Human Metapneumovirus

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Author Disclosure

Dr Schuster has disclosed no financial relationships relevant to this article. Dr Williams has disclosed that he serves on the Scientific Advisory Board of Quidel. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gaps

1. Respiratory viruses are a leading cause of global pediatric morbidity and mortality. Human metapneumovirus is the second leading cause of pediatric viral lower respiratory tract infection. Because human metapneumovirus is a newly recognized pathogen, many clinicians are unfamiliar with the epidemiology, pathogenesis, and clinical signs and symptoms of infection.
2. Knowledge of the biology of human metapneumovirus is important to understand the pathogenesis of human metapneumovirus and how best to treat it.
3. Diagnosis of human metapneumovirus is challenging, and clinicians should be aware of the sensitivity and specificity of available tests.

Objectives

After completing this article, readers should be able to:

1. Discuss the current epidemiology of human metapneumovirus.
2. Recognize clinical manifestations of human metapneumovirus.
3. Identify populations most susceptible to human metapneumovirus.
4. Discuss laboratory studies available for the diagnosis of human metapneumovirus.

Report of a Case

A 3-year-old girl undergoing induction chemotherapy for pre-B-cell acute lymphoblastic leukemia presents with a history of temperatures to 38.9°C. She has a 2-day history of cough and nasal congestion. She is refusing solid food and taking minimal liquids. She had one episode of nonbloody, nonbilious emesis. On physical examination, she appears ill and is having difficulty breathing. Her temperature is 39.5°C, heart rate is 130 beats per minute, respiratory rate is 40 breaths per minute, blood pressure is 90/60 mm Hg, and oxygen saturation on room air is 92%. She has a bulging, erythematous, nonmobile right tympanic membrane and clear rhinorrhea. Her lung examination findings are notable for tachypnea with retractions and diffuse wheezing.

Viral infection is suspected, but because she is undergoing chemotherapy, she merits evaluation for serious bacterial infection. White blood cell count is 1200/ μ L (12.0×10^9 /L) (80% lymphocytes, 10% neutrophils, 10% monocytes), hemoglobin level is 8.9 mg/dL (89 g/L), and platelet count is 169×10^3 / μ L (169×10^9 /L). Blood culture is performed. Chest radiography reveals diffuse perihilar infiltrates. Because she is febrile and neutropenic, broad-spectrum antibiotics are administered, and she is admitted to the hospital. She receives intravenous fluids and oxygen via nasal cannula.

During the next 48 hours, her respiratory status worsens, and she requires intubation and mechanical ventilatory support. Blood culture result remains negative. After 5 days, her respiratory status improves, and she is extubated. A nasopharyngeal wash result is positive for human metapneumovirus by polymerase chain reaction (PCR) testing and negative for other pathogens.

Abbreviations

HIV: human immunodeficiency virus
MPV: metapneumovirus
PCR: polymerase chain reaction
PIV: parainfluenza virus
RSV: respiratory syncytial virus

Introduction

Human metapneumovirus (MPV) is a respiratory pathogen with worldwide prevalence that produces disease clinically

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similar to respiratory syncytial virus (RSV). Although the virus was not identified until 2001, antibodies to MPV were detected in archived human sera, demonstrating that the virus has been circulating since at least the 1950s. Multiple reasons likely contributed to the delayed identification of the virus. Trypsin supplementation is required for growth in culture, and slow replication kinetics lead to delayed cytopathic effect and identification in cell culture. Furthermore, many laboratory cell lines are not permissive for MPV infection. Within the last 12 years, researchers have defined the epidemiology of MPV, developed rapid diagnostic testing, and are investigating host immune responses to guide vaccine development.

Virology

MPV, like other members of the Paramyxovirus family, is an enveloped, single-stranded, negative-sense RNA virus. It is most closely related to avian metapneumovirus type C, the other member of the *Metapneumovirus* genus, and it is in the Pneumovirinae subfamily with RSV. The fusion protein is required for attachment and entry and requires trypsin for cleavage to the active form. The other external proteins, glycoprotein and small hydrophobic protein, are not required for entry. The virus contains 9 structural proteins. Integrins and heparan sulfate have been identified as host receptors. The genome is approximately 13 kb in length. Phylogenetic analysis identifies 2 groups (A and B), each with 2 subgroups (A1, A2, B1, and B2). Clinical disease is similar for all subgroups.

Viral Replication

Similar to other respiratory viruses, MPV spreads by respiratory droplets. The incubation period is thought to be 4 to 9 days, although in nonhuman primate models a shorter period has been observed. Shedding occurs for 7 to 14 days. Virus can remain infectious on fomites for 8 hours, although viral RNA has been isolated from noninfectious particles up to 7 days after inoculation. MPV has been implicated in both hospital and institutional nosocomial outbreaks, emphasizing the importance of appropriate precautions, particularly around immunocompromised children.

Epidemiology

MPV has a worldwide prevalence, with the incidence varying yearly and by geographic location. The virus has been isolated year-round, but the peak seasonal incidence in temperate regions is February to April, later than the usual peak of RSV infection. In subtropical climates, MPV is most prevalent during the spring and summer

seasons. Incidence varies from 5% to 20% and is generally lower than RSV. Rates of MPV are comparable to other respiratory viruses, such as influenza and parainfluenza virus (PIV) types 1 to 3 combined. One large, multicenter, prospective study enrolled children with acute respiratory infection among inpatient, emergency department, and clinic settings; MPV was the second most common virus after RSV in this study. In retrospective, multiyear, epidemiologic studies, researchers have noted that one subgroup may dominate, but this varies among geographic locations and from year to year. Coinfection with other respiratory pathogens, such as rhinoviruses, RSV, PIV, and adenovirus, has been documented in a few MPV infections. Most studies have found that viral coinfections are not more severe clinically than MPV-alone infection. In addition, data from animal and small human studies suggest that MPV may be associated with increased development of bacterial coinfections with *Streptococcus pneumoniae*.

Large-scale evaluation of adult serum samples has demonstrated that nearly all adults are seropositive for MPV. In most geographic locations, seroprevalence is 100% in children older than 5 years. The mean age of children hospitalized with MPV-associated lower respiratory tract infection is 6 to 12 months, older than those hospitalized with RSV. Maternal antibodies may provide protection to young infants. Studies have demonstrated symptomatic subsequent infection with viruses from different subgroups in young children, although in animal models evidence of serologic cross-protection occurs. MPV is less frequently identified in older children, likely because of this cross-protective immunity.

Prospective studies demonstrate that MPV is a leading cause of viral respiratory infections in older adults, with hospitalization rates similar to influenza and RSV. The virus has been identified as a cause of community-acquired pneumonia and chronic obstructive pulmonary disease exacerbations in adults. However, healthy young adults may demonstrate MPV seroconversion without clinical illness.

Pathology

Cotton rat and mouse models exhibit peribronchial inflammation with an increase in mononuclear and lymphocytic cells. Perivascular edema is present. The most severe condition in these models has been noted on days 5 to 7, although abnormalities are present on days 1 to 14. Nonhuman primate models demonstrate inflammatory and erosive changes in the airway mucosa. Replication occurs only in ciliated epithelial cells of the respiratory tract; there is no evidence of viremia in humans or animal models. Lung disease in humans is more difficult to characterize because of barotrauma related to ventilation,

although increased alveolar macrophages are present, similar to nonhuman primates.

Host Response

Multiple studies have evaluated the cytokine response to MPV. Although a vigorous cytokine response is described, the interaction between the virus and production of different cytokines remains unclear. Despite the variable findings regarding the increase and decrease of assorted cytokines, several studies have demonstrated decreased interferon γ secretion after infection.

Antibodies alone can protect against infection, including cross-protection from infection with other subgroups. However, immunity appears to wane over time. In nonhuman primates, low-level replication with secondary infection by a virus from the same subgroup occurred 12 weeks after primary infection despite detectable serum antibodies. In the same study, no evidence of protection was seen when animals were challenged 11 months after primary infection. Subsequent infection in children has been documented, usually with a virus from a different subgroup; most of these presented with lower respiratory tract illness during primary infection and upper respiratory tract illness during secondary MPV infection. Some studies have identified a decrease in MPV-specific antibody in elderly adults compared with younger adults. Additional prospective studies have noted that baseline MPV antibody levels are lower in patients who subsequently become infected with the virus compared with those who do not acquire infection.

Studies that evaluated cytotoxic T-cell responses have identified responses to multiple proteins, including the fusion protein, which is highly conserved in subgroups. However, recent studies suggest that MPV and other respiratory viruses cause impairment of lung CD8⁺ T lymphocytes, leading to increased viral replication. Impairment of cytotoxic CD8⁺ T cells and decreased levels of interferon γ provide potential avenues for further investigation of MPV and other viruses' ability to hijack the host immune system. Further, this T-cell impairment may contribute to the ability of the virus to reinfect individuals despite preexisting antibodies.

Clinical Manifestations

MPV causes both upper and lower respiratory tract disease. Rhinorrhea and coryza are common, whereas laryngitis and croup are described but are less frequent. Children also experience dysphagia associated with decreased oral intake, and pharyngitis has been associated with more than 40% of cases in studies that evaluated

upper respiratory tract disease. Fever is present in up to 50% of children with MPV-associated respiratory tract infection. Conjunctivitis has been identified in a small subset of patients. Large epidemiologic studies have identified MPV as a cause of upper respiratory tract infections at a similar rate as RSV, influenza, and PIV.

Acute otitis media is a common complication of MPV. In one case series, almost one-quarter of children with MPV had acute otitis media. Another report noted that 13% of children with acute otitis media had MPV-positive nasopharyngeal specimens. The virus has been isolated alone in tympanic fluid; however, in most cases, middle ear fluid cultures yield other bacterial pathogens, particularly *S pneumoniae*.

Manifestations of lower respiratory tract infection include cough, wheeze, rhonchi, and dyspnea. Epidemiologic studies have demonstrated that a greater number of children infected with MPV are diagnosed as having pneumonia vs bronchiolitis, especially when compared with RSV (Table 1). Hypoxia and cyanosis can occur with severe lower respiratory tract disease. Radiographic abnormalities include diffuse findings, such as perihilar infiltrates and alveolar disease, and focal findings, including bronchopneumonic changes, lobar pneumonia, and effusions (Fig 1).

MPV has been isolated in both children and adults hospitalized for asthma exacerbations. In one study, 7% of children with asthma exacerbations had MPV isolated from nasopharyngeal swabs. Another large-scale epidemiologic study noted that 14% of children with MPV had asthma as a discharge diagnosis. This finding was similar to the percentage of children with RSV and a discharge diagnosis of asthma; however, rhinovirus was more frequently associated with asthma exacerbations in the same study. Another study noted that MPV bronchiolitis in infancy was more associated with a subsequent asthma diagnosis between 3 and 5 years of life than RSV bronchiolitis in infancy. In children ages 2 to 17 years hospitalized with asthma, MPV was the second most commonly (5%) isolated viral pathogen after rhinovirus.

Other clinical symptoms of MPV infection may include nonrespiratory manifestations. In some studies, up to half of all children with MPV had vomiting and/or diarrhea. Between 5% and 10% of children develop a rash during the infection. Febrile seizures have been reported uncommonly in patients with MPV infection. MPV has been isolated rarely by PCR from nasal washes of children with encephalitis, and one report detected MPV in the cerebrospinal fluid of a child with encephalitis. Identification of MPV outside the respiratory tract is rare, and children are generally not thought to be viremic during infection.

Table 1. Comparison of general clinical and epidemiologic features of MPV- and RSV-associated lower respiratory tract infection.

Feature	MPV	RSV
Peak age	Older infant (6–12 months)	Young infant (<6 months)
Sex	Slight male predominance	Slight male predominance
Seasonality	February–April	November–January
Clinical symptoms	Fever, rhinorrhea, cough, wheezing, vomiting, and diarrhea	Fever, rhinorrhea, cough, wheezing, vomiting, and diarrhea
Radiographic findings	Consolidation, perihilar infiltrates, atelectasis, hyperinflation	Peribronchial thickening, consolidation, atelectasis, hyperinflation
Diagnosis	Pneumonia Bronchiolitis Asthma exacerbation	Bronchiolitis Pneumonia Asthma exacerbation
Risk factors	Prematurity, underlying comorbidity, young age	Prematurity, young age, underlying comorbidity, daycare

MPV=metapneumovirus; RSV=respiratory syncytial virus.

High-Risk Patients

Premature infants have increased morbidity and mortality from MPV infection. Multiple studies have demonstrated that premature and high-risk infants are more likely to be hospitalized with MPV infection when compared with

infants without medical problems. A prospective study in Argentina following up high-risk and premature infants noted that 30% of children with MPV infection had moderate to severe disease. Other epidemiologic studies have noted that between 34% and 88% of children

Figure 1. A. Portable chest radiograph of a 5-month-old girl with fever, cough, and increased work of breathing. The lungs are mildly hyperexpanded, with perihilar interstitial prominence, peribronchial cuffing, and fine alveolar perihilar opacities. There is a confluent density seen in the right mid lobe, silhouetting the heart border. B. Portable chest radiograph of a 4-month-old boy with fever, cough, and increased work of breathing. The lungs are hyperinflated, with multifocal atelectasis affecting the right upper lobe and medial lung bases bilaterally. The airspace opacities affecting the right upper lobe are more confluent compared with elsewhere.

hospitalized with MPV infection had underlying medical conditions, including prematurity, cardiopulmonary disease, or immunodeficiency. In a South African study, human immunodeficiency virus (HIV)-positive children were significantly more likely than HIV-negative children to be infected with MPV.

In an adult population, MPV was identified in 3% of bronchoalveolar lavage specimens in patients who underwent hematopoietic stem cell transplantation and had lower respiratory tract symptoms. Of these patients, 80% of the patients died of respiratory failure, indicating that in a susceptible population MPV can cause high mortality. Therefore, the host immune system may play a significant role not only in clearing the infection but also in disease morbidity.

In the pediatric population, prolonged shedding has been observed in solid organ transplant recipients. Furthermore, active infection was associated with acute graft rejection. Mortality has been reported in pediatric patients with leukemia, including one patient who was infected with 2 genetically different strains of MPV during 10 months and died of acute respiratory distress syndrome during the second MPV infection. Another case report detailed a premature infant who required extracorporeal membrane oxygenation due to MPV-associated acute respiratory distress syndrome.

Although the predominance of morbidity and mortality occurs in high-risk children, case reports describe previously healthy children without underlying immunodeficiency succumbing to MPV infection. These children typically

present with sepsis and can develop pulmonary hemorrhage and/or acute respiratory distress syndrome. One study demonstrated that higher MPV viral loads were associated with increased disease severity as manifested by fever, prolonged hospital stay, and increased bronchodilator use.

Daycare does not seem to be as significant a risk factor for MPV infection compared with other respiratory viruses. Prospective studies of children in daycare demonstrate a lower transmission rate of MPV compared with RSV and PIV. Other prospective studies in daycare identified MPV infection in approximately 10% of all children; however, this accounted for 2% of all acute respiratory tract infections.

Diagnosis

MPV was initially identified in cell culture; LLC-MK2 monkey kidney cells are commonly used for the growth of MPV, but viral cultures take up to 10 to 14 days and are, therefore, not useful clinically. MPV produces small round plaques with occasional syncytia and can take between 3 and 23 days to produce a cytopathic effect (Fig 2). Shell vial culture has demonstrated increased sensitivity compared with traditional culture. Direct and indirect fluorescent antibody testing has similar sensitivity and specificity to shell vial culture. Currently, the gold standard for diagnosis is PCR testing. Reverse transcriptase-PCR testing has a high sensitivity for virus detection, and laboratories have developed primers targeted at many of the conserved proteins. In many clinical laboratories,

Figure 2. Cytopathic effect caused by human metapneumovirus (MPV). A. Uninfected LLC-MK2 cell monolayer. B. MPV-infected LLC-MK2 cells. Arrows indicate syncytia.

MPV has been incorporated into multiplex diagnostic PCR assays used to simultaneously evaluate for multiple respiratory pathogens.

Treatment

No Food and Drug Administration–approved antiviral drug against MPV exists. Supplementary oxygen and assisted ventilation may be needed in the hospitalized setting. Intravenous fluids can be used for hydration when vomiting and diarrhea occur or a patient is unable to tolerate oral hydration because of tachypnea or dyspnea. Bronchodilators and steroids may be used in the management of MPV contributing to asthma or chronic obstructive pulmonary disease exacerbations, and antibiotics may be needed in cases of bacterial superinfection, such as acute otitis media or suspected community-acquired bacterial pneumonia.

In vitro data suggest that ribavirin and intravenous immunoglobulin inhibit MPV infection. Ribavirin has been found to decrease inflammation in a mouse model. Ribavirin and intravenous immunoglobulin have been used together to treat immunocompromised adults and children in isolated case reports. However, data are limited, and no case-control studies have been performed. In animal models, monoclonal antibodies have been effective prophylactically and therapeutically at decreasing viral titer, although no data are available in humans.

Prevention

Similar to other respiratory viruses, good hand hygiene and curtailing respiratory secretions are currently the only preventive measures. However, vaccine discovery efforts are under way. The fusion protein is immunogenic and highly conserved, making it an excellent target for vaccine research. Soluble fusion protein vaccines reduce viral titers in animal models, and vectored vaccines encoding the fusion protein are protective.

Researchers have generated live-attenuated temperature-sensitive strains of MPV, which produce low levels of replication in the upper respiratory tract and no active disease in the lower respiratory tract. High antibody titers were produced, and subsequent infection with wild-type virus in a hamster model demonstrated no lower respiratory tract infection and decreased viral replication in the upper respiratory tract. Thus, cold-passaged MPV may prove to be a useful vaccine approach. Other recombinant strains that lack the small hydrophobic protein and glycoprotein are attenuated and demonstrate evidence of subsequent reduction in viral titers on wild-type infection. Therefore, recombinant viruses may prove to

be an effective vaccine strategy. Other strategies for prevention include the generation of monoclonal antibodies that could potentially be used as prophylaxis in high-risk populations.

Summary

- On the basis of strong research evidence and consensus, (1) (2) (3) (4) human metapneumovirus is a leading cause of upper and lower respiratory tract infections in children.
- On the basis of research evidence and consensus, (3) (5) (6) (7) the clinical features of MPV-associated disease are similar to those of RSV. MPV is an important cause of asthma exacerbations, bronchiolitis, and pneumonia. Bacterial superinfection can occur.
- On the basis of research evidence and consensus, (2) (3) (8) the mean age of infection is 6 to 12 months, and nearly all school-age children are seropositive. However, infection can recur, likely in part due to impaired CD8⁺ T-cell response.
- On the basis of research evidence and consensus, (9) (10) (11) morbidity and mortality are the highest in patients who are premature, are immunosuppressed, or have underlying cardiopulmonary abnormalities.
- On the basis of research evidence and consensus, (2) commercially available diagnostic tests exist, and reverse transcriptase–PCR is the most commonly used.
- On the basis of consensus, because of a lack of relevant clinical studies, recombinant virus vaccines and monoclonal antibodies may be useful as prophylactics or therapeutics. (10)

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PIR Quiz

This quiz is available online at <http://pedsinreview.org>. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

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1. A 12-month-old boy is admitted to the hospital with rhinorrhea, cough, wheezing, and respiratory distress. The results of studies on nasopharyngeal fluid wash for respiratory syncytial virus, influenza, and parainfluenza are negative. Which of the following laboratory studies on nasopharyngeal fluid wash should be ordered to diagnose the most likely etiologic agent?
 - A. Direct fluorescent antibody testing.
 - B. Indirect fluorescent antibody testing.
 - C. Reverse transcriptase–polymerase chain reaction testing.
 - D. Shell viral culture.
 - E. Viral culture.
2. Acute otitis media (AOM) is a common complication of metapneumovirus (MPV) respiratory infection in children. Research data regarding MPV and increased risk of bacterial coinfection are consistent clinically with which of the following pathogens identified in children with MPV-associated AOM?
 - A. Anaerobic bacteria.
 - B. *Haemophilus influenzae*.
 - C. *Moraxella catarrhalis*.
 - D. *Streptococcus pneumoniae*.
 - E. *Streptococcus pyogenes*.
3. A 2-year-old child presents in early April with fever, rhinorrhea, and coryza. A viral cause is suspected for this child's illness. Which of the following additional signs or symptoms is most likely to indicate that MPV is the etiologic agent?
 - A. Conjunctivitis.
 - B. Cough.
 - C. Croup.
 - D. Laryngitis.
 - E. Pharyngitis.

4. In which group of pediatric patients has prolonged viral shedding of MPV been observed?
- A. Chronic pulmonary disease patients.
 - B. Congenital heart disease patients.
 - C. Human immunodeficiency virus–positive patients.
 - D. Premature infants.
 - E. Solid organ transplant recipients.
5. A few pediatric patients with severe morbidity and mortality secondary to MPV disease are previously healthy children without underlying disorders. Which of the following is a typical presentation for this group of children?
- A. Encephalitis.
 - B. Pneumonia.
 - C. Seizures.
 - D. Sepsis.
 - E. Vomiting, diarrhea, and dehydration.

Corrections

In the print version of the November 2013 article "Cephem Antibiotics: Wise Use Today Preserves Cure for Tomorrow" (Parker S, Mitchell M, Child J. *Pediatrics in Review*. 2013;34;11:510–524, doi: 10.1542/pir.34-11-510), in the Selected References introduction, the link to the complete reference list should be: http://pedsinreview.aappublications.org/content/34/11/510/suppl/DCSupplementary_Data. The link is correct in the online version of the journal. The journal regrets the error.

In the print version of the November 2013 article "Chronic Cough in Children: a Primary Care and Subspecialty Collaborative Approach" (Kaslovsky R and Sadof M. *Pediatrics in Review*. 2013;34(11):498–509, doi: 10.1542/pir.34-11-498), the following phrase appeared above the quiz questions but should have been part of Question 1: "Some clinical signs are highly suggestive of a given condition. In the scenarios below, match the clinical presentation with the most likely cause of the patient's cough." The phrase appears correctly in the online version of the journal CME quiz. The journal regrets the error.