



Children Hospitalized with Rhinovirus Bronchiolitis Have Asthma-Like Characteristics

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Children with bronchiolitis often are considered a homogeneous group. However, in a multicenter, prospective study of 2207 young children hospitalized for bronchiolitis, we found that children with respiratory syncytial virus detected differ from those with rhinovirus detected; the latter patients resemble older children with asthma, including more frequent treatment with corticosteroids. (*J Pediatr* 2016;172:202-4).

Bronchiolitis, the leading cause of hospitalization for US infants, is caused by a diverse group of viruses.¹ Respiratory syncytial virus (RSV) is the most common virus associated with severe bronchiolitis (ie, bronchiolitis requiring hospitalization), and rhinovirus is the second most common.² The 2014 American Academy of Pediatrics bronchiolitis clinical practice guideline recommends that clinicians not test children with bronchiolitis for viruses because identifying the viral etiology will not change the child's management.³ In other words, the guidelines suggest that bronchiolitis should be treated by clinicians as a homogeneous condition despite different viral etiologies.

Emerging evidence suggests that bronchiolitis actually is a heterogeneous condition with different short-term and long-term outcomes. Based on small studies ($n < 280$), children with rhinovirus-associated bronchiolitis have different demographics, are more likely to have a prior history of wheezing, and more often are treated with corticosteroids in the acute setting compared with young children infected with other viruses.^{4,5} Moreover, children hospitalized with rhinovirus-associated bronchiolitis have been shown, in 2 separate populations, to have a shorter length of stay than children with RSV bronchiolitis.^{2,6} In addition to these short-term differences, early childhood rhinovirus-associated wheezing illnesses, such as bronchiolitis, are associated with an increased risk of school-age asthma compared with RSV-induced wheezing illnesses.⁷ Taken together these findings suggest that bronchiolitis is not a homogeneous condition.

We recently completed a prospective, multicenter, multi-year study of over 2000 children hospitalized with bronchiolitis.² In this secondary analysis, we hypothesized that children hospitalized with rhinovirus-associated bronchiolitis would be more likely than their counterparts with RSV infection to have asthma-like characteristics (ie, prior wheezing, atopic characteristics, and more frequent treatment with corticosteroids).

Methods

This is a secondary analysis of the 30th Multicenter Airway Research Collaboration prospective observational study of children hospitalized with bronchiolitis. The study design, setting, participants, and methods of data collection have been described previously.² Briefly, site teams at 16 hospitals across 12 US states enrolled children age <2 years with an attending physician diagnosis of bronchiolitis for up to 3 consecutive years during the 2007-2010 winter seasons using a standardized protocol. All medical decisions, including testing for viruses, were at the discretion of the treating clinicians. During the study period, no sites were routinely testing for rhinovirus. The institutional review board at each participating hospital approved the study.

Investigators conducted structured interviews assessing patients' demographic characteristics, medical history, and details of the acute illness. Pre-admission and daily hospital clinical data were obtained by chart review. Nasopharyngeal aspirates were collected using a standardized protocol.² Polymerase chain reaction assays used single-plex or duplex 2-step real-time polymerase chain reaction for RSV types A and B, rhinovirus, parainfluenza virus types 1, 2, and 3, influenza virus types A and B, 2009 novel H1N1, human metapneumovirus, coronaviruses NL-63, HKU1, OC43, and 229E, enterovirus, adenovirus. This testing was conducted from 2008-2010, as described previously.²

ED	Emergency department
RSV	Respiratory syncytial virus

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Statistical Analyses

We focused this analysis on RSV and rhinovirus, the 2 most common viruses causing severe bronchiolitis,² by creating 3 nonoverlapping categories RSV+, RSV/rhinovirus coinfection, and rhinovirus+. The RSV+ and rhinovirus+ categories include all other viral coinfections except RSV/rhinovirus. In sensitivity analyses, we assessed different virus combinations, stratified by age (<6 months, 6-11.9 months, ≥12 months), and restricted the analysis to children with first-time wheezing. Data were analyzed using χ^2 tests for unadjusted analyses and multivariable logistic regression for adjusted analyses. For the multivariable analysis, we examined the association between virus detection and receiving corticosteroids in both the emergency department (ED) and during the hospitalization; a composite outcome that only included children prescribed corticosteroids by either of 2 different care teams (ie, ED and inpatient). Data are presented as proportions, medians with IQRs, and ORs with 95% CIs. All analyses were performed using Stata 12.0 (StataCorp, College Station, Texas).

Results

Over the 3-year study period, we enrolled 2207 children hospitalized for bronchiolitis. The median age was 4 months (IQR, 2-9 months), 1311 (59%) were male, and 539 (24%) were black. Among these 2207 children, 1302 (59%) were RSV+, 287 (13%) had RSV/rhinovirus coinfection, and 277 (13%) were rhinovirus+. There were 341 (15%) children with non-RSV and nonrhinovirus infections or no identified viral infections that were excluded from the current analysis. As shown in **Table I**, children positive for rhinovirus were

more likely to be older, have a history of wheezing, and have a history of eczema. No differences were observed with respect to parental history of asthma. Children with rhinovirus were also more likely to receive systemic corticosteroids in the ED and during the current hospitalization. In a multivariable model controlling for age, sex, race, history of wheezing, history of eczema, treatment with inhaled corticosteroids in the past week, and clustering by site, children with rhinovirus were more likely to be prescribed systemic corticosteroids in the ED and the hospital than children who were RSV+ (OR 2.48; 95% CI 1.62-3.78; $P < .001$). Children with RSV/rhinovirus coinfections did not have a higher odds of being prescribed corticosteroids than children who were RSV+ (OR 1.43; 95% CI 0.83-2.48; $P = .20$). Results did not materially change in sensitivity analyses comparing different combinations of viruses, including RSV-only, rhinovirus-only, or when stratifying by age (<6 months, 6-11.9 months, ≥12 months), or restricting the analytic cohort to children with first time wheezing (**Table II**; available at www.jpeds.com).

Discussion

In this large multicenter, multiyear study of children hospitalized with bronchiolitis, we found that children with rhinovirus-associated bronchiolitis resembled older children with asthma. Compared with children with RSV-associated bronchiolitis, children with rhinovirus-associated bronchiolitis were more likely to be older and have a prior history of wheezing and eczema. Furthermore, in the multivariable

Table I. Asthma-like characteristics (older age, history of wheezing, history of eczema) in children hospitalized with bronchiolitis, by virus

	RSV+* (n = 1302)	RSV-rhinovirus (n = 287)	Rhinovirus+† (n = 277)	P value
Age				<.001
<6 mo	899 (69%)	203 (71%)	116 (42%)	
6-11.9 mo	242 (19%)	63 (22%)	97 (35%)	
12+ mo	161 (12%)	21 (7%)	64 (23%)	
Sex				.06
Male	756 (58%)	173 (60%)	182 (66%)	
Female	546 (42%)	114 (40%)	95 (34%)	
Race				.10
White	824 (63%)	173 (60%)	160 (58%)	
Black	291 (22%)	78 (27%)	81 (29%)	
Other	187 (14%)	36 (13%)	36 (13%)	
History of wheezing	239 (18%)	60 (21%)	99 (36%)	<.001
History of eczema	182 (14%)	43 (15%)	63 (23%)	.001
Family history of asthma				.53
Neither parent	881 (68%)	187 (65%)	180 (65%)	
Either mother or father	355 (27%)	79 (28%)	84 (30%)	
Both parents	46 (4%)	12 (4%)	9 (3%)	
Don't know/missing	20 (2%)	9 (3%)	4 (1%)	
Inhaled corticosteroids in past week	178 (14%)	41 (14%)	50 (18%)	.17
Systemic corticosteroids in ED and inpatient setting	89 (7%)	22 (8%)	63 (23%)	<.001

*RSV+ includes RSV alone or coinfections with any other virus[‡] except rhinovirus.

†Rhinovirus+ includes rhinovirus alone or coinfections with any other virus[‡] except RSV.

‡Other viruses include adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, enterovirus, influenza A, influenza B, human metapneumovirus, novel H1N1, parainfluenza type 1, parainfluenza type 2, parainfluenza type 3.

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