A review of pathogens causing lower respiratory tract infection in the pediatric hematopoietic stem cell transplant recipient

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Abstract. Pediatric hematopoietic stem cell transplant recipients are at risk for acquiring a variety of lower respiratory tract infections (LRTI), which result in frequent pediatric intensive care unit admission with high mortality. Recent advances in conditioning regimens, opportunistic infection prophylaxis, diagnostic tools, and treatment modalities have broadly impacted our understanding of LRTI among these vulnerable patients. In this review, the most common bacteria, viruses, and fungi causing LRTI in pediatric hematopoietic stem cell transplant patients are discussed.

Keywords: Pediatric, bone marrow transplant, hematopoietic stem cell transplant, intensive care unit, critical care, pulmonary, lower respiratory tract, infection, pneumonia, immunocompromise

1. Introduction

Over 2,500 children underwent hematopoietic stem cell transplantation (HSCT) for life-threatening diseases in the United States in 2013 [1]. Approximately two/three of these transplants were allogeneic, of which 70% were from unrelated donors [1]. As the number of pediatric HSCT performed continues to increase, the indications for HSCT are becoming

increasingly varied. The leading indication for pediatric HSCT continues to be acute leukemia, but bone marrow failure disorders, primary immunodeficiencies, and an increasing number of metabolic and storage disorders, malignancies, hemoglobinopathies, and rheumatologic diseases now contribute to the heterogeneity of the pediatric HSCT population [1].

Of children who undergo HSCT, 17–44% will require pediatric intensive care unit (PICU) admission within one yr of diagnosis [2–5], and 73–88% of these PICU admissions are due to pulmonary complications [2, 3, 6, 7]. Pulmonary complications are defined as clinical signs of lower respiratory tract dysfunction (i.e.: increased work of breathing, hypoxia,

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abnormal auscultation) with associated radiographic correlates [8]. They occur within 100 days post-HSCT in up to 40% of pediatric HSCT patients, and reach 74% incidence when pediatric HSCT patients are followed to a median of 5 yr [8]. The causes of pulmonary complications in this population are diverse and include infection, non-infectious inflammation, treatment-related lung injury, fluid overload, and recurrent primary disease [9, 10].

Lower respiratory tract infections (LRTI) constitute 35–50% of pulmonary complications for children with HSCT [6, 8, 11, 12] and are a leading cause of death, with current mortality rates exceeding 45% [13–18]. While mortality has decreased significantly in recent years due to reduced intensity conditioning regimens, aggressive infection prophylaxis, and improvements in PICU care, LRTI in pediatric HSCT patients remains one of the deadliest disease entities in the field of pediatrics [3, 7].

2. Immune reconstitution

Like other infections, risk for LRTI is dependent on the stage of immune reconstitution. Following HSCT, the pre-engraftment stage is marked by profound pancytopenia, including leukopenia of all lineages [19]. This usually lasts 3–4 wk and correlates with the greatest risk for bacterial infections, although nosocomial fungal infections can present as well. Approximately 5% of autologous and 10% of allogeneic recipients will have an LRTI in this phase, which in total account for approximately half of all post-HSCT LRTI [20, 21].

The early post-engraftment period is marked by restoration of the innate immune system, starting with monocytes and followed by granulocytes, macrophages, and natural killer cells [19]. This period correlates with a reduction in the risk of bacterial LRTI and a concomitant increase in the risk for viral and fungal LRTI. This phase may last approximately 3 mo, although functional assays measuring macrophage and neutrophil chemotaxis, phagocytosis, and bacterial killing within the lungs have demonstrated impairment well beyond the resolution of absolute peripheral blood cell counts [22–24].

The late post-engraftment period correlates with slow restoration of B and T-cell adaptive immunity and may last beyond 1 yr [19]. Immunoglobulin (Ig) G, IgM, and IgA class and subclass deficiencies can persist beyond 1 yr and are associated with graft versus

host disease (GVHD) and poor response to vaccines [25]. Even after restoration of peripheral blood cell counts, mitogen proliferation and cytokine production remain impaired in both alveolar B and T-cells, contributing to lasting susceptibility to LRTI [24, 26–29].

The overall pace of immune reconstitution is variable among patients and affected by total body irradiation, myeloablative conditioning, stem cell source, donor type and match, graft T-cell depletion (including *ex vivo* T-cell depleted grafts and *in vivo* antibody administration with agents such as anti-thymocyte globulin or alemtuzumab), GVHD, and cytomegalovirus (CMV) reactivation [15, 17, 19]. Other factors predisposing HSCT patients to LRTI include previously compromised lung health, pre-transplant pulmonary function testing, and pulmonary veno-occlusive disease [8, 30].

3. Diagnostics

LRTI can be diagnosed with modified centers for disease control criteria that take into account fever, radiographic changes, and at least two characteristic pulmonary symptoms (i.e.: dyspnea, rhonchi, sputum, cough, and/or rales) [31, 32]. Conventional chest roentgenography may be normal in 40–56% of patients [32, 33] and should not be used to exclude LRTI; high resolution computerized tomography (HR-CT) identifies abnormalities in 66–94% of patients [33, 34]. Diagnostic testing fails to identify a pathogen in up to one third of LRTI cases; in such cases, the diagnosis can be made based on clinical suspicion and response to antimicrobial treatment [15]. When diagnostic testing does identify a pathogen, the majority of positive specimens come from the serum or upper respiratory secretions (63%), with the minority coming from bronchoalveolar lavage (BAL, 29%) and open lung biopsy (OLB) (8%) [15].

Invasive testing typically occurs after empiric broad-spectrum antimicrobial treatment fails; at this point, pathogen yield for BAL is 27–73% [6, 8, 13, 35–46] and pathogen yield for OLB is 22–57% [44, 45, 47–51], with up to 67% concordance between the two procedures [47, 51]. BAL performed within four days of respiratory symptom onset has been associated with better pathogen yield and decreased mortality compared with BAL performed after 4 days [52]. When BAL and OLB do not yield pathogens, they are often useful in differentiating LRTI from non-infectious lung

pathology and have been shown to lead to an overall change in specific therapy in 30–63% of BAL and 17–90% of OLB [13, 36, 37, 39, 43, 47–49], although these therapy changes have not been consistently associated with reduced mortality, perhaps due to their frequent reservation until late in the course of illness. With these data in mind, we advocate for early and comprehensive diagnostic workup with the goal of tailoring treatment to circumvent disease progression where possible. Despite diagnostic efforts, post-mortem analyses have identified invasive pulmonary pathogens in up to 30% of patients undergoing autopsy [43, 53].

4. Bacteria

Bacterial LRTI occurs in up to 15% of pediatric HSCT patients; nearly 50% of these occur in the first 100 days post-HSCT [30]. Approximately 29% of cases will isolate a pathogen from peripheral blood culture and 25% from uncontaminated sputum [15, 30]. The remainder may undergo invasive diagnostic testing or may be diagnosed based on improvement with antibacterial therapy [15, 30]. When present, chest radiograph findings include segmental (71%), lobar (19%), and patchy infiltrates (10%) [15, 30]. HR-CT findings include nodular opacities (81%), air space consolidation (69%), and ground glass opacities with or without halo (35%, Fig. 1) [34]. Pathogenesis of bacterial LRTI usually occurs via hematogenous spread to the lungs rather than direct respiratory tract migration. Bacteremia occurs in 20–30% of HSCT patients; 22% of these will present with concomitant LRTI [54–56]. While bacteremia is more frequently Gram-positive

(58–80%) than Gram-negative (16–38%) [55, 57–59], bacteremia with concurrent LRTI is equally likely to be Gram-positive as Gram-negative [60].

Bacteremia is largely due to central line associated blood stream infection or gut translocation secondary to mucositis or GVHD [61]. Improvements in central line associated blood stream infection prevention efforts such as line hub cleansing and minimizing the number of times a line is accessed have significantly decreased hematogenous seeding by skin flora and nosocomial contaminants [58]. Despite this, virulent skin flora including *Staphylococcus aureus*, *Staphylococcus epidermidis*, and other coagulase negative staphylococci have been implicated in LRTI in this population.

Duration of mucositis is closely related to myeloablative conditioning intensity and neutropenia [55, 62]. The viridans streptococcus species (including *Staphylococcus mitis* and *Staphylococcus oralis*) are well-recognized to cause bacteremia with associated LRTI in patients with mucositis. In one cohort with viridans streptococcal bacteremia, 46% of patients needed supplemental oxygen and 31% required mechanical ventilation [54]. Patients with viridans streptococcal LRTI have high rates of pulmonary hemorrhage and acute respiratory distress syndrome; mortality estimates exceed 50% [54, 63].

Intestinal mucositis and GVHD also facilitate bacteremia and allow hematogenous seeding of the lungs. Some data suggest that *Escherichia coli* and *Klebsiella* bacteremia have significantly lower mortality than *Enterobacter*, *Citrobacter*, and *Serratia* organisms or *Pseudomonas aeruginosa* (<3%, 25%, 40%, respectively) [55], but the associated rates of LRTI

Fig. 1. High-resolution computerized tomography of the thorax of an 11-year-old with T-cell acute lymphocytic leukemia, day +397 status post matched related donor peripheral blood stem cell transplant. There is a right lower lobe pulmonary nodule surrounded by a ground glass halo. Pseudomonal lower respiratory tract infection was diagnosed based on bronchoalveolar lavage culture. Co-infections included cytomegalovirus (grown in bronchoalveolar lavage culture), oral candidiasis, and transient pseudomonal bacteremia. Views are; a) axial view, b) coronal view, and c) sagittal view.

in cases of enteric Gram-negative bacteremia are not well-described.

Although less common, bacterial pneumonia can also occur due to direct respiratory tract inoculation. *Streptococcus pneumoniae* LRTI has been documented for HSCT patients with and without anti-pneumococcal prophylaxis, with increased risk in patients with chronic GVHD [61, 64]. *H. influenza* has been isolated from BAL specimens [47]. Multiple *Bordetella* species infections have been linked to LRTI in HSCT patients, including *Bordetella pertussis* [65–68]. *Legionella* has been documented in HSCT patients as well, with presentation ranging from cavitary lesions to pulmonary abscesses requiring pneumonectomy [69–73]. Intracellular pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been implicated in LRTI [13]. Tuberculous and non-tuberculous mycobacteria have been isolated from blood, sputum, lower respiratory tract secretions, OLB, and autopsy in patients with LRTI [74–78], often despite negative purified protein derivative skin tests and the absence of HR-CT findings [37, 48, 74–80]. The incidence of mycobacterial LRTI in pediatric HSCT patients outside of endemic areas is low but reaches 16% in endemic parts of the world [81]. Evaluation should include traditional diagnostics as well as reverse transcription polymerase chain reaction (PCR) for mycobacterial DNA in sputum and BAL fluid [82].

Prevention of bacterial infections relies on strict transmission precautions among both healthcare workers and visitors [83, 84]. Fluoroquinolone prophylaxis may reduce risk for LRTI in adults but is not standard practice for pediatrics [15]. Antimicrobial gut decontamination has conflicting evidence for reducing the incidence of bacteremia and is not standard practice [59]. Surveillance blood cultures in asymptomatic individuals are of unclear benefit as well [85, 86]. Intravenous immunoglobulin (IVIG) is sometimes used for severe post-transplant hypogammaglobulinemia to reduce risk of infection [61]. Vaccination series should be repeated in HSCT patients but are not typically possible until late immune reconstitution [87].

When suspected, bacterial LRTI should be treated with broad-spectrum antibiotics with attention paid to local resistance patterns [55]. An alarming increase in multi-drug resistant (MDR) isolates in the HSCT population has been documented and includes up to one third of pseudomonal isolates; these MDR pathogens are associated with higher mortality than non-MDR

strains [88]. Overall mortality for bacterial LRTI in pediatric HSCT patients is 22% [30].

5. Viruses

Recognition of the role of respiratory viruses as pulmonary pathogens in pediatric HSCT patients has increased significantly in the last 30 yr due to the widespread availability of advanced diagnostic tools such as multiplex and quantitative PCR. While respiratory viruses are well-implicated in the pathogenesis of upper respiratory tract infections (URIs), they are being increasingly isolated as pathogens in severe and fatal LRTIs [89].

Cohort studies of pediatric HSCT patients presenting with either URI or LRTI identify viruses in over 33% of children via testing of nasopharyngeal secretions [11], although the true incidence of viral infection is likely higher. Viral co-infection is common and occurs in 8–10% of upper respiratory aspirates [11]. Patients who undergo invasive testing (BAL, OLB) represent a select subgroup with severe and often undifferentiated disease, and these procedures implicate a virus in 10–34% of patients [40, 45, 47, 52].

Respiratory viruses in pediatric HSCT patients can broadly be divided into two groups—community respiratory viruses (CRVs) and herpesviruses. Although CRVs are often considered community-acquired, up to 50% of CRV URIs and 75% of CRV LRTIs in the pediatric HSCT population may be acquired during inpatient hospital stays [11].

5.1. CRVs

The natural history of CRVs post-HSCT varies significantly by geography, season, diagnostic strategy, and cohort. CRVs are typically newly-acquired infections, although some patients may have chronic infection that intensifies to cause symptomatic illness. As infection may be mild or asymptomatic in immunocompetent hosts, transmission precautions are crucial. CRV progression from URI to LRTI occurs in 38–55% of HSCT patients [11, 90] and risk for LRTI has been associated with lymphopenia, allogeneic HSCT, and GVHD [91].

5.1.1. Adenovirus

Adenoviridae are particularly pathogenic due to their ability to cause viremia and multi-system

disease. Pulmonary findings include severe pneumonitis, pulmonary hemorrhage, and hypoxemic respiratory failure [92]. There are six subgenera A-F that account for at least 51 known viral subtypes with regional variation in strain prevalence and overall sequence homology of <25%, and therefore a comprehensive PCR platform is mandatory to ensure accurate detection [93]. Other accepted diagnostic tools include viral culture and identifying adenoviral nuclear inclusions on microscopy. Identification of adenovirus in the nasopharynx and sputum has been associated with LRTI [94, 95].

Multiple surveillance studies have been attempted with the goal of early detection. The incidence of detection in peripheral blood post-HSCT is 8–17%, with up to 73% of those patients developing LRTI as part of multi-organ dysfunction syndrome. Mortality occurs in 60–100%, even in cohorts receiving antiviral treatment [93, 95–97]. Surveillance of stool and urine are important for local disease but of unclear significance for pulmonary disease, although identification in 2+ sites correlates with positivity in peripheral blood [93, 98–100].

In all body fluids, increase in copy number, rather than absolute viral load, is associated with development of clinical symptoms [93]. Patients who received T-cell depleted allografts (i.e.: *in vivo* with antibody and *ex vivo* with CD34+ positive selection), allografts from mismatched family members or unrelated donors, or total body irradiation have increased rates of adenovirus positivity [93, 97, 101].

Delay between detection and initiation of treatment is associated with mortality [97]. Lymphocyte recovery is the most important factor in clearing adenoviremia and treating adenovirus LRTI [96]. Speed of lymphocyte recovery may be hastened by withdrawal of immunosuppression but is primarily influenced by T-cell reduction of the graft [96]. High-dose IVIG and vidarabine are of unclear benefit [97]. Ribavirin has had little success with LRTI or disseminated disease [92, 96, 97]. Cidofovir with probenecid is a promising approach to limit viral replication and bridge time to lymphocyte recovery [96, 97, 102, 103]. Donor leukocyte infusions may also be beneficial [97, 104, 105].

5.1.2. Respiratory syncytial virus (RSV)

Paramyxoviridae are single stranded ribonucleic acid (RNA) viruses that include RSV, parainfluenza virus (PIV), and human metapneumovirus (hMPV). They can cause isolated URI, isolated LRTI, or

URI progressing to LRTI [106]. RSV is particularly pathogenic due to its ability to cause airway epithelial cell necrosis and lymphocyte-mediated airway inflammation [107]. HR-CT findings for RSV in HSCT patients include centrilobular nodules <1 cm (53%), air space consolidation (33%), and ground glass attenuation (23%), but may be absent in up to 20% of patients [34]. Inhaled ribavirin has been shown to reduce progression from URI to LRTI and may be more effective when started early [108]. Current treatment options include oral or aerosolized ribavirin, immunoglobulin, or monoclonal antibodies, although practice varies by center [91, 109, 110].

5.1.3. PIV

PIV has four serotypes and is pathogenic due to varying expression of anti-interferon accessory proteins [111]. It may cause severe laryngotracheitis, necessitating invasive mechanical ventilation to bypass upper airway obstruction. Co-infection with other viruses is common [106, 112]. Antiviral therapy has been of limited benefit; aerosolized ribavirin has been tried with some success when used early in URI [112–114]. The addition of IVIG has been tried with little success [112].

5.1.4. hMPV

Since discovery in the Netherlands in 2001 [115], hMPV has been implicated in a variety of URI and LRTI in both immunocompetent and immunocompromised hosts. In HSCT cohorts, it has been identified in numerous patients with URI [116] and has been implicated in severe and fatal LRTI, both as a monopathogen and as a co-infection [11, 117, 118]. IVIG and ribavirin have been attempted as treatment but are not considered standard therapy [119, 120].

5.1.5. Influenza virus

Influenza is a single stranded RNA orthomyxovirus well-known to cause fever, myalgia, and rhinorrhea in the pediatric HSCT population [121]. There is a high rate of progression from URI to LRTI (18%), which can be partially ameliorated by early antiviral treatment [122]. In addition, isolated LRTI has been confirmed without clinical or microbiologic URI [122]. Rimantadine, amantadine, inhaled zanamivir, and oseltamivir have been used efficaciously when started early [121, 123]. Choice of appropriate antiviral medication is dependent on circulating strain sensitivity and

local availability of medication type and delivery formulation.

5.1.6. *Rhinovirus*

Rhinovirus is a picornavirus that is one of the most common causes of self-limited URI in immunocompetent hosts. Although it has been implicated as both an isolated pathogen and co-pathogen in fatal LRTI in pediatric HSCT patients, its role in LRTI pathogenesis is poorly understood [124–126]. There are no antiviral medications with proven efficacy at this time.

5.1.7. *Other CRVs*

Case reports of coronavirus and measles virus related LRTI exist but are infrequent [11, 18, 127, 128].

5.2. *Herpesviruses*

Exposure to herpesviruses is common in childhood and leads to chronic infection. Viral suppression is linked to T cell function, and therefore the majority of LRTI associated with herpesviruses is due to endogenous latent reactivation during periods of absolute and functional lymphopenia. Accordingly, 28–47% of patients will develop herpesvirus viremia within 1 yr post-HSCT [129]. This hematogenous spread makes peripheral blood screening crucial, although primary disease via direct inoculation of the respiratory tract has been described [130–132]. Viral shedding can often be detected in body fluids and may not correlate with clinical disease; therefore repeat testing aimed at quantifying rate of viral replication is crucial [129].

5.2.1. *CMV*

CMV reactivation in the lungs can cause air-space consolidation, bronchial wall thickening, interstitial pneumonia, and pleural effusions [133, 134]. HRCT findings include ground glass opacification (68%), multiple nodules <1 cm (59%), air space consolidation (31%), and large nodules >1 cm (14%) [34]. The most severe pulmonary presentations occur in seropositive recipients of seronegative allografts [135].

Aggressive surveillance is standard and evidence exists that detection of CMV in the urine, throat, and blood can precede LRTI [136]. However, CMV LRTI can occur in the absence of viremia [137]. Screening techniques include detection of circulating antigen of the CMV structural protein pp65 as well as quantitative PCR of DNA and mRNA. In patients with

symptomatic LRTI, a BAL with culture, microscopy, and PCR should be performed. PCR in BAL fluid has high negative predictive value but the cutoff beyond which viral detection correlates with clinical disease is unknown since pulmonary shedding is common even in asymptomatic patients [138, 139].

Co-infection with other herpesviruses (human herpesvirus-6 [HHV-6] and human herpesvirus-7 [HHV-7]) is common due to their ability to suppress the anti-CMV immune response [135]. CMV positivity is also associated with increased risk of bacterial and fungal infections, particularly aspergillus [137, 140].

Prompt treatment based on early detection is associated with improved outcomes [135]. Standard therapy is ganciclovir with either pooled IVIG or CMV-specific immunoglobulin, although the use of immunoglobulin is currently under debate [141–143]. Of note, ganciclovir may cause cytopenias and nephrotoxicity [141]. Ganciclovir resistance testing should be performed [137]; cidofovir or foscarnet are available as alternatives or additions. Adoptive immunotherapy with CMV-specific cytotoxic T lymphocytes is also being developed and has shown early success [144]. The case fatality rate is 75–93% without treatment [13, 145–148] and 30–50% with treatment [149].

5.2.2. *Herpes simplex virus (HSV)*

Both HSV-1 and HSV-2 can cause LRTI with dyspnea, productive cough, focal consolidation, bronchial wall thickening, centrilobular nodules, and ground glass attenuation [34, 130, 134]. Disease may be preceded by mucocutaneous HSV in up to 85% [130] or concurrent HSV tracheitis or esophagitis in up to 50% [130]. However, patients may have isolated HSV LRTI without other signs of disseminated HSV disease [150]. Co-infections have been reported [151]. Intravenous acyclovir is standard therapy, though cases of acyclovir-resistant HSV emphasize the need for antiviral genomic testing when possible [151].

5.2.3. *HHV-6*

Asymptomatic reactivation of HHV-6 in the peripheral blood is common after HSCT (30–50%) [152, 153]. HHV-6 has been identified alone and as a co-pathogen in lung tissue; radiographic presentations include alveolar, nodular, and interstitial pneumonias [154–158]. Although HHV-6 is known to optimize the local environment for opportunistic infection and supports the growth of other herpesviruses, it is unclear if HHV-6 is pathogenic on its own [157]. HHV-6 may

directly or indirectly trigger acute GVHD and may proliferate in response to GVHD-induced cell damage [154, 155]. HHV-6 is associated with poor clinical outcomes including non-relapse mortality [159, 160]. Due to a poor understanding of the pathogenicity of HHV-6 in pulmonary disease, it is unclear if treatment is warranted. Ganciclovir has been shown to reduce HHV-6 viremia as well as non-pulmonary clinical symptoms when used early [161]. Foscarnet has also been used.

5.2.4. Epstein-Barr virus (EBV)

EBV reactivation most commonly presents as post-transplant lymphoproliferative disorder (PTLD); case reports of severe and often fatal EBV LRTI in the setting of PTLD exist [162, 163]. Diffuse lung infiltrates may be seen on HR-CT and lung biopsy may show interstitial pneumonia with intra-alveolar B-cell infiltrates [162, 163]. Rituximab-based therapies have been attempted but mortality remains above 50% [164]. Whether EBV reactivation can cause LRTI in the absence of PTLD is unclear due to high viral shedding in the lung [165], although at least one case of severe LRTI due to primary EBV infection post-HSCT has been reported [131].

5.2.5. Varicella zoster virus (VZV)

Although VZV may reactivate in up to 30% of HSCT patients, disseminated zoster is unusual and case reports of VZV LRTI are rare in the era of antiviral prophylaxis [18, 132, 166]. VZV LRTI can be clinically indistinguishable from CMV LRTI in the absence of comorbid zoster.

6. Fungi

The warm, humidified respiratory tract is an ideal environment for opportunistic fungal proliferation in leukopenic hosts [167–170]. Fungi are resilient and replicate slowly, making them difficult to eradicate. Diagnosis is challenging due to a high rate of nasopharyngeal colonization [171], which frequently necessitates invasive BAL or OLB. The most common fungi implicated in LRTI include *Aspergillus* (60–75%), *Mucormycoses* (7–20%), and *Candida* (1–10%) [167, 171–175]. *Cryptococcus*, *Coccidioides*, *Blastomyces*, *Histoplasmosis*, and other fungi have also been reported as causes of fungal LRTI [175].

6.1. *Aspergillus*

Aspergillus species, including *Aspergillus niger*, *Aspergillus fumigatus*, and *Aspergillus flavus*, are environmental molds and are a leading cause of fungal death in the pediatric HSCT population [77, 176]. Five to fifteen percent of patients will acquire infection [176–178] and 75–90% of these infections will present as LRTI [179–181]. Infection occurs via spore inhalation and is augmented by lack of hospital-based laminar air flow equipment, local construction or dust aerosolization, unrelated donor transplant, GVHD, and concurrent use of corticosteroids [177, 178, 182–185]. Clinical presentations span from mild respiratory distress to fulminant respiratory failure [186]. Airway invasion may cause complete lobar collapse and angioinvasion may cause pulmonary infarction and hemorrhage [187].

Conventional roentgenography may show cavitary lesions (38%), segmental or subsegmental consolidations (22%), patchy infiltrates (21%), and nodular infiltrates (11%) [188], but has been reported to miss up to 50% of cases identified on HR-CT [186]. HR-CT may show centrilobular nodules (81%), peribronchovascular consolidation (44–69%), ground glass attenuation (44–56%), the halo sign (37%), and cavitation (16%) [34, 189, 190] (Fig. 2). Serum galactomannan and β -D-glucan assays are highly specific (82–97%) but less sensitive (58–86%) [191–193]. Blood cultures are rarely positive but peripheral blood DNA PCR is a promising tool [193–195]. Sputum cultures are positive in less than 10% of patients and may reflect colonization [188]. Definitive diagnosis depends on BAL or OLB with PCR, fungal culture, and silver stain demonstrating septate and branching hyphae [196, 197].

Anti-*aspergillus* prophylaxis is not standard but voriconazole and posaconazole are options for at-risk patients, which includes patients with active leukemia at the time of transplant, those who received mismatched related donor or unrelated donor and have post-transplant CMV infection, iron overload, or prolonged neutropenia, and patients with GVHD [198–200]. Chronic azole therapy may predispose to fungal infections by non-albicans *Candida* species, *Mucormycoses*, and azole-resistant *Aspergillus* [199, 201–203]. Alternative prophylaxis options include intermittent liposomal amphotericin B and micafungin [199, 204, 205]. Since 2003, voriconazole has been the accepted first line treatment for *aspergillus*

Fig. 2. High-resolution computerized tomography of the thorax of a 16-year-old with acute myeloid leukemia, day +37 status post matched unrelated donor peripheral blood stem cell transplant. There is a 2.6×2.5 cm left lower lobe pulmonary nodule surrounded by a ground glass halo. *Aspergillus* lower respiratory tract infection was diagnosed based on highly elevated serum galactomannan antigen. Co-infections included human herpesvirus-6 viremia (although only 600 copies/mL) and urine BK viruria ($>90,000,000$ copies/mL). Bronchoalveolar lavage was not performed. Views are; a) axial view, b) coronal view, and c) sagittal view.

LRTI and has been demonstrated to be superior to other first-line options including amphotericin [206, 207]. Salvage therapy options are limited and include amphotericin, but favorable response is seen in less 30% of patients [207–209]. Surgical resection may be beneficial in patients with focal disease [210]. Unfortunately, mortality rates are 68–91% once infection has been established [177, 178, 210–213].

6.2. *Mucormycoses*

Mucormycoses, previously called zygomycoses, are caused by ubiquitous environmental saprophytes of the order Mucorales, which includes *Rhizopus* spp, *Mucori* spp, and *Lictheimia* spp [214]. The incidence has drastically risen in the past two decades to over 1,000 cases reported in the literature [178, 215–218], which many suspect is related to the use of fluconazole and voriconazole for *Candida* and *Aspergillus* prophylaxis [202, 215, 217, 219, 220]. Mucormycosis is most often acquired by inhalation, making pulmonary and rhinocerebral manifestations the most common sites of infection [216, 221]. Mucorales are angioinvasive, which may lead to disease patterns of rapid progression along tissue and blood vessels [218, 222]. Diagnosis relies on BAL or OLB culture and microscopy.

Mucormycosis treatment consists of a combination of aggressive surgical resection, systemic antifungal therapy, and modulation of immunosuppression when possible [218, 222, 223]. First line therapy is amphotericin B, as neither fluconazole nor voriconazole adequately block Mucorales ergosterol synthesis [218, 224, 225]. Posaconazole does have both *in vitro* and

in vivo activity against Mucorales and has been used successfully in patients who fail or cannot tolerate amphotericin [224–226]. Despite treatment, mortality rates exceed 90% [178, 215, 217].

6.3. *Candida*

Candida species are commensal budding yeasts that colonize the mouths of up to 80% of children [227]. Despite frequent colonization, primary candidal LRTI occurring via direct spread or aspiration of oropharyngeal organisms is exceedingly uncommon [187, 228]. Secondary candidal LRTI occurs via hematogenous seeding in the context of candidemia, which most often originates from mucositis or central vascular catheters [229]. Historically, candidemia affected up to 20% of pediatric HSCT patients [230], which prompted the widespread use of azole prophylaxis [203, 231]. Recent data show that candidemia occurs in $<1\%$ of pediatric HSCT patients; 6–10% of these cases present with concomitant candidal LRTI [203, 232, 233]. Patients at risk include those with broad-spectrum antibiotic use, persistent neutropenia, GVHD, and CMV reactivation [232, 234]. Symptoms include rapid-onset fever, productive cough, and respiratory distress, often in the setting of fungemic sepsis [235].

Diagnosis of candidal LRTI is challenging due to widespread detection in respiratory secretions and up to 30% of BAL samples, particularly in mechanically ventilated patients [236]. Sputum and BAL cultures have 71–85% sensitivity and 57–60% specificity [237], suggesting that they may be useful in ruling out candidal LRTI but not in confirming the diagnosis. Chest

roentography findings include bilateral miliary nodular disease (80%), pleural effusions (25%), and unilateral disease (20%) [187, 238]. HR-CT findings include centrilobular nodules (50%), diffuse nodules (45%), peribronchovascular consolidation (30–41%), ground-glass attenuation (35–75%), the halo sign (29–32%), and cavitation (4–6%) [189, 190, 235]. The halo sign cannot reliably distinguish between candidal and aspergillus LRTI [189]. Diagnosis requires histologic demonstration of candida invasion into lung tissue [229].

Fluconazole remains the standard recommended therapy for invasive disease due to its documented improvement in long-term outcomes [231, 239, 240]. Since the advent of azole prophylaxis, there has been a shift of candida species away from *Candida albicans* such that azole-resistant species including *Candida krusei* and *Candida glabrata* now account for more than 50% of candidal infections [172, 233, 241, 242]. Therefore, fluconazole, amphotericin B, caspofungin, and voriconazole are all treatment options depending on sensitivity of the isolate [167, 172, 242–244]. Mortality among pediatric HSCT patients with candidal LRTI ranges from 20–50% [172, 233, 245].

6.4. *Pneumocystis jirovecii*

Pneumocystis jirovecii (formerly *carinii*) is a ubiquitous fungus that causes pneumonia, named *Pneumocystis carinii* pneumonia (PCP) in immunocompromised hosts. The transmission of pneumocystis is not fully understood, although recent evidence supports airborne person-to-person transmission with the supposition that healthy individuals may be asymptomatic carriers [246, 247]. Common symptoms of PCP include fever, progressive dyspnea, non-productive cough, hypoxemia, and a lack of URI symptoms [247–249]. Typical radiographic findings include bilateral perihilar interstitial infiltrates [247, 248, 250]. The organism cannot be cultured *in vitro*; therefore, induced sputum or BAL with DNA PCR and microscopy are required for diagnosis [246, 247]. PCP occurs almost exclusively in patients with CD4 T-cell levels <200 [251, 252] and children under 2 yr of age may be at increased risk following transplant [246, 253].

In the absence of prophylaxis, PCP develops in 5–15% of pediatric HSCT patients, with mortality rates of up to 63% [254–256]. Since the introduction of prophylactic regimens, PCP incidence

is now estimated to be <5%; with most infections occurring in the late post-transplant period after prophylaxis has been discontinued [256–258]. Trimethoprim-sulfamethoxazole has been shown to be highly effective for PCP prophylaxis, lowering incidence by 91% and reducing mortality by 85% when used correctly [252]. Trimethoprim-sulfamethoxazole is also first-line treatment for active infection; it may be useful to add a corticosteroid for adjunct treatment of inflammation-mediated pathology [248].

In conclusion, opportunistic infections of the lower respiratory tract continue to be a significant source of morbidity and mortality for pediatric HSCT recipients. Despite recent advancements in care, further reduction in disease burden will require vigilant infection prevention, improved diagnostic strategies, and new aggressive therapies.

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