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Viral Pneumonia in Patients with Hematopoietic Cell Transplantation and Hematologic Malignancies

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KEYWORDS

- Pneumonia • Hematopoietic cell transplantation • Hematologic malignancy
- Community respiratory virus infection • Cytomegalovirus

KEY POINTS

- Viral pneumonia is a common pulmonary complication in patients with HCT/HM and is associated with high morbidity and mortality.
- Because of nonspecific imaging findings, and high rates of coinfection with other viral, bacterial, and fungal pathogens, microbiologic diagnosis generally requires bronchoalveolar lavage with samples sent for culture, direct fluorescent antibody and nucleic acid testing as available.
- CMV remains the most common cause of viral pneumonia in HCT/HM, but adoption of preemptive therapy strategies and changes in transplant techniques over the last few decades have resulted in significant improvement in the incidence and mortality associated with CMV pneumonia.
- Community respiratory virus (CRV) infections, such as influenza, parainfluenza, and respiratory syncytial virus, are common. Fewer patients develop lower tract disease; however, once established, mortality rates are high.
- Infection prevention practices in the community and health care setting are critical in limiting the acquisition and spread of CRVs in this highly susceptible patient population.

INTRODUCTION

Patients undergoing hematopoietic cell transplantation (HCT) or treatment of hematologic malignancy (HM) have profound impairment of cell-mediated and humoral immunity. As such they are at risk of lower respiratory tract infection from reactivation of latent infections, such as cytomegalovirus (CMV), and progression of community-acquired upper respiratory tract

infections, such as respiratory syncytial virus (RSV) influenza A and B. The clinical presentation of these infections is varied, and diagnosis is often complicated by high rates of coinfection with bacterial, fungal, and other viral pathogens (**Table 1**).¹⁻⁴ This article reviews the epidemiology of the major viral pathogens for pneumonia in patients with HCT/HM with discussion of evidence-based prevention strategies and treatments.

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Table 1
Incidence of infection, incidence of pneumonia, associated mortality rates, and treatments of most common causes of viral pneumonia in patients with HCT or HM

Virus	Incidence of Infection	Progression to Pneumonia	Mortality	Treatment
Cytomegalovirus	50%–90% seroprevalence	1%–8% after allogeneic HCT with pre-emptive therapy 1%–5% other populations with no surveillance	60%–80%	Ganciclovir or foscarnet
Influenza A and B (FluA and FluB)	33% of symptomatic patients	14%–30%	15%–28%	Oseltamivir or other neuraminidase inhibitors
Respiratory syncytial virus	14%–30% of symptomatic patients	40%–75%	28%–55%	No direct-acting therapy; inhaled ribavirin most studied
Parainfluenza virus	1%–10% of all patients	30%	17%–46%	None currently licensed; DAS-181 in phase III trials
Adenovirus	8%–17% after allogeneic HCT, 6% after autologous	~8%	N/A	Cidofovir

DIAGNOSIS OF VIRAL PNEUMONIA

Clinical Presentation

Presenting signs and symptoms of viral pneumonia are variable. Most patients have fever and cough, with hypoxia and increased work of breathing of varying degrees depending on the extent of the infection. Upper respiratory tract infection symptoms, such as nasal congestion, rhinorrhea, sinusitis, myalgias, and fatigue, may be present for infections caused by community respiratory viruses (CRVs).

Imaging

Computed tomography (CT) is helpful in distinguishing between infectious and noninfectious causes of lung disease in this patient population and also between viral and fungal or bacterial infections.^{5,6} Viral pneumonias are similar in appearance on CT often demonstrating small centrilobular nodules, patchy bilateral areas of ground glass opacities and consolidation, bronchial wall thickening, and tree-in-bud opacities (Fig. 1). If there is significant bronchiolitis, air trapping can also be evident.^{5–10}

Diagnostic Sampling

Fiberoptic bronchoscopy with bronchoalveolar lavage is the predominant sampling method to

confirm a diagnosis of viral pneumonia in the HCT/HM population. Although sampling of the upper respiratory tract with nasopharyngeal aspirate/wash may provide an early identification of the involved virus or viruses, sampling of the lower tract is usually recommended to confirm the diagnosis and to exclude other copathogens. Because of the risk of hemorrhage in these patients who often have thrombocytopenia, endobronchial biopsy is usually avoided. Surgical lung biopsy, which was once the principle method by which lung abnormalities were evaluated after HCT, is now rarely performed.¹¹

Virologic Diagnosis

Standard viral cultures are of waning utility in the diagnosis of viral pneumonias because it can take up to 2 weeks to become positive and several more recently identified respiratory viruses, such as human metapneumovirus, coronaviruses, and bocavirus, are notoriously difficult to isolate in culture. For most viral pathogens, molecular methods of viral detection, such as direct or indirect fluorescent antibody tests or nucleic acid tests, can be used to give reliable results with a rapid turnaround time. Multiplex polymerase chain reaction (PCR) panels have the advantage of being able to test for multiple viruses at the same time and are more sensitive than fluorescent antibody tests.^{12–17}

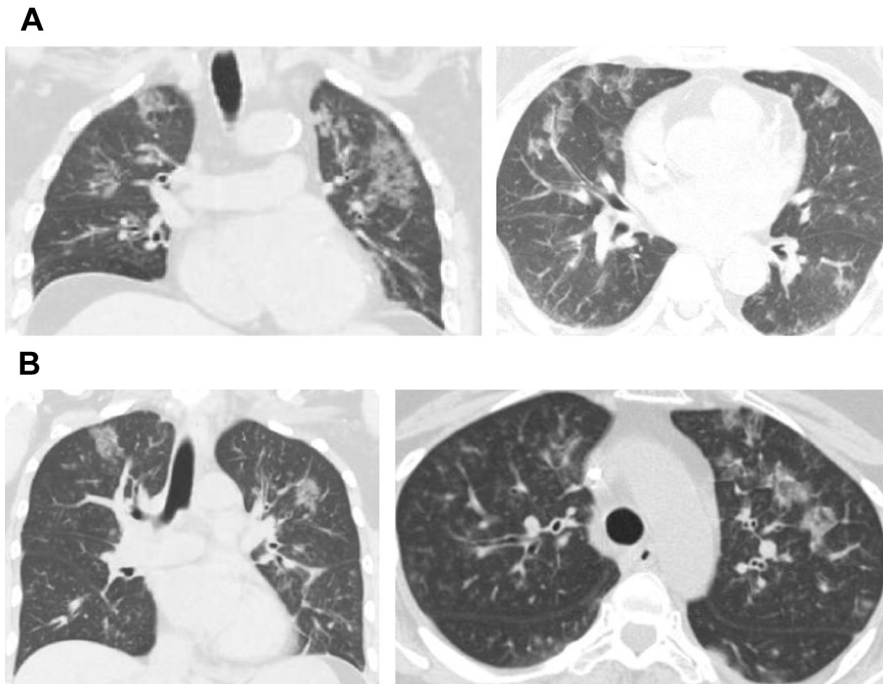


Fig. 1. (A) Transverse and coronal views of CT imaging for a patient with HCT with adenovirus and rhinovirus pneumonia, demonstrating patchy bilateral infiltrates with ground glass opacities and tree-in-bud pattern. (B) Transverse and coronal view of CT imaging for a patient with HCT with pneumonia caused by parainfluenza virus type 3. Note scattered nodular infiltrates with ground glass opacities.

The diagnosis of CMV pneumonia, however, continues to rely on the use of standard viral or shell vial culture, histopathology, or immunohistochemical testing.¹⁸ The assumption has been that the CMV PCR tests would be too sensitive and have a low positive predictive value for CMV pneumonitis.^{19–22} However, because of the operational advantages of PCR testing with much faster turnaround time, efforts are underway to estimate a quantitative CMV viral load threshold that would be more predictive of CMV pneumonitis rather than asymptomatic shedding.

CYTOMEGALOVIRUS

Epidemiology

CMV is the most common cause of viral pneumonia after allogeneic HCT. Early reports indicated an incidence of 20% to 70% with an associated mortality of 85% to 90%.^{23–25} The development of ganciclovir resulted in significant improvements in the mortality associated with CMV pneumonia but with mortality rates still 60% to 80% focus shifted to prevention of disease.^{26–29} The use of ganciclovir for prophylaxis decreased the incidence of pneumonitis and other CMV end-organ disease, but was associated with increased rates of neutropenia and late-occurring

disease (ie, after Day 100 posttransplant).^{25,30–33} In the current era of preemptive therapy, where patients are monitored for CMV replication with either pp65 antigen or CMV DNA PCR in the blood or plasma and antiviral treatment is initiated before the development of CMV pneumonia, the incidence of CMV pneumonia is now only 1% to 3% in the early posttransplant period (100 days posttransplant).^{34–36} An additional 1% to 8% of patients develop CMV pneumonia within the first year after transplant.^{36–38}

Risk factors for development of CMV pneumonia after allogeneic HCT are CMV seropositivity, recipient of a cord blood graft, HLA-mismatched donors, myeloablative conditioning regimens, acute and chronic graft-versus-host disease (GVHD), and use of T-cell-depleted stem cells.^{34,36,39–43}

CMV pneumonia is much less common in patients who have received an autologous transplant, or in patients receiving treatment of HM with incidence of 1% to 5% reported in the absence of surveillance and preemptive therapy.^{44–48}

Treatment

Ganciclovir (5 mg/kg intravenous [IV] every 12 hours) remains the first-line treatment for CMV

pneumonitis.⁴⁹ Based on the results of three non-randomized studies,^{50–52} CMV immunoglobulin was often recommended as adjunctive treatment. However, more recent analyses have called into question the additional benefit of this therapy.^{29,47,53,54} Duration of treatment is generally induction therapy for 21 to 28 days, followed by 21 to 28 days of maintenance therapy (ganciclovir, 5 mg/kg IV every 24 hours). Foscarnet (90 mg/kg IV every 12 hours) may be used in the setting of neutropenia because it is associated with less bone marrow suppression than ganciclovir, but commonly causes significant nephrotoxicity.

Antiviral resistance mutations have been identified in the viral encoded UL97 kinase, required only by ganciclovir, and the viral DNA polymerase, the target of ganciclovir, foscarnet, and cidofovir.⁵⁵ Fortunately, antiviral resistance is a rare occurrence in patients with HCT/HM occurring in 0% to 4% of patients with CMV reactivation.^{56–58} Foscarnet, cidofovir, and brincidofovir (an oral nucleotide analogue and prodrug of cidofovir) could be used for treatment of resistant CMV caused by UL97 mutations. Maribavir and letermovir, two agents currently undergoing clinical trials, have distinct mechanisms of action that may make them useful for treatment of resistant CMV disease; however, little is known of their genetic barrier to resistance.^{59–62}

Other Herpesviruses

Reactivation of latent varicella zoster virus and herpes simplex virus in immunocompromised patients can result in disseminated disease with pneumonia and was a significant clinical problem for patients with HCT/HM.^{63,64} Long-term prophylaxis with acyclovir or valacyclovir has been the standard of care for more than a decade.^{65–68} Cases still rarely occur in patients who have discontinued acyclovir prophylaxis, but generally respond well to high-dose parenteral acyclovir.^{69–71}

COMMUNITY RESPIRATORY VIRUSES

CRVs are a common cause of infection in patients with HCT/HM; however, the risk of pneumonia varies by virus type and patient risk factors. Several of the viruses, such as influenza and RSV, have significant seasonal variation of incidence, whereas others, such as parainfluenza virus (PIV) and adenovirus, tend to cause disease year round. Outbreaks on oncology and HCT hospital wards and ambulatory clinics have been described for many of these viruses,^{72–76} emphasizing the importance of infection-prevention policies and procedures that can prevent the

transmission of viruses among highly susceptible patients. This is particularly challenging with this patient population because of prolonged viral shedding, which often lasts weeks or months.^{77–79}

Influenza

Influenza is diagnosed in approximately 1% of patients with HCT/HM during treatment, and in 33% of patients presenting with respiratory virus symptoms.^{80–82} Progression to pneumonia occurs in 14% to 30% of patients and is associated with mortality rates of 15% to 28%.^{80–83} During the 2009 H1N1 influenza pandemic, rates of pneumonia were much higher (>50%), but mortality was similar.⁸⁴ Risk factors for development of pneumonia include lymphopenia (<100 cells/ μ L), neutropenia (<500 cells/ μ L), steroid use at time of diagnosis, and absence of antiviral treatment.^{80,81,83,84}

Neuraminidase inhibitors, primarily oseltamivir, are currently the standard of care for influenza treatment and postexposure prophylaxis. Oseltamivir resistance has been described but remains uncommon.^{85–88} In the setting of documented or suspected oseltamivir resistance, or in patients who have impaired enteric absorption, inhaled zanamivir or the newly licensed parenteral peramivir have been used.^{89–91}

Seasonal vaccination with the trivalent inactivated vaccine is recommended for all health care workers caring for patients with HCT/HM, family members, and household contacts. Additionally, it is recommended that patients undergoing treatment of leukemia and lymphoma are vaccinated because it may reduce the risk of hospitalization for respiratory illness.^{92–95} Ideally, vaccine should be administered at least 2 weeks before any cytotoxic therapy. For HCT recipients, vaccination of patients less than 6 months after transplant is ineffective and is generally not recommended.^{66,95,96} Chemoprophylaxis after exposure is recommended for patients with HCT within 1 year of transplant or for patients with HM during chemotherapy.^{66,97}

Respiratory Syncytial Virus

Infection with RSV is more common than influenza, occurring in 7% to 10% of patients undergoing allogeneic HCT.^{98,99} Among patients with HCT/HM presenting with viral respiratory symptoms, RSV is diagnosed in 14% to 30%.^{81,99} Involvement of the lower respiratory tract occurs in 40% to 75% of infected patients.^{81,98,99} Risk factors for progression to pneumonia include patient age, allogeneic HCT, mismatched or unrelated donor, GVHD, myeloablative conditioning

regimens, infection less than 30 days post-transplant, prolonged lymphopenia, and lack of ribavirin-based therapy.^{81,98–101} RSV pneumonia is associated with mortality rates of 28% to 55%.^{100,102,103} Treatment with inhaled ribavirin has been shown in several retrospective studies to be associated with decreased rates of progression and a 67% to 83% reduction in the risk of mortality after RSV infection.^{100,102} Based on these data, many centers use inhaled ribavirin (2 g for 2 hours every 8 hours for 10 days) in select, high-risk patient populations.^{66,104} However, because of recent increases in the cost of this formulation, the use of systemic (oral or parenteral) ribavirin is increasing despite a paucity of evidence to support this practice.^{102,105,106} There are a few noteworthy agents with novel mechanisms of action that are currently in trial: GS5806, an oral RSV entry inhibitor; and ALS8176, a nucleoside RSV polymerase inhibitor.^{107,108} Finally, pneumonia caused by RSV has been associated with a significant airflow decline by 1 year posttransplant, an important long-term sequela of this common infection.¹⁰⁹

Parainfluenza Virus

Unlike influenza and RSV, PIV infections occur without much seasonal variation. The incidence of PIV infection in patients with HCT/HM is 1% to 10%, and 30% of infected patients develop pneumonia; most cases are caused by PIV type 3.^{110–113} Death occurs in 17% to 46% of patients who develop pneumonia.^{110,112,113} Risk factors for development of pneumonia include high-dose corticosteroid use, lymphopenia, neutropenia, infection occurring early posttransplantation, the presence of copathogens, and a higher Acute Physiology and Chronic Health Evaluation II score.^{110,113,114} There are currently no licensed treatments for PIV pneumonia. Ribavirin has been used with little noted improvement in mortality or clinical response.^{110,114} DAS181, an investigational sialidase fusion protein that works by removing sialic acid-containing receptors from respiratory epithelial cells, preventing PIV from binding, has been successfully used in several cases of adult and pediatric PIV pneumonia in HCT/HM and is currently in phase III clinical trials.^{115,116}

Adenovirus

Human adenovirus (HAdV) infections can cause significant disseminated disease in patients with HCT/HM, including severe pneumonia. The most severe disease occurs after HCT, especially in children, and in patients with HM treated with

alemtuzumab.^{117–119} Adenovirus infection occurs in 8% to 17% of patients undergoing allogeneic HCT, with most cases occurring in children.^{120,121} A total of 10% of patients develop HAdV end-organ disease; the lungs are involved in 75% of these cases.^{120,121} Infection is less common after autologous HCT, occurring in only 6% of patients, and end-organ disease including pneumonia is rare. In addition to T-cell depletion, risk factors for HAdV disease are lymphopenia, receipt of cord blood grafts, GVHD requiring increased or prolonged immunosuppression, and absence of HAdV-specific T-cell responses.¹²² Patients with adenoviral pneumonia often have involvement at other sites, such as the gut and liver, and mortality rates with disseminated disease are high. First-line treatment of HAdV disease including pneumonitis is cidofovir (5 mg/kg once weekly, or 1 mg/kg three times weekly) and reduction in immunosuppression whenever possible.^{66,122–124}

Other Community Respiratory Viruses

Other common CRVs, such as human metapneumovirus, novel coronaviruses (eg, SARS-CoV, MERS-CoV), and even human rhinovirus, cause lower respiratory tract infection in patients with HCT/HM.^{125–128} Although each of these viruses have their own specific biology and epidemiology, the risk factors for pneumonia that have been identified for other CRVs, such as lymphopenia and infection occurring early after HCT, are shared. Because there are yet no direct-acting treatments for these viruses, efforts to prevent infection in these highly immunosuppressed patients remains paramount. Current guidelines recommend preventing contact from symptomatic health care workers and family members, daily screening of health care workers and visitors to inpatient units for symptoms, active surveillance for CRV disease, and isolation of symptomatic patients with recognition that viral shedding is prolonged in this patient population.^{129,130}

SUMMARY

The profound and prolonged immunosuppression experienced by patients undergoing HCT and intensive chemotherapy for HM results in rates of viral pneumonia that far surpass the incidence in the general population. Patients with viral pneumonia generally present with fever; hypoxia; and often bilateral, patchy nodular infiltrates with or without surrounding ground glass opacities on high-resolution CT imaging. Because the imaging findings do not help distinguish among different viral etiologies, and these patients commonly have other viral, bacterial, and fungal coinfections,

a microbiologic diagnosis typically requires fiberoptic bronchoscopy with bronchoalveolar lavage.

Although CMV remains the most common cause of viral pneumonia in this population, efforts to treat CMV replication early in its course and changes in transplant practices have resulted in improvements in the incidence and associated mortality of CMV pneumonia. Taken together, CRV infections also occur commonly in this patient population. However, the rates of progression to pneumonia vary depending on the virus with influenza, RSV, and PIV causing lower tract disease more commonly than adenovirus, human metapneumovirus, and rhinovirus, and patient risk factors relating to the degree of immunosuppression (ie, lymphopenia, early posttransplant, steroid use). Once established, however, pneumonia caused by these infections is associated with high mortality rates in part because of the lack of direct-acting antiviral agents for most of these viruses. Infection prevention practices that limit the acquisition of CRVs by patients with HCT/HM and decrease the risk of spread within the clinics and inpatient settings are of particular importance.

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