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Childhood asthma: New insights into management

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Recently, a concerted effort has been made to reverse the trend of increasing asthma mortality and morbidity. One additional strategy might be to recognize patients at risk for persistent asthma and to intervene early. This review summarizes new information on asthma pathogenesis that has helped shape a new direction in managing childhood asthma. At the core is the recognition that asthma is a chronic inflammatory disease. Subsequently, inhaled steroids, the most potent anti-inflammatory asthma medications, have emerged as the cornerstone of the management of persistent asthma. The recent report of the National Heart, Lung, and Blood Institute's Childhood Asthma Management Program provides a comprehensive "profile of performance" for 3 treatment choices for the management of persistent asthma. This study answers questions regarding the benefits and shortcomings of the medications evaluated and prompts a closer evaluation of the long-term effects of other treatment strategies, including medications currently being developed. Although intervention with inhaled steroids offers new opportunities to control the development of asthma, one must be cognizant of potential risks in early and long-term therapeutic intervention. This review provides a perspective on our present knowledge, the rationale for early intervention, and opportunities for more aggressive therapy, as well as speculation on how ongoing clinical research will continue to play a role in advancing asthma care and moving toward a "cure" for this life-threatening disease. (*J Allergy Clin Immunol* 2002;109:3-13.)

Key words: *Bronchodilators, childhood asthma, Childhood Asthma Management Program, cromolyn, inhaled corticosteroids, long-term control therapy, theophylline*

Abbreviations used

CAMP: Childhood Asthma Management Program

FVC: Forced vital capacity

PEF: Peak expiratory flow

Over the last 15 years, we have gained tremendous insight into the pathogenesis of asthma¹ and consequently introduced several new classes of therapy—namely, inhaled steroids and leukotriene antagonists. We have also turned our attention to earlier recognition of the disease as well as to earlier intervention with environmental control and long-term control therapy. It is expected that this evolution of understanding and managing asthma will continue at today's rapid pace as we learn more and more about the pathogenesis and treatment of the disease, especially inasmuch as advances in immunology and genetics are sure to open doors to new treatment modalities. This new direction stimulates questions regarding criteria for the diagnosis of asthma as well as the development of methods by which to carefully monitor the disease. Recent data suggest that inhaled steroid therapy has played a role in controlling the rise in asthma morbidity and mortality, but there is still a great deal of room for improvement.²

This review begins by summarizing how we reached our current strategy in the management of asthma and speculates on where we appear to be heading. Knowledge about asthma has increased tremendously with the application of some new tools for evaluating airway pathology in combination with the relatively rapid introduction of new medications as well as the reformulation of old medications to improve drug delivery to the lung. Ongoing discussions about asthma now entertain the provocative thought of a "cure" for this disease by recognizing it early and intervening appropriately. The goals now are to define how to "recognize it early" and to identify the most effective and safe interventions for early intervention and long-term control.

WHERE ARE WE NOW?

Less than 20 years ago, we thought of asthma as a disease manifested by intermittent and unpredictable episodes of respiratory distress. These episodes were more likely to occur with respiratory infections, with

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allergen exposure, or after exercise. Sputum examination revealed eosinophils and mucous plugs. It was thought that such episodes of respiratory distress occurred primarily because of smooth muscle bronchoconstriction following the release of bronchoconstrictive mediators, such as histamine from mast cells.

Less than 50 years ago, the treatment of asthma was limited to medications that relieved episodes of bronchospasm; epinephrine was the preferred medication because of its rapid onset of action and rapid relief of a significant exacerbation. It was also recognized that systemic steroids were helpful in overcoming severe, life-threatening exacerbations.

The 1970s marked the evolution of theophylline as the preferred maintenance therapy for asthma. Also in the late 1970s, the role of allergy in triggering a pulmonary response was well characterized. It was recognized that a single allergen inhalation challenge in a sensitized patient could precipitate several types of pulmonary response, an immediate reduction in pulmonary function within minutes of exposure, and, in some patients, a late pulmonary response representing another drop in pulmonary function several hours after the single exposure. Continuing airway hyperresponsiveness could last for days, weeks, or even months after a single allergen challenge in some individuals.

In the 1980s, the unique attribute of inhaled cromolyn in blocking the early and late pulmonary responses to allergen challenge in sensitized patients, as well as in blocking resultant airways hyperresponsiveness, was discovered. This observation not only provoked interest in other methods of preventing pulmonary response to allergen challenge but also ushered in the era of preventative anti-inflammatory therapy for asthma. Cromolyn emerged as a first-line therapy for childhood asthma, especially in young children, despite limited evidence of efficacy in this patient population. Although cromolyn was effective in reducing symptoms in mild forms of persistent asthma, it had recognized shortcomings in the treatment of moderate to severe asthma.

Principles of inhaled steroid therapy dosing evolved in the late 1970s and through the 1980s; at the same time, a series of articles was appearing that provided clear evidence of efficacy in adults and children with asthma.³ An era also emerged in the mid 1980s that demonstrated the effect of inhaled steroids on reducing airway inflammation on the basis of information obtained from the application of bronchoscopy and biopsy.⁴ At present, 5 inhaled steroids are available in the United States and approved for use in children as young as 4 years of age for the breath-actuated forms of the disease. In addition, a nebulized form of budesonide has been recently approved for use in children as young as 1 year of age.⁵ Therefore, inhaled steroids can now be effectively delivered to children at a very early age.⁶⁻⁸

In the mid 1990s, several important new classes of medications were introduced. Given the recognized benefits of the short-acting β_2 -agonists, attention was directed to extending the duration of effect of the β_2 -adrenergic

agonists. As a result, long-acting β_2 -adrenergic agonists with a 12-hour duration of action were introduced; these medications were salmeterol and formoterol. To limit the adverse effects of short-acting β -agonists, the stereoisomer of albuterol, levalbuterol, was developed and introduced.⁹ In addition, the class of leukotriene modifiers was introduced, including a 5-lipoxygenase inhibitor, zileuton, and 2 leukotriene D_4 -antagonists, zafirlukast (Accolade, Zeneca) and montelukast (Singulair, Merck). Furthermore, the oral leukotriene antagonist montelukast has emerged as a popular first-line, long-term control therapy in children because of the availability of dosage guidelines and the demonstration of its safety in children as young as 2 years of age.¹⁰ In addition, renewed interest has developed with regard to the combination of medications into single formulations, such as fluticasone plus salmeterol; this approach is based on evidence of additive effects, convenience for the patient, and the potential to further reduce the risk of significant exacerbations.¹¹ With the implementation of the Montreal Protocol and the introduction of alternative propellants to replace chlorofluorocarbon propellants, alternative delivery systems—specifically, hydrofluoroalkane-based and dry-powder, breath-activated systems—have been introduced. The smaller particle size and improved peripheral distribution of some hydrofluoroalkane-based metered dose inhalers have also raised questions about improved delivery to peripheral airways.¹² With the availability of numerous medications, it is obviously important to organize the approach to medication selection. Attempts have been made to do this through the formulation of expert panels and the publication of guidelines for the diagnosis and management of asthma.¹³⁻¹⁵

WHAT IS THE CURRENTLY RECOMMENDED APPROACH FOR MANAGING CHILDHOOD ASTHMA?

Current guidelines for asthma management emphasize environmental control, objective monitoring, cooperative management, and pharmacotherapy as the core elements of asthma management. Asthma has been classified as intermittent, mild persistent, moderate persistent, and severe persistent on the basis of symptoms, nighttime episodes, and pulmonary function (Fig 1). The following approach to asthma pharmacotherapy is recommended for adults and for children more than 5 years of age^{13,14}:

- **Intermittent asthma.** Characterized as episodic bronchospasm. Therapy includes as-needed β -adrenergic agonists to relieve symptoms. Symptoms can also be prevented by administering β -adrenergic agonists before exercise or cromolyn/nedocromil before anticipated exposure to allergen.
- **Mild persistent asthma.** Characterized by frequent episodes of bronchospasm—eg, more than twice per week but less than once per day—with marginal compromise in pulmonary function—eg, a peak expiratory flow (PEF) variability of 20% to 30%. According to National Asthma Education and Prevention Program 2

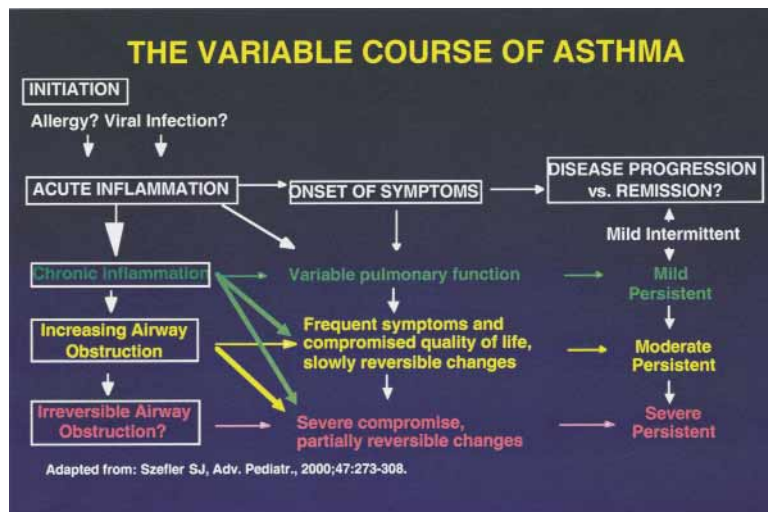


FIG 1. Asthma has many forms. Some children have recurrent wheezing as infants but will not go on to develop persistent asthma. Other children have a progressive course that might lead to irreversible loss in pulmonary function over time. Persistent asthma is thought to be a consequence of chronic airway inflammation. The magnitude of chronic inflammation is related to the severity of asthma. The level of severity can fluctuate significantly over time. In general, the longer the duration and the greater the level of severity, the less likely that a patient will remit even while on continuous therapy. Reprinted with permission from Adv Pediatr 2000;47:273-308.

guidelines, first-line therapy may begin with an inhaled glucocorticoid (low dose), cromolyn, or nedocromil as preferred therapy, or alternatively with sustained-release theophylline, with a leukotriene synthesis inhibitor (zileuton [Zyflo, Abbott], for which dosing information is limited to children aged ≥ 12 years) or with a leukotriene receptor antagonist (zafirlukast [Accolate, Zeneca], montelukast [Singulair, Merck]). Currently, however, the leukotriene antagonists, especially montelukast, are the favored alternatives to inhaled steroids because of their convenience of administration and dosage recommendations for children as young as 2 years of age. The inhaled glucocorticoid dosing strategy is now described as low, medium, or high, and information is provided in the National Heart, Lung, and Blood Institute's (NHLBI) Expert Panel Report 2 (EPR-2) on these dose levels for each of the preparations available at the time of publication.¹⁴ Inhaled β -adrenergic agonists are used as needed for breakthrough symptoms.

- **Moderate persistent asthma.** Characterized by daily symptoms, exacerbations that affect activity and sleep, or pulmonary function compromise—specifically, $>60\%$ and $<80\%$ FEV₁ or PEF or a within-day PEF variability of $>30\%$. Inhaled glucocorticoids (medium dose) or low-dose inhaled glucocorticoids plus a long-acting β_2 -adrenergic agonist are the recommended base of treatment. A long-acting bronchodilator can be added for nighttime symptoms in the form of an inhaled β_2 -agonist (salmeterol), sustained-release theophylline, or a long-acting oral β_2 -agonist. Recent studies suggest that leukotriene modifiers could be

effective as additive therapy with inhaled steroids but are somewhat less effective than a long-acting β_2 -adrenergic agonist/inhaled steroid combination.¹⁶

- **Severe persistent asthma.** Characterized by continual symptoms, limited physical activity, frequent daytime and nocturnal exacerbations, low pulmonary function ($<60\%$ PEF or FEV₁), or a $>30\%$ within-day variability in pulmonary function. Inhaled glucocorticoids at high doses are primary therapy. Other medications are added on the basis of need—eg, a long-acting β -adrenergic agonist (salmeterol) or theophylline therapy to control nighttime symptoms and prevent intermittent breakthrough symptoms. Short-acting β -adrenergic agonists (albuterol, terbutaline, pirbuterol) are used to relieve breakthrough symptoms. Oral glucocorticoids are used for severe exacerbations and are occasionally needed as maintenance therapy. To date, a single study, conducted by Robinson et al,¹⁷ has observed no beneficial effect of montelukast on improving peak expiratory flow and symptom control in patients with moderate to severe asthma who were inadequately controlled with inhaled corticosteroids. Once control is established, as indicated by a significant reduction in the need for rescue bronchodilator and systemic glucocorticoid therapy, medications are reduced and discontinued in a step-down manner in reverse order, beginning with the maintenance oral glucocorticoids.

Asthma is now considered a progressive disease, one of its components being a reduction in pulmonary function over time (Fig 2). It is not clear when this reduction occurs, who is susceptible to such reduction, and what medications can prevent the decline in pulmonary function over time.

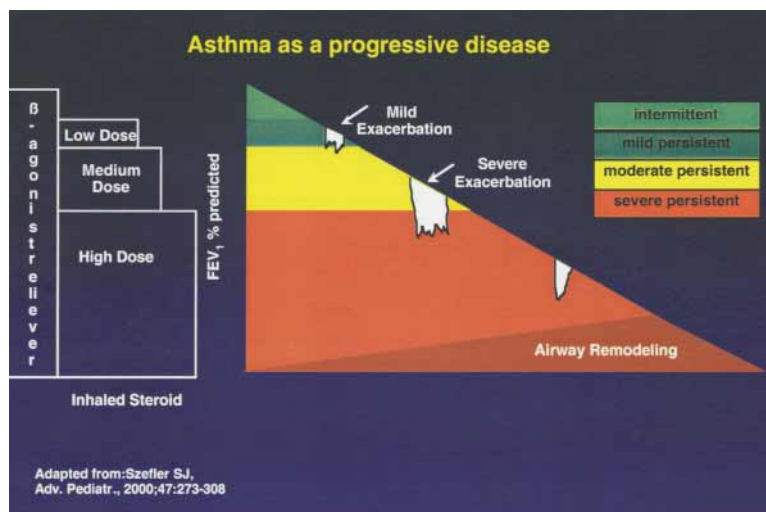


FIG 2. Conceptual model of declining lung function and airway remodeling. Inhaled glucocorticoids are recommended in increasing doses for increasing severity of persistent asthma. For exacerbations of asthma, β -adrenergic agonists are the medication of choice. Systemic or high-dose inhaled corticosteroids are used to resolve significant exacerbations. Reprinted with permission from *Adv Pediatr* 2000;47:273-308.

WHAT IS THE CURRENT APPROACH FOR MANAGING ASTHMA IN YOUNG CHILDREN?

Current therapy is based on the concept that chronic inflammation is a major feature of asthma. Because persistent asthma can occur early in life, attention is moving toward early recognition and early intervention. It is assumed but not yet proven that early recognition and early treatment with anti-inflammatory therapy could modify the disease process and the natural history of asthma.^{13,14,18} Although this approach is attractive in concept, prospective randomized control studies are needed to verify whether long-term outcome can be significantly altered through use of it.

Asthma management in young children is particularly challenging. Although the approach to asthma control is similar and the same classification is used, there are limitations to the assessment of asthma in young children. The assessment is primarily based on symptoms, because pulmonary function cannot be measured reliably in young children. Environmental control measures can be applied if allergen sensitivity is defined. In addition, limiting exposure to viral respiratory infections could also reduce the frequency of significant acute exacerbations. Pharmacotherapy can also be a challenge, inasmuch as the route of administration for inhaled medication administration must be adjusted to patient cooperation, given that adequacy of medication delivery is a major question. Another problem is the limited information on the appropriate dose of medications for children less than 5 years of age. First-line therapy might begin with cromolyn or nedocromil or low-dose inhaled glucocorticoid with spacer/holding chamber and face mask. As indicated previously, a nebulized budesonide preparation has recently been approved for use in children as young as 1 year of age, and there are now dosage guidelines for this age group.⁸ In addition,

montelukast is now available in a formulation that can be administered to children as young as 4 years of age. Because both of these medications have only recently been approved, an expert panel has not yet provided insight with respect to the order of placement of nebulized budesonide and oral montelukast as first-line and additive therapy in young children with persistent asthma.

For moderate persistent asthma, medium-dose inhaled glucocorticoids can be used and supplemented with nedocromil or long-acting bronchodilator (theophylline). For more severe asthma, high-dose inhaled glucocorticoids are recommended, and if needed, systemic glucocorticoid can be used with adjustment to the lowest dose daily (or on alternate days) that stabilizes symptoms. This algorithm will obviously be refined as we obtain more information on the efficacy of the available medications approved for young children.

WHAT HAVE WE LEARNED FROM THE CHILDHOOD ASTHMA MANAGEMENT PROGRAM?

The NHLBI's Childhood Asthma Management Program (CAMP) was initiated in 1991 and designed to evaluate whether continuous long-term treatment with either an inhaled steroid (budesonide) or an inhaled non-steroid (nedocromil) control medication could improve lung growth safely over a 4- to 6-year treatment period in comparison with treatment based on frequency and severity of symptoms (albuterol and, if necessary, prednisone administered as needed).¹⁹ Secondary outcomes included airway responsiveness, morbidity, and physical and psychological growth and development. Furthermore, concerns about the effects of inhaled steroids on linear growth prompted a careful evaluation of the long-term role of inhaled steroids in childhood asthma, partic-

ular attention being paid to their potential for suppression of bone growth, bone density, and sexual maturation and for development of cataracts.

CAMP, a National Institutes of Health/NHLBI-sponsored research program, was organized as a multicenter trial with 8 clinical centers and a Data Coordinating Center. The initial 4- to 6-year treatment phase of the study lasted from November 1993 to June 1999, and a 4-month washout phase was completed by October 1999. A 4½-year continuation study (the CAMPCS) is now in progress; this is a cohort investigation designed to further evaluate the effect of the intensive treatment period on long-term outcomes—specifically, lung and body growth.

Observations on the study population

Many factors, including heredity, atopic status, and environment, have been implicated in the determination of asthma severity. Relatively little is known about the degree to which asthma duration influences asthma severity. The extensive CAMP baseline cross-sectional data were used to examine the relationship of asthma duration, spirometry, bronchial responsiveness, symptomatology, and markers of atopy to asthma severity.²⁰ Of interest, the duration of asthma in the study cohort from the time of diagnosis until randomization into CAMP ranged from 0.3 to 12.1 years (mean, 5.0 years). Asthma duration was associated with lower levels of several lung functions or increased methacholine reactivity, prebronchodilator and postbronchodilator percent of predicted FEV₁, and prebronchodilator and postbronchodilator FEV₁/forced vital capacity (FVC), as well as with higher levels of symptoms and borderline greater use of albuterol for symptoms during the 28-day screening period. Duration of asthma was also significantly associated with increased asthma severity, as determined by physician/nurse assessment and other historical measures of medication use.

Nelson et al²¹ evaluated the relationship between sensitivity and exposure to inhalant allergens and lung function and bronchial responsiveness in the children enrolled in CAMP. Of interest, allergen sensitization was not associated with reduced lung function but was associated with increased bronchial hyperresponsiveness. There was a strong direct correlation between increased sensitivity to methacholine and skin test sensitivity to tree, weed, *Alternaria*, cat, dog, and indoor molds. The skin test sensitivities showing the strongest associations with the concentration of methacholine that caused a 20% fall in FEV₁ were dog, *Alternaria*, and cat. Children sensitive to any one of the aeroallergens tested were compared for the presence or absence of exposure to that allergen at the time when the methacholine challenge was performed. Those who were sensitive and exposed to weed and cat had greater methacholine sensitivity than those similarly sensitized but not exposed. These observations support the important role that sensitization to certain allergens plays in modulating bronchial responsiveness. Interestingly, dust mite and cockroach sensitivity and exposure were not associated with increased methacholine sensitivity.

Investigation of the complex relationship between illness progression and psychological development was a secondary objective of the psychological battery test. Evaluation of baseline data revealed that psychological disorders and cognitive impairment were not increased in children with mild to moderate asthma. Mild to moderate asthma imposed modest effects on the daily life of this group of children but did not significantly alter their psychological health.²² Scores on cognitive tests were not different from published norms for the general population, did not differ between children with mild asthma and children with moderate asthma, and were not associated with asthma outcomes such as pulmonary test results and symptom scores.²³

CAMP STUDY OUTCOMES: ANSWERS TO MAJOR QUESTIONS

The major outcomes study addresses many questions that have been raised regarding the beneficial and adverse effects of long-term control therapy.²⁴ It also raises a number of questions for future studies.

What is the effect of treatment on lung growth?

Postbronchodilator FEV₁ percent of predicted was selected as the parameter by which to assess lung growth as a measure of maximal lung capacity because it minimizes the effects of airway constriction and has less variability over time than prebronchodilator measurements. The study was designed to identify a 3.5% difference from placebo as a significant treatment effect.¹⁹

Budesonide treatment improved postbronchodilator FEV₁ from a mean of 103.2% of predicted to a mean of 106.8% of predicted within 2 months, but this measurement gradually diminished to 103.8% of predicted by the end of the treatment period (Fig 3, A). At this time, the postbronchodilator FEV₁ percent of predicted in the budesonide group was not significantly different from that in the placebo group. The nedocromil group was similar to the placebo group in this measure throughout the treatment period.

The finding that neither budesonide nor nedocromil improved lung function, as measured by the percentage-of-predicted value for FEV₁ after the administration of a bronchodilator, was not expected on the basis of a previous report of inhaled steroid effect in asthmatic children.¹⁸ However, that study did not examine postbronchodilator FEV₁ measurements. In fact, there have been few, if any, studies in childhood asthma that used postbronchodilator FEV₁ as the primary outcome variable. Because a decline in FEV₁ has been interpreted as an indication of airway remodeling, the CAMP study results raise questions about whether airway remodeling is occurring in this population of children with mild to moderate persistent asthma and whether inhaled steroids have any effect on preventing this change in airway pathology. The results indicate that FEV₁ percent of predicted did not decline in either the placebo group or the inhaled nedocromil group. Furthermore, the

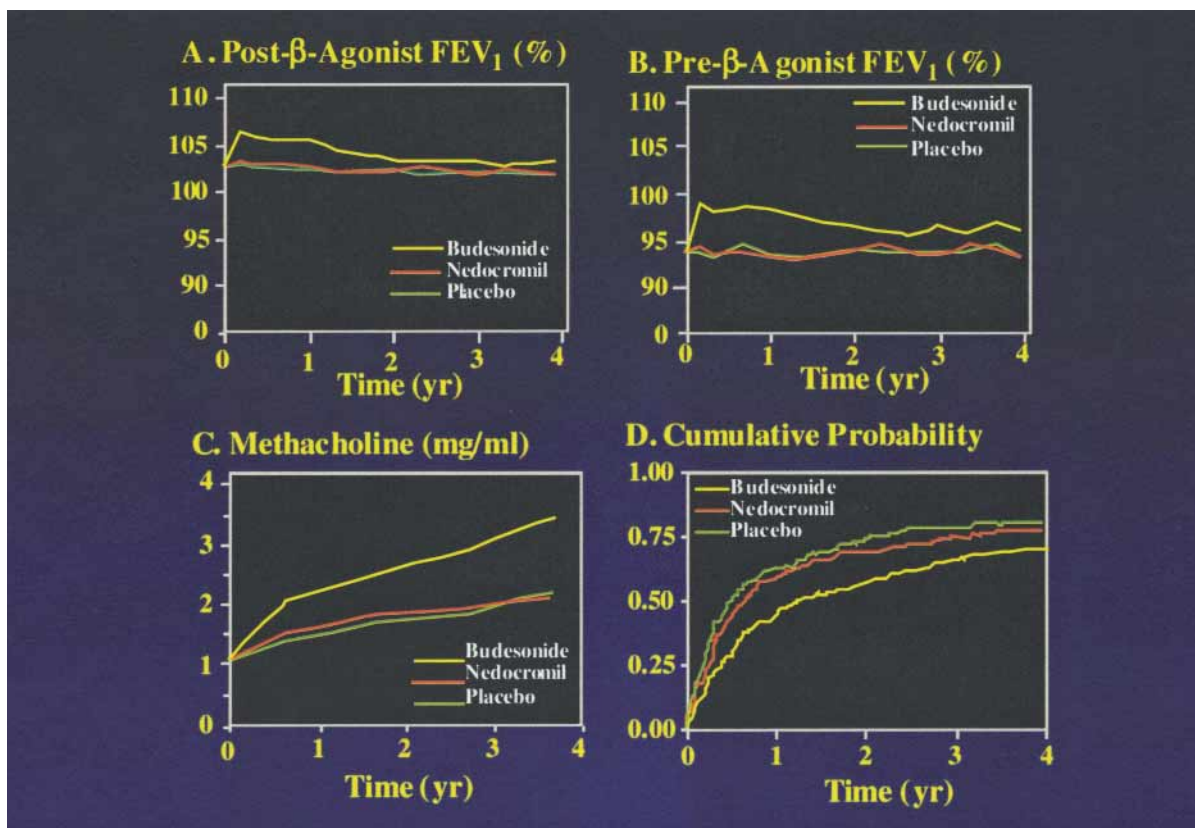


FIG 3. Results of the CAMP Study. *Panel A* depicts the change in postbronchodilator FEV₁ during the duration of the study. There was an initial improvement in postbronchodilator FEV₁ in patients receiving budesonide, but by the end of the study there were no differences among the 3 treatment groups. *Panel B* depicts the change in prebronchodilator therapy. Budesonide resulted in a modest yet statistically significant improvement in prebronchodilator FEV₁ throughout the treatment period in comparison with placebo. *Panel C* depicts the change in methacholine responsiveness over time. Note that all subjects had improvement in bronchial hyperresponsiveness, as indicated by the increase in methacholine PC₂₀ values over the 4 to 6 years of the trial. Patients randomized to budesonide had a significantly greater reduction in bronchial hyperresponsiveness in comparison with the placebo-treated patients. *Panel D* shows a Kaplan-Meier curve describing the cumulative probability of a first course of prednisone during 4 years of follow-up in the budesonide-, nedocromil-, and placebo-treated children. Reprinted with permission from N Engl J Med 2000;343:1054-63. Copyright 2000 Massachusetts Medical Society. All rights reserved.

temporary increase in postbronchodilator FEV₁ percent of predicted after the initiation of treatment was not sustained over the treatment period and was comparable to that seen in the placebo group.

For several reasons, these results might not reflect airway remodeling. First, FEV₁ might not be sufficiently sensitive to serve as an indicator of airway remodeling. Second, given that the study design limited enrollment to patients with mild to moderate persistent asthma, patients susceptible to airway remodeling or a progressive loss in FEV₁ might have been screened out. Third, the mean duration of asthma in the study population was 5 years, and it is possible that the most significant effect on FEV₁ or airway remodeling occurred before entry into the study; if that is true, then emphasis should be placed on early recognition and early intervention.

What was the effect of treatment on other lung function measures?

Other measures of postbronchodilator spirometry, including FEV₁ (in liters), FEV₁/FVC, FVC percent of predicted, and FEV₁/FVC, were not significantly different on completion of the treatment phase. For prebronchodilator measurements of pulmonary function, the treatment and placebo groups differed with respect to several parameters. At the end of the treatment period, the difference in prebronchodilator FEV₁ percent of predicted after inhaled budesonide treatment in comparison with baseline exceeded that in the placebo group (2.9 vs 0.9; $P = .02$; Fig 3, *B*). The FEV₁ percent of predicted could be interpreted as indicating that functional airway caliber on completion of the treatment phase exceeded that in the placebo arm.

Although statistically significant, the total value of 2.0% for the difference in FEV₁% was not impressive.

Prebronchodilator FEV₁ percent of predicted was higher than that for placebo and that for inhaled nedocromil for the first 2 years of treatment. However, the inhaled nedocromil group did not differ from the placebo group during any point of the treatment phase, indicating that there was no detectable effect of this treatment on prebronchodilator FEV₁ percent of predicted. For change in FEV₁/FVC, the difference attributed to inhaled budesonide was less than that after placebo treatment (−0.2 vs −1.8; $P = .001$). This indicates that the decline in FEV₁/FVC, another measure of airway obstruction, was less with inhaled budesonide over the course of treatment. Because FEV₁ (in liters) demonstrated no difference among the treatments, the difference in FEV₁/FVC decline is likely due to a reduction in FVC (in liters) with inhaled steroid treatment in comparison with placebo treatment (1.29 vs 1.35; $P = .001$).

For inhaled nedocromil, the only difference between prebronchodilator and postbronchodilator spirometry values in comparison with placebo was observed with prebronchodilator FEV₁ (in liters). The end result indicated that the difference at the end of treatment from baseline was less for inhaled nedocromil than for placebo (0.6 vs 2.4; $P = .02$). Furthermore, all values of prebronchodilator and postbronchodilator spirometry were comparable for the 3 treatment groups after the 4-month discontinuation of active study medication, indicating that the effect observed on any pulmonary function parameter was lost within 4 months of discontinuing treatment.

What is the effect of long-term treatment on airway hyperresponsiveness?

The most distinct effect observed on a measure of pulmonary function was a significant and consistent effect of inhaled budesonide on reducing airway hyperresponsiveness (Fig 3, C). This effect was revealed by the first measurement 8 months after the beginning of treatment. The ratio of smallest provocative dose required to produce a 20% decrease/fall in FEV₁ (PC₂₀) by the end of treatment to that at baseline was 3.0 for inhaled budesonide; this compared with 1.9 for placebo ($P < .001$). Once again, no difference was seen in a comparison of inhaled nedocromil and placebo throughout the treatment period.

Although it was anticipated that the washout effect of inhaled budesonide on methacholine response would be slow, a surprising observation was that all 3 treatment groups were comparable for methacholine PC₂₀ after the 4-month washout phase. Therefore, this additional surrogate marker of airway remodeling is not permanently affected by inhaled steroid therapy in comparison with the other 2 treatment options.

What is the effect of treatment on clinical outcome measures?

During the treatment course, the most consistent effects on changes in a panel of clinical outcomes were observed with inhaled budesonide treatment in compari-

son with placebo treatment. For inhaled budesonide, numbers of hospitalizations (2.5 vs 4.4 per 100 person-years; $P < .04$), urgent care visits (12 vs 22 per 100 person-years; $P < .001$), and prednisone courses (70 vs 122 per 100 person-years; $P < .001$; Fig 3, D) were significantly lower than those seen in the placebo arm by approximately 45%. Other inhaled budesonide measures showing a difference from measures for placebo included a lower symptom score ($P = .005$), a greater number of episode-free days per month ($P = .01$), and a smaller number of albuterol inhalations per week ($P < .001$).

Although several retrospective epidemiologic studies have indicated a reduction in hospitalizations with inhaled steroids,^{25,26} this is the first prospective, longitudinal, randomized clinical trial to demonstrate a reduction in significant asthma exacerbations that lead to hospitalizations, urgent care visits, and courses of systemic corticosteroid therapy. On the contrary, treatment with inhaled nedocromil demonstrated effects only on reduction of urgent care visits (16 vs 22 per 100 person-years; $P < .02$) and prednisone courses (102 vs 122 per 100 person-years; $P < .01$) in comparison with placebo treatment.

Did continuous long-term control therapy reduce the need for supplementary therapy?

Two additional measures of asthma control over the course of the treatment period included the time to the first significant exacerbation requiring prednisone therapy and the time for intervention with inhaled beclomethasone dipropionate. Inhaled budesonide was distinctly different from placebo with respect to the proportion of courses and the time for the first course of prednisone (Fig 3, D). Similarly, the time for intervention with inhaled beclomethasone therapy, along with the proportion of patients requiring this intervention, was much lower in the inhaled budesonide group. For both of these measures, inhaled nedocromil was comparable to placebo.

WHAT ARE THE ADVERSE EFFECTS ASSOCIATED WITH LONG-TERM ASTHMA TREATMENT?

What is the effect of continuous, long-term inhaled steroid therapy on linear growth?

A major benefit of this extended period of observation was the assessment of growth velocity and height percentiles. Of interest, the mean increase in height in the inhaled budesonide group was 1.1 cm less than that seen in the placebo group ($P = .005$). This change occurred primarily in the first year of treatment. Until this time, it had been assumed that inhaled steroids could reduce growth velocity by 1 cm per year for each year of continuous treatment. The concern was that this effect on growth would be cumulative. The CAMP results clearly indicate that the reduction in growth velocity effect occurs in the first year of treatment and is persistent but not progressive. Further support of the finding that the growth suppression associated with inhaled glucocorticoid use is transient comes from a long-term prospective

study from Denmark,²⁷ the results of which were published in the same issue of the *New England Journal of Medicine* in which the CAMP report appeared. Agertoft and Pedersen²⁷ followed the growth of a cohort of 142 children with mild to moderate asthma until they reached adult height; the subjects had received a mean dose of budesonide of 412 $\mu\text{g}/\text{day}$ for a mean of 9.2 years. The adult height of the members of this cohort on long-term inhaled budesonide therapy was 0.3 cm greater than expected. Long-term inhaled budesonide thus had no long-term growth-suppressive effects. Of note, the investigators also observed transient growth suppression soon after inhaled glucocorticoid therapy was initiated, but after 2 years of treatment, the growth suppression was no longer statistically significant.

In the CAMP study, a bone age measurement was obtained at the end of the treatment period in each subject. This measurement, along with the subject's linear height, was used to estimate the subject's final adult height by the method of Tanner et al.²⁸ The calculation indicated that the members of the 3 groups would reach comparable adult height, no significant differences being seen between either inhaled steroid or inhaled nedocromil and placebo. The results of this evaluation were reassuring in the light of the previous studies, each of which had been limited to a maximum of 1 year of treatment.

What is the effect of treatment on bone density and body development?

After the 4- to 6-year period of follow-up, the increase in bone density for the inhaled steroid group was 0.17 g/cm^2 , which was not significantly different from that for the placebo group. Similarly, other measures of body growth and development were not significantly different for the inhaled steroid and inhaled nedocromil groups in comparison with the placebo group. This observation alleviates concerns that inhaled steroids could result in decreased bone mineralization or delayed sexual development.

Are there any effects on the incidence of ocular disorders?

At the end of the treatment course, photographic evaluation of each child's lenses was obtained.²⁴ One child in the inhaled budesonide group had a questionable posterior subcapsular cataract in the right eye and was found on slit lamp examination to have a minuscule cataract; this did not affect visual acuity. Furthermore, this child had received additional steroid therapy in the form of systemic steroids for periodic breakthrough exacerbations and supplementary inhaled steroids for poor asthma control. In general, the results are encouraging in the light of recent reports from epidemiologic retrospective studies indicating a higher risk for ocular disorders after long-term, high-dose inhaled steroid therapy in elderly adults with asthma.^{29,30}

In summary, the major conclusions in the CAMP outcomes report were that neither inhaled budesonide nor nedocromil provides a therapeutic advantage for lung growth as measured in terms of postbronchodilator FEV₁ percent of predicted. The results of CAMP offer a "profile

of performance" for the 3 treatment arms studied and provide considerable insight for the prescribing clinician into what might be expected in the form of clinical and pulmonary function outcomes for these 3 treatment strategies. The inhaled steroid group had much less hospitalization, fewer emergency room visits and prednisone courses, and less need for rescue therapy, corresponding to reduced symptoms. Side effects were limited to a small, apparently transient reduction in growth velocity during the first year of treatment. Accordingly, inhaled steroids are safe and effective for long-term use in childhood asthma.

Postbronchodilator FEV₁ percent of predicted was selected as the measure of lung growth. Although inhaled budesonide provided a temporary increase, this measure gradually declined to the pretreatment value by the end of the study and did not differ from what was seen with the other 2 treatments. In addition, deterioration in lung growth was not detected in the placebo group. More work is needed to define adequate measures of airway remodeling and to determine whether any treatment is effective in altering the natural history of asthma, especially in those who are at risk for chronic, irreversible changes. Perhaps FEV₁ percent of predicted is not sufficiently sensitive to detect these changes in airway pathology.

The CAMP results challenge conclusions that have been derived in short-term studies, especially those related to pulmonary function and growth measures. It is also clear that the medications used in CAMP did not completely eliminate the morbidity associated with asthma; there is certainly room for improvement in this area.

CAN WE EXPECT TO LEARN MORE FROM CAMP?

The rich CAMP database will continue to be evaluated as the CAMPCS progresses. Further work will be conducted to evaluate subpopulations and their responses to treatment—eg, the effect of age, sex, duration of disease, and race will be evaluated on the various outcome parameters, including pulmonary function, clinical outcomes, psychosocial features, and body growth and development. A series of adjunct studies were conducted during the course of CAMP and will continue to be evaluated. Ancillary studies were conducted on medication adherence, markers of inflammation, and family assessment. The CAMPCS is specifically designed to evaluate the long-term effects of treatment on lung development and growth. The CAMP subjects will be followed into late adolescence and early adulthood in an attempt to define maximal lung and body growth parameters.

WHERE DO WE GO FROM HERE?

CAMP has provided answers to many questions regarding the effect of continuous long-term use of the 3 treatment options available for the management of childhood asthma. Although the answers from CAMP will be applicable to children with established persistent asthma, the obvious question is whether the results apply to younger



FIG 4. The asthma treatment dilemma. The clinician must carefully weigh the benefits and risks of each medication in the treatment of childhood asthma.

children. Additional studies must be developed to look at earlier intervention as well as at the effects of other medications, such as leukotriene receptor antagonists, on clinical outcomes and the natural history of asthma.

Information is now becoming available on the risk factors for persistent asthma.^{13,14,31} The potential consequence of undertreatment might be a loss of pulmonary function over time that is greater than that observed in patients without asthma and similar to that usually observed in chronic obstructive pulmonary disease and cystic fibrosis. This decline in pulmonary function could have an overall effect on outcome. Obviously, patients differ markedly with respect to clinical presentation and susceptibility to this decline in lung function.

It has been proposed that early intervention with inhaled steroid therapy can be effective in preventing the progression of the disease and lowering the risk of irreversible changes in the airways that could contribute to the persistence of symptoms. This study is currently in progress as part of the NHLBI Childhood Asthma Research and Education Network.

At the other extreme, patients with severe asthma show evidence of persistent inflammation.³²⁻³⁴ Their disease often has its onset in early childhood. Does this information suggest that children who manifest persistent inflammation in the presence of anti-inflammatory therapy are at increased risk for disease progression? If so, it will be important to recognize these patients and to provide more effective interventions at critical stages of their disease progression. Furthermore, it would then be important to measure inflammation and use this as another gauge for adjusting therapy.

WILL INHALED GLUCOCORTICOIDS REMAIN THE CORNERSTONE OF ASTHMA THERAPY?

One of the most difficult challenges for the physician is selection of the initial long-term control medication for a child with persistent asthma. This decision must include a careful assessment of the benefits and risks of each available medication, as well as a consideration of other factors, including cost, taste, ease of administration, and patient acceptance (Fig 4).

Numerous studies have shown that inhaled glucocorticoids improve asthma management and reduce inflammation in the airways. In comparison studies, inhaled glucocorticoids have almost always been shown to be superior to, and have never been shown to be less effective than, nonsteroid long-term controllers such as cromolyn, nedocromil, theophylline, and leukotriene modifiers for overall asthma control.³⁵ Furthermore, several studies have now demonstrated that inhaled steroids reduce the deposition of several tissue components—specifically, collagen and tenascin—that are associated with airways remodeling.³⁶⁻³⁸ β -adrenergic agonists, including the new long-acting β -adrenergic agonists, such as salmeterol (when used alone), do not alleviate airways inflammation but do have an additive effect on asthma control when combined with inhaled corticosteroids.³⁹ Theophylline and leukotriene modifiers have some effect on reducing airway inflammatory cells, though studies involving direct comparison with inhaled steroids are not available. Theophylline alters the number of lymphocytes, and leukotriene antagonists reduce the pulmonary response to an allergen challenge.⁴⁰⁻⁴² This

might be related to differences in mechanism of action among the various long-term controllers. Some medications, such as inhaled steroids, alter the synthesis of mediators, such as leukotrienes and cytokines, that contribute to the inflammatory response or control cell-to-cell communication.

The choice of first-line therapy, once persistent asthma has been diagnosed, is a major clinical question (Fig 4). In general, long-term nonsteroid controller medications—eg, theophylline, leukotriene modifiers, long-acting β_2 -agonists, cromolyn, and nedocromil—relieve and even prevent symptoms as well as improve pulmonary function; however, their effect on long-term control of airways inflammation and disease progression is less than clear in comparison with the available information on inhaled steroids. The question remains as to whether the use of long-term controllers in place of inhaled steroids could mask the symptoms of chronic inflammation and thus lead to disease progression and less favorable long-term outcomes. It is thus difficult to adjust inhaled glucocorticoid doses, given that the indirect measures of inflammation, such as pulmonary function, can be easily ablated by nonsteroid long-term controllers.

IS A "CURE" ON THE HORIZON?

The effort to understand the natural history of asthma is a current area of interest in childhood asthma. Although it is becoming clear that patients with asthma are susceptible to a more rapid decline in pulmonary function than is seen in normal subjects, it is not clear how this decline can vary among patients. Long-term studies that begin with the onset of early asthma will be helpful in determining whether some patients have a rapid decline in pulmonary function and then a continuing slow loss in pulmonary function or whether the decline is always relatively constant over time—or whether both patterns (or even additional ones) occur.

It is possible that early indicators of asthma, such as increased symptoms or altered lung growth in children, could prompt early intervention. With the right intervention, it is possible that the disease could continue to be controlled and that thus, in a sense, a remission or relative "cure" could be sustained. Current interest centers on the comparative effects of inhaled steroids and leukotriene antagonists; however, it might be that neither of these agents is sufficient to control asthma progression. A new area of genetics—including pharmacogenetics in relation to medication response—has also emerged.⁴³⁻⁵¹ Studies are also in progress within the NHLBI Childhood Asthma Research and Education (CARE) Network to study the response to asthma medications, including an inhaled steroid and a leukotriene antagonist, in relation to asthma characteristics and potentially in relation to genetics. It is becoming increasingly important to define risk factors for patients likely to develop persistent asthma, patients predisposed to life-threatening severe exacerbations, patients with severe persistent asthma requiring extensive therapy, and patients with steroid-insensitive or independent asth-

ma. Advances in genetic associations could help define patients so that treatment could be individualized.

Advances are also occurring in the recognition of significant allergens and methods of controlling environmental exposure. In addition, there are new medications on the horizon—cytokine antagonists, anti-IgE, and adhesion molecule antagonists, to name but a few. Each of these medications has a potential use for asthma, but their placement in asthma therapy will have to be defined. As such, there are several forces whose activity has emerged to facilitate advances in therapy, and the future will indeed be interesting.

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