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Bronchodilator Use for Acute Chest Syndrome Among Large Pediatric Hospitals in North America

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Abstract

The utility of bronchodilators to treat acute chest syndrome (ACS) in patients with sickle cell disease is unknown. Our objectives were to examine the variability in bronchodilator use for ACS among pediatric hospitals contributing to a large database and to examine the relationship between bronchodilator use and length of stay (LOS) and mortality. Between 2005 and 2011, bronchodilators were used during 6812/11 328 hospitalizations (60.1%) and use varied from 0.0% to 97.0% (median = 46.0%, interquartile range = 37.0% to 74.0%). Median LOS was 4 days, and interquartile range was 2 to 6 days. Bronchodilator use was associated with a 13.2% increase in LOS (95% confidence interval = 9.2% to 17.3%, $P < .001$). However, in the subgroup with asthma, bronchodilator use was associated with a 17.9% decrease in LOS (95% confidence interval = 1.7% to 31.4%, $P = .03$). There is wide variability in bronchodilator use for ACS, and it has variable association with LOS, depending on comorbid asthma. Prospective trials are needed to evaluate bronchodilators for ACS.

Keywords

acute chest syndrome; bronchial hyperreactivity; bronchodilators; pediatrics; sickle cell disease

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Author Contributions

LSK, WKL, and MCM planned and performed the data analysis, which was approved by all other authors. LSK wrote the first draft of the manuscript and all authors advised, edited, and approved on the final manuscript.

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Declaration of Conflicting Interests

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Introduction

Sickle cell disease (SCD) is a hemolytic anemia that is inherited in an autosomal recessive fashion, based on a single-point mutation in the gene encoding for the β -globin chain of hemoglobin (Hb).¹ It is an extremely common monogenetic disease worldwide, affecting an estimated 1% to 4% of infants born in Sub-Saharan Africa² and approximately 1 in 500 African Americans.³ Acute chest syndrome (ACS) is a common cause for hospitalization among patients with SCD⁴ and is the leading cause of mortality.⁵ It is typically defined as a new pulmonary infiltrate involving at least one complete lung segment on chest radiograph, as well as respiratory signs or symptoms such as chest pain, tachypnea, wheeze, cough, hypoxemia, or fever.² The causes of ACS include infection, fat embolism, and pulmonary infarction.⁶

Children with SCD are known to have high rates of airway hyperreactivity (AHR) even in the absence of asthma,^{7–11} and this AHR may be more prominent during episodes of ACS. A case series of 4 subjects with SCD, but without asthma, demonstrated over 15% improvement in peak flow with albuterol use during episodes of ACS, which was not present when tested 8 weeks later when the subjects were stable.¹² In theory, AHR and consequent bronchoconstriction could lead to ventilation-perfusion mismatching, contributing to hypoxia.¹³ This, in turn, may lead to the deoxygenation and subsequent polymerization of Hb S, resulting in sickling of red blood cells, and ultimately, further occlusion of the pulmonary microvasculature and infarction of pulmonary parenchyma, which may worsen the ACS as part of a “vicious cycle.”¹⁴ Rapid-onset bronchodilators, which are typically used to treat AHR in diseases such as asthma,¹⁵ may prevent this hypothetical scenario and consequently may play an important role in the management of patients with ACS.

Rapid-onset bronchodilators are medications used to relax airway smooth muscle and thereby provide rapid symptom relief in the setting of bronchoconstriction. This class of medications includes short-acting β -adrenergic receptor agonists such as albuterol and terbutaline, which act by binding to the β -2 adrenergic receptors on bronchial smooth muscle,¹⁶ as well as the anticholinergic agent ipratropium bromide, which is a muscarinic receptor antagonist.¹⁷ While bronchodilators have been reported to improve forced expiratory volume in 1 second in a proportion of subjects with ACS and reactive airways disease,⁶ their ability to improve other clinical outcomes are unknown. A recent Cochrane review found no randomized controlled trials evaluating bronchodilators for ACS.¹⁸

Our primary aim was to examine the variability in rapid-onset bronchodilator use for ACS among pediatric hospitals. We hypothesized that there would be a large amount of variability, reflecting the paucity of clinical evidence to guide best practice. Our secondary aim was to examine the relationship between rapid-onset bronchodilator use for ACS and outcomes including length of hospital stay and mortality.

Methods

Description of the Database

Data for this retrospective analysis were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 43 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. The data warehouse function for the PHIS database is managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, hospitals provide discharge/encounter data including demographics, diagnoses, and procedures and resource utilization data (eg, pharmaceuticals, imaging, and laboratory) into PHIS. Data are de-identified at the time of data submission and are subjected to a number of reliability and validity checks before being included in the database. For this study, pharmacy data for hospitalizations that met our case definition were available from 43 hospitals. For a subgroup analysis of hospitalizations with a co-diagnosis of asthma, data were available from 41 hospitals.

This study was approved by the Institutional Review Board of Boston Children's Hospital.

Case Definition

We included all cases of ACS aged 0 to 21 years between years 2005 and 2011. We defined ACS as an International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis of sickle cell crisis (282.62, 282.64, 282.42, or 282.69) *and* either pneumonia (486, 481, 483.0, 480.8, or 482.8) *or* ACS (517.3). ICD-9 codes for pneumonia were included in order to avoid missing cases of ACS that were miscoded as pneumonia. This case definition was consistent with that used in a prior study that utilized the PHIS database.

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Statistical Analysis

Descriptive Statistics—When describing the patient cohort on demographic and clinical characteristics, we used χ^2 tests for categorical variables and *t* tests or Wilcoxon tests for dimensional variables, depending on the normality of distribution of the variable.

Variability in Bronchodilator Use—The unit of analysis was each distinct hospitalization. The primary outcome was any use of bronchodilator during the hospitalization, including inhaled albuterol sulfate, levalbuterol HCl, ipratropium bromide, albuterol sulfate and ipratropium bromide, or parenteral terbutaline sulfate. We examined the variability between hospitals in the use of any bronchodilator among their respective ACS patients. We standardized each hospital's use of bronchodilators for ACS by adjusting for the hospital case mix (a relative value indicating the average complexity or severity of illness in each hospital relative to the other hospitals). We examined variability in bronchodilator use for the entire cohort as well as the subgroup of hospitalizations for which there was a co-diagnosis of asthma (defined as ICD-9 codes 493, 493.01, 493.02, 493.1, 493.11, 493.12, 493.9, 493.91, or 493.92). We also examined variability in bronchodilator use in the

subgroup whose primary diagnosis was defined as sickle cell crisis and ACS (not pneumonia), to ensure that our findings were not dependent on our case definition.

Length of Stay—To examine length of stay, the unit of analysis was each distinct hospitalization. Because length of stay was highly positively skewed, we employed a Poisson regression to evaluate the association between bronchodilator use and length of stay. Generalized estimating equations were utilized to account for clustering of multiple hospitalizations per patient. A comprehensive model was made. Potential confounders, comprising multiple indicators of disease severity and acuity, were determined a priori based on clinical concern and previous literature.¹⁹

These included subject-level covariates (age, gender, race, HbSS genotype, primary insurance payer, and diagnosis of asthma), treatments associated with asthma (inhaled steroids and systemic steroids), treatments during the hospitalization that could act as markers of severity of acute and/or chronic illness (use of narcotics, antibiotics, oxygen, mechanical ventilation, blood transfusion, inhaled nitric oxide, and hydroxyurea, and admission to an intensive care unit), other markers of severity (subject having ≥ 3 admissions for sickle cell crisis in the last year and the All Patient Refined Diagnosis Related Groups [APR-DRGs] severity subclass, a 4-point scale indicating severity of illness, with higher level indicating more severe illness), and hospital-level covariates (discharge year to account for changes in practice over time, and average number of admissions for SCD per year to account for hospital experience with the disease).

Subgroup Analysis—We repeated the Poisson regression analysis in the subgroups of patients with and without a comorbid ICD-9 diagnosis of asthma (as defined above), in order to verify whether the association between bronchodilator use and length of stay was different in these populations.

Mortality—We used a χ^2 test to evaluate the association between bronchodilator use and mortality. Since this outcome was extremely rare in this cohort, we did not estimate a multivariate model. Therefore, the unadjusted odds ratio is presented.

Analyses were conducted using IBM SPSS statistics version 19.0.

Results

Characteristics of Hospitalizations

There were 11 328 hospitalizations (5903 individual subjects) that met our case definition across the 43 hospitals. The mean number of cases of ACS per hospital was 300.0 (standard deviation = 200.3). Bronchodilators were used in 60.1% of hospitalizations, and albuterol was the most frequently prescribed bronchodilator. There were 792 hospitalizations (7.0%) with a co-diagnosis of asthma, of which bronchodilators were used in 704 cases. Table 1 shows the characteristics of the hospitalizations for the entire cohort, subdivided by bronchodilator use. The group that received bronchodilators was statistically significantly more likely to be male, black, have the HbSS genotype, require admission to an intensive

care unit, have more severe disease (APR-DRGs severity subclass 4), have a diagnosis of asthma, receive inhaled or systemic steroids, and other treatments related to ACS (Table 1).

Variability in Bronchodilator Use

The likelihood of receiving bronchodilators, after adjusting for the average case mix of the entire cohort, ranged from 0.0% to 97.0% (median = 46.0%, interquartile range (IQR) = 37.0% to 74.0%; Figure 1). Similar results were obtained when the analysis was performed using only those cases defined using ICD-9 codes for sickle cell crisis and ACS (excluding cases defined using pneumonia codes), with a range of 0.0% to 98.0%, median = 50.4%, and IQR = 37.6% to 76.4%.

When limiting the analysis to hospitalizations of patients with a co-diagnosis of asthma (N = 792 hospitalizations among 41 hospitals), the variability ranged from 0.0% to 100.0%, but with a median of 98.2% and IQR = 73.7% to 100.0%, suggesting more frequent use.

Bronchodilator Use and Length of Stay

The median length of stay for the entire cohort was 4 days, IQR = 2 to 6 days. In the unadjusted model, bronchodilator use was associated with a 24.4% increase in length of stay (95% confidence interval [CI] 19.7% to 29.4%, $P < .001$). In the adjusted model, bronchodilator use was associated with an expected 13.2% increase in length of stay (95% CI = 9.2% to 17.3%, $P < .001$; Table 2).

Subgroup Analysis

When confining the analysis to subjects without comorbid asthma, the expected length of stay remained increased by 14.5% in the group that received bronchodilators (95% CI = 10.5% to 18.6%, $P < .001$). However, when confining the analysis to subjects with comorbid asthma, bronchodilator use was associated with a decrease in expected length of stay by 17.9% (95% CI = 1.7% to 31.4%, $P = .03$).

Bronchodilator Use and Mortality

Mortality was very rare (N = 11, corresponding to 0.1% of the cohort). There was no difference in mortality between the group that received bronchodilators (n = 7, 0.1%) versus the group that did not receive bronchodilators (n = 4, 0.1%).

Discussion

We demonstrate that there is high variability in the use of bronchodilators during admissions for ACS among large pediatric hospitals in North America, ranging from 0.0% to 97.0%. We also report that bronchodilator use during admissions for ACS is associated with longer length of hospital stay, after adjusting for multiple potential confounders. However, in the subcohort of patients with a co-diagnosis of asthma, bronchodilator use is associated with a decreased length of stay. Bronchodilator use is not associated with mortality, which is a very rare outcome in this population. This is the first study that we are aware of to report on variability in bronchodilator use, as well as the association between bronchodilator use and length of stay for ACS.

The high variability we found in the use of bronchodilators for ACS likely reflects the dearth of published evidence regarding their efficacy in the SCD population¹⁸ as well as conflicting expert recommendations. Some authors suggest using bronchodilators only in patients with a known history of asthma or as a trial in those who are wheezing on physical examination,²⁰ while others recommend that AHR should be assumed to be present in all patients and bronchodilators should be used universally.⁶ Not surprisingly, our analysis shows that among patients with a co-diagnosis of asthma, there was less variability in bronchodilator use and a greater proportion of patients received bronchodilators during the admission for ACS (median = 98.2%). The increased use of bronchodilators in this population may be explained by the known association between patients with SCD and comorbid asthma and higher rates of pain crisis⁴ and higher risk of death,²¹ which may prompt initiation of bronchodilator treatment more readily.

Our results show that bronchodilator use is associated with a modest increase in length of hospital stay for patients admitted with ACS. It is possible that the adverse effects of bronchodilators such as tachycardia, anxiety, and hyperactivity¹⁸ may be contributing to a longer length of stay. In subgroup analysis, we found that length of stay was increased with bronchodilator use among subjects who did not have a co-diagnosis of asthma; however, in subjects with a co-diagnosis of asthma, bronchodilator use was associated with a decreased length of stay. This suggests that bronchodilators may be effective during ACS only in those patients with asthma and actually are potentially harmful in patients without asthma. However, caution should be taken in interpreting this finding as it may be a result of confounding by indication. Bronchodilator use was associated with multiple measures of severity and sicker patients tend to receive more medication, including bronchodilators. We attempted to control for severity of illness using 2 possible confounders (APR-DRGs score and ≥ 3 admissions for sickle cell crisis in the last year) as well as multiple other measures of disease severity, including requirement for mechanical ventilation and intensive care unit admission, but there may be remaining unmeasured confounders that we were unable to assess given the nature of the dataset. This needs to be clarified with prospective studies in the future.

It should be noted that the increased length of stay of 13.2%, while statistically significant, may not be clinically significant because it represents an estimated increase of approximately only 5 hours. However, the fact that this association held up when looking at the subpopulation of patients without asthma, and that a statistically significant decrease in length of stay was identified among those patients with asthma, provides convincing evidence of a signal in these data. Perhaps other severity outcomes, such as oxygenation and lung function, which were impossible to evaluate in this study due to the nature of the database, would have shown more robust results.

Our study has several strengths. By using a large database encompassing data from multiple hospitals across North America, we were able to capture a very large number of hospitalizations (>11 000). We were also able to control for a large number of potential confounders in our models.

The nature of this study presents a few potential limitations. The PHIS database is collected for administrative purposes and not for clinical research; therefore, there may be errors in coding that caused us to miss cases of ACS. However, we accounted for this by defining cases as those with a diagnosis of either ACS or pneumonia in an effort to include all with an infiltrate on chest radiograph. The PHIS database also provides data on billed services and pharmaceutical codes, but this does not necessarily equate to administered services and treatments. Finally, while we attempted to control for various measures of severity, acuity, and co-diagnosis of asthma, it is impossible to completely eliminate the possibility of confounding by indication with a retrospective analysis.

Conclusion

There is wide variability in bronchodilator use during hospitalizations for ACS in patients with SCD. Bronchodilator use for ACS may be associated with longer length of stay but not with mortality. The finding of an association between bronchodilator use and longer length of stay in our study may indicate that bronchodilators are potentially harmful in this population, but it is also possible that this finding was secondary to confounding by indication. Interestingly, bronchodilator use is associated with shorter length of stay among patients with a co-diagnosis of asthma, suggesting this subpopulation likely benefits from their use during admissions for ACS. There is sufficient uncertainty and clinical equipoise to justify a randomized, double-blinded, placebo-controlled trial to establish whether bronchodilators are effective and safe for use during ACS. Such a trial is needed to help inform clinical practice.

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Figure 1.
Variation in bronchodilator use for acute chest syndrome, by hospital.
Each vertical bar represents an individual hospital in the database ($N = 43$). Data standardized to entire cohort.

Table 1.

Demographics and Characteristics of Hospitalizations^a.

	Whole Cohort (N = 11 328)	Bronchodilator (n = 6812, 60.1%)	No Bronchodilator (n = 4516, 39.9%)	Odds Ratio (95% Confidence Interval)	P ^b
Age, years (median, range)	9 (0-21)	9 (0-21)	10.2 (0-21)	NA	<.001
Female	5056 (44.6)	2978 (43.7)	2078 (46.0)	0.9 (0.8-1.0) ^c	.02
Black ^d	10 414 (92.8)	6314 (93.5)	4100 (91.8)	1.3 (1.1-1.5)	.001
HbSS	9520 (84.0)	5771 (84.7)	3749 (83.0)	1.1 (1.0 ^e -1.3)	.02
Bronchodilator use				NA	
Albuterol sulfate	6265 (55.3)		None		
Levalbuterol HCl	860 (7.6)		None		
Ipratropium bromide	696 (6.1)		None		
Albuterol sulfate and ipratropium bromide	23 (0.2)		None		
Terbutaline sulfate	10 (0.1)		None		
Primary payer ^f				NA	<.001
Public	7280 (64.3)	4339 (63.7)	2941 (65.1)		
Private	2093 (18.5)	1148 (16.9)	945 (20.9)		
Other	1223 (10.8)	765 (11.2)	458 (10.1)		
Asthma	792 (7.0)	704 (10.3)	88 (1.9)	5.8 (4.6-7.3)	<.001
Inhaled corticosteroid	2369 (20.9)	2175 (31.9)	194 (4.3)	10.5 (9.0-12.2)	<.001
Systemic corticosteroid	1772 (15.6)	1611 (23.6)	161 (3.6)	8.4 (7.1-9.9)	<.001
Narcotic	8016 (70.8)	4892 (71.8)	3124 (69.2)	1.1 (1.0 ^e -1.2)	.003
Antibiotic	10653 (94.0)	6693 (98.3)	3960 (87.7)	7.9 (6.5-9.7)	<.001
Oxygen	4254 (37.6)	2874 (42.2)	1380 (30.6)	1.7 (1.5-1.8)	<.001
Ventilation	917 (8.1)	820 (12.0)	97 (2.1)	6.2 (5.0-7.7)	<.001
Transfusion	1147 (10.1)	725 (10.6)	422 (9.3)	1.2 (1.0 ^e -1.3)	.03
Nitric oxide	79 (0.7)	66 (1.0)	13 (0.3)	3.4 (1.9-6.2)	<.001
Hydroxyurea	2520 (22.2)	1693 (24.9)	827 (18.3)	1.5 (1.3-1.6)	<.001
Required ICU admission	1222 (10.8)	940 (13.8)	282 (6.2)	2.4 (2.1-2.8)	<.001

	Whole Cohort (N = 11 328)	Bronchodilator (n = 6812, 60.1%)	No Bronchodilator (n = 4516, 39.9%)	Odds Ratio (95% Confidence Interval)	<i>P</i> ^b
≥ 3 SCD admissions in past 12 months	1937 (17.1)	1137 (16.7)	800 (17.7)	0.9 (0.8-1.0) ^c	.16
DRG severity level ^g					
1	3138 (27.7)	1846 (27.1)	1292 (28.6)		
2	4863 (42.9)	2834 (41.6)	2029 (44.9)		
3	2803 (24.7)	1753 (25.7)	1050 (23.3)		
4	524 (4.6)	379 (5.6)	145 (3.2)		
Discharge year					
2005	1601 (14.1)	858 (12.6)	743 (16.5)		
2006	1489 (13.1)	915 (13.4)	574 (12.7)		
2007	1588 (14.0)	904 (13.3)	684 (15.1)		
2008	1694 (15.0)	979 (14.4)	715 (15.8)		
2009	1963 (17.3)	1234 (18.1)	729 (16.1)		
2010	1761 (15.5)	1130 (16.6)	631 (14.0)		
2011	1232 (10.9)	792 (11.6)	440 (9.7)		
Average annual SCD admissions/hospital (mean, SD)	300.0 (200.3)	327.6 (208.7)	257.6 (179.0)	NA	<.001

Abbreviations: HbSS, hemoglobin SS; NA, not available; ICU, intensive care unit; SCD, sickle cell disease; DRG, diagnosis-related groups.

^aData shown as count (%) unless otherwise indicated.

^bBolded *P* values indicate significant differences between the group that received bronchodilators and the group that did not.

^cRounded to 1.0, actual value < 1.0.

^dN = 11 220.

^eRounded to 1.0, actual value > 1.0.

^fN = 10 596.

^gDRG severity level: All-Patient Refined Diagnosis-Related Groups (APR-DRGs) severity subclass, a 4-point scale indicating severity of illness.

Table 2.
Poisson Regression Model: Association Between Bronchodilator Use and Length of Stay.

Parameters	Incidence Rate Ratio	95% Confidence Interval	<i>p</i> ^a
Bronchodilator	1.13	1.09-1.17	<.001
Age	1.02	1.02-1.03	<.001
Female	1.07	1.03-1.11	.001
Black	0.90	0.82-0.98	.02
HbSS	1.21	1.14-1.28	<.001
Primary payer			
Public	Reference		
Private	1.00	0.96-1.05	.92
Other	1.03	0.98-1.08	.20
Asthma	0.98	0.91-1.07	.69
Inhaled corticosteroid	0.99	0.95-1.03	.62
Systemic corticosteroid	1.11	1.06-1.16	<.001
Narcotic	1.46	1.41-1.51	<.001
Antibiotic	1.15	1.01-1.32	.03
Oxygen	1.13	1.09-1.16	<.001
Ventilation	1.28	1.21-1.36	<.001
Transfusion	1.14	1.07-1.21	<.001
Nitric oxide	1.40	1.16-1.68	<.001
Hydroxyurea	1.07	1.02-1.12	.007
Required ICU admission	1.13	1.07-1.20	<.001
≥ 3 SCD admissions in past 12 months	1.18	1.12-1.23	<.001
DRG severity level ^b			
1	Reference		
2	1.19	1.15-1.23	<.001
3	1.43	1.36-1.49	<.001
4	2.16	2.01-2.33	<.001
Discharge year			
2005	Reference		

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Parameters	Incidence Rate Ratio	95% Confidence Interval	<i>P</i> ^a
2006	0.94	0.88-0.99	.03
2007	0.93	0.88-0.98	.005
2008	0.90	0.85-0.95	<.001
2009	0.89	0.84-0.94	<.001
2010	0.90	0.84-0.95	.001
2011	0.91	0.85-0.97	.003
Average annual SCD admissions/hospital ^c	0.97	0.96-0.98	<.001

Abbreviations: HbSS, hemoglobin SS; ICU, intensive care unit; SCD, sickle cell disease; DRG, diagnosis-related groups.

^aBolded *P* values indicate statistically significant independent association between the variable and length of stay.

^bDRG severity level: All-Patient Refined Diagnosis-Related Groups (APR-DRGs) severity subclass, a 4-point scale indicating severity of illness.

^cPer 100 SCD admissions.