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Beyond Respiratory Syncytial Virus and Rhinovirus in the Pathogenesis and Exacerbation of Asthma
The Role of Metapneumovirus, Bocavirus and Influenza Virus

Andrea M. Coverstone, MD[a], Leyao Wang, PhD, MPH[b],
Kaharu Sumino, MD, MPH[c],*

KEYWORDS

- Human metapneumovirus • Bocavirus • Influenza virus • Wheezing • Asthma

KEY POINTS

- Respiratory viruses other than rhinovirus or respiratory syncytial virus can be associated with acute wheezing illness.
- Contribution to recurrent/wheezing is not well studied.
- Children with human metapneumovirus lower respiratory tract infection may have increased risk of subsequent recurrent wheezing over the several years after initial infection.

With the dissemination of the use of sensitive molecular methods for viral detection, the opportunities to evaluate the role of respiratory viruses in acute and chronic respiratory illness has expanded in the past decade. Acute wheezing illnesses are common, especially in young children, and viral agents have been shown to be found in 60% to 100% of these episodes using these sensitive detection methods.[1–3] Multiple

viruses are associated with acute wheezing illness, including rhinovirus (RV), respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza virus, parainfluenza virus, adenovirus, human bocavirus (HBoV),[1] coronavirus, and enterovirus (**Table 1**). These viruses have also been shown to be associated with asthma exacerbations.[4,5] RV and RSV are the most frequently detected pathogens (see **Table 1**), with RSV more prevalent in younger children in winter months and RV more prevalent in older children.[2] There is a large body of evidence implicating the association of RV[6–8] and RSV[9,10] with the subsequent development of recurrent wheezing and/or asthma. Viruses other than RV or RSV can be detected in 50% of wheezing illnesses,[1,11,12] but there are limited data regarding the association of these other viruses and asthma. Conducting studies to evaluate the long-term consequences of these other viruses has been challenging for several reasons. First, the detection rate of these viruses is often lower compared with RV and RSV, so a much larger cohort is required to perform a study with adequate representation of patients infected with these other viruses. The prospective study that investigated the role of hMPV infection in the development of wheezing and asthma required screening of more than 400 children infected with hMPV over a 5-year period of recruitment.[13] Second, establishing appropriate animal models has been challenging and existing models may not adequately model human infection to evaluate long-term outcomes. Third, it is difficult to tease out the specific contribution of other viruses because the association of RV and RSV can confound the analysis given the high rate of coinfection with these viruses. For instance, in a community cohort of 147 children with high atopic risk, wheezy, febrile lower respiratory tract infection (LRTI) during the first year of life was associated with a higher risk of persistent wheezing (odds ratio [OR], 3.5) and asthma (OR, 4.9) at age 10 years if they were atopic by age 2 years.[3] Respiratory virus was detected in 62% of these patients with febrile LRTI with a large proportion (60%–70%) of the detected viruses being RV or RSV, so this observed association may be primarily caused by the effect of RV or RSV infection. However, there are data suggesting that viral infection in early life with any cause may be important in increasing the risk of asthma. In a high-risk birth cohort study in Demark, the number of respiratory episodes in the first year of life was associated with the development of asthma at age 7 years regardless of virus type.[14]

This article focuses on 3 viruses (hMPV, HBoV, and influenza virus) in which an association with wheezing illness has been most studied. It provides an aggregate of

Table 1	
Frequency of viruses detected in acute wheezing illness in children	
Virus	**Frequency (%)**
RV	28–76
RSV	16–29
Enterovirus	4–27
Bocavirus	5–18
Parainfluenza virus	8–9
HMPV	3–6
Adenovirus	3–7
Coronavirus	2–5
Influenza virus	2–4

Data from Refs.[1–3]

available data reviewing the current research investigating the role of these viruses in acute and chronic respiratory disease.

HUMAN BOCAVIRUS

hMPV is a paramyxovirus first discovered by van den Hoogen and colleagues[15] in 2001. Similar to RSV, hMPV is a single-stranded RNA virus belonging to the Pneumoviridae subfamily, and causes many of the same symptoms as RSV. Typical symptoms of hMPV infection include mild, self-limiting, acute upper respiratory tract infections to more severe LRTIs, with wheezing and pneumonia. It is a frequent cause of bronchiolitis in young children.[16] Cough, rhinorrhea, wheeze, and fever are commonly reported symptoms in children infected with hMPV.[17–22]

Virtually all children have evidence of exposure to hMPV by age 5 years.[15] hMPV is responsible for a significant portion (2%–12%) of respiratory tract infections[16,17,19,23–26] and is associated with a large burden of hospitalizations and outpatient visits in younger children.[18,20] It tends to peak during the late winter and spring seasons, typically between December and April,[16,19,22,24] often peaking in February and March. Compared with infection with other viruses, there have been conflicting data on whether hMPV infections result in greater hypoxemia or duration of hospitalization or intensive care unit (ICU) stays.[23,24] The severity of illness is worse in those with a history of extreme prematurity.[25]

Although hMPV causes wheezing and lower respiratory tract symptoms, the contribution of hMPV to asthma exacerbations varies among different populations. In those with asthma exacerbations, the detection rate of hMPV is approximately 5% worldwide,[4] whereas in those with hMPV LRTI a much higher proportion have a diagnosis of asthma. In a study of children with hMPV LRTIs in the United States, 14% to 33% carried a diagnosis of asthma or history of wheezing.[16,19] In a study of children with hMPV in Spain, 60.7% of those infected with hMPV alone carried a diagnosis of recurrent wheeze or asthma, which was higher than rates in RSV or adenovirus but similar to that of RV or HBoV. Children with RSV were more likely to have a diagnosis of bronchiolitis than children with hMPV.[24] hMPV can cause an illness consistent with bronchiolitis, but children may be diagnosed less often with this term, given that it often is synonymous with RSV infections in young children. Nonetheless, hMPV causes wheezing in young children; can often precipitate episodes of wheezing in those prone to do so, such as asthmatics; and is an important cause of viral-induced asthma exacerbations. In children with asthma, studies have shown synergistic effects of allergic characteristics of the host (ie, immunoglobulin E level, house dust sensitization) and the severity of asthma exacerbation by RV,[27,28] but the interaction of allergy of the host and hMPV infection has not been well studied.

In contrast with the large number of studies reporting the association of hMPV in early childhood with acute wheezing illnesses or asthma at the time of illness,[16,23] there are sparse data on the long-term consequences after the acute infection. One study from Garcia-Garcia and colleagues[26] retrospectively identified children 2 to 5 years of age who were hospitalized with hMPV or RSV bronchiolitis in their first 24 months of life and contacted them to assess their diagnosis of asthma at the time of the study. Of 101 children with hMPV-positive bronchiolitis (without coinfection) over the course of the prior 5 years (October 2000 to June 2005), they were able to obtain follow-up on 23 children with no prior history of wheezing. They then selected a random sample of children in that same time period with RSV bronchiolitis and obtained follow-up on 32 of those children. A diagnosis of recurrent wheezing and asthma was more frequent in children with a history of hMPV bronchiolitis or RSV

bronchiolitis compared with control children who were hospitalized around the same time because of rotavirus. hMPV bronchiolitis was the strongest independent risk factor for asthma (OR, 15.9; confidence interval [CI], 3.6, 70.5), followed by RSV bronchiolitis (OR, 10.1; CI, 2.5, 40.1) and allergic rhinitis (OR, 4.9; CI, 1.2, 40.1) at age 3 to 5 years. Another study prospectively followed premature infants with viral LRTI and, although it did not track wheezing or asthma status, found that airway resistance measures were increased at 1 year of age, although this study included only 4 infants with hMPV.[29]

Stronger evidence for the long-term effect of hMPV LTRI was found in a recent prospective study that evaluated the effects of hMPV infection on wheezing and asthma outcomes. Children less than 5 years of age hospitalized or treated in the emergency room with hMPV LRTI and no prior history of wheezing were prospectively followed along with a control group, with outcome assessment every 3 to 6 months for up to 3 years, and a final follow-up as late as 6.5 years.[13] This prospective study design enabled the investigators to obtain the child's wheezing history and capture the outcome securely in a longitudinal fashion. Follow-up data were collected on 29 children with hPMV LRTI and 27 controls. Children with hMPV LRTI had a higher likelihood of wheezing episodes during the follow-up period (hazard ratio [HR], 2.8; CI, 1.4, 5.8) than controls. In addition, children with hMPV LRTI had earlier onset of recurrent wheezing, both with and without colds, than the control children (**Fig. 1**). The association with the development of asthma was not statistically significant (HR, 2.5; CI, 0.8, 8.1; P = .12), although the number of children diagnosed with asthma was larger in the hMPV group (9 of 29) than the control group (4 of 27). There is more to learn, but these studies suggest an increased risk of asthma development following hMPV infection early in life.

The mechanism of short-term and long-term pathologic effects of hMPV infection is not well studied compared with that of RSV. Infection with hMPV in mice was shown to lead to persistence of viral RNA, pulmonary inflammation, and airway hyperresponsiveness several months after the infection,[30] suggesting long-term pathologic changes can occur after hMPV infection.
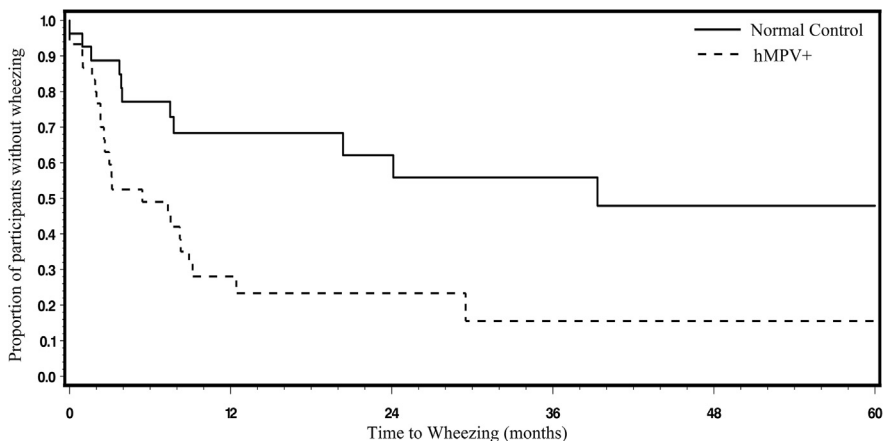
Fig. 1. Survival analysis for wheezing and asthma after hMPV LRTI. Kaplan-Meier estimates of freedom from any wheezing episodes, P = .004; hMPV LRTI subjects had wheezing earlier in follow-up compared with control subjects. (*From* Coverstone AM, Wilson B, Burgdorf D, et al. Recurrent wheezing in children following human metapneumovirus infection. J Allergy Clin Immunol 2018;142(1):299; with permission.)

Studies in both mice and humans have suggested several different molecular mechanisms of hMPV affect airway inflammation and function at the time of acute infection, often comparing these mechanisms with those of other viral causes. Alveolar macrophage activity may be augmented in hMPV infection, leading to detrimental effects on the airway, whereas alveolar macrophage depletion was seen in RSV and may provide protection against the harmful effects of the virus.[31] The chemokine profile of nasal secretions was also shown to differ in hMPV, with high concentrations of interleukin (IL)-8 (neutrophil chemotactic factor) and low concentrations of RANTES (regulated on activation, normal T-cell expressed and secreted) (eosinophil chemotactic factor) in individuals infected with hMPV compared with the increased RANTES concentrations seen in RSV.[17] In another study of children 1 to 14 years of age with hMPV infection, differences in measures of cell-mediated immunity distinguished hMPV from other respiratory viruses, such as RSV and influenza.[22] Thymic stromal lymphopoietin (TSLP) as well as IL-4 plasma levels were higher in children with wheezing and hMPV than in those without wheezing and hMPV or without wheezing and another respiratory virus. TSLP has been implicated as a mediator in the pathway of pediatric asthma, with higher plasma TSLP levels correlating with poor asthma control.[32] TSLP promotes basophil production and type 2 inflammation.[33] Infection of human airway epithelial cells with hMPV induced expression of TSLP, as well as leading to upregulation of IL-8 and IL-33, whereas TSLP blockade led to reduced lung inflammation,[34] indicating activation of the TSLP pathway initiating airway inflammation by hMPV acute infection. These studies may suggest the involvement of the TSLP pathway as a molecular mechanism for how hMPV leads to a recurrent wheezing and asthma phenotype, although further investigation is warranted.

HUMAN BOCAVIRUS

HBoV is a parvovirus that was discovered in 2005 from pooled nasopharyngeal samples by molecular screening.[35] Subsequent studies have shown that HBoV genotype 1 is commonly detected in respiratory samples from children with acute wheezing.[1,12] In children with acute wheezing for the first time, HBoV was detected in 18%.[12] However, it is also known that the coinfection rate of HBoV with other viruses is very high (15%–100%). In addition, detection in asymptomatic individuals is also frequent. HBoV was found to be present in 17% of healthy controls admitted to the hospital for elective surgery,[36] and in participants in a household study in which symptoms and nasal samples were prospectively collected for 12 months, 50% of HBoV detection occurred in those without symptoms.[37] Viral persistence is thought to be responsible for the high frequency of coinfection.[37,38] HBoV 1 is implicated to be an important respiratory pathogen by many,[39,40] but the precise pathologic contribution of HBoV in acute respiratory disease is still not accurately defined and HBoV may be both a passenger and a causative pathogen.[36,41] HBoV may interfere with RV-induced immune responses during acute wheezing. Lukkarinen and colleagues[42] compared the T-helper (Th) 1, Th2, proinflammatory cytokine response profile in young children with RV, HBoV, and RV-HBoV coinfection with acute wheezing illness. Unlike RV, HBoV infection was not associated with systemic proinflammatory or Th2-type responses and the RV-HBoV coinfection resulted in a non–Th2-type immune response.

Although bocavirus is frequently detected and seems to be associated with acute wheezing episodes, the data on long-term consequences after the acute infection are sparse. One retrospective study from Spain identified children who were previously hospitalized with HBoV (n = 10) or RSV bronchiolitis (n = 80) in their first 24 months of life and evaluated them to assess clinical outcomes, including a

diagnosis of asthma and presence of atopy at age 5 to 7 years.[43] All children in the HBoV group developed recurrent wheezing. Fifty percent in the HBoV group and 23% in the RSV group had a diagnosis of asthma at age 5 to 7 years. The proportion of those with atopy was similar among those with HBoV and RSV. Another study in children hospitalized for acute viral wheezing showed that 13 children with HBoV-associated bronchiolitis had recurrent wheezing 2 years after the initial hospitalization less often than children with RV-associated bronchiolitis (HBoV 40% vs RV 60%).[42] The association of HBoV LRTI in early life and asthma is inconclusive and larger prospective studies are required to confirm these findings.

INFLUENZA VIRUS

Influenza viruses are responsible for an average of 3.1 million annual hospitalized days, and 31.4 million outpatient visits,[44] and is one of the frequently detected viruses during asthma exacerbations. It has long been identified as a precipitant of asthma exacerbations in all age groups.[2,4,45] In people with asthma exacerbations, the detection rate of influenza virus is approximately 10% worldwide,[4] but, during a flu season, the prevalence of influenza viruses can be as high as 20% in wheezing infants and 20% to 25% in adults with acute asthma exacerbations.[2,46,47] Although involvement of influenza virus is common in asthma exacerbation, influenza virus is an infrequent cause of acute wheezing illness in younger children.[1–3] The authors are not aware of any studies evaluating the role of influenza virus LRTI on the development of recurrent wheezing and/or asthma later in life.

The cytokine IL-33 is implicated as an important driver for influenza-induced asthma exacerbations in animal studies.[48,49] In the influenza-infected mouse models, IL-33 expression is upregulated, shifting the balance of Th1/Th2 immunity.[48,50] A recent study has shown that IL-33 is produced by ciliated bronchial cells and type II alveolar cells on viral-induced exacerbation in human and mice and dampened innate and adaptive Th1-like and cytotoxic responses, which subsequently results in increased viral loads and enhanced airway inflammation underlying the influenza-induced asthma exacerbation.[49] Meanwhile, heightened IL-33 production induces substantial IL-13 production in type 2 innate lymphoid cells (ILC-2), Th2 cytokine–producing cells that promote allergic inflammation in mouse models of asthma and atopic dermatitis.[51] In another study, influenza A infection induced acute airway hyperreactivity that was medicated by ILC-2, suggesting the importance of the IL-33–IL-13 axis in influenza-induced acute asthma exacerbations.[52]

Whether asthmatics are more frequently infected by influenza virus is still a matter of debate. It has been shown that patients with asthma have reduced type 1 interferon (IFN) responses on RV infection,[53,54] but a few studies did not confirm this observation.[55,56] Human bronchial epithelial cells from patients with asthma show increased IFN-lambda 1 levels and preserved IFN-beta levels when infected with influenza A virus, although viral levels were higher in asthmatics compared with non-asthmatics.[56] In a US study, children with asthma were found to be infected twice as often as nonasthmatics by H1N1 influenza when monitored by weekly nasal samples and symptoms scores during the 2009 to 2010 season.[57] Regardless, it has been accepted that asthma is a risk factor of severe disease with influenza once acquired, and patients with asthma have been listed as a priority population for vaccination.[58] The population studies in the 2009 H1N1 pandemic have provided interesting observations regarding this susceptibility. Having asthma was found to be a risk factor for hospitalization for H1N1[59,60] and was found in 10% to 20% of the hospitalized

patients worldwide.[61] Nonetheless, an observation has also been made that having asthma may be protective once patients are hospitalized from influenza. Patients with asthma had decreased risk of ICU stay, mechanical ventilation, and death from H1N1, compared with other chronic conditions, such as cardiovascular diseases and obesity.[62–64] The observed protective effect may be in part explained by early hospital admission and/or a favorable response to steroids.[65] In mouse models, this protective effect of allergic asthma on influenza infection has been recapitulated and the increased eosinophil levels in asthmatic airways may be one of the mechanisms.[66] With putative antigen-presenting functions, eosinophils enhanced influenza-specific CD8+ T cells after infection, mediating the viral clearance of influenza virus in a mouse asthma model.[66] Rapid induction of type III IFNs, natural killer cells, and TGF-beta was also observed in asthmatic mice on influenza infection, indicating a potential mechanism for enhanced antiviral immunity against influenza in asthmatics.[66–68]

Influenza vaccine is recommended for patients with asthma in many countries, but there has not been clear evidence showing a protective benefit. The most recent Cochrane Review, in 2013, which included 18 trials across the world, concluded that inactivated influenza vaccine did not provide significant reduction in the number or duration of influenza-related asthma exacerbations.[69] Safety concern was raised in an earlier study that showed a decrease in peak flow following the administration of the inactivated influenza vaccine.[70] A subsequent study in the Netherlands[71] and a large study in the United States[72] enrolling more than 2000 patients with asthma confirmed that there is no increase in risk for adverse events including asthma exacerbation within 2 weeks following the injection. This Cochran Review also conducted a systematic review in 3 trials comparing intranasal vaccine with intramuscular infection in infants and older children and concluded that event rates for asthma exacerbation and wheezing were similar in both vaccine types.[69] A more recent study in the United Kingdom evaluated the safety of intranasal live attenuated influenza vaccine in atopic children with well-defined allergy to eggs. Sixty-seven percent of children had asthma in addition to their egg allergies. There was no systemic reaction following the injections and 8 mild self-limiting symptoms after 433 doses given in 282 children, which also ensured safety.[73]

SUMMARY

Respiratory viruses other than RV or RSV, especially hMPV, influenza virus, and HBoV, can be detected frequently in acute wheezing illness. The interaction of these other viruses with an allergic host, and their contribution in the development of asthma after acute infection, are not well understood, although there is evidence to suggest that children with hMPV LRTI have a higher likelihood of subsequent and recurrent wheezing over the several years after initial infection.

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