

The effect of drug therapy on long-term outcome of childhood asthma: A possible preview of the international guidelines

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Background: International guidelines classify childhood asthma as mild, moderate, and severe and recommend treatment with "as needed" bronchodilators, cromolyn sodium, and inhaled corticosteroids, respectively. Recently, some investigators proposed inhaled corticosteroids as first-line therapy to avoid possible irreversible airway obstruction. This article describes a retrospective study assessing the effect of the guidelines' approach on the long-term outcome of childhood asthma and the possible effect of delaying initiation of administration of corticosteroids.

Methods: A retrospective review was performed on the charts of 175 children, and an end-of-study questionnaire plus results of spirometry completed the data. The mean age at start of study was 6.5 years, and the children were followed up for 2.2 to 16.8 years (mean, 8.4 years). Treatments included bronchodilators as needed only (patients with mild asthma), cromolyn sodium (patients with moderate asthma), and inhaled corticosteroids (patients with severe asthma).

Results: Frequency of symptoms, unscheduled doctors' visits, emergency department visits, hospitalizations, and missed school days decreased for the whole group. Statistically significant between-treatment differences favored both antiinflammatory therapies over as-needed bronchodilator treatment (cromolyn sodium: symptoms, $p < 0.05$; hospitalizations, $p < 0.05$; corticosteroids: emergency department visits, $p < 0.05$; hospitalizations, $p < 0.05$). Mean spirometry results improved, and the postbronchodilator values approached normal by study end. Assessed by treatment, spirometry decreased with bronchodilators but improved in patients treated with cromolyn sodium or inhaled corticosteroids. Delay in starting administration of cromolyn sodium had an unfavorable effect on clinical outcomes ($p < 0.01$) and spirometry ($p < 0.05$); delay in starting administration of corticosteroids did not.

Conclusions: Treatment with antiinflammatory drugs (cromolyn sodium or inhaled corticosteroids), but not as-needed bronchodilators alone, improves the long-term prognosis of asthma. It is possible that starting administration of nonsteroid antiinflammatory agents earlier than the present recommendations could further improve clinical outcomes, but prospective studies are needed. (*J Allergy Clin Immunol* 1996;98:1103-11.)

Key words: Asthma, antiinflammatory, cromolyn sodium, corticosteroids, β -agonists, prn bronchodilators, clinical outcomes, retrospective study

The International Guidelines classify asthma according to severity as mild, moderate, and severe.¹ Previous studies investigating the long-term

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Abbreviations used

ED:	Emergency department
FEF _{25%-75%} :	Forced expiratory flow, mid-expiratory phase
FVC:	Forced vital capacity
prn:	As needed

outcome of childhood asthma have established that a certain percent of patients will stop wheezing. Specifically, the percent varies widely between 18% and 80%.^{2,3} Several factors seem to influence the progression of asthma in children. One contro-

versial factor is the age at onset of the disease. In one report investigators found early onset to be a poor prognostic factor,⁴ yet other investigators concluded that early age at onset was a good prognostic sign.⁵ However, most investigators found that early onset had no prognostic value for childhood asthma.^{2, 3, 6, 7} There is better consensus regarding correlation of other factors and asthma prognosis, including the coexistence of allergic rhinitis or eczema.^{2, 6, 8-10} However, among all the factors that may be related to disease progression, the most generally accepted conclusion was that patients with severe asthma were less likely to outgrow their disease.^{2-4, 6-9, 11}

Three studies investigated the possible role of pharmacotherapy on the long-term outcome of childhood asthma. Martin et al.¹¹ concluded that pharmacotherapy had no influence on long-term outcome of the disease. Kokkonen and Linna⁹ also concluded that the improvement rate was similar in patients receiving antiinflammatory therapy when compared with patients receiving as-needed (prn) bronchodilators only. Agertoft and Pedersen¹² studied the effect of budesonide in children for 3 to 6 years and found that the annual increase in FEV₁ inversely correlated with the delay in starting administration of budesonide. From these results, the authors conclude that delay in initiating inhaled corticosteroids may result in irreversible airway obstruction.

Current recommendations for asthma management include a stepwise approach based on anti-inflammatory therapy.^{1, 13-15} This approach begins with the use of prn bronchodilator therapy for mild asthma, cromolyn sodium for moderately severe asthma, and inhaled corticosteroid therapy for severe asthma.

Over the last 20 years, asthma management in our practice has closely resembled these international asthma treatment guidelines.¹⁶ Specifically, the International Consensus Report defines moderately severe asthma as "having exacerbations more than two times a week."¹ Similarly, our definition for moderately severe disease includes asthma symptoms present for more than 3 days per week. These patients were treated with cromolyn sodium, and if this treatment did not control the patients' disease, they were switched to inhaled corticosteroid therapy. Patients with symptoms that occurred less than three times per week were treated only with prn bronchodilator therapy. All patients had access to prn bronchodilators for rescue therapy.

Given the close similarities between the treatment strategies for our patients with asthma and

the step-care approach currently recommended by international guidelines, a retrospective analysis from our clinic provides a preview of the possible outcome of long-term management of asthma in children.¹ Because our practice reserved the use of inhaled corticosteroid therapy for severe asthma, this assessment also investigated whether delay in starting inhaled corticosteroid therapy may lead to irreversible airway obstruction, as suggested by Agertoft and Pedersen.¹²

METHODS

Subjects

Patients under the care of the Pediatric Pulmonary-Allergy Division at the University of Missouri-Columbia were included in the analysis. Entry criteria were: (1) patients were followed up originally in our clinic for at least 6 months, and (2) at least 2 years had passed since their first visit to our clinic. Exclusion criteria were: the presence of concomitant chronic lung disease (e.g., cystic fibrosis, bronchopulmonary dysplasia, congenital emphysema) and age over 17 years.

The diagnosis of asthma was considered in the presence of recurrent episodes of cough, wheezing, and dyspnea or chronic cough fulfilling the characteristics of cough-variant asthma.¹⁷ In patients old enough to perform pulmonary function tests, proof of reversible airway obstruction and/or the presence of bronchial hyper-reactivity (determined by exercise or methacholine challenge) were used to confirm the diagnosis.

The severity of the disease was determined by history, physical examination, symptom diaries,¹⁸ results of spirometry at each clinic visit, and home peak flow measurements when necessary. The initial severity was determined in the first 6 months of assessment in our clinic. Asthma severity was based on the following classification:

1. Mild, intermittent asthma: having symptoms on 3 or fewer days per week. These patients were treated only with bronchodilators on a prn basis, mostly inhaled β -adrenergic agents, usually with a backup bronchodilator (either anticholinergic agent or oral theophylline) for more severe or prolonged symptoms.
2. Moderately severe asthma: having symptoms on more than 3 days per week. The treatment for these patients was cromolyn sodium in an age-appropriate delivery system (nebulized in patients under 4 to 5 years and dry powder or metered-dose inhaler in older children). The dosage was usually four times daily at start and three times daily after 1 month (rarely was twice daily dosing used). At times of prolonged exacerbation or respiratory infections, the drug was sometimes given five to six times daily.¹⁹
3. Severe asthma: not satisfactorily controlled with a trial of cromolyn sodium. The treatment for this group was inhaled corticosteroids, mostly beclomethasone dipropionate. The dose was 400 to 800 μ g

TABLE I. Clinical outcomes at start of study (mean $\pm$ SD)

Group	Days with symptoms/wk	Days of school missed/yr	Unscheduled doctors' visits/yr	ED visits/yr	Hospitalizations/yr
Mild	1.5 $\pm$ 0.5	2.0 $\pm$ 0.8	1.9 $\pm$ 0.8	1.2 $\pm$ 0.5	0.6 $\pm$ 1.2
Moderate	1.7 $\pm$ 0.4*	2.4 $\pm$ 0.8*	2.2 $\pm$ 0.8	1.6 $\pm$ 0.8*	1.3 $\pm$ 1.9*
Severe	1.6 $\pm$ 0.5	2.3 $\pm$ 0.7	2.1 $\pm$ 0.8	1.6 $\pm$ 0.8*	1.4 $\pm$ 1.8*

Patients in the mild group were treated with prn bronchodilators, those in the moderate group were treated with cromolyn sodium, and those in the severe group were treated with inhaled corticosteroids.

* $p < 0.05$ relative to mild (prn bronchodilator only) group.

initially (mean $\pm$ SD, 675 μ g $\pm$ 199), tapered down to the lowest effective dose or raised as high as 1000 to 2000 μ g/day as necessary. The mean dose in the last year of the study was 670 $\pm$ 630 μ g.

All patients treated with the steroid and nonsteroid antiinflammatory medications were also given prescriptions for prn bronchodilators to use "as needed" for rescue therapy. At regular clinic visits, if control of the disease with the original treatment regimen was judged unsatisfactory (on the basis of evaluation of both symptoms and pulmonary function), the patient was stepped up to the next level of treatment. Alternatively, patients whose conditions improved were stepped down to a lower level of medication.

Patient evaluation included skin testing for prevalent regional allergens in most cases; and patient education included allergen avoidance and environmental control when appropriate.

At the end of the follow-up period, the patients were interviewed by a pulmonary nurse or respiratory therapist who completed a questionnaire on the degree of asthma control and the medication used. Many of the patients were no longer under our clinic's care at the follow-up review. However, information on symptoms and medications was collected from these patients also, including the periods not under our care.

Protocol

Heights and weights were included in the chart data for all patients and were also measured at the follow-up clinic visit at the end of the study. Standard deviation scores were calculated on the basis of published data for normal subjects.²⁰ Historical data taken from the patients' charts also included the frequency of asthma symptoms, the number of unscheduled doctors' visits, emergency department (ED) visits, hospitalizations, and missed school days per year. Spirometry (forced vital capacity [FVC], FEV₁, forced expiratory flow, mid-expiratory phase [FEF_{25%-75%}]) had been performed and recorded at every clinic visit with standardized methods.²¹ If the baseline values were outside the normal range (FVC or FEV₁ <80% of predicted value; FEF_{25%-75%} <70%), an inhaled bronchodilator was administered, and spirometry was repeated. Pulmonary function testing at the end of the follow-up period was performed after administration of an inhaled broncho-

dilator, even if the baseline values were within the normal range, because of the possibility of irreversible airway obstruction.

The equipment for spirometry changed during the years included in this retrospective study and included equipment from the following manufacturers: Collins, Med Science, Auto-spiro, Multispiro, and Med Graphics. Predicted normal values were taken from several sets of data.²²⁻²⁶

The project was approved by the Institutional Review Board, and written informed consent was obtained.

Statistical analysis

A chi square test was used to compare severity groups with regard to final clinical outcome (improved or not). Wilcoxon signed-rank tests were used to determine significant changes in continuous variables. To determine differences in continuous variables between independent groups, Kruskal-Wallis tests were used. Spearman's correlation coefficients were calculated to determine whether relationships between continuous variables exist. A p value of less than 0.05 was considered significant.

RESULTS

Demographics

A total of 248 patients were identified as suitable for inclusion in the analysis on the basis of chart review, but 73 (29.4%) could not be located or could not be enrolled mostly because of relocation. The remaining 175 patients constituted the study group. There were 117 (66.9%) male patients and 58 (33.1%) female patients included in the study. The mean age at the start of the study was 6.5 years (range, 0.2 to 16.8 years); median age at start was 6.0 years. The mean age at onset of asthma was 2.6 years (range, 0.1 to 12.3 years), and the mean duration of asthma was 3.9 years (range, 0.1 to 16.8 years). The mean length of the study follow-up was 8.4 years (range, 2.2 to 16.8 years). The majority of the patients (172) were followed up for 3 years or longer; the duration of follow-up was less than 30 months for three patients included in the analysis. There were no significant differences in demographic characteristics or asthma severity between

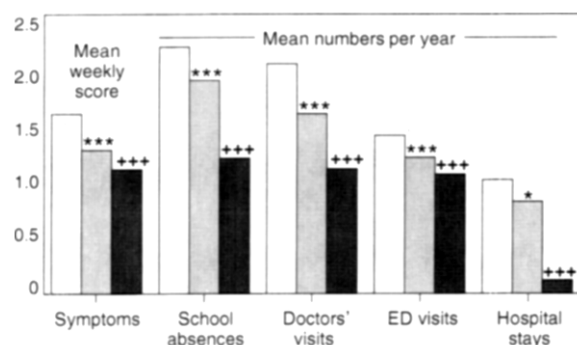


FIG. 1. Mean weekly asthma symptom frequency (days with symptoms/week) and mean yearly days of school missed, ED visits, and hospitalizations for treatment of asthma. Open bars, Baseline; lightly shaded bars, at end of first year of treatment; darkly shaded bars, at end of study. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ relative to baseline. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ relative to end of first year of treatment.

the patients included in the study and the 73 patients who could not be enrolled.

Patients were divided into mild ($n = 84$, 48%), moderate ($n = 57$, 33%), and severe ($n = 34$, 19%) categories. In terms of severity classification, there were no significant between-group differences for gender ratio or age at onset of asthma. However, the moderately severe group was significantly younger than the severe group at the start of the study review period ($p < 0.05$). The duration of the initial treatment in the study ranged from 13 months to 59 months (prn bronchodilators, 13.3 months; cromolyn sodium, 24.4 months; inhaled corticosteroids, 58.4 months).

Growth parameters

Height and weight scores in the whole group increased significantly from the beginning to the end of the review period. Analyzed by severity, the mild group significantly increased in mean height score but not in mean weight score; the moderate group increased in mean weight score but not in mean height score; and no significant changes occurred in the severe group. Between-group differences did not attain statistical significance either for the start of chart review, the end of the follow-up period, or in terms of the change from start to end.

Frequency of symptoms, unscheduled doctor's visits, ED visits, hospitalizations, and missed school days

When the historical data taken at the first clinic visit were used for comparison (Table I), all mean

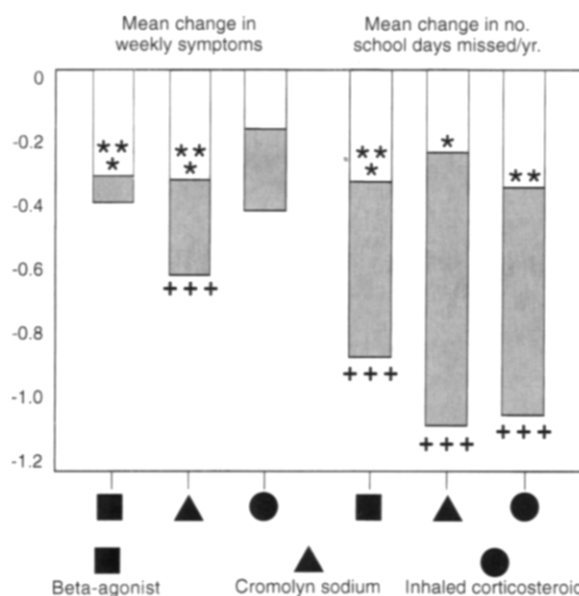


FIG. 2. Mean changes in weekly symptom scores and in number of missed school days per year. Open bars, Change after 1 year of treatment; shaded bars, change at end of study. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ after first year of treatment relative to baseline; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ at end of study relative to end of first year of treatment.

clinical outcomes for the whole group were significantly improved after the first year of treatment. Analyzed by severity group, at the start of chart review the mild group had significantly fewer symptoms ($p < 0.05$), ED visits ($p < 0.05$), hospitalizations ($p < 0.05$), and missed school days ($p < 0.05$) than the moderate group and significantly fewer ED visits ($p < 0.05$) and hospitalizations ($p < 0.05$) than the severe group. The mean weekly frequency of asthma symptoms and yearly frequencies of school absences, ED visits, and hospitalizations for the entire group of patients are shown in Fig. 1. The mean frequencies of clinical outcome events significantly decreased after the first year of treatment compared with baseline and also at study end compared with the end of the first year of treatment. The changes in mean outcome scores are shown by severity group in Figs. 2 and 3. By the end of the follow-up period, all outcomes were significantly improved across the three treatment groups. In addition, statistically significant reductions in clinical outcomes were determined between the first year of treatment and the last year of follow-up for all therapies (with the exception of a nonsignificant reduction in symptoms in the prn bronchodilator and corticosteroid groups). By the last year of the follow-up period, all three groups

had improved, but the moderate (cromolyn sodium) and severe (inhaled corticosteroids) groups improved significantly more than the mild (prn bronchodilator) group. Thus the cromolyn sodium group improved more than the prn bronchodilator group on frequency of symptoms ($p < 0.05$) and hospitalizations ($p < 0.05$), whereas the inhaled corticosteroid group improved more than the prn bronchodilator group on ED visits ($p < 0.05$) and hospitalization ($p < 0.05$). As a result, there were no further significant differences between the groups in the last year of follow-up.

Final clinical outcome

Four severity categories were determined at the end of the study: mild, moderate, severe, and a new group of patients who were free of symptoms and had not received any medication for at least 1 year. Only changes significant enough to jump severity groups were included in this analysis. There was a trend for reduction in severity for the whole group: by the end of the review period, 26 patients (14.9%) were free of symptoms; 88 (50.3%) were classified as mild, 18 (10.3%) were classified as moderately severe, and 43 (24.6%) were classified as severe.

Analyzed according to disease severity at start, approximately 50% of patients treated with either the nonsteroid or steroid antiinflammatory drugs showed improvement throughout the follow-up years (49% with cromolyn sodium and 47% with inhaled corticosteroids), as compared with 16.7% of the patients with mild asthma treated only with prn bronchodilators (Fig. 4). In the cromolyn sodium group 28% of patients needed inhaled corticosteroids by the end of the study, whereas of the patients initially treated with inhaled corticosteroids, 6% were receiving cromolyn sodium and 29% were receiving prn bronchodilator. More patients who began therapy with inhaled corticosteroids were receiving bronchodilators rather than cromolyn sodium at the end of the study because our practice was mostly to skip the cromolyn sodium stage when reducing medication (the step-down phase). The percentage of patients whose asthma deteriorated or remained unchanged was significantly higher ($p < 0.001$) in the prn bronchodilator group (83.3%) than in either the cromolyn sodium group (51.8%) or the inhaled corticosteroid group (52.9%). Thus at the end of the follow-up period, the majority of patients classified as "mild" were those who were originally placed in the mild (prn bronchodilator only) group. The percentage of patients who were free of

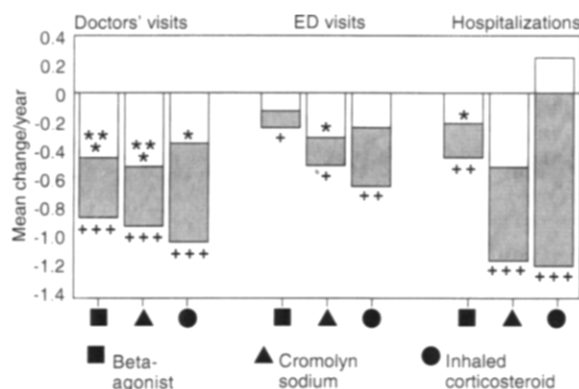


FIG. 3. Mean yearly changes in unscheduled doctors' visits, ED visits, and hospitalizations. *Open bars*, Change after 1 year of treatment; *shaded bars*, change at end of study. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ after first year of treatment relative to baseline; + $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$ at end of study relative to end of first year of treatment.

symptoms by the end of the follow-up period was not different among the three groups (16.7%, 14%, and 11.8% for the mild, moderate, and severe groups, respectively).

Age at onset of asthma and duration of asthma had no significant effect on the final clinical outcome. However, being in the original groups receiving either cromolyn sodium or inhaled corticosteroid had a significant positive effect ($p < 0.001$ for both).

The effect of delaying the start of antiinflammatory treatment (defined as the interval between the first visit and the start of antiinflammatory therapy) was analyzed by comparing the time to starting antiinflammatory treatment for patients whose asthma remained the same or deteriorated and patients whose asthma improved. With cromolyn sodium, there was a significantly longer delay (14.3 months) in those patients whose asthma remained the same or deteriorated than in those whose asthma improved (1.3 months, $p < 0.01$). Delay in starting inhaled corticosteroid therapy was not significantly different between the two groups (20.0 and 18.7 months, respectively). The delay in starting inhaled corticosteroid therapy, calculated from the onset of the disease, was 78.1 ± 41.9 months, and there was no significant difference between those whose asthma remained the same or deteriorated and those whose asthma improved.

Pulmonary function tests

Change from start to end of study review (in those patients tested both at start and end). The results for those patients who were old enough to perform

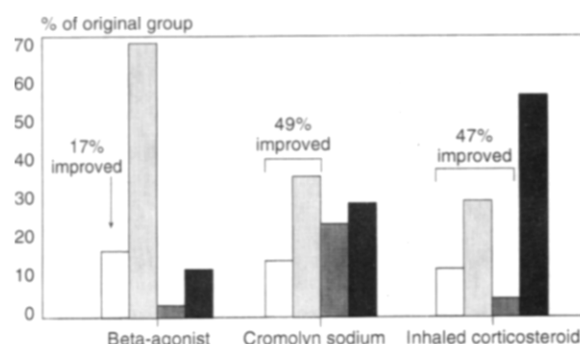


FIG. 4. Asthma severity classifications at end of the study. Severity categories are shown according to the original three treatment groups (prn β -agonist, mild asthma; cromolyn sodium, moderate asthma; inhaled corticosteroids, severe asthma). Open bars, Free of symptoms (not receiving any antiasthma medications); light gray bars, mild asthma (treated with prn bronchodilators only); dark gray bars, moderate asthma (treated with cromolyn sodium); black bars, severe asthma (treated with inhaled corticosteroids).

spirometry at the beginning of the study review period ($n = 109$) showed that the two groups of patients treated with antiinflammatory drugs had improvements that reached statistical significance for FEV_1 ($p < 0.05$) and $FEF_{25\%-75\%}$ ($p < 0.05$) in the cromolyn sodium group and for FVC ($p < 0.05$) in the inhaled corticosteroid group. The group treated with prn bronchodilators showed a nonsignificant deterioration in FVC and FEV_1 , but a significant improvement in $FEF_{25\%-75\%}$ ($p < 0.05$).

Between-group comparisons of the changes from the start to the end of the study showed a significant difference in FVC, favoring the steroid-treated group over the prn bronchodilator group ($p < 0.01$).

Within-treatment changes

Because the analyses comparing data from the start to the end of the study could be affected by some patients being switched to different treatments, another analysis was done, in which a starting point at the initiation of a treatment and an end point at the time of treatment change (or the end of follow-up if the patient continued to receive the same treatment) were used. This analysis showed statistically significant decreases in FVC ($p < 0.05$) and FEV_1 ($p < 0.05$) and a decrease in $FEF_{25\%-75\%}$ (which did not reach statistical significance) with prn bronchodilator treatment alone (Fig. 5). The cromolyn sodium-treated group showed no significant changes, and

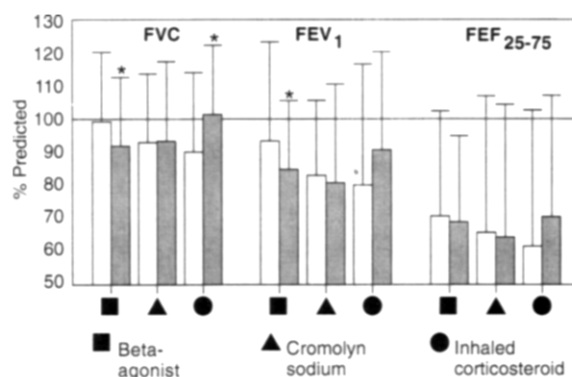


FIG. 5. Mean ($\pm$ SD) within-treatment changes in pre-bronchodilator pulmonary function test results reported as percentage of predicted normal value. Data represent start to end of treatment, regardless of whether the end of treatment was the end of the study or represented a change in therapeutic agent. β -Agonist, $n = 44$; cromolyn sodium, $n = 28$; inhaled corticosteroid, $n = 26$. Open bars, Start of treatment test results; shaded bars, end of treatment test results. * $p < 0.05$.

the patients treated with inhaled corticosteroid showed a statistically significant increase in FVC ($p < 0.05$). Between-group comparisons of changes showed significant differences in favor of inhaled corticosteroids over bronchodilator in FVC ($p < 0.01$) and FEV_1 ($p < 0.05$). No other statistically significant between-group differences were found.

Pulmonary function test results in all patients (including those who were too young to be tested at start)

Mean spirometry values for the whole group showed a tendency for improvement, and final postbronchodilator values approached normal. The pulmonary function test results are shown by severity classification in Table II. At the start of the study, the best values for all spirometric tests were obtained in the mild (prn bronchodilator only) group. At the end of the follow-up period, the moderately severe group showed the highest pulmonary function test results; and even the severe group demonstrated better results than the mild group in two of three pulmonary function measures (FVC and FEV_1). However, none of these differences reached statistical significance.

Age at onset of asthma and duration of asthma had no effect on final pulmonary function. FEV_1 (prebronchodilator) was significantly higher in female subjects than in male subjects ($p < 0.05$). Final FVC (before bronchodilator use) was positively affected by treatment with cromolyn sodium ($p < 0.05$) or inhaled corticosteroids ($p < 0.05$).

TABLE II. Mean pulmonary function tests for all patients ($n = 157$) reported as the percent predicted (mean $\pm$ SD)

	Start of study		End of study	
	Before bronchodilator	After bronchodilator	Before bronchodilator	After bronchodilator
FVC				
β -Agonist	98.3 $\pm$ 18.3	100.3 $\pm$ 19.2	95.5 $\pm$ 15.0	97.0 $\pm$ 15.0
Cromolyn sodium	92.0 $\pm$ 20.0	99.0 $\pm$ 22.7	102.4 $\pm$ 16.2	104.1 $\pm$ 16.9
Inhaled steroid	90.0 $\pm$ 27.1	99.6 $\pm$ 30.0	101.6 $\pm$ 18.7	103.8 $\pm$ 17.8
FEV ₁				
β -Agonist	92.0 $\pm$ 24.3	96.2 $\pm$ 21.2	88.8 $\pm$ 15.8	94.2 $\pm$ 15.0
Cromolyn sodium	80.3 $\pm$ 22.7	86.6 $\pm$ 25.2	92.4 $\pm$ 17.2	100.2 $\pm$ 15.8
Inhaled steroid	79.9 $\pm$ 31.7	88.4 $\pm$ 30.2	88.9 $\pm$ 19.5	95.5 $\pm$ 19.6
FEF _{25%-75%}				
β -Agonist	70.3 $\pm$ 29.8	82.5 $\pm$ 27.9	75.2 $\pm$ 23.2	87.2 $\pm$ 22.7
Cromolyn sodium	61.6 $\pm$ 37.6	72.1 $\pm$ 30.0	76.1 $\pm$ 30.3	93.5 $\pm$ 28.4
Inhaled steroid	61.2 $\pm$ 40.3	67.1 $\pm$ 32.7	67.3 $\pm$ 30.9	82.4 $\pm$ 36.2

Delay in starting cromolyn sodium therapy had a negative effect on the patients' final FVC prebronchodilator values ($\rho = -0.336$, $p < 0.05$) and FVC postbronchodilator values ($\rho = -0.332$, $p < 0.05$). Delay in starting inhaled corticosteroid therapy, calculated from the onset of the disease or from the start of the study, had no significant correlation with any of the final pulmonary function test results.

DISCUSSION

This retrospective study suggests that the stepwise approach to asthma therapy recommended by current national and international guidelines will produce positive long-term outcomes. In addition, our observations support the supposition that patients with asthma treated with an antiinflammatory drug (cromolyn sodium or an inhaled corticosteroid) will likely show greater improvements over time in clinical outcome measures and in pulmonary function test results as compared with patients treated only with prn bronchodilators. Similar percentages of the three original severity groups became free of symptoms, even though the moderate (cromolyn sodium) and severe (inhaled corticosteroid) groups needed greater levels of improvement than the mild (prn bronchodilator) group. This is in contrast to what might be expected on the basis of the natural history of the disease, which would predict a worse prognosis for patients with more severe asthma, and suggests at least a partial reversal of disease progression.^{2-4, 6-9, 11}

Two other published reports investigating the effect of drug therapy on the long-term outcome of asthma differ from this study in that neither study was

specifically designed to investigate the effect of drug therapy on disease progression.^{9, 11} The Australian study¹¹ was performed when the availability of anti-inflammatory drugs and their indications were very different from current treatment practices. Cromolyn sodium became available 3 years into the 14-year study, and even then, "appropriate" treatment in patients with frequent symptoms was considered to be either cromolyn sodium or continuous bronchodilators. Inhaled corticosteroids became available 7 years after the start of the study. Possibly, the conclusion that "appropriate" treatment had no effect on the long-term outcome was due to less use of anti-inflammatory drugs than in this study.¹¹

The Finnish study⁹ started in 1965. For the first few years, neither cromolyn sodium (first published study appeared in 1967²⁷) nor inhaled corticosteroids (first published studies of children appeared in the early 1970s^{28, 29}) were available. The authors do not describe the indications for use of these drugs; therefore, it is not possible to directly compare their results with those of this study. Agertoft and Pedersen¹² have suggested that delay in starting inhaled corticosteroid therapy may cause irreversible airway obstruction. Their study was not designed to identify irreversible obstruction because no attempt was made to reverse the airway obstruction, and only prebronchodilator (baseline) spirometry was measured. Furthermore, all their patients were treated with frequent β -adrenergic agents. In contrast to the conclusions of these investigators, our study shows a significant improvement in pulmonary function in patients treated with cromolyn sodium and not a deterioration, as one would expect on the basis of

their conclusions.¹² It is possible that the smaller increase in baseline spirometry with longer delays in starting budesonide therapy was due to the frequent use of β -adrenergic agents in their study. Several studies have suggested that continuous administration of β -adrenergic drugs for treatment of asthma can cause deterioration of clinical control and pulmonary function.^{30, 31} In this study delay in starting inhaled corticosteroid therapy had no detrimental effect on the long-term outcome, either in clinical condition or pulmonary function test results. On the other hand, delay in starting cromolyn sodium therapy adversely affected both clinical outcome measures and pulmonary function. On the basis of up to 16 years of follow-up, the important delay identified in this study is the time to initiation of administration of the first antiinflammatory drug, in this case, cromolyn sodium; and the time taken for a trial of a nonsteroid antiinflammatory agent does not appear to have any negative effect on long-term outcomes.

There were several confounding factors in this study. One is that at the end of the study many patients were no longer under our clinic's supervision. Although we have data on the medication that these patients received, we cannot be sure that determinations of asthma severity used clinical indicators similar to those described here. Analyses of spirometry at the last visit in our clinic supported the results at the end of the study, showing greater improvements in the patients treated with either the steroid or the nonsteroid antiinflammatory drugs as compared with patients treated only with prn bronchodilators. Another confounding factor is the change in treatment that, for many patients, occurred during the course of this retrospective study. Thus for most patients the final results were not simply due to a single drug regimen. A within-treatment analysis, based on data obtained only from the original treatment period, eliminated this factor and showed that only the patients treated with prn bronchodilators alone had significant deterioration in pulmonary function. The drop in spirometry for the bronchodilator group at the end of the study (Table II) was relatively modest because some patients were switched during the study to cromolyn sodium or inhaled corticosteroids. However, the within-treatment drop in FEV₁ from 93.3% to 84.6% is very likely clinically significant. The larger question to be addressed is determination of the clinically significant end point, that is, that level of pulmonary function deterioration at which antiinflammatory therapy should be initiated in a patient with "relatively" mild asthma.

The patients with moderate and severe asthma had more symptoms and worse pulmonary function and, perhaps, greater room for improvement than the patients with mild asthma (treated with prn bronchodilators only) at the start of the study. However, the natural history of asthma indicates that patients with more severe asthma have worse prognoses.^{2-4, 6-9, 11} In this study asthma status improved with antiinflammatory therapy in both the severe and moderate asthma groups. The fact that within-treatment changes showed significant decrements in pulmonary function only in the prn bronchodilator-treated group (patients with mild asthma) supports the idea that the improvements observed in the moderate and severe groups were due to their treatment regimen and not simply a function of the potential for improvement in those patients.

There was no evidence in this study that age of onset or duration of asthma had any effect on the long-term clinical outcome. Most other investigators have concluded that age of onset has no long-term effect.^{2, 3, 6, 7} There was no significant difference in gender ratio between the different severity groups, but final pulmonary function test results showed better FEV₁ in female subjects. Williams and McNicol⁴ concluded that even though up to the age of 10 years boys and girls are equally likely to have mild asthma, after that age more boys are found to have the more persistent (severe) form of asthma.

Overall, this study suggests that a stepwise approach to treatment, similar to that recommended by the International Consensus Report,¹ results in both clinical and functional improvements. This is an encouraging sign for the future if the principles of these guidelines are applied on a wide scale. The primary conclusion of this study is that the critical step is the initiation of antiinflammatory therapy. Of the children whose asthma did not improve, the time to initiation of antiinflammatory therapy was significantly longer than that for those whose asthma did improve. Specifically, delay in starting cromolyn sodium therapy (from therapy with prn bronchodilators) had a negative effect on clinical outcomes. A delay in starting inhaled corticosteroid therapy (in patients treated with cromolyn sodium) had no detrimental effect. Initiation of cromolyn sodium therapy in these children was done by using criteria similar to those recommended by the International Consensus Report.¹

The results of this study suggest that earlier introduction of nonsteroid antiinflammatory drugs, such as cromolyn sodium, will improve the long-term outcome of childhood asthma. There

are no other published studies of long-term outcomes of childhood asthma based on the presently recommended stepwise treatment provided by the International Consensus Report.¹ In the new era of managed health care, long-term clinical outcomes are relevant not only in terms of quality of care, but also in terms of overall costs associated with the disease. It is important, therefore, to note that the two groups treated with antiinflammatory drugs showed greater improvements than the patients treated only with prn bronchodilators, not only in symptoms and pulmonary function, but also in ED visits and hospitalizations. These "urgent care services" now constitute the largest component of the cost of care for asthma in the United States.³² Our results suggest that the current consensus recommendations regarding mild asthma may not be the optimal treatment and that antiinflammatory treatment should be started earlier. However, because this study was retrospective, prospective long-term studies are needed to confirm the observations made and to permit appropriate recommendations for initiating antiinflammatory therapy to be made with greater certainty.

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