Pediatric Radiology (2022) 52:2017–2028
https://doi.org/10.1007/s00247-022-05403-w

THORACIC IMAGING

Early pulmonary complications related to cancer treatment in children

Cara E. Morin[1] · Morgan P. McBee[2,3] · Lama Elbahlawan[4] · Lindsay M. Griffin[5] · Gabriela M. Maron[6] · HaiThuy N. Nguyen[7,8] · Akshay Sharma[9] · Elizabeth J. Snyder[10] · Jean Jeudy[11]

Received: 8 December 2021 / Revised: 1 March 2022 / Accepted: 14 May 2022 / Published online: 2 July 2022

Abstract
In this review, we summarize early pulmonary complications related to cancer therapy in children and highlight characteristic findings on imaging that should be familiar to a radiologist reviewing imaging from pediatric cancer patients.

Keywords Cancer therapy · Children · Complications · Computed tomography · Oncology · Pulmonary · Thoracic

Introduction

Pulmonary complications are common early in the course of cancer treatment and might be related to chemotherapy, radiation therapy or hematopoietic cell transplant. However, detecting early pulmonary complications related to cancer therapy can be challenging for the radiologist because of pre-existing co-morbidities and the co-existence of infectious and non-infectious etiologies, many of which have overlapping imaging findings. Prompt recognition of these pulmonary conditions, especially those with distinctive radiologic features, can lead to earlier appropriate intervention. In the hematopoietic cell transplant population, complications are commonly divided into early phase (< 100 days) and late phase (> 100 days) after transplant. Pulmonary complications follow a predictable timeline after hematopoietic cell transplant, and thus it is important for the radiologist to know how long after transplant the images are obtained. Early pulmonary complications (first 100 days after transplant) are often subdivided into the neutropenic, or pre-engraftment, period (within 30 days of transplant) and early post-transplant period (30–100 days after transplant). We use that general definition in this article, primarily focusing on complications that arise following hematopoietic cell transplant, although we include complications that can be related to chemotherapy and radiation.

Because many of the imaging findings of early pulmonary complications can be subtle, nonspecific or overlapping, chest radiography has been shown to have limited utility in this population; therefore, we focus on CT imaging findings [1–5]. In the early setting, single-phase (inspiratory) chest CT with or without intravenous contrast agent and with thin slices (< 3 mm) is sufficient for imaging purposes. Next, we

✉ Cara E. Morin
cara.morin@cchmc.org

1 Department of Radiology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229, USA

2 Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

3 Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

4 Division of Critical Care Medicine, St. Jude Children's Research Hospital, Memphis, TN, USA

5 Ann & Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

6 Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, USA

7 Singleton Department of Radiology, Texas Children's Hospital, Houston, TX, USA

8 Department of Radiology, Baylor College of Medicine, Houston, TX, USA

9 Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN, USA

10 Department of Radiology and Radiological Science, Vanderbilt University Medical Center, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

11 Department of Diagnostic Radiology & Nuclear Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

summarize some early pulmonary complications and present recent updates, highlighting characteristic findings indicating specific complications of cancer therapy.

Hematopoietic cell transplantation

More than 23,000 individuals undergo a hematopoietic cell transplant in the United States each year, with about 2,000 of these performed in children younger than 18 years [6, 7]. In an allogeneic hematopoietic cell transplant (alloHCT), hematopoietic stem and progenitor cells from an unaffected donor are infused into a recipient with a blood disorder after administering a conditioning regimen. It is a potentially curative treatment for high-risk hematologic malignancies and several non-malignant diseases of the hematopoietic system. An autologous hematopoietic cell transplant (autoHCT) involves reinfusion of a patient's own hematopoietic stem and progenitor cells that have been collected and cryopreserved to rescue the patient's hematopoiesis after administration of high-dose chemotherapy. A conditioning (or preparative) regimen consisting of a combination of chemotherapy, radiation and T cell–directed antibodies is generally used prior to graft infusion, to eliminate malignant cells, prepare the recipient to receive the graft and make space in the recipient bone marrow for incoming cells. The hematopoietic cell graft is obtained from donors by either performing a bone marrow harvest or mobilizing the hematopoietic stem and progenitor cells and collecting them from the peripheral blood. Umbilical cord blood, collected at the time of birth, can also be used as a source of hematopoietic stem and progenitor cells. Donors are generally matched to the recipient using human leukocyte antigen (HLA), though mismatched or half-matched (haploidentical) donors are increasingly used because of improvements in post-transplant immune therapeutics and graft manipulation techniques. Immunosuppressive drugs are often used after an alloHCT to prevent immunological complications such as graft rejection and graft vs. host disease (GVHD). GVHD prophylaxis is not required after an autoHCT because there is no immune mismatch between the graft and the recipient.

All hematopoietic cell transplant recipients are at a high risk of both infectious and non-infectious complications. Infections can be caused by multiple bacterial, fungal and viral pathogens, with morbidity and mortality from infections being much higher in this vulnerable population than in immunocompetent individuals [8–12]. Infectious complications occur in about 71% of people undergoing hematopoietic cell transplant, with death in up to 20% [13–15]. Many factors increase the infection risk in hematopoietic cell transplant recipients, including the breakdown of skin and mucosal barriers from the conditioning regimen [16, 17], delayed/poor immune reconstitution [18] and use of immunosuppressive agents during conditioning and after hematopoietic cell transplant for GVHD prevention. Immune reconstitution is further dependent on the donor type (e.g., umbilical cord blood or mismatched unrelated donor transplantations), graft source (bone marrow vs. peripheral blood vs. cord blood), graft manipulation (T cell depletion), use of serotherapy (anti-thymocyte globulin vs. alemtuzumab) and occurrence of GVHD as well as post-transplant GVHD prevention strategies like pharmacologic immunosuppression [18–21].

Non-infectious pulmonary complications of hematopoietic cell transplant are common and unfortunately have poor outcomes [22–24]. Non-infectious pulmonary complications occur in 12–30% of pediatric patients following hematopoietic cell transplant and account for 16% of deaths [25–32]. Early non-infectious pulmonary complications include pulmonary edema, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome (PERDS), pulmonary veno-occlusive disease (PVOD) and acute radiation pneumonitis.

The defining imaging characteristics, predisposing factors, clinical signs and symptoms, and treatments are summarized for infectious (Table 1; Figs. 1, 2, 3 and 4) and non-infectious (Table 2; Figs. 5, 6, 7, 8, 9 and 10) early pulmonary complications.

Infectious complications

First 30 days

In the first 30 days post-hematopoietic cell transplant, the frequencies of infectious and non-infectious complications are similar [33]. In the neutropenic phase, infectious complications commonly include bacterial pneumonia, respiratory viruses and invasive fungal pneumonia [34].

Bacterial pneumonia characteristically produces focal segmental or lobar pulmonary opacities. Commonly reported pathogens include *Enterococcus, Pseudomonas aeruginosa, Stenotrophomonas* and *Staphylococcus aureus* [34]. Respiratory viruses commonly reported in this period include respiratory syncytial virus, rhinovirus, parainfluenza virus and coronaviruses including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [35–37]. Respiratory viral infections often have nonspecific imaging findings, ranging from normal CT scans to single findings or combinations of nodules, ground-glass attenuation and consolidation [38–40]. Guidelines exist for imaging diagnosis of invasive pulmonary mold diseases. Diagnosis of probable pulmonary aspergillosis requires the presence of at least one of the following patterns on CT: dense, well-circumscribed lesion(s) with or without a halo sign (Fig. 1); air crescent sign; cavity (Fig. 2); or wedge-shape and segmental or lobar consolidation (Fig. 1) [41, 42]. For other

Table 1 Diagnostic characteristics for early (< 100 days) infectious pulmonary complications following cancer treatment

Entity	Predisposition	Typical onset	Clinical signs/symptoms	CT findings	Treatment
Bacterial pneumonia	AlloHCT, autoHCT, chemo	< 30 days	Fever, hypoxia, cough	Focal segmental or lobar pulmonary opacities	Antibacterial therapy
Respiratory viruses (respiratory syncytial virus, rhinovirus, parainfluenza, coronaviruses, influenza, human meta-pneumovirus)	AlloHCT, autoHCT, chemo	< 30 days 30–100 days	Fever, cough, increased work of breathing, hypoxia	Normal CT scans to single findings or combinations of nodules, ground-glass attenuation, consolidation	Supportive care; antivirals in select cases
Invasive fungal pneumonia	AlloHCT, autoHCT, chemotherapy, immunosuppressive cancer therapies, GVHD grades III and IV	< 30 days 30–100 days in children with GVHD and receiving IST	Fever, chest pain, hemoptysis, hypoxia	Pulmonary aspergillosis: 1 of the following findings in CT: dense, well-circumscribed lesion(s) with or without a halo sign (Fig. 1); air crescent sign; cavity (Fig. 2); or wedge-shape and segmental or lobar consolidation (Fig. 1). For other pulmonary mold diseases include prior criteria with addition of reversed halo sign	Antifungal therapy (triazoles, polyenes, echinocandins)
Herpes virus (HSV, VZV, CMV, HHV6)	AlloHCT, autoHCT	30–100 days	Fever, tachypnea	Diffuse or multifocal areas of ground-glass attenuation, consolidations, and/or nodules	Supportive care, antivirals
Pneumocystis jiroveci pneumonia	AlloHCT, autoHCT, immunosuppressive cancer therapies	30–100 days	Tachypnea, hypoxemia	Bilateral, diffuse ground-glass opacities with interstitial opacities, miliary pattern (Fig. 4)	TMP-SMZ

alloHCT allogeneic hematopoietic cell transplant, *autoHCT* autologous hematopoietic cell transplant, *Chemo* chemotherapy, *CMV* cytomegalovirus, *GVHD* graft versus host disease, *HCT* hematopoietic cell transplantation, *HHV6* human herpesvirus 6, *HSV* herpes simplex viruses, *IST* immunosuppressive therapy, *TMP-SMZ* trimethoprim and sulfamethoxazole, *VZV* varicella zoster virus

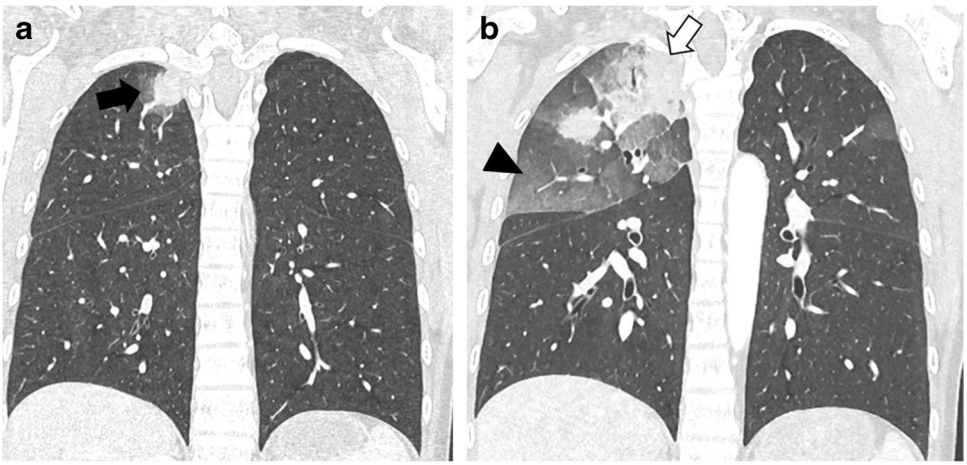

Fig. 1 Invasive pulmonary aspergillosis in a 17-year-old girl with relapsed acute myelogenous leukemia (AML) post hematopoietic cell transplant, on salvage therapy undergoing evaluation for chimeric antigen receptor T cell therapy. **a** Coronal CT image obtained 1 month after start of therapy demonstrates the halo sign with a right upper lobe nodular opacity with surrounding peripheral ground-glass opacity (*arrow*). **b** Two months after start of therapy, coronal CT shows that the right upper lobe opacity has increased in size with a wedge-shape area of consolidation (*arrow*) and adjacent ground-glass opacity (*arrowhead*)

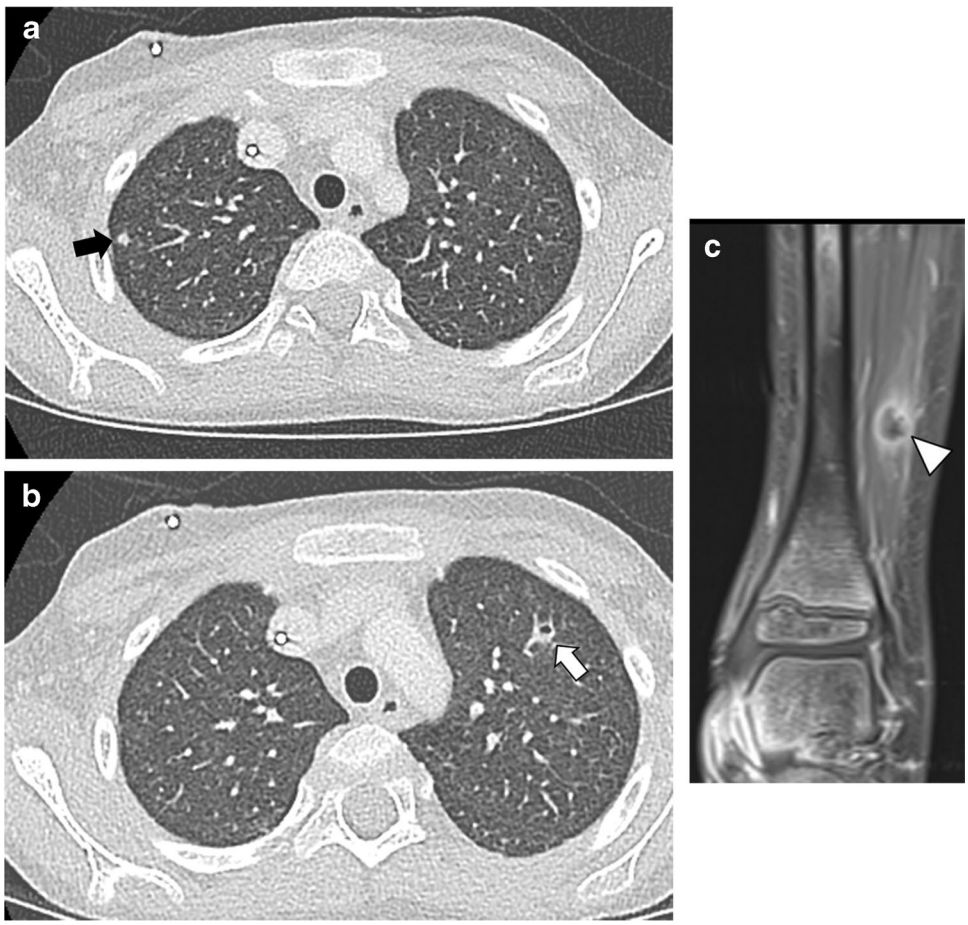

Fig. 2 Disseminated fungal infection (trichosporonosis) in a 6-year-old boy with B cell acute lymphocytic leukemia (ALL) on induction day 36 admitted for febrile neutropenia. **a, b** Axial CT images of the right and left upper lobes show a nodular opacity in the right upper lobe (*arrow* in **a**) and a nodular opacity with central cavitation in the left upper lobe (*arrow* in **b**). **c** Post-contrast T1-weighted fat-saturated coronal MR image of the ankle in the same boy shows a peripherally enhancing intramuscular collection (*arrowhead*), consistent with abscess

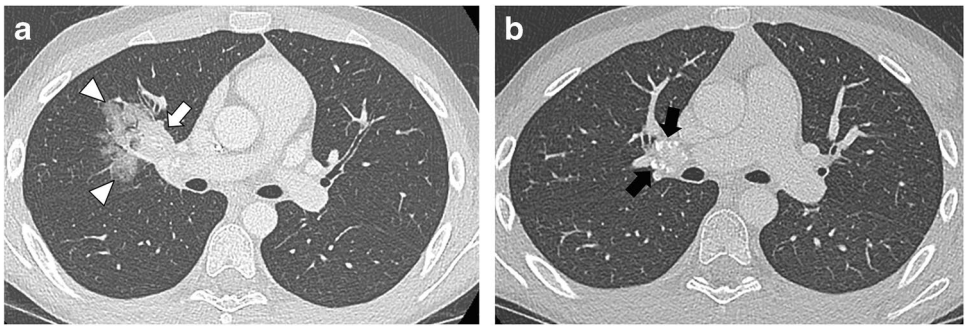

Fig. 3 Reactivation histoplasmosis in an 11-year-old boy with osteosarcoma of the humerus on week 9 of chemotherapy. He presented with mild upper respiratory symptoms, fever and neutropenia. **a** Axial CT image shows a right hilar mass (*arrow*) with adjacent intraparenchymal ground-glass opacities (*arrowheads*). **b** Axial CT image shows central calcifications (*arrows*) within the hilar mass. Because the parenchymal opacities were not present on baseline imaging (not shown), there was some concern that this might represent disease progression during therapy; however, infectious disease consultants were confident this represented reactivation histoplasmosis given a positive yeast antigen test, and the parenchymal abnormality resolved on follow-up imaging

pulmonary mold diseases, the same four criteria apply with the addition of a reverse halo sign. However, several case series have demonstrated that compared to adults, children are less likely to present with cavitation or the air crescent or halo signs [43]. In endemic areas, relevant mycoses such as *Histoplasma*, *Blastomyces* and *Coccidioides* should be considered. In pediatric oncology patients, CT findings of pulmonary histoplasmosis might manifest as parenchymal consolidation or as a hilar mass (Fig. 3) [44].

30–100 days

More than 30 days post-hematopoietic stem cell transplant, as the immune system reconstitutes, the frequency of infectious complications and the spectrum of causative agents change. Viral infections from respiratory viruses remain common, including influenza and human metapneumovirus as well as infections from herpes viruses (e.g., herpes simplex, varicella-zoster, cytomegalovirus, human herpesvirus 6) and adenoviruses [34, 35]. As with respiratory viruses, findings of infections with herpes viruses are nonspecific and can include diffuse or multifocal areas of ground-glass attenuation, consolidations and nodules [39, 45]. *Pneumocystis jiroveci* pneumonia (PJP) might present in this period, with radiographic features of bilateral ground-glass opacities, nodular opacities with or without cavitation, or a miliary pattern (Fig. 4) [41, 42]. It should be noted that while the incidence of PJP has tremendously decreased as a result of universal prophylaxis, breakthrough cases are still observed and a high index of suspicion must be maintained to establish a diagnosis. Radiologic examination, along with clinical suspicion, remains the cornerstone to establish a diagnosis of PJP. Invasive fungal infections in this period can present in children receiving immunosuppressive therapy with steroids or other recognized T cell immunosuppressants, and those with steroid-refractory grades III or IV GVHD [41, 42]. Radiologic criteria are the same as previously described.

Non-infectious complications

First 30 days

Non-infectious complications in the first 30 days include pulmonary edema and idiopathic pneumonia syndrome. The most common in the first 30 days is pulmonary edema, which is often multifactorial, related to either direct hydrostatic changes (e.g., fluid overload) or inflammation-related increased permeability (e.g., direct toxicity of chemotherapy) [33]. Pulmonary edema manifests as enlargement of pulmonary vessels, diffuse ground-glass opacification and septal thickening on CT (Fig. 5). The combination of diffuse ground-glass opacities and intralobular and interlobular septal thickening can cause a crazy-paving pattern. These children might also have cardiomegaly and pleural effusions, which can help differentiate pulmonary edema from other causes.

Transfusion-related acute lung injury is an increasingly recognized specific cause of pulmonary edema in transplant patients defined as acute respiratory distress and new bilateral lung infiltrates on anteroposterior/posteroanterior chest radiograph within 6 h of transfusion in the absence of cardiac dysfunction or other cause of lung injury [46, 47]. Imaging findings are the same as pulmonary edema from other causes.

30–100 days

In the early post-transplant period (30–100 days after hematopoietic stem cell transplant), idiopathic pneumonia

Table 2 Diagnostic characteristics for early (< 100 days) non-infectious pulmonary complications following cancer treatment

Entity	Predisposition	Typical onset	Clinical signs/symptoms	CT findings (Fig. X)	Treatment
Pulmonary edema	AlloHCT, autoHCT, chemo, prior XRT may contribute	< 30 days	Hypoxia, dyspnea, ± cardiomegaly, peripheral edema (if cardiogenic)	Enlargement of pulmonary vessels, diffuse ground-glass opacification, septal thickening (Fig. 5), cardiomegaly, pleural effusions	Diuresis + supportive care + Rx of the underlying cause
Idiopathic pneumonia syndrome	AlloHCT	< 100 days	Rapidly progressive respiratory failure	Focal or diffuse airspace or reticular opacities (Fig. 6)	Supportive; steroids, TNF-inhibitors
Diffuse alveolar hemorrhage	AlloHCT, autoHCT, rarely after chemotherapy alone	< 30 days	Dyspnea, hypoxia, hemoptysis in ~ 66% of cases	Diffuse ground-glass opacities, "crazy-paving" pattern (Fig. 7)	Steroids, correct coagulopathies if applicable, inhaled tranexamic acid, inhaled recombinant activated factor VII
Peri-engraftment respiratory distress syndrome (PERDS)	AlloHCT (more common), autoHCT	< 30 days	Skin rash, fever, hypoxia, capillary leak	Diffuse ground-glass opacification, which can be associated with thickening of the interlobular septa, perihilar or peribronchial consolidation, and pleural effusions (Fig. 8)	Steroids, supportive care
Acute GVHD	AlloHCT only	< 100 days	Rare; may have a rash, dyspnea, abdominal pain	Diffuse parenchymal opacities that resemble pulmonary edema	Steroids
Pulmonary VOD		< 100 days	Dyspnea	Dilatation of the main pulmonary artery, right-side cardiac chamber enlargement, centrilobular ground-glass opacities, smooth interlobular septal thickening, and mediastinal lymph node enlargement (Fig. 9)	Steroids and defibrotide
Acute radiation pneumonitis	XRT	< 6 months	Dyspnea, cough	Ground-glass and/or consolidative opacities in the radiation field (Fig. 10)	Delay treatment, steroids

alloHCT allogeneic hematopoietic cell transplant, *autoHCT* autologous hematopoietic cell transplant, *Chemo* chemotherapy, *GVHD* graft versus host disease, *Rx* treatment, *TNF* tumor necrosis factor, *VOD* veno-occlusive disease, *XRT* radiation therapy

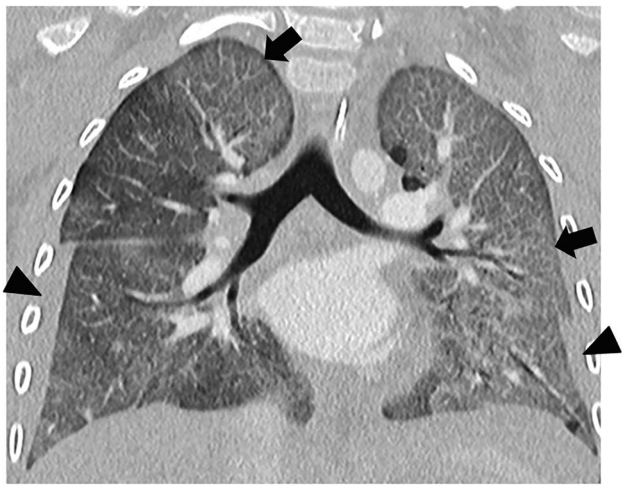

Fig. 4 *Pneumocystis jiroveci* pneumonia in a 6-year-old male with acute lymphocytic leukemia (ALL) on week 14 of therapy with prolonged febrile neutropenia and respiratory distress requiring intensive care admission. He was diagnosed with *Pneumocystis jirovecii* pneumonia by bronchoaveolar lavage (BAL). Coronal CT image shows diffuse ground glass opacification (*arrows*). Small pleural effusions are present (*arrowheads*), which are atypical in PCP

syndrome continues to be a common cause of respiratory symptoms. Additionally, acute pulmonary GVHD can occur, although it is very rare. CT findings of acute pulmonary GVHD are nonspecific and might include diffuse parenchymal opacities that resemble pulmonary edema [33].

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome is an acute lung dysfunction of noninfectious etiology [48]. Idiopathic pneumonia syndrome includes a constellation of clinical presentations and is characterized by widespread alveolar injury in the absence of cardiac, renal, iatrogenic fluid overload, or infectious organisms [48]. As defined by the American Thoracic Society, multiple etiologies are included under the umbrella term "idiopathic pneumonia syndrome" based on the site of injury. Acute injury might involve the pulmonary parenchyma (e.g., acute respiratory distress syndrome and radiation pneumonitis), the vascular endothelium (e.g., diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome and pulmonary veno-occlusive disease), or the airway epithelium (e.g., organizing pneumonia, described in the accompanying article on late pulmonary complications). Frequently, it is not possible to specifically categorize patients and some remain unclassifiable [48] (Fig. 6). Major risk factors of idiopathic pneumonia syndrome, regardless of specific etiology, include a myeloablative conditioning regimen including total body irradiation and the occurrence of acute GVHD. The incidence of idiopathic pneumonia syndrome has been declining; mortality, however, continues to be high with a reported survival rate of only 30% within a year post-hematopoietic cell transplant [49]. Current evidence indicates that many children diagnosed with idiopathic pneumonia syndrome in fact have an occult infection. Half of people post-transplant diagnosed with idiopathic pneumonia syndrome had pathogens detected in bronchoalveolar lavage and the most frequent organism was human herpesvirus-6 (HHV-6) [50]. Patients are usually treated with corticosteroids and tumor necrosis factor (TNF) inhibitors like etanercept. CT findings are nonspecific and might include focal or diffuse airspace or reticular opacities in the setting of rapidly progressive respiratory failure (Fig. 6). Next, we review some additional etiologies under the umbrella of idiopathic pneumonia syndrome and their imaging findings.

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage occurs in 2% of the pediatric hematopoietic cell transplant recipients with a median onset time of 1.7 months. Unfortunately, the prognosis remains dismal, with a mortality rate as high as 76% within 100 days post-transplant and 84% within 6 months [25]. Children present with fever, nonproductive cough, dyspnea and hypoxia. Hemoptysis suggests diffuse alveolar hemorrhage, but it occurs in only 66% of cases [48]. The diagnosis is usually established by bronchoscopy with

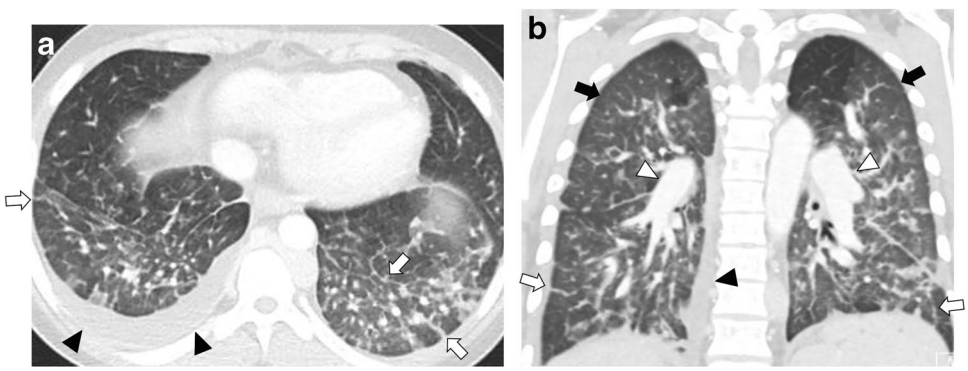

Fig. 5 Pulmonary edema in a 16-year-old boy with relapsed acute myelogenous leukemia (AML) and history of cardiac defect. **a**, **b** Axial (**a**) and coronal (**b**) CT images show widespread ground-glass opacity (*black arrows*) with regions of smooth interlobular septal thickening (*white arrows*). The pulmonary arteries are enlarged (*white arrowheads*). There is also a small layering right pleural effusion (*black arrowheads*)

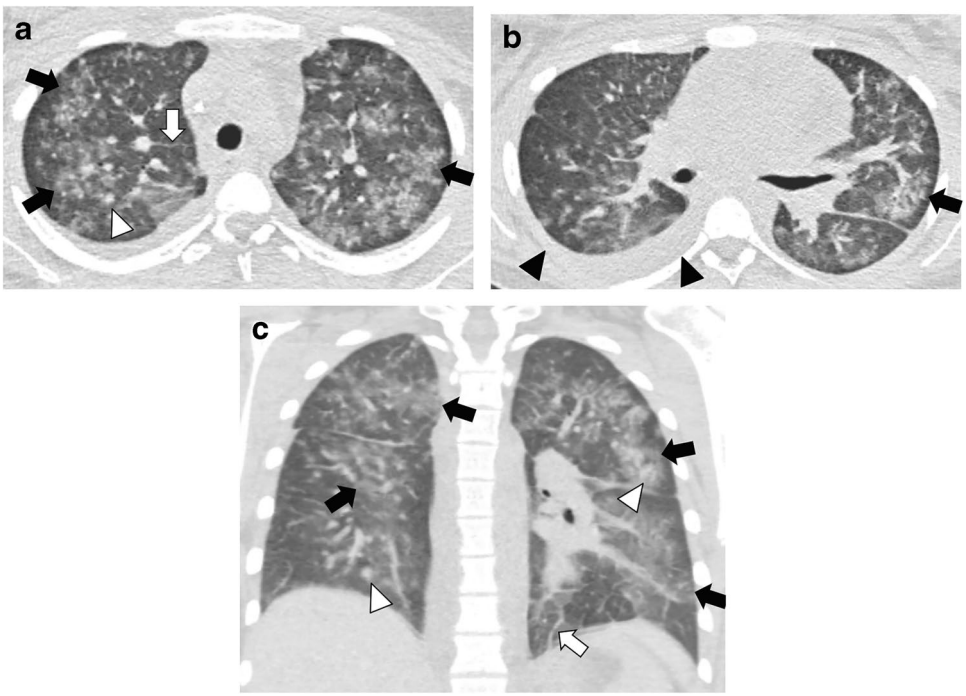

Fig. 6 Unclassified idiopathic pulmonary syndrome (IPS) in a 16-year-old girl with history of acute lymphocytic leukemia (ALL) day 13 post allogeneic hematopoietic cell transplant (alloHCT). IPS was diagnosed clinically based on respiratory status and absence of findings of infection. The girl improved clinically and radiographically (*not shown*) after treatment with steroids and etanercept. **a**-**c** Axial (**a** and **b**) and coronal CT (**c**) images show patchy ground-glass opacities (*black arrows*) with interspersed regions of more consolidative nodular opacities (*white arrowhead*) and reticular opacities (*white arrows*). There is also a small right pleural effusion (*black arrowheads*)

increasingly bloodier lavage return or ≥ 20% hemosiderin-laden macrophages. Pathogenesis is thought to be related to lung vascular injury with loss of integrity in the alveolar–capillary basement membrane, secondary to inflammation, conditioning regimen, thrombotic microangiopathy or occult infection. As a result, the distal alveolar airspace is obliterated by blood, fibrin and inflammatory cells, which impairs gas exchange, and refractory hypoxemia and acute respiratory failure follow. Treatment includes systemic corticosteroids, inhaled tranexamic acid and inhaled recombinant activated factor VII. CT findings include diffuse ground-glass opacities and crazy-paving pattern, related to intra- and interlobular septal thickening (Fig. 7). These children typically do not have cardiomegaly, prominent

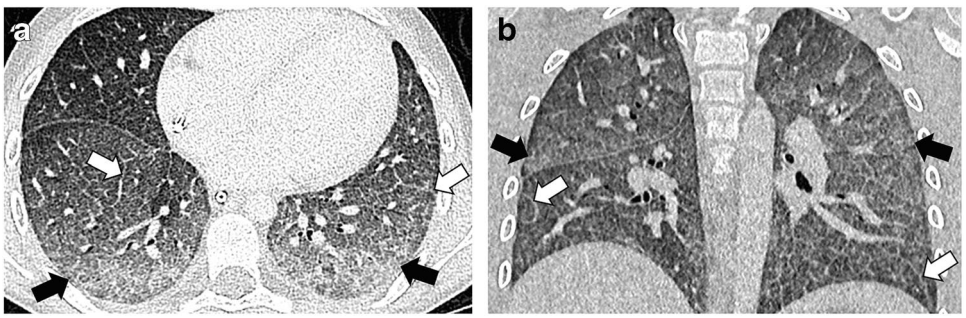

Fig. 7 Diffuse alveolar hemorrhage in a 13-year-old male with a primary diagnosis of relapsed acute myelogenous leukemia (AML), admitted to intensive care for respiratory distress. Bronchoscopy revealed diffuse hemorrhage and no identified infectious etiology. **a**, **b** Axial (**a**) and coronal CT (**b**) images show a "crazy paving" pattern with a mosaic pattern secondary to diffuse ground-glass opacities (*black arrows*) with intralobular and interlobular septal thickening (*white arrows*)

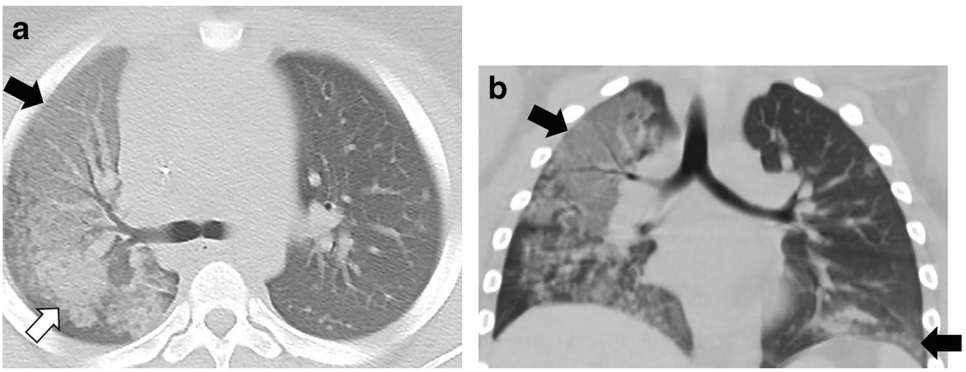

Fig. 8 Peri-engraftment respiratory distress syndrome (PERDS) in a 14-year-old girl with severe aplastic anemia on day 19 after bone marrow transplant with worsening respiratory symptoms. **a**, **b** Axial (**a**) and coronal (**b**) CT images show ground-glass opacities (*black arrows*) and areas of consolidation (*white arrow*)

pulmonary vessels or effusions, differentiating this entity from pulmonary edema.

Peri-engraftment respiratory distress syndrome (PERDS)

Peri-engraftment respiratory distress syndrome (PERDS) is an early pulmonary complication that can be encountered at the time of engraftment on days 5–21 post-transplant. Proinflammatory cytokine release at the time of neutrophil engraftment results in pulmonary edema and lung injury. These children usually develop fever, erythematous rash and hypoxia. Transient encephalopathy and hepatic and renal dysfunction might also occur. Acute respiratory failure occurs in 2% of children undergoing hematopoietic cell transplant but usually is transient with a good prognosis and greater than 80% overall survival [51]. Treatment is geared toward fluid management, especially given that capillary leak is common during this phase and a brief course of corticosteroids is typically used to ameliorate the inflammatory response. CT findings include diffuse ground-glass opacification, which can be associated with thickening of the interlobular septa, perihilar or peribronchial consolidation, and pleural effusions (Fig. 8). These children typically do not have cardiomegaly or other findings of pulmonary edema. Clinically, the presence of a skin rash and fever might be helpful to make the diagnosis.

Pulmonary veno-occlusive disease (PVOD)

Pulmonary veno-occlusive disease (PVOD) is an uncommon but fatal pulmonary complication post-transplant. Underlying pathology involves the obliteration of pulmonary venules with intimal fibrosis and luminal obstruction. These changes lead to pulmonary hypertension that might not respond to vasodilators. In fact, hypoxia can worsen with vasodilator therapy secondary to pulmonary edema with increased pulmonary blood flow in the setting of fixed post-capillary obstruction [52]. The onset of PVOD is typically weeks to months following transplant, although a minority of cases manifest within days. Dyspnea is an early symptom in this population. Unfortunately, treatment is usually not effective and includes corticosteroids and defibrotide [53]. On CT, findings include centrilobular ground-glass opacities, smooth interlobular septal thickening and mediastinal lymph node enlargement [52, 54]. Additional CT findings can include dilatation of the main pulmonary artery, right-side cardiac chamber enlargement, nodules, and pleural or pericardial effusions (Fig. 9) [54].

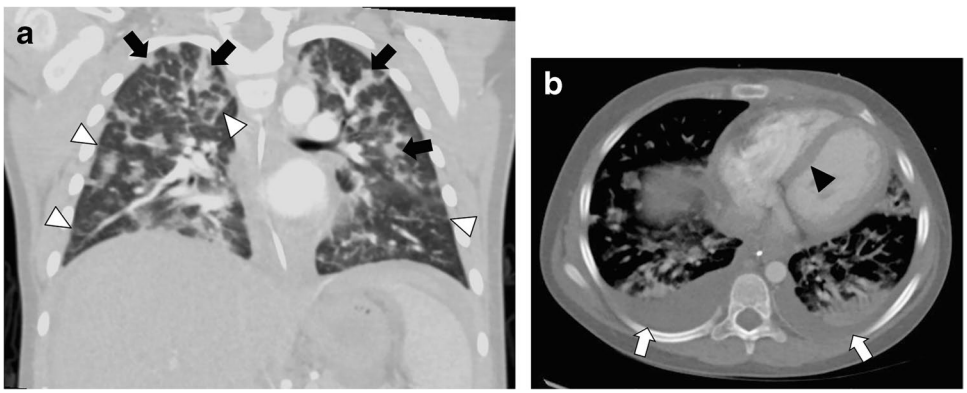

Fig. 9 Pulmonary veno-occlusive disease (PVOD) in a 7-year-old girl with history of status post allogeneic hematopoietic cell transplant (alloHCT) (day + 40) and history of hepatic veno-occlusive disease. **a**, **b** Coronal CT image in lung window (**a**) shows scattered nodular opacities (*black arrows*) with smooth interlobular septal thickening (*white arrowheads*). Axial CT image in bone window (**b**) shows small bilateral pleural effusions (*white arrows*) and leftward bowing of the interventricular septum (*black arrowhead*)

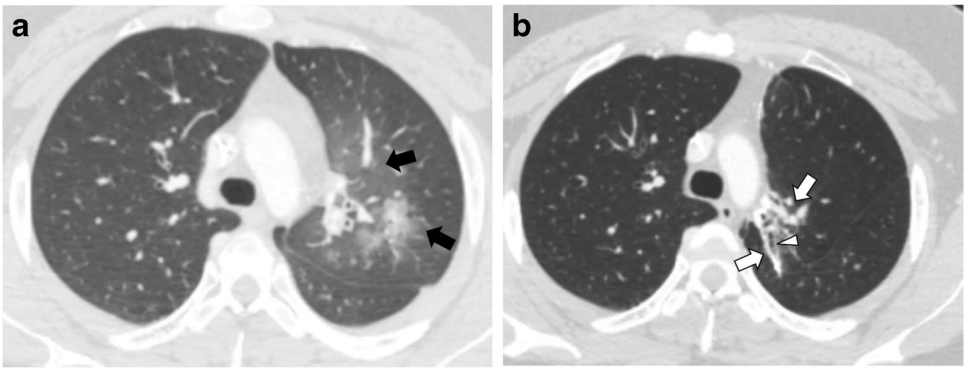

Fig. 10 Radiation pneumonitis in a 17-year-old boy with Ewing-like sarcoma of the left lung post radiation and chemotherapy. **a** Axial CT image in the acute phase shows areas of ground-glass opacity in the radiation field (*arrows*). **b** One year later, axial CT shows fibrosis as evidenced by the volume loss and architectural distortion (*arrows*) and traction bronchiectasis (*arrowhead*)

Acute radiation pneumonitis

Acute radiation pneumonitis can occur in children receiving radiation therapy for primary or metastatic lesions of the lung or the chest wall. Because of advances in modes and delivery of radiation to primary mediastinal lymphomas, radiation pneumonitis is becoming less common in these children (~6% of pediatric patients in one study) [55]. While total body irradiation as part of the conditioning regimen is not a typical cause of acute radiation pneumonitis, total lymphoid irradiation, which specifically targets the thymus, thoracic and cervical lymph nodes, sometimes causes localized pneumonitis. CT findings of acute radiation pneumonitis include ground-glass opacities and consolidation localized to the irradiated field with a well-demarcated border between the airspace opacities and the normal lung (Fig. 10) [56, 57]. Over time, imaging findings typically evolve to localized fibrotic change with volume loss, architectural distortion and traction bronchiectasis [56].

Conclusion

Early pulmonary complications following cancer therapy and hematopoietic cell transplant are common and frequently present with similar, nonspecific imaging findings. It is important to interpret imaging findings in the context of clinical signs and symptoms as well as the type and timing of treatments, ideally with close collaboration between the radiologist and the oncology, infectious disease, pulmonary and critical care teams.

Declarations

Conflicts of interest Dr. A. Sharma has received a consultant fee from Spotlight Therapeutics and Medexus Inc. He has also received research funding from CRISPR Therapeutics and honoraria from Vindico Medical Education. He is the St. Jude Children's Research Hospital site principal investigator of clinical trials for genome editing of sickle cell disease sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics (NCT03745287) and by Novartis (NCT04443907). The industry sponsors provide funding for the clinical trial, which includes salary support paid to Dr. Sharma's institution. These disclosures are not directly related to the content in this manuscript. Dr. Sharma also acknowledges support from the American Society of Hematology (ASH) Scholar Award. The other authors report no conflicts of interest.

References

1. Heussel CP, Kauczor HU, Heussel GE et al (1999) Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol 17:796–805
2. Graham NJ, Müller NL, Miller RR, Shepherd JD (1991) Intrathoracic complications following allogeneic bone marrow transplantation: CT findings. Radiology 181:153–156
3. Barloon TJ, Galvin JR, Mori M et al (1991) High-resolution ultrafast chest CT in the clinical management of febrile bone marrow transplant patients with normal or nonspecific chest roentgenograms. Chest 99:928–933
4. Korones DN, Hussong MR, Gullace MA (1997) Routine chest radiography of children with cancer hospitalized for fever and neutropenia: is it really necessary? Cancer 80:1160–1164
5. Roberts SD, Wells GM, Gandhi NM et al (2012) Diagnostic value of routine chest radiography in febrile, neutropenic children for early detection of pneumonia and mould infections. Support Care Cancer 20:2589–2594
6. D'Souza A, Fretham C, Lee SJ et al (2020) Current use of and trends in hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant 26:e177–e182
7. Phelan R, Arora M, Chen M (2020) Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary

slides. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx. Accessed 23 Mar 2022
8. Omer AK, Ziakas PD, Anagnostou T et al (2013) Risk factors for invasive fungal disease after allogeneic hematopoietic stem cell transplantation: a single center experience. Biol Blood Marrow Transplant 19:1190–1196
9. Zając-Spychała O, Wachowiak J, Pieczonka A et al (2016) Bacterial infections in pediatric hematopoietic stem cell transplantation recipients: incidence, epidemiology, and spectrum of pathogens: report of the Polish Pediatric Group for Hematopoietic Stem Cell Transplantation. Transpl Infect Dis 18:690–698
10. Caldas Teixeira D, Martins Oliveira Diniz L, Orlandi Mourão PH et al (2018) Infection surveillance in pediatric hematopoietic stem cell transplantation recipients. Eur J Haematol 100:69–74
11. Lindemans CA, Leen AM, Boelens JJ (2010) How I treat adenovirus in hematopoietic stem cell transplant recipients. Blood 116:5476–5485
12. Rowe RG, Guo D, Lee M et al (2016) Cytomegalovirus infection in pediatric hematopoietic stem cell transplantation: risk factors for primary infection and cases of recurrent and late infection at a single center. Biol Blood Marrow Transplant 22:1275–1283
13. U.S. Centers for Disease Control (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Accessed 2 Nov 2021
14. Engels EA, Ellis CA, Supran SE et al (1999) Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk. Clin Infect Dis 28:256–266
15. Junghanss C, Marr KA, Carter RA et al (2002) Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. Biol Blood Marrow Transplant 8:512–520
16. Tomblyn M, Chiller T, Einsele H et al (2009) Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 15:1143–1238
17. van der Velden WJFM, Herbers AHE, Feuth T et al (2010) Intestinal damage determines the inflammatory response and early complications in patients receiving conditioning for a stem cell transplantation. PLoS One 5:e15156
18. Bock AM, Cao Q, Ferrieri P et al (2013) Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. Biol Blood Marrow Transplant 19:102–108
19. Servais S, Lengline E, Porcher R et al (2014) Long-term immune reconstitution and infection burden after mismatched hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 20:507–517
20. Ramaprasad C, Pouch S, Pitrak DL (2010) Neutrophil function after bone marrow and hematopoietic stem cell transplant. Leuk Lymphoma 51:756–767
21. Ferrara JLM, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373:1550–1561
22. Kaya Z, Weiner DJ, Yilmaz D et al (2009) Lung function, pulmonary complications, and mortality after allogeneic blood and marrow transplantation in children. Biol Blood Marrow Transplant 15:817–826
23. Rowan CM, Gertz SJ, McArthur J et al (2016) Invasive mechanical ventilation and mortality in pediatric hematopoietic stem cell transplantation: a multicenter study. Pediatr Crit Care Med 17:294–302
24. Zinter MS, Logan BR, Fretham C et al (2020) Comprehensive prognostication in critically ill pediatric hematopoietic cell transplant patients: results from merging the Center for International Blood and Marrow Transplant Research (CIBMTR) and Virtual Pediatric Systems (VPS) registries. Biol Blood Marrow Transplant 26:333–342
25. Broglie L, Fretham C, Al-Seraihy A et al (2019) Pulmonary complications in pediatric and adolescent patients following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 25:2024–2030
26. Eikenberry M, Bartakova H, Defor T et al (2005) Natural history of pulmonary complications in children after bone marrow transplantation. Biol Blood Marrow Transplant 11:56–64
27. Elbahlawan L, Srinivasan A, Morrison RR (2016) A critical care and transplantation-based approach to acute respiratory failure after hematopoietic stem cell transplantation in children. Biol Blood Marrow Transplant 22:617–626
28. Park M, Koh KN, Kim BE et al (2011) Clinical features of late onset non-infectious pulmonary complications following pediatric allogeneic hematopoietic stem cell transplantation. Clin Transplant 25:E168–E176
29. Elbahlawan L, Rains KJ, Stokes DC (2017) Respiratory care considerations in the childhood cancer patient. Respir Care 62:765–775
30. Lucena CM, Torres A, Rovira M et al (2014) Pulmonary complications in hematopoietic SCT: a prospective study. Bone Marrow Transplant 49:1293–1299
31. Elbahlawan L, Galdo AM, Ribeiro RC (2021) Pulmonary manifestations of hematologic and oncologic diseases in children. Pediatr Clin North Am 68:61–80
32. Patriarca F, Poletti V, Costabel U et al (2009) Clinical presentation, outcome and risk factors of late-onset non-infectious pulmonary complications after allogeneic stem cell transplantation. Curr Stem Cell Res Ther 4:161–167
33. Peña E, Souza CA, Escuissato DL et al (2014) Noninfectious pulmonary complications after hematopoietic stem cell transplantation: practical approach to imaging diagnosis. Radiographics 34:663–683
34. Gertz SJ, McArthur J, Hsing DD et al (2020) Respiratory pathogens associated with intubated pediatric patients following hematopoietic cell transplant. Transpl Infect Dis 22:e13297
35. Fisher BT, Danziger-Isakov L, Sweet LR et al (2018) A multicenter consortium to define the epidemiology and outcomes of inpatient respiratory viral infections in pediatric hematopoietic stem cell transplant recipients. J Pediatric Infect Dis Soc 7:275–282
36. Vicent MG, Martinez AP, Trabazo Del Castillo M et al (2020) COVID-19 in pediatric hematopoietic stem cell transplantation: the experience of Spanish Group of Transplant (GETMON/GETH). Pediatr Blood Cancer 67:e28514
37. Barhoom D, Mohseni R, Hamidieh AA et al (2021) Clinical effects of COVID-19 on hematopoietic stem cell transplant outcomes in pediatric patients. Exp Clin Transplant 19:501–507
38. Franquet T, Rodriguez S, Martino R et al (2006) Thin-section CT findings in hematopoietic stem cell transplantation recipients with respiratory virus pneumonia. AJR Am J Roentgenol 187:1085–1090
39. Escuissato DL, Gasparetto EL, Marchiori E et al (2005) Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. AJR Am J Roentgenol 185:608–615
40. Bayramoglu Z, Canıpek E, Comert RG et al (2021) Imaging features of pediatric COVID-19 on chest radiography and chest CT: a retrospective, single-center study. Acad Radiol 28:18–27
41. Alexander BD, Lamoth F, Heussel CP et al (2021) Guidance on imaging for invasive pulmonary aspergillosis and mucormycosis: from the Imaging Working Group for the Revision and Update of the Consensus Definitions of Fungal Disease from the EORTC/MSGERC. Clin Infect Dis 72:S79–S88
42. Donnelly JP, Chen SC, Kauffman CA et al (2020) Revision and update of the consensus definitions of invasive fungal disease

from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 71:1367–1376
43. Burgos A, Zaoutis TE, Dvorak CC et al (2008) Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics 121:e1286-1294
44. Adderson EE (2004) Histoplasmosis in a pediatric oncology center. J Pediatr 144:100–106
45. Chong S, Kim TS, Cho EY (2010) Herpes simplex virus pneumonia: high-resolution CT findings. Br J Radiol 83:585–589
46. Kleinman S, Caulfield T, Chan P et al (2004) Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 44:1774–1789
47. Bux J, Sachs UJH (2007) The pathogenesis of transfusion-related acute lung injury (TRALI). Br J Haematol 136:788–799
48. Panoskaltsis-Mortari A, Griese M, Madtes DK et al (2011) An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. Am J Respir Crit Care Med 183:1262–1279
49. Wenger DS, Triplette M, Crothers K et al (2020) Incidence, risk factors, and outcomes of idiopathic pneumonia syndrome after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 26:413–420
50. Seo S, Renaud C, Kuypers JM et al (2015) Idiopathic pneumonia syndrome after hematopoietic cell transplantation: evidence of occult infectious etiologies. Blood 125:3789–3797
51. Elbahlawan L, Morrison R, Li Y et al (2020) Outcome of acute respiratory failure secondary to engraftment in children after hematopoietic stem cell transplant. Front Oncol 10:584269
52. Montani D, Lau EM, Dorfmüller P et al (2016) Pulmonary veno-occlusive disease. Eur Respir J 47:1518–1534
53. Bunte MC, Patnaik MM, Pritzker MR, Burns LJ (2008) Pulmonary veno-occlusive disease following hematopoietic stem cell transplantation: a rare model of endothelial dysfunction. Bone Marrow Transplant 41:677–686
54. Resten A, Maitre S, Humbert M et al (2004) Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. AJR Am J Roentgenol 183:65–70
55. Lewis GD, Agrusa JE, Teh BS et al (2018) Radiation pneumonitis in pediatric Hodgkin lymphoma patients receiving radiation therapy to the chest. Pract Radiat Oncol 8:e364–e368
56. Käsmann L, Dietrich A, Staab-Weijnitz CA et al (2020) Radiation-induced lung toxicity — cellular and molecular mechanisms of pathogenesis, management, and literature review. Radiat Oncol 15:214
57. Ikezoe J, Takashima S, Morimoto S et al (1988) CT appearance of acute radiation-induced injury in the lung. AJR Am J Roentgenol 150:765–770