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Multicenter Study of Viral Etiology and Relapse in Hospitalized Children with Bronchiolitis

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Abstract

Background—It is unclear whether the infectious etiology of severe bronchiolitis affects short-term outcomes, such as post-hospitalization relapse. We tested the hypothesis that children hospitalized with rhinovirus (RV) bronchiolitis, either as a sole pathogen or in combination with respiratory syncytial virus (RSV), are at increased risk of relapse.

Methods—We performed a 16-center, prospective cohort study of hospitalized children age <2 years with bronchiolitis. During the winters of 2007 to 2010, researchers collected clinical data and nasopharyngeal aspirates from study participants; the aspirates were tested using real-time polymerase chain reaction. The primary outcome was bronchiolitis relapse (urgent bronchiolitis visit or scheduled visit at which additions to the bronchiolitis medications were made) during the 2 weeks after hospital discharge.

Results—Among 1836 enrolled children with 2-week follow-up data, the median age was 4 months and 60% were male. Overall, 48% had sole RSV infection, 8% had sole RV infection, and 13% had RSV/RV co-infection. Compared with children with sole RSV infection, and adjusting for 10 demographic and clinical characteristics and clustering of patients within hospitals, children

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with sole RV infection did not differ in their likelihood of relapse (OR, 0.99; 95%CI, 0.52–1.90; $P=0.98$), whereas those with RSV/RV co-infection were more likely to have relapse (OR, 1.54; 95%CI, 1.03–2.30; $P=0.03$).

Conclusions—In this prospective, multicenter, multiyear study of children hospitalized with bronchiolitis, we found that RSV/RV co-infection was independently associated with a higher likelihood of bronchiolitis relapse. Present data support the concept that the infectious etiology of severe bronchiolitis affects short-term outcomes.

Keywords

Bronchiolitis; virology; relapse; respiratory syncytial virus; rhinovirus

INTRODUCTION

Bronchiolitis is the leading cause of hospitalization for US infants, accounting for 18% of all infant hospitalizations.^{1,2} Although most children with bronchiolitis recover with few complications after either emergency department or hospital discharge, some children experience a clinical “relapse” leading to unscheduled return visits and readmissions.^{3–5} Despite its obvious clinical importance, sparse evidence exists to predict which of the children discharged home from the hospital may develop bronchiolitis relapse and require further healthcare utilization.

It has long been the conventional wisdom that the infectious etiology of severe bronchiolitis does not affect outcomes. However, the recent advent of molecular diagnostic techniques demonstrated that a diverse group of infectious pathogens is associated with severe bronchiolitis (i.e., bronchiolitis requiring hospitalization) and that the specific viral etiology may affect outcomes.^{6–10} Although respiratory syncytial virus (RSV) is the most common pathogen associated with bronchiolitis,^{6,11,12} a growing number of studies reported that rhinovirus (RV) bronchiolitis have a strong association with development of recurrent wheezing and asthma in children.^{13–18} Furthermore, a recent study showed that children with RSV/RV co-infections had a significantly longer bronchiolitis hospital length of stay, compared to children with RSV infection alone.⁶ Despite its potential clinical relevance, the relationship between RV bronchiolitis (either as a sole pathogen or in combination with RSV) and bronchiolitis relapse has not been studied.

In this context, we therefore sought to further elucidate the impact of viral etiology on the risk of bronchiolitis relapse. We hypothesized that children hospitalized with RV bronchiolitis – either as a sole pathogen or in combination with RSV – are at a higher risk of developing relapse following the hospital discharge, compared to children with RSV infection only.

MATERIALS AND METHODS

Study Design

We conducted a multicenter, prospective cohort study during the 2007 to 2010 winter seasons for 3 consecutive years, as part of the Multicenter Airway Research Collaboration

(MARC), a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org).^{6,19,20} 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 enrolled a target number of consecutive patients from the inpatient wards and the intensive care unit (ICU). We aimed to enroll 20% of the total sample from the ICU; to achieve this over sampling from the ICU, the ward and ICU enrollments were monitored separately. If the site reached their target enrollment for that month (for both ward patients and ICU patients), the site stopped all enrollment until the start of the next 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. Patients were enrolled within 18 hours of admission. The exclusion criteria were previous enrollment or transfer to a participating hospital >48 hours after the original admission time. 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. Relevant comorbid medical disorders included respiratory, cardiac, neurologic, gastrointestinal, and immunologic diseases. Medical records were reviewed to obtain clinical data from the pre-admission evaluation (clinic or emergency department) and the child's inpatient course, including vital signs, medical management, and disposition. The follow-up data, including unscheduled visit, follow-up visit, and readmission, were collected by telephone interview 2 weeks after the hospital discharge. Data were manually reviewed at the EMNet Coordinating Center and site investigators were queried about missing data and discrepancies identified.

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 98% of 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 to the central laboratory at Baylor College of Medicine, where they were stored at -80°C .

Polymerase Chain Reaction (PCR) assay

All PCR assays were conducted as singleplex or duplex two-step real time PCR. Real time reverse transcriptase-PCR was used for the detection of RNA respiratory viruses which included RSV types A and B, RV, 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, and enterovirus. Real time PCR was used for the detection of DNA pathogens

which included adenovirus, *M. pneumoniae*, and *B. pertussis*. Details of the primers and probes have been described elsewhere.^{21–23} All real time PCR assays were tested in duplicate and samples with incongruent values (one well positive) were retested. To reduce carryover contamination, sample preparation, RNA/DNA extraction, cDNA and amplification were performed in separate areas. All PCR runs had extraction and reagent positive and negative controls.

Outcome Measure

The primary outcome was bronchiolitis relapse, defined as either (1) an urgent (unscheduled) bronchiolitis visit, or (2) a routine check-up, follow-up visit or visit for another health problem at which additions to the child's bronchiolitis medications were made (e.g., adding a bronchodilator or corticosteroid) during the 2 weeks after hospital discharge. The reproducibility of this relapse outcome has been validated previously.⁴

Statistical Analyses

Our primary analyses focused on RSV and RV, the most commonly detected viruses in children with severe bronchiolitis.⁶ For the purposes of this analysis, we combined RSV-A with RSV-B as the distinction between these subtypes was clinically unremarkable.⁶ In addition, according to previous literature,⁶ we created a categorical variable that reflected possible combinations of RSV/RV status: RSV only, RV only, RSV in combination with RV, RSV in combination with non-RV pathogens, RV in combination with non-RSV pathogens, and neither RSV nor RV.

To examine potential risk factors for bronchiolitis relapse among patients hospitalized for bronchiolitis, we performed unadjusted analyses using chi-square, Fisher's exact test, and Kruskal Wallis test, as appropriate. Then, we performed multivariable logistic regression to determine the association between RV infection – either as a sole pathogen or in combination with RSV –and bronchiolitis relapse. A set of potential confounders was chosen based on biological plausibility and a priori knowledge. These selected variables included age, sex, primary care provider status, history of prematurity (i.e., gestational age <37 weeks), special care facility use at birth (e.g., ICU and premature nursery), family history of asthma, history of infant wheeze, relevant comorbid medical disorder, inpatient apnea, and hospital length of stay. Additionally, the model was fit by using generalized estimating equations to account for potential clustering of patients within hospitals. Age was dichotomized at 2 months according to the previous literature.⁴ Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

In the first sensitivity analysis, to assess the consistency of association between the viral etiology and the primary outcome, we stratified the multivariable analysis by history of wheezing.⁴ Additionally, we repeated the analysis using a more restrictive definition of bronchiolitis relapse (i.e., only those children with an urgent bronchiolitis visit during the 2 weeks after hospital discharge). All analyses were performed using Stata 11.2 (Stata Corp, College Station, TX). All *P*-values were two-tailed, with *P*<0.05 considered statistically significant.

RESULTS

Of 2207 enrolled children, 1836 (83%) had 2-week follow-up data and were eligible for the current analysis. The analytic cohort and those children without 2-week follow-up were similar in age, sex, hospital length of stay, and viral etiology (all $P>0.05$; data not shown). Among the analytic cohort, the median age was 4 months (IQR, 2–8 months), 60% were male, 63% were white, and 37% were Hispanic. Additionally, 1,171 children (64%) had a single virus infection and 542 (30%) had 2 or more viruses; the remaining 123 (6%) had no pathogen identified from the testing panel. More specifically, 886 children (48%) had RSV only, 144 (8%) had RV only, 233 (13%) had RSV plus RV, 189 (10%) had RSV plus non-RV pathogens, 93 (5%) had RV plus non-RSV pathogens, and 291 (16%) had neither RSV nor RV.

During the 2-week follow-up period, 139 children (8%; 95% CI, 6%–9%) had a bronchiolitis relapse, including 56 children (3%; 95% CI, 2%–4%) with an urgent bronchiolitis visit and 83 children (5%; 95% CI, 4%–6%) with a routine check-up, follow-up visit or visit for another health problem at which additions to a child's bronchiolitis medications were made. The median number of days from hospital discharge to relapse was 3 (IQR, 1–5 days); 55% (95% CI, 46%–64%) of bronchiolitis relapse occurred within 3 days of the hospital discharge.

Unadjusted associations between various demographic and clinical characteristics and relapse are shown in Table S1 (see Supplemental Digital Content 1). Children with family history of asthma, gestational age less than 37 weeks, special care facility use at birth, and comorbid medical disorders were more likely to have a bronchiolitis relapse. By contrast, clinical factors, such as hospital length of stay and viral etiology, were not associated with an increased likelihood of relapse.

The multivariable logistic regression model for bronchiolitis relapse is presented in Table 1. Adjusting for 10 demographic and clinical characteristics, as well as clustering of patients within hospitals, significant independent predictors for a bronchiolitis relapse were family history of asthma, shorter hospital length of stay (<3 days), and viral etiology. Compared to children who had only RSV infection, children with RV infection alone had no significant difference in the chance of relapse (adjusted OR, 0.99; 95% CI, 0.52–1.90; $P=0.98$), whereas those with RSV/RV co-infection were more likely to have relapse (adjusted OR, 1.54; 95% CI, 1.03–2.30; $P=0.03$).

Although statistical power was limited, we performed sensitivity analyses to further examine this novel finding (Table S2, see Supplemental Digital Content 2). For example, in the subset of children without previous wheezing ($n=1425$), of whom 96 experienced relapse, those with RSV/RV co-infection also had a non-significant increased odds of relapse (OR, 1.49; 95% CI, 0.86–2.57, $P=0.15$) compared to those with RSV infection only. Similarly, in the analysis using the more restrictive definition of bronchiolitis relapse ($n=56$ urgent events), children with RSV/RV co-infection also had a non-significant increased odds of relapse (OR, 1.48, 95% CI, 0.77–2.83; $P=0.24$) compared to those with RSV infection only.

DISCUSSION

This large, multicenter, multiyear prospective cohort study of children hospitalized with bronchiolitis demonstrated that 8% of the children had a sole RV infection and 13% had a RSV/RV co-infection. Additionally, we found that 8% had a bronchiolitis relapse during the 2-week follow-up period. In comparison with children with a sole RSV infection, children with a RSV/RV co-infection had a significantly higher likelihood of bronchiolitis relapse, even after adjusting for many clinical factors and hospital length of stay. Taken together with other data from our group⁶ and others,^{7,24} our observations challenge the conventional wisdom that the infectious pathogen of severe bronchiolitis does not affect short-term outcomes.

Despite its obvious clinical importance, few prior studies have examined relapse and readmission after emergency department or hospital discharge in children with bronchiolitis. One single-center retrospective study of 409 children with severe bronchiolitis in the early 2000s found that 4% of children (n=16 cases) had a readmission for bronchiolitis within 30 days of hospital discharge and that clinical parameters have limited value for predicting the outcome.⁵ However, their inferences were potentially limited by type-II error and potential problems with generalizability. In addition, their outcome – readmission – would underestimate our patient-centered outcome: bronchiolitis relapse. By contrast, in our previous emergency department-based study of 722 children with bronchiolitis, we found that 11% of children (n=80 cases) developed a bronchiolitis relapse within 2 weeks after discharge from the emergency department.⁴ Additionally, the present study demonstrated that 8% of children hospitalized with bronchiolitis had a subsequent relapse. Differences in study design, patient population, clinical setting and definition of the outcome – or possible interactions among these factors – may help explain the differences across these studies.

In addition, to our knowledge, this is the first study to examine the impact of viral etiology on the risk of bronchiolitis relapse. Although the literature has linked RV infection to later development of recurrent wheezing of childhood^{16,17} and asthma,^{13–15} short-term outcomes, such as bronchiolitis relapse, are less clear. Furthermore, the clinical significance of multiple pathogen infections remains unclear.^{6,24,25} Indeed, the literature has shown that the clinical severity of RSV/RV bronchiolitis is less than,⁷ no different than,^{10,26} and greater than^{6,24} bronchiolitis caused by RSV alone. For example, a single-center study in Greece of 118 children with severe bronchiolitis found that the viral etiologies were not associated with clinical severity score at hospital admission but children with RSV/RV co-infection were hospitalized later in the course of their diseases.²⁶ Parallel to this Greek study, our previous study showed that children with RSV/RV co-infections had a significantly longer hospital length of stay, compared to those with RSV infection only.⁶ Furthermore, in the present study, we found that children with RSV/RV co-infections had a higher likelihood of relapse than did those with RSV alone. These observations collectively suggest that children with RSV/RV co-infections may not have a higher severity of illness but rather a protracted clinical course.

It may be intuitive for some clinicians that children infected with multiple respiratory virus pathogens should have either a more severe or a protracted clinical course than those with a

single virus infection. Indeed, it has been previously hypothesized that in concomitant respiratory virus infections, adenoviruses or picornavirus could serve as modifying factors functioning additively or synergistically in bronchiolitis.²⁵ However, the potential mechanism for how RSV/RV co-infections influences severity of bronchiolitis is unclear and likely multifactorial. Plausible explanation includes an enhanced RV replication due to impaired interferon- γ response and disrupted airway epithelium associated with RSV infection.^{24,27,28} An alternative mechanism consistent with a protracted clinical course is an increase in the expression of the main RV receptor, intercellular adhesion molecule 1, on RSV-infected epithelium cells, increasing the likelihood of co-infection.^{29–31} All of these mechanisms may promote the emergence of long-term damage to airway structures.

In addition to RSV/RV co-infections, we also found that a shorter hospital length of stay was independently associated with an increased risk of bronchiolitis relapse. This finding may suggest that some children might have been discharged prematurely, thereby resulting in a relapse. In contrast, other studies have not shown an association of hospital length of stay with readmission – a subset of relapse – in other common pediatric illnesses (e.g., asthma).³² Nevertheless, recent studies have reported variability in hospital length of stay for children with bronchiolitis,^{33,34} and thereby highlight ongoing uncertainty about when exactly children are ready for discharge to home. Although identifying predictors of safe discharge is beyond the scope of the present analysis, our finding underscores the need of research that improves the ability of clinicians to identify children who can be discharged safely after bronchiolitis hospitalization.

We acknowledge several potential limitations to the study. First, 17% of children did not have two-week follow-up data and this exclusion is a potential source of bias. However, the analytic cohort and children without follow-up were similar across demographic characteristics, hospital length stay, and viral etiology. This similarity across groups argues against a selection bias. Second, PCR detects low amounts of virus; indeed, RV is detected in up to 24% of infants without respiratory symptoms.³⁵ It is, therefore, possible that the RV we detected was not the causative agent of the child's bronchiolitis. However, our data also demonstrated that 8% of children with severe bronchiolitis had RV as the sole pathogen and that children with the specific type of co-infection – RV in combination with RSV – had a higher chance of relapse. Additionally, the literature reported that RV detection by PCR has been associated with systemic immune responses in young children with wheezing.³⁶ These observations collectively suggest that at least some RV infections play an important role in the clinical course of bronchiolitis. Third, one may surmise that the 2-week duration of follow-up in our study may not have been long enough to identify all of the children who had an acute relapse. However, the literature shows that respiratory illnesses in this age group lasting longer than 2 weeks are likely to be due to new infection with a different viral strain rather than persistent infection from the same strain.³⁷ Thus, our 2-week follow-up time frame should have been long enough for follow-up of the initial illness. Fourth, in this multicenter observational study, we did not employ standard criteria for hospitalization and discharge. Therefore, institutional variability in care is possible. However, this potential variability in care is less likely to be associated with the viral etiology of bronchiolitis – the primary exposure of interest; therefore, this variable is less likely to be a confounding variable. Fifth, bronchiolitis is a clinical diagnosis without a common international

definition.^{38,39} Therefore, it is possible that we included other respiratory illnesses, such as asthma, in this population. However, in the sensitivity analysis limiting to children without previous wheezing, children with RSV/RV co-infection still had an increased odds of relapse, with a limited statistical power. Finally, the study participants were enrolled in academic medical centers; therefore, our inferences may not be generalizable to community medical centers. Furthermore, caution is needed when generalizing the results beyond those with severe bronchiolitis (e.g., to children with bronchiolitis in ambulatory care setting). Nevertheless, our data are of likely relevance to hundreds of thousands of hospitalized children each year.^{2,40}

In conclusion, this prospective, multicenter, multiyear study of children hospitalized with bronchiolitis demonstrated for the first time that RSV/RV co-infections are independently associated with a higher likelihood of bronchiolitis relapse. The present data support the concept that the infectious etiology of severe bronchiolitis affects short-term outcomes. For researchers, a major implication is that randomized trials that combine all children with bronchiolitis into one group or that categorize children by RSV status alone (yes/no) may obscure true associations. Therefore, bronchiolitis research should include viral testing for both RSV and RV, which may in turn yield important insights for the management of bronchiolitis. For clinicians, as RV nosocomial outbreaks have been reported,^{41,42} our inferences challenge the conventional cohorting efforts relying on RSV and influenza virus testing alone; disregard of RV status has the potential to increase the risk of co-infections with RV and thereby contribute to patient morbidity. Furthermore, our findings also suggest a new line of research that may one day improve the ability of clinicians to create more personalized discharge counseling for parents and guardians.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Principal Investigators at the 16 participating sites in MARC-30

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Dorothy Damore, MD	New York Presbyterian Hospital, New York, NY
Michelle Stevenson, MD	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 1

Multivariable Predictors of Bronchiolitis Relapse Two Weeks After Hospital Discharge

Primary Analysis (n=1836 cases)			
	OR	95% CI	P value
Age <2 months	1.08	0.75 – 1.57	0.68
Female	0.71	0.45 – 1.12	0.14
Has primary care provider	0.45	0.19 – 1.05	0.07
Gestational age <37 weeks	1.22	0.78 – 1.90	0.39
Required special care facility at birth (e.g. ICU, premature nursery)	1.56	0.97 – 2.50	0.07
Family history of asthma			
No	1	Reference	–
Mother, father, or both parents	1.54	1.06 – 2.24	0.03
Don't know	1.02	0.27 – 3.90	0.97
History of infant wheeze	1.33	0.92 – 1.92	0.13
Major, relevant, comorbid medical disorder	1.25	0.83 – 1.86	0.29
Presence of apnea (chart)	1.29	0.72 – 2.32	0.40
Length of stay 3 days	0.65	0.47 – 0.90	0.01
Virology			
RSV only	1	Reference	–
RV only	0.99	0.52 – 1.90	0.98
RSV + RV	1.54	1.03 – 2.30	0.03
RSV and/or non-RV pathogen	1.18	0.58 – 2.43	0.65
RV and/or non-RSV pathogen	1.15	0.56 – 2.33	0.71
Neither RSV nor RV*	0.74	0.43 – 1.28	0.28

OR denotes odds ratio; CI, confidence interval; ICU, intensive care unit; RSV, respiratory syncytial virus; RV, rhinovirus.

–, not applicable.

* Included parainfluenza virus types 1, 2, and 3; influenza A, B, and the 2009 novel H1N1; human metapneumovirus; coronaviruses NL-65, HKU1, OC43, and 229E; enterovirus; adenovirus; *M. pneumoniae*; *B. pertussis*; and no pathogens identified from the testing panel.