

Chest radiographic features of human metapneumovirus infection in pediatric patients

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Abstract

Background Human metapneumovirus (HMPV) was identified in 2001 and is a common cause of acute respiratory illness in young children. The radiologic characteristics of laboratory-confirmed HMPV acute respiratory illness in young children have not been systematically assessed.

Objective We systematically evaluated the radiographic characteristics of acute respiratory illness associated with HMPV in a prospective cohort of pediatric patients.

Materials and methods We included chest radiographs from children <5 years old with acute respiratory illness who were

enrolled in the prospective New Vaccine Surveillance Network (NVSN) study from 2003 to 2009 and were diagnosed with HMPV by reverse transcription-polymerase chain reaction (RT-PCR). Of 215 HMPV-positive subjects enrolled at our tertiary care children's hospital, 68 had chest radiographs obtained by the treating clinician that were available for review. Two fellowship-trained pediatric radiologists, independently and then in consensus, retrospectively evaluated these chest radiographs for their radiographic features.

Results Parahilar opacities were the most commonly observed abnormality, occurring in 87% of children with HMPV. Hyperinflation also occurred frequently (69%). Atelectasis (40%) and consolidation (18%) appeared less frequently. Pleural effusion and pneumothorax were not seen on any radiographs.

Conclusion The clinical presentations of HMPV include bronchiolitis, croup and pneumonia. Dominant chest radiographic abnormalities include parahilar opacities and hyperinflation, with occasional consolidation. Recognition of the imaging patterns seen with common viral illnesses like respiratory syncytial virus (RSV) and HMPV might facilitate diagnosis and limit unnecessary antibiotic treatment.

Keywords Bronchiolitis · Chest · Children · Human metapneumovirus · Infection · Lungs · Radiography · Respiratory tract

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Introduction

Human metapneumovirus (HMPV) was discovered in 2001 [1]. Human metapneumovirus is a member of the pneumovirus family of negative-sense, single-stranded ribonucleic acid (RNA) viruses that also includes respiratory syncytial virus (RSV). Human metapneumovirus has emerged

as a significant contributor to upper and lower respiratory tract infections in infants and children and older adults, especially those with chronic medical conditions such as asthma, chronic obstructive pulmonary disease (COPD), and immune system compromise [2–11]. Human metapneumovirus is therefore a target for improved rapid diagnostic tests, as well as antiviral and vaccine development.

The burden of HMPV infection was evaluated in children in a prospective study undertaken by the Centers for Disease Control and Prevention (CDC) New Vaccine Surveillance Network (NVSN) from 2003 to 2009 [5]. Patients and healthy controls <5 years old were enrolled at three U.S. centers: Nashville, TN; Cincinnati, OH; and Rochester, NY. More than 10,000 children younger than 5 years were enrolled from outpatient clinics and emergency departments and as inpatients. The annual rate of hospitalization associated with HMPV was 1 per 1,000, similar to the rate for influenza virus and parainfluenza virus types 1–3 combined (1 per 1,000), but lower than the rate for RSV (3 per 1,000). Infants <6 months old with HMPV were more likely to be hospitalized than older children, and there was a high rate of outpatient visits associated with HMPV. Human metapneumovirus-associated visits to the outpatient clinic and emergency department continued until age 5 years [5]. It is important to note that HMPV is rarely detected in asymptomatic children [5, 6, 12, 13]. There are very rare reports of central nervous system disease associated with HMPV, but the biological mechanism of this is unclear [14, 15].

A subset of enrolled children identified as HMPV-positive at our institution in this prospective study had chest radiographs obtained as part of their routine clinical care. Thus we sought to describe the chest radiographic features of HMPV infection.

Materials and methods

The full design and methods of NVSN surveillance have been reported [5, 16–19]. Subjects included in the current study were enrolled in the winter and spring months from Nov. 1 through May 31 in the years 2003 through 2009. At our study site (Nashville), a total of 3,993 children younger than 5 years with acute respiratory illness or fever were enrolled. Hospitalized children were enrolled 4 days a week, outpatient surveillance was conducted 1–2 days per week, and subjects in the emergency department were enrolled 1–4 days per week. Acute respiratory illness was defined as an illness presenting with fever or one or more of the following symptoms: cough, earache, nasal congestion, rhinorrhea, sore throat, vomiting after coughing, wheezing, and labored, rapid or shallow breathing. Children were excluded if symptoms were present for >14 days, if they had chemotherapy-associated

neutropenia, or if they had been hospitalized within the previous 4 days. Viral testing was performed in the research lab, and the results were not available to clinicians; thus clinical diagnoses were assigned by the patients' health care providers independent of viral detection. A total of 215 subjects enrolled at our site tested positive for HMPV by reverse-transcriptase polymerase chain reaction (RT-PCR) [20]. We queried the NVSN database to identify subjects who had chest radiographs obtained; of these 215 HMPV-positive children, 77 (36%) underwent chest radiography at the discretion of the treating clinician. We retrieved the radiographic images for these subjects. Nine of the children had been enrolled at outlying hospitals in Nashville and the chest radiographs were unavailable. The remaining 68 HMPV-positive children with available chest radiographs made up our study population. The Vanderbilt University Institutional Review Board approved the study.

The subjects' presenting chest radiographs were reviewed independently by two fellowship-trained pediatric radiologists (M.A.H. and S.P.S.), both with certificates of added qualification (CAQ) in pediatric radiology and more than 20 years of combined experience in pediatric radiology. The radiologists were blinded to the parameters and outcomes of the initial clinical study and were only told the patient population had tested positive for the virus. They systematically assessed the radiographs for a variety of common chest radiographic findings, including consolidation, parahilar opacities, peribronchial thickening, atelectasis, hypo-inflation, hyperinflation, pleural effusion, nodules and pneumothorax. Atelectasis was defined as present if there were signs of volume loss and if the opacity was not well defined and was present only on one view. Consolidation was defined as opacity visible on both anteroposterior and lateral views. There was no formal definition for interstitial disease, which was left at the discretion of the radiologist. Other abnormalities could be noted if present. These categories were decided a priori based on experience with radiologic assessment of bacterial and viral respiratory tract infections. The findings were entered into an electronic research database, REDCap [21], independently by each reviewer. Once the radiographs were independently reviewed, the radiologists performed a consensus review to discuss and resolve discrepancies.

Results

The 68 subjects had a median age of 15 months (mean 18 months, range 0–59 months). Forty-nine (72%) were inpatients, 18 (26%) were emergency department patients, and one was seen in the outpatient clinic. Thirty-six (53%) were male, with 21 (31%) white, 24 (35%) black, 13 (19%) Hispanic and 10 (15%) other race/ethnicity. Only four subjects had

Table 1 Radiologic findings among all subjects

| Chest radiograph findings | Incidence |
|---------------------------|-------------|
| Parahilar opacities | 87% (59/68) |
| Hyperinflation | 69% (47/68) |
| Atelectasis | 40% (27/68) |
| Consolidation | 18% (12/68) |
| Peribronchial thickening | 3% (2/68) |
| Hypo-aeration | 3% (2/68) |
| Pleural effusion | 0% (0/68) |
| Pneumothorax | 0% (0/68) |
| Normal | 3% (2/68) |

underlying medical conditions, which included chronic lung disease, developmental delay and congenital heart disease, genetic metabolic disease, and neurological disorder. The clinical diagnoses included pneumonia ($n=34$, 50%), asthma ($n=25$, 37%), bronchiolitis ($n=14$, 21%) and croup ($n=1$, 1%). Some children were assigned more than one diagnosis: 10 subjects were diagnosed with both asthma and pneumonia, and 2 children were diagnosed with both bronchiolitis and pneumonia. The mean age of children diagnosed with bronchiolitis was 10 months, while the mean age for both pneumonia and asthma was 20 months. No children were diagnosed with apnea or

bacteremia. Of 49 children with complete records, 23 (47%) required supplemental oxygen, 7 (14%) were admitted to the intensive care unit and 5 (10%) required mechanical ventilation. There were no deaths.

The observed proportional agreement between the two radiologists' independent interpretations was 96%. When considering overall radiologic findings, parahilar opacities were the most commonly observed abnormality, present in the majority of the patients (Table 1). Hyperinflation was another common finding, present in 69% of cases. Three of the children presented with hyperinflation only. Atelectasis and consolidation were observed less frequently but were not rare, at 40% and 18%, respectively. Pleural effusion and pneumothorax were not seen in any HMPV-infected child. Two of the subjects' chest radiographs were normal.

Subjects with different clinical diagnoses had different radiologic findings (Table 2). Children diagnosed with pneumonia were more likely to have consolidation and parahilar/peribronchial opacities, though consolidation was present only in 12 of 23. In contrast, children with asthma and bronchiolitis were more likely to have hyperinflation. Figures 1, 2, 3, and 4 demonstrate representative chest radiographic findings in HMPV-infected children with different clinical diagnoses and severity ranging from mild to severe disease, thus illustrating the wide spectrum of HMPV illness.

Table 2 Radiologic findings in subjects with single clinical diagnoses

| Diagnosis | Consolidation | Effusion | Peribronchial thickening | Parahilar/peribronchial opacities | Atelectasis | Hyperinflation | Hypo-aeration |
|----------------------|---------------|----------|--------------------------|-----------------------------------|-------------|----------------|---------------|
| Pneumonia $n=23$ | 34.8% | 0% | 0% | 95.7% | 39.1% | 65.2% | 4.3% |
| Asthma $n=16$ | 0% | 0% | 6.3% | 81.3% | 18.8% | 75.0% | 0% |
| Bronchiolitis $n=12$ | 0% | 0% | 0% | 83.3% | 25.0% | 83.3% | 0% |

Fig. 1 Radiography in a 19-month-old HMPV-infected previously healthy boy who presented with fever, upper respiratory tract symptoms and diarrhea. Physical exam revealed coarse breath sounds; complete blood count was normal. He was administered intravenous saline and discharged from the emergency department with the diagnoses of febrile illness and dehydration. **a, b** Anteroposterior (**a**) and lateral (**b**) chest radiographs show parahilar opacities. *HMPV* human metapneumovirus

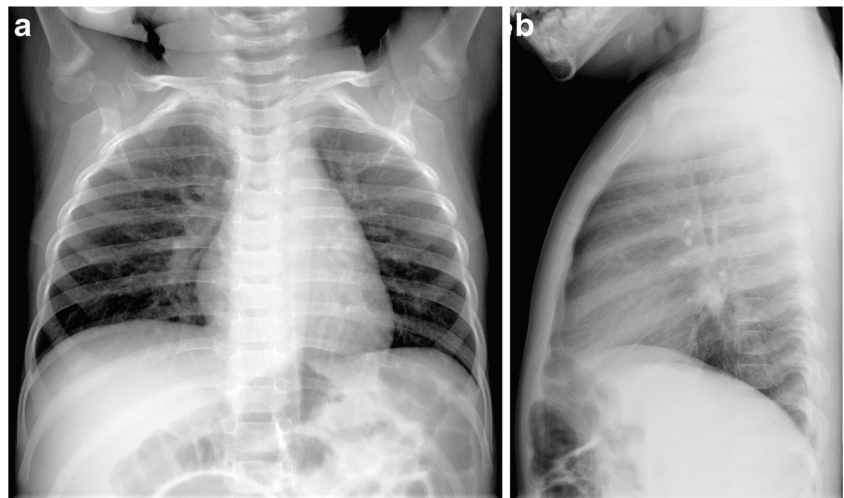
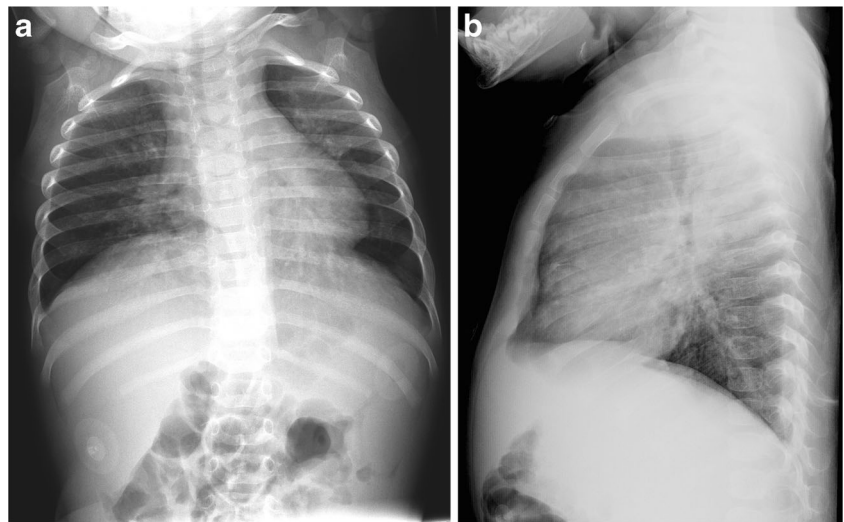


Fig. 2 Radiography in a 1-year-old HMPV-infected boy with history of occasional wheezing who presented with 5 days of fever, congestion and worsening cough. Physical exam revealed tachypnea, hypoxia, diffuse wheezes and bibasilar crackles. He was hospitalized with the diagnosis of pneumonia and treated with intravenous fluid, nebulized albuterol, supplemental oxygen and ceftriaxone. **a, b** Anteroposterior (a) and lateral (b) chest radiographs show parahilar opacities and hyperinflation. *HMPV* human metapneumovirus



Discussion

Radiography is commonly obtained as part of the clinical evaluation of children experiencing respiratory symptoms, primarily to exclude alternative diagnoses such as bacterial pneumonia and its complications, or foreign body aspiration. Recent guidelines for the management of community-acquired pneumonia in children recommend that chest radiographs be obtained only for outpatients with suspected or documented hypoxemia, significant respiratory distress or failed initial antibiotic therapy. Chest radiographs are recommended for all children hospitalized for pneumonia [22]. In contrast, chest radiographs are not recommended for the routine

management of bronchiolitis [23]. Although chest radiograph findings might have influenced the clinical diagnosis for these children, the radiographs were ordered by clinicians with no knowledge of a viral pathogen.

Radiologists, particularly pediatric radiologists, are aware of the common viruses causing respiratory disease in children, namely RSV, influenza, parainfluenza and adenovirus. In the last decade human metapneumovirus has been recognized as a leading pathogen among viruses causing significant disease burden in children. As more rapid diagnostic tests for HMPV become available, radiologists should recognize this pathogen and its imaging findings. Our studies found parahilar opacities and hyperinflation to be the most prominent findings, but they also noted consolidation. Several reports have described some of the radiographic features of HMPV infection [24–27]; however most of these included fewer subjects, comprised retrospective convenience samples, or did not systematically evaluate radiographs. One report of 11 chest radiographs in children with radiologically diagnosed community-acquired pneumonia caused by HMPV described pulmonary infiltrates (alveolar or interstitial), hyperinflation and atelectasis [28]. Another report of chest CT findings in immunocompromised adults with HMPV reported asymmetrical pulmonary findings consisting of ground-glass opacity, airspace consolidation or bronchial wall thickening, in contrast to more symmetrical bilateral pulmonary infiltrates in immunocompromised adults with RSV-pneumonia [29].

The findings on chest radiographs of HMPV infection are similar to those associated with other common viral causes of lower respiratory tract infection, such as RSV, parainfluenza and influenza [30–33]. The radiographic findings of RSV infection and other viral respiratory tract infections have been described as parahilar peribronchial infiltrates and hyperexpansion [34]. These findings are not completely specific and are also noted in adenovirus, influenza and parainfluenza virus infections, although hyperexpansion was reported more commonly with



Fig. 3 Radiography in a 4-month-old HMPV-infected boy presenting with fever, cough and increased work of breathing. Physical exam revealed tachypnea and dyspnea; peripheral white blood count was $18.9 \times 10^3/\mu\text{L}$. He was hospitalized with the diagnosis of pneumonia and treated with ceftriaxone. Blood culture was negative. His anteroposterior portable chest radiograph (slightly rotated) showed hyperinflation, increased parahilar opacities and multiple areas of atelectasis. There was more confluent consolidation in the right upper lobe, a less frequent finding in children with HMPV. *HMPV* human metapneumovirus

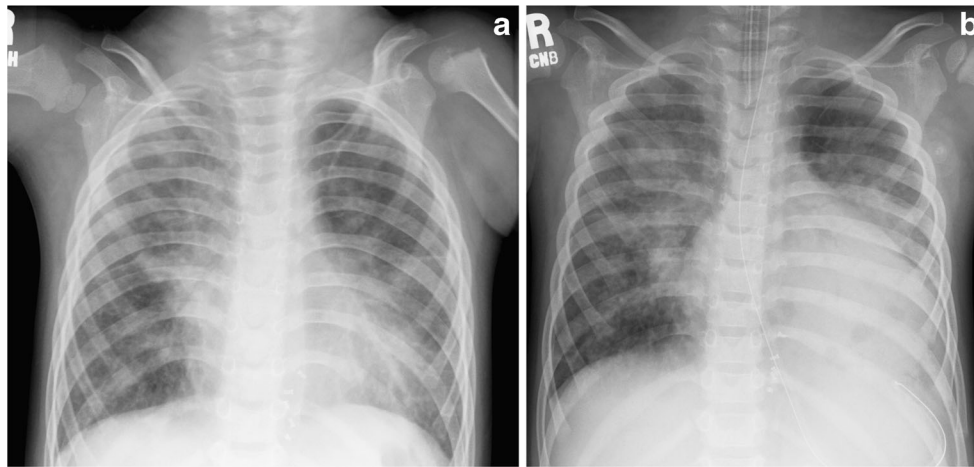


Fig. 4 Radiography in a 3-year-old boy with trisomy 21, atrioventricular septal defect, asthma and reflux. **a** Anteroposterior (AP) chest radiograph obtained at baseline 11 weeks prior to admission. The boy presented acutely with fever and dyspnea and required intubation and tested HMPV-positive. He was admitted to the intensive care unit and treated with intravenous antibiotics. Tracheal and blood cultures were negative. **b**

Portable AP chest radiograph on admission shows multifocal consolidation and worsening parahilar opacities, a change from baseline. He experienced a prolonged hospitalization complicated by chylous left pleural effusion 3 weeks after admission. HMPV human metapneumovirus

RSV, and hilar adenopathy was seen more often with adenovirus [34]. Kern et al. [35] described central pneumonia and peribronchitis as common chest radiographic findings in young children with RSV infection. Because terms placed in a radiographic report are not uniform and are interpreted by clinicians in different ways, the terms “central pneumonia” and “parahilar infiltrates” are likely describing the same findings [36]. Pleural effusions and lobar pneumonia were reported to be uncommon with RSV infection, similar to our findings for HMPV infection. One study reported frequent hilar adenopathy associated with RSV infection [37], but we did not observe this in any child with HMPV infection. Some of the findings we observed could be caused by chronic lung disease; however only 4 children out of 68 had underlying medical conditions.

Although radiologists should recognize these viral infection patterns on chest radiographs, they cannot definitively identify the virus without laboratory confirmation. Similarly, the clinical signs and symptoms do not reliably discriminate among these pathogens [13]. It is important to identify parahilar opacities and hyperinflation consistent with a viral pattern of disease because the child can be treated supportively without antibiotics in the absence of a confirmed superimposed bacterial pneumonia.

Our study has some limitations. We present a retrospective review of radiographs in children with HMPV infection from only one of the three initial study sites. Furthermore, not all children who tested positive for HMPV underwent chest radiography and those who did undergo chest radiography might have had more severe symptoms. Moreover, the clinical diagnoses were assigned with knowledge of the initial chest radiograph reading, which likely influenced the choice of diagnosis. In addition, upon review of the chest radiographs, the study radiologists were aware of the diagnosis, and perhaps were biased toward finding abnormalities.

Conclusion

Human metapneumovirus is a leading cause of acute lower respiratory infection in children and adults, with a substantial disease burden similar in degree to that of influenza virus [5]. There are no vaccines or antiviral drugs available against HMPV. Radiologists should be aware of this new pathogen, and to that end this study serves to document radiographic findings in young children with HMPV infection, most commonly parahilar opacities and hyperinflation without effusions or lobar consolidation.

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Compliance with ethical standards

Conflicts of interest J.V. Williams is on the Scientific Advisory Board for Quidel, Inc., and the Independent Data Monitoring Committee for GlaxoSmithKline. M.A. Hilmes, F.D. Dunnavant, S.P. Singh, W.D. Ellis, D.C. Payne, Y. Zhu, M.R. Griffin and K.M. Edwards have no conflicts to disclose.

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