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Risk factors for requiring intensive care among children admitted to ward with bronchiolitis

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Abstract

Objective—To examine risk factors for transfer of bronchiolitis patients from the ward to the intensive care unit (ICU) and/or initiation of critical care interventions.

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 primary outcome was late intensive care use, defined as a transfer to the ICU and/or use of mechanical ventilation (regardless of location) after the child's first inpatient day.

Results—Among 2,104 children hospitalized with bronchiolitis, 1,762 (84%) were identified as initial ward patients, comprising the analysis cohort. The median age was 4 months (interquartile range, 2–9 months), 1,048 (59%) were male. The most frequently detected pathogens were respiratory syncytial virus (72%) and rhinovirus (25%). After the first inpatient day, 47 (3%; 95% CI, 2%–4%) were subsequently transferred to the ICU or required mechanical ventilation. In the multivariable logistic regression model predicting subsequent transfer to the ICU or mechanical ventilation use, the significant predictors were birth weight <5 pounds (OR, 2.28; 95% CI, 1.30–4.02; $P=0.004$) and respiratory rate high of 70 per minute on the first inpatient day (OR, 4.64; 95% CI, 2.86–7.53; $P<0.001$).

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Conclusions—In this multicenter study of children hospitalized with bronchiolitis, low birth weight and tachypnea were significantly associated with subsequent transfer to the ICU and/or use of mechanical ventilation.

Keywords

bronchiolitis; hospitalization; intensive care unit; mechanical ventilation; risk factors

INTRODUCTION

As a leading cause of pediatric hospitalizations, bronchiolitis is managed in diverse settings from freestanding children's hospitals to community-based general hospitals.¹ Most children with bronchiolitis have an uneventful course; however, approximately one in ten are hospitalized.² Prior studies identified risk factors associated with severe bronchiolitis requiring hospitalization, such as prematurity, younger age, environmental factors (e.g., passive smoking, crowded household), and comorbidities (e.g., chronic pulmonary disease, congenital heart disease, immunodeficiency, neurologic disease).^{2,3} Furthermore, 2 to 3% of hospitalizations with bronchiolitis involve mechanical ventilation.⁴

Unfortunately, there is both a dearth and variable geographic distribution of pediatric intensive care units (ICUs) available for this level of care.⁵ Furthermore, the difficulty in determining the appropriate level of care for children with bronchiolitis is well documented by marked variability in acute management and disposition.⁶ The limited resources and the observed variability in care highlight the need for evidence-based assessments for risk of clinical deterioration which could improve triage and management decisions at both referring and receiving hospitals. A single-center retrospective study of 17 children with bronchiolitis requiring ICU transfers found that clinical parameters have limited value for predicting clinical deterioration; however, these inferences were potentially limited by type-II error.⁷ Additionally, our previous multicenter analysis identified several factors that predict the use of mechanical ventilation for children with bronchiolitis.⁸ However, the subgroup of children with subsequent clinical deterioration after hospitalization remains poorly defined in the literature.

To address this knowledge gap, using a prospective multicenter cohort of hospitalized children with bronchiolitis, we aimed to investigate the risk factors for transfer of bronchiolitis patients from the ward to the intensive care unit and/or initiation of critical care interventions.

METHODS

Study Design

This study was a secondary analysis of a prospective observational cohort data of children hospitalized with bronchiolitis. The study setting, methods of measurement, and measured variables have been reported previously.^{8,9} Briefly, we conducted a multicenter, prospective cohort study during the 2007 to 2010 winter seasons for three consecutive years, as part of the Multicenter Airway Research Collaboration (MARC), a program of the Emergency

Medicine Network (EMNet).^{8–11} 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 ICU.

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. 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. Medical records were reviewed to collect clinical data from the pre-hospitalization evaluation (clinic or emergency department) and the child's inpatient course, including vital signs, medical management, and disposition. Data were manually reviewed at the EMNet Coordinating Center and site investigators were queried about missing data and discrepancies identified.

Investigators also collected nasopharyngeal aspirates using a standardized protocol. 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. The aspirates were tested using singleplex or duplex two-step real time PCR. Details of the primers and probes have been described elsewhere.^{12–14}

Statistical Analyses

For the purpose of this analysis, we first identified all "initial ward" patients (i.e., children admitted to observation unit, ward, or step-down unit who did not require non-invasive or invasive mechanical ventilation on their first inpatient day). Non-invasive mechanical ventilation included continuous positive airway pressure ventilation. First inpatient day was defined as the calendar day of hospitalization. The primary outcome of this analysis was "late intensive care use" which was defined as a transfer to the ICU and/or use of mechanical ventilation (regardless of location) after the child's first inpatient day. We performed multivariable logistic regression with the use of generalized estimating equations to investigate predictors of late intensive care use and to account for the clustering of patients at the site level. We chose the covariates (ie, age, sex, birth weight, respiratory rate, and virology results [RSV status and HRV status]) based on clinical plausibility and *a priori* knowledge.^{2,3,7–9,15} In sensitivity analyses, we fit two additional models adding two covariates (i.e., exposure to tobacco smoke, duration of difficulty breathing) separately. We also conducted a sensitivity analysis excluding late intensive care use without mechanical ventilation from the primary outcome. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs); all *P*-values were two-tailed, with *P*<0.05 considered statistically significant. All analyses were performed using Stata 11.2 (Stata Corp, College Station, TX).

RESULTS

Of the 2207 enrolled children, 2,104 had disposition data (95%). Among these 2104 children, 342 (16%) were hospitalized to the ICU on the first inpatient day. Consequently, 1,762 (84%) were identified as initial ward patients, comprising the analysis cohort. Overall, the median age was 4 months (interquartile range, 2–9 months), 1,048 (59%) were male; 1,060 (60%) were white. The most frequently detected pathogens were respiratory syncytial virus (72%) and rhinovirus (25%). After the first inpatient day, 47 (3%; 95% CI, 2%–4%) were subsequently transferred to the ICU or required mechanical ventilation. Among these, 18 (38%) were transferred to the ICU but did not require mechanical ventilation. Additionally, of these 47 late intensive care use, 30 (64%) occurred on the second day; 11 (23%) occurred on the third day.

Table 1 shows unadjusted associations between patient characteristics and late intensive care use. Compared to children who did not require intensive care, children with late intensive care use were more likely to be age <6 months, have a higher respiratory rate, and more likely to receive nebulized albuterol and epinephrine on the first inpatient day (all $P<0.05$). By contrast, there were no significant differences in the proportion of children with comorbid disorders and virology results between the two groups.

In the multivariable logistic regression model predicting late intensive care use (Table 2), the significant predictors were birth weight <5 pounds (OR, 2.28; 95% CI, 1.30–4.02; $P=0.004$) and respiratory rate high of 70 per minute on the first inpatient day (OR, 4.64; 95% CI, 2.86–7.53; $P<0.001$). In sensitivity analyses, the adjusted associations of these two predictors with late intensive care use persisted with the inclusion of the different covariates and the exclusion of late intensive care use without mechanical ventilation from the primary outcome (Table 3).

DISCUSSION

In this large, multicenter, multiyear, prospective cohort study, we found that 3% of children hospitalized with bronchiolitis were subsequently transferred to the ICU or required mechanical ventilation and that this rate was similar to the previous smaller study.⁷ Our data also demonstrated that birth weight <5 pounds and a respiratory rate 70 on the first inpatient ward day were independently associated with late intensive care use. These multicenter data support "conventional wisdom" but also reveal new findings that merit further study.

Low birth weight and tachypnea are consistently identified as risk factors for severe bronchiolitis, as measured by risk of hospitalization.¹⁶ In the current study, we demonstrated that these two clinical factors independently predicted late intensive care use, even after adjusting for demographic and clinical characteristics. While these factors might assist in better defining critical respiratory distress in hospitalized children, they also might be markers of being born with a reduced lung function.¹⁷ Nevertheless, in a previous single-center study of hospitalized children with bronchiolitis, tachypnea was shown to have low

sensitivity in predicting the ICU transfer outcome, suggesting a potentially limited clinical significance of this variable.⁷

Interestingly, two-thirds of late intensive care use occurred on the second inpatient day. This finding emphasizes the need for further studies on the monitoring and triage criteria in the inpatient setting to facilitate best patient placement and efficient transfer to ICU care when needed.

Our study has potential limitations. First, the observed associations do not necessarily prove causality and might be confounded by unmeasured factors, such as previous history of bronchiolitis. Second, our model did not include oximetry data because approximately 20% of children had missing data for room air oximetry on the first inpatient day. However, in sensitivity analysis (data not shown), this missing information was a significant predictor of the outcome. We suspect that missing information may be a proxy for being on supplemental oxygen and, therefore, more severe illness. Third, we are unable to differentiate between the patients who were directly admitted to the ICU and those who were admitted initially to the ward and then transferred to the ICU on their first inpatient day. We suggest that these children with early transfer are a mix of limited ICU bed availability, mistaken clinician assessment of severity, and true clinical deterioration. Disentangling these possibilities would be very challenging across the many sites in our study. By contrast, we believe that our patient population is more likely to represent children who experienced a true clinical deterioration. Finally, our inferences may not be generalizable to other clinical settings. For example, the study population was enrolled in large urban medical centers. Likewise, institutional variation in resource utilization for children with bronchiolitis may limit generalizability.¹⁸ The multicenter design mitigates this concern, as does our focus on a major intervention with associated adverse events,¹⁹ which should have less variation than other aspects of bronchiolitis care.

Based on our prospective multicenter data, we found that low birth weight and tachypnea were significantly associated with subsequent transfer to the ICU and/or use of mechanical ventilation. As bronchiolitis research moves forward, the subgroup of children with subsequent clinical deterioration will be of particular interest. Although our ability to identify this specific subgroup is limited,⁷ our findings underscore for researchers the need for continued work on more accurate prediction of clinical deterioration. Furthermore, our data facilitate studies to examine why and how these children differ from the majority of children who do not require late intensive care use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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WHAT'S NEW

In this 16-center prospective study of 1,762 children hospitalized with bronchiolitis on the ward, 3% subsequently required intensive care (including mechanical ventilation). Low birth weight and tachypnea on the first inpatient day were predictors of requiring late use of intensive care.

Table 1

Characteristics of Children with Bronchiolitis on the Ward, According to Clinical Course

Characteristics	No intensive care use (n=1,715)	Late intensive care use (n=47)	P-value
Study year			0.12
2007–2008 winter season	21%	30%	
2008–2009 winter season	39%	26%	
2009–2010 winter season	40%	44%	
Age, mo			0.04
<6	62%	77%	
6	38%	23%	
Sex			0.77
Male	60%	57%	
Female	40%	43%	
Race			0.59
White	60%	55%	
Black	26%	26%	
Other or missing	14%	19%	
Hispanic ethnicity	37%	40%	0.61
Gestational age, weeks			0.20
<32	7%	13%	
32–36.9	17%	17%	
37	77%	70%	
Birth weight, pounds			0.07
<5	12%	21%	
5	88%	79%	
Exposure to tobacco smoke	13%	17%	0.39
Major relevant, comorbid medical disorder*	21%	24%	0.66
Previously admitted overnight to a hospital (any cause)	20%	30%	0.10
Kept in ICU, premature nursery, or any type of special care facility when born (%)	25%	36%	0.09
When difficulty breathing began prior to index visit			0.11
<24 hours or no difficulty breathing	29%	38%	
1–3 days	43%	47%	
4 days	28%	15%	
Vital signs on first day of admission			
Highest respiratory rate, per minute (median, IQR)	52 (44–60)	56 (48–70)	0.003
<70	92%	70%	<0.001
70	8%	30%	
Lowest O2 saturation on room air [†] , % (median, IQR)	94 (92–96)	91 (87–95)	0.003
Given nebulized albuterol on first day of admission	34%	55%	0.003
Given nebulized epinephrine on first day of admission	7%	19%	0.01
Given steroids on first day of admission	15%	21%	0.28

Characteristics	No intensive care use (n=1,715)	Late intensive care use (n=47)	P-value
Received high flow oxygen on first day of admission	2%	21%	<0.001
Virology results of nasopharyngeal aspirate [‡]			
RSV	72%	72%	0.95
HRV	25%	28%	0.71
Adenovirus	8%	11%	0.59
HMPV	8%	9%	0.78
Number of viral pathogens detected from nasopharyngeal aspirate			1.00
0	5%	4%	
1	65%	66%	
2	30%	30%	

Abbreviations: IQR, interquartile range; ICU, intensive care unit; RSV, respiratory syncytial virus; HRV, human rhinovirus; HMPV, human metapneumovirus.

* Relevant comorbid medical disorders include respiratory, cardiac, neurologic, gastrointestinal, and immunologic diseases.

[‡] Data are available for 1401 patients.

[‡] Percentages do not sum up to 100% because of co-infections.

Table 2Multivariable Logistic Regression of Factors Associated with Late Intensive Care Use^{*}

Variables	Odds ratio (95% CI)	P-value
Age, mo [†]		
<6	2.05 (0.95–4.39)	0.07
6	Reference	-
Female	1.14 (0.70–1.84)	0.60
Birth weight, pounds [‡]		
<5	2.28 (1.30–4.02)	0.004
5	Reference	-
Highest respiratory rate on first day of admission [‡] , per minute		
<70	Reference	-
70	4.64 (2.86–7.53)	<0.001
Virology		
RSV only	Reference	-
HRV only	0.55 (0.12–2.48)	0.44
Others [‡] or none	1.07 (0.63–1.80)	0.80

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; HRV, human rhinovirus.

^{*} Good model fit (P=0.87) by Hosmer-Lemeshow test.[†] Variables were dichotomized in the multivariable model.[‡] Others includes adenovirus, human metapneumovirus, and co-infections.

Table 3
Sensitivity Analyses of Multivariable Logistic Regression of Factors Associated with Late Intensive Care Use

Variables	Late intensive care use (47 cases)			Late intensive care use excluding cases without mechanical ventilation use (29 cases)		
	Model 1*	Model 2 [†]	Model 3	Model 1*	Model 2 [†]	Model 3
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, months [‡]		0.06		0.08		<0.001
<6	2.05 (0.96–4.37)		2.03 (0.91–4.51)		5.64 (2.52–12.64)	
6	Reference		Reference		Reference	
Female	1.13 (0.70–1.83)	0.61	1.09 (0.66–1.80)	0.74	1.05 (0.49–2.24)	0.91
Birth weight, pounds						
<5	2.33 (1.31–4.16)	0.004	2.22 (1.30–3.78)	0.003	2.46 (1.25–4.87)	0.009
5	Reference		Reference		Reference	
Exposed to tobacco smoke	1.47 (0.83–2.60)	0.19	-	-	-	-
When difficulty breathing began prior to index visit						
<24 hours or no difficulty breathing	-	-	Reference		-	-
1–3 days	-	-	0.88 (0.29–2.66)	0.82	-	-
4 days	-	-	0.41 (0.14–1.19)	0.10	-	-
Highest respiratory rate first day of admission						
<70	Reference		Reference		Reference	
70	4.67 (2.84–7.69)	<0.001	4.72 (2.88–7.74)	<0.001	3.19 (1.72–5.94)	<0.001
RSV/HRV status						
RSV only	Reference	-	-	-	-	-
HRV only	0.52 (0.12–2.35)	0.40	-	-	-	-
Others [§] or none	1.06 (0.62–1.83)	0.82	-	-	-	-

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; HRV, human rhinovirus.

* Adding exposure to tobacco smoke to the original model.

[†] Adding duration of difficulty breathing and removing the virus pathogens from the original model.

[‡] Variables were dichotomized in the multivariable model.

§ Others includes adenovirus, human metapneumovirus, and co-infections.

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