Early Use of Bronchodilators and Outcomes in Bronchiolitis

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abstract

BACKGROUND AND OBJECTIVES: There are no effective interventions to prevent hospital admissions in infants with bronchiolitis. The American Academy of Pediatrics recommends against routine bronchodilator use for bronchiolitis. The objective of this study was to characterize trends in and outcomes associated with the use of bronchodilators for bronchiolitis.

METHODS: This is a multicenter retrospective study of infants <12 months of age with bronchiolitis from 49 children's hospitals from 2010 to 2018. The primary outcomes were rates of hospital admissions, ICU admissions, emergency department (ED) return visits after initial ED discharge, noninvasive ventilation, and invasive ventilation. Multivariable logistic regression was used to evaluate the rates of outcomes among hospitals with high and low early use of bronchodilators (on day of presentation).

RESULTS: A total of 446 696 ED visits of infants with bronchiolitis were included. Bronchodilator use, hospital admissions, and ED return visits decreased between 2010 and 2018 (all $P <$ .001). ICU admissions and invasive and noninvasive ventilation increased over the study period (all $P <$ .001). Hospital-level early bronchodilator use (hospitals with high versus low use) was not associated with differences in patient-level hospital admissions, ICU admissions, ED return visits, noninvasive ventilation, or invasive ventilation (all $P >$ .05).

CONCLUSIONS: In a large study of infants at children's hospitals, bronchodilator therapy decreased significantly from 2010 to 2018. Hospital-level early bronchodilator use was not associated with a reduction in any outcomes. This study supports the current American Academy of Pediatrics recommendation to limit routine use of bronchodilators in infants with bronchiolitis.

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Dr Shanahan and Dr Bachur conceptualized and designed the study, coordinated and supervised the data collection, conducted data analyses and interpretation, and drafted the initial manuscript; Dr Monuteaux conceptualized and designed the study, collected data, and conducted data analyses and interpretation; Dr Nagler conceptualized and designed the study and interpreted data; and all authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The American Academy of Pediatrics Clinical Practice Guideline recommends against routine use of bronchodilators for bronchiolitis. Bronchodilators have not been shown to change outcomes in bronchiolitis in several systematic reviews.

WHAT THIS STUDY ADDS: The use of bronchodilators for bronchiolitis decreased from 2010 to 2018. In a large group of infants, hospital-level bronchodilator use was not associated with hospital admissions, intensive care admissions, emergency department return visits after initial emergency department discharge, or ventilatory support.

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Bronchiolitis is the most common lower respiratory tract infection in infants in the United States, accounting for almost 300 000 emergency department (ED) visits per year.[1,2] Although hospitalizations for bronchiolitis are declining, they account for 18% of admissions for infants and are associated with rising costs, ~$734 million in 2016 alone.[3,4] There is currently no known single effective intervention to reduce the likelihood of admission for bronchiolitis in the ED.[5]

The American Academy of Pediatrics (AAP) Clinical Practice Guideline recommends against the routine use of bronchodilators to treat bronchiolitis.[5] Bronchodilators have not been shown to benefit in the management of bronchiolitis in several systematic reviews and a meta-analysis.[6–8] A 2014 meta-analysis revealed a trend toward reduction in hospitalization rates with bronchodilator administration that was not statistically significant.[7] Limited data exist on the ability of bronchodilators to reduce the need for noninvasive and invasive ventilation in bronchiolitis. These findings have not been validated in a large cohort sufficiently powered to detect small changes in hospitalizations or changes in outcomes with low incidence, including invasive ventilation. In addition, recent national trends in bronchodilator use in the ED and their impact on outcomes in bronchiolitis are not known. Single institutions have performed effective quality improvement campaigns to reduce ED bronchodilator use in infants with bronchiolitis.[9]

The objectives of this study were to describe temporal trends in and associations between ED bronchodilator therapy and outcomes, including hospitalization, noninvasive and invasive ventilation, and ED return visits after initial ED discharge for bronchiolitis. The current study extends previous research on bronchodilators in bronchiolitis by characterizing trends in clinical outcomes, providing the opportunity to identify potential unintended consequences of widespread changes in clinical practices around bronchodilators. In addition, this large, national study of infants with bronchiolitis provides a large sample of outcomes with low incidence, which have been historically challenging to study.

METHODS

Study Design and Setting

This was a multicenter, retrospective, cross-sectional study of infants presenting to the ED with bronchiolitis. Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, ED, ambulatory surgery and observation encounter-level data from >49 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Lenexa, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge and encounter data, including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource use data, including pharmaceuticals, imaging, and laboratory, into PHIS. Data are deidentified at the time of submission and subjected to a number of reliability and validity checks before being included in the database. The Committee on Clinical Investigation at Boston Children's Hospital approved this study with a waiver of informed consent.

Study Population

Infants <12 months of age who were diagnosed with bronchiolitis in the ED were included. In the analysis of trends, infants presenting between January 1, 2010, and December 31, 2018, were included. The analysis of outcomes was limited to infants presenting between January 1, 2015, and December 31, 2018. This time period was selected to reflect current hospital-level practice patterns, which may be distinct from clinical practices before the publication of the newest AAP guidelines in 2014.[3,5] Infants with bronchiolitis were identified by using the *International Classification of Diseases, Ninth Revision, Clinical Modification*, (ICD-9-CM) code of 466.1 or *International Classification of Diseases, 10th Revision, Clinical Modification*, (ICD-10-CM) code of J21 as the primary discharge diagnosis. Infants with complex chronic conditions were identified according to the pediatric complex chronic conditions classification and excluded.[10,11]

Measurements

Patient demographics (sex, age, race, ethnicity, primary insurance, and disposition) as well as hospital characteristics (ED to inpatient admission rate and ED patient volume) were measured. Primary insurance was classified as public payer, private payer, or other. Diagnoses and procedures were identified by using ICD-9-CM, ICD-10-CM, Current Procedural Terminology, and PHIS-specific clinical transaction codes. Illness severity was measured by using All Patient Refined Diagnosis Related Group (APR-DRG) severity scores, a marker of the severity of illness and

risk of death in hospitalized children.[12]

Outcomes and Predictor Variables

The primary outcomes were the rates of bronchodilator use, hospitalization, admission to an ICU, ED return visit within 3 days of initial ED discharge, noninvasive ventilation, and invasive ventilation among the study sample.

Hospital-level rates of "early" (as defined by administration on the date of presentation) bronchodilator use among the study sample were calculated. Hospitals in the lowest and highest quartiles of bronchodilator use were classified as low and high users, respectively. Early bronchodilator use was defined as the administration of a nebulized bronchodilator on the calendar day of presentation.

Bronchodilator use and invasive and noninvasive ventilation were identified by using ICD-9-CM, ICD-10-CM, Current Procedural Terminology, and PHIS clinical transaction codes. Bronchodilators included nebulized albuterol, racemic epinephrine, ipratropium, and levalbuterol. Noninvasive ventilation was defined by using codes for continuous positive airway pressure, bilevel positive airway pressure, noninvasive positive pressure ventilation, and noninvasive ventilation. Invasive ventilation was defined by using the mechanical ventilation flag created by PHIS, which includes codes for continuous invasive mechanical ventilation, respiratory ventilation, and mechanical ventilation.

Statistical Analysis

Descriptive statistics were used to characterize the demographic features of the patients, by using frequencies with proportions and medians with interquartile ranges for categorical and continuous variables, respectively. To compare patient demographics between hospitalizations with and without bronchodilator therapy, χ^2 and Wilcoxon rank tests were used for categorical and continuous variables, respectively. Patient demographics included race and ethnicity as a means of describing the population of infants with bronchiolitis in the study.

Logistic regression models were used to assess linear trends over time in the rates of any bronchodilator use, hospital admission, admission to an ICU, ED return visit within 3 days of initial ED discharge, noninvasive ventilation, and invasive ventilation. The independent variable for these models was calendar year.

Descriptive statistics were used to characterize the use of bronchodilators as well as patient-level and hospital-level factors at hospitals with high and low early bronchodilator use. χ^2 and Kruskal-Wallis rank sum tests were used to compare patient and hospital factors between hospitals with high and low early bronchodilator use for categorical and continuous variables, respectively.

Multivariable logistic regression was used to test the association of hospital-level early bronchodilator use (high versus low users) with patient-level hospitalization, admission to an ICU, noninvasive and invasive ventilation on the initial hospital day, and ED return visit after initial ED discharge. The model was adjusted for patient-level age and median APR-DRG severity scores for all infants with bronchiolitis in the study at each hospital. Age has been previously identified as the strongest predictor of disease severity in children with bronchiolitis.[13] The medians of APR-DRG severity scores for all infants with bronchiolitis in the study at each hospital were used as a marker of severity of illness of the patients with bronchiolitis seen at each center.[14] The model used robust SEs clustered on hospital to account for intrahospital correlation among patients.

Odds ratios (ORs) for the outcomes and 95% confidence intervals (CIs) were calculated. All tests were 2-tailed, and α was set at .05. Statistical analyses were conducted by using Stata SE, version 15 (Stata Corp, College Station, TX).

RESULTS

Study Population

A total of 466 696 emergency visits of infants with bronchiolitis from 49 hospitals were included in the analysis. The median age was 5 months (interquartile range: 2–8). More infants were male (59.9%), white (49.9%), non-Hispanic (65.3%), and publicly insured (71.5%). Overall, 142 873 (32.0%) were treated with bronchodilators. Infants who received bronchodilators were more likely to be male, an older age, Black, non-Hispanic, and publicly insured than those who did not (Table 1; all $P < .001$).

Trends in Bronchodilator Use and Outcomes

Bronchodilator use decreased from 51.5% to 22.8% between 2010 and 2018 (linear trend by year [OR: 0.83; 95% CI 0.83–0.83]; Fig 1). Hospital admissions decreased from 34.4% to 33.1% (OR: 0.98; 95% CI 0.98–0.99), and ICU admissions increased from 2.4% to 4.3% (OR: 1.06; 95% CI 1.05–1.06; Fig 1). ED visits within 3 days after initial ED discharge declined from 5.9% to 5.2% (OR: 0.98; 95% CI 0.98–0.99) over the study period. Noninvasive ventilation increased from 1.0% to 2.9% (OR: 1.15; 95% CI 1.14–1.16), and invasive ventilation increased

TABLE 1 Demographics of Infants Presenting to the ED for Bronchiolitis

Demographic Characteristics	Bronchodilators (n = 142 873 [32.0%])	No Bronchodilators (n = 303 823 [68.0%])	P
Sex, female, n (%)	52 870 (37.0)	126 307 (41.5)	<.001
Age in mo, median (IQR)	6 (3–9)	4 (2–7)	<.001
Race, n (%)			<.001
White	62 850 (44.0)	160 216 (52.7)	
Black	44 171 (31.0)	72 542 (24.5)	
Asian	2742 (1.9)	5711 (1.9)	
Other	24 575 (17.2)	48 912 (16.1)	
Not reported	8535 (6.0)	14 442 (4.8)	
Ethnicity, Latino, n (%)	34 409 (24.1)	86 091 (28.3)	<.001
Primary insurance, n (%)			<.001
Public	104 386 (73.1)	214 967 (70.8)	
Private	32 435 (22.7)	69 484 (22.9)	
Not reported	6052 (4.2)	19 372 (6.4)	

IQR, interquartile range.

from 0.7% to 1.5% (OR: 1.06; 95% CI 1.04–1.07).

Hospital Practice Patterns in Bronchodilator Use and Association With Outcomes

Patient Characteristics

The study included 111 310 infants in the hospital-level analysis, with 56 852 and 54 458 infants at hospitals with high and low early use of bronchodilators, respectively. Rates of early bronchodilator therapy for infants with bronchiolitis ranged from 13.6% to 53.7% and 3.3% to 12.8% at hospitals categorized as having high and low early use of bronchodilators, respectively.

Hospital Characteristics

Infants admitted to hospitals with high early use of bronchodilators for bronchiolitis were older than those admitted to hospitals with low early use of bronchodilators ($P < .001$). Hospitals with high early use of bronchodilators had lower overall ED admission rates, higher annual ED volumes, and higher median APR-DRG severity scores than hospitals with low early use of bronchodilators (all $P < .001$; Supplemental Table 3).

Multivariable Hospital-Level Analysis

There were no significant differences in any outcomes in patients at hospitals with high versus low early use of bronchodilators (Table 2). Hospital admissions (OR: 0.93; 95% CI 0.7–1.3), ICU admissions (OR: 1.5; 95% CI 0.7–3.1), ED return visits after initial ED discharge (OR: 1.2; 95% CI 0.99–1.4), noninvasive ventilation (OR: 3.5; 95% CI 0.7–19.1), and invasive ventilation (OR: 8.2; 95% CI 0.99–67.5) did not differ significantly between hospitals with high and low early bronchodilator use.

In the multivariable models, the odds of all outcomes decreased significantly with increasing age in months, including hospital admissions (OR: 0.91; 95% CI 0.89–0.93), ICU admissions (OR: 0.93; 95% CI 0.89–0.96), invasive ventilation (OR: 0.92; 95% CI 0.89–0.95), noninvasive ventilation (OR: 0.94; 95% CI 0.91–0.98), and ED return visits after initial ED discharge (OR: 0.91; 95% CI 0.90–0.93).

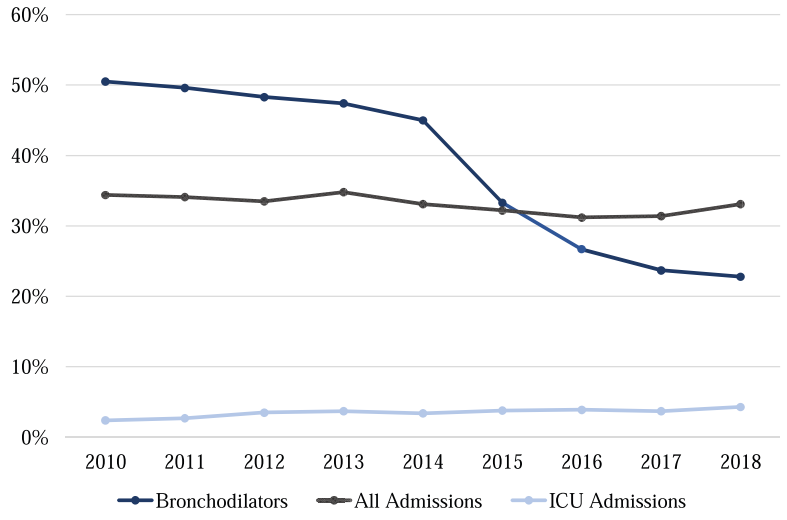

FIGURE 1
Percentage of all infants receiving bronchodilators and admissions for bronchiolitis, 2010 to 2018.

DISCUSSION

In a large study of infants at pediatric centers, bronchodilator use in the ED for bronchiolitis declined significantly from 2010 to 2018. Despite this decline, there was a statistically significant but small and clinically unremarkable decrease in hospital admissions. However, ICU admissions and invasive and noninvasive

TABLE 2 Rates of Outcomes at Hospitals With High and Low Use of Bronchodilators

Outcome	Hospitals With High Use of Bronchodilators (n = 56 767)[a]	Hospitals With Low Use of Bronchodilators (n = 52 819)[a]	OR (95% CI)
Admission, n (%)	18 223 (32.0)	18 312 (33.6)	0.93 (0.7–1.3)
ICU admission, n (%)	2683 (4.7)	1762 (3.2)	1.5 (0.7–3.1)
ED[b] return visit, n (%)	2097 (5.7)	1707 (5.0)	1.2 (0.99–1.4)
Noninvasive ventilation,[b] n (%)	1488 (2.6)	409 (0.8)	3.5 (0.7–19.1)
Invasive ventilation,[b] n (%)	645 (1.1)	77 (0.1)	8.2 (0.99–67.5)

[a] High and low use are defined as the lowest and highest quartiles of hospital-level bronchodilator use for bronchiolitis.
[b] Intervention on initial or following hospital day.

ventilation have risen during this time period. In adjusted analyses, hospital-level early bronchodilator use is not associated with reduction in hospital admission, ICU admission, return visits to the ED after initial ED discharge, invasive ventilation, or noninvasive ventilation.

No Clinical Increase in Admission Rates Despite Substantial Reductions in Bronchodilators for Bronchiolitis

Between 2010 and 2018, infants treated with bronchodilators for bronchiolitis decreased by two-thirds. These trends in bronchodilator use were likely driven by the growing literature suggesting that bronchodilators are not an effective therapy in bronchiolitis as well as the clinical practice guideline on the management of bronchiolitis from the AAP recommending against their use published in 2014.[5–8]

Despite this extensive reduction in bronchodilator use, admissions and ED return visits after initial ED discharge during the study period slightly declined. These contemporaneous trends do not show any adverse associations with the reductions in bronchodilator use for stable patients. However, critical care admissions, invasive ventilation, and noninvasive ventilation have risen. These trends are similar to published increases in noninvasive and invasive ventilation for bronchiolitis from 2000 to 2016.[3] The rising use of noninvasive ventilation for bronchiolitis may have driven this rise in critical care admissions, which may represent a lower threshold to initiate noninvasive ventilation or increasing illness severity among infants with bronchiolitis over the study period. The increasing use of high-flow nasal cannula may also contribute to rising rates of critical care admissions because of some institutional policies requiring critical care admission for its administration.[15,16] This study provides further support that the use of bronchodilators does not improve measurable outcomes when used in the management of bronchiolitis in stable patients who are likely to be discharged from the ED or admitted to the inpatient ward. The simultaneous rising rates of invasive ventilation as bronchodilator use has decreased raises the question of whether these trends are associated.

Hospital-Level Bronchodilator Use and Patient-Level Outcomes in Bronchiolitis

This study suggests that early use of bronchodilators is not associated with reductions in hospital admissions in infants with bronchiolitis, which is consistent with previous literature.[5–8] The study adds to the existing literature as a large, hospital-level analysis aimed to characterize association with ED discharge. Anecdotally, some physicians may sense that there is a subgroup of infants with bronchiolitis who show response to bronchodilators. This large study was performed because it had adequate power to identify small changes, which may have been the first step to identifying that population. Yet, no difference in any outcomes, including admission rates, between hospitals with high and low early use of bronchodilators was identified. Therefore, this study provides further evidence that bronchodilators are not an effective therapy for bronchiolitis.

Strengths, Limitations, and Future Investigations

The strengths of this study include the large sample size and assessment of hospital-level practice patterns in early bronchodilator use as a predictor to mitigate the problem of confounding by indication, which occurs when using patient-level treatment as a predictor. The limitations of this study include the challenges associated with the administrative nature of these data sources, including insufficient patient-level data to quantify illness severity, and preclude conclusions of causality in associations. In addition, administrative data are at risk for recording errors. The PHIS database includes data from tertiary care children's hospitals only, limiting generalizability to patients in other settings. Further investigation is needed to potentially characterize a subgroup of infants with

bronchiolitis who may benefit from bronchodilators.

CONCLUSIONS

In a large, national study of infants admitted to children's hospitals for bronchiolitis, early bronchodilator therapy for bronchiolitis declined markedly from 2010 to 2018, whereas admissions and ED return visits declined slightly. Hospital-level bronchodilator use was not associated with a meaningful difference in hospital admissions for bronchiolitis. This large, multicenter study presents further evidence that bronchodilators are not an effective therapy in bronchiolitis. Future study may define a subgroup of infants with bronchiolitis who respond to bronchodilators.

ABBREVIATIONS

AAP: American Academy of Pediatrics
APR-DRG: All Patient Refined Diagnosis Related Group
CI: confidence interval
ED: emergency department
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
ICD-10-CM: *International Classification of Diseases, 10th Revision, Clinical Modification*
OR: odds ratio
PHIS: Pediatric Health Information System

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