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# 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<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Studies of patients with HM/HSCT suggest that viral URITs progress to pneumonia 35% to 58% of the time, depending on the center, virus, underlying condition, and transmission patterns.<sup>4–8</sup> 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.<sup>9</sup> 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<sup>10–12</sup> and remains low in patients with autologous HSCT<sup>13–15</sup> and HM without transplant.<sup>16</sup>

## 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/ $\mu$ L). Chemaly and colleagues<sup>8</sup> 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/ $\mu$ L. Studies by Martino and colleagues<sup>7</sup> and Ljungman and colleagues<sup>17</sup> prospectively corroborated these findings, and similar observations were made in smaller studies involving influenza,<sup>18</sup> PIV,<sup>19,20</sup> and HEV/HRV.<sup>21</sup> A single-center prospective HSCT case-control autopsy study also identified lymphopenia as an independent risk factor for CMV pneumonia.<sup>11,22</sup>

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.<sup>23,24</sup>

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.<sup>25,26</sup> The use of these agents appears especially important for the risk of developing CMV disease in HSCT recipients.<sup>11,27–29</sup> Furthermore, because infection with viruses such as influenza and RSV can directly impair lymphocyte function in previously healthy patients,<sup>30</sup> 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.<sup>7</sup> Similar findings are described for HSCT patients who develop CMV disease<sup>12,31–33</sup> and other individual respiratory viruses.<sup>10,11,34–37</sup>

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

donor status, are at the highest risk for reactivation of latent virus.<sup>33</sup> Alternately, as seronegative recipients (R-) face limited reactivation risk, their rate of CMV pneumonia is lower than R+ recipients, even with seropositive donors (D+).<sup>38</sup>

Additional risk factors for the progression of viral URTI to viral pneumonia identified by multivariate analyses include age greater than 65 years,<sup>8</sup> hypoalbuminemia,<sup>39</sup> and cumulative dose of corticosteroids.<sup>20,37,40,41</sup>

### **Environmental Risk Factors**

Exposure to viruses is prominently driven by seasonal variation in viral carriage. In general, influenza, RSV, and hMPV infections peak in late autumn and continue through winter. HRV demonstrates biphasic peaks in autumn and spring. Parainfluenza rates are highest in spring and summer, although certain subtypes are present all year. Pandemics and localized outbreaks further increase risk.

Although most viruses are acquired through community or household contacts, nosocomial outbreaks also result in significant morbidity and mortality due to intensive exposures to the health care environment coupled with disease-related susceptibility to viral infections. Careful molecular typing of viral isolates has demonstrated that nosocomial outbreaks persist in the outpatient and inpatient settings despite established infection control practices.<sup>42-49</sup>

### **CLINICAL PRESENTATION**

Rhinorrhea, sore throat, cough, and fever are characteristic of most respiratory viral infections and thus cannot be used to reliably distinguish viral URTI, viral pneumonia, or other infections.

The acute febrile illness that typically characterizes influenza infections in the general population is less consistently observed in HM/HSCT patients.<sup>18</sup> In a study by Claus and colleagues,<sup>50</sup> the Centers for Disease Control and Prevention (CDC) influenza-like illness criteria (fever  $\geq 100^{\circ}\text{F}$  with cough and/or sore throat) was applied to patients with solid organ transplant or HSCT who presented with influenza. They found a positive predictive value of only 50% and a negative predictive value of 82% using these criteria. Ferguson and colleagues<sup>51</sup> applied a clinical prediction score using URTI and LRTI symptoms to HSCT recipients and found a positive predictive value of 28.7% and a negative predictive value of 84.5%. These studies suggest that symptoms common to viral infections in immunocompetent patients are moderately sensitive but poorly specific in patients with HM/HSCT.

In RSV pneumonia, fever, cough, dyspnea, and wheezing are common, whereas rhinorrhea and sore throat are less frequently observed.<sup>52</sup> In a large retrospective study of patients with HSCT and PIV, 87% of patients presented with upper respiratory tract symptoms and 6% presented with both upper and lower respiratory tract symptoms.<sup>53</sup> HRV infections usually exacerbate symptoms associated with an underlying chronic lung disease and include dyspnea, chest tightness, and wheezing.<sup>54-57</sup> HEV presents frequently with cough, even when lower respiratory involvement is not suspected.<sup>58</sup> Limited information is available for hMPV, but cough, wheeze, and fever predominate.<sup>36,59</sup> Symptoms of CMV pneumonia are nonspecific but are usually consistent with a non-suppurative pneumonitis, including nonproductive cough, dyspnea, and hypoxia. The presence of fever is variable.<sup>60</sup> Because CMV pneumonia may also be coincident with CMV viremia, symptoms of fever, malaise, arthralgia, cytopenias, and elevation of liver associated enzymes may also occur.

### **DIAGNOSTIC CONSIDERATIONS**

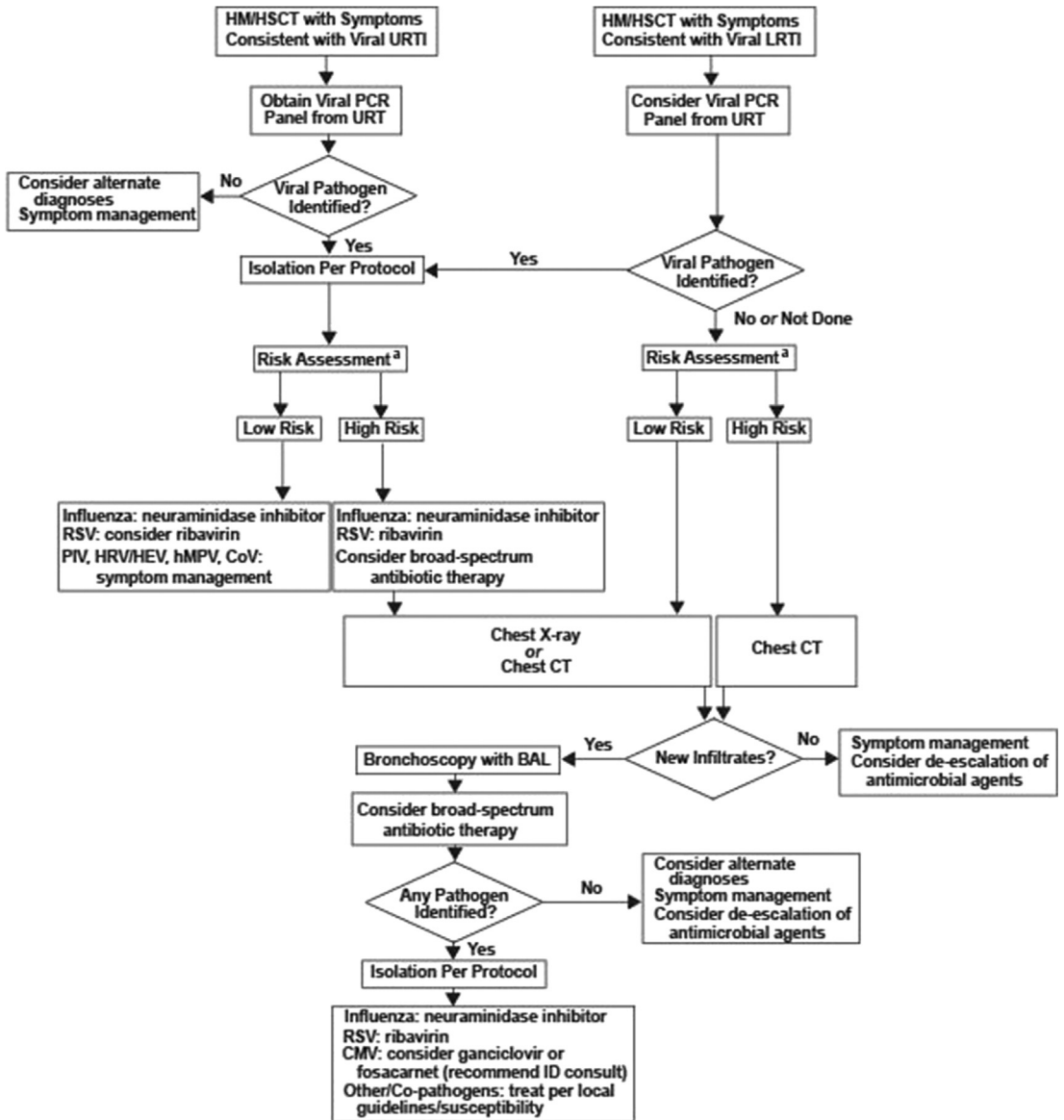
Patients with HM/HSCT have many potential causes of respiratory symptoms, pulmonary infiltrates, and fevers. Thus, a high degree of suspicion is essential for diagnosing viral pneumonia in a patient with nonspecific symptoms. The clinician must remain vigilant in consideration of patient risk factors, time of year, and exposure history, and those suspected of having a viral infection should be promptly referred for laboratory and radiographic evaluation. **Fig. 1** presents an algorithmic approach to patients presenting with syndromes suggestive of viral respiratory infections.

#### **Virus Isolation**

Viral nucleic acid amplification techniques using PCR, microarray, or DNA chip technologies have largely supplanted direct fluorescent antibody stains and conventional viral culture for the diagnosis of respiratory viruses. These techniques have been specifically validated in patients with HM/HSCT.<sup>61-63</sup> Samples for nucleic acid assays are commonly obtained from the nasopharynx using sterile swabs or washings. Similar test performance is observed when analyzing sputum samples, tracheal aspirates, and BAL fluid.

#### **Radiographic Characteristics**

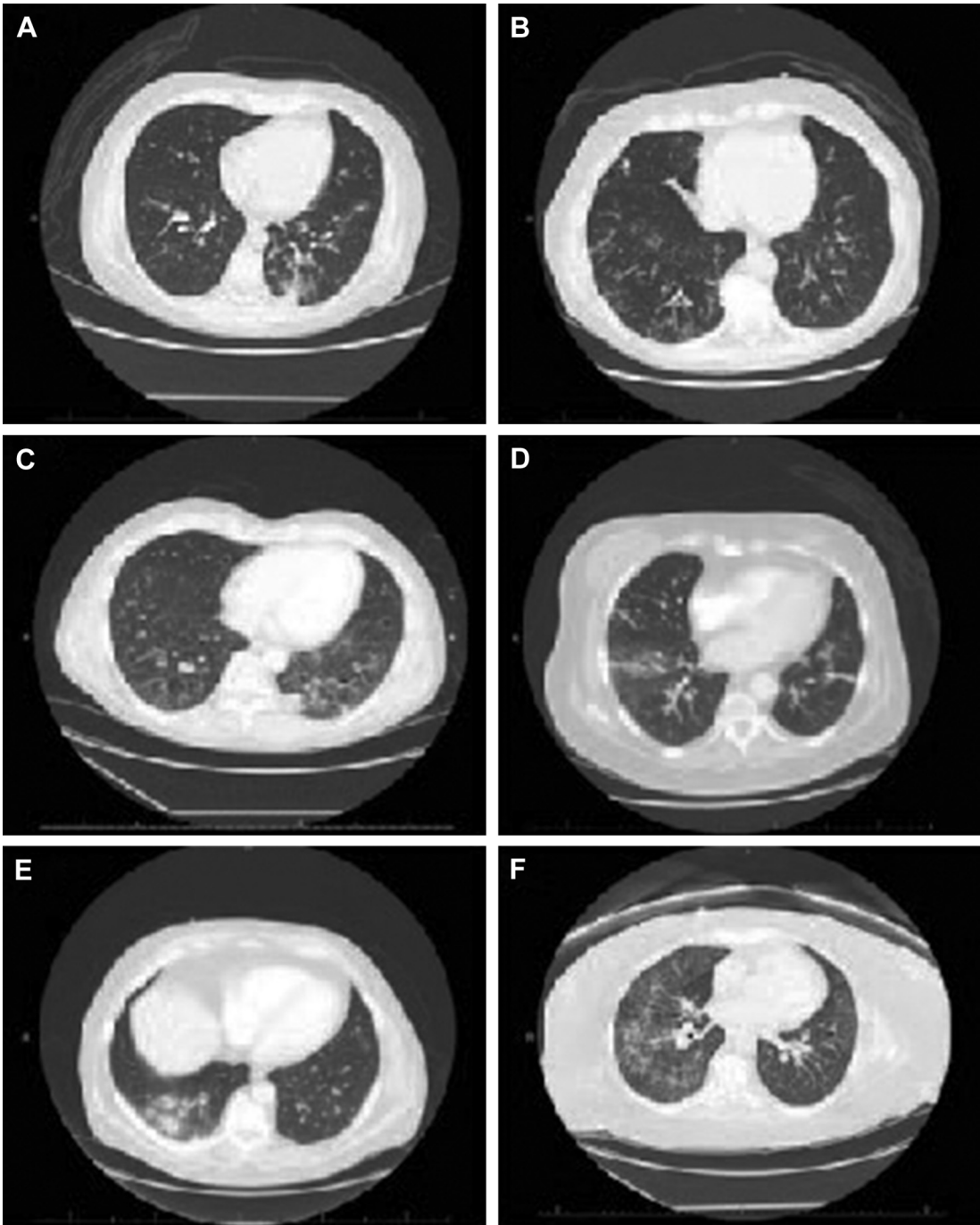
Although plain CXR can demonstrate lower respiratory tract involvement of viral infections, they



**Fig. 1.** Algorithmic approach to the HM/HSCT patient with suspected viral infection. ID consult, consultation with infectious disease expert; PCR Panel, PCR-base viral nucleic acid detection panel. <sup>a</sup> High-risk patient characteristics: lymphopenia, neutropenia, active GVHD, T-cell-depleting regimens, myeloablative conditioning, high-dose corticosteroids, age >65 years, hypoalbuminemia.

are nonspecific and have a poor negative predictive value, particularly in HM/HSCT patients. In a study by Logan and colleagues,<sup>64</sup> radiologist-interpreted CXR predicted the correct type of infection in immunocompromised patients with pneumonia only 34% of the time. Heussel and colleagues<sup>65</sup> compared CXR with chest CT in adult patients presenting with febrile neutropenia. Forty-eight percent of patients whose chest CT was suggestive of pneumonia were found to have a CXR that was interpreted as normal.

As shown in **Fig. 2**, the CT patterns most commonly observed in viral pneumonias are ground glass opacities (GGOs), nodules, interlobular septal thickening, bronchial wall thickening, and subtle changes in attenuation. Although it is widely presumed that these distinct radiographic patterns relate to unique histopathologic injury caused by different viruses, there is considerable histopathologic and radiographic overlap between respiratory viruses, rendering the findings nonspecific.<sup>66</sup> Furthermore, patients with HM/HSCT and



**Fig. 2.** Radiographic presentations of BAL-documented viral pneumonia. (A) Mucus plugging and consolidative opacities in a patient with hMPV and multiple myeloma following autologous HSCT. (B) Mucus plugging and GGOs in a patient with RSV and acute myelogenous leukemia following allogeneic HSCT. (C) Bronchial wall thickening and consolidative opacities in a patient with rhinovirus and chronic lymphocytic leukemia following allogeneic HSCT. (D) Multifocal GGO and micronodules in a patient with PIV and acute myelogenous leukemia receiving clofarabine. (E) Focal consolidative opacity in a patient with influenza A and untreated acute myelogenous leukemia. (F) Diffuse GGOs and micronodules in a patient with CMV pneumonitis and acute myelogenous leukemia following matched-unrelated donor allogeneic HSCT.

viral pneumonia frequently have coinfection with bacterial or fungal pathogens, and their radiographic patterns may be further confounded by noninfectious conditions.

Influenza virus is associated with bronchial thickening, mucus plugging of the terminal bronchioles, GGOs, and nodules that may evolve into confluent opacities.<sup>67,68</sup> Severe influenza may be associated with secondary infections and/or the acute respiratory distress syndrome, potentially presenting with consolidative opacities. In a case series of adult patients with HM/HSCT with RSV pneumonia, the most common patterns were centrilobular subcentimeter nodules, airspace consolidation, GGOs, and bronchial wall thickening.<sup>69</sup> PIV manifests most often with multiple peribronchial subcentimeter nodules and GGOs.<sup>70</sup> The predominant pattern in hMPV is a mixture of bilateral GGOs and subcentimeter nodular opacities without a predilection for lung zones.<sup>71</sup> Little data are available for HRV viral pneumonia, but bilateral diffuse GGOs are described.<sup>72</sup> CMV may present with a miliary pattern or a diffuse interstitial pneumonitis with GGOs, small centrilobular nodules, and air space opacities.<sup>73–75</sup>

### **Bronchoscopy**

In order to assess progression to the lower respiratory tract and to detect additional pathogens, BAL is frequently recommended in HM/HSCT patients with respiratory symptoms and identified virus from an upper respiratory sample, particularly in the setting of an abnormal CXR or CT. A meta-analysis of BAL and lung biopsy in patients with cancer and HSCT demonstrated an overall yield of 43% for any infectious cause by BAL, with 13% of all samples containing identifiable virus.<sup>76</sup> The diagnostic yield of BAL is reduced substantially in HSCT patients if bronchoscopy is delayed more than 4 days after presentation for any infectious cause.<sup>77</sup>

BAL diagnostic performance in CMV pneumonia depends on the analytical modality chosen. Shell vial culture has high sensitivity but poor specificity for diagnosing tissue-invasive disease.<sup>78</sup> Cytologic examination with demonstration of CMV intracytoplasmic inclusions is highly specific but poorly sensitive.<sup>79</sup> PCR is highly sensitive and specific if the pretest clinical suspicion for CMV pneumonia is high.<sup>80–82</sup> In patients without respiratory symptoms, PCR-based results may result in false positives because pulmonary shedding of virus is common in patients with CMV infection without tissue-invasive disease.<sup>83,84</sup> In theory, false positives could be mitigated with quantitative PCR

techniques, but a viral DNA threshold has not been established.<sup>85–87</sup>

The prognostic value of isolating virus from the lower respiratory tract by BAL has been the subject of recent investigation. Seo and colleagues<sup>88</sup> found that HSCT patients with new pulmonary infiltrates and BAL-detected PIV had worse 90-day survival than did patients with new infiltrates and PIV detected only in the upper respiratory tract (45% vs 85%). Alternatively, a study by Campbell and colleagues<sup>89</sup> evaluated the prognostic value of quantitative PCR in BAL samples but found high viral copy numbers of PIV was not a predictor of outcome.

The role of lung biopsy, either surgical or endoscopic, is unclear. Although lung biopsy is superior to BAL in diagnosing noninfectious lung abnormality, it is associated with significant complications and procedure-related mortality.<sup>76</sup> High clinical suspicion for a diagnosis other than viral pneumonia would be needed to justify tissue biopsy in HM/HSCT patients with new pulmonary infiltrates.

## **PREVENTION AND TREATMENT**

### **Prevention**

Three main principles of preventing respiratory virus infections in HM/HSCT patients are infection control, chemoprophylaxis, and vaccination. Given the high attendant mortality and the variable efficacy of antiviral treatments, effective prevention likely offers the greatest potential for a mortality benefit.

Standard infection control practices should be instituted for all patients with suspected respiratory viral infection. These infection control practices include the use of personal protective equipment, patient isolation, and frequent hand hygiene. A systemic review demonstrated that these practices are a low, cost-effective way of reducing transmission.<sup>90</sup> The American Society for Blood and Marrow Transplant published extensive guidelines on infection prevention in transplant recipients.<sup>91</sup> Additional measures include early and aggressive testing for respiratory viral infections with rapid diagnostic methods, reverse isolation with face mask, and strict policies for family members and health care staff with symptoms of a respiratory infection.

Despite these practices, nosocomial transmission remains high. A likely contributor is noncompliance with infection control practices by staff members, visitors, and patients. Maziarz and colleagues<sup>48</sup> described successfully curtailing a nosocomial outbreak of PIV in the outpatient setting by establishing a rigorous 7-step protocol. During an RSV outbreak, Lehnert and

colleagues<sup>45</sup> described isolation of contacts for up to 8 days, routinely swabbing to monitor viral shedding and requiring 3 consecutive negative throat swabs before lifting isolation. These extra precautions, along with strict compliance with routine measures, are likely required for effective prevention and management of outbreaks.

The CDC recommends annual influenza vaccination for all persons aged 6 months or older who do not have contraindications.<sup>92</sup> Vaccination in patients with HSCT is complicated by impaired immunologic response. If vaccination is given before 6 months after transplant, vaccine efficacy is significantly impaired.<sup>93–95</sup> The addition of a second dose has little effect.<sup>96</sup> Vaccination before transplant has theoretic advantages, although HSCT candidates with HM also often have an impaired immunologic response to vaccination, especially while receiving highly myelosuppressive chemotherapy.<sup>97–100</sup> If vaccination is performed, only the intramuscular preparation with inactivated influenza should be used. Vaccinations for other respiratory viruses are under investigation.

Chemoprophylaxis with antiviral therapy can limit the spread of infection during outbreaks or high-risk seasons. Higa and colleagues<sup>101</sup> demonstrated that neuraminidase (NA) inhibitors may be effective at preventing nosocomial transmission of influenza in hospitalized patients. In a study of HSCT recipients who reside in an outpatient residential facility while undergoing treatment, oseltamivir was provided to all residents after several patients were diagnosed with influenza.<sup>102</sup> After initiation, no new cases of influenza were diagnosed for the duration of the influenza season, which compared favorably with matched controls in previous years.

The humanized monoclonal antibody palivizumab (PVZ) is effective at reducing the rate of RSV transmission in children with HSCT. In a study by Kassis and colleagues,<sup>103</sup> 16 children with HSCT on an inpatient ward who were considered high risk for contracting RSV during an outbreak received PVZ, and none contracted RSV.

Chemoprophylaxis against CMV in recipients of HSCT is critically important in preventing tissue-invasive disease. Prevention strategies are multimodal with a focus on preventing primary CMV infection when possible, preventing CMV reactivation in seropositive HSCT recipients, and preemptive therapy in patients with early indications of CMV reactivation.

Chemoprophylaxis is not yet available for other respiratory viral infections. Given unpredictable virus exposure patterns, profound immune defects in HM/HSCT patients, and narrow specificity of available chemopreventive agents, broad

stimulation of antiviral responses via host-directed therapies may provide an opportunity to enhance survival in these populations. Several groups are focused on stimulating antiviral protection through manipulation of pattern recognition receptors.<sup>104–108</sup>

### **Approved Therapies**

There are 2 classes of antiviral agents approved for the treatment of influenza. M2 proton channel inhibitors amantadine and rimantadine have antiviral activity against influenza A virus. NA inhibitors oseltamivir (oral), zanamivir (inhaled), and peramivir (intravenous) have activity against influenza A and B virus. Given high levels of resistance (in some series reported as >99%) to M2 inhibitors in influenza A H1N1 and H5N3, the CDC now recommends empiric therapy with an NA inhibitor in high-risk patients.<sup>109</sup> All patients with HM/HSCT are considered high risk, and NA inhibitors should be started without delay in those with confirmed or suspected influenza infection, because this confers a mortality benefit in HM<sup>110</sup> and HSCT<sup>111</sup> in both inpatient and outpatient settings.<sup>112</sup> For most studies, the average duration of NA therapy was 5 days; however, the optimal duration is unknown because patients with HM/HSCT frequently demonstrate prolonged viral shedding.

Aerosolized ribavirin, delivered via facemask in a scavenging tent, is approved for the treatment of RSV infection in children and is used frequently in high-risk adults. Data supporting its use in adults with HM/HSCT are mainly from retrospective studies that demonstrate improved mortality but no reduction in the progression to pneumonia.<sup>8,113,114</sup> Combination therapy with intravenous immunoglobulin (IVIG)<sup>114,115</sup> or PVZ<sup>116–118</sup> also seems to reduce mortality, but similarly does not clearly reduce progression to pneumonia.<sup>119</sup> Duration of therapy is usually 5 to 7 days but may be longer in severe disease. Aerosolized ribavirin can cause bronchospasm in patients with asthma or chronic obstructive pulmonary disease (COPD). It is also associated with high treatment cost, especially when combined with IVIG or PVZ.

Compassionate use of ribavirin and IVIG in patients with PIV and hMPV pneumonia has been described, but no mortality benefit or reduction in the rate of progression to pneumonia was demonstrated.<sup>34,36,120</sup>

CMV pneumonia is generally treated with intravenous ganciclovir or foscarnet in combination with IVIG or CMV-specific immunoglobulin (CMV-Ig),<sup>121–124</sup> with an intensive induction phase followed by maintenance therapy. Duration of



treatment depends on patient risk factors, viral burden, response to treatment, and institutional preference. Although generally considered the first-line agent, treatment with ganciclovir is limited by myelosuppression and is considered contraindicated in the pre-engraftment phase of transplant and in neutropenic patients. Ganciclovir resistance is also a significant concern. Foscarnet use is limited by nephrotoxicity. Combination therapy has been described in CMV-antigenemia and may play a role in select cases.<sup>125</sup> The oral valine esters valganciclovir and valacyclovir are not recommended. No randomized trials comparing antiviral therapy with or without immunoglobulins are available, and the benefit of immunoglobulins is debatable.<sup>126,127</sup> However, given the high mortality associated with CMV pneumonia and the limited toxicity profile of IVG and CMV-Ig,

combination therapy is favored. The choice of immunoglobulin is based on cost, availability, and institutional preference.

### **Future Therapies**

Several novel therapies are under development for a variety of respiratory viruses in HM/HSCT patients. **Table 1** presents an annotated list of promising antiviral therapies.

### **Coinfection and Underlying Disease**

Rates of bacterial, fungal, and viral copathogen infection are high in HM/HSCT patients with viral infections. Exact rates are difficult to estimate due to confounding elements of related studies, but when identified, prompt treatment of copathogens is imperative. Patients with HM/HSCT and comorbid

**Table 1**

**Select antiviral agents in development for use in hematologic malignancy/hematopoietic stem cell transplant populations**

<b>Name</b>	<b>Target</b>	<b>Mechanism of Action</b>	<b>Stage</b>
DAS181	Parainfluenza	Sialidase fusion protein that enzymatically cleaves sialic acids on respiratory epithelium preventing viral binding	Phase II ongoing to determine efficacy in immunocompromised patients (NCT01644877)
BCX2798 BCX2855	Parainfluenza	Selective inhibitors of hemagglutinin-NA glycoprotein	Preclinical animals studies completed <sup>140,141</sup>
PUL-042	Broad antiviral	Toll-like receptor-mediated stimulation of lung epithelial cells to activate antiviral responses in target cells of respiratory viruses	Phase I completed in health volunteers (NCT02124278); phase II in HSCT recipients planned
Presatovir	RSV	Small molecule inhibitor of RSV F protein preventing viral-envelope fusion with host-cell membrane	Phase II ongoing to determine efficacy in HSCT recipients (NCT02254408, NCT02254421)
ALN-RSVO1	RSV	Small interfering RNA directed against nucleocapsid gene required for replication	Phase IIb completed for bronchiolitis obliterans (BO) in lung transplant recipients <sup>142</sup>
Maribavir	CMV	Selective inhibitor of viral encapsidation and nuclear egress of viral particles from infected cells through binding of CMV protein kinase UL97	Phase III completed for prophylaxis in HSCT recipients <sup>143</sup>
Brincidofovir	CMV	Lipid conjugate prodrug of cidofovir, which is a selective inhibitor of viral DNA polymerase	Phase II completed for prophylaxis in HSCT recipients <sup>144</sup> Phase III ongoing for prophylaxis in HSCT recipients (NCT01769170)
Letermovir	CMV	Selective inhibitor of viral terminase subunit pUL56	Phase II completed for prophylaxis in HSCT recipients <sup>145</sup> Phase III ongoing for prophylaxis in HSCT recipients (NCT02137772)

underlying lung disease, particularly asthma and COPD, are at increased risk of respiratory failure, especially with HRV infection. Appropriate therapy for bronchospasm and airway inflammation should be part of the treatment algorithm.

## PROGNOSIS

There is significant heterogeneity reported for studies of mortality caused by respiratory viral infections in HM/HSCT patients, and most are based on single-center experience. Published mortalities for influenza pneumonia vary depending on the center, use of NA inhibitors, and influenza strain. Data from a large cancer center during the 1991 to 1992 influenza A epidemic demonstrated a 17% mortality from influenza A pneumonia in HSCT patients who had not received NA inhibitors or influenza prophylaxis.<sup>128</sup> Prospective data from several European centers between 1997 and 1998 demonstrated an all-cause mortality in patients with HSCT and influenza of 25%.<sup>17</sup> In a study with early initiation of oseltamivir in HSCT patients with influenza A or B in Brazil, mortality was 0% in 39 patients studied.<sup>111</sup> During the 2009 H1N1 outbreak, a prospective survey of HSCT recipients at several European centers reported an H1N1-attributable mortality of 6.3%.<sup>129</sup>

Mortality from RSV pneumonia is high, with rates reported between 29% and 88%.<sup>5,6,17,52,130</sup> Mortality from HRV-associated pneumonia is commonly associated with coinfection and is between 38% and 83%.<sup>21,39,131</sup> Overall mortality in patients with PIV who developed pneumonia in 2 large retrospective studies was 17%<sup>20</sup> and 35%<sup>53</sup> at 30 days. Very limited data are available for hMPV but mortalities of 0%,<sup>59,132</sup> 12.5%,<sup>36</sup> and 43%<sup>133</sup> have been reported. Risk of mortality from HEV and nonepidemic CoV appears low, but more data are needed.<sup>35,58</sup> Overall 6-month mortality from CMV-pneumonitis in patients with HSCT was 30% in a large transplant center.<sup>134</sup>

Respiratory virus infection may also result in progressive loss of lung function, particularly in patients with HSCT. Erard and colleagues<sup>134</sup> retrospectively studied 132 patients with HSCT over a 12-year period and found that 58% of patients developed airflow limitations that did not improve following resolution of their infection. Viral infections were also independently associated with bronchiolitis obliterans syndrome and idiopathic pulmonary syndrome in HSCT.<sup>135,136</sup>

Viral infections may also impact graft function. Toupin and colleagues<sup>137</sup> described 3 patients with HSCT and severe PIV pneumonia who developed engraftment failure. Grewal and colleagues<sup>138</sup> described 2 patients with Hurler

syndrome who underwent HSCT that had secondary marrow failure coincident with PIV infection. CMV has also been shown to alter gene expression in the stromal environment of bone marrow transplant recipient and inhibit engraftment.<sup>139</sup>

## SUMMARY

Respiratory viruses are increasingly recognized as a cause of pneumonia in patients with HM/HSCT and are associated with notable morbidity. Modern molecular diagnostic tools coupled with a high index of suspicion can assist identification of patients with viral pneumonia. CXR or CT scans should be considered in all patients with symptoms and signs of lower respiratory tract involvement, and referral to bronchoscopy should not be delayed. Prompt empiric antivirals followed by tailored therapy should be administered when treatments are available, and careful management of copathogens and comorbid pulmonary disease is critical. Patients with HM/HSCT should receive yearly influenza vaccination. Patients, families, and health care workers should be routinely educated on hand hygiene and isolation practices while institutional policies for infection control should be strictly enforced. Much remains understudied and large prospective studies are needed to improve the understanding of the role respiratory virus play in patients with HM and HSCT.

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