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Measuring the Severity of Respiratory Illness in the First 2 Years of Life in Preterm and Term Infants

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Objective To develop a valid research tool to measure infant respiratory illness severity using parent-reported symptoms.

Study design Nose and throat swabs were collected monthly for 1 year and during respiratory illnesses for 2 years in a prospective study of term and preterm infants in the Prematurity, Respiratory Outcomes, Immune System and Microbiome study. Viral pathogens were detected using Taqman Array Cards. Parents recorded symptoms during respiratory illnesses using a Childhood Origins of Asthma (COAST) scorecard. The COAST score was validated using linear mixed effects regression modeling to evaluate associations with hospitalization and specific infections. A data-driven method was also used to compute symptom weights and derive a new score, the Infant Research Respiratory Infection Severity Score (IRRISS). Linear mixed effects regression modeling was repeated with the IRRISS illness data.

Results From April 2013 to April 2017, 50 term, 40 late preterm, and 28 extremely low gestational age (<29 weeks of gestation) infants had 303 respiratory illness visits with viral testing and parent-reported symptoms. A range of illness severity was described with 39% of illness scores suggestive of severe disease. Both the COAST score and IRRISS were associated with respiratory syncytial virus infection and hospitalization. Gestational age and human rhinovirus infection were inversely associated with both scoring systems. The IRRISS and COAST scores were highly correlated (r = 0.93; $P < .0001$).

Conclusions Using parent-reported symptoms, we validated the COAST score as a measure of respiratory illness severity in infants. The new IRRISS score performed as well as the COAST score. *(J Pediatr 2019;214:12-9)*.

Respiratory infections are among the most common illnesses encountered in infancy and early childhood.[1,2] When symptomatic, these infections induce a range of disease severity, from mild congestion to severe respiratory distress requiring hospitalization. Respiratory infections in infancy have also been associated with respiratory morbidity in later childhood suggesting the importance of these infections to health and the need to fully understand how early infections relate to later disease.[3-5]

Much has been learned about the epidemiology of respiratory pathogens causing early life infections owing to the introduction of molecular detection methods.[6,7] However, there is a significant need for a validated research assessment tool to measure the severity of respiratory illnesses among infants to understand disease risk as well as clinical and biological modifiers of respiratory disease severity. There are no widely accepted research tools to measure illness severity in infants with respiratory infections except those with bronchiolitis.[8-13] Most respiratory illnesses and infections in infants do not require hospitalization or medical intervention; thus, to measure the full range of respiratory symptom severity, a tool reflecting outpatient symptoms is needed.

Physicians trust parents to be good judges of their child's health and to identify serious symptoms to seek care. Yet, the data for the accuracy of parental reports of respiratory symptoms are mixed.[14-17] The Childhood Origins of Asthma Study (COAST) developed a scorecard for parents of full term infants at risk for wheezing, asthma, and atopy to quantify respiratory symptoms to alert the study staff of a probable viral infection and the need for a research visit.[18-20] Although the COAST score has been used as a measure of respiratory illness severity, it has not been fully validated. Additionally, the usefulness in

AUC	Area under the curve
COAST	Childhood Origins of Asthma Study
ED	Emergency department
ELGANS	Extremely low gestational age newborns
hRV	Human rhinovirus
IRRISS	Infant Research Respiratory Infection Severity Score
LMER	Linear mixed effects regression modeling
PRISM	Prematurity, Respiratory Outcomes, Immune System and Microbiome
RSV	Respiratory syncytial virus

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measuring illness severity in preterm infants or those not at risk for atopy or allergy has not been demonstrated previously.

We undertook a large, prospective cohort study of term and preterm infants focused on Prematurity, Respiratory Outcomes, Immune System and Microbiome, the PRISM study (www.urmc.rochester.edu/respiratory-pathogens-research-center/projects.aspx). One of the aims of PRISM is to identify symptomatic and asymptomatic respiratory infections over the first 2 years of life to understand the effect of repeated infections on respiratory morbidity in early childhood. The ability to measure respiratory illness symptomatology and severity is a key component of this aim and the subject of this report. As such, we first determined the validity of the COAST Scorecard for measuring illness severity in the PRISM birth cohort, including both term and preterm infants, selected without regard to risk of wheezing. As a secondary aim, we developed a new data-driven scoring system of disease severity based on the 10-day illness diary cards kept by parents for the PRISM infants and young children. We compared the new scoring system with the COAST score in an attempt to create a more broadly applicable, sensitive, and specific measure of respiratory illness severity to be used as a tool for research.

Methods

The PRISM study enrollment strategy has been previously published and registered at ClinicalTrials.gov (NCT01789268).[21] Briefly, preterm (<36 weeks of gestation) and term (≥37 weeks of gestation) newborns, ≤7 days of age, born at the University of Rochester Medical Center, Rochester, New York, were eligible for enrollment. Exclusion criteria included airway/chest wall abnormalities, neuromuscular or cardiac disorders (except patent ductus arteriosus or isolated atrial septal defect), genetic disorders of immune system or respiratory function, maternal HIV infection, and nonviability. The Research Subjects Review Board approved the study and all parents provided informed consent.

Study Protocol

Nose and throat swabs were obtained from each newborn on study day 1, weekly during hospitalization, monthly after discharge until 12 months corrected gestational age, and during respiratory illnesses after the birth hospitalization in the first 2 years of life. Additionally, the use of the COAST scorecard was reviewed with each family via a printed diary form before discharge from the birth hospitalization and at each visit. Families were reminded to begin filling out the scorecard and to notify the study team when their child developed respiratory symptoms resulting in a score of ≥3 and to continue completing the scorecard daily until 10 days had elapsed or the child's symptoms dropped below a score of 3.[18-20] The scorecard assigns points to the presence or absence of fever ≥100°F, hoarseness, wheezing, retractions, tachypnea, cyanosis, apnea, being ill for >4 days, and the degree of cough and rhinorrhea. Maximal possible score is 31 with higher scores indicating more severe symptoms. The PRISM study sought to identify all respiratory infections with the full range of severity so a threshold score of 3 was chosen as a sensitive measure of illness. When parents reported a COAST score of ≥3, a study visit was completed and respiratory samples obtained. Staff followed up with families to ensure scorecard completion and also reviewed the 3 days before when a score of 3 was reached, so that the full range of illness was recorded. For participants with baseline respiratory symptoms such as retractions or wheezing, the families were instructed to assign points only when findings were greater than baseline.

Hospitalizations and emergency department (ED) visits were recorded and chart review was completed only for those related to respiratory illnesses. Hospitalizations, ED visits, and research illness visits for respiratory illnesses were included in the analysis only if they occurred within 12 days of a parental COAST scorecard report and had respiratory pathogen testing completed. There had to be a minimum of 12 days between illnesses to count as a new event. The number of ED visits that met criteria were so small they were combined with research illness visits in the analyses. Results of clinical respiratory viral testing were included if obtained from 2 days before to 7 days after the first COAST scorecard entry.

Specimens

Separate flocked swabs (Copan, FLOQSwabs catalog # 525CS01, Copan, Murrieta, California) were used to sample the nares and oropharynx/tonsillar region, combined in 3 mL of Universal Transport Media (UTM, Cat # 330CHL, Quidel [formerly Diagnostic Hybrids], Athens, Ohio), shaken, placed on ice, and transported to the laboratory.[21]

Laboratory Methods: Real-Time Polymerase Chain Reaction

TaqMan Array Card technology was used as previously described.[21] Targets included influenza A and B; respiratory syncytial virus (RSV); human metapneumovirus, parainfluenza virus 1, 2, and 3; human rhinovirus (hRV); enterovirus, human parechovirus, coronavirus 1-4 (229, NL63, OC43, and HKU1); adenovirus; and human bocavirus. The detection of the human RNase P gene was a positive control confirming the presence of cellular material.[22]

Statistical Analyses

Our first goal was to determine whether we could validate the COAST scorecard in our population of term and preterm infants. In the COAST study the detection of known viral respiratory pathogens was significantly associated with disease severity as measured by the scorecard.[18] Therefore, we used the identification of respiratory viruses as a validation measure. Because hospitalization is also a measure of disease severity, we chose it as an additional validation measure. The associations between the preterm and term cohorts

and their characteristics, prevalence of hospitalizations, reported illnesses, and viruses identified were explored using the Pearson χ^2 test. The same approach was used to evaluate symptoms and validation measures.

COAST scorecard data were summarized by using the maximum COAST score assigned by a parent or the area under the curve (AUC) of the daily score averaged over the full course of illness to control for different lengths of illness. Linear mixed effects regression modeling (LMER) was used to evaluate the associations between the detection of viral infections (RSV, hRV, and any other viral infections combined), hospitalization, and the maximum COAST score or the average AUC COAST score. Random intercepts were included in the model to account for between subject variations. Illness visits with >1 viral pathogen detected were included in the analysis of each virus (RSV, hRV, or other viral infections).

Second, a novel, data-driven approach to severity scoring was developed to more precisely determine the contribution of the clinical information from each symptom to the overall score. With day 1 of reporting (score of ≥3) having the most abundant diary data, a factor analysis with polychoric correlation matrix of symptoms reported on day 1 was used to determine the symptom weights for cough, tachypnea, fever, hoarseness, retractions, rhinorrhea, sick for >4 days, and the presence of wheeze as reported on the scorecard. Cyanosis and apnea were rare, so were not considered. A value of 10 was added to each weighted score to produce all positive values. The first factor explained the largest amount of the variance in the data (51.2%) and was used to assign weights to the variables in the new Infant Research Respiratory Infection Severity Score (IRRISS). LMER models were again used to validate the IRRISS with the detection of a viral respiratory pathogen as well as hospitalization as measures of disease severity. Finally, severity scores were calculated similarly but separately for the term and preterm subjects to explore potential heterogeneity among age cohorts, and the performance of each score was compared with the IRRISS and COAST score.

All LMER models were controlled for gestational age at birth, race, birthweight z-score, number of people in the household separated into 3 categories (2-3, 4-6, or 7-10), and a family history of asthma.

Results

From April 2013 to April 2017, 267 newborns were enrolled in the PRISM study including 64 born at <29 weeks of gestation or extremely low gestational age newborns (ELGANs), 84 late preterm (29-<36 weeks of gestation), and 119 term infants ($\geq 37^{0/7}$ weeks of gestation). To be included in the analyses, subjects had to have had a minimum of 1 follow-up visit ≥1 month after hospital discharge and ≥1 illness visit with an accompanying parent reported COAST score and viral testing data. During the study period there were 208 active subjects, 118 subjects (Table I), had a qualifying illness visit (1-12 per subject) resulting in a total of 346 illness visits. Of these, 303 visits (88%) had matching viral testing and parent reported COAST scorecards that form the basis of this report. Sixteen hospitalizations were included for 13 subjects; 89% of illness visits (269) with a matching COAST Scorecard reported ≥3 days of illness symptoms and 70% had ≥7-10 days of data. Twelve hospitalizations were in the ELGANS group, 2 in late preterm infants, and 2 in term infants with an overall hospitalization rate that was significantly higher in the ELGANS group (15.2%) than the late preterm (1.9%) or term infants (1.7%; $P < .001$; Table II).

There were 249 samples (82%) from the 303 illness visits that had a viral respiratory pathogen identified with 8 viral co-detections including 7 with RSV and hRV and 1 with hRV and human bocavirus (Table II). The rate of viral detection at illness visits was significantly greater than at well visits (383 of 1114 well visits [34%]; $P < .001$). The

Table I. Participant characteristics

Characteristics	Term (n = 50)	Late preterm (n = 40)	ELGANs (n = 28)	Total (n = 118)	*P* value
Sex					
Female	15 (30.0)	19 (47.5)	17 (60.7)	51	.025
Male	35 (70.0)	21 (52.5)	11 (39.3)	67	
Race					
African American	6 (12.0)	6 (15.0)	8 (28.6)	20	.138
Other	14 (28.0)	5 (12.5)	6 (21.4)	25	
White	30 (60.0)	29 (72.5)	14 (50.0)	73	
Birth weight					
Average for gestational age	42 (84.0)	34 (85.0)	27 (96.4)	103	.086
Large for gestational age	4 (8.0)	0 (0.0)	1 (3.6)	5	
Small for gestational age	4 (8.0)	6 (15.0)	0 (0.0)	10	
Family history of asthma					
No	37 (74.0)	29 (72.5)	12 (42.9)	78	.012
Yes	13 (26.0)	11 (27.5)	16 (57.1)	40	
No. of people in home					
2-3	16 (32.0)	8 (20.0)	6 (21.4)	30	.397
4-6	33 (66.0)	28 (70.0)	20 (71.4)	81	
7-10	1 (2.0)	4 (10.0)	2 (7.1)	7	

Values are number (%).

Table II. Comparison of illness visits, hospitalizations, and respiratory viral infections in the term and preterm participants

Variables	Term	Late preterm	ELGANs	*P* value
Total illness visits	121	103	79	
Hospitalization	2 (1.7)	2 (1.9)	12 (15.2)	<.001
hRV infection	47 (38.8)	57 (55.3)	37 (46.8)	.048
RSV infection	19* (15.7)	15† (14.6)	10‡ (12.7)	.836
Other than hRV/RSV	38§ (31.4)	17 (16.5)	17 (21.5)	.029
Any virus infection	102 (84.3)	85 (82.5)	62 (78.5)	.572

Values are number (%).
There were 7 hRV and RSV coinfections: *1 in a term baby, †4 in late preterm, ‡2 in ELGANs, and §1 hRV and human bocavirus coinfection in a term baby.

rate of pathogen detection at illness visits did not differ by gestational age group with 79% of illness visits in the ELGANS, 83% in the late preterm group, and 84% in the term cohort associated with the detection of a viral pathogen (P = .57). In contrast, a respiratory virus was detected at 28% of well visits in ELGANs, 36% in the late preterm group, and 38% of well visits in term babies, suggesting that babies born at <29 weeks of gestation are significantly less likely to have asymptomatic viral respiratory infections (P = .03). The preterm cohorts were also more likely to have rhinovirus-associated illness visits (47% ELGANS and 55% late preterm) than term (39%) infants (P = .05; **Table II**). The percentage of illness visits associated with RSV infection was not different between the 3 groups (P = .84; **Table II**). In the PRISM study, 75% of ELGANS and 10% of late preterm infants received palivizumab prophylaxis. Of the 79 illness visits in ELGANS, 10 were due to RSV. Four hospitalizations and 5 illness visits occurred in subjects who received palivizumab, with 1 RSV illness visit in an ELGANS subject who had not received palivizumab. Nine illness visits occurred in late preterm subjects who received palivizumab, none of which were due to RSV infection, whereas 15 RSV illness visits occurred in late preterm infants who did not receive palivizumab, 1 of which was associated with hospitalization (**Table III**; available at www.jpeds.com).

COAST Score

Seven percent of illness visits had maximum COAST scores of ≤3, suggesting mild upper respiratory symptoms only. However, 39% of illnesses were associated with a maximal COAST score of >10, implying more severe disease. In general, ELGANS had a greater number of illness visits associated with higher scores (**Figure 1**).

LMER models were used to examine associations between the detection of viral infections as a measure of disease severity and either the maximal COAST score or the average AUC COAST score. Results focus on the maximum scores for ease of presentation as the maximum scores and average AUC scores provided similar results. We chose to examine the associations with RSV, hRV, and other viral infections because the original COAST study showed an association between the identification of a respiratory pathogen and illness severity. The models were repeated using hospitalization as an alternative measure of construct validity.

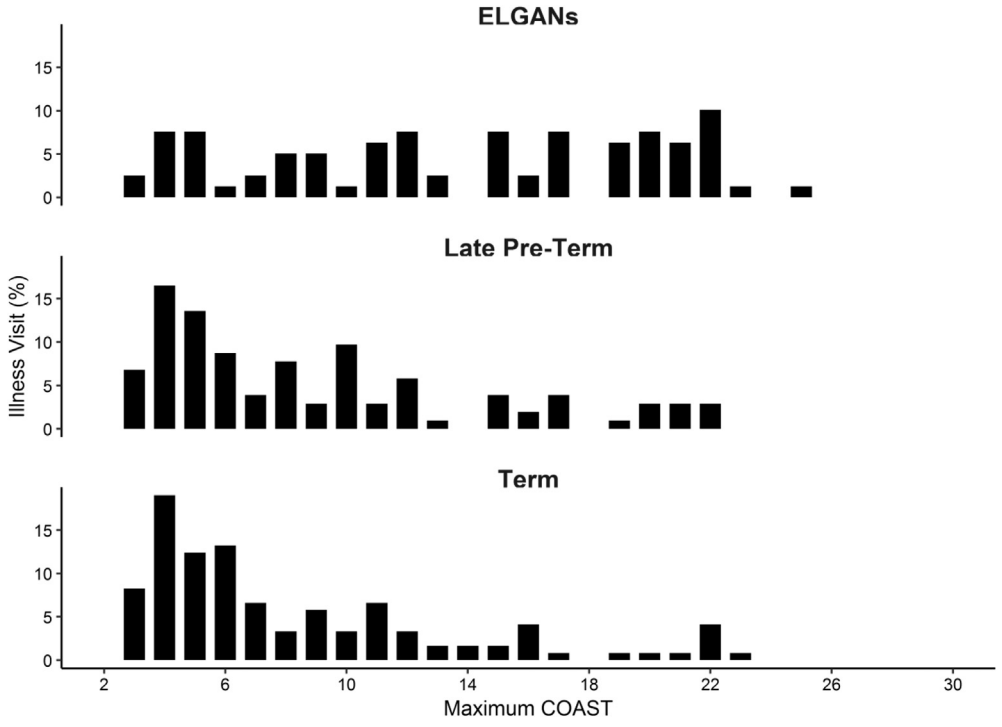

Figure 1. Frequency distribution of the parent-reported maximal COAST score for respiratory illness visits by cohort.

The presence of RSV in the respiratory sample during an illness visit was positively associated with the COAST score in each model (Table IV and Table V [available at www.jpeds.com]). The detection of hRV was inversely associated with the COAST score (Tables IV and V). Hospitalization was also positively associated with the COAST score ($P < .001$). African American race was consistently positively associated with the COAST score and gestational age at birth was inversely associated.

Development of a New Severity Score, the IRRISS

Based on the respiratory symptom components of the COAST scorecard, we next performed a factor analysis to develop a data-driven severity scoring system. The aim was to develop an alternative system to accurately summarize the contribution of each respiratory symptom to disease severity to determine if this approach would improve upon the COAST score. Using the new score the associations with viral infection and hospitalization were reexamined.

When developing the new scoring system we initially explored individual associations of symptoms with one another to evaluate the biological plausibility of including each one of the symptoms in the new scoring system. A cluster dendrogram based on a dissimilarity matrix classified the symptoms into 2 main groups—those more associated with lower respiratory tract infection such as retractions and tachypnea compared with those consistent with upper respiratory tract infection (Figure 2; available at www.jpeds.com). Pearson χ^2 test analyses identified the presence of retractions, tachypnea, and wheeze as significantly associated with hospitalization (Table VI; available at www.jpeds.com). Cough was associated with the detection of RSV and hRV infection was associated with fever and a longer duration of illness (Table VI). Viral infections other than hRV or RSV were also associated with fever and hoarseness. Next, a factor analysis was performed to compute weights for each of the 8 symptoms and to derive the new severity scoring system, the IRRISS, with a range of 9-14 (Figure 3; available at www.jpeds.com).

Repeating the LMER models using the IRRISS identified the presence of RSV infection and hospitalization to be positively associated with the IRRISS in both models (Table IV and Table V). Infection with hRV was inversely associated with the IRRISS when compared with all hRV-negative illness, visits which were predominantly due to RSV and other viral respiratory pathogens (Table VII; available at www.jpeds.com). Gestational age at birth was also negatively associated with the IRRISS. When comparing the IRRISS and the COAST score, they were highly correlated ($r = 0.93$; $P < .0001$; Figure 4; available at www.jpeds.com).

A sensitivity analysis was performed to confirm the associations between the IRRISS and COAST scores and hospitalization and specific viral infections with ELGANS subjects removed. RSV infection and hospitalization continued to be significantly associated with both the maximal COAST score and IRRISS with an inverse association with hRV infections. A family history of asthma was now significantly associated with the average AUC of the IRRISS in all analyses.

Next, separate preterm and term infant severity scores were derived in a similar fashion as the IRRISS using factor analysis to determine if symptoms interacted differently between term and preterm infants. In the preterm cohort the COAST score, IRRISS and preterm factor score were consistently associated with RSV infection and hospitalization ($P = .022$ to $P = .028$ for RSV infection and $P < .001$ for hospitalization) and inversely associated with hRV infection ($P = .002$ to $P = .002$). Findings were not consistent when the full-term cohort was analyzed separately. There was an association between RSV infection and the maximal IRRISS score, but no association with the maximal COAST score or the maximal term factor score. Hospitalization was significantly associated with the COAST score, the average AUC of the term factor score and marginally significant with the average AUC of the IRRISS ($P = .05$) in term babies despite few hospitalizations in this cohort. No associations were noted for hRV.

Despite these differences, the separate term and preterm factor scores were highly correlated with the IRRISS score (term score $r = 0.97$, preterm score $r = 1$; both $P < .001$)

Table IV. Results of the linear mixed effects regression models of the maximum COAST score and IRRISS

	COAST score		IRRISS	
Variables	**Estimate**	***P* value**	**Estimate**	***P* value**
Hospital admission				
Hospitalization	0.621	<.001	0.087	<.001
Gestational age at birth	−0.022	<.001	−0.004	<.001
African American vs white	0.195	.038	0.027	.110
Other race vs white	0.054	.551	0.013	.426
Family history of asthma	0.088	.253	0.016	.234
4-6 vs < 4 people in home	−0.060	.456	−0.008	.576
7-10 vs < 4 people in home	−0.073	.673	0.004	.899
Birth weight Z-score	0.072	.075	0.007	.331
Other virus infection				
Other than hRV/RSV	0.159	.022	0.024	.056
Gestational age at birth	−0.028	<.001	−0.005	<.001
African American vs white	0.216	.023	0.030	.075
Other race vs white	0.074	.417	0.016	.326
Family history of asthma	0.130	.092	0.023	.098
4-6 vs < 4 People in home	−0.074	.361	−0.010	.498
7-10 vs < 4 People in home	−0.143	.416	−0.006	.854
Birth weight Z-score	0.096	.019	0.010	.151
RSV infection				
RSV infection	0.253	.002	0.056	<.001
Gestational age at birth	−0.029	<.001	−0.005	<.001
African American vs white	0.193	.049	0.025	.141
Other race vs white	0.045	.636	0.010	.561
Family history of asthma	0.123	.121	0.021	.135
4-6 vs < 4 people in home	−0.062	.458	−0.006	.681
7-10 vs < 4 people in home	−0.156	.382	−0.007	.826
Birth weight Z-score	0.081	.053	0.007	.318
hRV infection				
hRV infection	−0.159	.007	−0.026	.013
Gestational age at birth	−0.029	<.001	−0.005	<.001
African American vs white	0.190	.051	0.026	.131
Other race vs white	0.058	.534	0.013	.415
Family history of asthma	0.130	.098	0.023	.102
4-6 vs < 4 people in home	−0.067	.419	−0.008	.567
7-10 vs < 4 people in home	−0.151	.395	−0.007	.828
Birth weight Z-score	0.090	.030	0.010	.189

and the COAST score (term score, r = 0.94; preterm score, r = 0.93; both $P < .0001$; results not shown).

Discussion

In the PRISM study, we used parent reported symptom data included on the COAST scorecard to signal the need for a respiratory illness research visit and to quantitate the type and degree of symptoms throughout the illness as a measure of disease severity.[18,19] From these reports, we examined both the validity of the COAST score for measuring respiratory disease severity and developed ex nihilo data-driven severity scores, the IRRSS, and separate term and preterm factor scores, using the presence of RSV, hRV, and hospitalization to evaluate construct validity.

As linear combinations of 8-10 separate symptoms clinically associated with acute respiratory illnesses, the COAST score and the newly derived scores demonstrate face validity. Evaluating individual components of the COAST score, we found associations between hospitalization and specific symptoms associated with lower tract disease. In addition, associations between RSV, hRV, and other viral infections with 7 of the 10 symptoms were identified. The cluster dendrogram linked 8 symptoms together, suggesting a physiologic relationship between them with differences possibly owing to predominant lower airway vs upper airway viral replication and injury. These 8 symptoms were then included in the development of alternative scores for assessing severity of respiratory illnesses up to 24 months of age. We also examined score performance relative to gestational age at birth.

Prior reports demonstrated an association between the frequency of viral detection and the magnitude of the COAST score, categorized as mild (1-4), moderate (5-9), and severe disease (>9), which validated that the score was indeed identifying viral respiratory infections.[18,23] RSV infection causes more severe respiratory illness with a higher rate of hospitalization than other viral respiratory infections in infants.[24-26] Houben et al found that term infants with RSV infection had greater disease severity using the COAST score than infants with other viral infections providing preliminary validation of the score.[27] Although modifications of the COAST score have been used in subsequent respiratory disease studies, further efforts to validate the score to measure disease severity have not been reported.[28,29] Marginal analysis of our data confirmed an association between a COAST score of ≥3 and the presence of a viral infection. Multivariate modeling analyses further demonstrated that the maximal COAST score reported over a 10-day period for each illness and the average AUC of the COAST score were both associated with the presence of a symptomatic RSV infection and hospitalization in our cohort. In addition, our analyses consistently identified an inverse association between the COAST score and infection with hRV, as compared with infections with other viruses. This finding is in keeping with hRV infections generally causing milder respiratory disease.[26,30] The COAST score was also consistently inversely related to gestational age at birth. These data provide validation of the COAST score to measure respiratory disease severity in the first 2 years of life in a new cohort of term and preterm infants.

We further used the symptom components of the COAST score to develop the new IRRISS respiratory severity score. Our aim was to determine if the data would provide more accurate weightings of symptoms in measuring illness severity than the original investigator-assigned symptom weights. Additionally, we sought to develop a more accurate score that would be useful in the research setting with both preterm and term infants without regard to a family history of asthma or atopy, risk factors required in the COAST study. The IRRISS score demonstrated very good construct validity; it was significantly associated with RSV infections and hospitalization in both the maximal and average AUC scores, similar to the COAST score. Like the COAST score, the IRRISS score was also inversely associated with hRV infections. Separating the cohort into preterm and term sets and estimating individual factor models for each group did not provide consistent results. The COAST score and IRRISS also did not perform as well when applied only to the term infants included in our cohort, which may be due to the smaller number of subjects and illnesses in each group.

Although both the COAST and IRRISS severity scores performed well in our cohort of preterm and term infants, gestational age at birth remained a significant variable in explaining respiratory illness severity, confirming prior reports of prematurity as a risk factor for severe, recurrent, respiratory disease, irrespective of the viral etiology.[29,31,32] ELGANS not only had higher hospitalization rates, but they were also less likely to have asymptomatic respiratory viral infections in the current study and had higher COAST and IRRISS scores with respiratory illnesses. An additional consistent finding was that hRV infections were negatively associated with illness severity when compared with illness mostly owing to RSV and other viral respiratory infections. This finding is in keeping with prior reports of generally milder illness in infants with hRV infections, as noted.[26,30] Although previous research identified hRV as a cause of severe lower respiratory infections in infants, the association with disease severity seems to be due to underlying comorbidities such as prematurity, rather than virus type.[30,31,33]

The strengths of this study include the prospective, 2-year longitudinal design in a large cohort with state-of-the-art molecular detection methods to identify respiratory pathogens. We also included preterm and term infants in our study without regard to a predisposition to atopy or asthma and were able to evaluate the characteristics of the severity scores on both groups, a novel contribution.

Limitations include relying on caregivers to alert the study team with symptoms of respiratory illness, correctly using the COAST scorecard, and being available for a respiratory illness visit. We attempted to mitigate variability in parent report by frequent, typically monthly, contact and review of illness reporting. Study staff also reviewed the daily scoring of each illness with caregivers at the 10-day mark, which we believe

enhanced information recovery and consistency. The staff also specifically taught caregivers the meaning of "wheeze" as chest sounds to be distinguished from upper airway noisy breathing. Despite these interventions, we acknowledge that illnesses may be underreported in our dataset.

Although we did review electronic medical records, we did not include data from hospitalization or ED visits that were missing parent report. Although illness severity could be determined from the electronic medical record, we reasoned that the assessment of symptoms by health care workers is not necessarily comparable with that of parents and should not be included in an analysis of parental reports. We believe partnering with caregivers to identify significant respiratory symptoms is a clinically relevant and feasible approach in a research setting.

Despite these limitations, our data suggest that parent-reported symptoms can be reasonably used to score respiratory disease severity in infants. The finding that the COAST score and the IRRISS were highly correlated is not unexpected, because they are based on the same constellation of symptoms. However, the IRRISS assigned weightings to symptoms based upon the data as a means to accurately capture the influence of each symptom on severity. However, these data-driven methods provided only marginal improvement over the original COAST score in this cohort. The ease of use of the COAST scorecard by parents makes it a simple tool for collecting symptom data in studies of respiratory illnesses in the first 2 years of life. Analysis of the PRISM study supports the COAST scorecard as a valid tool for measuring respiratory illness severity in preterm and term infants without regard to risk for atopy and asthma. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Monto AS, Malosh RE, Petrie JG, Thompson MG, Ohmit SE. Frequency of acute respiratory illnesses and circulation of respiratory viruses in households with children over 3 surveillance seasons. J Infect Dis 2014;210:1792-9.
2. Yorita KL, Holman RC, Sejvar JJ, Steiner CA, Schonberger LB. Infectious disease hospitalizations among infants in the United States. Pediatrics 2008;121:244-52.
3. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013;368:1791-9.
4. Stein RT, Martinez FD. Respiratory syncytial virus and asthma: still no final answer. Thorax 2010;65:1033-4.
5. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354:541-5.
6. Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD, et al. Epidemiology of respiratory infections in young children: insights from the new vaccine surveillance network. Pediatr Infect Dis J 2004;23:S188-92.
7. Regamey N, Kaiser L, Roiha HL, Deffernez C, Kuehni CE, Latzin P, et al. Viral etiology of acute respiratory infections with cough in infancy: a community-based birth cohort study. Pediatr Infect Dis J 2008;27:100-5.
8. Bekhof J, Reimink R, Brand PL. Systematic review: insufficient validation of clinical scores for the assessment of acute dyspnoea in wheezing children. Paediatr Respir Rev 2014;15:98-112.
9. Destino L, Weisgerber MC, Soung P, Bakalarski D, Yan K, Rehborg R, et al. Validity of respiratory scores in bronchiolitis. Hosp Pediatr 2012;2:202-9.
10. Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. J Asthma 2013;50:1056-61.
11. Feldman AS, Hartert TV, Gebretsadik T, Carroll KN, Minton PA, Woodward KB, et al. Respiratory severity score separates upper versus lower respiratory tract infections and predicts measures of disease severity. Pediatr Allergy Immunol Pulmonol 2015;28:117-20.
12. Mosalli R, Abdul Moez AM, Janish M, Paes B. Value of a risk scoring tool to predict respiratory syncytial virus disease severity and need for hospitalization in term infants. J Med Virol 2015;87:1285-91.
13. Parker MJ, Allen U, Stephens D, Lalani A, Schuh S. Predictors of major intervention in infants with bronchiolitis. Pediatr Pulmonol 2009;44:358-63.
14. Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child 1985;60:473-4.
15. Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. Arch Dis Child 2001;84:31-4.
16. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000;82:327-32.
17. Dales RE, White J, Bhumgara C, McMullen E. Parental reporting of childrens' coughing is biased. Eur J Epidemiol 1997;13:541-5.
18. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116:571-7.
19. Gern JE, Brooks GD, Meyer P, Chang A, Shen K, Evans MD, et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. J Allergy Clin Immunol 2006;117:72-8.
20. Gern JE, Martin MS, Anklam KA, Shen K, Roberg KA, Carlson-Dakes KT, et al. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. Pediatr Allergy Immunol 2002;13:386-93.
21. Caserta MT, Yang H, Gill SR, Holden-Wiltse J, Pryhuber G. Viral respiratory infections in preterm infants during and after hospitalization. J Pediatr 2017;182:53-8.e3.
22. Weinberg GA, Schnabel KC, Erdman DD, Prill MM, Iwane MK, Shelley LM, et al. Field evaluation of TaqMan Array Card (TAC) for the simultaneous detection of multiple respiratory viruses in children with acute respiratory infection. J Clin Virol 2013;57:254-60.
23. Lee WM, Lemanske RF Jr, Evans MD, Vang F, Pappas T, Gangnon R, et al. Human rhinovirus species and season of infection determine illness severity. Am J Respir Crit Care Med 2012;186:886-91.
24. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360:588-98.
25. Kristjansson S, Bjarnarson SP, Wennergren G, Palsdottir AH, Arnadottir T, Haraldsson A, et al. Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local TH2-like response. J Allergy Clin Immunol 2005;116:805-11.

26. Luchsinger V, Ampuero S, Palomino MA, Chnaiderman J, Levican J, Gaggero A, et al. Comparison of virological profiles of respiratory syncytial virus and rhinovirus in acute lower tract respiratory infections in very young Chilean infants, according to their clinical outcome. J Clin Virol 2014;61:138-44.
27. Houben ML, Coenjaerts FE, Rossen JW, Belderbos ME, Hofland RW, Kimpen JL, et al. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. J Med Virol 2010;82:1266-71.
28. Wishaupt JO, van den Berg E, van Wijk T, van der Ploeg T, Versteegh FG, Hartwig NG. Paediatric apnoeas are not related to a specific respiratory virus, and parental reports predict hospitalisation. Acta Paediatr 2016;105:542-8.
29. Wishaupt JO, van der Ploeg T, de Groot R, Versteegh FG, Hartwig NG. Single- and multiple viral respiratory infections in children: disease and management cannot be related to a specific pathogen. BMC Infect Dis 2017;17:62.
30. Costa LF, Queiroz DA, Lopes da Silveira H, Bernardino Neto M, de Paula NT, Oliveira TF, et al. Human rhinovirus and disease severity in children. Pediatrics 2014;133:e312-21.
31. Miller EK, Bugna J, Libster R, Shepherd BE, Scalzo PM, Acosta PL, et al. Human rhinoviruses in severe respiratory disease in very low birth weight infants. Pediatrics 2012;129:e60-7.
32. Miller JE, Hammond GC, Strunk T, Moore HC, Leonard H, Carter KW, et al. Association of gestational age and growth measures at birth with infection-related admissions to hospital throughout childhood: a population-based, data-linkage study from Western Australia. Lancet Infect Dis 2016;16:952-61.
33. Ricart S, Marcos MA, Sarda M, Anton A, Munoz-Almagro C, Pumarola T, et al. Clinical risk factors are more relevant than respiratory viruses in predicting bronchiolitis severity. Pediatr Pulmonol 2013;48:456-63.

50 Years Ago in *The Journal of Pediatrics*

Antimicrobial Treatment of Pertussis

Bass JW, Klenk EL, Kotheimer JB, Linnemann CC, Smith MH. J Pediatr 1969;75:768-81.

Bass et al concluded that erythromycin is the most effective drug to render a child with pertussis as non-infectious, based on a prospective study of 50 children with microbiologically confirmed disease. The study population consisted of 5 groups of 10 patients each, administered no antibiotics, ampicillin, oxytetracycline, chloramphenicol, or erythromycin, for at least 7 days. None of the 4 drugs altered the clinical course of pertussis when given in paroxysmal stage. Nasopharyngeal clearance was achieved in those receiving erythromycin, oxytetracycline, and chloramphenicol. The erythromycin group was rendered noninfective within 3 days. All 3 drugs showed bacteriologic relapse in some of the cases. Pertussis hyperimmune globulin also did not alter the clinical or bacteriologic course of the illness.

Fifty years later, macrolides remain the gold standard to eradicate nasal bacterial carriage of *Bordetella pertussis* and for pre-exposure prophylaxis in asymptomatic contacts. However, their effectiveness for the treatment of pertussis is still questionable. Erythromycin may be effective in shortening the illness only when given in pre-paroxysmal stage. Due to the toxic profile of erythromycin and its causative association with idiopathic hypertrophic pyloric stenosis in newborns, in 2005 the Centers for Disease Control and Prevention recommended azithromycin as the preferred macrolide for infants <1 month age with pertussis.[1] The American Family Physician Society and the American Society of Microbiology have recommended azithromycin as the first-line drug for pertussis at all age groups.[2,3] Trimethoprim-sulfamethoxazole also is recommended as an alternative drug for infants >2 months of age.[4] The American Family Physician Society also has shortened the duration of antibiotic administration (azithromycin 5 days, clarithromycin 7 days, and erythromycin 14 days), as shorter courses of these antibiotics were found to be equally effective with lesser toxic profile.[4] Pertussis immunoglobulin still has not shown any definite beneficial effects on clinical course of disease. All said and done, the status of treatment of pertussis remains by and large unchanged in last 50 years.

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References

1. Tiwari T, Murphy TV, Moran J , National Immunization Program, CDC. Recommended Antimicrobial Agents for Treatment and Postexposure Prophylaxis of Pertussis CDC Guidelines 2005. MMWR Recomm Rep 2005;54:1-16.
2. Kline JM, Lewis WD, Smith EA, Tracy LR, Moerschel SK. Pertussis: a re-emerging infection. Am Fam Physician 2013;88:507-14.
3. Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: microbiology, disease, treatment, and prevention. Clin Microbiol Rev 2016;29:449-86.
4. Altunaiji S, Kukuruzovic R, Curtis N, Massie J. Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev 2007;CD004404.

Figure 2. Cluster dendrogram of respiratory symptoms. The dendrogram was created with data from the dissimilarity matrix analyses of respiratory symptoms including wheeze, cough, hoarseness, tachypnea, retractions, sick for >4 days, runny nose and fever. It suggests a physiologic relationship among these 8 symptoms.

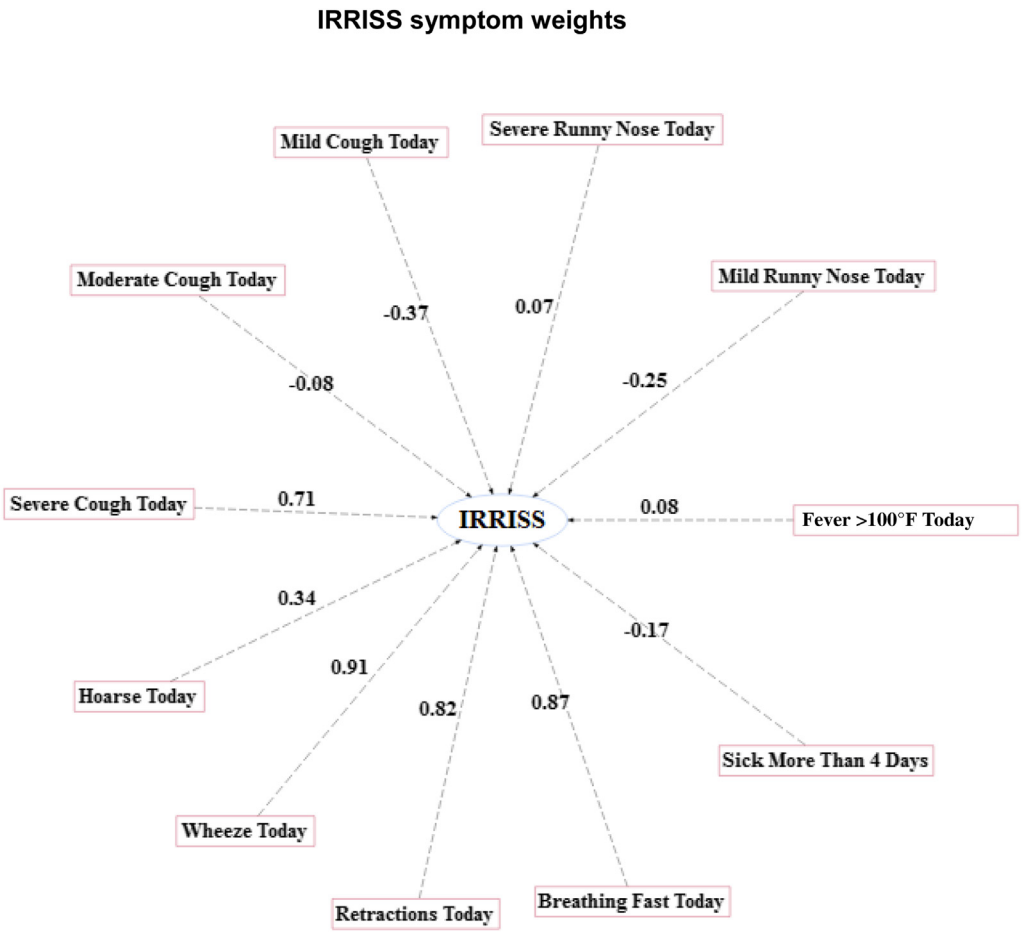

Figure 3. Computation of the IRRSS score. Respiratory symptom weights were computed via factor analysis with polychoric correlation matrix of symptoms. The final IRRSS was computed as: IRRSS = 0.07 × Severe runny nose today − 0.25 × Mild runny nose today + 0.08 × Fever >100°F today − 0.17 × Sick >4 days + 0.87 × Breathing fast today + 0.82 × Retractions today + 0.91 + Wheeze Today + 0.34 × Hoarse today + 0.71 × Severe cough today − 0.08 × Moderate cough today − 0.37 × Mild cough today + 10.

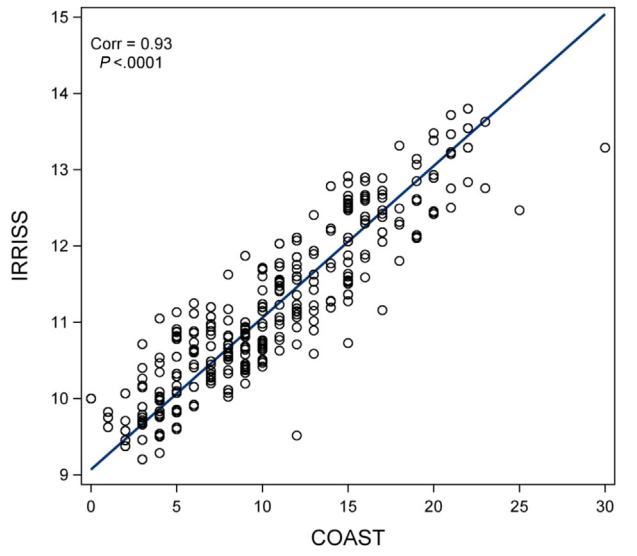

Figure 4. Correlation between the maximal COAST score and the maximal IRRSS. The scores were significantly correlated (r = 0.93; $P < .0001$).

Table III. Illness visits and respiratory virus detection in preterm infants by palivizumab status

	Late preterm			ELGANS		
		Palivizumab received			Palivizumab received	
Visits	All	No	Yes	All	No	Yes
Total illness visits	103	94	9	79	15	64
Research illness visits						
Illness visits	101	92	9	67	14	53
No virus identified						
hRV−						
RSV−	18	16	2	15	–	15
Virus infection identified						
hRV−						
RSV−	16	14	2	14	4	10
RSV+	10	10	–	5	–	5
hRV+						
RSV−	53	48	5	32	9	23
RSV+	4	4	–	1	1	–
Hospital admission						
Illness visits	2	2	–	12	1	11
No virus identified						
hRV−						
RSV−	–	–	–	2	–	2
Virus infection identified						
hRV−						
RSV−	1	1	–	3	1	2
RSV+	1	1	–	3	–	3
hRV+						
RSV−	–	–	–	3	–	3
RSV+	–	–	–	1	–	1

Table V. Results of the linear mixed effects regression models of the average AUC of the COAST score and the IRRISS

	COAST score		IRRISS	
Variables	**Estimate**	***P* value**	**Estimate**	***P* value**
Hospital admission				
Hospitalization	0.548	<.001	0.067	<.001
Gestational age at birth	−0.018	.002	−0.003	.003
African American vs white	0.195	.016	0.028	.029
Other race vs white	0.077	.326	0.023	.065
Family history of asthma	0.080	.227	0.019	.071
4-6 vs < 4 people in home	−0.069	.318	−0.011	.327
7-10 vs < 4 people in home	−0.053	.721	−0.022	.357
Birth weight Z-score	0.047	.172	0.005	.314
Other virus infection				
Other than hRV/RSV	0.050	.399	0.002	.845
Gestational age at birth	−0.023	<.001	−0.003	<.001
African American vs white	0.209	.012	0.029	.023
Other race vs white	0.091	.255	0.024	.049
Family history of asthma	0.115	.087	0.023	.027
4-6 vs < 4 people in home	−0.090	.205	−0.013	.220
7-10 vs < 4 people in home	−0.126	.412	−0.031	.191
Birth weight Z-score	0.067	.061	0.008	.154
RSV infection				
RSV infection	0.272	<.001	0.048	<.001
Gestational age at birth	−0.024	<.001	−0.003	<.001
African American vs white	0.189	.025	0.026	.042
Other race vs white	0.064	.426	0.020	.105
Family history of asthma	0.108	.113	0.022	.034
4-6 vs < 4 people in home	−0.066	.359	−0.009	.434
7-10 vs < 4 people in home	−0.124	.417	−0.030	.201
Birth weight Z-score	0.053	.135	0.006	.309
hRV infection				
hRV infection	−0.103	.040	−0.017	.032
Gestational age at birth	−0.024	<.001	−0.003	<.001
African American vs white	0.194	.021	0.027	.036
Other race vs white	0.083	.304	0.023	.063
Family history of asthma	0.116	.087	0.023	.026
4-6 vs < 4 people in home	−0.081	.261	−0.011	.307
7-10 vs < 4 people in home	−0.124	.417	−0.030	.207
Birth weight Z-score	0.064	.072	0.007	.176

Table VI. Correlations between respiratory symptoms and hospitalization, RSV, hRV, and other viral infections

Variables	**Hospitalization**	**hRV infection**	**RSV infection**	**Other than hRV/RSV**
Fever	.303	.003	.065	<.001
Rhinorrhea	.358	.055	.812	.257
Sick >4 days	.211	.016	.056	.524
Retractions	<.001	.436	.167	.293
Tachypnea	<.001	.315	.403	.438
Hoarseness	.219	.957	.182	.037
Cough	.851	.063	.001	.252
Wheeze	.021	.931	.633	.101

Values are *P* values.

Table VII. Viral respiratory pathogens identified other than hRV at illness visits included in the analyses

Target	**Frequency**
Adenovirus	15
Bocavirus	25
Corona virus 2	12
Corona virus 3	14
Corona virus 4	3
Enterovirus	11
Influenza A	7
Influenza B	2
Parainfluenza virus 1	3
Parainfluenza virus 2	6
Parainfluenza virus 3	17
Parechovirus	5
RSV	44
Metapneumovirus	16