Viral Pneumonia in Patients with Hematologic Malignancy or Hematopoietic Stem Cell Transplantation

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KEYWORDS

- Viral pneumonia • Hematologic malignancy • Stem cell transplant
- Immunocompromised host pneumonia

KEY POINTS

- Viral pneumonias in patients with hematologic malignancies and recipients of hematopoietic stem cell transplantation cause significant morbidity and mortality.
- Advances in diagnostic techniques have enabled rapid identification of respiratory viral pathogens from upper and lower respiratory tract samples.
- Lymphopenia, myeloablative and T-cell–depleting chemotherapy, graft-versus-host disease, and other factors increase the risk of developing life-threatening viral pneumonia.
- Chest imaging is often nonspecific but may aid in diagnoses. Bronchoscopy with bronchoalveolar lavage is recommended in those at high risk for viral pneumonia who have new infiltrates on chest imaging.
- Early initiation of antiviral therapy in patients with influenza or respiratory syncytial virus is recommended.

POPULATION AND DEFINITIONS

This review focuses on common community-acquired respiratory viruses transmitted via aerosolized droplets or direct contact to patients with hematologic malignancy (HM) and hematopoietic stem cell transplant (HSCT) recipients. These viruses include influenza virus, respiratory syncytial virus (RSV), parainfluenza virus (PIV), human enterovirus (HEV), human rhinovirus (HRV), coronavirus (CoV), and human metapneumovirus (hMPV). Cytomegalovirus (CMV) has also been included, because CMV pneumonia plays an important role among immunocompromised patients. Other latent endogenous viruses associated with viral pneumonia in this population are less prevalent and are beyond the scope of this article.

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No standard definition for viral pneumonia is accepted. A distinction is generally made between viral upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). Viral LRTI includes viral tracheitis, bronchitis, bronchiolitis, and alveolitis. Viral pneumonia is typically understood to describe an infectious syndrome with (1) symptoms consistent with a respiratory infection (eg, cough, rhinorrhea, dyspnea); (2) isolation of a viral pathogen known to cause respiratory infections from either nasal, oropharyngeal, tracheal, or bronchoalveolar secretions; and (3) new infiltrates on chest radiograph (CXR) or computed tomography (CT).

CMV pneumonia is considered separately, but similarly lacks a uniform definition. In a recent review of CMV infection and disease, Ljungman and colleagues[1] defined CMV pneumonia in HSCT patients as "the presence of signs and/or symptoms of pulmonary disease combined with the detection of CMV in bronchoalveolar lavage fluid or lung tissue sample." However, the updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation published in 2013 recommends histologic or immunohistochemical demonstration of tissue invasive disease, because bronchoalveolar lavage (BAL) culture or quantitative polymerase chain reaction (PCR) may not consistently correlate with disease.[2] CMV infection is an umbrella term to describe detection of CMV in a blood sample. CMV antigenemia indicates blood samples positive for CMV antigens (usually pp65). CMV disease refers to tissue-invasive disease.

SCOPE OF THE PROBLEM

Pneumonia is a major cause of morbidity and mortality in patients with HM/HSCT. Bacteria and fungi account for most of the documented pathogens, but advances in DNA-based diagnostic tools highlight the larger role of respiratory viruses as a cause of pneumonia. A recent epidemiologic study of community-acquired pneumonia in US adults, irrespective of immune status, isolated viral pathogens in 23% of patients.[3] Studies of patients with HM/HSCT suggest that viral URTIs progress to pneumonia 35% to 58% of the time, depending on the center, virus, underlying condition, and transmission patterns.[4–8] The incidence of respiratory viral infections among HM/HSCT patients mirrors the incidence observed among immunocompetent patients, although the HM/HSCT population frequently demonstrates more severe disease.[9] The incidence of CMV pneumonia in allogeneic HSCT recipients has decreased following widespread use of posttransplant chemoprophylaxis but remains around 1% to 8% in both the early and the posttransplant periods[10–12] and remains low in patients with autologous HSCT[13–15] and HM without transplant.[16]

RISK FACTORS

Patient Risk Factors

A limited number of characteristics have been identified as risk factors for developing viral pneumonia in HM/HSCT patients. The best established is severe lymphopenia (absolute lymphocyte count <200 cells/μL). Chemaly and colleagues[8] retrospectively found that 52% of patients with HM/HSCT with a viral URTI and severe lymphopenia progressed to viral pneumonia compared with 31% for patients with absolute lymphocyte count greater than 200 cells/μL. Studies by Martino and colleagues[7] and Ljungman and colleagues[17] prospectively corroborated these findings, and similar observations were made in smaller studies involving influenza,[18] PIV,[19,20] and HEV/HRV.[21] A single-center prospective HSCT case-control autopsy study also identified lymphopenia as an independent risk factor for CMV pneumonia.[11,22]

Patients who receive more intensely myeloablative conditioning regimens before HSCT face higher risk of progression to viral pneumonia, although this is controversial for CMV. Data from a large retrospective study of HSCT recipients and a smaller case-control study failed to detect a difference in the incidence of CMV disease following myeloablative therapy.[23,24]

Patients receiving T-cell–depleting chemotherapeutic agents (eg, alemtuzumab, fludarabine, or antithymocyte globulin) appear to remain at elevated risk both during treatment and, in some cases, for years after treatment has been completed.[25,26] The use of these agents appears especially important for the risk of developing CMV disease in HSCT recipients.[11,27–29] Furthermore, because infection with viruses such as influenza and RSV can directly impair lymphocyte function in previously healthy patients,[30] even moderate chemotherapy-induced lymphopenia and/or lymphocyte dysfunction may place HM/HSCT patients at elevated risk of viral pneumonia.

In a large single-center study, 44% of HSCT patients with acute graft-versus-host disease (GVHD) developed viral pneumonia, compared with 22% among patients without GVHD.[7] Similar findings are described for HSCT patients who develop CMV disease[12,31–33] and other individual respiratory viruses.[10,11,34–37]

CMV pneumonia principally arises from disease reactivation. HSCT recipients who are seropositive for CMV (R+) before transplant, irrespective of