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PROGRAM INFORMATION

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Dear Subscriber,

Welcome to the premier issue of eNeonatalReview, a CE-accredited e-newsletter designed specifically for the NICU Health Care Professional.

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Our focus this month is on a newly described pathogen that may be relatively unknown to many health care providers: Human Metapneumovirus (HMPV).

Children with Bronchopulmonary Dysplasia (BPD) suffer from increased respiratory morbidity due to viral infections, particularly RSV. Clinicians have speculated that chronic infectious diseases may play an important role in the development of BPD, and currently consider the ureaplasma and mycoplasma species to be the most commonly implicated organisms.

While the prevalence of HMPV in newborn nurseries is not presently recognized, this virus may play an important role in the future of neonatal medicine.

Several recently published articles help categorize this new pathogen:

Commentary & Reviews by Edward E. Lawson, MD, Lawrence Noguee, MD, and Christoph U. Lehmann, MD

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Our guest editor opinion

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A newly discovered human

Guest Editors of the Month

Edward E. Lawson, MD
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pneumovirus

- **Confirmation**
Characterization of the virus
- **Clinical Manifestation (I)**
Incidence of clinical symptoms
- **Clinical Manifestation (II)**
Challenges in identification
- **Incidence**
HMPV and hospitalization rates

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Guest Faculty Disclosures

Edward E. Lawson, MD

Faculty Disclosure: Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

Lawrence M. Noguee, MD

Faculty Disclosure: Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories

Christoph U. Lehmann, MD

Faculty Disclosure: No relationship with commercial supporters.

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No faculty member has indicated that their presentation will include information on off label products.

COMMENTARY

HMPV is a newly identified pathogen that should be of great interest to neonatologists and pediatricians, as it is present before six months of age in most infants and affects almost every child by age 5. Unlike the SARS-associated corona virus, HMPV has received little public attention: a Google search on SARS resulted in more than 4.5 million hits, compared to only 2000 for HMPV. Yet the high prevalence of HMPV sero-positive children in the studies presented this issue demands further investigation.

Although information on the mode of transmission and virulence is not currently available, HMPV infection is likely present throughout the world. HMPV appears to provide only partial immunity following infection and, like RSV, can re-infect individuals, potentially leading to repeated episodes of illness. Symptoms of HMPV infection are similar to other respiratory pathogens, making diagnosis based on clinical criteria impossible. Most of us will remember the infant or toddler admitted to the pediatric floor with respiratory distress, where an extensive evaluation including all possible viral studies yielded no definitive etiologic diagnosis. In two of the above cited reports, 5-10% of infants with symptomatic acute respiratory illness admitted to the hospital were positive for HMPV. HMPV may thus be responsible for a considerable portion of the more than 150,000 cases of infants and children hospitalized annually with bronchiolitis. In fact, most health care professionals will be many times more likely to encounter a patient with HMPV this winter than with SARS.

The potential for nosocomial infection also poses a significant risk to the population in the NICU. Given the available data on its prevalence, if we look for HMPV in our NICUs, it is very likely that we will find it. Until the development of

commercially available tests to diagnose HMPV infection, research on the mode of infection and risks of transmission is needed to evaluate the dangers of nosocomial outbreaks. In the meantime we are left to worry about the adequacy of our current isolation protocols and cohorting criteria.

As underlying medical conditions such as BPD were increased in patients with HMPV infection, we must now add HMPV to the long list of potential complications and problems for our NICU graduates. When the impact of HMPV on morbidity, mortality, hospitalization and lost income are better understood, pressure for development of a vaccine or products providing passive immunity, such as for RSV infection, may emerge.

IDENTIFICATION

Van den Hoogen et al., from the Erasmus Medical Center in Rotterdam, Netherlands, were the first to describe a new viral pathogen that causes respiratory illness in children and newborns: "Human Metapneumovirus".

van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, Osterhaus AD. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med. 2001 Jun;7(6):719-24.

Nasopharyngeal aspirates of 28 children under the age of 6 with lower respiratory tract infections were found to be free of known viral pathologic agents such as parainfluenza, respiratory syncytial (RSV), and influenza viruses. Using tertiary monkey kidney cells, the authors were able to isolate 28 unidentifiable viruses from these nasopharyngeal aspirates. Evaluating biochemical properties, the authors concluded that the unknown virus was a member of the Paramyxoviridae family. All 28 viruses reacted with developed antisera, indicating that the viruses were serologically identical or related. The authors demonstrated genetic heterogeneity in 9 of the 28 viruses, finding two subgroups.

On screening human sera of Netherlands infants, the authors found that 25% of those 6-12 months old had antibodies to the new HMPV, and that by age 5 years almost all the children tested were seropositive. In addition, human serum samples from 1958 were tested, and also revealed the presence of antibodies to this virus.

This study did not prove a causal association of HMPV with a specific respiratory infectious process. However: a) the virus was found in the aspirates of children with respiratory infections reminiscent to RSV; b) other viruses were not found in these aspirates; and c) the virus was not present in 400 samples from children under 2 years of age without respiratory symptoms. Hence a causal relationship was considered likely.

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CONFIRMATION

Researchers at the CDC and in Canada were able to duplicate the identification of HMPV in symptomatic humans.

Peret TC, Boivin G, Li Y, Couillard M, Humphrey C, Osterhaus AD, Erdman DD, Anderson LJ. Characterization of human metapneumoviruses isolated from patients in North America. J Infect Dis. 2002 Jun 1;185(11):1660-3.

Isolates from ten patients (ages ranging from 2 months to 87 years) with acute respiratory illness were negative for influenza A and B, parainfluenza 1, 2 and 3, rhinovirus and RSV. Electron-microscopic examination showed that viruses from all specimens had morphologic characteristics consistent with paramyxovirus. Similar to the results from the Netherlands, two subgroups were found on sequencing studies, which were both present during the same year. In one instance, a child with two isolates ten-months apart was found to carry a HMPV subtype in the second isolate as well as the first, suggesting a re-infection.

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CLINICAL MANIFESTATION (I)

Jartti et al. describe the incidence of clinical symptoms associated with HMPV infection in children.

Jartti T, van den Hoogen B, Garofalo RP, Osterhaus AD, Ruuskanen O. Metapneumovirus and acute wheezing in children. Lancet. 2002 Nov 2;360(9343):1393-4.

The authors conducted a study of 132 children between September 2000 and May 2001 on the efficacy of systemic glucocorticoids in acute expiratory wheezing. Nasopharyngeal aspirates were evaluated for the presence of viruses known to cause respiratory illness, including influenza A & B, adenovirus, RSV, parainfluenza 1, 2 & 3, corona virus, rhinovirus, and enterovirus, as well as human metapneumovirus. A potential viral agent was found in 88% of the children: 31% had rhinovirus, 22% had enterovirus, 16% had non-typable picornavirus, 14% had RSV, and 9% (10 patients) had HMPV. Of note is that HMPV was only detected between January and April.

Of these 10 children: the average age was 7 months (range 4-25), 7 had HMPV alone, and none of the children had used glucocorticoids before. Diagnoses included bronchiolitis (N=5), wheezy bronchitis (N=4) and newly diagnosed asthma (N=1). Prior symptoms included cough (mean 9 days, SD 10), rhinitis (mean 4, SD 5), expiratory wheezing (mean 3, SD 2) and fever (mean 3, SD 2). Two of the seven children with HMPV alone were diagnosed with otitis media.

During the period from January to April, 31, children with wheezing were admitted to the study and ten (32%) of these were found to be positive for HMPV. Interleukin 8 and RANTES (Regulated by Activation, Normal T-cell Expressed and Secreted) concentration in nasopharyngeal aspirates was different than previously described in RSV patients.

The authors conclude that HMPV may be a causative agent of wheezing with a distinctive epidemic pattern when other causes (RSV, rhinovirus) of respiratory symptoms were not prevalent. Overall, 9% of children presenting with acute expiratory wheezing were found to be positive for HMPV, only slightly less than the incidence of RSV.

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CLINICAL MANIFESTATION (II)

Yale-New Haven Hospital researchers evaluated 357 respiratory specimens from 296 individuals in which a viral pathogen could not be identified by direct fluorescent antibody.

Esper F, Boucher D, Weibel C, Martinello RA, Kahn JS. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. Pediatrics. 2003 Jun;111(6 Pt 1):1407-10.

A total of 20 HMPV infections were identified in 19 individuals by PCR. Clinical symptoms of HMPV related infections were similar to previous reports: cough (69%), rhinorrhea (69%), fever (63%) and wheezing (50%). Hypoxia developed in 31% of patients. All HMPV infections occurred in a six-week interval in January and February 2002. The authors report a nosocomial infection in at least 1 patient: the infant never left the hospital after birth and became symptomatic in the 25th week of life.

These authors report the first cases of HMPV in the US. Bronchiolitis was the most common diagnosis in children infected with HMPV, and a significant number developed hypoxia.

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INCIDENCE

In the latest HMPV study, researchers from Quebec, Canada attempted to estimate the relative contribution to children's hospitalization for acute respiratory tract infections.

Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis [serial online] 2003 Jun [07/28/2003].

Nasopharyngeal aspirates were analyzed in 208 cases for HMPV, RSV and influenza A & B. The positivity rates were 5.8% for HMPV, 51% for RSV, 21.6% for influenza A and 0% for influenza B. The peak age for hospitalization was 0-2 months for RSV and 3-5 months for HMPV. The median duration of hospitalization was similar for HMPV (4.5 days), RSV (5.0 days) and Influenza A (4.0 days). None of the children with HMPV was admitted to the intensive care unit, in contrast to 15% with RSV and 16% with Influenza A. Patients with HMPV had underlying medical conditions in 25%, opposed to 7% in RSV and 10% in Influenza A patients. At discharge, 67% of children with HMPV were given the diagnosis bronchiolitis, compared to 84% in the RSV and 51% in the influenza A group. Pneumonitis was less common in the HMPV group (17%) than the RSV (25%) and Influenza A (37%) groups.

The authors of this study compared the data to results from a virology laboratory for the general population. They noticed that the end of their sample collection was stopped shortly after the peak incidence of HMPV in the general population, and therefore probably underestimated the incidence of HMPV.

Key conclusions of the study: a) HMPV results in clinical symptoms similar to RSV, although in smaller numbers and perhaps causing less severe illness; b) seasonal patterns of RSV, HMPV, and Influenza A appear to differ.

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Target Audience [back to top](#)

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Learning Objectives [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Evaluate the research that has recently identified a potentially important new pathogen;
- Understand how HMPV may be affecting your patients;
- Use your increased awareness of HMPV to provide more optimal neonatal care.

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- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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