HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2021 June 10.

Published in final edited form as:

Clin Infect Dis. 2020 June 10; 70(12): 2712–2714. doi:10.1093/cid/ciz961.

Severe Human Metapneumovirus and Group A *Streptococcus* Pneumonia in an Immunocompetent Adult

Holly M. Biggs[1], **Chris A. Van Beneden**[2], **Katie Kurkjian**[3,4], **Miwako Kobayashi**[2], **Teresa C. T. Peret**[1], **John T. Watson**[1], **Eileen Schneider**[1], **Susan I. Gerber**[1], **Jayashree Ravishankar**[5]

[1]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA,

[2]Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA,

[3]Division of State and Local Readiness, Center for Preparedness and Response, Centers for Disease Control and Prevention, Atlanta, Georgia, USA,

[4]Virginia Department of Health, Richmond, Virginia, USA,

[5]Infectious Diseases, St Mary's Hospital, Richmond, Virginia, USA

Abstract

An immunocompetent adult with asthma developed severe human metapneumovirus (HMPV) illness complicated by group A *Streptococcus* coinfection, progressing to acute respiratory distress syndrome and shock. Several coworkers had less severe HMPV infection. HMPV can cause severe respiratory illness in healthy adults and should be considered as a potential cause of community respiratory outbreaks.

Keywords

human metapneumovirus; respiratory virus; group A *Streptococcus*; acute respiratory distress syndrome; pneumonia

Human metapneumovirus (HMPV) causes acute respiratory illness among people of all ages, particularly during the winter and spring in temperate climates [1]. Infection can be asymptomatic or result in mild to severe respiratory illness [2]. Most children have been infected with HMPV by age 5, but immunity is incomplete and reinfection can occur. Among adults, severe HMPV disease is more common in persons who are older, who are immunocompromised, or have underlying cardiopulmonary disease [2, 3]. HMPV can cause severe lower respiratory tract infection, including acute respiratory distress syndrome

Correspondence: H. M. Biggs, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30333 (hbiggs@cdc.gov).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

(ARDS), in healthy adults; however, it is not always recognized as a potential etiology of severe pneumonia and intensive care unit (ICU) admission in this population [3, 4]. Outbreaks, including cases of severe illness and death, have been reported in long-term care, rehabilitation, and other healthcare settings [5].

CLINICAL NARRATIVE

A 40-year-old man with a history of asthma presented to an emergency department (ED) in Virginia during spring with fever, cough, and dyspnea. Two days before ED presentation he developed malaise, mild headache, diffuse myalgia, and non-productive cough. The following day, he had a fever of 39.3°C (102.8°F) and sought care at an urgent care center where a rapid test for influenza was negative. He was prescribed oseltamivir. Early the next morning, he developed severe shortness of breath, generalized weakness, nausea, and back pain that radiated to the lower left chest. He was transported to the ED by emergency medical services (EMS). He reported working in an office setting where several coworkers were currently experiencing flu-like symptoms and at least 1 coworker had been diagnosed with pneumonia. He denied recent international travel and exposure to livestock or wildlife. No family members were ill. He was a nonsmoker. Medications included fluticasone furoate and a vilanterol inhaler for asthma, fexofenadine for allergic rhinitis, and atorvastatin for hyperlipidemia.

Initial assessment by EMS showed a respiratory rate of 38 breaths per minute, heart rate of 130 beats per minute, and oxygen saturation of 92% on room air. In the ED, he was febrile (38.3°C [100.9°F]) and developed progressive hypoxia. Lung auscultation revealed diffuse rhonchi bilaterally. Initial complete blood count showed a white blood cell count of 6.5 K/μL (82% neutrophils, 10% bands, 4% lymphocytes, and 4% monocytes), hemoglobin of 14 g/dL, and platelets of 132 K/μL. Erythrocyte sedimentation rate was 41 mm/hour (reference range, 0–15 mm/hour) and C-reactive protein was 30 mg/dL (reference range, 0–0.6 mg/dL). Initial chest radiography showed widespread bilateral patchy perihilar airspace disease. Chest computed tomography revealed extensive multifocal airspace disease throughout both lungs (Figure 1). Broad-spectrum antibiotics were initiated, including vancomycin, meropenem, and levofloxacin; oseltamivir was continued. He was admitted as an inpatient.

Within 24 hours of presentation, he developed ARDS and was intubated. He initially required a fraction of inspired oxygen of 100% and positive end expiratory pressure of 10 cm H_2O. He received inhaled nitric oxide in the setting of marginal oxygenation despite maximal ventilator support. Bronchoscopy revealed purulent secretions with a bronchoalveolar lavage (BAL) fluid white blood cell count of 1360 cells/μL (72% neutrophils, 11% lymphocytes, 17% monocytes). He required vasopressor support in the setting of septic shock. A nasopharyngeal (NP) swab and BAL fluid were tested for respiratory pathogens using molecular assays (NP: FilmArray Respiratory Panel, BioFire Diagnostics, Salt Lake City, Utah; BAL: Genmark RVP, Genmark Diagnostics, Carlsbad, California) and were positive for only HMPV; influenza polymerase chain reaction (PCR) was negative. BAL fluid culture grew group A *Streptococcus* (GAS). Blood cultures drawn before administration of antibiotics were negative. Additional infectious diseases diagnostic evaluation was negative, including urinary antigen tests for *Legionella* and *Streptococcus*

pneumoniae, serology for leptospirosis and tularemia, BAL fluid cultures for acid-fast bacilli and fungi, and PCR for *Pneumocystis jirovecii*. Aggressive hemodynamic support was continued and antibiotics were tailored to include ceftriaxone and clindamycin to optimize GAS coverage. He was weaned off vasopressors on hospital day (HD) 8, extubated on HD 13, transferred out of the ICU on HD 15, and discharged to a rehabilitation facility on HD 22.

An NP swab and BAL fluid collected on HD 2 were sent to the Centers for Disease Control and Prevention (CDC) for additional testing. Using the genes F, SH, and G to categorize the HMPV genotype, HMPV subgroup B subtype 2 was confirmed from both specimens; full genome sequencing revealed no unusual characteristics in the F or SH genes. A 6-nucleotide insertion was present in the G gene in comparison to a reference strain. Real-time reverse-transcription PCR (rRT-PCR) assays for influenza and other respiratory viral pathogens were negative. Using whole genome sequencing at CDC, the GAS isolate was identified as *emm*3.1 subtype and multilocus sequence type (MLST) 15 [6]. The isolate was positive for virulence markers often associated with *emm*3, including the inactived *rocA* regulatory gene, and an upregulated promoter for the co-transcribed genes encoding the streptolysin O and NAD-glycohydrolase extracellular virulence factors. It was positive for only 2 exotoxin genes (*speG* and *ssa*).

Nine coworkers of the patient had reported acute respiratory illness during the past month, including 2 diagnosed with pneumonia who were treated as outpatients, 1 diagnosed with bronchitis, and 6 with upper respiratory tract infection (URTI) symptoms. All but 1 of the ill employees, including the case patient, reportedly worked in a large, open office area populated with cubicles. NP and oropharyngeal specimens from 2 coworkers, including 1 with pneumonia and 1 with URTI, were tested for selected viral and bacterial pathogens at CDC (HMPV rRT-PCR assay and TaqMan array card multipathogen assay). Specimens from both coworkers were positive for HMPV, and 1 was additionally positive for rhinovirus; neither tested positive for GAS.

DISCUSSION

This adult patient with underlying asthma developed HMPV infection complicated by secondary GAS bacterial infection, which resulted in ARDS and shock. The epidemiology, consistent with a workplace cluster of HMPV infection, supports HMPV as the patient's primary infection. HMPV subgroup B subtype 2, detected in this patient, is 1 of 4 HMPV subtypes (2 subgroups, A and B, each with 2 subtypes) that can circulate concurrently, with no consistent evidence of differences in disease severity. The 6-nucleotide insertion present in the HMPV G gene was not considered remarkable; duplications of up to 180 bases have been observed in HMPV [7]. The GAS isolate in this study was subtype *emm*3.1 and MLST type 15, which are the most common *emm* subtype and MLST type, respectively, for *emm*3 isolates [6]. Infection with *emm* types 1 and 3 have been found to be independently associated with death [8]. Isolation of GAS from this patient's lower respiratory (BAL) specimen is consistent with GAS pneumonia. Invasive GAS infection, when it occurs, is often severe; approximately 16% of invasive GAS infections in the United States present with pneumonia, and 18% of patients with pneumonia die [8].

Secondary infection with bacteria that colonize the nasopharynx or oropharynx, particularly *Streptococcus pneumoniae*, *Staphylococcus aureus*, and less frequently, GAS, is well described as a contributor to influenza morbidity and mortality. Secondary bacterial infection is less commonly documented with noninfluenza respiratory viruses, including HMPV; however, a study of hospitalized adults with acute respiratory infections at 1 institution over 3 seasons showed similar proportions and types of bacterial coinfections with noninfluenza respiratory viruses as with influenza [9]. In general, mechanisms for viral infection predisposing to bacterial infection are not completely understood. Possible mechanisms include enhanced bacterial adhesion resulting from viral damage to the respiratory epithelium, and impaired immune response to bacteria caused by a virus-induced inflammatory response [10]. Interactions between HMPV infection and *S. pneumoniae* in vitro and in murine models suggest increased *S. pneumoniae* adherence to the bronchial epithelial cells [11] and increased susceptibility to severe pneumococcal infection with preceding HMPV infection [12].

HMPV infection can result in severe respiratory illness and ARDS without apparent bacterial coinfection, including in young, otherwise healthy adults [4]. Underlying asthma in this patient may have also increased his risk for severe HMPV disease and pneumonia. The patient was prescribed an inhaled corticosteroid (ICS) and long-acting β_2 agonist combination. Most studies of pneumonia risk among patients who use an ICS for management of asthma or chronic obstructive pulmonary disease (COPD) show a small increase in risk that might vary by drug combination or dose [13, 14]. However, studies have less commonly addressed pneumonia risk among younger adults who use an ICS for asthma in contrast to older adults with COPD, and data on risk with newer ICS formulations are limited.

In summary, HMPV should be considered as a cause of pneumonia and severe respiratory illness, even among generally healthy young adults, particularly during winter and spring in temperate climates. Although HMPV causes severe illness without concurrent bacterial coinfection, appropriate bacterial diagnostics should be considered in severely ill patients, as secondary bacterial infection may also complicate HMPV disease. Outbreaks of HMPV are recognized among higher-risk adults in long-term care settings [5], but HMPV should also be considered as a cause of respiratory outbreaks in the community, including among younger, relatively healthy persons. Adhering to good respiratory hygiene, including handwashing and covering coughs, and staying home when ill, is important to prevent and control respiratory virus outbreaks, including in office settings.

Acknowledgments.

The authors thank Senthil Kumar Sakthivel, Brett Whitaker, Xiaoyan Lu, and Shifaq Kamili (Division of Viral Diseases, Centers for Disease Control and Prevention [CDC]) and Jonas Winchell, Maureen Diaz, and Bernard Wolff (Division of Bacterial Diseases, CDC) for performing confirmatory laboratory testing; the Division of Consolidated Laboratory Services, Richmond, Virginia, for performing confirmatory laboratory testing and facilitating transfer of specimens; the Division of Bacterial Diseases *Streptococcus* Laboratory for the group A *Streptococcus* strain genomic sequence data; Melissa Arons and Agathe Hoffer-Schaefer, Virginia Department of Health/Alexandria Health Department; Tracy Hess, Arlington Health Department; Denise Sockwell, Virginia Department of Health; and Jennifer Milucky, Division of Bacterial Diseases, CDC.

References

1. Haynes AK, Fowlkes AL, Schneider E, Mutuc JD, Armstrong GL, Gerber SI. Human metapneumovirus circulation in the United States, 2008 to 2014. Pediatrics 2016; 137. doi:10.1542/peds.2015-2927. [PubMed: 27543009]
2. Walsh EE, Peterson DR, Falsey AR. Human metapneumovirus infections in adults: another piece of the puzzle. Arch Intern Med 2008; 168:2489–96. [PubMed: 19064834]
3. Hasvold J, Sjoding M, Pohl K, Cooke C, Hyzy RC. The role of human metapneumovirus in the critically ill adult patient. J Crit Care 2016; 31:233–7. [PubMed: 26572580]
4. Contentin L, Guillon A, Garot D, Gaudy-Graffin C, Perrotin D. Acute respiratory distress syndrome secondary to human metapneumovirus infection in a young healthy adult. Intensive Care Med 2013; 39:533–4. [PubMed: 23287871]
5. Peña SA, Davis SS, Lu X, et al. Severe respiratory illness associated with human metapneumovirus in nursing home, New Mexico, USA. Emerg Infect Dis 2019; 25:383–4. [PubMed: 30666949]
6. Chochua S, Metcalf BJ, Li Z, et al. Population and whole genome sequence based characterization of invasive group A streptococci recovered in the United States during 2015. MBio 2017; 8.
7. Saikusa M, Kawakami C, Nao N, et al. 180-Nucleotide duplication in the G Gene of human metapneumovirus A2b subgroup strains circulating in Yokohama City, Japan, since 2014. Front Microbiol 2017; 8:402. [PubMed: 28352258]
8. Nelson GE, Pondo T, Toews KA, et al. Epidemiology of invasive group A streptococcal infections in the United States, 2005–2012. Clin Infect Dis 2016; 63: 478–86. [PubMed: 27105747]
9. Falsey AR, Becker KL, Swinburne AJ, et al. Bacterial complications of respiratory tract viral illness: a comprehensive evaluation. J Infect Dis 2013; 208:432–41. [PubMed: 23661797]
10. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: illuminating the immunologic mechanisms of disease. Infect Immun 2015; 83:3764–70. [PubMed: 26216421]
11. Lai SH, Liao SL, Wong KS, Lin TY. Preceding human metapneumovirus infection increases adherence of *Streptococcus pneumoniae* and severity of murine pneumococcal pneumonia. J Microbiol Immunol Infect 2016; 49:216–24. [PubMed: 24931548]
12. Kukavica-Ibrulj I, Hamelin ME, Prince GA, et al. Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. J Virol 2009; 83:1341–9. [PubMed: 19019962]
13. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014; 3:CD010115.
14. McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. Chest 2013; 144:1788–94. [PubMed: 23990003]

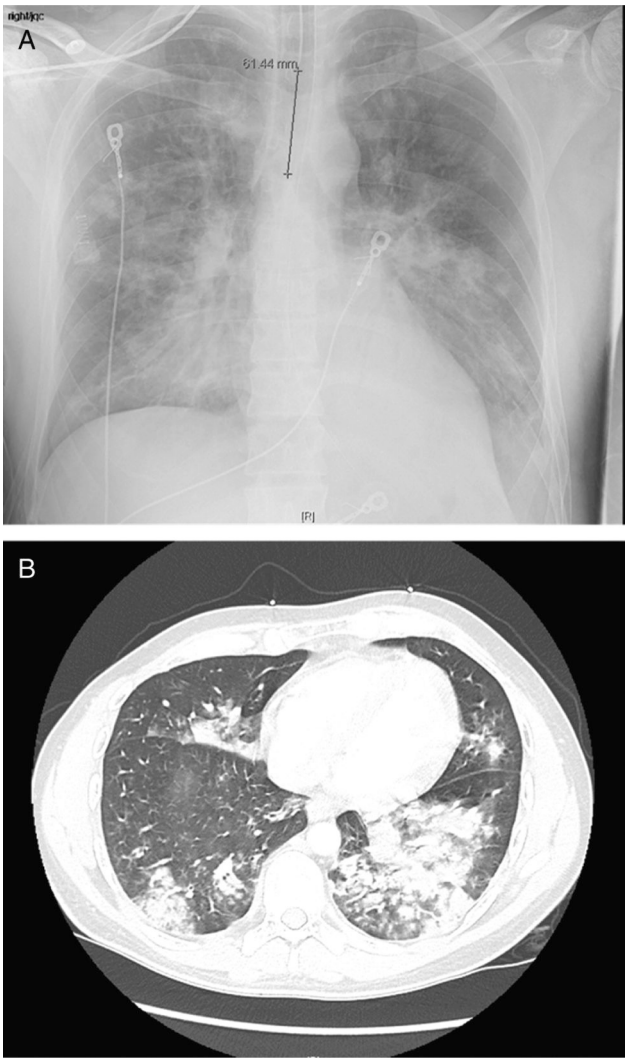

Figure 1.

A, Chest radiograph performed on hospital day 2, demonstrating widespread bilateral patchy perihilar airspace disease. *B*, Computed tomographic scan of the chest performed on hospital day 1 demonstrating extensive multifocal patchy airspace consolidation throughout both lungs, with more focal consolidation throughout the right middle lobe and left lower lobe.