

Managing Childhood Asthma: Challenge of Preventing Exacerbations

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ABSTRACT

Acute episodes of airway obstruction followed by periods of apparent wellness are the main clinical manifestations of the disease for many children with persistent asthma. Although currently available asthma controllers decrease the risk for acute asthma exacerbations, 30% of children taking these medicines still have ≥ 1 episode requiring oral corticosteroid treatment per year. There is increasing evidence that neutrophilic inflammation, against which inhaled corticosteroids are not very effective, plays a major role in the pathogenesis of asthma exacerbations. New therapeutic approaches are needed for this frequent cause of consultation in pediatric practice. One approach could be the development of drugs that target neutrophilic inflammation specifically. Studies in adults have shown that use of inhaled corticosteroids every time a bronchodilator is needed may decrease the frequency of asthma exacerbations. This strategy is currently being tested in a large clinical trial involving children with mild persistent asthma. *Pediatrics* 2009;123:S146–S150

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Key Words

prevention, control, childhood asthma, acute disease

Abbreviation

CAMP—Childhood Asthma Management Program

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IN THE PAST 20 years, significant advances have been made in our understanding of the natural history, pathogenesis, and risk factors of childhood asthma. In addition, the availability of controller medications that can effectively decrease airway inflammation provides the opportunity for most children with asthma to lead normal lives. These advances notwithstanding, there is still much to learn regarding the inception of childhood asthma and the mechanisms that trigger acute and chronic manifestations. One area that requires particular attention, and in which advances have been less evident, involves the mechanisms of asthma exacerbations and the potential therapies for their prevention and treatment.

ROLE OF EXACERBATIONS IN ASTHMA MORBIDITY

Asthma is a variable disease, particularly in children. The latest version of the National Asthma Education and Prevention Program guidelines distinguishes 2 dimensions in the assessment of asthma severity and control, namely, impairment and risk.¹ The impairment dimension includes all of the traditional factors that in previous versions of the guidelines were considered to determine the type and intensity of therapy needed by children and adults with asthma, that is, frequency of asthma symptoms, frequency of nocturnal awakenings, use of quick-relief medications, and level of lung function. Risk is a new dimension; its most important component is the likelihood of asthma exacerbations. Under the new guidelines, determining asthma morbidity involves considering both the patient's daily symptoms and the risk of the patient having more-severe disease expression that requires more-frequent use of quick-relief medications and eventually oral corticosteroid treatment. In support of this view, Schatz et al² reported that, when discriminant analysis was performed to identify independent dimensions of the clinical expression of asthma, exacerbations clustered separately from daily symptoms and lung function, which suggests that the factors that determine the risk for exacerbations may differ from those that determine the more-traditional markers of asthma control.

This new view is particularly relevant in the evaluation of children. In most cases of asthma involving preschool-aged children, the main expression of the disease is a relatively sudden deterioration in health status, usually associated with a cold that results in signs of airway obstruction, cough, and wheezing.³ Although this is the usual definition of an asthma exacerbation, the severity of clinical symptoms and lung function impairment used to identify an exacerbation varies markedly; changes in lung function suffice in some studies, whereas oral corticosteroid treatment is necessary for classification of a deterioration in clinical status as an asthma exacerbation in other studies. Regardless of what criterion is used, it is now evident that this pattern of expression of asthma is also the most prevalent in school-aged children.⁴ For the great majority of such children, levels of lung function between exacerbations are normal or nearly normal, and a significant proportion of asthma morbidity is associated with exacerbations.

Exacerbations also have the greatest impact on health care utilization and treatment costs for children with asthma. In one of the most-comprehensive studies of that impact, Hoskins et al⁵ studied >12 000 patients with

asthma in the United Kingdom over a 1-year period; almost 4000 children ≤ 15 years of age were included in the analyses. The study found that patients who experienced an acute asthma attack incurred health care costs that were 3 times higher than those of patients who did not experience an attack. Even after subtraction of the costs of hospital stays, which represented $\sim 44\%$ of total expenditures for the attack group, the average costs per patient in that group were still twice as high the incurred health care costs in the nonattack group. Similarly, costs for both primary care consultation and medication prescription coverage were 2.4 and 1.7 times higher, respectively, for patients who experienced an acute attack, compared with those who did not experience an attack. Other studies showed that asthma exacerbations also are the most important cause of loss of school days for children with asthma.⁶

There is conclusive evidence that establishment of an appropriate asthma controller program and adherence to such a program significantly reduce the risk of exacerbations for schoolchildren with asthma and toddlers at high risk for the disease. In the Childhood Asthma Management Program (CAMP) study, for example, children who received 200 μg of budesonide twice daily required 70 prednisone courses per 100 person-years, whereas those who received placebo required 122 such courses (a highly significant difference).⁷ In the same study, children who received 8 mg of nedocromil twice daily also required significantly fewer prednisone courses (102 courses per 100 person-years), compared with children who received placebo. Use of daily oral montelukast treatment among children with asthma was shown to decrease the likelihood of mild (but not severe) asthma exacerbations, compared with placebo.⁸ Among children 2 to 5 years of age and at high risk for asthma who were enrolled in the Prevention of Early Asthma in Kids study, children who received fluticasone (88 μg , twice daily) demonstrated a significant difference in the frequency of exacerbations, compared with those who received placebo.⁹ Taken together, these findings clearly suggest that currently available controllers are effective in preventing asthma exacerbations in children ≥ 2 years of age.

This conclusion should not obscure the fact that, even when adherence to therapy has been ascertained objectively, children treated with adequate doses of controller medications still have unacceptably high rates of asthma exacerbations. In the CAMP study, for example, 30% of children who were treated with adequate doses of budesonide experienced asthma exacerbations during the first year of treatment.⁷ Similarly, in the Pediatric Asthma Controller Trial, children who were treated with fluticasone (100 μg , twice daily) or with a combination of fluticasone (100 μg , once daily) and salmeterol (50 μg , twice daily) had $\sim 30\%$ risk of experiencing exacerbations during the 48-week treatment period.¹⁰ These results clearly suggest that a large proportion of children with asthma experience exacerbations even when given appropriate doses of asthma controllers. Another important consideration is that these rates of asthma exacerbations were ascertained as part of highly controlled

clinical trials; it is plausible that rates of exacerbation would be even higher under "real-life" conditions, in which adherence is more difficult to obtain and subjects are not prescreened for adherence (as they are for clinical trials).

PATHOGENESIS OF ASTHMA EXACERBATIONS

There are convincing data showing that evidence of a viral infection (usually attributable to rhinovirus) is present for the majority of patients who experience an asthma exacerbation.¹¹ Although this evidence strongly suggests that many, if not most, asthma exacerbations are caused by viral infections, studies in which subjects with asthma were infected with experimental strains of such viruses (eg, rhinovirus 16) were seldom successful in triggering an asthma attack or significant asthma symptoms.¹² Although this lack of success may be related to the virus strains used in these experimental studies, it is also possible that, to trigger an exacerbation, asthma-related viruses need to encounter conditions in the patient that cannot be easily mimicked in the laboratory. For example, an observational study suggested that asthma deteriorations occur when both viral infections and increased exposure to allergens occur in sensitized subjects.¹³

The nature of the immune response to the virus also may be an important determinant of the risk for an asthma exacerbation. Wark et al¹⁴ suggested that bronchial epithelial cells obtained from subjects with asthma had deficient innate immune responses to viruses. When the investigators infected the cells with rhinovirus 16, they found that viral RNA expression and late virus release into the supernatant were increased 50-fold and sevenfold, respectively, in cells obtained from subjects with asthma, compared with cells obtained from healthy control subjects. When the investigators examined the early cellular responses to infection, they noted impairment of virus-induced apoptotic responses in the cultures of cells from subjects with asthma. Moreover, cells obtained from subjects with asthma in early phases after viral infection produced >2.5 times less interferon- β messenger RNA than did cells obtained from healthy subjects. Addition of interferon- β to the cell cultures partially restored the immune responses in cells from subjects with asthma. More recently, Contoli et al¹⁵ reported that primary bronchial epithelial cells and alveolar macrophages obtained from subjects with asthma demonstrated deficient induction of interferon- λ when infected with rhinovirus. Interferon- λ was described as an important participant in immune responses to viral infection.^{16,17} Taken together, these results suggest that genetic and/or developmental factors may determine a pattern of immune responses to viruses that makes patients with asthma susceptible to the development of inappropriate responses to viruses. These inappropriate responses may trigger acute asthma symptoms and bronchial obstruction, which are enhanced by remodeled and hyperresponsive airways.

HETEROGENEITY OF ASTHMA EXACERBATIONS

The availability of noninvasive methods to obtain cells and fluids from the central airways through sputum induction during asthma exacerbations has provided important new information about the nature of these exacerbations.¹⁸ Three different patterns have been observed: (1) a neutrophilic pattern in which a large proportion of neutrophils are observed, with few or no eosinophils; (2) an eosinophilic pattern, in which both eosinophils and an increased proportion of neutrophils are observed; and (3) a paucigranulocytic pattern, in which neither eosinophils nor increased numbers of neutrophils are observed.¹⁹ The fact that neutrophils are the predominant cells in a significant proportion of asthma exacerbations¹⁸ has suggested the possibility that these types of exacerbations may be less sensitive to current controllers, given that neutrophilic conditions are less sensitive to glucocorticosteroids²⁰; however, the data supporting this contention are scanty. Jayaram et al²¹ provided the strongest evidence. They studied 117 adults with asthma who entered into a multicenter, randomized, parallel-group, effectiveness study for 2 treatment strategies over a 2-year period. In the clinical strategy, treatment was based on symptoms and spirometric findings. With the sputum strategy, sputum cell counts were used to guide corticosteroid therapy, with the objective of maintaining eosinophil levels of $\leq 2\%$. The authors reported that monitoring sputum cell counts in the manner described benefited patients with moderate/severe asthma by reducing the number of eosinophilic exacerbations and the severity of both eosinophilic and noneosinophilic exacerbations during the follow-up period. Surprisingly, the sputum strategy had no effect on the frequency of noneosinophilic exacerbations, which represented the majority of exacerbations observed for the study population. Because the adjustments made in both strategies entailed mainly changes in the doses of inhaled corticosteroids given to the patients, it is tempting to speculate that adjustments of doses of inhaled corticosteroids are effective in decreasing the frequency of eosinophilic exacerbations but have no effect on the frequency of noneosinophilic (most often neutrophilic) exacerbations. If this were the case, then many children with asthma would be left insufficiently protected against exacerbations even if they complied with current, guideline-based, therapeutic strategies. Nevertheless, the role of inhaled corticosteroids in the treatment of neutrophilic inflammation in asthma remains controversial. Maneechotesuwan et al²² showed recently that the incidence of asthma exacerbations after inhaled corticosteroid withdrawal in adults was associated with increased sputum interleukin 8 and neutrophil levels. Therefore, it is possible that the timing and dosages of inhaled corticosteroid treatment may play roles in preventing asthma exacerbations.

NEW STRATEGY TO PREVENT ASTHMA EXACERBATIONS: AS-NEEDED INHALED CORTICOSTEROID TREATMENT

The consensus paradigm for the treatment of persistent asthma is daily use of inhaled corticosteroids to decrease the baseline level of airway inflammation, which is

thought to persist even when patients are experiencing no asthma symptoms.²³ As explained earlier, however, asthma is by nature a variable disease. Although certain degrees of bronchial hyperresponsiveness and airway inflammation are present in most patients with asthma even when symptoms are in remission, both of these characteristics fluctuate with time, and these fluctuations correlate (often loosely) with the likelihood of experiencing asthma symptoms and exacerbations. Therefore, it was reasonable to propose that a strategy that combined daily inhaled corticosteroid treatment with supplemental inhaled corticosteroid treatment when the patient needed relief for symptoms of airway obstruction could be more successful in preventing asthma exacerbations than one in which inhaled corticosteroids were used only on a regular, twice-daily basis.

O'Byrne et al²⁴ tested this hypothesis in a study in which subjects were assigned randomly to 3 arms: (1) low maintenance doses of a budesonide/formoterol combination, with short-acting β -adrenergic receptor agonists as quick-relief medication; (2) high maintenance doses of budesonide twice daily, with short-acting β -adrenergic receptor agonists for quick relief; or (3) low maintenance doses of the budesonide/formoterol combination twice daily, with the same combination used for quick relief any time the subject would have used a short-acting β -adrenergic receptor agonist. The authors reported that the frequency of exacerbations requiring oral corticosteroid treatment was remarkably lower for subjects who used the budesonide/formoterol combination as a quick-relief medication, compared with subjects in either of the other 2 arms (which showed similar frequencies of asthma exacerbations). That study suggested that inhaled corticosteroids titrated in a way that increased doses when the patient needed a quick-relief medication could better match inhaled corticosteroid use with increased airway inflammation and could decrease the likelihood of asthma exacerbations.

The study by O'Byrne et al²⁴ raises several issues. First, formoterol was used as a quick-relief medication, and it is not approved for this type of use in the United States. Moreover, there are concerns regarding the potential for long-acting β -adrenergic receptor agonists used regularly to increase the risk of severe asthma exacerbations and death for a small minority of patients.²⁵ Until recently, the possibility that short-acting β -adrenergic receptor agonists could replace long-acting ones in strategies similar to those used by O'Byrne et al²⁴ had not been explored. Papi et al²⁶ investigated whether symptom-driven use of a combination of beclomethasone dipropionate and albuterol in a single inhaler could be as effective as regular use of inhaled beclomethasone and superior to as-needed use of inhaled albuterol. The investigators conducted a 6-month, double-blind, double-dummy, randomized, parallel-group trial. A total of 455 adult patients with mild asthma were assigned randomly to 4 groups: (1) the as-needed combination group received placebo twice daily plus 250 μg of beclomethasone and 100 μg of albuterol in a single inhaler as needed; (2) the regular beclomethasone group received 250 μg of beclomethasone twice daily and 100 μg of

albuterol as needed; (3) the as-needed albuterol group received placebo twice daily plus 100 μg of albuterol as needed; and (4) the regular combination group received 250 μg of beclomethasone and 100 μg of albuterol in a single inhaler twice daily plus 100 μg of albuterol as needed. The authors reported that the numbers of exacerbations per subject per year were lower in the as-needed combination group and the regular beclomethasone group than in the as-needed albuterol group ($P < .001$) and the regular combination group ($P < .001$). The proportion of subjects with ≥ 1 exacerbation was not significantly different in the group that received as-needed combination therapy, compared with the group that received regular beclomethasone therapy or the group that received regular combination therapy. The proportions of subjects with ≥ 1 exacerbation were significantly smaller in the group that received as-needed combination therapy (4.9%) and in the group that received regular beclomethasone therapy (5.7%) than in the group that received as-needed albuterol therapy (17.8%). Kaplan-Meier analyses showed that the time to first exacerbation differed significantly between the groups, with the shortest time to first exacerbation being observed in the as-needed albuterol group.²⁶ Most interesting from the point of view of childhood asthma was the finding that the cumulative dose of inhaled beclomethasone was significantly lower in the group that received as-needed combination therapy (18.5 \pm 25.3 ng), compared with the group that received regular beclomethasone therapy (77.0 \pm 17.4 mg; $P < .001$) or the group that received regular combination therapy (77.1 \pm 17.6 mg; $P < .001$). The numbers of adverse events did not differ significantly among the treatment groups.

The studies by O'Byrne et al²⁴ and Papi et al²⁶ indicated that, in cases of mild persistent or moderate/severe persistent asthma, an entirely new therapeutic approach is possible, that is, use of a combination of inhaled corticosteroids and bronchodilators on an as-needed basis. The results of the study by O'Byrne et al²⁴ suggested that use of formoterol plus budesonide as quick-relief medication plus regular use of the same combination for patients with more-severe asthma produced better results than those obtained with regular use of the combination therapy plus use of short-acting β -adrenergic receptor agonists for quick relief. The study by Papi et al²⁶ suggested that use of a combination of beclomethasone and albuterol as needed could replace daily use of inhaled corticosteroids for adults with mild asthma, at least from the point of view of the prevention of asthma exacerbations. More studies are needed to confirm the validity of these strategies and to determine the exact role that these types of as-needed therapies should have in the treatment of childhood asthma.

INHALED CORTICOSTEROIDS DO NOT MODIFY THE NATURAL HISTORY OF ASTHMA

Until recently, an objection that could have been made to studies such as those by O'Byrne et al²⁴ and Papi et al²⁶ was that there was the potential for regular use of inhaled corticosteroids to prevent long-term deterioration in airway function and subsequent development of

more-severe symptoms in children with asthma. However, an indication that inhaled corticosteroids were unlikely to have long-term effects on the natural history of asthma was provided by the previously mentioned CAMP study.⁷ In that study, regular use of inhaled corticosteroids for a period of 4 to 6 years had no effect on airway function growth when children who were assigned to that treatment were compared with those who were treated for a similar period with either nedocromil or placebo. Because only school-aged children were included in the CAMP study, it became important to determine whether use of inhaled corticosteroids at an even earlier age could have positive effects on lung function and asthma outcomes. Studies in the United States, the United Kingdom, and Denmark used different therapeutic strategies to test this hypothesis. In the US study, regular use of fluticasone twice daily for 2 years by 2- to 3-year-old children with significant asthma symptoms (recurring wheezing) who were at high risk for the development of asthma was compared with placebo in the effects on respiratory symptoms during a third year, in which no study medicine was given.⁹ In the British study, infants at high risk for asthma received either regular fluticasone or placebo as a function of the intensity of their symptoms; this treatment strategy was extended during most of their preschool years.²⁷ In the Danish study, children at high risk for asthma were given short courses of inhaled corticosteroids during the first 2 years of life and 48 hours after the onset of an acute lower respiratory illness.²⁸ The results of all 3 studies were very similar; the use of inhaled corticosteroids had no long-term beneficial effects, although better clinical outcomes were observed in the US study when the children were receiving fluticasone regularly.

The results of these studies strongly support the contention that the regular, long-term use of inhaled corticosteroids cannot be predicated on the basis of their potential to change the natural course of asthma. Parents are often very reluctant to give inhaled corticosteroids for long periods to children with asthma. Therefore, the possibility that a strategy in which inhaled corticosteroids are used on an as-needed basis in combination with short-acting β -adrenergic receptor agonists offers a new, less-burdensome approach to the prevention of asthma exacerbations, at least among children with mild persistent asthma. This strategy is currently being tested in a large placebo-controlled study.

CONCLUSIONS

Preventing exacerbations remains the most important challenge in asthma treatment, particularly during childhood. The studies discussed above offer hope that asthma exacerbations can be dramatically decreased or eliminated in the near future. New treatments that translate the knowledge that has been acquired regarding the heterogeneity of asthma exacerbations into usable medications are needed. In addition, studies showing the safety and efficacy of inhaled corticosteroids in combination with bronchodilators on an as-needed basis, either as add-on therapy for children with more-severe asthma or as an alternative to the regular use of

inhaled corticosteroids for children with mild persistent asthma, are urgently needed.

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