

Human metapneumovirus in the preterm neonate: current perspectives

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Abstract: Premature birth (<37 weeks gestation) occurs in ~11% of all births in the US. These infants are at risk of chronic lung disease and respiratory conditions, including bronchopulmonary dysplasia. Respiratory viruses are important causes of acute respiratory illness (ARI) in preterm infants, leading to rehospitalization, increased health care burden, and long-term morbidity. Human metapneumovirus (HMPV) is a paramyxovirus discovered in 2001 that is related to respiratory syncytial virus. Epidemiologic studies show that HMPV is a leading cause of ARI in children and adults worldwide. Prematurity is a major risk factor for severe HMPV disease, requiring hospitalization. Moreover, limited data suggest that HMPV infection during infancy is associated with asthma and recurrent wheezing, which are common long-term pulmonary complication of prematurity. HMPV causes nosocomial outbreaks of ARI in hospitals and long-term care facilities, although there are few studies of the prevalence of HMPV in neonatal intensive care unit populations. HMPV is a common and important virus in premature infants, and caregivers for preterm infants should consider this virus in patients with acute respiratory symptoms.

Keywords: prematurity, chronic lung disease, human metapneumovirus, bronchiolitis, BPD

Human metapneumovirus

Human metapneumovirus (HMPV) was first reported in 2001 by Dutch investigators who collected a number of unidentified virus isolates from children with lower respiratory infection (LRI) over a 20-year period.¹ Electron microscopy, biochemical studies, and sequence analysis of the virus genome identified it as a member of the Pneumovirus subfamily of the Paramyxoviridae that includes respiratory syncytial virus (RSV). HMPV is most closely related by sequence homology to avian metapneumovirus (AMPV) type C. AMPV, discovered in 1979, is an important agricultural pathogen of poultry, causing severe respiratory disease in chickens and turkeys.² Evolutionary analysis suggested that HMPV diverged from AMPV type C several hundred years ago.³⁻⁵ However, birds cannot be productively infected with HMPV, indicating that while the virus had a zoonotic origin, it has evolved to become an established human pathogen.⁶

Phylogenetic analysis of HMPV genes defines two major genetic subgroups of HMPV, designated A and B, each with two minor subgroups.^{3-5,7} Longitudinal epidemiologic surveillance identified changes in subgroup dominance over time, suggesting that subtle changes between subgroups facilitate reinfection.⁸ Reinfection with either homologous or heterologous strains of HMPV occurs readily, even during early childhood.⁹⁻¹¹ It is not

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clear whether the ability of HMPV to reinfect humans is due to infections with different subgroup viruses that are antigenically distinct, incomplete or waning immunity, or CD8⁺ T-cell impairment induced by respiratory virus infections.¹² Serum neutralizing titers in adults appear to correlate with risk of reinfection.¹³ There are no definitive human data determining the degree of cross-protection between different HMPV subgroups. Animal studies show that these subgroups are not fully antigenically distinct and that there is cross-protective immunity.^{7,14–16} Therefore, similar to RSV, a single-antigen vaccine or prophylactic antibody would suffice.

HMPV infections occur in annual epidemics during the late winter and early spring months in temperate locations such as North America and Europe. The HMPV season overlaps with those of RSV and influenza viruses, but the peak incidence of HMPV typically occurs 1–2 months later than the peak of RSV. Prospective surveillance studies conducted over 25 years showed that HMPV was present in every season, although the year-to-year prevalence varied.^{9,17} Different genetic subgroups of HMPV frequently circulate during the same winter season, although one subgroup may predominate in a given year.^{8,17} Viruses from each subgroup are capable of causing severe LRI, and different subgroup viruses have not been associated convincingly with differing severity of disease.^{18,19} In most studies of patients with acute respiratory tract infection, the percentage of HMPV detection varies from 6% to 25%. HMPV infection usually causes clinical disease; the virus is rarely detected in asymptomatic children.^{9,20–26} Studies of hospitalized and outpatient children worldwide have found HMPV to be associated with 6%–40% of acute respiratory illness (ARI) in a given season.^{9,17,24,27–43} HMPV is usually ranked second after RSV in most studies and has prevalence comparable to or greater than that of influenza or parainfluenza viruses (PIV).^{24,25,32}

Hospitalization of children for HMPV infection occurs primarily in the first year of life, although many studies report that the peak age of hospitalization for HMPV is between 6 and 12 months of age and thus later than the peak age of hospitalization for RSV at 2–3 months.^{24,30,41,44–46} Males appear to be at greater risk of LRI due to HMPV compared with females, similar to sex difference in severity observed for other respiratory viruses. HMPV infections are more severe in patients with underlying medical conditions such as asthma, prematurity, cardiopulmonary disease, or immune compromise.^{9,22,24,27,28,32,37,40,46,47} Importantly, adults can be productively reinfecting with HMPV throughout life, and thus family members and care providers are potential vectors to transmit infection to young infants.^{48,49}

Premature infants and respiratory viruses

Approximately 11% of live births in the US and Europe occur at <37 weeks of gestation.⁵⁰ In addition, preterm birth is more common in certain populations, notably African-Americans.⁵⁰ These preterm infants are at risk of significant respiratory morbidity, especially during the first year, typically recurrent or chronic wheezing or recurrent ARI.^{51,52} One prospective cohort study followed 124 very-low-birth-weight (VLBW <1,500 g) premature infants. At 1 year of age, 9% of the infants had been diagnosed with asthma, 11% had been hospitalized for ARI, and nearly half had required more than one health care visit.⁵¹ Another group evaluated a cohort of 28 VLBW infants with bronchopulmonary dysplasia (BPD) at a mean age of 9.5 years.⁵² Children with BPD, compared to matched VLBW controls without BPD, had higher rates of chronic respiratory symptoms (36% vs 8%), higher rates of asthma (21% vs 0%), and lower lung function by formal pulmonary function testing. A study of 797 preterm infants found that the frequency of chronic respiratory disease correlated inversely with gestational age and weight at birth, displayed a male predominance, and was more common in those who meet criteria for the diagnosis of BPD.⁵³ Depending on differences in definition, race/ethnicity, and clinical management, ~35%–45% of infants born before 28 weeks of gestation develop BPD.⁵⁴ A large California state database study of >263,000 infants born prematurely between 1992 and 2000 found that 15% required at least one rehospitalization within the first year of life, most commonly with ARI.⁵⁵ Notably, only ~23% of the readmits for ARI were due to RSV, while the rest were other infectious causes. Numerous studies document an increased risk of LRI due to respiratory viruses in premature infants, though many studies focus on RSV.^{56–59} In preterm infants, respiratory viral LRI in the first years are later associated with long-term pulmonary consequences and diminished lung function.^{60–63}

Respiratory viruses in the neonatal intensive care unit

Preterm infants are especially vulnerable to respiratory infections. RSV has been the virus of primary concern to neonatologists, with HMPV rarely recognized as an important source of morbidity in this population. HMPV has seldom been documented in the neonatal intensive care unit (NICU). However, viral infections often are not recognized as either causative or complicating factors in NICU patients' respiratory illnesses, except during virulent and rapidly contained

outbreaks. Adenovirus and rhinovirus, for example, have been implicated in such isolated events.^{64,65} Thus, clinicians may not test for community respiratory viruses in a closed NICU, among a population of infants already at risk of respiratory symptoms due to lung disease associated with prematurity. Some studies suggest that apart from nosocomial outbreaks, viral respiratory infections are uncommon in the NICU. In one of the largest studies of viral infections in the NICU, including 5,396 infants admitted over a 12-year period, only 51 had a viral infection (29% of these RSV), representing ~5% of all documented infections.⁶⁶ In a report of postmortem autopsies of NICU infants who died of respiratory illness, none had HMPV or RSV.⁶³ However, there are few published prospective studies of viral ARI in the NICU. Moreover, the absence of documented HMPV in the available data may simply be due to the recent discovery of HMPV and use of viral culture in many studies, since sensitive detection of HMPV requires RT-PCR (reverse transcription polymerase chain reaction).⁶⁷ The recent VIRIoN-I study used multiplex PCR to show that 6% of 135 NICU patients evaluated and treated for late-onset sepsis due to respiratory symptoms had a viral infection.⁶⁸ RSV has been reported in numerous outbreaks of nosocomial NICU infection.^{69–75} Thus, the prevalence of community respiratory viruses in NICU populations is likely underappreciated. Future studies using routine screening with PCR or other molecular diagnostic methods will likely allow the detection of nosocomial HMPV infections as well.

HMPV in preterm infants

Preterm infants remain at high risk of morbidity from viral infections even after discharge, with readmissions and emergency department visits for ARI representing the majority of health care costs in the first year.^{51,55,56} Since the highest rates of hospitalization for HMPV are during the first year of life, it is likely in this age range that the greatest burden of HMPV LRI occurs among premature infants.^{24,32} The presenting symptoms of HMPV are often similar to those of RSV (apnea, cough, increased respiratory rate, wheezing, retractions).^{9,24} However, prematurity may contribute to a more frequent severe presentation of HMPV. A large prospective study of >10,000 children in three US cities found that of children evaluated in the emergency department, HMPV-positive subjects were more likely to have been born prematurely than HMPV-negative children (13% vs 11%, $P=0.009$). Similarly, hospitalized HMPV-positive children were more likely to be premature than HMPV-negative subjects (24% vs 16%, $P=0.006$).²⁴ A Brazilian 1-year cohort study of 303

premature infants identified 461 episodes of LRI and detected HMPV in 17% of these illnesses, half of which required hospitalization.⁵⁷ In a longitudinal study of Spanish children hospitalized for LRI, HMPV was more frequently identified in preterm than term infants ($P=0.017$).⁷⁶ HMPV was also detected in 9.5% of recurrent wheezing episodes in preterm infants. Numerous other studies have identified prematurity as a risk factor for hospitalization for HMPV infection.^{24,28,31,32,47}

HMPV respiratory illness, when recognized, is also associated with substantial morbidity, with at least one report of HMPV infection in a premature infant requiring extracorporeal membrane oxygenation support.⁷⁷ In a study comparing clinical features and risk factors for HMPV with RSV, HMPV was associated with more severe disease in premature infants, with more preterm infants hospitalized with HMPV than RSV (21.3% vs 12.4%, respectively).⁷⁸ In the outpatient clinic setting, all gestational age groups were equally represented for RSV and HMPV. However, hospitalized infants with severe HMPV were more likely to be born at earlier gestational ages than the late preterm period ($P=0.002$). Significantly more infants who received palivizumab were HMPV, rather than RSV, positive (11.3% vs 2.0%, respectively). However, this finding may simply point to palivizumab receipt as a marker of extreme prematurity and is consistent with the lack of neutralizing activity by palivizumab against HMPV in vitro or in vivo.⁷⁹ There are no published data regarding a protective effect of maternally derived antibodies on the incidence and severity of HMPV in neonates. However, infants with high levels of maternally acquired antibodies against the related viruses RSV and PIV type 3 are better protected against lower respiratory tract illness than those with lower levels.^{80,81} Infants do have maternally derived HMPV-specific antibodies at birth that wane during the first year of life.^{82,83} Thus, it is likely that infants born before the majority of maternal antibody are transported across the placenta in the third trimester will have diminished protection against HMPV. Moreover, this would present a challenge for a strategy of maternal vaccination, since vaccine-induced antibodies would not be present in the highest risk infants born before 28–32 weeks.⁸⁴

Overall, prematurity conferred the greatest odds ratio for severe HMPV disease (13.97, 95% confidence interval: 1.50–130.0), far more than all other risk factors for severity of HMPV combined (female sex, genotype of HMPV, household crowding). Prematurity only conferred an odds ratio of 3.08 (95% confidence interval: 1.63–5.83) for severe RSV disease, suggesting that premature infants may be at

greater risk of severe HMPV disease.⁷⁷ The increased severity of HMPV in preterm infants persisted after the first year, with pediatric intensive care data demonstrating that 34% of hospitalized infants with HMPV were preterm and had significantly worse hypoxemia, increased need for ventilation, and longer hospitalizations.⁸⁵

Simultaneous coinfection with HMPV and RSV has been described. Dual infection with RSV and HMPV increased the risk of severe disease and pediatric intensive care unit admission compared to RSV alone in one small study,⁸⁶ but this finding was not confirmed by subsequent larger reports.^{19,87–89}

Consequences of HMPV infection on lung remodeling may also be worse than those of RSV for preterm infants. Pulmonary function testing at 1 year done on preterm infants who experienced LRI demonstrated differential effects of HMPV, RSV and other viruses on lung function. HMPV LRI were associated with clinically significant increases in airway resistance, which were worse than in RSV LRI ($P=0.002$).⁶¹ HMPV may therefore have more severe short- and long-term consequences in preterm infants than term infants, without the current recognition or treatment options available for RSV.⁵⁸ An investigation of possible reasons for the differential effects of HMPV on the context of prematurity may provide insight into mechanisms and future therapeutic strategies.

The increased susceptibility of preterm infants to viral infection is incompletely understood and may involve a combination of prenatal and postnatal inflammatory conditions, immunologic immaturity, and genetics.⁶² In mouse models of prematurity, the degree of maturation of the immune system at the time of infection can influence response to initial and subsequent viral challenges. Preterm infants exhibit immature but also dysfunctional humoral immune responses with limited or inefficient repertoire formation and low IgG levels in the first 6 months.⁹⁰ While leukocytes increase throughout gestation, the increase in CD3⁺ cells occurs in inverse proportion to an increase in CD4⁺ cells, which are often dysregulated, resulting in a functional immunosuppression. The inflammatory milieu is also postulated to increase susceptibility to infection with dysfunctional shifts in Th1/Th2 balance and long-term effects on cytokine responses to infection.

In the case of HMPV, this altered inflammatory response has been noted in formerly hospitalized preterm children. One study reported a lower IFN γ /IL-4 ratio (thus increased Th2 bias) in term infants infected with HMPV.⁹¹ In contrast, another study found that term infants hospitalized with HMPV infection had increased IFN γ , CCL5 and IL-10 levels, with increased Th1/Th2 ratios compared to uninfected controls,

but preterm infants exhibited minimal cytokine responses and no elevation in IFN γ /IL-4 ratio.⁸⁵

Alterations in the preterm microbiome due to frequent antibiotic exposures and delayed or limited feedings of maternal milk have also been hypothesized to play a role in immune system dysfunction. While evidence exists for a role of the microbiome in gut and lung immune susceptibility to bacterial pathogens or diseases such as necrotizing enterocolitis or pneumonia, it is unclear at this time whether a similar association exists with LRI-causing viruses or HMPV.

The increased severity of viral diseases and likelihood of pathological responses to viral illness are associated with disruption of normal development of the lung and the immune system. In particular, abnormal postnatal lung growth and iatrogenic lung injury may contribute to respiratory disease of prematurity. Preterm infants are at risk of significant respiratory morbidity in the first year of life but also at school age,⁹² when they present with symptoms similar to those of reactive airways disease, and upper or lower respiratory tract infections.⁵¹ Infants born at lower gestational ages are more likely to experience these morbidities, especially if they have BPD. While BPD is incompletely characterized, large prospective studies have demonstrated a pro-/anti-inflammatory cytokine imbalance,⁹³ which could influence the pathogenesis of HMPV infection. Furthermore, extremely preterm infants with BPD are often discharged home on supplemental oxygen to support lung growth and development. However, hyperoxia can increase the severity of viral illnesses through exaggerated inflammatory responses to infection.^{94,95}

While BPD is often associated with a high burden of morbidity and health care utilization after discharge from the NICU, even preterm infants without BPD exhibit more severe symptoms than term infants, such as more days of cough and wheeze after LRI. This may be related to lung injury during the perinatal period (even in the absence of infection), as 78% of children born at <26 weeks of gestation have evidence of airway obstruction, ventilation inhomogeneity, gas trapping, and airway hyperresponsiveness at 11 years of age.^{60,96} Preterm infants with similar lung function at 36 weeks postmenstrual age will differentially develop increased airway resistance at 1 year if they experience LRI in infancy.⁶²

The immune system of preterm infants may play a role not only in susceptibility to HMPV but also in the severity of response. In particular, low levels of IFN γ in cord blood are associated with childhood wheezing and atopy. It is hypothesized that the ability to have an initial increase in

IFN γ in response to the first presentation of a virus may limit excessive antigen presenting cell function and allow for protective immune response and viral clearance without immunopathogenesis. Two reports suggest that HMPV infection during infancy is associated with asthma or impaired lung function later in life.^{61,97} Preterm infants with poor initial IFN γ responses may therefore have more severe symptoms upon LRI viral infections in infancy and beyond. Finally, a genetic susceptibility to morbidity after RSV infection may also contribute to severity of disease after LRI,⁹⁸ and it is possible that such associations exist with HMPV.

Treatment and prevention of HMPV

For infants who require hospitalization, the primary therapies are supplemental oxygen and intravenous hydration. Extracorporeal membrane oxygenation support has been used in cases of respiratory failure refractory to mechanical ventilation.^{77,99} There are anecdotal reports of the empiric use of bronchodilators and corticosteroids, but there are no controlled trials of these medications for HMPV and no data to support efficacy. Bronchodilator and corticosteroid treatment appeared to offer benefit in experimentally infected cotton rats.¹⁰⁰ Aerosolized ribavirin is the only currently licensed antiviral agent for treatment of RSV. Ribavirin and polyclonal human immunoglobulin exhibited in vitro virus-inhibiting activity against HMPV.¹⁰¹ However, there are no published animal or human data for these interventions. Anecdotal reports exist of ribavirin use in profoundly immunocompromised HMPV-infected patients, usually in conjunction with intravenous immunoglobulin, but there are no controlled data, and so this therapy should be considered experimental.^{102–107}

A number of candidate vaccines against HMPV have been tested using animal models. Recombinant chimeric bovine/human PIV type 3 and Bacillus Calmette–Guérin vaccines expressing HMPV fusion (F) protein were immunogenic and protective in rodents.^{108,109} Investigators have generated recombinant HMPV strains that lack various genes or that possess avian metapneumovirus gene insertions.^{110–113} Many of these recombinant viruses caused attenuated infection in rodents or nonhuman primates but were highly immunogenic, inducing neutralizing antibodies and protection against challenge with wild-type HMPV. Virus-like particles can be generated by expressing the viral fusion and matrix genes in mammalian cells to produce enveloped particles that are morphologically similar to viruses, but contain no genome and are noninfectious.¹¹⁴ These particles are effective at inducing B- and T-cell

responses in animal models and confer protection against viruses of both subgroups.^{116,115}

HMPV-specific human monoclonal antibodies analogous to palivizumab have shown prophylactic and therapeutic efficacy in rodent models.^{116,117} Strikingly, some of these monoclonal antibodies exhibit broadly neutralizing activity in vitro and in vivo against RSV as well as HMPV.^{79,118} A live attenuated vaccine has been tested in humans, although only ~30% developed a neutralizing antibody response.¹¹⁹ Thus, several potential vaccine candidates and prophylactic antibodies are in development, offering potential future intervention in premature infants.

Infection control is an important aspect of HMPV prevention in premature infants. HMPV can persist as infectious particles for hours on nonporous surfaces,¹²⁰ and thus environmental cleaning and personal protective equipment are important to reduce the risk of nosocomial transmission. While there are few reports as yet of nosocomial HMPV in the NICU, multiple reports exist of nosocomial outbreaks of HMPV in long-term care facilities for children and adults.^{121–124} Healthy adults can be productively reinfectd with HMPV under experimental conditions,¹¹⁹ illustrating the potential for health care worker transmission. However, a 1-year prospective study of 170 pediatric health care workers detected only one episode of HMPV shedding in a subject with cough and rhinorrhea.¹²⁵

Conclusion

HMPV is a recently identified paramyxovirus, yet it is a leading cause of LRI in children and adults. Premature infants are at high risk of viral LRI and chronic lung disease related to prematurity. Although the data are limited thus far, HMPV is clearly an important respiratory pathogen among these preterm infants. Clinical features are similar to RSV, and the virus may be associated with long-term sequelae. Nosocomial infections likely occur but are underappreciated. Future studies are needed to fully define the burden of disease due to HMPV in preterm infants and to develop therapeutic or preventive strategies for this high-risk population.

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