Human Metapneumovirus Pneumonia in Adults: Results of a Prospective Study

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We prospectively collected clinical, laboratory, and radiographic data regarding community-acquired human metapneumovirus (hMPV) infection in consecutive adults hospitalized with pneumonia. hMPV infection was diagnosed using highly accurate reverse-transcription–polymerase chain reaction analysis of nasopharyngeal samples. Eight (4%) of 193 patients had hMPV RNA present, all detected during influenza season. hMPV is an important cause of pneumonia in adults.

Human metapneumovirus (hMPV) is a recently described respiratory virus [1]. Most descriptions of the clinical characteristics of hMPV infection have focused on children, although the picture in adults is slowly emerging [2–8]. hMPV is thought to cause a spectrum of disease in adults, ranging from upper respiratory tract illness to community-acquired pneumonia (CAP).

The presentation of CAP due to hMPV in adults has not been well characterized, and the incidence may be underestimated. We undertook a prospective etiology study to better describe the clinical, radiographic, and laboratory characteristics and outcomes of hMPV in consecutive adults hospitalized with CAP.

Methods. From August 2004 through March 2006, 300 consecutive consenting patients were entered into a prospective study to determine the etiology of CAP. The study included patients who were >17 years old and who had been hospitalized because of CAP at all 5 Edmonton, Canada, hospitals. We excluded patients who were pregnant, who were immunocompromised (because of receipt of >10 mg of prednisone/day for >1 month, receipt of other immunosuppressive agents, or HIV infection with CD4 cell count of <250 cells/μL), or who had tuberculosis or cystic fibrosis. All patients provided written informed consent, and the Health Research Ethics Board of the University of Alberta approved the study.

Pneumonia was defined as an acute respiratory tract illness with ≥2 of the following symptoms or signs: cough, productive cough, fever, chills, dyspnea, pleuritic chest pain, crackles, or bronchial breathing; in addition, an opacity or infiltrate on chest radiograph interpreted as pneumonia by a radiologist was required. Symptom severity was graded on a 6-point scale from 0 (no symptom) to 5 (very severe symptom), as described elsewhere [9]. To characterize the severity of pneumonia itself, we calculated the Pneumonia Severity Index using the methods of Fine et al. [10].

We collected routine blood and sputum specimens and nasopharyngeal swabs for each patient according to a study protocol. Nasopharyngeal swabs submitted for detection of viral pathogens first had routine viral tests performed according to laboratory test algorithms, including direct fluorescent antibody tests for respiratory syncytial virus, parainfluenza virus, and influenza virus types A and B (Imagen; DakoCytomation); rapid respiratory virus plate cultures; and traditional viral cultures. In addition to routine microbiological and virological investigations, expanded testing of nasopharyngeal samples was done for a range of respiratory pathogens by nucleic acid amplification techniques using extraction and amplification methods described previously [11]. In brief, total nucleic acid extraction (DNA and RNA) was undertaken from 200 μL of nasopharyngeal swab material into an elution volume of 100 μL with 5 μL of eluted nucleic acid used in each amplification.

Nucleic acid amplification techniques included an RT-PCR designed to amplify and detect all lineages and sublineages of hMPV, as well as sensitive and specific assays for influenza A virus, influenza B virus, respiratory syncytial virus, parainfluenzaviruses 1–4, adenoviruses, rhinoviruses, enteroviruses, coronaviruses (OC43, 229E, and NL63), Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila. We included all patients with an RT-PCR result positive for hMPV in our analysis. The limit of detection for the hMPV RT-PCR is <100 copies input for all hMPV lineages, with no reported
Table 1. Clinical characteristics of 8 adult patients with community-acquired pneumonia due to human metapneumovirus.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years/sex</th>
<th>Comorbidities</th>
<th>Vaccination up to date</th>
<th>Smoking status</th>
<th>Symptoms and signs</th>
<th>PSI class</th>
<th>Chest radiographic findings</th>
<th>Length of stay, days</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Polysaccharide pneumococcal</td>
<td>Influenza</td>
<td>Former</td>
<td>Cough, dyspnea, fatigue, sputum</td>
<td>IV</td>
<td>Infiltrates LLL and RLL and pleural effusions</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>91/F</td>
<td>IHD, cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>Former</td>
<td>Cough, dyspnea, fatigue, sputum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31/F</td>
<td>Asthma, IHD, depression</td>
<td>No</td>
<td>No</td>
<td>Nonsmoker</td>
<td>Cough, dyspnea, fatigue, sputum, vomiting</td>
<td>II</td>
<td>Infiltrates LLL, LUL, and lingula</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>79/F</td>
<td>IHD, cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>Former</td>
<td>Cough, dyspnea, fatigue, sputum</td>
<td>IV</td>
<td>Infiltrates RLL, RML, LLL, and lingula and pleural effusions</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>33/M</td>
<td>HIV, COPD, substance abuse</td>
<td>Yes</td>
<td>Yes</td>
<td>Current</td>
<td>Cough, dyspnea, fatigue, sputum</td>
<td>II</td>
<td>Infiltrates RUL</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>56/F</td>
<td>COPD, CHF, home oxygen</td>
<td>Yes</td>
<td>Yes</td>
<td>Former</td>
<td>Cough, dyspnea, fatigue sputum</td>
<td>II</td>
<td>Infiltrates LUL, lingula, RML</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>91/M</td>
<td>COPD, IHD, CHF, home oxygen</td>
<td>Yes</td>
<td>No</td>
<td>Former</td>
<td>Cough, dyspnea, fatigue</td>
<td>IV</td>
<td>Infiltrate LLL and pleural effusion</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>85/F</td>
<td>Asthma, COPD, IHD</td>
<td>Yes</td>
<td>No</td>
<td>Nonsmoker</td>
<td>Cough, dyspnea, fatigue, sputum</td>
<td>IV</td>
<td>Infiltrate LLL and pleural effusion</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
<td>IHD</td>
<td>No</td>
<td>No</td>
<td>Nonsmoker</td>
<td>Cough, dyspnea, fatigue</td>
<td>III</td>
<td>Infiltrate RML</td>
<td>2</td>
</tr>
</tbody>
</table>

**NOTE.** CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; LLL, left lower lobe; LUL, left upper lobe; PSI, Pneumonia Severity Index; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
cross-reaction with other common respiratory pathogens (i.e., 100% specificity) [12].

**Results.** A total of 300 patients were enrolled in the study, and 193 had evaluable nasopharyngeal samples collected; this latter group is our final study sample. Overall, 9 patients had evidence of hMPV RNA detected in the nasopharyngeal swab; 1 had evidence of coinfection (Streptococcus pneumoniae detected by blood culture) and was therefore excluded from analysis. Eight (4%) of 193 patients had hMPV RNA detected without evidence of coinfection with other microorganisms (i.e., no organisms were cultured from blood or sputum specimens or detected by nasopharyngeal swab examination) and were considered to have hMPV CAP. All cases of hMPV infection occurred during the period of December through April.

The characteristics of the 8 patients with CAP due to hMPV are summarized in table 1. Ages ranged from 31 to 91 years (mean, 62 years), 5 (63%) of 8 patients were female, and all patients had underlying cardiac or pulmonary disease. One-half of the patients had severe pneumonia (defined as a Pneumonia Severity Index class IV or V).

All patients with pneumonia due to hMPV had cough, dyspnea, and fatigue. The cough was described by all 8 patients as “severe enough to require cough suppressants,” and a productive cough was described by 6 patients; 5 described their sputum as purulent. Dyspnea was described as “at least most of the time” in 4 patients. Seven patients reported that their fatigue involved being “tired most of the time, comfortable only at rest.” Of note, only 1 patient had myalgias, and only 1 had gastrointestinal illness.

Only 1 patient was febrile (oral temperature, >38°C), and the mean temperature of the 8 patients was 37.6°C (range, 36.2°C–40.4°C). The mean respiratory rate was 25 breaths/min (range, 20–36 breaths/min), but only 1 patient was tachypneic (defined as respiratory rate of >30 breaths/min). Nevertheless, most patients were hypoxic, and only 2 of 8 had room air oxygen saturations of >92%. The mean pulse rate was 103 beats/min (range, 73–116 beats/min), and no patient had a systolic blood pressure of <90 mm Hg.

The leukocyte count was normal (defined as a leukocyte count of 4.5–11 × 10^9 cells/L) in 7 patients (mean, 8.0 × 10^9 cells/L; range, 3.5–15.10 × 10^9 cells/L). Lymphopenia (lymphocyte count, <1.3 × 10^9 cells/L) occurred in all but 1 patient (mean lymphocyte count, 0.9 × 10^9 cells/L; range, 0.2–3.0 × 10^9 cells/L); conversely, neutrophilia (neutrophil count, >7.5 × 10^9 cells/L) occurred in 3 patients (mean neutrophil count, 6.6 × 10^9 cells/L; range, 2.5–12.8 × 10^9 cells/L).

Infiltrates could be seen in either upper (3 patients), midzone (4 patients), or lower lobes (5 patients) of admission chest radiographs, and in 50% of patients, the radiographs demonstrated multilobar abnormalities. Only 3 patients had bilateral infiltrates. Small unilateral pleural effusions were seen in 4 patients.

All patients received empirical therapy with levofloxacin, in accordance with the hospitals’ pneumonia care map [13]. The average length of stay was 7 days (range, 2–11 days); no patient required intubation, ventilation, or admission to the intensive care unit, and no patient died.

**Discussion.** In this prospective cohort study, we found that hMPV accounted for 4% of all cases of CAP, and it was more prevalent in winter months (the usual peak of influenza activity) and had a tendency to affect elderly patients with cardiopulmonary disorders. We have shown that the prevalence of hMPV pneumonia was similar to the previously reported 4.4% prevalence of respiratory syncytial virus pneumonia in adults [14]. Our findings are consistent with those of Hamelin et al. [3], who reported that the incidence of hMPV infection among patients with CAP or chronic obstructive pulmonary disease exacerbations was 4.1%, although their study population included patients with evidence of coinfection with other pathogens.

The prominent clinical features of hMPV pneumonia in our sample included severe (often productive) cough, dyspnea, fatigue, and the absence of fever, consistent with most previous case reports and small case studies of hMPV infection in adults [2, 5]. In contrast, Hamelin et al. [3] described fever as an important sign among patients with CAP due to hMPV (again, bear in mind that they included patients with potential coinfecting pathogens, such as S. pneumoniae and influenza virus). In our series of patients without detectable coinfection, hMPV pneumonia seemed to be distinguishable from influenza because of the absence of fever, myalgias, and gastrointestinal symptoms—symptoms that previous literature suggests should play a prominent role in influenza [14]. Should this observation prove to be replicated when studied in a larger cohort, earlier recognition of CAP due to hMPV may help avoid use of unnecessary empirical antivirals.

The outcome of CAP due to hMPV in this study was good; no patients died or required admission to an intensive care unit. In contrast, hMPV infection in immunocompromised hosts has been associated with significant morbidity and mortality [15, 16]. A diagnosis of hMPV infection may have important infection control implications, because hospitals will want to avoid placing patients with known CAP due to hMPV with those who are immunocompromised. This is germane, given recent reports of hMPV as a cause of outbreaks of respiratory infection in schools, long-term-care facilities, and assisted-care centers [7, 8, 12]. The strengths of this study include its prospective and comprehensive data collected from a cohort of consecutive patients requiring admission to hospital. Our sample size precludes meaningful statistical comparisons with the rest of the study.
cohort; however, our intent was to describe the clinical entity, not compare its presentation with that of pneumonias due to other etiologies. Limitations include the fact that patients were recruited from only 5 hospitals and the possibility of false-negative and false-positive hMPV diagnoses, although RT-PCR reportedly has excellent sensitivity and specificity [12], and a recent publication by Falsey et al. [17] concluded that asymptomatic carriage of hMPV is extremely uncommon. The possibility exists that some patients had bacterial superinfection, although the fact that fever was absent and WBCs were normal potentially mitigates against this [14]. Viral coinfection was unlikely, given the use of RT-PCR to exclude many potential viruses.

In summary, hMPV is a common cause of pneumonia in adults, constituting 4% of all cases of CAP in our cohort. We recommend routine testing for hMPV in adults admitted to hospital with CAP when the virus is known to be circulating, because early recognition may aid in limiting transmission of hMPV, particularly to immunocompromised hosts.

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