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Oral Prednisolone for Preschool Children with Acute Virus-Induced Wheezing

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ABSTRACT

BACKGROUND

Attacks of wheezing induced by upper respiratory viral infections are common in preschool children between the ages of 10 months and 6 years. A short course of oral prednisolone is widely used to treat preschool children with wheezing who present to a hospital, but there is conflicting evidence regarding its efficacy in this age group.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial comparing a 5-day course of oral prednisolone (10 mg once a day for children 10 to 24 months of age and 20 mg once a day for older children) with placebo in 700 children between the ages of 10 months and 60 months. The children presented to three hospitals in England with an attack of wheezing associated with a viral infection; 687 children were included in the intention-to-treat analysis (343 in the prednisolone group and 344 in the placebo group). The primary outcome was the duration of hospitalization. Secondary outcomes were the score on the Preschool Respiratory Assessment Measure, albuterol use, and a 7-day symptom score.

RESULTS

There was no significant difference in the duration of hospitalization between the placebo group and the prednisolone group (13.9 hours vs. 11.0 hours; ratio of geometric means, 0.90; 95% confidence interval, 0.77 to 1.05) or in the interval between hospital admission and signoff for discharge by a physician. In addition, there was no significant difference between the two study groups for any of the secondary outcomes or for the number of adverse events.

CONCLUSIONS

In preschool children presenting to a hospital with mild-to-moderate wheezing associated with a viral infection, oral prednisolone was not superior to placebo. (Current Controlled Trials number, ISRCTN58363576.)

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Attacks of wheezing that are induced by viral infections of the upper respiratory tract are common in children under the age of 6 years.[1,2] The majority of preschool children with virus-triggered wheezing have few or no interval respiratory symptoms and no chronic lower airway eosinophilia.[2-5] Furthermore, the propensity to wheeze with upper respiratory viral infections often resolves by school age.[6,7] National guidelines, which are based on the efficacy of systemic corticosteroids in reducing the duration of hospitalization in school-age children and adults with classic atopic asthma,[8-10] recommend the use of oral corticosteroids for preschool children with virus-induced wheezing who present to a hospital.[11-13] However, the results of trials that have specifically addressed the question of efficacy of systemic corticosteroids in young children with acute wheezing are contradictory.[14-17] In a previous study, we found that a 5-day course of oral prednisolone that was initiated by parents at home at the first sign of an attack of wheezing did not significantly reduce parent-assessed symptom scores and the need for hospitalization.[18] Thus, the role of oral corticosteroids for virus-induced wheezing remains controversial.[19]

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=344)	Prednisolone (N=343)
Male sex — no. (%)	216 (62.8)	227 (66.2)
Age — mo	26.2±14.7	25.8±13.3
Previous wheezing — no./total no. (%)	229/337 (68.0)	211/332 (63.6)
Age at first onset of wheezing		
No. of patients	326	327
Mean — mo	15.8±12.3	16.6±12.0
Coughing or wheezing without a cold during previous year — no./total no. (%)	59/333 (17.7)	47/330 (14.2)
Conditions previously diagnosed by physician — no./total no. (%)		
Asthma	55/337 (16.3)	63/333 (18.9)
Eczema	132/335 (39.4)	136/330 (41.2)
Hay fever	24/324 (7.4)	26/324 (8.0)
Food allergy	22/331 (6.6)	33/327 (10.1)
Bronchiolitis	85/328 (25.9)	71/323 (22.0)
Family history of asthma — no./total no. (%)		
Mother	82/337 (24.3)	87/327 (26.6)
Father	80/333 (24.0)	83/326 (25.5)
Smokers in household — no./total no. (%)	121/337 (35.9)	117/331 (35.3)
No. of wheezing attacks in the previous year — no./total no. (%)		
0	119/324 (36.7)	127/329 (38.6)
1–3	117/324 (36.1)	104/329 (31.6)
4–6	65/324 (20.1)	62/329 (18.8)
6–10	18/324 (5.6)	23/329 (7.0)
>10	5/324 (1.5)	13/329 (4.0)
No. of previous presentations to hospital with acute wheezing — no./total no. (%)		
0	271/333 (81.4)	260/330 (78.8)
1–2	50/333 (15.0)	49/330 (14.8)
3–4	9/333 (2.7)	13/330 (3.9)
≥5	3/333 (0.9)	8/330 (2.4)

Table 1. (Continued.)

Characteristic	Placebo (N=344)	Prednisolone (N=343)
Parent-reported fever associated with symptoms on admission — no./total no. (%)	99/333 (29.7)	101/329 (30.7)
Previously prescribed medication — no./total no. (%)		
Inhaled albuterol as required	191/340 (56.2)	172/340 (50.6)
Daily inhaled corticosteroids	65/340 (19.1)	61/340 (17.9)
Oral montelukast	1/340 (0.3)	2/340 (0.6)
No. of courses of oral corticosteroids for wheezing in the previous year — no./total no. (%)		
0	240/328 (73.2)	242/330 (73.3)
1–2	69/328 (21.0)	63/330 (19.1)
3–4	17/328 (5.2)	14/330 (4.2)
≥5	2/328 (0.6)	11/330 (3.3)
Baseline PRAM score†		
No. of patients	340	339
Mean — units	4.27±2.18	4.32±2.31

* Plus–minus values are means ±SD. The results do not include baseline data on the second admission of 10 children who had been recruited on a previous occasion and data for 3 children for whom study-group assignments could not be determined. Included are baseline data for 3 children who were randomly assigned to receive a study drug but for whom primary-outcome data were not recorded. Data are missing for patients for whom a parent or guardian was unsure of the response. There were no significant differences between the two groups in baseline variables.

† Scores on the Preschool Respiratory Assessment Measure (PRAM)[21] range from 0 to 12, with higher scores indicating a greater severity of respiratory distress; scores were determined 5 minutes after the administration of a dose of inhaled albuterol.

In this study, we assessed the efficacy of a short course of therapy with oral prednisolone in children presenting to a hospital with virus-induced wheezing. We sought to ensure that at least one dose of oral prednisolone was administered by a health care professional and that a validated assessment of the severity of the child's symptoms was included.

METHODS

PATIENTS

From March 2005 through August 2007, we conducted the study in three hospitals in the United Kingdom: the University Hospitals of Leicester National Health Service Trust Children's Hospital, Nottingham City Hospital, and University Hospital Queen's Medical Centre in Nottingham. We enrolled children between the ages of 10 months and 60 months who had an attack of wheezing that a physician judged to be preceded by the symptoms and signs of a viral infection of the upper respiratory tract and who were either referred to the hospital by a clinician or brought to an emergency department by a parent or guardian. The presence of an upper respiratory viral infection was determined clinically.

The lower age limit of 10 months was chosen to reduce the recruitment of infants with wheezing associated with bronchiolitis, a condition that is defined in the United Kingdom as a primary lower respiratory tract infection of infants, resulting in hypoxemia and bilateral chest crackles.[20] We excluded children who were in shock or who had clinical evidence of bacterial sepsis. Children who had known heart or lung disease, who were receiving immunosuppressive therapy or had an immunodeficiency, or who had active varicella infection or had recently been exposed to varicella were also excluded.

Children who presented to a hospital with wheezing on auscultation were screened for eligibility by a pediatrician after they had received 10 puffs of albuterol, administered through a metered-dose inhaler and Volumatic spacer (Allen and Hanburys) with a face mask, or nebulized albuterol (2.5 mg if the child was <3 years of age or 5.0 mg if the child was ≥3 years of age). Each cen-

ter kept a record of the number of children who were screened.

Five minutes after patients who were enrolled in the study had received a dose of inhaled albuterol, a clinician calculated the baseline score on the Preschool Respiratory Assessment Measure (PRAM)[21] scale, which ranges from 0 to 12, with higher scores indicating a greater severity of respiratory distress (Table 1 and the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). A medical history was obtained by the clinician with the use of a standardized data-collection form that included questions about the number and severity of previous wheezing attacks, the presence or absence of physician-diagnosed eczema, and the interval of symptoms. The clinician subsequently recorded the PRAM score shortly after the administration of inhaled albuterol at 4, 12, and 24 hours in children remaining in hospital.

The study was approved by the U.K. National Health Service Multicenter Research Ethics Committee and by local institutional review boards and was approved by the U.K. National Health Services Medicines for Children Research Network. Written informed consent was obtained from the parent or guardian of each child who was enrolled in the study.

CLINICAL MANAGEMENT

Children were initially treated in the pediatric emergency department by a clinician trained in pediatric care. The hospitals' care pathway for preschool children with virus-induced wheezing is to discharge children home if they have no or minimal wheezing on auscultation after inhalation of albuterol, if the oxygen saturation is more than 92% while breathing ambient air on pulse oximetry, and if the clinician judges that the child will remain clinically stable at home receiving inhaled albuterol as required (up to a maximum of four to six puffs at 4-hour intervals through a metered-dose inhaler and Volumatic spacer). For children remaining symptomatic after the administration of albuterol, clinicians either continue treatment in the emergency department or transfer the patient to a short-stay observation-and-assessment ward associated with the emergency department or to a pediatric ward. In some cases, selection of the treatment site is influenced by nonclinical factors, including the time of day and the availability of beds.

In this study, the treatment-and-observation policy was identical at all study centers, including the emergency department, and monitoring was always done by nursing staff with pediatric training. The decision to discharge a patient from the hospital was based on the judgment of physicians, taking into consideration the clinical variables described above.

RANDOMIZATION

We used a double-blind randomization design that was stratified according to study center. Study numbers were assigned sequentially, and randomization was achieved by generating numerical codes in random permuted blocks of 10. Randomization and packaging of placebo and prednisolone were done by Nova Laboratories. Placebo and prednisolone were packaged in identical capsules containing an identical volume of lactose in identical containers labeled with the patient's number only. Staff members were unaware of study-group assignments. Randomization codes were locked in a hospital pharmacy department until the entry of all data entry was complete. Randomization was applied to children who were found to be eligible and whose parents agreed to have them participate.

STUDY INTERVENTION

During administration of the study drugs, a nurse broke open a white capsule containing either prednisolone or placebo and mixed the white powder with 10 ml of a strongly flavored drink (usually black-currant flavored). The dose of oral prednisolone was in accordance with guidelines of the British Thoracic Society,[12] which recommends 10 mg of oral prednisolone once a day for 5 days for children 24 months of age or younger and 20 mg once a day for 5 days for children over 24 months of age. Treatment in the hospital was left to the discretion of the supervising clinician, who also could stop the study drug and start a definitive course of systemic corticosteroids. Treatment was in accordance with the British Thoracic Society guidelines[12]: inhaled albuterol as required and oxygen delivered by face mask if the child had hypoxemia while breathing ambient air.

The time of discharge was recorded by administrative personnel as part of normal hospital record keeping. In the hospital, parents were provided with a diary card for reporting respiratory symptoms after discharge from the hospital[18] (see the Methods section in the Supplementary Appen-

dix). On discharge from the hospital, parents or guardians were provided with the remaining capsules to complete the course and were instructed in their use.

OUTCOME MEASURES

The primary outcome was the duration of hospitalization, which was divided into two time periods — the time from enrollment to the time of actual discharge from the hospital and the time from enrollment to the time that the patient was deemed to be "fit for discharge" (signoff for discharge) — since the time of actual discharge may be influenced by nonclinical factors. Secondary outcomes were the PRAM scores at 4, 12, and 24 hours (as assessed shortly after the administration of inhaled albuterol); the total dose of inhaled albuterol during hospitalization (with 2.5 mg of the drug considered to be equivalent to 10 actuations of a metered-dose inhaler); the mean 7-day symptom score, as assessed by a parent or guardian; the mean number of actuations of albuterol given at home during a 7-day period; the time required for the child to be "back to normal"; and hospital readmission for wheezing within a month after discharge.

ADVERSE EVENTS

Children were monitored for adverse events during hospitalization. Adverse events after discharge were monitored by telephone follow-up. An independent data and safety monitoring committee, whose members were not involved with the enrollment of patients, tracked any adverse events.

STATISTICAL ANALYSIS

We determined the required power for the study from prospectively collected data from 208 preschool children presenting to the University Hospitals of Leicester National Health Service Trust with a physician-diagnosed attack of virus-induced wheezing. We calculated that 350 in each group would give a power in excess of 80% to detect a difference of 5 hours in the geometric mean of duration of hospital stay with a two-sided alpha level of 0.05. An interim analysis was not included in the statistical analysis plan. Differences in continuous outcomes between the two study groups were assessed by obtaining mean differences with 95% confidence intervals from a linear regression model incorporating the study center as a variable. The mean duration of hospital stay was log transformed before analysis, since this variable was positively skewed. The treatment effect thus refers to the ratio of geometric means for the primary outcome. In addition, we calculated the difference in the median duration of hospital stay with 95% confidence intervals, which were obtained with the use of the bootstrap method.[22] The duration of hospital stay was also shown graphically with the use of Kaplan–Meier survival estimates. For other positively skewed variables, 95% confidence intervals for differences in means were obtained by the bootstrap method.[22] Differences between categorical variables were expressed as odds ratios with 95% confidence intervals, obtained from a logistic-regression model incorporating the study center as a variable.

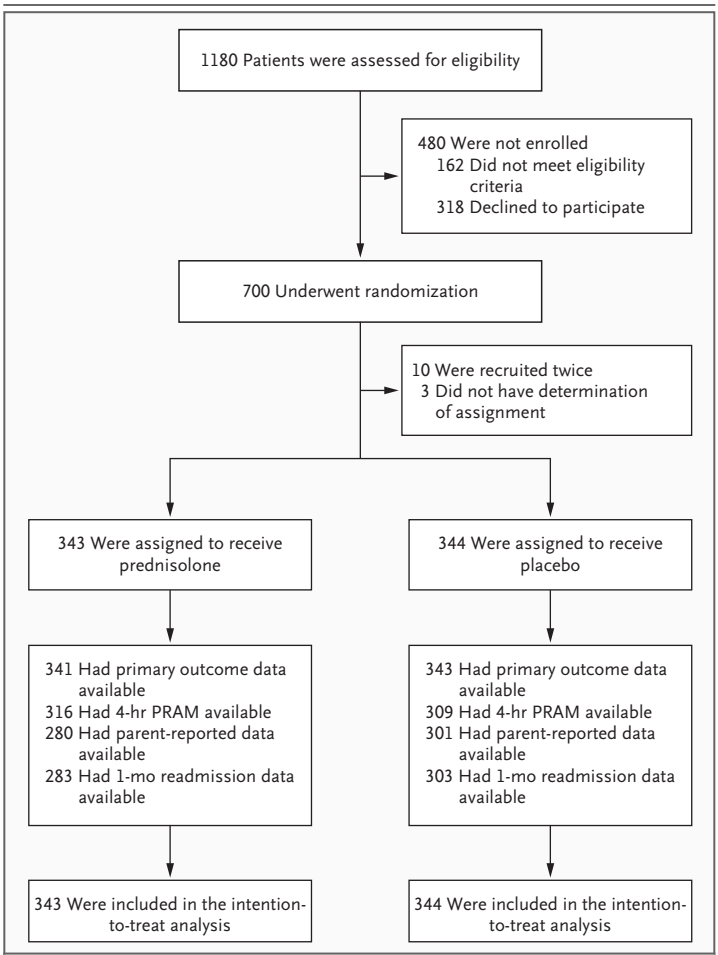

Figure 1. Enrollment and Outcomes.

The majority of children who did not meet the inclusion criteria were judged by a clinician to be asymptomatic after a single dose of inhaled albuterol, administered through a metered-dose inhaler and spacer. PRAM denotes Preschool Respiratory Assessment Measure.

Table 2. Duration of Hospitalization (Primary Outcome).*

Duration	Placebo	Prednisolone	Difference (95% CI)	P Value
Interval between presentation and signoff for discharge				
No. of patients	342	340		
Median (hr)	12.0	10.1	–1.9 (–6.5 to 4.1)	
Log_e mean	2.40±1.11	2.28±1.02		
Ratio of geometric means (95% CI)	NA	0.89 (0.76–1.05)		0.16
Interval between presentation and actual discharge				
No. of patients	343	341		
Median (hr)	13.9	11.0	–2.9 (–8.7 to 2.4)	
Log_e mean	2.46±1.09	2.36±1.02		
Ratio of geometric means (95% CI)	NA	0.90 (0.77–1.05)		0.18

* Plus–minus values are means ±SD. The mean duration of hospital stay was log transformed before analysis, since this variable was positively skewed. The treatment effect thus refers to the ratio of geometric means for the primary outcome. The primary outcome was not recorded for three children who were randomly assigned to receive a study drug. NA denotes not applicable.

The only prespecified subgroup analysis involved children who were at increased risk for atopic asthma. This subgroup, which was based on the clinical index for an increased risk of asthma in preschool children reported by Castro-Rodríguez et al.,[23] was defined as children with a history of four or more wheezing episodes who had a parent with asthma or who had physician-diagnosed eczema. There were two post hoc subgroup analyses, stratified according to PRAM score and age. For each subgroup analysis, heterogeneity was assessed by adding an interaction term with treatment to the model. PRAM scores at 12 and 24 hours were analyzed only for patients who were still in the hospital.

All analyses were performed with the use of Stata 10 statistical software, version 10.0. All P values are two-sided and have not been adjusted for multiple testing.

RESULTS

PATIENTS

We screened 1180 children for study eligibility (Fig. 1). Of these children, 162 did not meet the eligibility criteria, and 318 parents declined to participate. A total of 700 children underwent randomization. For three sequential children, the trial bottle number was not recorded and group assignment could not be determined, thus reducing the number of study participants to 697. Ten children who presented to the hospital on a second occasion were enrolled in error. These 10 children were assigned to receive a study drug, but data from the second admission were removed from the study database. The remaining 687 children were included in the intention-to-treat analysis; 343 children were assigned to receive prednisolone and 344 to receive placebo. The primary outcome was not recorded for one child in the placebo group and for two children in the prednisolone group. There were no significant differences between the two study groups in baseline demographic characteristics and PRAM scores (Table 1).

OUTCOMES DURING HOSPITALIZATION

The time to actual discharge from the hospital was relatively short in both the placebo group and the prednisolone group (median, 13.9 and 11.0 hours, respectively) (Table 2 and Fig. 2). There was no significant difference between the study groups in the time to actual discharge from the hospital (ratio of geometric means, 0.90; 95% confidence interval [CI], 0.77 to 1.05; P=0.18) or in the time to signoff for discharge (ratio of geometric means, 0.89; 95% CI, 0.76 to 1.05; P=0.16) (Table 2). There was no significant difference between the groups in the number of albuterol actuations administered in the hospital, in PRAM scores at 4 to 24 hours, and in the very small proportion of children in

whom a study drug was stopped by a clinician and substituted with a definitive systemic corticosteroid (Table 3).

A total of 124 children (58 in the placebo group and 66 in the prednisolone group) were classified as being at high risk for asthma at school age. In this subgroup, there was no significant difference between the placebo group and the prednisolone group in the duration of hospitalization and no evidence of a differential treatment effect, as compared with children who were not in the high-risk group (test for interaction, P=0.31). In a post hoc analysis, we found no evidence of a significant differential treatment effect for the time to actual discharge stratified according to the PRAM score or age (Table 2 in the Supplementary Appendix).

OTHER OUTCOMES

There were no significant differences between the two study groups in parent-assessed 7-day mean symptom scores, the time to return to normal activities (just over 5 days), and the number of albuterol actuations given at home during a 7-day period. The two study groups also did not differ significantly in the number of readmissions to the hospital for wheezing within a month (6.3% in the placebo group and 7.4% in the prednisolone group) (Table 4).

ADVERSE EVENTS

No clinically significant adverse events were reported to the patient safety committee. In one child in the prednisolone group, parents attributed excess vomiting to the study drug and discontinued the medication after discharge from the hospital.

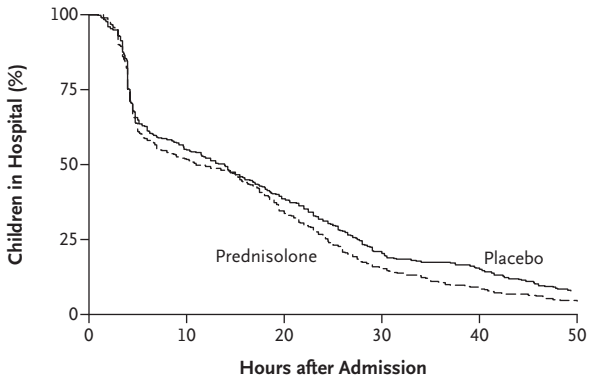

Figure 2. Kaplan–Meier Estimates of the Proportion of Children Remaining in the Hospital.

DISCUSSION

In this three-center trial of a 5-day course of oral prednisolone for preschool children with an attack of virus-induced wheezing, we found no significant reduction in the duration of the actual hospital stay, the interval between hospital admission and signoff for discharge, PRAM scores at any interval, 7-day parent-reported scores of symptom severity, and readmission to the hospital within 1 month after discharge.

This study's results are consistent with our findings of no significant effect of a 5-day course of oral prednisolone in a previous community-based study of parent-initiated oral prednisolone for virus-induced wheezing among preschool children.[18] However, two studies have reported a beneficial effect of systemic corticosteroids in preschool children who presented to the hospital with acute wheezing. First, Csonka et al.[14] assessed a 3-day course of oral prednisolone (at a dose of 2 mg per kilogram of body weight per day) in 230 children under 3 years of age who presented to the hospital with virus-induced wheezing. Although corticosteroid treatment did not significantly reduce the proportion of children who were still hospitalized after 4 hours, significantly fewer children receiving corticosteroids required additional treatment in the hospital than in the placebo group. Second, Tal et al.[15] assessed the efficacy of a course of intramuscular methylprednisolone (at a dose of 4 mg per kilogram) in 70 children who were 7 months to 54 months of age and who presented to the hospital with acute wheezing. The investigators reported that more children who received corticosteroids were discharged at 3 hours than those in the placebo group.

A major difference between these two studies and our study is that we included the PRAM score, a measure that has been validated against preschool lung function[21] and that has a good internal consistency and reliability among raters.[24] For short-term outcomes, we found no significant difference between the two study groups in the 4-hour PRAM score and in the proportion of children who had been discharged home by 6 hours. The initial PRAM results suggest that the majority of children had mild-to-moderate wheezing,

Table 3. Secondary Outcomes during Hospitalization.*

Variable	Placebo	Prednisolone	Difference (95% CI)†
Treatment site — no. (%)			
Exclusively in emergency department	3 (0.9)	1 (0.3)	
On observation ward	151 (43.9)	157 (45.8)	
On pediatric ward	190 (55.2)	185 (53.9)	
Use of albuterol			
No. of patients	341	342	
Total metered-dose inhaler actuations — no.	66.70±88.10	52.80±74.50	−14.08 (−26.62 to 1.54)
PRAM score‡			
At 4 hr			
No. of patients	309	316	
Score — units	2.74±2.30	2.48±2.20	−0.29 (−0.65 to 0.06)
At 12 hr			
No. of patients	163	149	
Score — units	2.28±2.03	2.49±1.98	0.20 (−0.24 to 0.64)
At 24 hr			
No. of patients	97	65	
Score — units	1.58±1.64	1.52±1.75	−0.06 (−0.57 to 0.51)
Antibiotics administered in hospital — no./total no. (%)§	43/331 (13.0)	40/337 (11.9)	
Substitution of a study drug and introduction of definitive systemic corticosteroid — no./total no. (%)¶	19/305 (6.2)	13/288 (4.5)	

* Plus–minus values are means ±SD.
† Differences between groups were calculated with the use of linear regression models with the study center as a variable; confidence intervals were calculated with the use of the bootstrap method.
‡ Scores on the Preschool Respiratory Assessment Measure (PRAM)[21] range from 0 to 12, with higher scores indicating a greater severity of respiratory distress; scores were determined after the administration of inhaled albuterol. Confidence intervals for PRAM scores were determined by the bootstrap method.
§ The odds ratio in the prednisolone group was 0.91 (95% CI, 0.57 to 1.44).
¶ The odds ratio in the prednisolone group was 0.70 (95% CI, 0.34 to 1.46). The substitution of a study drug was done either by a pediatrician in the hospital or by a community physician after discharge. No child received oral montelukast during hospitalization.

rather than severe wheezing.[24] However, PRAM scores were assessed after the administration of high-dose inhaled albuterol and therefore did not reflect the maximum severity of wheezing. No significant effect of prednisolone was found in the longer-term outcomes, as assessed by parents after discharge, although these results were limited by the lack of validation of parent-assessed symptom scores against lung function.

The most likely explanation for the difference between our negative result and the positive results reported in other studies is that the majority of children who were recruited into our trial did not have the classic atopic asthma phenotype that is responsive to a short course of oral corticosteroids.[10] This explanation is supported by robust epidemiologic data showing that acute wheezing is not associated with atopy in a majority of affected children[7] and that it has a high likelihood of complete resolution by school age.[6] Many clinicians justify the routine treatment of all preschool children who present with virus-induced wheezing in order to preclude overlooking potentially responsive subgroups.[25] One putative corticosteroid-responsive subgroup is the small minority of preschool children in whom atopic asthma will

Table 4. Secondary Outcomes after Discharge from the Hospital.*

Variable	Placebo	Prednisolone	Difference (95% CI)†
Respiratory-symptom score at 7 days‡			
Daytime			
No. of patients	228	204	
Mean score — units	1.10±0.65	1.00±0.69	–0.06 (–0.18 to 0.07)
Nighttime			
No. of patients	234	204	
Mean score — units	0.99±0.81	0.84±0.77	–0.14 (–0.29 to 0.01)
Actuations of albuterol at 7 days‡			
No. of patients	222	198	
Mean no.	10.80±9.50	10.60±8.30	–0.24 (–1.95 to 1.45)
Time to return to normal activities			
No. of patients	301	280	
No. of days	5.10±3.84	5.13±3.90	0.06 (–0.59 to 0.67)
Hospital readmission for wheezing within 1 month after discharge — no./total no. (%)§	19/303 (6.3)	21/283 (7.4)	

* Plus–minus values are means ±SD.
† Differences between groups were calculated with the use of linear regression models with the study center as a variable; confidence intervals were calculated with the use of the bootstrap method.
‡ Parents were provided with a respiratory-symptom diary card.[18] The severity of daytime and nighttime symptoms and disruption of daytime activity were recorded on a scale of 0 to 3 once daily for 7 days. Parents chose the score that best described the severity of symptoms and the recorded frequency of use of inhaled albuterol.
§ The odds ratio for the prednisolone group was 1.19 (95% CI, 0.62 to 2.26).

develop at school age.[6,7] To date, no predictive index for the development of asthma at school age has proved to be sufficiently accurate to be clinically useful in preschool children. However, in a subgroup analysis using the combination of variables reported by Castro-Rodríguez et al.,[23] we found no evidence of responsiveness to corticosteroids in children who were at statistically high risk for asthma at school age. Although we did not assess blood immunoglobulin E levels, recent data from the longitudinal German Multicenter Allergy Study suggest that blood markers of atopy have poor sensitivity and poor positive predictive value for school-age asthma.[6]

A further limitation of our study is that since we did not collect clinical data from the substantial proportion of children whose parents declined to have them participate in the study, it remains possible that we selected children whose risk for atopic asthma was lower because of either increased symptom severity or parental perception of an increased risk of atopic asthma. It is also important to note that we have not ruled out a small difference between the two study groups, since the lower bound of the 95% confidence interval for the time to signoff for discharge was –6.5 hours. From our data, we calculated that the demonstration of a lack of effect of prednisolone would require a trial enrolling 4400 children to show that those given prednisolone had a duration of hospital stay that was within approximately 2 hours of those in the placebo group.

We did not perform polymerase-chain-reaction analysis, immunofluorescence, or viral cultures to identify viruses associated with upper respiratory infections. An infecting virus is detected in up to 95% of preschool children with clinical virus-induced wheezing,[1] and clinical assessment alone is therefore a valid method of diagnosis. However, a recent study has raised the possibility of a differential response to corticosteroids as a function of the infecting virus.[25] Jartti et al.[16] performed a randomized, placebo-controlled trial of oral prednisone (at a dose of 2 mg per kilogram per day for 3 days) in children 3 months to 16 years of age presenting to the hospital with acute wheezing. In the subgroup of preschool children, oral prednisolone did not significantly reduce the primary

outcome of the time to signoff for discharge.[16] However, in a secondary analysis, prednisolone treatment was associated with significantly fewer relapses for wheezing after discharge in the subgroup infected with rhinovirus.[16] Subsequently, post hoc analyses reported that prednisolone reduced the duration of symptoms and subsequent recurrent wheezing in rhinovirus-infected children.[17,26] To our knowledge, no trial has used virus-associated specificity to oral prednisolone as a primary outcome, and evidence for this phenomenon remains weak, since it is derived from post hoc, secondary analyses of subgroups of children in a small trial.

In summary, in a large, randomized, double-blind trial of a 5-day course of oral prednisolone for preschool children with virus-induced wheezing who presented to the hospital, we found no evidence that a short course of an oral corticosteroid significantly shortened the duration of hospitalization or significantly reduced markers of the severity of symptoms, as assessed by either physicians or parents. Our results suggest that oral prednisolone should not be routinely given to preschool children presenting to the hospital with acute, mild-to-moderate virus-induced wheezing.

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