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Prospective, multicenter study of viral etiology and hospital length-of-stay in children with severe bronchiolitis

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Abstract

Objective—To determine if hospital length-of-stay (LOS) for acute bronchiolitis is influenced by the infecting pathogen

Design—Prospective observational cohort over 3 consecutive years.

Setting—16 US hospitals

Participants—Children age <2 years hospitalized with bronchiolitis

Main Exposure—Nasopharyngeal aspirate (NPA) polymerase chain reaction pathogen results

Main Outcome Measure—Hospital LOS

Results—Of 2,207 participants, 72% had respiratory syncytial virus (RSV), 26% had human rhinovirus (HRV), while all other viruses and bacteria were each ≤8%. Multiple pathogen infections were present in 30%. There were 1,866 (85%) children with either RSV and/or HRV. Among these 1,866 children, the median age was 4 months and 60% were male. The median LOS was 2 days (interquartile range [IQR], 1–4). Compared to children with RSV alone, LOS ≥3 days was less likely among children with HRV alone (adjusted odds ratio [AOR], 0.36; 95% confidence interval [CI], 0.20–0.63; $P<0.001$) and those with HRV + non-RSV pathogens (AOR, 0.39; 95%CI, 0.23–0.66; $P<0.001$), but more likely among children with RSV + HRV (AOR, 1.33; 95%CI, 1.02–1.73; $P=0.04$), controlling for 15 demographic and clinical factors.

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Conflict of Interest Disclosures
All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported

Author Contributions
Drs Mansbach and Camargo have participated sufficiently in the work to take public responsibility for the whole content.
Study concept and design: Mansbach, Piedra, Sullivan, and Camargo
Acquisition of data: Mansbach, Piedra, Teach, Sullivan, Forgey, Espinola, and Camargo
Analysis and interpretation of data: Mansbach, Piedra, Teach, Clark, Espinola, and Camargo
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Study supervision: Camargo

Conclusions—In this multicenter study of children hospitalized with bronchiolitis, RSV was the most common viral etiology, but HRV was detected in one-quarter of children. Since 1 in 3 children had multiple virus infections and HRV was associated with LOS, these data challenge the effectiveness of current RSV-based cohorting practices, the sporadic testing for HRV in bronchiolitis research, and current thinking that the infectious etiology of severe bronchiolitis does not affect short-term outcomes.

Bronchiolitis is one of the most common infectious respiratory conditions of early childhood [1] and the leading cause of hospitalization for infants. [1, 2] The most common pathogen associated with severe bronchiolitis (i.e. bronchiolitis requiring hospitalization) is respiratory syncytial virus (RSV) [3] and the second most common is human rhinovirus (HRV).[4, 5] With the advent of molecular amplification techniques, however, it has become clear that a diverse group of pathogens is associated with severe bronchiolitis and these pathogens may infect children in isolation or in combination as co-infections. [5–7]

The clinical relevance of identifying the specific pathogen or combination of pathogens infecting a child with severe bronchiolitis remains unclear. [8–10] As a result, children with bronchiolitis, no matter the infecting pathogen, are considered to have essentially the same disease. Indeed, the 2006 American Academy of Pediatrics bronchiolitis clinical practice guideline recommends that clinicians limit viral diagnostic testing when caring for children with bronchiolitis.[8] Children with HRV, however, may have different short- and long-term outcomes than children with RSV. [5, 11–14] Specifically, children with HRV bronchiolitis may have shorter acute clinical courses [5, 11] and may be at increased risk of recurrent wheezing and asthma [12–14] when compared to children with RSV bronchiolitis. To examine the clinical utility of identifying an infectious etiology, we conducted a prospective, multicenter, multiyear study of >2000 children hospitalized with bronchiolitis. We hypothesized that children infected with HRV alone would have shorter hospital length-of-stay (LOS) than children infected with RSV alone.

Methods

Study Design

We conducted a prospective, multicenter cohort study for 3 consecutive years during the 2007 to 2010 winter seasons, as part of the Multicenter Airway Research Collaboration (MARC), a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org). The number of participating sites varied over the 3 years: 13 sites in year 1; 16 sites in year 2; and 14 sites in year 3. Each month from November 1 until March 31, site investigators across 12 US states used a standardized protocol to enroll a target number of consecutive patients from the inpatient wards and the intensive care unit (ICU). Once the site reached their target enrollment for that month, the investigators would stop enrollment until the beginning of the following month.

All patients were treated at the discretion of the treating physician. Inclusion criteria were an attending physician's diagnosis of bronchiolitis, age <2 years, and the ability of the parent/guardian to give informed consent. The exclusion criterion was previous enrollment. All consent and data forms were translated into Spanish. The institutional review board at each of the 16 participating hospitals approved the study.

Data Collection

Investigators conducted a structured interview that assessed patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. Relevant comorbid medical disorder included review of respiratory, cardiac, neurologic, gastrointestinal, and immunologic diseases. Emergency department (ED) and

daily hospital chart review provided further clinical data, including respiratory rates, daily respiratory rate trends, clinical assessment of degree of retractions (collapsed for analysis into none, mild, and moderate/severe), oxygen saturation, daily oxygen saturation trends, medical management, and disposition. These data were reviewed at the EMNet Coordinating Center and site investigators were queried about missing data and discrepancies identified by manual data checks.

Nasopharyngeal aspirate collection and virology testing

Nasopharyngeal aspirates (NPAs) were performed using a standardized protocol. Designated site personnel were trained using a lecture, written instructions, and video. All of the sites used the same collection equipment (Medline Industries, Mundelein, IL) and collected the samples within 24 hours of a child's arrival on the medical ward or ICU. Once collected, the NPA sample was added to transport medium. After collection, the NPA samples were immediately placed on ice and then stored at −80°C. Frozen samples were batch shipped on dry ice overnight to the central laboratory at Baylor College of Medicine, where they were stored again at −80°C.

PCR assay

All PCR assays were conducted as singleplex or duplex two-step real time PCR (rtPCR). Real time reverse transcriptase-PCR (rtRT-PCR) was used for the detection of RNA respiratory viruses which included RSV types A and B, human rhinovirus (HRV), parainfluenza virus (PIV) types 1, 2 and 3, influenza virus types A and B, 2009 novel H1N1, human metapneumovirus (hMPV), coronaviruses NL-65, HKU1, OC43 and 229E, and enterovirus. rtPCR was used for the detection of DNA pathogens which included adenovirus, *M. pneumoniae*, and *B. pertussis*. These tests are routinely conducted in the central laboratory of one of the investigators (PAP) and details of the primers and probes have been described. [15–17]

Statistical Analyses

All analyses were performed using Stata 11.2 (Stata Corp, College Station, TX). Data are presented as proportions with 95% confidence intervals (95%CIs) and medians with interquartile ranges (IQR). Our primary analyses focused on RSV and HRV, the most commonly detected viruses in children with severe bronchiolitis. For the purposes of this analysis we combined RSV-A with RSV-B since the clinical distinction between the two subtypes of RSV was unremarkable. For analyses, we created a categorical variable that reflected the possible combinations of RSV/HRV status: (1) RSV only infection, (2) HRV only infection, (3) RSV in combination with HRV, (4) RSV in combination with non-HRV pathogens, and (5) HRV in combination with non-RSV pathogens.

We performed univariate analyses using chi-square, and Fisher's exact test, and Kruskall Wallis test, as appropriate. All *P*-values were two-tailed, with $P<0.05$ considered statistically significant. Multivariable logistic regression analyses were conducted to evaluate independent predictors of longer LOS (≥3 days; defined using the median value of 2 days) and other measures of severity: ICU admission and continuous positive airway pressure (CPAP)/intubation. Factors were selected for inclusion in the model if they were found to be associated with the outcome in unadjusted analyses ($P<0.20$) or were potentially clinically significant. All regression models account for potential clustering by site. To further investigate independent predictors of LOS, a zero-truncated negative binomial model was also used to evaluate the relationship between demographic and clinical factors and LOS in days (continuous outcome). Children who were hospitalized for <1 day were assigned 0.5 days LOS. Results of the zero-truncated negative binomial model are reported as incidence rate ratios (IRRs) with 95%CIs.

Results

Of 3,910 eligible children with severe bronchiolitis, 2,207 (56%) were enrolled. Enrolled and non-enrolled children were similar in both age and gender ($P>0.05$) but enrolled children were more likely to be white (61% vs 50%; $P<0.001$) and Hispanic (36% vs 29%; $P<0.001$). Enrolled children also were less likely to have a LOS ≥3 days (44% vs 49%; $P=0.007$).

Of the 2,207 enrolled children, (1,410 [64%]) tested positive for a single virus infection while 658 (30%) had two or more viruses; the remaining 139 (6%) children had no pathogen identified from our testing panel. Among all enrolled children, the pathogens detected were RSV-A (43%) and RSV-B (30%); HRV (26%); PIV types 1,2, and 3 (3%); influenza A, B, and novel H1N1 (1%); hMPV (7%); coronaviruses NL-65, HKU1, OC43 and 229E (7%); enterovirus (5%); adenovirus (8%); *M. pneumoniae* (1%); and *B. pertussis* (0.2%). Children with RSV and/or HRV represented 1,866 (85%) of the 2,207 children. At least one other virus was detected in 32% of children who tested positive for RSV, in 23% who tested negative for RSV, in 70% of children with HRV, and in 16% without HRV.

Given the high frequency of RSV and HRV, we restricted this analysis to the 1,866 children with RSV and/or HRV. Among these 1,866 children, the median age was 4 months (IQR, 2–8 months), 60% were male, 62% were white, and 36% were Hispanic. The median LOS was 2 days (IQR, 1–4 days). Moreover, 1,075 (58%) had RSV only infections, 167 (9%) had HRV only infections, 287 (15%) had RSV + HRV, 227 (12%) had RSV + non-HRV pathogens, and 110 (6%) had HRV + non-RSV pathogens. We examined the demographic and clinical characteristics according to these five groups (Table 1).

Unadjusted associations between various demographic and clinical characteristics and LOS (<3 days versus ≥3 days) are presented in Table 2. In general, younger children, white children, and those with gestational age <32 weeks were more likely to have longer LOS. Furthermore, clinical factors such as more severe retractions, lower oxygen saturations, apnea, inadequate oral intake, and ICU admission all were associated with longer LOS. Additionally, two other unadjusted multivariate models were generated with ICU and CPAP/intubation as outcomes, but RSV/HRV status did not significantly predict either severity outcome (data not shown).

The multivariable logistic regression model for LOS ≥3 days is shown in Table 3. Controlling for 15 demographic and clinical characteristics as well as site, significant independent predictors for longer LOS were: age <2 months, gestational age <32 weeks, having retractions, oxygen saturation <90%, ICU admission, and viral etiology. Compared to children with RSV alone, children with an HRV alone or HRV + any other non-RSV pathogen were less likely to have longer LOS (both $P<0.001$), whereas children with RSV + HRV infections were more likely to have a LOS ≥3 days ($P=0.04$). Even after restricting the analysis to the most common subset of children with bronchiolitis, those age<12 months and gestational age ≥37 weeks, the results remain robust.

The zero-truncated negative binomial model, which examines LOS as a continuous outcome, showed similar results for the demographic and clinical factors presented in Table 3 with LOS as a dichotomous outcome (data not shown). This model also supported the virus findings. Compared to RSV alone, the IRR for LOS was lower for children with HRV alone (IRR, 0.73; 95% CI, 0.54–0.98; $P=0.04$) and higher for children with RSV + HRV (IRR, 1.18; 95% CI, 1.02–1.36; $P=0.03$).

Comment

In this large, multicenter, multiyear prospective study of children hospitalized with bronchiolitis, we found that 30% of children had multiple pathogen infections. The two most common viral etiologies were RSV (72%) and HRV (26%) and children with these viruses had different short-term outcomes. In comparison to children with RSV only infections, multivariable models demonstrated that children infected with HRV alone or in combination with non-RSV viruses had a significantly shorter LOS while children with RSV/HRV co-infections had a significantly longer LOS even after adjusting for clinical and demographic factors associated with severity of illness. Therefore, based on this large sample from across the US, we submit that inpatient cohorting practices may not be as effective as once believed, that researchers consider testing for HRV more routinely in bronchiolitis studies, and that clinicians and researchers reconsider conventional wisdom that the infectious etiology of severe bronchiolitis does not affect short-term outcomes.

Although several studies have found that HRV lower respiratory tract infection in early childhood is associated with later wheezing [12, 18, 19] and asthma, [13, 14, 18] the short-term outcomes are less clear. Indeed, recent studies have shown that the clinical severity of HRV bronchiolitis is less than, [5] no different than, [4] and greater than [20] bronchiolitis due to RSV. Specifically, Marguet and colleagues performed a 4-center prospective study in France of 209 infants age <1 year with their first bronchiolitis hospitalization. [5] In a multivariable analysis, they found that the 15 children with HRV only infections had a reduced odds of staying in the hospital ≥5 days (OR 0.13; 95%CI, 0.03–0.57) compared to those children with RSV alone. However, a single-center study in Spain of 318 children age <2 years with severe bronchiolitis found no difference in LOS for the 24 children with HRV alone compared to RSV alone. [4] Another single-center prospective study in Greece of 118 children age <18 months with severe bronchiolitis found that the presence of HRV (i.e. alone or co-infection) increased the odds of having a clinical severity score higher than the median (adjusted OR 4.9; 95%CI, 1.2–18.7). [20] In the present multicenter study, we found that on average the 167 children with HRV only infections had shorter LOS than children with RSV only infections even after controlling for 15 factors associated with severity of illness. [21, 22]

It may seem intuitive that children infected with more than one virus should have a more severe clinical course than children infected by only one virus, but the data on multiple pathogen infections are unclear. [23–26] Interestingly, we found that HRV in combination with viruses other than RSV had shorter LOS. However, when HRV was paired with RSV, children with this specific co-infection had longer LOS than RSV alone. There are few data with which to compare our results, but Marguet and colleagues found that the 30 children with RSV/HRV co-infections had a reduced odds of staying in the hospital ≥5 days (OR=0.26; 95%CI, 0.09–0.76) compared to those children with RSV alone. [5] A different and more acute measure of severity of illness is ICU admission or CPAP/intubation. Although Papadopoulos and colleagues found that HRV increased an admission clinical severity score among 118 children with bronchiolitis, [20] we did not find that the infectious etiology increased the odds of admission to the ICU or use of CPAP/intubation. Therefore, based on our data children with RSV/HRV co-infections have a protracted severe illness, but not necessarily a higher intensity of illness as represented by the intensive care outcomes.

Although the pathophysiology of the interactions between RSV and HRV are beyond the scope of this analysis, it is interesting that without RSV as a cofactor, the clinical course of HRV parallels its more common, less severe, outpatient clinical course. [18, 27] There are at least two plausible theories for the increased severity of illness of RSV/HRV co-infections. One possibility is that a diminished interferon-γ response associated with RSV may allow for enhanced HRV replication; [28, 29] a similar pathogenesis occurs in airway epithelial cells

from people with asthma. [30, 31] Another possibility is that RSV-infected endothelial cells increase the cell surface expression of intercellular adhesion molecule-1 (ICAM-1), [32] the major receptor for HRV, [33, 34] setting the stage for a more severe HRV infection. [35]

Of direct relevance to all hospitals that have two or more beds per hospital room, are the infection control issues raised by these data. The current point-of-care virology tests used to develop care plans for children with lower respiratory tract infections are influenza and RSV. If hospitals cohort children with bronchiolitis, they do so by RSV status. However, given that one of three children with RSV and almost one of four without RSV will have a co-infection, the effectiveness of these cohorting practices is questionable, especially given that some of the co-infecting pathogens require droplet precautions and not just contact precautions. Some have suggested routinely using PCR to test for multiple respiratory viruses in critically ill children with lower respiratory infections, [36] but the expense of using molecular testing for all children with severe bronchiolitis may not outweigh the potential benefits for the family and clinicians. Although one possibility would be to limit the testing to RSV and HRV, the benefits of having a more complete picture of the infecting viruses, providing guidance about the potential severity of illness, possibly reducing antibiotic prescriptions, [37] and following the HRV positive children closely for the development of asthma, [12–14] most likely do not outweigh the expense of the molecular testing for HRV.

Testing for HRV in a clinical setting may not be practical currently, but we suggest that HRV testing become more common in bronchiolitis research. To date, no one has rigorously or effectively defined sub-groups of children with severe bronchiolitis who may respond differently to medications and/or have different clinical outcomes. Our results suggest that categorization by infectious pathogen (i.e. RSV and HRV) may be necessary to most accurately interpret the findings of randomized trials and other bronchiolitis research, especially when using LOS as an outcome. [38, 39] Trials that combine all children with clinical bronchiolitis into one group, or that categorize children by RSV status alone, may obfuscate real associations. Therefore, bronchiolitis investigators may be missing clinically meaningful results by not including HRV status in their analyses. [19]

The present study has potential limitations. PCR detects low amounts of virus in children and HRV in particular is detected in up to 24% of children age <1 year without fever or other respiratory symptoms. [40–43] Therefore, it is conceivable that the HRV we detected is a “bystander” virus [44] and these HRV infections are asymptomatic. [40–43] Alternatively, we may be detecting a recent infection from which the children were recovering and not the causative agent related to the hospitalization. Although it remains possible that some of the children with HRV were asymptomatic or in recovery, on the whole, these data suggest that in children with severe bronchiolitis, HRV plays a central role in the clinical course and is not asymptomatic. Another issue is that the study participants were hospitalized in academic medical centers. Consequently, these results are not necessarily generalizable to community medical centers or outpatients with bronchiolitis. Furthermore, bronchiolitis is a clinical diagnosis [8] without a common international definition. [8, 45] It is therefore possible that we included other respiratory disorders in this sample of children. However, when the data were restricted to resemble classic bronchiolitis, the results remained robust. Although the site teams enrolled 56% of children and there were statistical differences in racial and ethic groups, we do not think the level of enrollment or the statistical differences are clinically relevant or have provided biased results in this large, multicenter study.

In summary, on the basis of these prospective, multicenter, multiyear data, we found that 1 in 3 children with severe bronchiolitis have multiple virus infections and identified pathogen-based sub-groups of children with different hospital LOS. Accordingly, we believe that these data raise questions about the effectiveness of RSV-based hospital cohorting

practices.. Moreover, severe bronchiolitis medication trials and other related research probably would benefit from inclusion of viral testing for both RSV and HRV so that lingering questions about differential effects by virus do not remain after the completion of otherwise rigorous trials. Most importantly, our data challenge current thinking that the infectious etiology of severe bronchiolitis does not affect short-term outcomes.

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Appendix A

Collaborators in the MARC-30 Study:

Acquisition of data and *review of the manuscript:* All below

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Brian Pate, MD	Children's Mercy Hospital
Mark Riederer, MD and Paul Hain, MD	Children's Hospital at Vanderbilt
M Jason Sanders, MD	Children's Memorial Hermann Hospital
Alan Schroeder, MD	Santa Clara Valley Medical Center
Nikhil Shah, MD and Dorothy Damore, MD	New York Presbyterian Hospital - Cornell
Michelle Stevenson, MD	Kosair Children's Hospital
Erin Stucky, MD	Rady Children's Hospital
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Table 1

Demographic characteristics, medical history, and clinical course of children with severe bronchiolitis by respiratory syncytial virus and human rhinovirus infection status

Characteristics	RSV only infection (n=1,075), %	HRV only infection (n=167), %	RSV + HRV (n=287), %	RSV + non- HRV (n=227), %	HRV + non- RSV (n=110), %	P-value
Age in months						<0.001
<1 month	19	6	8	5	2	
1–1.9	19	13	18	11	7	
2–3.9	23	18	26	18	14	
4–5.9	12	10	18	17	11	
6–11.9	16	31	22	30	41	
≥12	11	22	7	19	25	
Female	42	34	40	40	35	0.20
Race						0.03
White	64	63	60	60	50	
Black	21	27	27	28	33	
Other or missing	15	10	13	12	17	
Hispanic	36	31	37	32	39	0.39
Family history of asthma						0.64
Neither parent	68	64	65	66	66	
Either Mother or Father	27	32	28	28	27	
Both Parents	4	3	4	4	4	
Don’t know/missing	1	1	3	3	3	
Maternal smoking during pregnancy	13	22	19	19	10	0.001
Gestational age, weeks						<0.001
<32	4	12	6	4	11	
32–36	16	22	18	16	25	
≥37 or ‘full term’	80	66	76	80	64	
History of eczema						0.004
No	86	76	83	81	76	

Arch Pediatr Adolesc Med. Author manuscript; available in PMC 2013 August 01.

Characteristics	RSV only infection (n=1,075), %	HRV only infection (n=167), %	RSV + HRV (n=287), %	RSV + non- HRV (n=227), %	HRV + non- RSV (n=110), %	P-value
Yes	13	24	15	17	21	
Missing	1	0	2	2	3	
History of intubation	7	16	8	7	18	<0.001
Major, relevant comorbid medical disorder	15	32	18	26	31	<0.001
Presence of apnea (chart)	8	5	8	5	10	0.38
Respiratory rate per minute, median (IQR)	48 (10–60)	48 (38–57)	50 (40–60)	45 (38–60)	48 (40–60)	0.16
Retractions						0.06
None	24	24	14	18	22	
Mild	42	37	43	42	38	
Moderate or severe	28	32	35	33	34	
Missing	7	8	8	6	6	
Oxygen saturation by pulse ox or ABG						0.63
<90	10	13	11	10	16	
90–93.9	17	14	17	17	13	
≥94	72	72	71	73	71	
Oral intake						0.01
Adequate	43	53	38	41	47	
Inadequate	44	33	49	43	34	
Missing	13	14	14	17	19	
ICU	17	16	18	17	18	0.98
Intubation and/or CPAP during admission	8	5	10	5	6	0.23
Length-of-stay ≥3 days	48	28	54	47	27	<0.001

Abbreviations: RSV indicates respiratory syncytial virus; HRV, human rhinovirus; IQR, interquartile range; ABG, arterial blood gas; ICU, intensive care unit; CPAP, continuous positive airway pressure.

Table 2

Demographic characteristics, medical history, and clinical course of children with severe bronchiolitis associated with respiratory syncytial and/or human rhinovirus by hospital length-of-stay

Characteristics	LOS <3 days, (n=1,018)	LOS ≥3 days, (n=848)	P-value
	column %		
Age in months			<0.001
<1 month	9%	18%	
1–1.9	15%	19%	
2–3.9	22%	21%	
4–5.9	13.5%	13.3%	
6–11.9	24%	18%	
≥12	15%	11%	
Female	39%	42%	0.13
Race			0.01
White	60%	64%	
Black	27%	21%	
Other or missing	13%	15%	
Hispanic	35%	37%	0.32
Family history of asthma			0.41
Neither parent	66%	68%	
Either Mother or Father	28%	27%	
Both Parents	4%	3%	
Don’t know/missing	1.7%	1.9%	
Maternal smoking during pregnancy	14%	16%	0.19
Gestational age, weeks			0.01
<32	4%	7%	
32–36	16%	19%	
≥37 or ‘full term’	80%	74%	
History of eczema			0.34
No	82%	85%	
Yes	17%	14%	
Missing	1.4%	1.2%	
History of intubation	8%	9%	0.52
Major, relevant comorbid medical disorder	19%	20%	0.57
Presence of apnea (chart)	5%	10%	<0.001
Respiratory rate per minute, median (IQR)	48 (40–60)	48 (40–60)	0.003
Retractions			<0.001
None	25%	17%	
Mild	43%	40%	
moderate or severe	25%	36%	

Characteristics	LOS <3 days, (n=1,018)	LOS ≥3 days, (n=848)	P-value
Missing	6%	8%	
Oxygen saturation by pulse ox or ABG			<0.001
<90	7%	17%	
90–93.9	16%	18%	
≥94	77%	65%	
Oral intake			<0.001
Adequate	50%	35%	
Inadequate	37%	50%	
Missing	13%	15%	
ICU	6%	30%	<0.001
Intubation and/or CPAP during admission	0.3%	15%	<0.001
RSV/HRV status			<0.001
RSV only infection	55%	60%	
HRV only infection	12%	5%	
RSV + HRV	13%	18%	
RSV + any other non-HRV pathogen	12%	13%	
HRV + any other non-RSV pathogen	8%	4%	

Abbreviations: IQR indicates interquartile range; ABG, arterial blood gas; ICU, intensive care unit; CPAP, continuous positive airway pressure; RSV, respiratory syncytial virus; HRV, human rhinovirus.

Table 3

Multivariable predictors of hospital length-of-stay ≥3 days among children with severe bronchiolitis associated with respiratory syncytial and/or human rhinovirus (n=1,866)

Characteristics	Odds Ratio (95%CI)	P-value
Age in months		
<1 month	2.57 (1.73–3.82)	<0.001
1–1.9	1.75 (1.14–2.69)	0.01
2–3.9	1.21 (0.89–1.66)	0.22
4–5.9	1.37 (0.94–2.00)	0.11
6–11.9	0.99 (0.69–1.43)	0.95
≥12	1.00 (reference)	
Female	1.12 (0.91–1.37)	0.30
Race		
White	1.00 (reference)	
Black	0.79 (0.62–1.01)	0.06
Other or missing	1.07 (0.75–1.53)	0.70
Maternal smoking during pregnancy	1.15 (0.86–1.55)	0.35
Gestational age, weeks		
<32	2.57 (1.44–4.57)	0.001
32–36	1.26 (0.94–1.68)	0.12
≥37 or ‘full term’	1.00 (reference)	
History of eczema		
No	1.00 (reference)	
Yes	1.15 (0.83–1.59)	0.41
Missing	0.59 (0.26–1.33)	0.20
History of intubation	0.95 (0.71–1.28)	0.75
Major, relevant comorbid medical disorder	1.14 (0.86–1.49)	0.36
Presence of apnea (chart)	1.14 (0.77–1.71)	0.51
Respiratory rate per minute	1.00 (0.99–1.01)	0.95
Retractions		
None	1.00 (reference)	
Mild	1.62 (1.23–2.12)	0.001
Moderate or severe	2.05 (1.45–2.91)	<0.001
Missing	1.64 (0.94–2.86)	0.08
Oxygen saturation by pulse ox or ABG		
<90	2.06 (1.45–2.93)	<0.001
90–93.9	1.26 (0.98–1.62)	0.07
≥94	1.00 (reference)	
Oral intake		
Adequate	1.00 (reference)	

Characteristics	Odds Ratio (95%CI)	P-value
Inadequate	1.31 (0.93–1.84)	0.12
Missing	1.19 (0.81–1.72)	0.37
ICU	5.33 (3.01–9.44)	<0.001
RSV/HRV status		
RSV only infection	1.00 (reference)	
HRV only infection	0.36 (0.20–0.63)	<0.001
RSV + HRV	1.33 (1.02–1.73)	0.04
RSV + any other non-HRV pathogen	1.06 (0.67–1.69)	0.79
HRV + any other non-RSV pathogen	0.39 (0.23–0.66)	<0.001

Abbreviations: IQR indicates interquartile range; ABG, arterial blood gas; ICU, intensive care unit; RSV, respiratory syncytial virus; HRV, human rhinovirus.