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### Human metapneumovirus infection in children hospitalized for wheezing

#### *To the Editor:*

Recently, the prevalence of viral respiratory tract pathogens associated with acute wheezing exacerbations was reported in a study of infants and children admitted to the Children's Hospital at the University of Virginia.<sup>1</sup> Subsequently, we analyzed the nasal washes from these children for human metapneumovirus (hMPV), a paramyxovirus closely related to respiratory syncytial virus (RSV). hMPV has also been shown to be a significant cause of respiratory tract illnesses in young children.<sup>2-4</sup>

The study we previously reported from the University of Virginia was an observational, case-control study of 133 children (age 2 months to 18 years) hospitalized for wheezing between April 1, 2000, and March 31, 2001. This represented 93% of all admissions for acute wheezing during the study period. Children who had evidence of cardiopulmonary disease or immunosuppression were excluded. The control subjects included 133 age-matched and gender-matched hospitalized children without wheezing. They were enrolled during the same season of each matched wheezing subject. Demographic information was obtained from parent-administered questionnaires and hospital charts. The Human Investigation Committee at the University of Virginia approved the study. Informed consent was obtained from parents, and assent was obtained from older children.

Nasal washes were obtained from patients to test for viruses by culture and for RSV and influenza by antigen testing. In addition, nucleic acids extracted from the samples had been tested previously by RT-PCR for rhinovirus, enterovirus, coronavirus, influenza virus, parainfluenza virus, and RSV, and by PCR for adenovirus.<sup>1</sup> Metapneumovirus testing was performed by a real-time RT-PCR assay on a Smart Cycler (Cepheid, Sunnyvale, Calif) using primers and probe for the N gene<sup>5</sup> with the Quantitect RT-PCR kit (Qiagen, Valencia, Calif). The probe was altered slightly, with BHQ-3 (Invitrogen, Carlsbad, Calif) substituted for 5-carboxytetramethylrhodamine as the 3' fluorescent quencher. These primers and probe have been shown to detect all 4 genetic lineages of hMPV, and the limit of detection in our assay was 50 copies of viral genome per reaction.

Patient demographic data and the frequencies for positive tests for virus among wheezing and control patients were analyzed by nonparametric exact methods. Exact 2-sided 95% CIs for the difference of proportion were constructed as described by Agresti and Min.<sup>6</sup> Multivariate analyses related to predicting wheezing as a function of the patient's atopic status and evidence for viral infection were performed by multiple logistic regression. Tests of association were evaluated on the basis of the generalized Wald  $\chi^2$  statistic, and 95% CI construction for the adjusted odds ratio was based on the Wald approximation. Total serum

IgE data were analyzed on the logarithmic scale by way of 1-way ANOVA.

Demographic characteristics of the study population were previously described in detail.<sup>1</sup> Thirteen children in this study tested positive for hMPV (10 children hospitalized for wheezing and 3 controls; Table I). Seven of the 10 wheezing children were <3 years old, and half were males. The mean age of the children <3 years old who were infected with hMPV was 7 months (range, 2-13 months). The majority of subjects with positive tests for hMPV (85%; 11/13) were hospitalized from January through April.

The prevalence of positive tests for hMPV among children <3 years old was 8.9% (7/79) in wheezing children compared with 1.3% (1/77) of controls ( $P = .035$ ). Overall, the children in this age group who tested positive for any virus (including hMPV) were more likely to be hospitalized for wheezing than the children who tested negative for virus (odds ratio, 6.48; 95% CI, 2.83-14.81;  $P < .001$ ). More wheezing children than controls who were younger than 3 years had positive tests for 1 or more viruses (32% compared with 16%;  $P = .02$ ). Among those who tested positive for hMPV, 3 of the wheezing subjects as well as the control tested positive for other viral pathogens (Table I). Only 1 of these 4 children (all admitted during the midwinter) tested positive for RSV, and none tested positive for influenza. Mean serum total IgE levels were not different between hMPV-infected children with wheezing and hMPV-infected controls.

Among the children 3 to 18 years old, the children who tested positive for any virus were more likely to be hospitalized for wheezing than the children who tested negative for virus (odds ratio, 6.00; 95% CI, 2.62-13.73;  $P < .001$ ). As previously reported,<sup>1</sup> rhinovirus was the dominant pathogen, whereas hMPV was not significantly associated with wheezing in this age group. Among children who were 3 through 9 years of age, hMPV was detected in 8.8% (3/34) of the wheezing subjects compared with 5.7% (2/35) of the controls ( $P = .71$ ). None of the children who tested positive for hMPV in this age group were coinfecting with another virus. No subject older than 9 years of age had a positive test for hMPV.

In this analysis, we found a significant association between hMPV infection and wheezing among children younger than 3 years, especially during the midwinter months. This is consistent with a highly significant association between hMPV and wheezing exacerbations observed in a 25-year prospective study of lower respiratory tract illness in otherwise healthy outpatient children (in Tennessee) who were younger than 5 years.<sup>3</sup> In contrast, hMPV was not significantly associated with wheezing requiring hospitalization among children 3 years of age and older in our study. Instead, rhinovirus was the dominant pathogen associated with severe exacerbations, which has also been observed in other studies of

**TABLE I.** Characteristics of subjects infected with hMPV

Group	Number	Age	Sex	Serum IgE	Month of admission
				level (IU/mL)	
Wheezing subjects	*1	2 mo	F	<2.0	Oct
	*2	2 mo	M	<2.0	Jan
	3	4 mo	M	<3.0	Jan
	4	8 mo	F	<2.0	Mar
	*5	9 mo	F	2.45	Feb
	6	12 mo	F	14.4	Mar
	7	13 mo	M	33.7	Jan
	8	5 y	F	27.6	Apr
	9	8 y	M	145	Apr
	10	9 y	M	548	Jan
			Mean, 128		
Control subjects	*11	6 mo	F	<2.0	Mar
	12	5 y	M	66.4	Feb
	13	9 y	F	1053	Oct
				Mean, 560	

\*These subjects also tested positive for other viruses, including parainfluenza virus (subject 1); cytomegalovirus (subject 2); adenovirus, RSV, cytomegalovirus, and parainfluenza virus (subject 5); and rhinovirus and parainfluenza virus (subject 11).

children hospitalized for wheezing.<sup>7</sup> In addition, the large majority (at least 80%) of the wheezing children age 3 years and older who were hospitalized in Virginia had striking atopic characteristics.<sup>1</sup>

Combined with test results for other viral pathogens reported previously in the same patients,<sup>1</sup> the detection of hMPV in our current analysis increased the overall prevalence of viral infections among the wheezing subjects younger than 3 years to almost 90%. These results confirm and strengthen the observation that viral respiratory tract pathogens are the dominant risk factor for wheezing exacerbations in early childhood. Similar to other viruses that are significantly associated with wheezing during early childhood, more information is needed about the infants who are infected with hMPV and their long-term prognosis with respect to persistent wheezing and their risk for developing asthma.<sup>8</sup>

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### Detection of novel latex allergens associated with clinically relevant allergy to plant-derived foods

To the Editor:

During the last decades, hypersensitivity to natural rubber latex proteins has become a serious occupational and public health problem. Several latex allergenic proteins have been purified and characterized thus far, and some of them have been shown to be responsible for the so-called latex-fruit syndrome caused by the presence of cross-reacting homologous proteins in fruits and vegetables.<sup>1,2</sup> Banana, avocado, chestnut, and kiwi are the most frequently implicated foods in this syndrome, but associations with several other fruits and vegetables, including pineapple, fig, passion fruit, mango, tomato, bell pepper, carrot, oregano, dill, and sage, have been reported.

The allergen responsible for most cases of latex-fruit syndrome is hevein (Hev b 6.02), the amino-terminal fragment of prohevein<sup>3</sup>; homologous proteins have been detected in avocado, chestnut, banana, kiwi, tomato, passion fruit, papaya, and mango.<sup>3</sup> Another latex allergen possibly causing food allergy is  $\beta$ -1,3-glucanase (Hev b 2), a 35-kd protein<sup>3</sup>; homologous proteins have been detected in avocado, chestnut, banana, kiwi, fig, and bell pepper.<sup>4</sup> Finally, cross-reactivity between Hev b 7 and patatin has been recently described.<sup>5</sup> In the present study we describe a patient who was sensitized uniquely to uncharacterized high-molecular-weight latex proteins cross-reacting with proteins in plant-derived foods.

A 53 year-old man was seen in September 2003 with a clinical history of eczematous dermatitis at the left foot for 12 years, at the left axilla for 1 year, and at the left ankle and both wrists for some months. Moreover, the