RESEARCH ARTICLE

Corticosteroid Therapy During Acute Bronchiolitis in Patients Who Later Develop Asthma

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ABSTRACT

BACKGROUND AND OBJECTIVE: Meta-analyses show that corticosteroids are not effective in patients with bronchiolitis. However, risk factors for asthma such as eczema or familial atopy prompt some practitioners to prescribe corticosteroids for bronchiolitis. We assessed if corticosteroid prescription is associated with shorter hospitalization for bronchiolitis among patients who later develop asthma.

METHODS: The Pediatric Health Information System database was interrogated for patients with bronchiolitis aged <2 years hospitalized between 2006 and 2015. Only patients who also later had a hospitalization for asthma and prescription of inhaled corticosteroids were included. For the initial bronchiolitis admission, use of mechanical ventilation defined "severe illness," and ICU admission without mechanical ventilation defined "moderate illness"; all other patients were deemed to have "mild illness." Variables associated ($P < .10$) with length of stay (LOS) in bivariate analysis were included in linear regression analysis.

RESULTS: During the bronchiolitis admission of 2479 children who were later hospitalized for asthma, corticosteroid prescription ($n = 857$) was associated with longer LOS in bivariate analysis (3 [2–4] vs 2 [2–4] days; $P < .01$) but not the multivariate model ($P = .18$) that included age, sex, comorbid conditions, bacterial pneumonia, and illness severity. Corticosteroid prescription was associated with shorter LOS among previously healthy children with moderate illness (4 [2–6] vs 5 [3–7] days; $P = .02$) but not those with mild or severe illness.

CONCLUSIONS: Corticosteroids were not associated with improved outcome in patients with bronchiolitis who were later hospitalized with asthma. Moderately ill patients with no comorbidities may warrant further study.

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Viral bronchiolitis is the most common indication for hospitalization among young children, accounting for ~20% of all postbirth admissions in children aged <2 years in the United States.[1–3] Currently, although no medication has sufficient evidence to support routine use,[4,5] practitioners continue to prescribe medications that they believe will help individual patients. For example, bronchodilators and systemic corticosteroids were prescribed in 58% and 16%, respectively, of recent bronchiolitis admissions in the United States.[6] Bronchodilators and corticosteroids are standard therapy for children with acute severe asthma, which similarly causes wheezing and dyspnea, but are not indicated for bronchiolitis.[7,8] In clinical practice, it may be challenging to distinguish if a dyspneic, wheezing child has bronchiolitis or is having a first asthma exacerbation. Asthma is characterized by a recurrent nature that is inherently absent during the first episode but is more likely to develop in children with eczema, familial asthma, and familial atopy.[9] The presence of such risk factors for developing asthma later in childhood is one of the largest reported influences on the decision to prescribe corticosteroids for bronchiolitis; these factors suggest a potential increased risk that the current episode includes a component of airways inflammation and reactivity that may respond to asthma medications.[9,10]

Providing corticosteroids to patients with bronchiolitis on the basis of risk factors for developing asthma is supported by 1 randomized trial.[11] In this study, corticosteroids reduced hospital length of stay (LOS) in children with eczema or a family history of asthma, although subgroup analyses of other trials did not show benefits in similar populations.[12–15] This inconsistency may reflect that corticosteroids are simply ineffective in bronchiolitis, even in patients who will later develop asthma. It might also be that corticosteroids are effective during bronchiolitis in patients who will later develop asthma, but eczema and family history are not sufficiently specific to identify these patients. Several scoring systems have been developed to predict if a young child who wheezes will later develop asthma (eg, the Asthma Predictive Index), but none of these systems is perfectly discriminatory, and none was designed for use during acute bronchiolitis episodes.[9,16–20]

Without an available method to identify for prospective study which patients with bronchiolitis will later develop asthma, a retrospective study design may best assess the hypothesis that corticosteroids are effective in inpatients with bronchiolitis who later develop asthma. With such a design, a remote cohort of patients with bronchiolitis who ultimately developed asthma in the subsequent years could be identified, and associations between corticosteroid use and clinical outcomes of the bronchiolitis episode could be tested. If that study found that corticosteroid use is associated with favorable outcomes, efforts to develop novel methods to identify these patients "destined" to have asthma during acute bronchiolitis would then be needed. Or, if there is no association with favorable outcomes, the practice of prescribing corticosteroids during bronchiolitis based on asthma risk factors would then be generally refuted.

In the present study, a quality-controlled database stemming from nearly 50 children's hospitals was used to investigate associations between corticosteroid prescription and hospital LOS in patients with bronchiolitis who later developed asthma.

METHODS

This retrospective, observational database study was performed with approval of the Children's Hospital Association (Overland Park, KS) and the investigational review board of University Hospitals of Cleveland. The Pediatric Health Information System (PHIS) database (Children's Hospital Association) was interrogated for data from pediatric inpatients discharged between January 1, 2006, and December 31, 2015. As previously reported,[6] bronchiolitis hospitalization was defined according to the following: (1) a primary inpatient diagnosis of acute bronchiolitis (*International Classification of Diseases, Ninth Revision* [ICD-9], codes of 4661, 46c611, or 46c619); (2) an All Patient Refined Diagnosis Related Groups diagnosis code of 138 (bronchiolitis and respiratory syncytial virus pneumonia); and (3) age at admission <2 years. Only children who had at least 1 subsequent hospitalization for asthma were included, using a previously reported definition of an admission between the ages of 2 and 18 years with a principal diagnosis of asthma (ICD-9 code of 493x).[21] In addition, we only included children who were prescribed an inhaled corticosteroid (ICS) (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, or triamcinolone, including combinations with long-acting β agonists) during the asthma admission.

For the initial bronchiolitis admission, data on age at admission, sex, race, and duration of hospitalization were extracted for each hospitalization. Comorbid conditions were identified by using 5 complex chronic condition "flags" (cardiovascular, neurologic and neuromuscular, other congenital or genetic defect, premature and neonatal, and respiratory).[22] Concurrent bacterial pneumonia was identified by any 1 of the following ICD-9 codes: 481 (*Streptococcus pneumoniae* pneumonia), 482.XX (other bacterial pneumonia), and 483.0 (*Mycoplasma pneumoniae* pneumonia). Bronchiolitis was defined as "severe" if the child received ICU care and mechanical ventilation, and "moderate" if the child was treated in the ICU but was not mechanically ventilated. All other children were defined as having "mild" illness. Corticosteroid treatment was defined as the presence of a billing code for dexamethasone, methylprednisolone, prednisolone, or prednisone administered via the oral, intravenous, or intramuscular route during hospitalization. Hospital regions were defined by using criteria from the Healthcare Cost and Utilization Project. Only the first extracted bronchiolitis admission was analyzed for each subject. Children who had an ICD-9 code for asthma (493x) during their bronchiolitis admission and children with incomplete pharmacy billing data were excluded.

Basic nonparametric (Wilcoxon rank-sum tests and Kruskal-Wallis analysis of

variance) methods were used to test for associations between hospital LOS and sex, race, comorbid conditions, illness severity, and corticosteroid treatment. The association between age and LOS was tested by using the Spearman rank order correlation. Any variable that was loosely associated with LOS in the bivariate analyses ($P < .10$) was included in the multivariate linear regression models. Exploratory bivariate subgroup analyses were performed to test for associations between corticosteroid treatment and LOS for cohorts defined according to illness severity (mild, moderate, and severe) and comorbid conditions. All analyses were performed by using SigmaPlot version 12.5 (Systat Software Inc, San Jose, CA). Data are shown as *n* (%) or median (interquartile range).

TABLE 1 Comparison of Children Prescribed Corticosteroids and Children Not Prescribed Corticosteroids

Variable	Prescribed Corticosteroids ($n = 857$)	Not Prescribed Corticosteroids ($n = 1622$)	*P*
Age, mo	10.8 (6.6–15.5)	5.8 (2.6–11.0)	<.01
Female	331 (38.6)	650 (40.1)	.51
Race/ethnicity			
African American	199 (23.2)	378 (23.3)	>.99
White	233 (27.2)	446 (27.5)	
Hispanic	151 (17.6)	282 (17.4)	
Other	274 (32.0)	516 (31.8)	
Region 1: Northeast	232 (32.0)	109 (68.0)	<.01
Region 2: Midwest	558 (34.1)	289 (65.9)	
Region 3: South	444 (39.3)	287 (60.7)	
Region 4: West	388 (30.7)	172 (69.3)	
Previously healthy	744 (86.6)	1432 (88.3)	.32
Complex chronic condition			
Cardiovascular	54 (6.3)	77 (4.7)	.12
Neurologic	22 (2.6)	39 (2.4)	.91
Genetic	45 (5.3)	73 (4.5)	.46
Prematurity	5 (0.6)	10 (0.6)	.86
Pulmonary	32 (3.7)	44 (2.7)	.20
Mild illness	701 (81.8)	1454 (89.6)	<.01
Moderate illness	133 (15.5)	149 (9.2)	
Severe illness	23 (2.7)	19 (1.2)	
Bacterial pneumonia	15 (1.8)	29 (1.8)	.93

Data are presented as median (interquartile range) or *n* (%). Statistical methods included the Wilcoxon rank-sum test and χ^2 analyses.

RESULTS

We identified 3997 children who were hospitalized for bronchiolitis and later developed asthma who required a subsequent hospitalization and were treated with an ICS. After excluding 702 repeat admissions and 816 bronchiolitis admissions that also included an ICD-9 code for asthma, 2479 subjects were included in the following analyses. The median age of the patient with bronchiolitis was 7.6 (3.5–13.3) months. More than one-half were male (60.4%), and most were white (27.4%), African American (23.3%), or Hispanic (17.5%). At least 1 comorbid condition was identified in 12.2% of the patients, which were most commonly either cardiovascular (5.3%) or genetic (4.8%). Concurrent bacterial pneumonia (1.8%) and severe illness (1.7%) were rare; 11.4% had moderate illness. The median LOS was 2 (2–4) days.

Approximately one-third (34.6%) of the patients were prescribed corticosteroids. Corticosteroid prescription was commonly initiated within 1 day of hospital admission (749 [87.4%] of 857 cases). Children prescribed corticosteroids (Table 1) were significantly older (10.8 [6.6–15.5] vs 5.8 [2.6–11.0] months; $P < .01$) and had higher illness severity than those not prescribed corticosteroids. Utilization among hospital regions ranged from 30.7% to 39.3% ($P < .01$) and was highest in the southern region. There were no significant differences in sex, race, comorbid conditions, or prevalence of bacterial pneumonia between treatment groups.

The bivariate analyses of associations with LOS are presented in Table 2. Corticosteroid prescription was significantly associated with a longer LOS (3 [2–4] vs 2 [2–4] days; $P < .01$). Age was also associated with longer LOS (Spearman coefficient: 0–0.16; $P < .01$). Other factors associated with longer LOS included female sex, comorbid conditions, bacterial pneumonia, and illness severity. Age, sex, hospital region, comorbid conditions (except prematurity), bacterial pneumonia, illness severity, and corticosteroid prescription were included in the multivariate linear regression model (Table 3). Corticosteroid prescription ($\beta = 0.46$; $P = .18$) was not significantly associated with LOS after adjusting for the other variables. Younger age, female sex, cardiovascular comorbidities, genetic comorbidities, bacterial pneumonia, and more severe illness were all significantly associated with LOS. When prematurity was included in the model, it was not significantly associated with LOS ($\beta = 0.40$; $P = .85$), and the parameters and *P* values for all other variables did not differ meaningfully from the results in Table 3.

Overall findings were also similar when only children aged <1 year were included. Corticosteroid prescription ($n = 487$) was associated in the bivariate analysis with increased LOS (3 [2–6] vs 2 [2–4] days; $P < .01$) compared with infants not prescribed corticosteroids ($n = 1267$). Female sex, genetic comorbidities, bacterial pneumonia, and more severe illness were associated with increased LOS in the linear regression model; corticosteroid prescription ($\beta =$

TABLE 2 Bivariate Associations Between Variables and Hospital LOS

Variable	*n* (%)	Length of Stay	*P*
Female	981 (39.6)	3 (2–4)	<.01
Male	1498 (60.4)	2 (1–4)	
Race/ethnicity			
African American	577 (23.3)	2 (2–4)	.94
White	679 (27.4)	2 (2–4)	
Hispanic	433 (17.5)	2 (2–4)	
Other	790 (31.9)	2 (2–4)	
Region 1: Northeast	341 (13.8)	2 (1–3.5)[a]	<.01
Region 2: Midwest	847 (34.2)	2 (1–4)[a]	
Region 3: South	731 (29.5)	3 (2–4)	
Region 4: West	560 (22.6)	2 (1–4)	
Previously healthy	2176 (87.8)	2 (1–4)	<.01
Not previously healthy	303 (12.2)	4 (2–8)	
CCC: cardiovascular	131 (5.3)	4 (2–8)	<.01
Not present	2348 (94.7)	2 (1–4)	
CCC: neurologic	61 (2.5)	4 (2–8)	<.01
Not present	2418 (97.5)	2 (2–4)	
CCC: genetic	118 (4.8)	4 (2–8)	<.01
Not present	2361 (95.2)	2 (2–4)	
CCC: prematurity	15 (0.6)	4 (2–8)	.12
Not present	2464 (99.4)	2 (2–4)	
CCC: pulmonary	76 (3.1)	4 (2–6.75)	<.01
Not present	2403 (96.9)	2 (2–4)	
Mild illness	2155 (86.9)	2 (1–4)	<.01
Moderate illness	282 (11.4)	4 (3–7)[b]	
Severe illness	42 (1.7)	6 (3.75–8.25)[b]	
Bacterial pneumonia	44 (1.8)	5 (3–8)	<.01
No bacterial pneumonia	2435 (98.2)	2 (2–4)	
Corticosteroids	857 (34.6)	3 (2–4)	<.01
No corticosteroids	1622 (65.4)	2 (2–4)	

LOS is presented as median (interquartile range). Statistical methods included the Wilcoxon rank-sum test and Kruskal-Wallis analysis of variance. CCC, complex chronic condition.

[a] $P < .05$ versus southern region (with post hoc testing using Dunn's test).

[b] $P < .05$ versus mild illness (with post hoc testing using Dunn's test).

0.62; $P = .23$), age, hospital region, and other comorbidities (cardiovascular, neurologic, and respiratory) were not.

Subgroup analyses of the entire cohort of patients with bronchiolitis who later developed asthma are presented in Table 4. Corticosteroid prescription was not associated with LOS among previously healthy children (2 [1.25–4] vs 2 [1–4] days; $P = .11$), but it was associated with longer LOS among children with comorbidities (6 [3–9] vs 3 [2–6.25] days; $P < .01$). In the subgroup without comorbidities, corticosteroid prescription was associated with a significantly shorter LOS among subjects with moderate bronchiolitis illness (ICU care without mechanical ventilation) but not in those with mild or severe illness. Corticosteroid prescription in children with comorbidities was associated with nominally longer LOS in all 3 illness categories, but the difference was only statistically significant in those with mild illness.

DISCUSSION

In this study of 2479 inpatients with bronchiolitis, all of whom later developed asthma that required hospitalization and treatment with an ICS, our main finding is that corticosteroid prescription was not associated with a shorter duration of the original bronchiolitis hospitalization. Corticosteroids continue to be prescribed for bronchiolitis despite expert recommendations to the contrary, and they are preferentially prescribed to children with factors that are associated with an increased risk for developing asthma, such as eczema and familial atopy.[4,6,10] Based on our analyses, we do not support the practice of prescribing corticosteroids during bronchiolitis simply because a patient exhibits risk factors for future asthma.

Our findings generally align with current expert guidelines that "clinicians should not administer systemic corticosteroids to infants with a diagnosis of bronchiolitis."[4] Corticosteroids were associated with increased LOS in the bivariate analysis but were preferentially prescribed to older children and patients with more severe disease. The prevalence of comorbidities, which are associated with unfavorable outcomes in bronchiolitis, did not differ between corticosteroid-treated patients and nontreated subjects.[23–25] Age, illness severity, and comorbidities were all associated with LOS in the bivariate analyses. When these factors were included in the multivariate model, there was no statistically significant association between corticosteroid prescription and LOS. Prematurity was not initially included in the model because of a P value >.10 in bivariate analysis, which was likely influenced by its low prevalence in our cohort, and the results were not significantly different when it was forced into the model.

The wheezing and dyspnea that are common in acute bronchiolitis can be caused by multiple pathophysiologic mechanisms, including obstruction of the airways with mucus and cellular debris, bronchospasm, edema, impaired ciliary function, and inflammation; these same mechanisms may cause symptoms of acute severe asthma.[5] The lack of a salutary effect of anti-inflammatory corticosteroids in the present cohort suggests that inflammation may play a lesser role in acute bronchiolitis than it

TABLE 3 Multivariate Linear Regression Model of Associations Between Variables and Hospital LOS

Variable	Coefficient	*P*
Corticosteroids	0.46	.18
Bacterial pneumonia	3.59	<.01
Severe illness	3.32	<.01
Moderate illness	2.19	<.01
Complex chronic condition		
Cardiovascular	1.61	.03
Genetic	1.89	.01
Neurologic	1.32	.20
Pulmonary	0.60	.52
Age, d	−0.004	<.01
Female sex	0.68	.03
Region 1: Northeast	−0.35	.52
Region 2: Midwest	−0.25	.56
Region 3: South	0.53	.23

All variables that were loosely ($P < .10$) associated with LOS in the bivariate analyses were included.

does in asthma, even in children who will later develop the recurrent episodes of acute bronchospasm and corticosteroid-sensitive inflammation that are the hallmark of asthma.

As seen in Table 2, LOS varied markedly according to comorbid conditions and illness severity. Corticosteroids were associated with longer LOS among children with comorbidities but not in otherwise healthy children. This finding may reflect an increased risk of adverse effects of corticosteroids, such as immunosuppression, in children with comorbid conditions. When these groups were divided according to illness severity, LOS was nominally longer in corticosteroid-treated children with comorbidities regardless of illness severity. Conversely, there was a statistically significant association between corticosteroid use and shorter LOS among the 224 previously healthy children who required ICU admission but not mechanical ventilation ("moderate illness"). This outcome may reflect a unique cohort that is sufficiently ill such that medications may improve outcomes but well enough to not be adversely affected by immunosuppressive therapy; this finding could also be a false-positive result. Prospective studies of otherwise healthy PICU patients with bronchiolitis who did not undergo mechanical ventilation may be warranted, especially if recently described biomarkers enable improved identification of future asthma cases at the time of bronchiolitis illness.[26]

There are several limitations to our study design. First, it used an administrative and billing database that does not include clinical variables (eg, physical examination findings) or diagnostic results (eg, pulmonary function testing, microbiology results) that may have optimized our diagnosis of both bronchiolitis and asthma. Two approaches were used to maximize the specificity of our definition of asthma. We used a previously reported definition which required that asthma was the primary diagnosis for hospitalization,[21] and we used ICS prescription as a marker for children who had actually been diagnosed with persistent asthma.[7] For the initial bronchiolitis cohort, we used a previously reported definition that required both a primary (not secondary) ICD-9 diagnosis of bronchiolitis and an All Patient Refined Diagnosis Related Groups code for bronchiolitis to ensure that these children were hospitalized primarily for bronchiolitis.[6] Multiple approaches were also used to minimize the inclusion of children with prior wheezing in the initial bronchiolitis cohort, such as including only the first hospitalization for bronchiolitis for children with >1 episode in the database, and excluding children with a secondary diagnosis of asthma during their bronchiolitis admission. Such strict definitions may have reduced the power of the present study, as did the inability to identify patients with asthma who did not require hospitalization or were hospitalized at non-PHIS hospitals. However, the use of strict criteria was necessary to maximize the validity of the study and to best evaluate the efficacy of corticosteroids during acute bronchiolitis hospitalizations of children who later develop asthma.

The second limitation was that only patients hospitalized with bronchiolitis were included, so even the subjects with "mild" illness were very ill. Third, several variables that may affect the relationship between corticosteroids and outcomes (physical examination findings, dyspnea scores, the interval between symptom onset and hospital admission date, and viral test results) are not available in this database.[27,28] Our results may have differed if such variables were included. Fourth, the study was retrospective and can only establish associations, not causation. Fifth, the PHIS database only provides LOS data as whole days; more granular measurement may have improved our analysis. LOS may also have been influenced by variables such as time of day and social factors that were not available in the database. Sixth, the database reports medications based on billing data, not medication administration records. Seventh, as has been done in earlier bronchiolitis studies using the PHIS database, we did not restrict our analysis to children started on corticosteroids at or shortly after admission.[6] It is possible that including the small minority of subjects who were only prescribed corticosteroids later in their hospital course may have biased our findings against corticosteroids. Finally, the PHIS database only includes

TABLE 4 Subgroup Analyses Based on Comorbidities and Severity of Illness

Variable	Previously Healthy Children					Children With Comorbidities				
	Corticosteroids		No Corticosteroids			Corticosteroids		No Corticosteroids		
	n	LOS	*n*	LOS	*P*	*n*	LOS	*n*	LOS	*P*
All patients	744	2 (1.25–4)	1432	2 (1–4)	.11	113	6 (3–9)	190	3 (2–6.25)	<.01
Mild illness	630	2 (1–4)	1291	2 (1–3)	.16	71	4 (2–8)	163	3 (2–5)	<.01
Moderate illness	99	4 (2–6)	125	5 (3–7)	.02	34	8.5 (3.75–13)	24	6.5 (4.5–9)	.29
Severe illness	15	6 (2–10)	16	5 (4–7.75)	.89	8	8.5 (5.5–14.5)	3	5 (3–7)	.13

LOS is presented as median (interquartile range). Statistical methods included the Wilcoxon rank-sum test.

data from freestanding children's hospitals, and thus our analyses may not be generalizable to other treatment locations. Despite these limitations, the PHIS database has been used to support bronchiolitis research in multiple leading pediatric journals.[6,29–31]

CONCLUSIONS

These retrospective data support the theory that inpatient prescription of corticosteroids has little salutary effect during bronchiolitis admissions, even in children who later require hospitalization for asthma. Future studies may attempt to identify a population of corticosteroid-responsive patients with bronchiolitis based on comorbid conditions, illness severity, and objective markers of future asthma. Until such studies can establish criteria for corticosteroid-responsive patients, our data support the current guidelines that corticosteroids should not be prescribed for bronchiolitis, even in the presence of asthma risk factors.

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