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TRANSPLANT INFECTIOUS DISEASE

REVIEW ARTICLE

Evaluation of pulmonary abnormalities in recipients of hematopoietic cell transplants and cellular therapies

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Abstract

Hematopoietic cell transplant (HCT) and chimeric antigen receptor T-cell (CAR-T) therapy recipients are susceptible to multiple pulmonary complications that are caused by infectious and noninfectious processes. Numerous variables can be associated with specific pulmonary diseases including time from transplantation, presence of graft versus host disease (GVHD), underlying disease, and prolonged neutropenia and lymphocytopenia. Most pulmonary complications are infectious in origin, with bacterial pneumonia remaining the most common pulmonary infection, particularly before neutrophil engraftment. Invasive fungal infections continue to affect this patient population even when antifungal prophylaxis is used. Noninfectious pulmonary complications include a wide differential of pathologies in this population, and as clinical presentations of these various pulmonary disorders often overlap, clinicians frequently will use a multidisciplinary approach in diagnosing these abnormalities. Radiography, particularly with chest computed tomography (CT) imaging, is an essential tool in identifying pulmonary pathology and potential sources. While standard microbiological cultures of respiratory specimens are still utilized, their role is limited by low sensitivity and diagnostic yield. The likelihood of obtaining a diagnosis can be improved by using other microbiological assays, including fungal antigen tests and molecular diagnostic methods, particularly if specimens are collected via bronchoscopy. This review will highlight the more common causes of pulmonary diseases encountered after HCT and CAR-T and will examine the different methods in their diagnosis.

KEYWORDS
Pulmonary complications in HCT and CAR-T

1 | INTRODUCTION

Recipients of hematopoietic cell transplants (HCT) and cellular therapies are a heterogeneous group with varying degrees of immunosuppression. Most of these patients have an underlying hematological malignancy and are at risk for multiple infectious complications due to their underlying disease and treatments, prolonged periods of neutropenia, lymphocytopenia, and hypogammaglobulinemia.[1–4] Those undergoing allogeneic HCT typically are most at risk due to these factors plus their augmented immunosuppression related to therapies to treat or prevent graft versus host disease (GVHD).[5,6] While autologous HCT recipients are not subject to the same risks associated with GVHD

therapies, they are still more susceptible to infectious complications, particularly during the pre- and periengraftment periods.[7] Chimeric antigen receptor T-cell (CAR-T) therapy recipients also receive multiple forms of immunosuppression, which can include treatments for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome .[8,9] Pulmonary complications, including infectious ones, can occur in up to a third of HCT recipients and lead to significant morbidity and mortality.[10] In this review, the pulmonary complications related to infectious and noninfectious causes in HCT and CAR-T recipients will be discussed, with a focus on the available methods to diagnose these abnormalities.

2 | INFECTIOUS CAUSES OF PULMONARY ABNORMALITIES

2.1 | Bacterial infections

Among the infectious causes of pulmonary abnormalities in HCT recipients, bacterial etiologies remain among the most common, particularly during the preengraftment period. In a study of four transplant centers evaluating infections in allogeneic HCT recipients, 30% of patients developed pneumonia, and more than half were bacterial.[11] Predisposing risk factors for bacterial pneumonia include prolonged neutropenia, acute leukemia, previous HCT, and GVHD.[12–14] Bacterial pulmonary infections occur in both autologous and allogeneic HCT recipients, but the incidence is higher in allogeneic HCT recipients.[15] The most common organisms associated with bacterial pulmonary infections include Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, and Gram-positive organisms include *Streptococcus pneumoniae* and *viridans*.[11,14] Levofloxacin prophylaxis administered in the pre-engraftment period after HCT has been shown to reduce the frequency of early bacterial pneumonia, but increases fluoroquinolone resistance.[14,16,17] Pneumonias caused by intracellular pathogens, such as *Legionella*, are reported rarely in this population which may also be correlated to the use of quinolone prophylaxis.[18] Late-onset bacterial pneumonias that occur more than 100 days after HCT occur less frequently, but in one review, 25% of HCT recipients developed pneumonia after 100 days, but only 9% were from a bacterial cause. Factors associated with late-onset pneumonia included older age, the use of an unrelated donor, and treatment for chronic GVHD.[19]

Less is known about bacterial pneumonias in recipients of CAR-T therapy. Up to 33% of CAR-T therapy recipients develop bacterial infections within the first 28 days from CAR-T infusion but more than half are blood stream infections, and few pneumonias are reported.[8,20–22]

Standard chest x-rays can have low sensitivity and specificity for predicting pulmonary abnormalities in neutropenic patients, whereas computed tomography (CT) imaging of the chest can have up to 88% sensitivity in detecting pneumonias in neutropenic HCT recipients.[23,24] Radiographically, bacterial pneumonias usually present with focal alveolar or interstitial infiltrates or consolidations (Table 1). Bacterial pulmonary infections presenting as lung nodules could be indicative of septic emboli from bacteremia, central venous line access, or right-sided endocarditis. Microbiological confirmation of bacterial pneumonias in HCT can be elusive, as one study showed that only 29% of pneumonia cases had a pathogen identified.[25] Bronchoscopy with BAL can improve the chances of identifying a pathogen, where the sensitivity of culture of alveolar lavage fluid can be as high as 75%,[26] though most bronchoscopy studies in neutropenic recipients show a diagnostic yield of 23–55%.[14,22] Utilizing plasma cell-free DNA testing to identify pneumonia pathogens is a promising noninvasive diagnostic tool. Studies in children with community-acquired pneumonia showed an 86% sensitivity compared to 47% using standard culture and polymerase chain reaction (PCR)-based methods. Studies evaluating cell-free plasma sequencing in immunocompromised populations, including those with hematological malignancies, have shown comparable results at identifying pathogens, particularly bacterial ones, in these populations.[27,28]

2.1.1 | Nocardia

Pulmonary *nocardia* infections occur rarely in HCT recipients, but cases can be severe with up to a 40% mortality rate.[29] *Nocardia* infections are more likely to occur after 100 days from transplant, with one review showing a median time of infection onset at 8 months. Radiographic imaging of the lungs can show both nodular and consolidative patterns (Table 1, Figure 1A). Most importantly, a diagnosis of nocardiosis in an HCT recipient requires imaging of the brain, as central nervous system (CNS) involvement occurs in a third of all cases.[30]

2.2 | Fungal Infections

Pulmonary fungal infections remain a leading cause of infection related morbidity and mortality in HCT recipients.[31,32] Pulmonary mold infections remain some of the most common causes of invasive fungal infections (IFI), as one review showed an estimated incidence of invasive aspergillosis as high as 15%.[33] Antifungal prophylaxis is routinely used in this population, though the specific antifungal agent used varies depending on institutional practice and the patient's individual risk factors. Prophylaxis that includes activity against molds, such as *Aspergillus* and *Mucor*, has been shown to reduce IFI by as much as 50% in HCT recipients.[32,34,35]

2.2.1 | Aspergillosis

Pulmonary infections from *Aspergillus* species continue to affect those who have undergone HCT, although outcomes have improved with the development of antimold triazole therapies.[36] Host factors significantly impact the risk of developing pulmonary aspergillosis including prolonged neutropenia, corticosteroid use, GVHD, and a previous history of IFI.[37,38] The diagnosis of IFI, such as pulmonary aspergillosis, poses significant challenges, therefore, comprehensive evaluation using both invasive and noninvasive testing should be utilized. A

TABLE 1 Common causes of pulmonary complications.

Pulmonary complication	Radiographic findings (CT scan)						Time From transplant	Highlights	Source
	Focal	Multifocal/ Diffuse	Ground glass	Nodular	Consolidative	Cavitating			
Bacterial	X			X	X	X	Any time; incidence decreases after 30 days	Gram-negative pathogens: *E. coli*, *P. aeruginosa* Gram-positive pathogens: *S. pneumonia*, *S. viridans*, *S. aureus*	97
Viral		X	X	X	X		Any time, LRTI most likely to occur ≤ 100 days	Respiratory viral infections Cytomegalovirus	54
Fungal	X	X[a]	X	X	X	X	≥2 weeks	Halo and reversed halo sign in pulmonary mold infections	98
Mycobacterial	X	X[b]	x	X	X	X	≥1 month	Rare but more common than in general population	74
Toxoplasmosis		X	X				1–3 months	*T. Gondii* IgG +	79
PERDS		X	X		X		≤5–7 days of neutrophil engraftment	Fever, diarrhea, rash may be present	46
DAH		X	X		X		7–40 days	Bloody BAL fluid	99
TACO/TRALI		X	X				6 (TRALI) to 12 (TACO) hours from transfusion	Pulmonary edema caused by fluid overload (TACO) or pulmonary endothelial injury/leakage (TRALI)	97
BOS		X	X				≥100 days from allogeneic HCT	Associated with GVHD. Parenchymal mosaicism and air trapping	100, 101
IPS		X	X		X		≤4 months	Negative infectious work up via bronchoscopy required	95
COP	X	X	X	X	X		2–12 months	2% incidence Risk factors: HLA disparity, female to male HCT and peripheral blood stem cell transplant	102–104
Drug toxicity		X	X				≤100 days	Bleomycin, busulfan, methotrexate amiodarone, cytarabine, chlorambucil, fludarabin	105

Abbreviations: BOS, bronchiolitis obliterans syndrome; CT, computed tomography; COP, cryptogenic organizing pneumonia; DAH, diffuse alveolar hemorrhage; GVHD, graft versus host disease; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; IPS, idiopathic pneumonia syndrome; LRTI, lower respiratory tract infection; PERDS, peri engraftment respiratory distress syndrome; TACO, transfusion-associated circulatory overload; TRALI, transfusion-associated lung injury .

[a] *Pneumocycstis jirovecii*.

[b] Miliary.

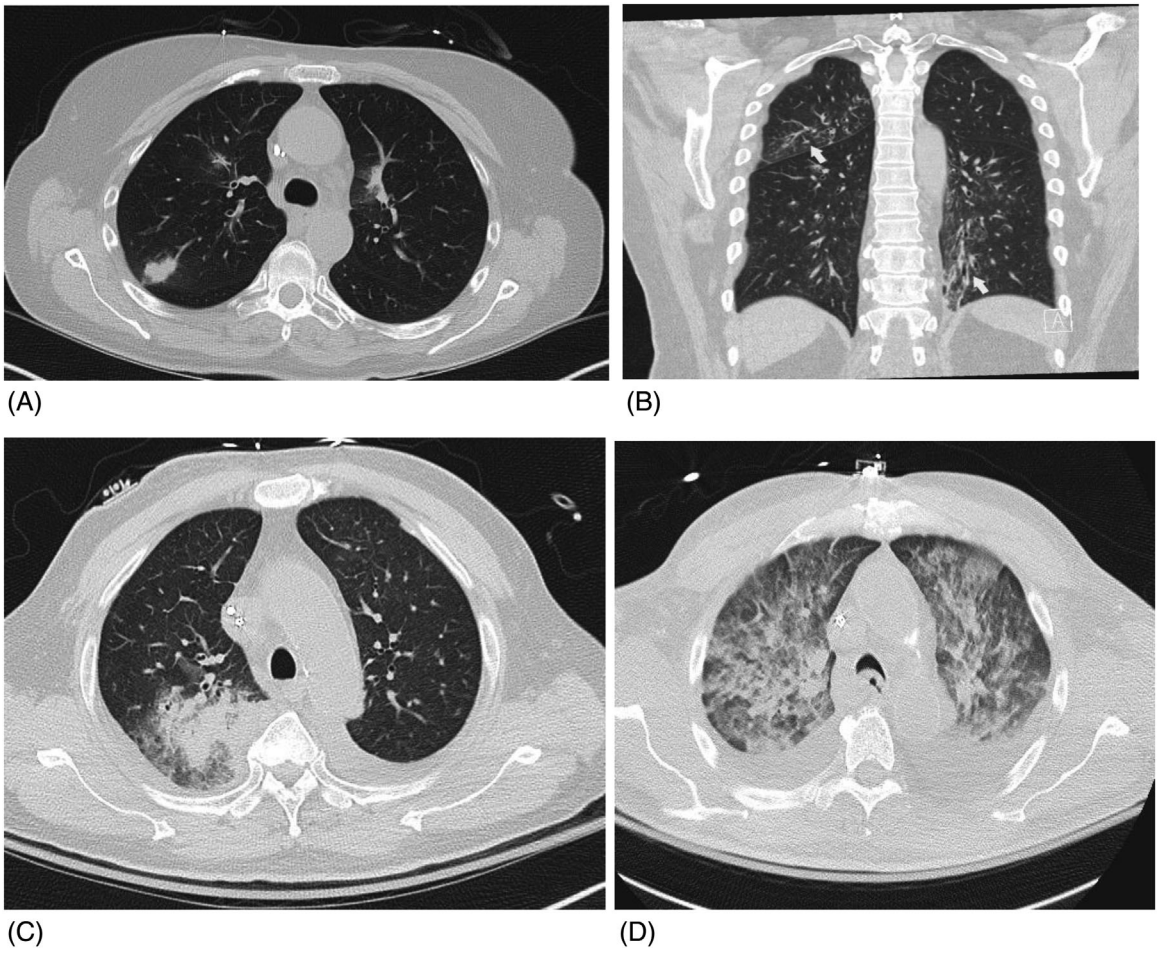

FIGURE 1 (A) Chest CT of allogeneic HCT recipient with fever. Multifocal nodular opacities. BAL nocardia culture and microbial cell free DNA with *Nocardia veterana*. (B) Chest CT of allogeneic HCT recipient with cough and fever. Tree-in-bud nodularities (left arrow) and peribronchial thickening (right arrow). Multiplex PCR of nares swab with human parainfluenza virus type 4. (C) Chest CT of allogeneic HCT recipient with fever and right pleuritic chest pain. Irregular consolidative and ground glass airspace disease in right upper lobe. BAL fungal culture and microbial cell-free DNA testing revealed *Rhizomucor miehei*. (D) Chest CT of autologous HCT recipient with rapid onset of dyspnea and hypoxia. Widespread bilateral ground glass airspace disease and moderate pleural effusions. Bronchoscopy confirmed diagnosis of diffuse alveolar hemorrhage.

CT of the chest, preferably with high resolution, is a noninvasive test with a potentially high negative predictive value for pulmonary aspergillosis.[37] There are several CT findings that are suggestive of pulmonary aspergillosis such as macronodules surrounded by a "halo sign" of ground-glass attenuation (Table 1). Tree-in-bud appearance of centrilobular nodules with bronchial wall thickening can be seen more with bronchoinvasive forms of infection. Consolidations may be pleural based, alveolar, or in patchy peribronchial areas. Cavity or air-crescent signs and pleural effusions can also be seen. As these findings are not specific for invasive pulmonary aspergillosis, radiographic evidence alone cannot be diagnostic.[37]

Culturing *Aspergillus spp*. can be technically difficult, even from tissue samples. The sensitivity of invasive aspergillosis with microscopy alone is at best 50%.[37] To improve diagnostic yield, more invasive procedures, such as bronchoscopy or biopsy, are often warranted. Additionally, tools other than culture and microscopy should be utilized such as fungal antigen assays. Galactomannan (GM) is a cell-wall component of *Aspergillus* that is released during fungal cell growth and can be an essential test to improve the diagnosis of invasive aspergillosis.[39] GM from blood and BAL is more sensitive than culture for diagnosing invasive aspergillosis, with BAL GM having superior sensitivity over blood GM in pulmonary infection (Table 2).[37] When interpreting GM results in HCT recipients, it is important to remember that (1) previous mold prophylaxis reduces the sensitivity of GM assays and (2) false-positive results occur more frequently in the first 100 days after transplant and in those with gut GVHD and mucositis.[39–42]

Another assay to aid in diagnosing IFI is 1-3-β-D-glucan (BDG), a component of the cell wall found in multiple different fungi. While the test can exhibit a high negative predictive value in immunocompromised populations, this assay has limitations with a high false positivity rate, particularly in those receiving immunoglobulin therapy, hemodialysis, or experiencing bacteremia.[42,43] Additionally, this assay has low specificity for *Aspergillus* species with cross-reactivity to other

TABLE 2 Sensitivity and specificity of common microbiological tests and assays.

Test	Sensitivity (%)	Specificity (%)	Diagnosis	Source
Serum galactomannan	43–100	78–92	Invasive aspergillosis	25, 36, 37
BAL Galactomannan	73–87	89–92	Invasive pulmonary aspergillosis	25, 106
Serum β-D-glucan	50–90	70–100	Invasive fungal infections	34, 107
BAL β-D-glucan	52–53	58–67	Invasive fungal infections	108, 109
BAL PJP PCR	70–100	81–100	PJP	47, 110
Respiratory virus multiplex PCR	70–80	96–98	Viral pulmonary infections	111
Plasma cell-free DNA	75–86	82–100	Various infections including pulmonary	26, 112
Serum cryptococcal antigen	93–100	93–100	Cryptococcal disease	113
NAAT MTB respiratory specimen	60–100	98–100	Pulmonary MTB	114, 115

Abbreviations: BAL, bronchoalveolar lavage; MTB, *Mycobacterium tuberculosis;* PJP, *Pneumocystis jirovecii* pneumonia; PCR, polymerase chain reaction; NAAT, nucleic acid amplification test.

fungal organisms.[44,45] Other diagnostic tools in evaluating pulmonary infections, including fungal causes, are described in Table 2.

2.2.2 | Mucormycosis

Various fungal organisms can cause pulmonary mucormycosis, and include *Rhizopus* spp., *Mucor* spp., *Cunninghamella spp*., and *Liththeimia* spp. Risk factors for pulmonary mucormycosis are similar to those seen with aspergillosis, as are the radiographic findings (Figure 1C). "Reverse halo" signs, which are ground-glass lesions, with a peripheral rim of consolidation, can be seen with many invasive mold infections but are most attributed to mucormycosis.[46,47] Many noninvasive tests, such as GM and BDG, do not detect mucormycosis and can be positive with other nonmucor fungal species, therefore, bronchoscopy with BAL and biopsy of the nodule for tissue visualization and culture are of high importance for diagnosis. Plasma cell-free DNA is a potential noninvasive test that can aid in diagnosis of mucormycosis as well as other pulmonary fungal infections.[27,28]

2.2.3 | Pneumocystis jirovecii

HCT recipients, particularly those with allogeneic donors, are at increased risk for *Pneumocystis jirovecii* pneumonia (PJP). Fortunately, with the standardization of prophylaxis, the incidence of PJP has been greatly reduced in patients undergoing HCT. Prior to standardization of prophylaxis, the incidence was 5–37%, with mortality rates as high as 34–62%. Risk factors for developing PJP include corticoid steroid use, prolonged lymphopenia, low $CD4^+$ T-cell count, GVHD, and medical nonadherence to prophylaxis.[48,49] Dyspnea and hypoxia are common with PJP, and CT of the chest typically shows diffuse, multifocal ground glass opacities.[50,51] The gold standard for diagnosing PJP has historically been direct visualization of cysts as *Pneumocystis* cannot be cultured.[52] Direct PCR testing of respiratory samples can improve sensitivity, but a positive result does not distinguish between colonization and infection.[53] Serum BDG assays are typically positive in the setting of PJP, therefore, a negative BDG result can be a useful tool in ruling out infection.[54–56]

2.2.4 | Endemic fungi

Endemic fungal infections, including cryptococcosis and histoplasmosis, are uncommonly encountered after HCT infection, likely attributable to the amount of triazole antifungal prophylaxis used in these populations. The incidence of cryptococcus in HCT recipients has varied in studies from 0.6 to 2%.[57,58] Cryptococcal disease is commonly diagnosed by serum cryptococcal antigen test, direct microscopic visualization in cultures, histopathologic or cytopathologic samples. CT imaging is helpful but not specific for pulmonary cryptococcus, with single to multiple nodules, cavitation, and consolidations seen. Given the risk for disseminated disease in this patient population, the diagnosis of pulmonary cryptococcosis should prompt evaluation for meningitis with lumbar puncture.[59]

While data are limited for IFIs following CAR-T, incidence rates appear to be lower compared to HCT recipients(1.2 vs 11.1%).[33,57,60] In a retrospective study of 280 patients receiving CAR-T cell therapy, eight patients developed IFIs, six of which were pulmonary infections.[57] CRS in CAR-T recipients has also been implicated in an increased risk for fungal infections, especially if patients receive steroids or tocilizumab.[22]

2.3 | Viral Infections

Pulmonary infections caused by respiratory viral infections (RVI) include a wide array of viruses including influenza, respiratory syncytial virus (RSV), parainfluenza virus, adenovirus, human metapneumovirus, and coronaviruses such as the severe acute respiratory syndrome coronavirus-2. Compared to immunocompetent populations, RVIs in HCT recipients are known to have higher rates of progression to lower

respiratory tract infections (LRTI) and mortality.[61] The incidence of RVI in these populations often correlates with the level of community activity and may be as high as 40%.[62] Outbreaks of certain respiratory viruses highlight the importance of strenuous infection prevention measures to reduce transmission of contagious viral infections. Another factor that may impair infection prevention measures is the prolonged periods of oral or mucosal viral shedding that is commonly seen in HCT recipients after RVI, even without the presence of any symptoms.[63] The clinical presentation for each respiratory virus is often indistinguishable from the others with upper respiratory tract symptoms (rhinorrhea, sore throat, nasal congestion) predominating. Evidence of LRTI includes hypoxia and abnormal chest imaging. Certain respiratory viruses have a seasonal distribution and are more likely to occur during the fall and winter months (RSV, influenza, and human metapneumovirus), while others can cause infection year-round (parainfluenza, adenovirus).

Morbidity from respiratory virus infections typically results from the development of LRTI. A review of RSV infections in HCT recipients showed that 44% of patients developed lower respiratory tract disease, and 9% died.[63] Studies evaluating risk factors for progression to LRTI have noted that infection in the early post-transplant period, neutropenia, lymphocytopenia, and augmented immunosuppression to treat GVHD all contribute to the risk of progression to LRTI.[64–66] An immunodeficiency scoring index was developed in RSV-infected HCT recipients to aid in the determining risk of progression to LRTI.[67] The scoring index includes such factors as age (greater than 40), neutropenia, lymphocytopenia, myeloablation, and presence of GVHD. This risk scoring system has also been validated in determining the progression risk for other RVIs including influenza and adenovirus.[68] Another issue related to RVIs in HCT recipients is the increased risk for coinfection with both bacteria and fungi.[69] There may also be an increased risk for GVHD and a decline in pulmonary function in those affected by RVIs.[70,71]

RVIs in CAR-T cell recipients are among the most common infections reported after infusion. In a review of 83 CAR-T recipients, 43% of patients had RVIs within the first 28 days of infusion, and 11% between 29 and 90 days after infusion. Most RVI cases were mild to moderate and occurred more frequently in patients with higher severity CRS and hypogammaglobulinemia.[20] COVID-19 infection in CAR-T recipients often causes severe disease with pneumonia, with one report noting a 41% mortality rate in infected patients.[72]

Radiographic findings for RVIs are included in Table 1. Pulmonary abnormalities in viral infections will more likely be multifocal, diffuse, and infiltrates will have a ground-glass appearance. Viral bronchiolitis manifests as micronodules, interlobular septal and bronchial wall thickening, and tree-in-bud opacities (Figure 1B).[73] As it is difficult to distinguish between viral infections based on chest imaging alone, molecular diagnostics have become the gold standard for diagnosing RVIs. Multiplex PCR panels performed on respiratory specimens collected from the upper respiratory tract (nares, nasopharyngeal, and oropharyngeal) and lower respiratory tract (BAL) and offer good sensitivity (Table 2), though they do not distinguish between asymptomatic infection or viral shedding.[74]

2.3.1 | Cytomegalovirus

Cytomegalovirus (CMV) pneumonia is a viral infection of the lung that differs from RVI in that it more commonly represents the reactivation of latent infection in allogeneic HCT recipients. The incidence of CMV pneumonia has decreased after HCT due to improved prophylaxis and monitoring strategies, but is more likely to occur in those with chronic GVHD and seropositive recipients.[75–77] CMV pneumonia can cause ground-glass opacities, but also nodular and consolidative abnormalities, usually bilateral.[78] Quantitative CMV DNA testing of the blood and BAL fluid can aid in diagnosis.[79] Pneumonia due to CMV or other herpesviruses in recipients of autologous HCT or CAR-T therapy is uncommon in comparison to allogeneic HCT recipients.[8,80]

2.4 | Mycobacteria

Mycobacterial tuberculosis (MTB) infections are 10 times more common in HCT recipients than the general population, but they are still rare. Incidence ranges between 1 and 16% depending on exposure history to endemic areas or individuals with a history of MTB.[81] For HCT recipients who develop MTB infection, about one-third will have extrapulmonary involvement so disseminated disease should be considered in this patient population. Latent tuberculosis can be difficult to diagnose in immunocompromised patients as they are more likely to have an attenuated response to tuberculin skin tests and indeterminate interferon-ϒ release assays (IGRA).[81] In a review evaluating the performance of IGRAs in immunocompromised patients, 20% of patients with a history of solid organ transplantation or HCT had indeterminate testing results.[82] Common chest CT findings for pulmonary MTB infections include pulmonary nodules, cavitary formation, tree-in-bud opacities, ground-glass opacifications, and pleural effusions.[81] Consolidations, especially in the lower lobes, are more often seen in reactivation versus upper lobe cavitary lesions seen with primary tuberculosis infections. Expedited diagnosis of pulmonary TB has been made possible using PCR techniques on induced AFB sputum, BAL, pleural fluid, or tissue biopsy cultures.[83] While histopathology of affected tissue usually shows caseating or noncaseating granulomas, these findings may be atypical or absent in HCT recipients.

Nontuberculous mycobacterium (NTM) infections are more common than tuberculosis infections in HCT even in TB-endemic areas.[84] The prevalence rates of NTM infections in HCT have been estimated between 0.4 and 10%.[85,86] Like with tuberculosis, diagnosis can be challenging as mycobacterial organisms are often slow to grow in cultures. CT chest imaging can be similar in appearance to that seen with MTB infections including cavitary changes (Table 1). Diagnosis of NTM relies on microscopic visualization of acid-fast bacilli in smears or cultures, but as certain NTM species can be nonpathogenic or transient colonizers, it important to interpret culture data carefully. Bronchoscopy with BAL or tissue biopsy with cultures can increase the chances of a diagnosis. In a study of 98 HCT recipients, 11% of patients were diagnosed with mycobacterial infection, with 82% of those diagnoses made by bronchoscopy with BAL.[87]

2.5 | Parasitic infections

2.5.1 | Toxoplasmosis

Pulmonary infections from *Toxoplasma gondii* can occur in HCT recipients, particularly in those who are seropositive prior to transplant, as these infections usually result from the reactivation of latent infection. The incidence of toxoplasmosis after HCT largely depends on prophylaxis and seroprevalence of the population. In a large systemic review of HCT recipients, 50 out of 399 cases of toxoplasmosis (13%) had evidence of pulmonary infection.[88] While most cases of toxoplasmosis in HCT occur in seropositive patients, up to 25% of those who develop toxoplasmosis infection are seronegative.[89] This issue highlights the fact that anti-*T. gondii* antibodies may be unreliable in a severely immunosuppressed stage. Serum *T. gondii* PCR techniques have been developed given this limitation.[90] CT chest imaging of pulmonary toxoplasmosis most commonly reveals patchy, bilateral ground-glass opacities, but rarely with nodules seen.[88] As toxoplasmosis commonly causes CNS disease, an evaluation for the presence of meningoencephalitis should be performed.

2.5.2 | Strongyloidiasis

Strongyloidiasis can cause chronic, latent infection, which may progress into dissemination and hyperinfection syndrome in the setting of immunosuppression. Multiple cases in HCT recipients have been reported, and pulmonary hyperinfection is a common presentation.[91] Mortality rates of this hyperinfection syndrome are estimated to be as high as 83% in HCT recipients.[92] Pulmonary strongyloidiasis can present as a fever and cough but progress to severe respiratory failure and septic shock. Peripheral eosinophilia may be absent in the setting of immunosuppression. CT chest imaging of active pulmonary infections can present as nonspecific diffuse ground glass opacities.[93] Serologic testing should be done prior to transplant in those with specific risk factors and empiric treatment should be considered for those who have lived in an endemic region.[94] Acute strongyloidiasis can be detected using the same serologic tests and direct microscopic visualization on sputum, BAL, or stool samples.[92]

3 | NONINFECTIOUS CAUSES OF PULMONARY ABNORMALITIES

Noninfectious pulmonary complications in HCT include a broad spectrum of pathology, and in one review, accounted for over a third of all pulmonary complications in HCT recipients.[95] Noninfectious pulmonary complications may be difficult to delineate from infectious, as clinical presentation and chest imaging findings can overlap. An infectious workup is often performed in the setting of noninfectious pulmonary complications. A negative infectious workup is often a key component in diagnosing various noninfectious pulmonary diseases (i.e., idiopathic pneumonia syndrome [IDS]).

3.1 | Pulmonary edema and infusion reactions

Acute pulmonary edema is the most common noninfectious complication after HCT and can result from both cardiogenic and noncardiogenic causes.[95] HCT recipients often receive multiple blood product transfusions and pulmonary edema related to transfusions can be severe. Transfusion-related acute lung injury (TRALI) is a form of noncardiogenic pulmonary edema that occurs within 6 h after blood product infusion and results from donor-antibody-mediated pulmonary endothelial injury and capillary leakage.[96] TRALI presents as sudden-onset dyspnea with hypoxia, or an increased oxygen requirement, in a mechanically ventilated patient. Fever or hypotension can also be present.[97] Chest imaging shows pulmonary edema (Table 1), though there are no other signs of cardiac dysfunction. Transfusion associated circulatory overload (TACO) presents similarly to TRALI, but there is evidence of cardiogenic or circulatory overload, such as an elevated BNP and pre-existing cardiac disease, and renal dysfunction. TACO can occur up to 12 h after a transfusion, and is usually not associated with fever and hypotension.[98,99]

3.2 | Periengraftment respiratory distress syndrome

During the period of neutrophil engraftment in HCT recipients, pulmonary complications related to engraftment syndrome, a systemic disorder associated with diffuse pulmonary capillary leakage, can occur. The pulmonary component of engraftment syndrome, or periengraftment respiratory distress syndrome (PERDS) presents as fever and hypoxia that occur within 5 days of neutrophil engraftment.[100] Other signs of engraftment syndrome may be present such as an erythematous rash, diarrhea, and rapid fluid retention.[101] Chest imaging shows bilateral pulmonary opacities and/or edema (Table 1).[51]

3.3 | Diffuse alveolar hemorrhage

One of the most potentially lethal pulmonary complications that can occur in the HCT population is diffuse alveolar hemorrhage (DAH). This entity occurs in roughly 5% of HCT recipients and occurs in both allogeneic and autologous HCT with a median time of onset of 23.5 days after transplant.[102] Diagnosis is confirmed via bronchoscopy, either with progressively bloody return of BAL fluid from sequential aliquots, or if more than 20% hemosiderin-laden macrophages are seen on cytological evaluation of BAL fluid.[103] Common signs include abrupt-onset tachypnea, hypoxia, fever, but hemoptysis is rare.[104] Chest imaging regularly shows diffuse or bilateral ground glass and consolidative opacities (Figure 1D).

3.4 | Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) in HCT recipients describes the condition of diffuse lung injury without the presence of infection, cardiac dysfunction, or fluid overload. Symptoms are identical to infectious pneumonia with fever, cough, and hypoxia but LRTI has been adequately ruled out with either BAL or lung biopsy that are negative for microbial pathogens. In a review of allogeneic HCT recipients, 3.7% of patients developed IPS a median of 25 days after transplant. Bilateral multilobar airspace opacities are the predominant findings on chest imaging. Those who have received myeloablative conditioning with high-dose total body irradiation have a higher risk for IPS.[105]

3.5 | Other noninfectious pulmonary complications

Other pulmonary complications encountered in HCT recipients are described in Table 1. Bronchiolitis obliterans syndrome (BOS) is a disease predominantly seen in allogeneic HCT recipients as a pulmonary manifestation of chronic GVHD. This obstructive lung disease causes significant morbidity in affected individuals, who often have signs of air trapping seen on radiographic imaging. Cryptogenic organizing pneumonia (COP) is another noninfectious complication seen in allogeneic HCT recipients that typically occurs after 2 months from transplant.[106] Pulmonary toxicity from drugs, including chemotherapeutic agents, will typically occur within the first 100 days from transplant.[107]

CAR-T recipients are at risk for many of the same noninfectious pulmonary complications as HCT recipients such as TACO, TRALI, and DAH. Up to one-half of CAR-T recipients may experience CRS, a systemic inflammatory process that can result in fever, hypotension, neurotoxicity, and organ injury. Hypoxia is a common feature of CRS, often ascribed to pulmonary edema, but CRS can also lead to acute respiratory distress syndrome.[108]

4 | CONCLUSION

HCT and CAR-T recipients are at risk for an array of pulmonary complications including those of infectious and noninfectious etiologies. Diagnosing these pulmonary abnormalities can be challenging, yet utilizing the available tools, such as CT imaging, bronchoscopy, antigen assays, and PCR, can assist in accurately identifying the underlying cause.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

This is an invited review article.

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