function differs over time after HSCT. Pulmonary complications caused by infectious vs. non-infectious etiologies have incidence ranging from 13.9%–54.8% to 10.2%–39.7%, respectively.

INFECTIOUS PULMONARY COMPLICATIONS

Infectious pulmonary complications occur at higher rates in both allogeneic and autologous HSCT (**Table 2**) (5, 15, 17, 21, 22). Infectious complications are higher in pre-engraftment and post-engraftment phases and occur in 20%–30% of patients. This increased risk is related to the impairment of immunological function due to proximity of conditioning regimen and stem cell infusion (14, 15, 21, 23). One study evaluating autologous HSCT demonstrated infectious etiology of pulmonary complications at an incidence of 13.9%, non-infectious at 10.2%, and patients experiencing both at 3.5% (5). Bacterial, viral, and fungal infections all contribute to pulmonary complications after HSCT.

Bacterial Infections

Bacterial pneumonia is the most prevalent type of infectious complication in all phases, with an incidence up to 45% (15, 21, 23, 24). In the pre-engraftment phase, the major causative agents include Gram-negative organisms (such as *Pseudomonas aeruginosa*) due to the poor mucosal barrier, acute GVHD, central lines, and protracted neutropenia (14, 15, 22, 25). In the late phase, infectious etiologies more commonly feature encapsulated organisms and are associated with chronic GVHD. This is likely due to continuation of immunosuppressive medications (14, 15, 25, 26).

Nocardia infection has a low cumulative annual incidence. One study noted a cumulative annual incidence of 1.75% throughout the course of treatment, predominantly occurring in the late phase (15, 27–29). Nocardial infection is more common in patients with allogeneic HSCT, those with a

TABLE 1 | Infectious and non-infectious etiologies of pulmonary complications after stem cell transplant further subdivided by time after transplant.

	Pre-Engraftment (Days 0–30)	Post-Engraftment (Days +30–100)	Late phase (over 100 days)
Infectious Diagnoses	**Bacterial** • Gram-negative organisms • Gram-positive organisms	**Bacterial** • Gram-positive organisms • Gram-negative organisms	**Bacterial** • Gram-positive organisms • Gram-negative organisms • Encapsulated bacteria • *Nocardia* • *Mycobacterium*
	Fungal • Candida	**Fungal** • Candida • Aspergillosis • Mucormycosis • PJP	**Fungal** • Aspergillosis • Mucormycosis • PJP
	Viral • Community-acquired viral pneumonia (e.g., influenza) • *Cytomegalovirus*	**Viral** • Community-acquired viral pneumonia (e.g., influenza) • *Cytomegalovirus*	**Viral** • Community-acquired viral pneumonia (e.g., influenza) • *Cytomegalovirus*
Non-infectious Diagnoses	• Pulmonary hypertension • Drug toxicity • Peri-engraftment syndrome • Diffuse alveolar hemorrhage • Idiopathic pneumonia syndrome • Pulmonary alveolar proteinosis	• Drug toxicity • Diffuse alveolar hemorrhage • Cryptogenic-organizing pneumonia • Idiopathic pneumonia syndrome • Pulmonary hypertension	• Cryptogenic-organizing pneumonia • Bronchiolitis obliterans • Pulmonary hypertension • Drug toxicity

PJP, Pneumocystis jirovecii pneumonia.

TABLE 2 | Infectious etiology summary (20).

Diagnosis	Laboratory Testing	Imaging	Treatment
Bacterial			
Gram-negative organisms	-BAL fluid culture -Blood cultures with imaging findings	CXR/CT chest: consolidation or pleural effusion	-Antibiotics based on biogram or sensitivities -Cephalosporins -Aminoglycosides - Fluoroquinolones -Carbapenems
Gram-positive organisms	-BAL fluid culture -Blood cultures with imaging findings	CXR/CT chest: consolidation or pleural effusion	-Antibiotics based on biogram or sensitivities -Cephalosporins -Vancomycin -Daptomycin -Penicillins
Encapsulated organisms	-BAL fluid culture -Blood cultures with imaging findings	CXR/CT chest: consolidation or pleural effusion	-Antibiotics based on biogram or sensitivities -Cephalosporins -Penicillins -Fluoroquinolones
Nocardia	-BAL fluid culture -Blood culture	CT chest: lobular and multinodular infiltrates, reticulonodular infiltrates	Sulfonamide -Trimethoprim-sulfamethoxazole
Fungal			
Aspergillosis	-BAL galactomannan -Serum galactomannan and aspergillosis serum PCR	CT chest: perinodular halos with ground-glass opacities	Antifungal based on sensitivities Azoles -Voriconazole -Posaconazole Polyenes -Amphotericin B
Candidiasis	-BAL fungal cultures -Serum fungal cultures	CT chest: tree-in-bud changes, ground-glass opacities, cavitation	Antifungal based on sensitivities Echinocandins -Micafungin Azoles -Voriconazole -Posaconazole
Mucormycosis	-BAL fungal cultures -Serum fungal cultures	CT chest: area of central ground glass necrosis surrounded by a ring of consolidation	Polyenes -Amphotericin B Surgical resection
Viral			
Cytomegalovirus	BAL: CMV PCR Serum: CMV PCR	CT chest: ground-glass opacities, air-space consolidations, and reticulonodular patterns	Purine nucleosides -Ganciclovir -Valganciclovir Pyrophosphate analog -Foscarnet -Cidofovir
Adenovirus	-BAL: Adenovirus PCR -Serum: Adenovirus PCR	CT chest: bilateral ground-glass opacities with a random distribution	Pyrophosphate analog -Cidofovir Immunoglobulins
Community-acquired viral pneumonia (RSV, HMPV, rhinovirus, and parainfluenza)	-BAL: Respiratory viral PCRs -Nasal swab: Respiratory viral PCRs	CT chest: multifocal patchy consolidation with ground-glass opacities. Can have centrilobular nodules with bronchial wall thickening	Supportive care Immunoglobulins
COVID-19	-BAL: COVID PCR testing -Nasal swab: Respiratory viral PCRs -Serum: Antibody testing	CT chest: Bilateral ground-glass opacities with peripheral distribution, consolidations, linear opacities, septal thickening, halo sign	Supportive care Steroids ± Remdesivir ± Tocilizumab

Infectious etiologies of pulmonary complications. Describes diagnostic testing, imaging results, and most commonly used treatments, though there is institutional variation. BAL, bronchoalveolar lavage; CMV, Cytomegalovirus; RSV, respiratory syncytial virus; HMPV, human metapneumovirus.

history of acute GVHD, and those actively being treated for chronic GVHD at the time of diagnosis (27, 28). Additional risk factors include other concurrent infections, in particular, CMV infection (27, 28). *Nocardia* tends to be disseminated at diagnosis but commonly has a pulmonary locus (30). There is some evidence that those who receive pentamidine prophylaxis for *Pneumocystis jirovecii* also have increased risk, but this is not consistently demonstrated throughout the literature (28, 30).

Mycobacterium infections including both tuberculosis and non-tuberculous subtypes occur at low incidence worldwide (0.1%–5.5%) and are more prevalent in those who have received an allogeneic HSCT. In the United States, incidence has been reported from 0.0014% to 3% (31–33). Infection typically occurs in the late phase, and while *Mycobacterium* infections can be disseminated, infection is predominantly in the lungs (31, 32). Tuberculosis infection is associated with older age and chronic GVHD (34). Most recommendations are for conservative management, with treatment if the patient has a tuberculosis exposure even with negative skin testing. Currently, there is no evidence for prophylaxis as incidence remains low (32). Studies have demonstrated that it is likely safe to treat after Day +100, and treatment consists of isoniazid, rifampin, ethambutol, and pyrazinamide for 6–9 months (33).

Fungal Infections

Overall, the reported incidence of fungal infections ranges from 4% to 34%, occurring most commonly in allogeneic HSCT patients and during the post-engraftment and late phases. Mortality can be up to 33.3% (3, 4, 17, 23). The most common fungal pulmonary complications in HSCT patients are invasive aspergillosis, followed by invasive candidiasis, then mucormycoses (17, 35). In one large multicenter study, incidence rates of each fungal infection were reported as 43%, 28%, and 8% respectively (35). There is an increase in fungal infections with protracted/continued neutropenia (60 days or longer) and concurrent GVHD (35).

Invasive aspergillosis has a reported incidence in autologous HSCT of 1% to 5%, most frequently diagnosed in post-engraftment and late phases (15, 35). Invasive aspergillosis cases have continued to decline with the integration of granulocyte colony-stimulating factor and azole prophylaxis in treatment (14, 25, 36). Aspergillosis is diagnosed using a combination of radiologic and serologic testing. Serum galactomannan and aspergillosis serum PCR testing can be sent for diagnosis, but the most sensitive/specific test is the BAL galactomannan (14, 25, 37). The accuracy of testing has been shown to be related to neutrophil count and underlying condition (38). The current recommended treatment is with antifungals such as voriconazole or amphotericin B (25, 37).

Overall, invasive candidiasis infections have been decreasing in incidence, in particular, *Candida albicans*. There has been an increase in the rate of *Candida glabrata* and *Candida krusei*, likely secondary to antifungal prophylaxis (15, 39); one study demonstrated that 70% of infections were attributed to that non-albican species when analyzing autologous HSCT recipients with *Candida* infections (35). *Candida* infections span the entire course of transplant, peaking in the post-engraftment phase before the first 120 days (35). Diagnosis is made through fungal cultures from both serum and BAL. Initial treatment of choice for *Candida* species is echinocandins (such as micafungin) or voriconazole, with further modification based on sensitivities of cultures (40).

Mucormycosis infections are also increasing in incidence with the use of azole antifungal prophylaxis (25, 41). One study showed an incidence of 8% with infections typically occurring in the late phase (35). CT scans can be helpful for diagnosis and can show reversed halo signs (an area of central ground-glass necrosis surrounded by a ring of consolidation); however, for diagnosis, BAL with fungal cultures are needed. Treatment is with amphotericin B and accompanied by surgical resection if without significant morbidity/mortality (14, 25, 41).

Of note, *P. jirovecii* pneumonia is a rare complication after HSCT, with an incidence of 0.63% in allogeneic HSCT and 0.28% in autologous HSCT recipients (42). In one study, when a patient was diagnosed, they were 6.87 times more likely to die when compared to their matched controls (42). Patients are at an increased risk if they have GVHD and/or poor immune reconstitution (42). As this complication is a rare cause of pulmonary complications, it will not be discussed in significant detail in this review.

Viral Infections

Viral pneumonia in all HSCT patients ranges between 4% and 21.9%, with a greater incidence in allogeneic HSCT patients. The most commonly reported viral infections are *Cytomegalovirus* (CMV) and adenovirus (17, 21, 23). In a study evaluating the changes in rates of infection over time, CMV disease fell from 8% to 5% from 1993–1997 compared to 2003–2007 (3). Mortality greatly varies between types of viral infection, viral quantities, and autologous vs. allogeneic HSCT. Respiratory syncytial virus (RSV), influenza, and parainfluenza are other common etiologies of viral pneumonia that are seen in HSCT patients (14).

CMV becomes a major cause of pneumonia starting at 3 weeks posttransplant and continues into the late phase. There have been improvements in infection rates through careful selection of donors, careful serology monitoring, and early intervention. The greatest predictor of CMV infection is the serology status of the recipient (14, 15, 23, 25, 43, 44). Autologous HSCT patients have a reported incidence of 1%–9% (15, 44). Again, acute GVHD and allogeneic HSCT patients have an increased risk of CMV infection (14, 43). Diagnosis requires radiologic and positive CMV PCR from BAL or viral cultures (14, 15). Mortality still approached 31% in one study focusing specifically on autologous HSCT recipients. While letermovir can be used for prophylaxis, it has not been used to treat active infections (45, 46). Treatment of CMV infection includes gancyclovir and foscarnet with/without CMV immunoglobulins (14, 15, 44). Resistance testing can be performed if continued breakthrough viremia or increasing viral count while on treatment. Some centers treat more persistent or severe infections with virus-specific T cells (targeted therapy) (14).

While a common community-acquired entity, RSV infection in HSCT patients (as well as rhinovirus, parainfluenza, and human metapneumovirus) has been shown in studies to progress to pneumonia between 35% and 58% of the time (15, 47, 48). These infections occur equally in autologous and allogeneic HSCT (15). Additional risk factors for developing a significant pneumonia from these common viruses include severe lymphopenia, T cell-depleting or myeloablative conditioning, and acute GVHD (47, 48). RSV can be particularly severe in HSCT patients, leading to additional complications such as acute respiratory distress syndrome or even diffuse alveolar hemorrhage (DAH) that results in invasive respiratory support (4, 49, 50). One study reported that up to 10% of their patients developed acute lung injury from RSV (50). Chemoprophylaxis with palivizumab in high-risk children (RSV outbreak or young infants) has been shown to have some benefit in prevention of RSV infection (47). Rapid RSV PCR is diagnostic, and in severe cases, aerosolized ribavirin and immunoglobulins can be considered, though there are little data to support an improvement in mortality (14, 25, 49).

Other viral infections that should not be excluded from evaluation are human herpesvirus 6 (HHV6), herpes simplex virus (HSV), and adenovirus. Going forward, additional studies will be needed on the novel coronavirus disease 2019 (COVID-19) virus in HSCT patients.

NON-INFECTIOUS COMPLICATIONS

While there has been significant reduction in developing infectious complications secondary to improved prophylaxis, improved diagnostic testing, and targeted antimicrobials, there has been no significant improvement in the incidence of non-infectious pulmonary complications in HSCT (**Table 3**) (8, 15, 51, 52). Two studies evaluating allogeneic and autologous HSCT show non-infectious pulmonary complications with an incidence of 28% and 10.2%, respectively (5, 17). Some main categories of non-infectious pulmonary complications in HSCT include peri-engraftment respiratory distress syndrome (PERDS), idiopathic pneumonia syndrome (IPS), DAH, drug toxicity, cryptogenic organizing pneumonia (COP), bronchiolitis obliterans (BO), and pulmonary veno-occlusive disease. These complications also have a typical time of presentation after stem cell infusion, which will be further discussed below. Diagnosis is often difficult due to significant overlap, poor diagnostic confirmatory testing, and increased risk of invasive procedure to identify the underlying etiology (8, 51, 52). This highlights the need for studies to further investigate and better determine the mechanism of these injuries, possible preventative measures, and elucidation of better treatment options for these complications.

TABLE 3 | Non-infectious causes of pulmonary dysfunction.

Diagnosis:	Laboratory Testing	Imaging	Treatment
Engraftment syndrome/ PERDS	- No definitive laboratory testing	- CXR/CT chest - Pulmonary edema	- Corticosteroids - Diuretics - Supportive care
IPS	-BAL fluid without signs of infectious process	-CXR/CT chest: multilobular infiltrates	IV corticosteroids -TNF alpha-binding protein -Supportive care
DAH	-BAL fluid: –hemosiderin-laden macrophages –Increasingly bloody samples	-CT chest: Lobular/lobar ground-glass opacities. Prominent segmental bronchi	-IV corticosteroids -Supportive care
Drug toxicity	-BAL fluid: without signs of infectious process -**Lung biopsy: hypersensitivity reaction with eosinophilic pneumonia	-CT chest: patchy ground-glass opacities, sometimes with septal thickening	-IV corticosteroids -Supportive care
COP	-Lung biopsy: patchy plugs of granulation tissues filling lumens of distal airways. Chronic interstitial inflammation and no prominent bronchiolar damage	-CT chest: patchy consolidations with elongated distribution and ground-glass opacities	-Corticosteroids (systemic)
PHTN	-None	-ECHO: increased pulmonary vascular resistance and elevated right ventricular pressure	-Supportive care -Oxygen therapy -Inhaled nitric oxide -Calcium channel blockers -Phosphodiesterase-5 inhibitors
BO	-Lung biopsy: constrictive bronchiolitis and submucosal bronchiolar fibrosis	-CT chest: small airway thickening or bronchiectasis -PFTs: Obstructive pattern, not responsive to albuterol	-Corticosteroids (inhaled and systemic) -TNF-alpha modulators

Describes diagnostic testing, imaging results, and most commonly used treatments, though there is institutional variation. BAL, bronchoalveolar lavage; PERDS, peri-engraftment respiratory distress syndrome; IPS, idiopathic pneumonia syndrome; DAH, diffuse alveolar hemorrhage; COP, cryptogenic organizing pneumonia; PHTN, pulmonary hypertension; BO, bronchiolitis obliterans; PVOD, pulmonary veno-occlusive disease; IV, intravenous; TNF, tumor necrosis factor.
***Not routinely performed.*

Peri-Engraftment Respiratory Distress Syndrome

PERD typically occurs within the first 5 days of engraftment (pre-engraftment phase) and is accompanied by established clinical criteria, with pulmonary edema seen on imaging (25). Clinical criteria include fever, rash, hepatic or renal dysfunction, weight gain, hypoxemia, and transient encephalopathy (15, 53). The etiology is not completely understood but thought to be secondary to pro-inflammatory cytokines (54). PERD does have a higher incidence in autologous HSCT patients, with studies showing an incidence between 2.5% and 20% (5, 14, 54, 55). Overall incidence seemed to increase over time, which is thought to be secondary to the introduction of granulocyte colony-stimulating factor during HSCT (56). Typically, there is a good response to steroids (14, 15, 53).

Idiopathic Pneumonia Syndrome

IPS usually presents with fever, acute respiratory distress, and alveolar damage that has an unknown underlying etiology (not caused by infection or end organ damage) (8, 51, 52). Currently, the best evaluation of etiology has come from murine models that suggest conditioning regimens including lung irradiation, cyclophosphamide, busulfan, or previous treatments with carmustine (BCNU), etoposide, bleomycin, and cisplatin all increased the risk of epithelial injury. This leads to activation of pulmonary macrophages and alloreactive T lymphocytes. Implicated cytokines include interleukin-6, interleukin-8, and in particular tumor necrosis factor (TNF)-alpha (52, 56, 57). Imaging is non-specific with multilobular infiltrates. BAL is typically performed to rule out an underlying infectious process (52, 58). Onset usually is in the later portion of pre-engraftment to the beginning of the post-engraftment phase (21, 51). There is a higher incidence in allogeneic HSCT with a mean up to 10% in allogeneic HSCT patients and 5.8% in autologous HSCT patients (14, 25, 51, 58). The onset for autologous HSCT is typically later in the mid-to-late post-engraftment phases (21, 58). Risk factors specifically for developing IPS include chest irradiation, older age, being female, or solid tumor diagnosis (58). Other risk factors that seem to increase the incidence of IPS include high-dose cyclophosphamide and adding busulfan to the conditioning regimen (52). Mortality is significant from 60%–80% in allogeneic transplants, with few recent studies specifically looking at mortality in autologous transplant patients (58). The patients who develop this complication have the highest rate of mortality once intubated (approaching 74%) (59).

Currently, first-line treatment with corticosteroids and supportive care is recommended; however, studies are mixed whether there is improvement in respiratory support or outcome (52, 59). Etanercept (TNF alpha binding protein), has been shown to reduce pulmonary vascular endothelial cell apoptosis; one study evaluating the combination of steroids and Etanercept demonstrated improvement in mortality, increasing D +28 survival to 73% (15, 57, 60). Thus, a randomized, double-blind, placebo-controlled trial was initiated comparing etanercept to placebo; all patients received methylprednisolone. This study was unable to produce significant results in mortality/outcome; however, the trial's results are difficult to interpret as it was halted due to poor study enrollment (25, 61). This demonstrates again an area that necessitates further investigation to find alternative treatment options and evaluate ways to improve outcomes. Treatment with agents such as etanercept should only occur after confirmation that there is not an underlying infectious etiology. IPS additionally encompasses subcategories including DAH and COP, which will be discussed later.

Diffuse Alveolar Hemorrhage

DAH is a subcategory of IPS that is defined by hemorrhagic alveolitis. In pediatric and adult allogeneic HSCT, incidence of DAH ranges from 5% to 12% with a median onset of 19 days as compared to autologous HSCT recipients where DAH incidence ranges from 2.1% to 12%, with a median time of onset of 12 days (5, 58, 62, 63). Definitive diagnosis requires a BAL sample with at least 20% of hemosiderin-laden macrophages, blood in 30% of alveolar surfaces, with increasingly bloody samples (15, 58, 64). In one study, DAH was associated with engraftment, an age over 40, solid malignancies, high fevers, severe mucositis, and/or with renal insufficiency (65). Currently, treatment recommendations include high-dose steroids and supportive care (5, 62). Small studies have been performed in patients with DAH (both transplant induced and not) that have evaluated inhaled/nebulized tranexamic acid ± recombinant activated factor VII with reported success; however, further investigation with a larger sample size is required before integrating this into standard of care (63, 66, 67). Despite early intervention and supportive care, mortality historically has been up to 80%–100% in allogeneic HSCT patients. Newer studies suggest that mortality for autologous HSCT patients is closer to 28% and 70% for allogeneic patients (21, 58, 62, 64, 67). If DAH occurs in the first 30 days, mortality is significantly lower (64).

Drug Toxicity/Delayed Pulmonary Toxicity Syndrome

Drug toxicity has a varying degree of severity—from mild dyspnea to respiratory failure requiring mechanical ventilation. Incidence ranges from 22% to 49% in autologous HSCT patients with a mean onset at Day +45 (post-engraftment phase); however, there is a wide range from 21 to 149 days (52, 58 68). Drug toxicity is seen more frequently in patients who have had regimens including BCNU, etoposide, cyclophosphamide, bleomycin, and cisplatin (52, 58, 68, 69). Radiologically, CT scans are not specific but can demonstrate patchy ground-glass opacities, sometimes with septal thickening. Biopsy can show hypersensitivity reaction with eosinophilic pneumonia or, if performed later, a thickening of the interstitium with early fibrosis (51, 52). The treatment of choice is corticosteroids, though little data are available on the overall mortality of this complication (58).

Cryptogenic Organizing Pneumonia

COP tends to be a more subacute process with fever, dyspnea, and cough (51). Incidence typically ranges from 0.9% to 10% and can occur in both allogeneic and autologous HSCT patients (14, 15, 51). For allogeneic patients, there is a well-described association with chronic GVHD, thus suggesting an immune-

mediated response (51). For autologous HSCT patients, the proposed mechanism is secondary to underlying infection or drug toxicity (51). COP usually occurs within the first 100 days and occurs more frequently in allogeneic HSCT patients. On chest CT, patchy consolidations with elongated distribution and ground-glass opacities can be seen (14, 51, 70). Diagnosis is confirmed *via* biopsy that shows patchy plugs of granulation tissues that fill lumens of distal airways (alveoli) with chronic interstitial inflammation and no prominent bronchiolar damage (15, 52). Corticosteroids remain the treatment of choice with a slow taper, usually with significant improvement. In one study, 78%–80% of patients demonstrated a good response (14, 15, 52, 71). However, there are no studies looking at what duration of steroid therapy is most appropriate. Additionally, COP tends to have a widely varied reported relapse rate of 9%–58%, which is likely secondary to no standardization of treatment across institutions (52, 70).

Pulmonary Hypertension

Pulmonary hypertension (PHTN) is characterized by increased pulmonary vascular resistance and elevated right ventricular pressure (72). The incidence of PHTN is not well defined but has been estimated between 15% and 28% with a mortality up to 55%–86% (73, 74). This complication most commonly occurs in the late phase with a reported median of Day +70; however, the range is wide from Day 0 to +365 (72). The underlying etiology in HSCT is not well understood; the proposed mechanism is endothelial injury in both pre/post-pulmonary capillary vasculature, leading to smooth muscle proliferation, fibroblast infiltration, and ultimately hypertrophy of the vasculature (72, 75). This damage can be instigated by other underlying disorders such as thrombotic microangiopathy and atypical hemolytic uremic syndrome (72, 73). Chemotherapy agents that have been implicated include mitomycin, bleomycin, cisplatin, vincristine, cyclophosphamide, and BCNU (76). Additional risk factors include high-dose preparative chemotherapy and radiation prior to transplantation. Diagnosis is usually obtained *via* electrocardiogram and echocardiogram, but sometimes more invasive measures are implemented, such as transesophageal echocardiology or cardiac catheterization (72, 75). Biopsy can be obtained to confirm the diagnosis and shows widespread fibrous proliferation in the pulmonary venules and small veins; however, this is not typically performed due to the morbidity and mortality associated with the procedure (76). Treatment includes supportive care, oxygen therapy, inhaled nitric oxide, calcium channel blockers, and phosphodiesterase-5 inhibitors (72). For long-term damage caused by PHTN, high-dose steroids can be used, though there are no studies evaluating the effectiveness of this treatment (76, 77). There are limited studies evaluating this complication, and further investigation is warranted.

Bronchiolitis Obliterans

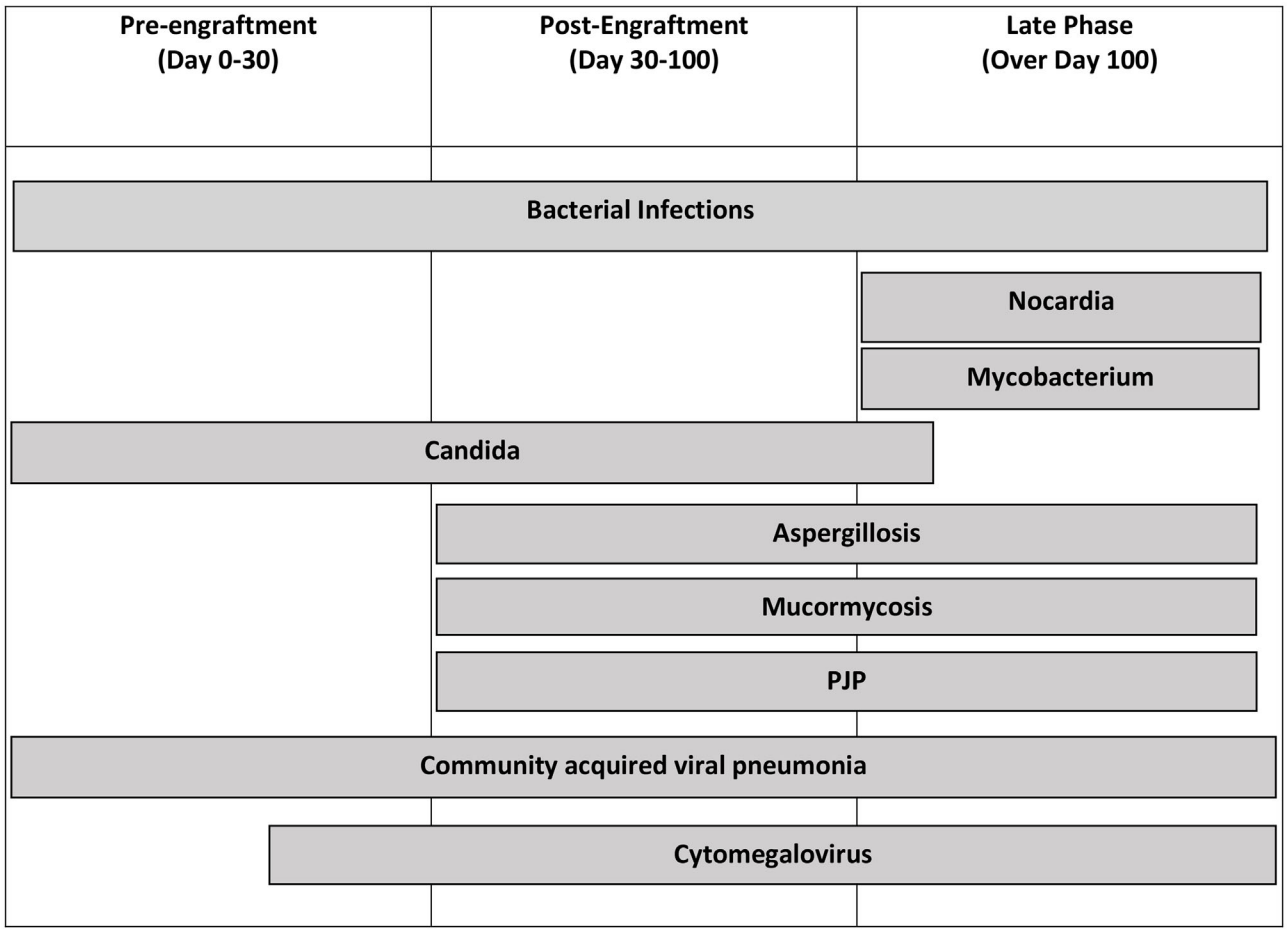
BO exclusively occurs in allogeneic HSCT patients and is one of the most common causes of late-phase complications (from Day +90 to 2 years) (15, 25, 51). Incidence ranges from 2% to 48%; this wide range is likely secondary to the inconsistencies in diagnostic criteria between studies (51). Associated features include acute GVHD, older age, non-related donor, total body irradiation, peripheral stem cell source, and busulfan-based conditioning regimen (14, 25, 51, 52). BO is a histologic diagnosis that can be made after lung biopsy, which shows constrictive bronchiolitis and submucosal bronchiolar fibrosis (15, 25, 51, 78). However, lung biopsies are not without significant morbidity and mortality. Thus, clinical criteria have been established through the National Institutes of Health Consensus Development Project to describe bronchiolitis obliterans syndrome (BOS). This requires four features to meet diagnostic criteria. First, FEV1/VC <0.7 (or 5th percentile of predicted). Second, FEV1 <75% of predicted with ≥10% decline over less than 2 years. FEV1 should not correct >75% with albuterol. Third, no identified infection. Fourth, evidence of air trapping/bronchiectasis on high-resolution chest CT or residual volume >120% of predicted value (79). While this is a useful outline, studies have shown that not all patients with histologic BO meet the established criteria of BOS. Treatment can include both inhaled and systemic steroids with other immunosuppressive medications, though very few studies demonstrated significant clinical benefit (51). For patients whose symptoms are steroid refractory, treatment can include Janus-associated kinase 1/2 inhibitors such as ruxolitinib (80, 81). Studies have been published reporting 59%–68% overall response rate with a tolerable safety profile (80, 82). Most common toxicities included reactivation thrombocytopenia and anemia; some studies have reported increased CMV reactivation, though this is not consistently demonstrated across all studies (80–83). However, these studies evaluated those 12 years of age or older; studies evaluating effectiveness/dosing in children younger than 12 and dosing are ongoing (81, 83). Other agents that are currently under investigation include belumosudil and ibrutinib, though further investigation is needed for use in pediatrics (84, 85). Despite aggressive treatment, most patients have acute flares with mortality rate being between 12% and 27% at 5 years due to secondary infection or respiratory complications (8, 51, 78).

Other entities that can cause pulmonary complications that are not discussed here include acute GVHD, pulmonary alveolar proteinosis, pulmonary cytolytic thrombi, and chronic GVHD.

TIMELINE/CLASSIFICATION OF PULMONARY COMPLICATIONS POSTTRANSPLANT

HSCT is associated with a variety of pulmonary complications that can be classified by time after stem cell infusion (**Tables 4**, **5**). Risk for developing pulmonary complications varies greatly by type of transplant (allogeneic vs. autologous), previous treatments (chemotherapy, radiation), and underlying demographics of the patient (age and primary diagnosis). Despite our increased knowledge surrounding pulmonary complications, arriving at the correct diagnosis requires thorough and often invasive evaluation.

TABLE 4 | Infectious complications and the most common times in which complication develops.



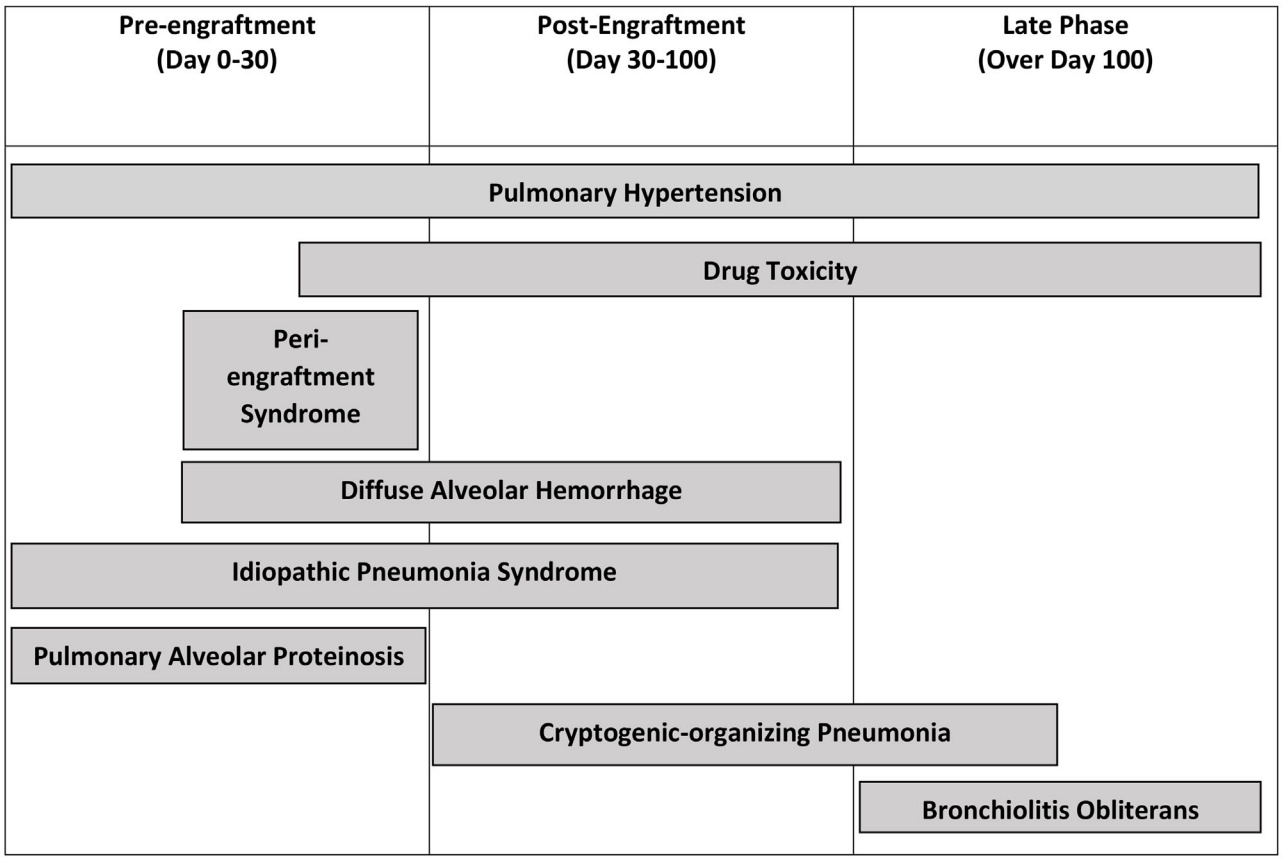
DIAGNOSIS OF PULMONARY COMPLICATIONS

In the acute phase, initial evaluation starts with imaging (**Table 6**). Chest X-rays are typically performed and can be helpful if an infiltrative process is found, which would indicate a BAL is needed for better evaluation (5, 23). However, chest X-rays can be normal in 15% of patients, and thus, if clear, it is prudent to proceed with a chest CT scan (5). Chest CT scans while sometimes suggestive are rarely diagnostic (25). Ultimately, patients most often require bronchoscopy with BAL or even lung biopsy to finalize diagnosis. Of note, these interventions have better diagnostic yield after imaging has been obtained (5).

Fiber-optic bronchoscopies are the next step to fully evaluate the etiology of pneumonitis and are well tolerated. Cytology and infectious studies (bacterial, fungal, and viral) are recommended. Multiple studies evaluating BAL show it can be diagnostic in about 50% of cases and is more likely to identify infectious etiologies compared to serologic testing and lung biopsies (4, 86–88). When BAL is obtained within the first 24 h of symptoms, yield can be as high as 75%; this is likely due to shorter duration of antibiotics (88). Despite this, there have not been consistent data showing that bronchoscopies have improved mortality likely due to skewed data, as only the sickest patients have bronchoscopies performed (4, 17). In the pre-engraftment/early phase, if the patient requires intubation for respiratory needs, at our institution, bronchoscopies are typically performed. The reasoning for this is multifactorial. If infection is suspected, this is confirmatory; if non-infectious complication is suspected or ultimately discovered to be the cause, ruling out concurrent infection is needed, as the treatment for many non-infectious complications involves further immunosuppression with steroids or other immunosuppressants. If developing in the late phase and more chronic in nature, bronchoscopies are carefully planned with input from pulmonology, bone marrow transplant, and anesthesia teams. Of note, a recent study evaluated pediatric patients' BAL's microbe-gene profile to see if a subset was more likely to develop pulmonary complications. What was found was that those with significant microbial depletion and concomitant natural killer/T-cell activation have higher incidence of pulmonary complication post-HSCT. This is a new and evolving field that may allow for predicting those with complications and ultimately help develop preventative measures (89).

The next diagnostic step can be a surgical lung biopsy; however, this does come with significant mortality. Biopsy was associated with a 4-fold higher procedure-related mortality of about 8% with common complications being pneumothorax,

TABLE 5 | Non-infectious complications and the most common times in which complication develops.



hemothorax, prolonged mechanical ventilation, and wound dehiscence (23, 86). This procedure has been more successful in identifying non-infectious causes of pneumonitis (86). In one study, a diagnosis was found 62% of the time, with a change in therapy made 57% of the time based on results (90). For those with a specific diagnosis, Day +30 and Day +90 outcomes were improved compared to those without a diagnosis (90). At our institution, lung biopsies are not routinely performed on patients with acute pulmonary deterioration but rather on the patients with chronic or refractory pulmonary disease. The workup mentioned above is almost always completed prior to proceeding with biopsy, and if there are continued clinical concerns or questions, biopsy is performed based on clinical stability of the patient and suspected clinical diagnosis. Unfortunately, there is limited literature to make uniformed recommendations and remains at each clinician's discretion.

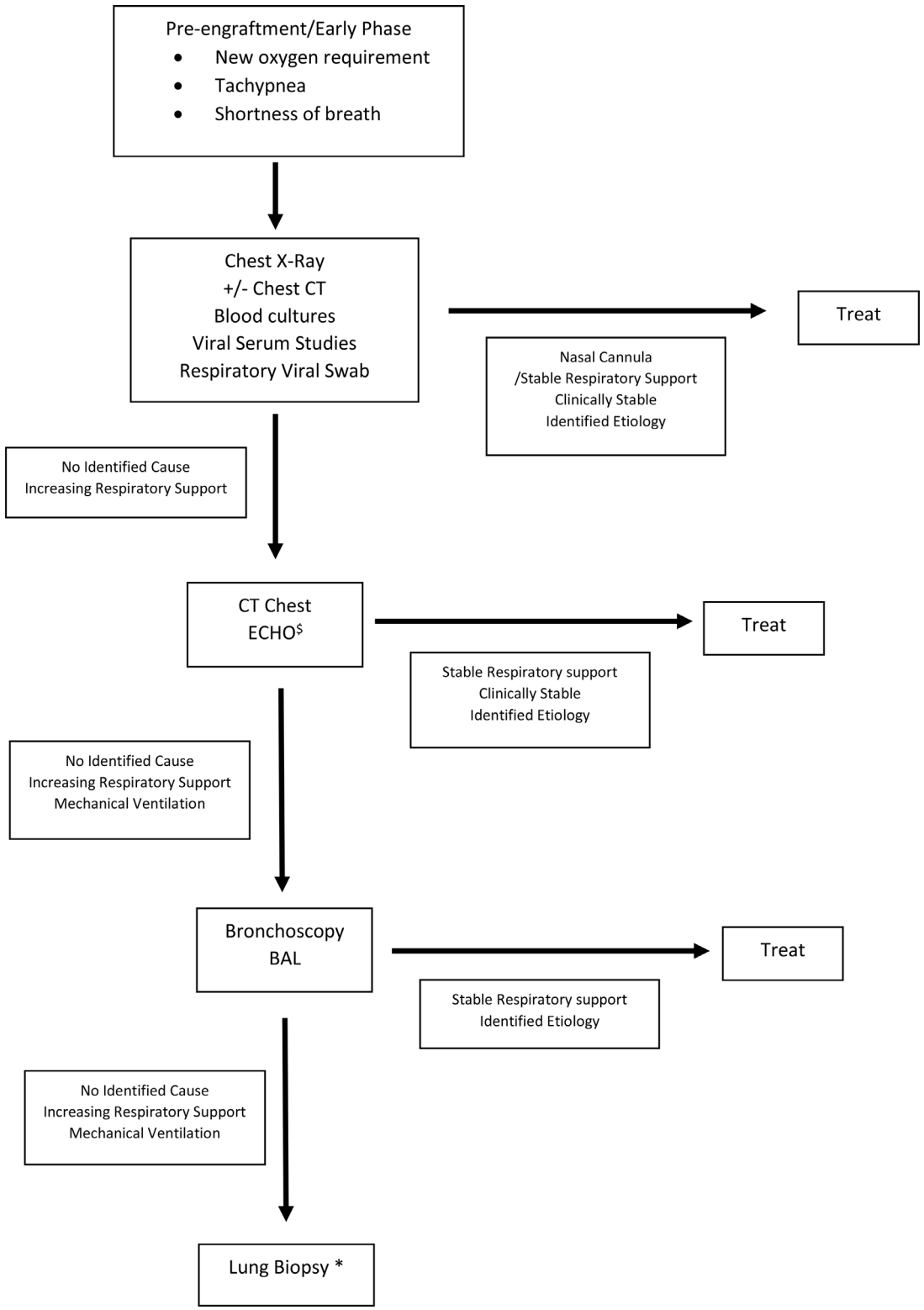
LONG-TERM FOLLOW-UP

In less acute phases, pulmonary function testing (PFT) with diffusion capacity [measured by diffusing capacity of the lungs for carbon monoxide (DLCO)] is used as a marker both pre- and post-HSCT to determine the risk of pulmonary complications during HSCT and risk of mortality after HSCT (5, 9, 17, 91, 92). The pre-HSCT PFTs establish a baseline and identify asymptomatic patients who have underlying pulmonary changes. Based on PFT results, further evaluation and adjustments can be made in conditioning regimens (22, 92). Studies have suggested that worsening spirometry measurements and DLCO are usually found immediately after transplant but recover partially then ultimately stabilize (91, 93, 94). When PFTs are abnormal, they typically show a restrictive rather than obstructive pattern (93–95). Studies, though variable, show poor baseline spirometry measurements, more pulmonary complications, and worse post-HSCT spirometry measurements if the patient had total body irradiation, lung metastasis, prior thoracotomy, lung radiation, and previous chemotherapy (9, 91–93, 95).

CONCLUSION

Pulmonary complications are common and cause significant morbidity and mortality for HSCT patients. Both allogeneic and autologous HSCT recipients experience these toxicities, though they occur most frequently in allogeneic HSCT patients. The process of the lung injury varies when comparing pre-engraftment, post-engraftment, and late phases and whether the underlying complication is infectious or non-infectious in

TABLE 6 | Diagnostic Algorithm of Pulmonary Complications after HSCT.



*Suggested diagnostic algorithm. Empiric treatment might be indicated depending on clinical status of patient. If patient requires intubation, all studies along the vertical access should be performed. $ECHO to evaluate for pulmonary hypertension, increased pulmonary vascular resistance, and elevated right ventricular pressure *Lung biopsy pending clinical evaluation and assessment of patient's ability to tolerate procedure.*

nature. Recently, the incidence of non-infectious complications has been increasing. Thus, a better understanding of the etiology, evaluation, and treatment of these disorders is needed. Additionally, there are very few studies evaluating autologous HSCT patients and the complications that affect these individuals. Recently, a growing number of patients at our institution experienced chemotherapy-induced pneumonitis, highlighting the need for a better understanding of this complication. Though murine models have helped elucidate a proposed mechanism of injury, this has been much harder to determine in our patients. Additionally, there are no readily available biomarkers or serologic testing that definitively point to chemotherapy-induced pneumonitis. Thus, it remains in large part a diagnosis of exclusion and clinical intuition. Ultimately, improved outcomes for patients with pulmonary complications can be achieved by understanding the underlying etiology and the mechanism of action of the resultant injury and by standardizing the workup and treatment (including duration).

AUTHOR CONTRIBUTIONS

TF wrote the first draft and assimilated data. KM contributed to editing the article with each subsequent draft. CT contributed to editing the article. MD helped with the figures and edited subsequent drafts. CD helped with final edits, primary research, and tables. All authors contributed to the article and approved the submitted version.

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