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Bedside clinical assessment predicts recurrence after hospitalization due to viral lower respiratory tract infection in young children

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Abstract

Infants requiring hospitalization due to a viral lower respiratory tract infection (LRTI) have a high risk of developing recurrent respiratory illnesses in early life and asthma beyond childhood. Notably, all validated clinical scales for viral LRTI have focused on predicting acute severity instead of recurrence. We present a novel clinical approach combining individual risk factors with bedside clinical parameters to predict recurrence after viral LRTI hospitalization in young children. A retrospective longitudinal cohort of young children (3 years) designed to define clinical predictive factors of recurrent respiratory illnesses within 12 months after hospitalization due to PCR-confirmed viral LRTI. Data collection was through electronic medical record. We included 138 children hospitalized with viral LRTI. Using automatic stepwise logistic model selection, we found that the strongest predictors of recurrence in infants hospitalized for the first time were severe prematurity (32 weeks' gestational age, OR=5.19; 95% CI 1.76 to 15.32; p=0.002) and a clinical score that weighted hypoxemia, subcostal retractions and wheezing (OR=3.33; 95% CI 1.59 to 6.98; p<0.001). After the first hospitalization, the strongest predictors of subsequent episodes were wheezing (OR=5.62; 95% CI 1.03 to 30.62; p=0.04) and family history of asthma (OR=5.39; 95% CI 1.04 to 27.96; p=0.04). We found that integrating individual risk factors (eg, prematurity or family history of asthma) with bedside clinical assessment (eg,

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wheezing, subcostal retractions or hypoxemia) can predict the risk of recurrence after viral LRTI hospitalization in infants. This strategy may enable clinically oriented subsetting of infants with viral LRTI based on individual predictors for recurrent respiratory illnesses during early life.

INTRODUCTION

Lower respiratory tract infections (LRTIs) caused by viruses such as respiratory syncytial virus (RSV) and rhinovirus (RV) are the top causes for recurrent respiratory illnesses in children during the first 3 years of life and are the leading cause of hospitalization for infants beyond the neonatal period.^{1–7} Although in general acute viral LRTI is a self-limited condition that can be managed conservatively at home without significant medical care, a non-negligible proportion of children often require hospitalization for observation and supportive therapy.⁸ Among infants requiring hospitalization due to viral LRTI, approximately 30%–50% will have recurrent respiratory illnesses and subsequently a much higher risk of asthma beyond childhood.^{9–11} Thus, it is critically important to define the clinical parameters that identify the subset of infants with high risk of recurrence after viral LRTI hospitalization.

The standardized clinical assessment of viral LRTI has largely focused on predicting severity instead of recurrence after hospitalization. In a recent systematic review of the instruments available to assess viral LRTI in infants (often termed viral bronchiolitis),¹² we found that all the validated clinical scales have been developed using parameters of respiratory distress correlated with markers of acute severity such as length of stay (LOS) or escalation of care (eg, critical care unit and mechanical ventilation). For that purpose, non-respiratory parameters are often combined with respiratory parameters to quantify overall effort (eg, heart rate (HR) added to wheezing and retractions). However, these severity scales are not well suited to subclassify viral LRTI according to longitudinal outcomes (eg, recurrence) because they do not take into account the heterogeneity of the pathogenesis and clinical presentation of this condition in infants. In young children, viral LRTI sometimes lead primarily to airway hyper-reactivity (wheezing) and air-trapping causing diaphragm flattening (subcostal retractions),^{113–15} while in other instances, it may manifest mostly as tachypnea and hypoxemia due to parenchymal compromise of alveolar gas-exchange units.^{113–15} Delineating these different pathogenic processes is critically important because it may predict prognosis and individual response to therapies.

The primary objective of this study was to test the hypothesis that a model that combines individual risk factors with clinical respiratory parameters can predict recurrent respiratory illnesses within 12 months after hospitalization due to PCR-confirmed viral LRTI in young children (< 3 years). The impact of this work is that it provides a simple bedside strategy to subclassify viral LRTI in infants based on individual predictors for recurrence. This approach may contribute to improve clinical care and facilitate the design of mechanistic studies and clinical trials to prevent the development of recurrent viral respiratory illnesses in infants during early life.

METHODS

Study design

We conducted an analytical single-center longitudinal retrospective study that included a random sample of children 3 years of age admitted with viral respiratory infection, confirmed by PCR analysis, at Children's National Health System (CNHS) during 2014. We included only those children hospitalized that had: (1) positive PCR for any of the viruses included in our panel, including RV, RSV, human metapneumovirus, influenza A/B, parainfluenza 1–3, and adenovirus; (2) had continued clinical care in CNHS for at least 12 months after discharge; and (3) had available electronic medical record (EMR) data (inpatient and outpatient) to ascertain predictors of interest (eg, clinical presentation) and main outcomes. We excluded cases with incomplete EMR data and children with: (1) congenital conditions (eg, pulmonary abnormalities, cyanotic heart disease, cystic fibrosis and airway abnormalities); (2) immunodeficiency; and (3) neuromuscular disorders. This study was approved by the Institutional Review Board of Children's National Medical Center, Washington, DC.

Outcome definition

The main outcome was the binary presence (0 or 1 episode) of a respiratory illnesses leading to hospitalization or ED visit within 12 months after the index hospitalization due to PCR-confirmed viral LRTI. We only counted as respiratory hospitalization or ED visits those in which the primary complaint was any type of respiratory sign or symptom (eg, cough, nasal/chest congestion, wheezing, respiratory distress and hypoxemia).

Clinical variables and respiratory assessment

Clinical data collection was through EMR review at the point of ER presentation or admission to the inpatient unit and included the following demographic, clinical, and microbiologic information: viral pathogen, date of admission, age (months), gender (male or female), race/ethnicity (white, black or Hispanic), gestational age (GA), family history of asthma (mother or father) and prior underlying disease conditions such as previous respiratory disease, congenital heart disease, and underlying neurologic disease (yes or no). We also recorded clinical features at presentation such as subcostal retractions, wheezing and hypoxemia defined as need of supplemental O₂, due to sustained desaturation of <91% based on our institution criteria, respiratory rate (RR), HR, LOS, need for non-invasive ventilation, high flow nasal cannula or mechanical ventilation. To better assess the contribution of airway hyper-reactivity (wheezing), air-trapping leading to diaphragm flattening (subcostal retractions),^{113–15} and parenchymal compromise of alveolar gas exchange units (hypoxemia), we also combined these three clinical parameters in a weighted score [*wheezing (0–1)+subcostal retractions (0–1) – hypoxemia (0–1)*] that was included (along with other clinical predictors) in regression models.

Statistical analysis

Continuous variables are presented as mean or median IQR, whichever is appropriate. Categorical variables are presented as numbers (percentage). Differences between groups on

continuous variables were analyzed using the unpaired t-test or the Mann-Whitney U test, whichever was appropriate. Associations between categorical variables were analyzed using the χ^2 test or Fisher's exact test, whichever was appropriate. To identify factors associated with the presence of recurrence after viral LRTI hospitalization, we adjusted logistic regression models (logit function). Variables that were considered to be able to influence the risk of recurrence were selected a priori for inclusion as predictor variables in multivariable models. In order to check that the models fit sufficiently well, we performed model diagnostics, including the inclusion of all the relevant variables and the possibility of overfitting and multicollinearity. The final model was chosen using automatic stepwise selection with an alpha to enter of <0.05 and an alpha to remove of >0.05 . Regression results are reported as ORs and their respective 95% CIs. All statistical tests were two tailed, and the significance level used was $p<0.05$. The data were analyzed with the Minitab Statistical Package V.18.1. (Minitab, Inc, State College, Pennsylvania, USA).

RESULTS

We included a total of 138 children hospitalized with viral LRTI patients in this study. The median age was 1 year (IQR 0.6–1.8) and 85 (62%) were male subjects. The most common pathogen was RV isolated in 79 subjects (57%) followed by RSV isolated in 21 cases (29%). Given that at the time of enrollment (index hospitalization) some infants already had a prior episode of severe LRTI leading to hospitalization or ED visit, we decided to categorize all study subjects in two groups: infants with the 'first episode' of severe LRTI ($n=82$) and those with a 'prior episode' of severe LRTI ($n=56$). A comparison of all the demographic and clinical characteristics measured in these two groups is presented in table 1.

As expected, we found that the group infants with already a prior episode of severe LRTI at enrollment had a significantly greater probability of subsequent recurrence (first episode $n=31$; 37% vs prior episode $n=43$; 77%, $p<0.01$, figure 1).

We first examined the clinical predictors of recurrence in infants with the first episode of severe LRTI. As shown in table 2, we evaluated all the predictive variables of subsequent recurrence in these infants grouping them in three different multivariate logistic models: (1) individual characteristics (GA ≥ 32 weeks, age ≥ 1 year, male gender, black race and family history of asthma); (2) clinical features (subcostal retractions, wheezing, hypoxemia, weighted clinical score and RSV (+) LRTI); and (3) severity markers (RR ≥ 60 bpm, HR ≥ 160 bpm, mechanical ventilation and LOS ≥ 5 days). Using stepwise regression in each of these models, we selected a final predictive model that included severe prematurity (< 32 weeks GA, OR=5.19; 95% CI 1.76 to 15.32; $p=0.002$) and a weighted respiratory clinical score of wheezing, subcostal retractions and hypoxemia (OR=3.33; 95% CI 1.59 to 6.98; $p<0.001$) as the best independent clinical predictors of recurrence in infants hospitalized for the first time with viral LRTI.

We conducted separate analyses to examine the clinical predictors of recurrence in the group of infants with already a prior episode of severe viral LRTI at the time of enrollment (index hospitalization). Using the same stepwise regression approach, we identified that the presence of wheezing (OR=5.62; 95% CI 1.03 to 30.62; $p=0.04$) and family history of

asthma (OR=5.39; 95% CI 1.04 to 27.96; p=0.04) were the best independent clinical predictors of subsequent recurrence after hospitalization among infants with a prior episode of severe viral LRTI (table 3).

DISCUSSION

The primary finding of this study is that a clinical model that integrates individual risk factors with bedside respiratory assessment can predict recurrence among infants hospitalized with viral LRTI within 12 months of discharge. This new information provides a simple strategy to subclassify infants with viral LRTI based on individual susceptibility for recurrent respiratory hospitalizations and ED visits during early childhood.

In subjects admitted for the first time due to viral LRTI, we identified that a history of severe prematurity, and a clinical picture consistent on wheezing and subcostal retractions without hypoxemia was associated with a higher risk of recurrence after the first hospitalization. The link between prematurity and recurrent illnesses after viral bronchiolitis is not surprising and is consistent with previous studies.^{15–18} However, to the best of our knowledge, the clinical respiratory predictors presented here have not been previously described in the literature. We developed a new weighted score system [*wheezing (0–1)+subcostal retractions (0–1) – hypoxemia (0–1)*] that predicted recurrence after the first viral LRTI hospitalization (Table 2). Our rationale for the proposed weighted score is that the respiratory manifestations of viral bronchiolitis cannot be grouped together because they represent distinct pathophysiological processes. We believe that the reason why infants with this clinical presentation are more likely to have recurrence is because wheezing and subcostal retractions most likely represent underlying airway hyper-reactivity (airway obstruction and air trapping, respectively),^{113–15} which could be triggered by subsequent viral respiratory infections. In contrast, infants with hypoxemia as primary manifestation of viral LRTI are more likely to have ventilation/perfusion and/or diffusion abnormalities due to lung parenchyma compromise, which is less likely to reoccur in otherwise healthy subjects. Notably, the use of weighted score systems, like the one presented in this study, is important because the clinical manifestations of airway hyper-reactivity and parenchymal lung disease may coexist in the same individual. For this purpose, we feel that it is essential to develop new viral LRTI ‘phenotypical scales’ that weight clinical parameters (subtracting or adding to define specific disease phenotypes) instead of simply adding respiratory and non-respiratory parameters to quantify acute severity. Indeed, in a recent systematic review, we identified that acute severity is currently the focus of all available instruments for the clinical evaluation of viral bronchiolitis.¹²

In this study, we also included a group of infants with already a prior episode of severe viral LRTI at the time of enrollment (index hospitalization). In this group of infants, wheezing (independently of other respiratory manifestations) and a family history of asthma showed the best prediction for subsequent recurrent episodes (Table 3). It is important to mention that based on the definition used in clinical trials and guidelines, this group of young children cannot be considered to have ‘viral bronchiolitis’ because it is not the first severe viral LRTI episode.¹⁹²⁰ In support of this notion, our study demonstrates that the antecedent of a single episode of severe viral LRTI is sufficient to consider these infants as a separate

category from viral bronchiolitis because they have a much higher risk for subsequent recurrence (Figure 1). Clinically, early life viral respiratory infections are usually divided in those presenting for the first time versus those presenting with prior respiratory episodes of hospitalizations because these two groups of viral LRTI have different risk factors and rates of recurrence.²¹ Thus, the misuse of the term viral bronchiolitis in infants with a prior episode is highly inappropriate and may lead to the mistaken idea, based on clinical trials and guidelines for viral bronchiolitis,¹⁹²⁰ that most respiratory therapies are not clinically indicated in young children with recurrent respiratory illnesses triggered by respiratory viruses such as RV or RSV. For instance, there is compelling evidence, based on randomized controlled clinical trials^{22–24} that corticosteroids are beneficial in young children with recurrent wheezing, which is often triggered by respiratory viruses.

Our study has a number of strengths and some limitations. We included a cohort of children hospitalized due to viral LRTI confirmed by PCR in all cases. We were able to investigate clinical manifestations (our EMR system provides automated options to document clinical parameters and physical findings) as well as longitudinal 12-month outcomes given that our institution encompasses the largest centralized system in Washington DC, which connects outpatient centers and emergency rooms in inner city and sub-urban areas. The main limitation of the present study is the retrospective collection of clinical data. We acknowledge the inherent bias in only including patients who had a viral PCR ordered. Given that we could not ascertain the presence of minor viral illnesses (eg, upper respiratory infection) at enrollment, we only recorded prior severe episodes of viral respiratory infections requiring ED visits or hospitalizations. In addition, it is important to emphasize that the study was conducted in a specialized, tertiary referral hospital, which makes it likely that the patients included represent the extreme of the spectrum of severity of all patients with viral respiratory infection, which could limit the generalization of results to other contexts. For instance, our population may have an over-represented amount of cases with severe prematurity (< 32 weeks' GA) because CNHS is the primary center caring for these infants in Washington DC. However, it is important to emphasize that our final models controlled by the presence of severe prematurity and our initial design excluded infants with severe cardiorespiratory comorbidities. Finally, because EMR information did not provide a complete medical history in all cases, including medication use (eg, compliance) and the potential presence of antibiotic therapy. We did not include in the multivariate analyses some potentially important predictors of recurrent respiratory illnesses, such as eczema, eosinophils counts,²⁵ socioeconomic status and environmental factors (eg, smoking and daycare attendance), and as is the case for other observational epidemiologic studies, residual confounding cannot be excluded, so interpretation of our results needs to be cautious.

In conclusion, our study identified that a model that integrates individual factors with bedside clinical assessment in young children can predict the risk of recurrence after viral LRTI hospitalization. During the first episode of viral LRTI (often termed viral bronchiolitis), the risk of recurrence was associated with a history of prematurity and the concomitant presence of wheezing and subcostal retractions without hypoxemia. In subsequent episodes (> 1 prior respiratory hospitalization/ED visit), a family history of asthma and the presence of wheezing (independently of other respiratory manifestations)

were the best predictors of recurrent respiratory illnesses. Further longitudinal studies integrating bedside clinical respiratory assessment with molecular phenotyping may elucidate new mechanisms of disease and phenotype-specific therapeutic strategies for primary prevention of preschool wheezing and asthma after early viral infection.

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Significance of this study

What is already known about this subject?

- Lower respiratory tract infections (LRTI) caused by viruses such as respiratory syncytial virus (RSV) and rhinovirus (RV) are the top causes for recurrent respiratory illnesses in children during the first 3 years of life and are the leading cause of hospitalization for infants beyond the neonatal period.
- Among infants requiring hospitalization due to viral LRTI, approximately 30%–50% will have recurrent respiratory illnesses and subsequently a much higher risk of asthma beyond childhood

What are the new findings?

- The primary finding of this study is that a clinical model that integrates individual risk factors with bedside respiratory assessment can predict recurrence among infants hospitalized with viral LRTI within 12 months of discharge.
- We identified that a history of severe prematurity and a clinical picture consistent on wheezing and subcostal retractions without hypoxemia was associated with a higher risk of recurrence after the first hospitalization. The clinical respiratory predictors presented here have not been previously described in the literature.
- In subsequent episodes (1 prior respiratory hospitalization/ED visit), a family history of asthma and the presence of wheezing (independently of other respiratory manifestations) were the best predictors of recurrent respiratory illnesses.
- We proposed the idea that is essential to develop new viral LRTI ‘phenotypical scales’ that weight clinical parameters (subtracting or adding to define a specific disease phenotypes) instead of simply adding respiratory and non-respiratory parameters to quantify acute severity.

How might these results change the focus of research or clinical practice?

- We found that the integration of individual risk factors (eg, prematurity or family history of asthma) with bedside clinical assessment (eg, wheezing, subcostal retractions or hypoxemia) can predict the risk of recurrence after viral LRTI hospitalization in infants. This strategy may enable clinically oriented subsetting of infants with viral LRTI based on individual predictors for recurrent respiratory illnesses during early life and guide therapeutic strategies for recurrent episodes of wheezing and asthma after early viral infection.

Figure 1. Probability of subsequent recurrence in infants with the first severe viral LRTI versus infants with a prior respiratory hospitalization/ED visit. ** = $p < 0.05$. LRTI, lower respiratory tract infection.

Table 1

Baseline characteristics of all infants hospitalized with viral LRTI

Variable	First episode (n=82)	Prior episode (n=56)	P value
Individual characteristics			
Age (years)	0.98	1.62	<0.01
Gender			
Male %	60	65	0.59
Race/ethnicity			
White %	17	7	0.07
Black %	51	68	0.05
Hispanic %	20	21	0.8
Severe prematurity (< 32 weeks GA) %	34	62	<0.01
Family history of asthma %	43	60	0.09
Hospitalization parameters			
Hypoxemia	54	43	0.2
Wheezing %	30	70	<0.01
Subcostal retractions %	56	84	<0.01
RR (mean bpm)	44	45	0.6
HR (mean bpm)	150	147	0.4
NIV/HFNC %	7	11	0.5
Mechanical ventilation %	13	9	0.4
Length of stay (LOS), (median days)	3	4	0.7
Viral pathogen %			
RV	56	59	0.7
RSV	22	20	0.7
HMPV	16	16	0.9
Parainfluenza	9	5	0.5
Influenza	5	9	0.5
Adenovirus	13	14	0.9
Mixed	22	20	0.7

GA, gestational age; HFNC, high flow nasal cannula; HMPV, human metapneumovirus; HR, heart rate; LOS, length of stay; LRTI, lower respiratory tract infection; NIV, non-invasive ventilation; RR, respiratory rate; RSV, respiratory syncytial virus; RV, rhinovirus.

Clinical predictors of recurrence in infants with the first episode of severe viral LRTI at enrollment determined through stepwise regression and multivariate analysis

Table 2

Model/variable	Simple regression		Stepwise regression	
	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Individual characteristics				
Severe prematurity [*]	4.42	(1.67 to 11.68)	<0.001	5.19 (1.76 to 15.32)
Age 1 year	1.59	(0.63 to 4.06)	0.32	
Male	1.38	(0.55 to 3.46)	0.49	
Black	1.26	(0.52 to 3.09)	0.61	
Family history of asthma	1.3	(0.44 to 3.87)	0.637	
Clinical features				
Subcostal retractions	4.52	(1.65 to 12.38)	<0.001	
Wheezing	2.99	(1.13 to 7.92)	0.03	
Hypoxemia	0.88	(0.36 to 2.14)	0.77	
Clinical score [†]	3.05	(1.54 to 6.06)	<0.001	3.33 (1.59 to 6.98)
RSV	2.56	(0.88 to 7.43)	0.08	
Severity markers				
RR 60 bpm	1.87	(0.62 to 5.63)	0.27	
HR 160 bpm	1.28	(0.52 to 3.15)	0.6	
Mechanical ventilation	0.58	(0.14 to 2.36)	0.43	
LOS 5 days	1.19	(0.49 to 2.93)	0.7	

Bold values highlight statistical significance.

^{*} Severe prematurity defined as 32 weeks' GA.

[†] Clinical score defined as (subcostal–retraction+wheezing–hypoxemia).

GA, gestational age; HR, heart rate; LOS, length of stay; RR, respiratory rate; RSV, respiratory syncytial virus.

Table 3

Clinical predictors of recurrence in infants with a prior episode of severe viral LRTI at enrollment determined through stepwise regression and multivariate analysis

Model/variable	Simple regression		Stepwise regression	
	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Individual characteristics				
Severe prematurity [*]	0.23	(0.05 to 1.16)	0.05	
Age 1 year	2.13	(0.41 to 11.06)	0.34	
Male	1.48	(0.40 to 5.50)	0.56	
Black	1.44	(0.40 to 5.26)	0.58	
Family history of asthma	5.37	(1.15 to 25.10)	0.03	(1.04 to 27.96)
Clinical features				
Subcostal retractions	3.38	(0.75 to 15.17)	0.12	
Wheezing	3.85	(1.05 to 14.12)	0.04	(1.03 to 30.62)
Hypoxemia	1.96	(0.52 to 7.33)	0.31	
Clinical score [†]	1.7	(0.78 to 3.73)	0.18	
RSV	0.26	(0.06 to 1.06)	0.06	
Severity markers				
RR 60 bpm	1.07	(0.19 to 5.92)	0.94	
HR 160 bpm	2.66	(0.52 to 13.63)	0.21	
Mechanical ventilation	1.23	(0.13 to 12.09)	0.86	
LOS 5 days	1.61	(0.38 to 6.79)	0.51	

^{*} Severe prematurity defined as 32 weeks' GA.

[†] Clinical score defined as (subcostal–retraction+wheezing–hypoxemia).

GA, gestational age; HR, heart rate; LOS, length of stay; RR, respiratory rate; RSV, respiratory syncytial virus.