

ORIGINAL ARTICLE

Intermittent Inhaled Corticosteroids in Infants with Episodic Wheezing

Hans Bisgaard, M.D., D.M.Sci., Mette Northman Hermansen, M.D.,
Lotte Loland, M.D., Ph.D., Liselotte Brydesholt Halkjaer, M.D.,
and Frederik Buchvald, M.D., Ph.D.

ABSTRACT

BACKGROUND

From the Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, Copenhagen.

N Engl J Med 2006;354:1998-2005.
Copyright © 2006 Massachusetts Medical Society.

We hypothesized that asthma is preceded by a stage of recurrent episodes of wheezing during the first years of life and that inhaled corticosteroid therapy during symptomatic episodes in this early phase may delay progression to persistent wheezing.

METHODS

We assigned one-month-old infants to treatment with two-week courses of inhaled budesonide (400 μ g per day) or placebo, initiated after a three-day episode of wheezing, in this single-center, randomized, double-blind, prospective study of three years' duration. The primary outcome was the number of symptom-free days; key secondary outcomes were the time to discontinuation due to persistent wheezing and safety, as evaluated by height and bone mineral density at the end of the study.

RESULTS

We enrolled 411 infants and randomly assigned 294 to receive budesonide at a first episode of wheezing. The proportion of symptom-free days was 83 percent in the budesonide group and 82 percent in the placebo group (absolute difference, 1 percent; 95 percent confidence interval, -4.8 to 6.9 percent). Twenty-four percent of children in the budesonide group had persistent wheezing, as compared with 21 percent in the placebo group (hazard ratio, 1.22; 95 percent confidence interval, 0.71 to 2.13) — a finding that was unaffected by the presence or absence of atopic dermatitis. The mean duration of the acute episodes was 10 days in both groups and was independent of respiratory viral status. Height and bone mineral density were not affected by treatment.

CONCLUSIONS

Intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life. (ClinicalTrials.gov number, NCT00234390.)

IT IS CONTROVERSIAL WHETHER EARLY INTERVENTION with inhaled corticosteroid therapy makes a difference in the long-term outcome among children with asthma.¹⁻⁷ We hypothesized that for such an intervention to be successful, it must be implemented in infancy, since asthma and the loss of lung function begin during the first years of life.⁸⁻¹³ It is difficult to diagnose asthma in young children, although most authorities agree that recurrent episodes of respiratory symptoms such as wheezing, coughing, and breathlessness portend the development of asthma.¹⁴⁻¹⁶ It is likely that such a symptomatic period before asthma is diagnosed — considered by some to be “pre-asthma” — reflects the earliest pathologic features of asthma.

In the Prevention of Asthma in Childhood (PAC) study, a double-blind, randomized, controlled trial, we tested the hypothesis that intermittent inhaled corticosteroid treatment triggered by episodes of pre-asthma may prevent or delay progression to persistent wheezing (or have an immediate effect on symptoms) in a cohort of infants whose mothers had received a diagnosis of asthma. We monitored daily the progression of asthmatic symptoms from birth through the first three years of life, using the number of symptom-free days as the primary outcome and the development of persistent wheezing as a secondary outcome.

METHODS

SUBJECTS AND STUDY DESIGN

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the ethics committee for Copenhagen (filing no., KF 02-118/98), the Danish Medicines Agency (no., 2602-581), and the Danish Data Protection Agency (no., 1998-1200-359). Before enrollment, written informed consent was obtained from the infants' parents. We ensured the validity of the data by complying with Good Clinical Practice guidelines and quality-control procedures. Data were collected online into an externally monitored, structured-query-language database. An audit trail was run routinely. The study was designed and the data were analyzed by the principal investigator, with input from the coauthors and sponsors. The sponsors made no decisions regarding interpretation or statements in the manuscript. The data are fully owned and controlled by the principal investigator.

The study was nested in the Copenhagen Prospective Study on Asthma in Childhood (COPSAC), a prospective, longitudinal, birth-cohort study.¹⁷ A total of 798 pregnant women with a history of physician-diagnosed asthma were invited to enroll in COPSAC; 452 agreed to participate, and 411 of their newborns were enrolled between August 1998 and December 2001. Although the infants were enrolled at one month of age, they were not randomly assigned to treatment until they had a first episode of wheezing.

Budesonide (Pulmicort, AstraZeneca), at a dose of 400 μg per day, or matching placebo was administered by pressurized metered-dose inhaler and a spacer for two weeks (as described in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org). The families kept the randomly assigned treatments at home and were instructed to initiate a two-week period of treatment after the third day of symptoms and to visit the clinic for clinical evaluation within 24 hours. In addition, the parents were provided with terbutaline (Bricanyl, AstraZeneca) to be administered by pressurized metered-dose inhaler with a spacer when it was perceived to be needed by the infant for symptomatic relief. At the discretion of the pediatricians (the authors) at the clinical research unit, open-label budesonide (400 μg each morning) could be added to the study treatment for periods of two weeks for children presenting with severe symptoms. No other asthma medication was allowed. Correct inhaler technique was ensured by parental education and practice at the clinic at visits every six months.

Symptoms and the use of β_2 -agonists were recorded by the parents daily in diaries during the infants' first three years of life. A comprehensive educational session, more than an hour in duration, was conducted at scheduled clinic visits that took place every six months; parents were taught to record their child's lung-related symptoms, with an emphasis on the lower airways, as opposed to simple cold symptoms and to note only symptoms that troubled the child (e.g., those affecting activity or sleep). Wheezing was explained to the parents as any symptom severely affecting the child's breathing and manifested as, for example, noisy breathing (wheezing or whistling sounds), breathlessness, shortness of breath, or persistent troublesome coughing and was recorded as a composite dichotomized score (yes or no). This symptom

definition and the diary entries were reviewed with the parents at each six-month visit. A dedicated book on asthma-like symptoms and treatment in young children was given to the parents (and is available at www.copsac.com). Episodes of wheezing were defined as three consecutive days on which the child had wheezing symptoms. The parents were requested to bring the child to the clinical research unit for examination by the unit doctor within 24 hours after every episode (i.e., on the fourth consecutive day of symptoms). Children attended the dedicated clinical research unit rather than other health care providers for any symptoms relating to the airways or skin. In addition, at the regular visits every six months, parents were interviewed with the use of structured questions and standardized response categories that focused on the child's lung-related symptoms, diagnoses, medication, use of health care resources, lifestyle, and home environment and that were assessed by the clinical-research-unit doctor.

Children discontinued participation in the trial if they had persistent wheezing, defined as five episodes (each lasting at least three consecutive days) within six months, daily symptoms for four weeks, or acute severe asthma symptoms (resulting in hospitalization or the need for systemic corticosteroid treatment, as judged by the clinical-research-unit doctors). Serious adverse events incompatible with study participation or insufficient adherence with the study procedures also led to discontinuation.

The safety of the study treatment was assessed when the children were three years of age by measuring height by Harpenden stadiometry and bone mineral density by ultrasonography at the phalanx.¹⁷

Nasal secretions were collected at every episode to allow evaluation for respiratory viruses (rhinovirus, respiratory syncytial virus, coronavirus, adenovirus, human metapneumovirus, influenza virus, and parainfluenza virus). Respiratory viruses were identified by reverse-transcriptase–polymerase-chain-reaction analysis (unpublished data).

Lung function and bronchial responsiveness were tested by the raised-volume rapid-thoracoabdominal-compression technique¹⁸ at enrollment, when the children were one month of age. Specific airway resistance was measured at the end of the trial, when the children were three years

of age, by whole-body plethysmography^{19,20} before and after the inhalation of 0.25 mg of terbutaline.

Allergies (to inhalants and food allergens, as determined by skin testing and specific and quantitative IgE analyses) and blood eosinophil counts were determined when the children were 6 and 18 months of age. Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka.²¹

STUDY OBJECTIVES

The primary objective of the PAC study was to assess the efficacy of inhaled budesonide relative to that of placebo after a first episode of wheezing in reducing subsequent respiratory symptoms during the first three years of life. The primary outcome variables were the number of symptom-free days, the number of days free of the use of rescue medication, the number of episodes, and the number of treatments with open-label budesonide.

The secondary objective was to assess the ability of inhaled budesonide to prevent or delay persistent wheezing (i.e., to prolong the time until discontinuation of study treatment because of persistent wheezing). Additional secondary outcomes were the time between the first and second episodes of wheezing, the immediate effect of treatment on symptoms, and potential side effects of treatment on height and bone mineral density.

STATISTICAL ANALYSIS

Efficacy and safety analyses included all randomly assigned children who took at least one dose of study medication. No prevalence data in a high-risk population for the primary outcome (symptom-free days) are available. A power calculation was therefore based on the assumptions that 36 percent of the children in this high-risk population would have persistent wheezing (a prevalence of 14 percent was reported in a study of children at normal risk²²) and that treatment would reduce this proportion to 22 percent.²³ This calculation suggested that at an alpha level of 5 percent and a statistical power of 80 percent, the enrollment of 356 children would be required, and this number was used as the predefined target in the protocol.

All hypothesis testing was two-sided, with a 5 percent threshold for statistical significance.

Symptom-free days, days free of wheezing, and days free of the need for rescue medication were compared between treatment groups by analysis of variance with treatment as a factor. Cumulative incidence was denoted as a proportion. The interaction between treatment and the outcome of viral testing was evaluated by including the factor virus–outcome and the interaction between virus–outcome and treatment in the analysis of variance. Treated episodes and treatment with add-on medication were compared between the groups with the use of Poisson regression. In the comparison of long-term outcomes, the first treatment episode was excluded. The time to discontinuation because of persistent wheezing was compared between the groups with the use of a Cox proportional-hazards model. Bone mineral density and height at the age of three years were compared between the groups with the use of analysis of variance with treatment group as a factor.

RESULTS

Four hundred eleven infants were enrolled at one month of age (i.e., more than the target of 356 children based on the power calculation); 301 of them were randomly assigned to treatment at a mean age of 10.7 months, and 294 received at least one treatment (Fig. 1). Fourteen infants in each group were withdrawn from the study (but not from the analyses) for reasons unrelated to study treatment. A total of 1661 episodes were identified in the diaries; 577 of the episodes did not result in a visit to the clinical research unit. The randomly assigned groups were similar with respect to baseline characteristics, lung function and bronchial responsiveness at 1 month of age, environmental tobacco exposure, allergy-test results and blood eosinophil counts at 18 months of age, and the presence or absence of atopic dermatitis by the age of 3 years (Table 1).

The proportions of symptom-free days and days free of the need for rescue medication, as well as the numbers of episodes and treatments with add-on medication, were similar in the two groups (Table 2). During the three-year trial, the frequency of episodes was 3.1 per child per year in the budesonide group and 2.7 per child per year in the placebo group after randomization (estimated hazard ratio, 1.16; 95 percent confidence interval, 0.95 to 1.41). Two-week open-label add-

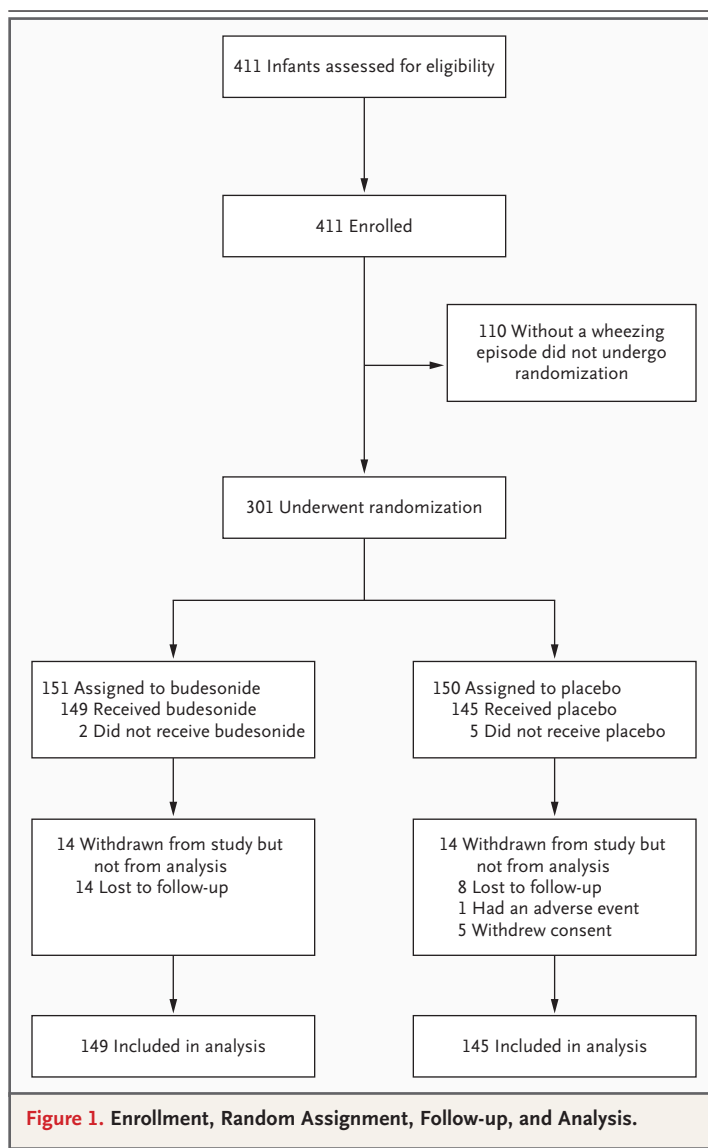


Figure 1. Enrollment, Random Assignment, Follow-up, and Analysis.

on treatment was needed on 59 occasions in the budesonide group and 37 occasions in the placebo group (risk ratio, 1.66; 95 percent confidence interval, 0.96 to 2.87).

The secondary outcome of persistent wheezing leading to study discontinuation was observed in 24 percent of the children receiving budesonide treatment and 21 percent of those receiving placebo (odds ratio, 1.22; 95 percent confidence interval, 0.71 to 2.13; P=0.48 by the chi-square test). The time to study discontinuation was similar in the two groups (P=0.41 by the log-rank test) (Fig. 2). The time from a first episode to a second episode of wheezing also did not differ significantly between the budesonide

Table 1. Characteristics of the Children.*

Characteristic	Budesonide (N = 149)	Placebo (N = 145)
Baseline demographic characteristics		
Male sex (no.)	78	82
White race (no.)†	144	140
Gestational age (wk)	39.7±1.6	40.0±1.6
Asthma in father (%)‡	14	9
Age at first dose of study treatment (mo)	10.8±6.9	10.4±6.7
Risk factors for wheezing and asthma		
FEV _{0.5} at 1 mo of age (ml)	68±19	68±17
Provocative-dose methacholine at 1 mo of age (μmol)§	1.1±2.4	1.3±3.2
Pneumonia at randomization (no.)	35	25
Pneumonia during double-blind treatment (no.)	76	73
Smoking by mother during 3rd trimester (cigarettes/wk)	9±27	11±32
Environmental tobacco exposure at home during first 3 yr of life (days/yr)	80	74
Allergy skin-test result at 18 mo of age (%)		
Positive	9	9
Negative	87	81
Not tested	5	10
Blood eosinophil count at 18 mo of age (28/mm ³)	28	26
Atopic dermatitis before 3 yr of age (%)	38	42

* Plus-minus values are means ±SD. FEV_{0.5} denotes forced expiratory volume in 0.5 second.

† Race was determined at enrollment by a doctor in the clinical research unit.¹⁷

‡ The mothers of all infants had a history of physician-diagnosed asthma.

§ The provocative dose was determined on the basis of incremental doses of methacholine administered with a dosimeter attached to a nebulizer; the response was measured as the forced flow volume obtained by the raised-volume rapid-thoracoabdominal-compression technique.¹⁸

and placebo groups (hazard ratio, 1.12; 95 percent confidence interval, 0.86 to 1.44; $P=0.40$). The treatment response was not significantly different between children with atopic dermatitis and those without atopic dermatitis before three years of age. Furthermore, specific airway resistance at three years of age was similar in the two groups, both at baseline and after bronchodilator use (Table 2), and was similar to our in-house reference value for healthy three-year-old children.²⁴

Respiratory symptoms during the acute episodes (i.e., during the 2-week treatment periods) were similar in the budesonide and placebo groups during the first episode and all episodes and lasted an average of 10 days (Fig. 3). A respiratory virus was identified in 369 of 583 episodes (63 percent), but the immediate treatment effect was not affected by viral status ($P>0.30$ for all symptom variables). The height at three years of age measured by stadiometry and bone min-

eral density measured by ultrasonography at the phalanx were unaffected by treatment group (see the Supplementary Appendix).

DISCUSSION

In this study, two-week treatments with inhaled budesonide during episodes of wheezing in high-risk infants during the first three years of life had no effect on the progression from episodic to persistent wheezing and also had no short-term effect. The development of persistent wheezing was similar in the two groups (24 percent with budesonide and 21 percent with placebo), and the mean duration of the acute symptomatic episodes (10 days) was unaffected by treatment. The response to treatment was independent of the presence or absence of concurrent atopic dermatitis and respiratory viruses.

The trial was based on the hypothesis that early treatment with inhaled corticosteroids modifies

Table 2. Effect of Budesonide on the Progression from Episodic to Persistent Wheezing.*

Variable	Budesonide (N=149)	Placebo (N=145)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)
Symptoms during the 3-yr study				
Symptom-free days (%)	83±24	82±27	1 (-4.8 to 6.9)	—
Days free of rescue medication (%)	91±16	94±13	-3 (-6.2 to 0.5)	—
Incidence of symptoms during the 3-yr study				
No. of episodes/child/yr	3.1	2.7	—	1.20 (0.95 to 1.41)
Withdrawal because of persistent wheezing (%)	24	21	—	1.22 (0.71 to 2.13)
No. of add-on treatments/child/yr	0.25	0.15	—	1.66 (0.96 to 2.87)
Lung function at 3 yr of age, assessed as airway resistance (kPa · sec · liter ⁻¹)†				
At baseline	1.32±0.25	1.31±0.28	0.01 (-0.10 to 0.09)	—
After bronchodilator use	1.08±0.17	1.11±0.21	-0.03 (-0.03 to 0.11)	—

* CI denotes confidence interval. Plus-minus values are means ±SD.

† Values were obtained in 132 children (64 in the budesonide group and 68 in the placebo group). The analysis includes children who completed the three-year study and excludes those who discontinued participation because of symptom severity and those who were unable to undergo whole-body plethysmography.

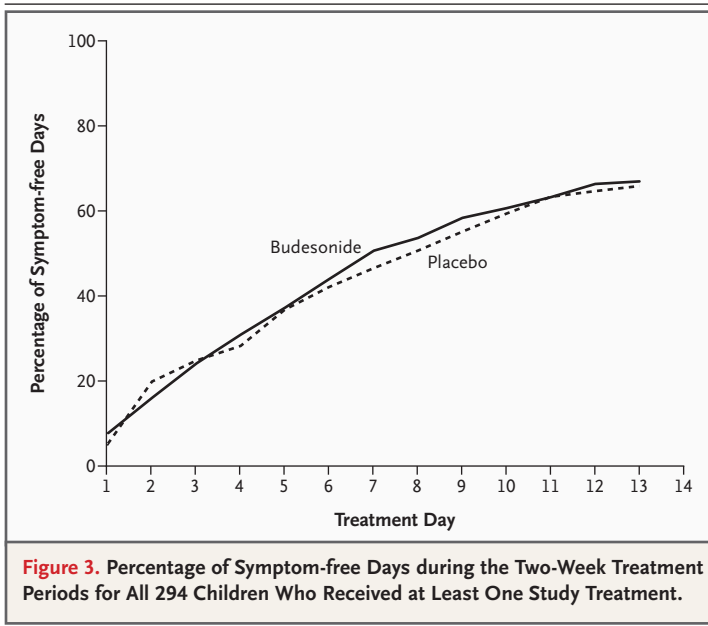
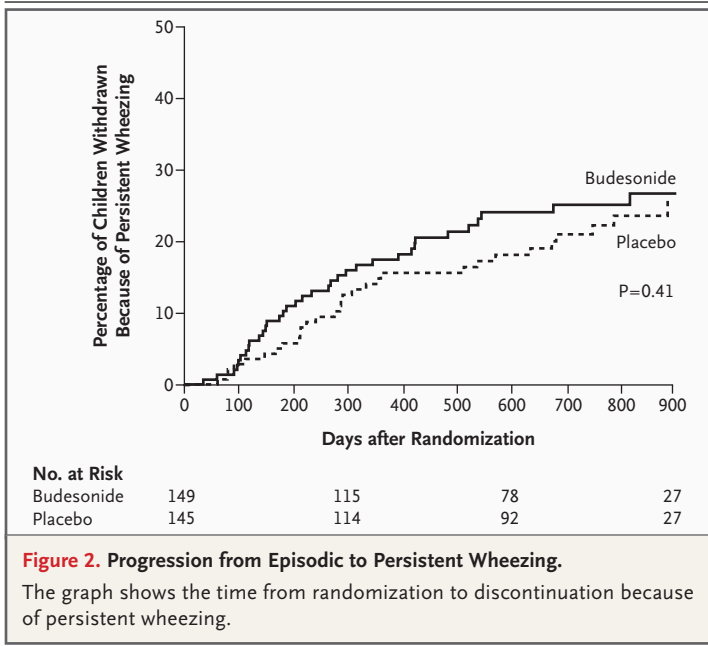
the progression of asthma — that is, the progression from episodic to persistent wheezing. Uncontrolled, prospective short-term³ and long-term^{2,25} follow-up data as well as data from randomized, double-blind, controlled trials with two to three years of follow-up^{1,5} have suggested that corticosteroid treatment initiated within the first years after the onset of asthma controls disease progression. In contrast, the randomized, controlled Childhood Asthma Management Program study, in which children were treated for four to six years, found a small improvement in lung function before the use of a bronchodilator but no benefit with respect to lung function after bronchodilator use⁷; however, these children had had asthma for at least five years before randomization. Overall, the data suggest that intervention after the first years of asthma can control symptoms but not alter the natural course of the disease.

Our study was designed to begin the treatment period even earlier and thus to determine the effect of inhaled-corticosteroid treatment during wheezy episodes of pre-asthma on the subsequent development of asthma. Such very early intervention is the distinguishing feature of this study. However, the study is confounded because in many children, symptoms of pre-asthma are present but asthma does not develop. Hence, pre-asthma reflects a common phenotype of heterogeneous etiologic factors, including virus-associated and atopy-associated respiratory symptoms and respiratory

symptoms that follow bronchiolitis, as well as asthma. Pre-asthma might be considered analogous to the heterogeneous stage preceding other diseases (e.g., hypertension and hypercholesterolemia^{26,27}). Our data show that episodic, short-term treatment in infants with pre-asthma symptoms does not provide benefit.

We used a single-center, birth-cohort design in which every infant was monitored prospectively from birth by means of daily diary cards. Thus, there was close follow-up and reasonable, but not perfect, adherence to the treatment regimen. Our study might be criticized because one third of the episodes retrospectively identified from the diaries did not result in a visit to the clinical research unit according to protocol, and such instances may reflect failure to initiate a treatment cycle. Still, this level of adherence probably exceeds the level that would prevail outside the aegis of a tightly controlled clinical trial.²⁸

Since the term “wheezing” may be difficult for some lay persons to understand,^{29,30} we defined wheezing according to the presence of symptoms severely affecting the child’s breathing, such as noisy breathing (wheezing or whistling sounds), breathlessness, shortness of breath, or persistent troublesome coughing (see the Supplementary Appendix). This approach probably resulted in a reasonable capture of data on lung-related symptoms. Furthermore, respiratory conditions were diagnosed and managed on a day-to-day basis by the



clinical-research-unit doctors (the authors) and according to predefined algorithms, thus minimizing the risk of symptom misclassification resulting from the variable diagnostic criteria and treatment traditions within the medical community.

The lack of an effect of early intervention with an inhaled corticosteroid may be interpreted in several ways. The concept of early intervention may be erroneous; our inhaled-corticosteroid strat-

egy may be incorrect, and regular (instead of intermittent) therapy may be required. However, elsewhere in this issue of the *Journal*, Guilbert et al.³¹ report that two years of inhaled corticosteroids did not change either the likelihood of the development of asthma or lung function in preschool children at high risk for asthma. Higher and more frequent doses may be necessary, or it may be necessary to initiate treatment earlier than the third day of symptoms. The treatment of episodes of wheezing, even in high-risk populations, may lack specificity. Many of the episodes treated were documented to be associated with a viral infection, but the response was not different in these instances. Children's status with respect to atopic dermatitis also did not affect the treatment response. It is possible that asthma early in life represents a pathologic process different from that seen later in life,³²⁻³⁵ and therefore, the first years of life may be too early for intervention with an inhaled corticosteroid. The effect of maintenance therapy with inhaled corticosteroids in young children with persistent wheezing is well documented,^{23,36-38} but this salutary effect is driven mainly by the inclusion of children with more severe symptoms and increases with age.^{39,40}

In summary, we found that early intervention with intermittent inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing in young children at high risk for asthma and no short-term effect on wheezing. Hence, our results caution against the widespread use of short courses of inhaled corticosteroids in the treatment of episodic wheezing while regular inhaled corticosteroid therapy should be reserved for young children with persistent wheezing.

Supported by AstraZeneca (Lund, Sweden), LEO Pharma, Pharmacia-Pfizer, and Yamanouchi Pharma. COPSAC is funded by the Pharmacy Foundation of 1991; the Lundbeck Foundation; Ronald McDonald House Charities; the Danish Medical Research Council; the Danish Pediatric Asthma Center; Direktør, K. Gad Andersen og Hustrus Familiefond; Aage Bangs Fond; Danish Lung Association; Kai Lange og Gunhild Kai Langes Fond; Direktør Ib Henriksens Fond; Gerda og Aage Hensch's Fond; Rosalie Petersens Fond; Hans og Nora Buchards Fond; Dagmar Marshalls Fond; Foundation of Queen Louise Children's Hospital; the Danish Hospital Foundation for Medical Research, Region of Copenhagen, Faroe Island, and Greenland; Gangsted Fond; Høj-mosegård-Legatet; Fonden til Lægevidenskabens Fremme; A.P. Møller og Hustru Chastine Mc-Kinney Møllers Fond til almene Formaal; the Danish Ministry of the Interior; and Health's Research Centre for Environmental Health.

Dr. Bisgaard reports having received consulting and lecture fees and sponsored grants from Aerocrine, AstraZeneca, Altana, GlaxoSmithKline, Merck, and MedImmune. He does not hold stock or options in any pharmaceutical company in the respira-

tory field. No other potential conflict of interest relevant to this article was reported.

We are indebted to the parents and infants participating in

this trial as well as to project coordinator Malene Stage, M.Sc., research assistants Lena Vind and Kirsten Mathiesen, and study nurse Marianne Hansen for skilled assistance.

REFERENCES

1. Haahntela T, Jarvinen M, Kava T, et al. Comparison of a β 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
2. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
3. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.
4. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103:376-87.
5. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.
6. Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. *Control Clin Trials* 1999;20:91-120.
7. *Idem*. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
8. Blair H. Natural history of childhood asthma: 20-year follow-up. *Arch Dis Child* 1977;52:613-9.
9. Gerritsen J, Koeter GH, Postma DS, Schouten JP, Knol K. Prognosis of asthma from childhood to adulthood. *Am Rev Respir Dis* 1989;140:1325-30.
10. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888-94.
11. Oswald H, Phelan PD, Lanigan A, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14-20.
12. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
13. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.
14. Global Initiative for Asthma: global strategy for asthma management and prevention. Update from the NHLBI/WHO workshop report 1995. Bethesda, Md.: National Heart, Lung, and Blood Institute, 2005. (NIH publication no. 02-3659.)
15. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics — 2002. *J Allergy Clin Immunol* 2002;110:Suppl:S141-S219. [Erratum. *J Allergy Clin Immunol* 2003;111:466.]
16. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
17. Bisgaard H. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): design, rationale, and baseline data from a longitudinal birth cohort study. *Ann Allergy Asthma Immunol* 2004;93:381-9.
18. Loland L, Buchvald F, Halkjaer LB, Anhoj J, Hall GL, Bisgaard H. Sensitivity of bronchial responsiveness measurements in young infants. *Chest* 2006;129:669-75.
19. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J* 1995;8:2067-75.
20. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest* 2005;128:355-62.
21. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92:Suppl:44-7.
22. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
23. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999;160:126-31.
24. Klug B, Bisgaard H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2-7 years. *Pediatr Pulmonol* 1998;25:322-31.
25. Selroos O, Lofroos AB, Pietinalho A, Riska H. Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study. *Respir Med* 2004;98:254-62.
26. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.
27. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
28. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
29. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82:327-32.
30. Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. *Arch Dis Child* 2001;84:31-4.
31. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
32. Le Bourgeois M, Goncalves M, Le Clainche L, et al. Bronchoalveolar cells in children <3 years old with severe recurrent wheezing. *Chest* 2002;122:791-7.
33. Saglani S, Malmstrom K, Pelkonen AS, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171:722-7.
34. Krawiec ME, Westcott JY, Chu HW, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1338-43.
35. Bisgaard H. Persistent wheezing in very young preschool children reflects lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1290-1.
36. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990;336:649-51.
37. de Blic J, Delacourt C, Le Bourgeois M, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;98:14-20.
38. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500-6.
39. Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108:540-6.
40. Hofhuis W, van der Wiel EC, Nieuwhof EM, et al. Efficacy of fluticasone propionate on lung function and symptoms in wheezy infants. *Am J Respir Crit Care Med* 2005;171:328-33.

Copyright © 2006 Massachusetts Medical Society.