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Clinical Profiles of Respiratory Syncytial Virus Subtypes A and B among Children Hospitalized with Bronchiolitis

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Abstract

In this analysis of a prospective, multicenter study of children hospitalized with bronchiolitis, 925 had RSV-A and 649 had RSV-B. Overall, bronchiolitis severity did not differ by RSV subtype. However, among children with RSV-only bronchiolitis, those children with RSV-A had higher risk of intensive care treatment (OR, 1.31; 95% CI, 1.00-1.71; $P=0.048$) when compared with those having RSV-B.

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Keywords

RSV; subtype; bronchiolitis; severity

Introduction

Bronchiolitis is the leading cause of hospitalization in young children, and occurs commonly during the winter months due to respiratory viral infections¹. Of the multiple viral etiologies, the most frequent is respiratory syncytial virus (RSV). Two antigenically different RSV subtypes exist, A and B. These two subtypes co-circulate during the same season, but in general, one predominates². Although some studies have shown that RSV-A is associated with an increased disease severity²⁻⁴, others have shown that either RSV-B is more severe⁵ or that the two subtypes have equivalent severity^{6, 7}. Most of these studies included one winter season or had small sample sizes, and in general used non-polymerase chain reaction (PCR) diagnostics which in most may have omitted the confounding effects of viral coinfections or led to ascertainment bias. Therefore, our objective was to determine whether RSV subtype is independently associated with increased disease severity in a multicenter, multiyear sample of children hospitalized for bronchiolitis that utilized PCR diagnostics.

Methods

Study Design

This is a secondary analysis of the 30th Multicenter Airway Research Collaboration (MARC-30) prospective cohort study of children hospitalized with bronchiolitis. Study design and data collection methods have been previously described⁸. Briefly, during three winter seasons (November-March) from 2007 through 2010, up to 16 sites across 12 states enrolled children who were hospitalized with bronchiolitis, were age <2 years, and for whom the parent/guardian provided informed consent. Children were identified by daily census review and enrolled using a standardized protocol and treated at the discretion of the attending physician. The institutional review board at all 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. Medical records were reviewed to obtain clinical data from the pre-admission evaluation and the child's inpatient course. Nasopharyngeal aspirates (NPAs) were collected using a standardized protocol and tested by PCR assays. Singleplex or duplex two-step real time PCR (rtPCR) were used to detect 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, *M. pneumoniae*, and *B. pertussis*⁸.

Statistical Analyses

To compare demographic and clinical characteristics between the RSV subtypes, we performed unadjusted analyses using chi-square, Fisher's exact test, and Kruskal-Wallis test, as appropriate. Data are presented as proportions with 95% confidence intervals (95% CIs) and medians with interquartile ranges (IQR). We used multivariable logistic regression analyses to examine the independent association between RSV subtype and bronchiolitis severity outcomes. The primary outcome measure was hospital length-of-stay (LOS) ≥ 3 days (i.e., an LOS greater than the cohort's median value of 2 days)⁸. The secondary outcome measure was the need for intensive care treatment, defined as admission to the intensive care unit (ICU) and/or the use of mechanical ventilation (continuous positive airway pressure [CPAP] and/or intubation use) during the inpatient stay. During the study period, one site routinely provided CPAP outside of the ICU setting. The models adjusted for 11 patient characteristics (age, sex, race, ethnicity, maternal smoking during pregnancy, premature birth, history of wheeze, history of eczema, comorbid medical disorder, duration of difficulty breathing prior to preadmission, any coinfections) and patient clustering by site. In the sensitivity analysis models, we isolated RSV-A and B infections by excluding patients with RSV plus any other coinfections. Results were reported as odds ratios (ORs) with 95% CIs. All *P*-values were two-tailed, with *P* < 0.05 considered statistically significant. All analyses were performed using Stata 13.1 (Stata Corp, College Station, TX).

Results

Among 2,207 children hospitalized with bronchiolitis, 1,589 (72%) tested positive for RSV. Of these, 925 (58%) had RSV-A, 649 (41%) had RSV-B, and 15 (0.9%) had both RSV-A and RSV-B. To discretely compare RSV subtypes, we limited this analysis to the 1,574 children with either RSV-A or RSV-B and excluded the 15 children infected with both subtypes.

The median age was 3.4 months (IQR, 1.5-7.2 months); 58% were male and 63% were white. When compared to those with RSV-B, children hospitalized with RSV-A bronchiolitis were more likely to be exposed in utero to tobacco (17% vs 12%, *P* = 0.01) and to have pulse oximetry level < 94% on admission (30% vs. 25%, *P* = 0.04). Detailed demographic characteristics and clinical course of the study population is included as Supplementary Digital Content, Table S1. The RSV-B subtype predominated in the 2008-2009 season (*P* < 0.001), and also consistently in all seasons during the month of January (32% vs. 26%) (Supplementary Digital Content, Figure S1).

Overall, there was no significant association of RSV subtypes with severity outcomes – i.e., LOS ≥ 3 days (adjusted OR, 0.92; 95% CI, 0.74-1.14; *P* = 0.45) and intensive care treatment (adjusted OR, 1.03; 95% CI, 0.85-1.24; *P* = 0.80). By contrast, in a sensitivity analysis restricted to RSV-only infections (i.e., children infected only with RSV-A or RSV-B and no other viruses), children with RSV-A infection had an increased odds of receiving intensive care treatment (adjusted OR, 1.31; 95% CI 1.00-1.71, *P* = 0.048) when compared to those with RSV-B (Table).

Discussion

In this multicenter, multiyear, prospective study of children hospitalized for bronchiolitis, we found that the severity of illness by RSV subtypes were similar. However, among children with RSV-only infections (i.e., no coinfecting viruses) we found that children with RSV-A were more likely to require intensive care treatment compared with children with RSV-B, even after controlling for 11 other patient characteristics.

Previous studies on RSV bronchiolitis in children have reported inconsistent associations of RSV subtype with severity of illness. In studying 81 hospitalized infants with bronchiolitis, Fodha et al showed no independent association between RSV subtype (determined by PCR) and increased disease severity⁷. On the contrary, Papadopoulos et al observed a small but statistically significant difference of increased disease severity caused by RSV-A, as determined by a composite clinical score index⁴. However, 41% of the specimens could not be subtyped by rtPCR, and the study was limited to a single winter season. Walsh et al also demonstrated an increased severity index by RSV-A infection in a 3-year prospective study of 265 infants with RSV infection (51% had RSV-A). The increased severity index was driven by differences in hypercarbia, apnea and need for mechanical ventilation². In contrast, our study did not detect significant differences in apnea or need for mechanical ventilation, but for ICU admission, one of the measures of disease severity (Table). We did not include arterial CO₂ in the analysis since it was rarely performed outside of the ICU setting or without the use of some form of advanced respiratory support. Multivariable analysis limited to those patients with sole RSV infection (i.e., no coinfections) showed that children with RSV-A infection had 1.31 higher odds of requiring intensive care treatment, although LOS ≥ 3 days was not different between the subtypes. This is noteworthy, since RSV subtypes were not identified at the participating hospitals during the study period and therefore, the RSV subtype would not have influenced the clinical decision to admit a child to the ICU and/or to provide mechanical ventilation. One way to reconcile the discrepant findings of the aforementioned studies is by recognizing that the outcomes of RSV subtype-specific bronchiolitis can be affected by the presence of viral coinfections; and that by analyzing RSV-only infections, the true biological effect can be ascertained. In this sense, our results would suggest that the peak severity of illness may be higher with RSV-A, without affecting the length of stay.

Major strengths of this study include the prospective and standardized data collection, the large sample size (n=1,574), and the case ascertainment method by rtPCR. Attending physicians were blinded to the virus subtype, as testing took place after each study season. Lastly, we believe the results should be generalizable to other geographic areas beyond the U.S. with similar therapeutic approach to severe bronchiolitis.

The study has several potential limitations. First, only hospitalized children were enrolled in this study, so results may not be generalizable to outpatients. However, our inferences are of direct relevance to hundreds of thousands of children with severe bronchiolitis every year. Second, we did not examine the association between viral genomic load and disease severity, or the variability in the genetic composition of circulating strains which may have conferred increased viral pathogenicity if subjects had no preexisting antibodies. Finally, we

did not use standard criteria for hospital discharge or intensive care use; therefore, institutional variability in care is possible. However, the significant associations persisted after accounting for clustering at the hospital level.

Conclusions

This large, prospective, multicenter, multiyear U.S. study of hospitalized children with bronchiolitis showed no difference in clinical severity between children with RSV-A and RSV-B. However, when we restricted the analysis to children with RSV-only infections, by excluding coinfections, we found that RSV-A had a modest, yet significant association with higher severity of illness. Subtype B was the prevalent circulating type during January for the three consecutive winter seasons. These findings suggest that preventive interventions (active or passive immunoprophylaxis) and antiviral therapies will be more beneficial for children if they are equally effective against both RSV subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

Principal Investigators at the 16 participating sites in MARC-30

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John Cheng, MD and Carlos Delgado, MD	Children's Healthcare of Atlanta at Egleston, Atlanta, GA
Dorothy Damore, MD and Nikhil Shah, MD	New York Presbyterian Hospital, New York, NY
Haitham Haddad, MD	Rainbow Babies & Children's Hospital, Cleveland, OH
Paul Hain, MD and Mark Riederer, MD	Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN
Frank LoVecchio, DO	Maricopa Medical Center, Phoenix, AZ
Charles Macias, MD, MPH	Texas Children's Hospital, Houston, TX
Jonathan Mansbach, MD, MPH	Boston Children's Hospital, Boston, MA
Eugene Mowad, MD	Akron Children's Hospital, Akron, OH
Brian Pate, MD	Children's Mercy Hospital & Clinics, Kansas City, MO
M. Jason Sanders, MD	Children's Memorial Hermann Hospital, Houston, TX
Alan Schroeder, MD	Santa Clara Valley Medical Center, San Jose, CA
Michelle Stevenson, MD, MS	Kosair Children's Hospital, Louisville, KY
Erin Stucky Fisher, MD	Rady Children's Hospital, San Diego, CA
Stephen Teach, MD, MPH	Children's National Medical Center, Washington, DC
Lisa Zaoutis, MD	Children's Hospital of Philadelphia, Philadelphia, PA

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Table
Multivariable Models Evaluating the Association between RSV Subtype and Bronchiolitis Severity Outcomes

		RSV-A vs. RSV-B(reference)					
		All subjects (n=1,574)			Restricted to sole RSV infection(n=1,075)		
Model outcomes [†]		OR	95%CI	P value	OR	95%CI	P value
Hospital length of stay		0.92	0.74-1.14	0.45	0.97	0.78-1.21	0.80
Intensive care treatment		1.03	0.85-1.24	0.80	1.31	1.00-1.71	0.048
•	ICU admission	1.03	0.85-1.24	0.78	1.37	1.02-1.84	0.03
•	Intubation and/or CPAP during admission [‡]	1.07	0.78-1.46	0.68	1.42	0.88-2.30	0.15

Abbreviations: RSV, respiratory syncytial virus; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; CPAP, continuous positive airway pressure.

[†]Models adjusted for: age, sex, race, ethnicity, maternal smoking during pregnancy, premature birth, history of wheeze, history of eczema, comorbid medical disorder, duration of difficulty breathing prior to preadmission, any comorbidities, and patient clustering by site.

[‡]Only one center routinely provided assisted ventilation (CPAP) outside of the ICU setting.