Human Metapneumovirus Infection in Immunocompromised Patients
Sharmeen Samuel, MD, Sowmya Nanjappa, MBBS, MD, Christopher D. Cooper, MD, and John N. Greene, MD

Summary: Human metapneumovirus (HMPV) is a pathogen associated with respiratory tract infection and is related to avian pneumovirus. Typically, children, the elderly, and those who are immunocompromised are the most susceptible to HMPV infection; however, the virus can infect persons of all ages. In otherwise healthy individuals, HMPV infection is generally self-limiting, but immunocompromised individuals can develop fatal complications. We present a case series of 3 severely immunocompromised patients who were infected with HMPV and describe their clinical course. All 3 patients had acute myeloid leukemia, histories of neutropenic fever, and prolonged hospitalization stays. This case series highlights the severe sequelae observed in individuals infected with HMPV, particularly among those who are immunocompromised.

Introduction
In 2001, van den Hoogen et al1 identified human metapneumovirus (HMPV) in children with respiratory tract infection, because they were able to obtain a genomic sequence of the pathogen via randomly primed polymerase chain reaction (PCR). The virus was found to be related to avian pneumovirus, a member of the Metapneumovirus genus.2 HMPV is an emerging pathogen associated with both upper and lower respiratory tract infections in all age groups, but it is more common in children (age < 5 years), in the elderly (age > 60 years), and in those with compromised immune systems.3,4 Although its formal discovery occurred 15 years ago, HMPV may have been responsible for respiratory tract infections for at least 60 years. 1

Case Reports
This series presents the cases of 3 immunocompromised patients treated at the H. Lee Moffitt Cancer Center & Research Institute (Tampa, FL) who were infected with HMPV. A summary of the case series is found in the Table.

Case 1
A Hispanic woman 47 years of age with acute myeloid leukemia (AML) had a clinical course complicated by central nervous system malignancy, bacterial enteritis, and diffuse alveolar and left-sided retinal hemorrhages. She was taking cladribine, cytarabine, and growth-factor therapy for AML and received multiple doses of intrathecal methotrexate.

Three months later she was readmitted to the hospital for blast crisis and reinduction chemotherapy. During that admission, she developed bacteremia with vancomycin-resistant enterococcus and Streptococcus mitis. She was subsequently treated with daptomycin, liposomal amphotericin B, cefepime, and acyclovir.

One month later she developed intermittent hemoptysis and mild dyspnea on ambulation that progressed to hypoxia (oxygen saturation = 90% on room air). She also experienced confusion, fever (temperature = 105.5 °F), bilateral scattered rhonchi, and crackles on auscultation. Noncontrast computed tomography (CT) of the thorax was obtained and revealed new focal consolidative infiltrates, including increased peripheral, dense consolidation of the right middle, left upper, and left lower lobes, widespread ill-defined nodules, and ground-glass infiltrates due to alveolar hemorrhage (Fig).

Bronchoalveolar fluid cultures obtained by bronchoscopy were negative for bacteria and fungi. However, HMPV was detected by PCR from nasopharynx swab sampling. Findings on PCR testing of other viral agents (adenovirus, influenza, parainfluenza, and rhinoviruses) were negative.

The patient was treated with oral ribavirin (RBV) 600 mg 3 times a day. After 14 days of therapy, her condition clinically improved and oxygen therapy was discontinued. Repeat CT showed improved multifocal pneumonia compared with the findings on the initial imaging study.

Case 2
An African American man 61 years of age with hepatitis B virus infection and non-Hodgkin lymphoma presented with fever and chills. Laboratory work-up studies were ordered and the results revealed pancytopenia. Findings on bone marrow biopsy were conclusive of AML. He was treated with cladribine, cytarabine, and...
growth factors and eventually achieved remission. Several months later, bone marrow biopsy was repeated, the results of which showed that the AML had relapsed; thus, cycle 1 of azacitidine therapy was initiated. The treatment course was complicated by pneumonia (presumed to be fungal in origin based on findings seen on CT of his chest). The patient was given daily liposomal amphotericin B to treat pneumonia.

On his hospital readmission for the second cycle of azacitidine, the patient developed submandibular cellulitis, transaminitis, and became infected with type 1 herpes simplex virus and respiratory syncytial virus. He was treated with intravenous meropenem every day for 6 weeks, weekly liposomal amphotericin B, acyclovir, and lamivudine. However, his clinical course was complicated by neutropenic fever and worsening dyspnea. Blood cultures grew Enterococcus faecium and multi-drug-resistant S maltophilia. Samples on bronchoscopy were positive for S maltophilia and Candida glabrata. He was treated with intravenous daptomycin and minocycline. Blood cultures were repeated and the results were negative after 6 days.

However, the patient again developed fever (temperature = 102.5°F), dry cough, and hypoxia (oxygen saturation = 92% on room air). Respiratory viral panel was repeated and HMPV was detected in his nasopharynx swab specimen. He was treated with oral RBV 600 mg 3 times a day. Repeat CT of his chest showed extensive bilateral ground-glass nodules consistent with bronchiolitis obliterans organizing pneumonia. His clinical presentation initially improved after oral RBV therapy, but he presented again with high-grade fever, tachycardia, and hypotension. He was started on meropenem, tobramycin, voriconazole, and acyclovir. Blood cultures were obtained and grew Escherichia coli. Despite aggressive treatment with antibiotics, the patient died the following day from septic shock.

**Case 3**

A Hispanic man 54 years of age with relapsed AML was admitted to the hospital for induction chemotherapy and was treated with cladribine, cytarabine, and growth-factor therapy. One week later while on neutropenic prophylaxis (ciprofloxacin, voriconazole, and acyclovir), the patient developed cough, mild dyspnea (oxygen saturation = 94% on room air), and fever (temperature = 103.0°F). Although findings on CT of the chest revealed bilateral patchy and nodular opacities consistent with an infectious process, sputum and bronchoalveolar fluid cultures were negative for bacteria and fungi. However, findings on respiratory viral panel from nasopharynx sampling were positive for HMPV.

The patient was treated with oral RBV 600 mg 3 times a day. Repeat CT of his chest showed extensive bilateral ground-glass nodules consistent with bronchiolitis obliterans organizing pneumonia. His clinical presentation initially improved after oral RBV therapy, but he presented again with high-grade fever, tachycardia, and hypotension. He was started on meropenem, tobramycin, voriconazole, and acyclovir. Blood cultures were obtained and grew Escherichia coli. Despite aggressive treatment with antibiotics, the patient died the following day from septic shock.

**Discussion**

HMPV is an enveloped virus with a nonsegmented, negative-sense RNA genome. Genetic analysis has elucidated 2 subgroups of the virus that often circulate together in a population. Although the virus is related to avian pneumovirus, HMPV does not cause illness in birds. Study results have shown that the inocula-

---

**Table. — Summary of the Case Series**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Underlying Malignancy</th>
<th>Etiology of Immunocompromised State</th>
<th>Clinical Signs and Symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AML CNS</td>
<td>Chemotherapy</td>
<td>Dyspnea Fever Hemoptysis</td>
<td>Oral RBV 600 mg TID</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>AML NHL</td>
<td>Chemotherapy</td>
<td>Cough Dyspnea Fever</td>
<td>Oral RBV 600 mg TID</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>AML</td>
<td>Chemotherapy</td>
<td>Cough Dyspnea Fever</td>
<td>Oral RBV 600 mg TID</td>
<td>Died</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia, CNS = central nervous system, NHL = non-Hodgkin lymphoma, RBV = ribavirin, TID = 3 times a day.
tion of HMPV in other nonhuman primates can lead to significant viral replication restricted to the respiratory tract with the subsequent development of upper respiratory tract symptoms. HMPV is commonly associated with respiratory tract infection, causing flulike symptoms, bronchiolitis, and pneumonia. HMPV infection may also be associated with exacerbations of asthma.

The data available are limited on the association of HMPV with infections of other organ systems beyond the respiratory tract. In a case report concerning a previously healthy child 14 months of age who died of encephalitis, HMPV RNA was detected in both brain and lung tissue, although HMPV antigens went undetected in these tissues via immunostaining.

Several studies have demonstrated the presence of HMPV and absence of other pathogenic organisms among patients with respiratory disease. Williams et al examined the nasal-wash specimens from children with lower respiratory tract infections during a 25-year period. A viral cause other than HMPV was identified in 41% of health care visits among 2,009 otherwise healthy infants and children presenting with acute symptoms. No viral or bacterial cause was identified in 59% of visits; of the available specimens for which no cause was previously identified, 20% tested positive for HMPV. This finding extrapolates to 12% of lower respiratory tract infections in their patient population. Thus, Williams et al concluded that HMPV infection is an important cause of respiratory tract illness, particularly during the first few years of life.

In general, transmission of HMPV is through direct or close contact via large-particle aerosols, droplets, and fomites. Many nosocomial infections have been reported in children and adults. Case 2 most likely represents a nosocomial infection, because the patient in this case was hospitalized for a prolonged duration prior to developing symptoms. HMPV infection also causes a variable array of clinical symptoms, including self-limiting cough, low-grade fever, rhinorrhea, severe respiratory failure, and death. The incubation period has not yet been defined but is thought to be 5 to 6 days in most cases. Little is known about the pathogenesis of HMPV, but an integrin alpha v beta 1 receptor has been identified that facilitates infection of the epithelial cells of the respiratory tract.

The most common reasons for hospitalization in children are bronchiolitis and pneumonia. Although HMPV has been associated with upper respiratory tract infections (rhinopharyngitis, laryngitis, croup), severe lower respiratory tract infection has been reported. The infection can occur in adults of all ages, although elderly persons with histories of long hospitalization stays and cardiopulmonary disease are at greater risk for becoming infected. The possible role of HMPV in the exacerbation of chronic obstructive pulmonary disease in adults is controversial.

Respiratory tract infections are a significant source of morbidity and mortality in immunocompromised patients, and this is especially true for individuals with hematological malignancies and those receiving hematopoietic stem cell transplantation (HSCT). Prospective and retrospective studies of patients receiving HSCT have provided data on the incidence of upper and lower respiratory tract infections caused by HMPV infection and the associated mortality rates. In these studies, cohorts of symptomatic and asymptomatic patients with HSCT were followed for 4 years, and the virus was identified through PCR testing of nasopharyngeal specimens. The incidence rates of HMPV infections in patients receiving HSCT ranged from 3% to 7% in those with any respiratory disease, whereas the rate increased to between 27% and 41% among patients with lower respiratory disease. The rate of deaths associated with lower respiratory tract infection was between 53% and 40%, and the rate of deaths related to overall infections (upper and lower respiratory tracts) was between 0% and 14%. In the retrospective study, bronchoalveolar lavage specimens were obtained for the work-up of pulmonary infiltrates from 163 patients after receiving HSCT; of these, 3% were positive for HMPV and 20% of patients died due to respiratory failure. These results highlight the potential severity of HMPV-related pneumonia in recipients of HSCT. Because many such patients have concurrent bacterial and fungal infections, describing the exact clinical features of HMPV infection can be difficult.

HMPV infection has important associations with respiratory tract illness in patients with hematological malignancies and those who have received lung transplants. A retrospective evaluation of 55 children (age range, 5 months–19 years) with laboratory-confirmed HMPV infection highlighted a number of associations. HMPV infection was associated with underlying hematological malignancy (44%), HSCT (15%), solid tumors (16%), and solid organ transplants (15%). Another report showed that 25% of study patients with hematological disease who tested positive for HMPV infection also had pneumonia. A review by Kamboj et al of 1,899 study patients with cancer showed that nearly 3% were positive for HMPV; more children were positive than adults.

To diagnose HMPV infection, reverse transcriptase (RT)-PCR is the most sensitive and commonly used method available; it detects the virus in nasal and bronchial secretions and is easy to perform. Other less-commonly used methods for detecting the virus include direct fluorescent antibody test, serology, and viral culture.

The incidence of HMPV infection increases during the winter and spring. Patients in cases 1 and 2 in our series were infected with HMPV in June 2015, and the patient in case 3 was infected in May 2014. Prior infection with HMPV does not protect against reinfection.
which can occur throughout life.\textsuperscript{4} A live recombinant vaccine for HMPV is still in preclinical trials.\textsuperscript{40} However, we must learn more about its pathogenesis, genetics, and serological properties to achieve a safe and effective vaccine against HMPV.

Treatment for HMPV infection is mainly supportive, and no data exist on any antiviral agent shown to have significant activity against the virus. No guidelines are available for treatment, but some centers use RBV and intravenous immunoglobulin; however, the usefulness of RBV in HMPV infection is controversial.\textsuperscript{27} Some animal models have shown that RBV reduces viral replication in HMPV-infected mice,\textsuperscript{28} and use of RBV to successfully treat the infection in humans has been previously described.\textsuperscript{29} Other study data show that RBV does not reduce mortality in immunocompromised patients and is not effective against the virus.\textsuperscript{30} Although case 1 in our series is an example of successful treatment against HMPV using oral RBV, this finding does not establish a beneficial effect of RBV against HMPV infection.

Conclusions

Discovered 15 years ago, human metapneumovirus (HMPV) can cause respiratory tract infections.\textsuperscript{1} Although data have been published on the prevalence of the virus in high-risk groups (eg, children < 5 years of age, persons > 60 years of age with comorbidities [eg, cardiopulmonary diseases], immunocompromised individuals), important information on the immunological properties and pathogenesis of the virus is still unknown.\textsuperscript{5} This case series presents the clinical courses of 3 severely immunocompromised patients infected with HMPV and describes the impact of the virus on their disease course. Infection with HMPV can add to the severity of an underlying malignancy, especially in immunocompromised patients, and can be a contributing factor toward the death of such patients. Therefore, it is important to prevent this viral infection in immunocompromised individuals. Measures to control such infection, including avoiding contact with large-particle aerosols and droplets, practicing proper hand hygiene, and, when possible, limiting the visitation of persons who are ill, can all help to prevent the spread of HMPV. A need exists for recommendations to guide treatment for HMPV infection in high-risk patient groups, such as the severely immunocompromised patients presented in this case series. Development of an HMPV vaccine is a reasonable goal for the prevention of this pathogen.

Acknowledgment: We gratefully acknowledge the help of Peter P. Karpawich, MD, from the Detroit Medical Center in Michigan for reviewing this case series.

References