

## Anti-Inflammatory Treatment for Recurrent Wheezing in the First Five Years of Life

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**Summary.** Medications identified for the treatment of recurrent wheezing in preschool children by the Expert Panel Report of the NHLBI Guidelines for the Diagnosis and Management of Asthma include inhaled corticosteroids, chromones, theophylline, and leukotriene pathway modifiers. However, these various agents differ in their mechanism, extent of action on the airway inflammatory process, and degree of clinical efficacy. Inhaled corticosteroids can control symptoms in many young children with even severe persistent wheezing, but data on their long-term safety when administered in preschool-age children are scarce. There is some information on the uninterrupted use of inhaled corticosteroids in school-age children and the absence of an adverse effect on ultimate adult height. Despite laboratory evidence of adrenal suppression in some studies, few pediatric cases of clinical adrenal insufficiency have been reported. Low-dose inhaled corticosteroid (<400 mcg/day for beclomethasone), which is adequate for controlling mild persistent symptoms, is generally safe. Chromones have a remarkable safety profile, but they are most effective for symptoms of mild severity. Promising data have been published on the efficacy and safety of leukotriene pathway modifiers when used in young children with persistent symptoms. It is uncertain whether early introduction and long-term administration of inhaled corticosteroids prevent development of irreversible airway obstruction. Nevertheless, they may be especially useful for patients with moderate to severe disease in whom other agents (chromones or leukotriene pathway modifiers) will most likely fail to control symptoms. **Pediatr Pulmonol.** 2003; 35:241–252. © 2003 Wiley-Liss, Inc.

**Key words:** beclomethasone dipropionate; budesonide; fluticasone propionate; cromolyn sodium; leukotriene receptor antagonists.

### INTRODUCTION

Asthma is an inflammatory disease characterized by recurrent episodes of airway obstruction and bronchial hyperresponsiveness to various stimuli.<sup>1</sup> Although airflow obstruction is reversible, either with or without treatment, this is not the case for all subjects. Some patients develop persistent deficits in lung function within the first 10 years of life, presumably due to airway remodeling resulting from untreated longstanding airway inflammation.<sup>2–6</sup> Since asthma usually begins in childhood,<sup>7</sup> it has been proposed that early introduction of inhaled corticosteroids may have a disease-modifying effect and may prevent development of irreversible airway obstruction.<sup>8,9</sup> This hypothesis is supported by a few studies demonstrating a negative correlation between lung function level and duration of symptoms before anti-inflammatory treatment was introduced,<sup>10,11</sup> but this correlation was not found by others.<sup>12</sup> In addition to the possible long-term effects of inhaled corticosteroids (prevention of airway remodel-

ing), important short-term benefits (control of symptoms) are associated with their use.

Nevertheless, concerns have been raised about “an early intervention” using inhaled corticosteroids for infants and young children with recurrent wheezing. *First*, some

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subjects with wheezing, who are 6 years of age or younger, do not have asthma later in life.<sup>3</sup> When early intervention is undertaken in children younger than 3 years of age, many of them will receive a prolonged course of inhaled corticosteroids, although they will never develop persistent asthma.<sup>3,8</sup> Only a minority of infants with wheezing will still be symptomatic in early and late childhood, and those are believed to have asthma with inflammation of the lower airways.<sup>3,13,14</sup> In fact, recently published data indicate that frequent wheezing in infancy associated with exposure to older children at home or other children at day care may protect against asthma later in childhood.<sup>15</sup>

*Second*, lung function deficits in asymptomatic asthmatic subjects do not necessarily indicate irreversible lower airway obstruction, as has been reported in the literature. Those deficits may alternatively represent chronic low-grade airway inflammation.<sup>16</sup>

*Third*, not all studies have detected a beneficial effect of inhaled corticosteroids on lung function measured in adulthood, when they were given for asthma of various severity in childhood.<sup>17</sup> A National Institutes of Health-funded multicenter trial of 5–12-year-old children with mild to moderate asthma found no differences in lung function after treatment with inhaled corticosteroid, nedocromil, or placebo for 4–6 years.<sup>18</sup> Moreover, there is evidence that long-term uninterrupted treatment with inhaled corticosteroids to achieve chronic control of airway inflammation in children is not completely devoid of adverse effects. For all the above reasons, caution has been suggested when using inhaled corticosteroids in the preschool age group.<sup>1,19</sup>

The present article reviews the benefits and harm of anti-inflammatory treatment for recurrent wheezing in patients 5 years of age or younger. The National Lung Heart and Blood Institute (NHLBI) *Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 2)* defined as anti-inflammatory those medications (corticosteroids, chromones, methylxanthines, and leukotriene pathway modifiers) that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (i.e., inflammatory cells or mediators) and thus decrease the intensity of airway hyperresponsiveness.<sup>1</sup> Corticosteroids are the only agents that acutely reverse a

range of inflammatory responses, whereas the others prevent a rather specific manifestation of inflammation. Our specific goals were: 1) to search for, critically appraise, and summarize the available literature; 2) to attempt interpretation of the reported efficacy, lack of efficacy, and adverse effects of various anti-inflammatory medications used for treatment of recurrent wheezing in preschool children; and 3) to identify gaps in the current knowledge and major research questions which are yet to be answered.

## METHODS

Four types of articles were reviewed: 1) systematic reviews; 2) randomized clinical trials; 3) nonrandomized or uncontrolled trials, and observational studies; and 4) consensus reports, narrative reviews, commentaries, and letters to medical journals expressing expert opinions. The literature search was not limited to systematic reviews and controlled clinical trials, since there are not enough evidence-based papers to provide answers to all the clinical questions which are relevant to the subject of the present article. In addition, randomized clinical trials for evaluation of rare adverse events of medications may be difficult to perform. Observational studies and expert opinions can be helpful to clinicians who try to make treatment decisions when methodologically sound studies are not available.

The literature search covered the period from January 1966–June 2002, and was performed using *MEDLINE* ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), the *Cochrane Library* ([www.update.cochrane.co.uk](http://www.update.cochrane.co.uk)), and the evidence-based textbook *Clinical Evidence* ([www.clinicalevidence.org](http://www.clinicalevidence.org)). To increase the yield of our search, the PubMed function “See Related Articles” was used, and the bibliographies of all retrieved papers were also examined manually. An effort was made to include only data concerning preschool children. When such data were not available, trials in older children or adults were referenced.

The collected papers were critically appraised based on principles previously described.<sup>20–22</sup> This task was accomplished using standard appraisal question checklists which can be found in the *Clinical Evidence* website and elsewhere.<sup>21,22</sup> After the critical review process was completed, the articles were summarized and classified into four levels of evidence similar to the NHLBI *GINA Report* (Global Initiative for Asthma).<sup>23</sup> *Level A* included well-designed randomized clinical trials and meta-analyses with substantial numbers of participants, while *Level B* included similar types of studies but with smaller patient groups. *Level C* incorporated observational studies, and *Level D*, expert opinions.

To interpret the reported efficacy, lack of efficacy, and adverse effects of various anti-inflammatory medications, a small number of original papers and review articles on the pharmacologic principles, pathophysiology, and

### ABBREVIATIONS

|              |                                           |
|--------------|-------------------------------------------|
| BDP          | Beclomethasone dipropionate               |
| BUD          | Budesonide                                |
| FP           | Fluticasone propionate                    |
| GINA         | Global Initiative for Asthma              |
| HPA axis     | Hypothalamic-pituitary-adrenal axis       |
| MDI          | Metered-dose inhaler                      |
| MDI + S      | Metered-dose inhaler + spacer             |
| MDI + S + FM | Metered-dose inhaler + spacer + face mask |
| N + FM       | Nebulizer + face mask                     |
| NHLBI        | National Heart Lung and Blood Institute   |

prognosis of recurrent wheezing in preschool years were referenced. When no appropriate evidence was available, suggestions about treatment decisions were based on data from older children and on expert opinion.

In this article, classification of disease severity (mild, moderate, or severe) was made according to the definitions of the NHLBI *Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 2)*,<sup>1</sup> with one important difference: preschool children frequently present with clinical features of certain disease severity for brief periods of time (mild, moderate, or severe *episodic* symptoms). Only a minority of them follow the clinical course of older children and adults suffering from continuous and unremitting symptoms (mild, moderate, and severe *persistent* symptoms).<sup>19</sup> Thus, classification of severity was based on either persistent or episodic symptoms.

## INHALED CORTICOSTEROIDS

### Inhaled Corticosteroids and Viral-Associated Wheezing: Amelioration of Acute Symptoms and Prevention of Recurrences

In the literature, the term viral-associated wheezing has been used to describe a history of episodic wheezing with upper respiratory infections and no symptoms between episodes.<sup>24,25</sup> Viral upper respiratory tract infections are associated in time with asthma exacerbations leading to hospital admission in both children and adults.<sup>26</sup> Viral upper respiratory infections have been identified in 80–85% of asthma exacerbations in school-age children in the community.<sup>27</sup> Furthermore, the majority of wheezing episodes in infants occur concomitantly with a viral respiratory infection.<sup>28</sup> It is unclear whether the pathophysiologic mechanisms of pure viral-associated wheezing in young children are the same with those of viral-induced exacerbations of asthma.<sup>29,30</sup>

A systematic review in the Cochrane Library evaluated inhaled corticosteroid treatment given intermittently or daily to children younger than 17 years of age for recurrent episodes of wheezing associated with viral upper respiratory tract infections.<sup>24</sup> Some of the reviewed studies had also included preschool children with viral-induced wheezing who received either high-dose inhaled corticosteroid at the onset of an upper respiratory infection,<sup>31–33</sup> or continuous treatment with a low dose of inhaled corticosteroid.<sup>34</sup>

The conclusion of the review was that episodic use of high-dose inhaled corticosteroid (0.8–3.2 mg/day of beclomethasone dipropionate or budesonide) decreased the severity of symptoms but not the need for systemic corticosteroids in children with mild wheezing induced by viral infection (*Evidence A*). No benefit in the severity of symptoms or the need for systemic corticosteroids was

identified with low-dose maintenance inhaled corticosteroid (0.4 mg/day of budesonide for 4 months) (*Evidence B*). This last conclusion was based on two randomized, double-blind, placebo-controlled trials, of which only one included preschool children. Specifically, 57 children were enrolled in the study, and 16 withdrew.<sup>34</sup> More studies are necessary to clarify the effects of low-dose maintenance inhaled corticosteroids in young children with recurrent viral-associated wheezing.

A short course of oral corticosteroids at the beginning of a viral-induced wheezing episode has been proposed as an effective way to improve symptoms and prevent emergency room visits and hospitalizations<sup>35</sup> (*Evidence D*). This expert opinion is supported by an open trial of 32 children younger than 6 years of age with a history of severe wheezing associated with upper respiratory tract infections.<sup>36</sup> Sixteen of 32 children received prednisone (1 mg/kg/day) with the first symptoms of upper respiratory tract infection in addition to bronchodilators, while the rest of the children were treated with bronchodilators only (control group). The corticosteroid-treated group had a significant decrease in the number of days with wheezing, number of wheezing attacks, visits to emergency department, and hospitalizations (*Evidence C*). In a second report, 74 patients aged 7–54 months, who presented to the emergency department with acute wheezing, were treated in a blinded way with either a single dose of intramuscular methylprednisolone (4 mg/kg) or normal saline as placebo. Corticosteroid treatment significantly reduced the hospital admission rate<sup>37</sup> (*Evidence B*).

### Inhaled Corticosteroids: Benefits to Preschool Children With Frequent Episodes of Wheezing or Persistent Wheezing

Currently, it is not possible to predict with certainty whether an infant or young child with frequent or persistent wheezing will continue having asthma symptoms in late childhood or adulthood. In the 2002 *Update of the NHLBI Guidelines for the Diagnosis and Management of Asthma* ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)), the Expert Panel suggested initiation of long-term control therapy in infants and young children with any of the following characteristics:

- 1) Symptomatic treatment required more than twice a week.
- 2) Severe exacerbations of wheezing less than 6 weeks apart.
- 3) More than 3 episodes of wheezing in the past year that lasted more than 1 day and affected sleep when risk factors for the development of asthma were present (e.g., parental history of asthma, physician-diagnosed atopic dermatitis, physician-diagnosed allergic rhinitis, wheezing apart from colds, or peripheral blood eosinophilia). (*Evidence D*).

A systematic review addressed the effectiveness of prophylactic inhaled corticosteroid in childhood asthma.<sup>38</sup> The review included 24 randomized, double-blind, placebo-controlled trials with a total of 1,087 subjects and ages 0–20 years that were published between January 1966–December 1996. Ten of 24 trials involved preschool children with frequent episodes of wheezing or persistent wheezing (377 subjects) who received placebo, beclomethasone dipropionate (0.15–0.4 mg/day), or budesonide (0.3–2 mg/day) for 4–24 weeks. Compared to placebo, inhaled corticosteroids decreased the mean total symptom score and mean concomitant  $\beta_2$ -agonist and oral steroid use, and increased mean peak expiratory flow rate in asthmatic children (*Evidence A*). There was no statistically significant difference in the rate of hospital admissions, but only 3 of 10 trials with preschool children provided such information (*Evidence B*).

Four more clinical trials of inhaled corticosteroids were published after the systematic review.<sup>39–42</sup> Some of their characteristics and findings are summarized in Table 1. They included a total of 861 children with ages 3 months to 8 years who had a history of recurrent episodes of wheezing and/or mild to moderate persistent wheezing. All trials were double-blind, randomized, and placebo-controlled and used a parallel-group design, and the analysis was done on an intention-to-treat group of children. A history of allergic rhinitis and/or eczema was reported in 27–63% of subjects in 3 of 4 studies.<sup>39,40,42</sup> Children were treated with inhaled placebo, budesonide, or fluticasone propionate.

In the largest of the four studies (481 subjects), the mean asthma symptom score changes in the budesonide-treated group were significantly greater compared to the placebo-treated group<sup>41</sup> (*Evidence A*). Subjects in the budesonide-treated group required rescue asthma medication for fewer days compared to subjects in the placebo-treated group (*Evidence A*). In the second largest study (305 subjects), patients with a baseline history of frequent symptoms who were treated with fluticasone propionate had significantly more days and nights without symptoms compared to those who were treated with placebo (*Evidence A*). This difference was not significant in the subgroup of patients with less frequent symptoms (less than three times a week).<sup>40</sup>

Pulmonary function tests were performed in a small number of infants (38 subjects) in two studies, with conflicting results. When comparing the budesonide-treated group with the placebo group,<sup>42</sup> there was a statistically significant effect of budesonide on cold-air challenge response, but not on specific airway resistance and methacholine challenge response (whole-body plethysmograph) (*Evidence B*). When comparing the fluticasone-treated group with the placebo group,<sup>39</sup> there was no statistically significant effect of fluticasone on either  $V'_{\text{maxFRC}}$  (rapid thoracoabdominal compression technique) or total respiratory system resistance (single-breath occlusion technique) (*Evidence B*).

### Inhaled Corticosteroids: Systemic Effects

Inhaled corticosteroids reach the systemic circulation and possibly cause side effects via two routes:<sup>1,43</sup> 1) Medication deposited in the mouth and pharynx may be swallowed, absorbed, and, depending on the degree of first-pass metabolism in the liver, may become systemically available. Newer inhaled corticosteroids (fluticasone propionate, budesonide) are minimally absorbed from the gastrointestinal tract and/or undergo extensive first-pass metabolism in the liver to products with very low glucocorticoid activity.<sup>44,45</sup> 2) Medication deposited in the lung reaches systemic circulation. In one trial, systemic availability of nebulized budesonide in patients aged 3–6 years was approximately 6%.<sup>43</sup>

To our knowledge, there are no systematic reviews or large long-term, double-blind, placebo-controlled trials designed specifically to identify systemic effects of inhaled corticosteroids in preschool children. One small study assessed the growth rate of the lower leg length in 18 toddlers of ages 13–36 months. They were randomized blindly through three consecutive 4-week treatment periods with placebo, budesonide 0.2 mg/day (low dose), or budesonide 0.4 mg/day (high dose). There was a statistically significant growth rate difference between the placebo treatment period and the high-dose corticosteroid treatment period<sup>46</sup> (*Evidence B*). In a different double-blind, placebo-controlled trial, 40 patients received 4 weeks of treatment with placebo, budesonide 0.4 mg/day, or fluticasone propionate 0.4 mg/day in random order.

**TABLE 1—Studies on Efficacy of Inhaled Corticosteroids in Preschool Children With Frequent Episodes of Wheezing or Persistent Wheezing<sup>1</sup>**

| Steroid (mg/day)              | Treatment duration | Age range        | Treated patients/controls                      | Fewer symptoms | Decreased albuterol use | Reference no. |
|-------------------------------|--------------------|------------------|------------------------------------------------|----------------|-------------------------|---------------|
| BDP (0.15–0.4) or BUD (0.3–2) | 4–24 weeks         | 0–6 years        | 377 (patients and controls, systematic review) | Yes            | Yes                     | 38            |
| FP (0.3)                      | 12 weeks           | 3–12 months      | 19/18                                          | Yes            | No                      | 39            |
| FP (0.2)                      | 12 weeks           | 12–47 months     | 152/153                                        | Yes            | Yes                     | 40            |
| BUD (0.25–1.0)                | 12 weeks           | 6 months–8 years | 386/95                                         | Yes            | Yes                     | 41            |
| BUD (0.8)                     | 8 weeks            | 2–5 years        | 19/19                                          | Yes            | Yes                     | 42            |

<sup>1</sup>BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate.

The growth rate of the lower leg length was significantly reduced during the inhaled steroid treatment periods<sup>47</sup> (*Evidence B*).

The short-term safety of budesonide inhalation suspension was also assessed in a multicenter, 12-week, double-blind, placebo-controlled trial of 1,017 infants and children (6 months–8 years old) with persistent asthma who were allocated randomly into one of the following treatment groups: placebo, or budesonide 0.25 mg/day, 0.5 mg/day, 1 mg/day, or 2 mg/day.<sup>48</sup> There were no significant differences between the placebo and the budesonide treatment groups in basal or ACTH-stimulated cortisol levels, physical examination, or clinical laboratory values (*Evidence A*).

The suspicion for systemic effects of inhaled corticosteroid when given to preschool children is confirmed indirectly by meta-analyses and randomized, placebo-controlled trials in older children. Two meta-analyses concluded that during the first 12 months of treatment with inhaled corticosteroids, there is a small decrease in the growth rate of school-age children. This decrease is 1.51–1.54 cm/year for beclomethasone dipropionate (0.328–0.4 mg/day administered for 7 months to 54 weeks) (*Evidence A*), and 0.43 cm/year for fluticasone propionate (0.1–0.2 mg/day administered for 52 weeks) (*Evidence B*).<sup>49,50</sup> A multicenter, randomized, double-blind, placebo-controlled study of 1,041 children (5–12 years of age) who received budesonide (0.4 mg/day), nedocromil, or placebo for 4–6 years revealed that the small decrease in growth rate of the corticosteroid-treated group (–1.1 cm/year) persisted only during the first year of treatment<sup>18</sup> (*Evidence A*). However, some “sensitive” subjects will experience stunting in growth persisting beyond the first year of treatment with doses of beclomethasone dipropionate as low as 0.2–0.3 mg/day<sup>51</sup> (*Evidence C*).

Some observational studies on the systemic effects of inhaled corticosteroids on adrenal function, bone metabolism, and linear growth in preschool children are summarized in Table 2. None of the presented observational studies (total of 212 infants and young children) identified systemic effects of beclomethasone dipropionate or budesonide on bone metabolism or linear growth (*Evidence C*). One of six studies revealed a suppres-

sion effect of inhaled budesonide on the hypothalamic-pituitary-adrenal (HPA) axis<sup>52</sup> (*Evidence C*).

A number of case reports of pediatric patients presenting with acute adrenal insufficiency following prolonged administration of inhaled corticosteroids have been published. Some representative cases of patients with acute adrenal insufficiency include: 1) a 6-year-old female receiving up to 1 mg/day of fluticasone propionate since age 3 years; 2) a 9-year-old female receiving 0.55 mg/day of fluticasone propionate for 6 months; and 3) a 7-year-old female receiving inhaled budesonide 0.4 mg/day and budesonide nasal spray 0.1 mg/day since age 5 years.<sup>58–60</sup> More recently, hypoglycemia as a result of acute adrenal insufficiency associated with high-dose inhaled corticosteroid treatment in asthmatic children was reported.<sup>61–63</sup> Symptoms of hypoglycemia (seizures, impaired level of consciousness) were described in 4–8-year-old asthmatic children receiving 0.5–1.5 mg/day of inhaled fluticasone propionate for 16 months to 5 years.<sup>62</sup> Furthermore, a 21-month-old asthmatic boy had a hypoglycemic seizure during a proven acute adrenal crisis secondary to high-dose nebulized budesonide treatment.<sup>63</sup>

Rare adverse effects of inhaled corticosteroids, such as immune suppression and tongue hypertrophy, have been described. For example, severe varicella infection and *Pneumocystis carinii* pneumonia have been reported in asthmatic children receiving prophylaxis with inhaled corticosteroids.<sup>64,65</sup> Hypertrophy of the tongue has been associated with inhaled beclomethasone treatment (200–400 mcg/day for 1–1.5 months) in premature infants with bronchopulmonary dysplasia.<sup>66</sup> This adverse effect appeared 2–4 weeks following initiation of treatment, and disappeared gradually after discontinuation of therapy.

## CHROMONES, LEUKOTRIENE PATHWAY MODIFIERS, AND THEOPHYLLINE

### Chromones: Safety Data and Anti-Inflammatory Effects

The safety of long-term administration of chromones to young children is supported by the lack of serious adverse effects in multiple studies. There are only rare reports of adverse incidents such as urticaria, angioedema,

**TABLE 2—Adverse Effects of Inhaled Corticosteroids in Preschool Children (Observational Studies)<sup>1</sup>**

| Steroid (mg/day) | Treatment duration | Age range      | Treated patients      | On adrenal function | On bone metabolism | On linear growth | Reference no. |
|------------------|--------------------|----------------|-----------------------|---------------------|--------------------|------------------|---------------|
| BUD (0.5–2.0)    | 18 weeks           | 5–47 months    | 102                   | Yes                 |                    |                  | 52            |
| BUD (0.4)        | 6 weeks            | 2–6 years      | 28 (cross-over trial) | No                  |                    |                  | 53            |
| BDP (0.5–0.86)   | 4.5–7.5 months     | 9–53 months    | 11                    |                     | No                 |                  | 54            |
| BUD (0.2)        | 12 months          | 3.5–7 years    | 16                    | No                  |                    | No               | 55            |
| BUD (1–4)        | 0.5–1.5 years      | 0.33–2.8 years | 40                    |                     |                    | No               | 56            |
| BUD (0.2)        | 3–5 years          | 2–7 years      | 15                    | No                  |                    | No               | 57            |

<sup>1</sup>BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate.

bronchospasm, anaphylaxis, and pulmonary infiltrates with eosinophilia, which have been summarized in a review article<sup>67</sup> (*Evidence C*). Nebulized cromolyn has been administered to patients who were a few days old without recognized side effects.<sup>68</sup> When airway biopsies were taken from adult asthmatic patients treated with disodium cromoglycate, it was found that there were decreased numbers of eosinophils, lymphocytes, and mast cells infiltrating the bronchial mucosa compared to placebo<sup>69</sup> (*Evidence B*).

### Chromones: Amelioration of Persistent Symptoms and Prevention of Recurrences

In the long-term randomized, controlled trial of 1,041 asthmatic children with ages 5–12 years which compared budesonide, nedocromil, and placebo, the inhaled corticosteroid improved airway responsiveness and provided better control of asthma symptoms than the inhaled chromone<sup>18</sup> (*Evidence A*). Table 3 summarizes double-blind, placebo-controlled trials on the efficacy of chromones with a parallel or cross-over design.<sup>70–79</sup> Cromolyn was useful in children over 1 year of age with mild to moderate symptoms<sup>75</sup> (*Evidence B*). The medication was not effective in some<sup>70–75</sup> but not all<sup>75–79</sup> studies, including patients younger than 12 months of age or subjects with moderate to severe symptoms (*Evidence B*).

The largest randomized, placebo-controlled study of inhaled cromolyn in preschool children with moderate asthma (218 subjects) concluded that cromolyn is not more effective than placebo.<sup>74</sup> An MDI with a spacer device and face-mask was used to administer 10 mg of cromolyn or placebo three times daily. This delivery system may have provided an inadequate amount of medication to the study subjects. Clinical efficacy improves when higher doses are used and more medication is deposited on the airway mucosa.<sup>80,81</sup> In the 2002 *Update of the NHLBI Guidelines for the Diagnosis and Management of Asthma* (www.nhlbi.nih.gov), the Expert Panel recommended nebulization as the preferred delivery method for cromolyn (*Evidence D*). The MDI formulation of 1 mg/puff available in the US is less able to decrease airway hyperresponsiveness compared to the MDI formulation of 5 mg/puff which is available elsewhere, apparently because it delivers less medication to the lower airway.<sup>82,83</sup>

A systematic review of 24 randomized, placebo-controlled trials, including more than 1,000 children, has been published.<sup>84</sup> About half of the children (11 trials) were of preschool age. Patient age was not a significant predictor of treatment effect. The meta-analysis concluded that there is insufficient evidence to support a beneficial effect of cromolyn when administered as maintenance treatment to children with asthma. However, only 24 of 251 articles identified by Medline search were analyzed. Many of the excluded trials are supportive of the use of

TABLE 3—Double-Blind, Controlled Studies on Efficacy of Chromones in Preschool Children With Recurrent Wheezing<sup>1</sup>

| Chromone (dosage)        | Method       | Treatment duration | Age range    | Treated patients/controls | Fewer symptoms | Fewer episodes | Reference no. |
|--------------------------|--------------|--------------------|--------------|---------------------------|----------------|----------------|---------------|
| Cromolyn (40 mg tid)     | N + FM       | 6 weeks            | 4–12 months  | 16/15                     | No             | No             | 70            |
| Cromolyn (20 mg qid)     | N + FM       | 8 weeks            | 21–53 months | 16 (cross-over trial)     | No             | No             | 71            |
| Cromolyn (20 mg tid)     | N + FM       | 2 months           | 4–24 months  | 23 (cross-over trial)     | No             | No             | 72            |
| Cromolyn (20 mg tid)     | N + FM       | 10 weeks           | 1–4 years    | 29/25                     | No             | No             | 73            |
| Cromolyn (10 mg tid)     | MDI + S + FM | 5 months           | 1–4 years    | 81/86                     | No             | Yes            | 74            |
| Cromolyn (20 mg qid)     | N + FM       | 4 weeks            | 3–11 months  | 20 (cross-over trial)     | No             | Yes            | 75            |
|                          |              |                    | 12–24 months | 24 (cross-over trial)     | Yes            | Yes            | 76            |
| Cromolyn (5 mg qid)      | MDI + S + FM | 3 weeks            | 4–31 months  | 16 (cross-over trial)     | Yes            | Yes            | 77            |
| Cromolyn (20 mg tid)     | N + FM       | 2 months           | 27–54 months | 17 (cross-over trial)     | Yes            | Yes            | 78            |
| Cromolyn (20 mg tid-qid) | N + FM       | 16 weeks           | 1–12 months  | 23/21                     | Yes            | Yes            | 79            |
|                          |              |                    | 13–23 months | 11/11                     | Yes            | No             |               |
| Cromolyn (20 mg qid)     | N + FM       | 6 months           | 14–49 months | 24 (cross-over trial)     | Yes            | No             |               |

<sup>1</sup>MDI + S, metered-dose inhaler + spacer; MDI + S + FM, metered-dose inhaler + spacer + face mask; N + FM, nebulizer + face mask.

cromolyn in children with wheezing.<sup>85</sup> The included trials were comprised mainly of hospital-based patients with moderate to severe disease, who are less likely to respond to chromones. In the majority of studies, duration of interventions did not exceed 4 weeks, which may be insufficient time to assess the efficacy of the medication. Finally, analysis of the data presented does show a small statistically significant effect of cromolyn on cough and wheeze, compared to placebo (95% confidence interval (CI) of additional decrease in cough score with cromolyn compared to placebo was  $-0.13$  to  $-0.27$ , and in wheeze score,  $-0.11$  to  $-0.26$ ).<sup>84,85</sup>

### **Leukotriene Pathway Modifiers: Anti-Inflammatory Effects**

The term *leukotriene pathway modifiers* describes two classes of medications: 1) leukotriene synthesis inhibitors (zileuton), and 2) competitive leukotriene receptor antagonists (montelukast, pranlukast, and zafirlukast). There is indirect evidence for the anti-inflammatory action of these agents in pediatric patients with asthma. In two clinical trials evaluating the use of leukotriene pathway modifiers in asthmatic children, a decrease in the concentration of exhaled nitric oxide was noted after 2–4 weeks of treatment with montelukast,<sup>86,87</sup> while in adult asthmatics, pranlukast inhibited airway inflammation, as documented by bronchial biopsy specimens<sup>88</sup> (*Evidence B*).

### **Leukotriene Pathway Modifiers: Efficacy Data in Preschool Children and Adverse Effects**

In a randomized, placebo-controlled study with cross-over design, montelukast administered to 13 asthmatic preschool children once daily for 2 days prevented bronchoconstriction induced by cold-air challenge<sup>89</sup> (*Evidence B*). In a multicenter, double-blind, placebo-controlled trial, 689 young children of ages 2–5 years and with persistent asthma were studied. Patients in the montelukast study group (4 mg daily for 12 weeks) improved significantly more than patients in the placebo study group in multiple parameters of asthma: daytime and overnight asthma symptoms, percentage of days without symptoms, need for  $\beta$ -agonist or oral corticosteroids, and physician global evaluation<sup>90</sup> (*Evidence A*). The additional improvement in cough and wheeze score with montelukast compared to placebo was small, and similar to the estimated effect of cromolyn in the recent systematic review.<sup>84</sup> The 95% CI of the additional decrease in cough score with cromolyn was  $-0.13$  to  $-0.27$ , and with montelukast,  $-0.06$  to  $-0.27$ . The 95% CI of the additional decrease in wheeze score with cromolyn was  $-0.11$  to  $-0.26$ , and with montelukast,  $0.00$  to  $-0.17$ .

Montelukast administered daily for 4 weeks offered a small additive effect on lung function and a decrease in the number of exacerbation days for 279 asthmatic children of

ages 5–15 years and incomplete control of symptoms by inhaled budesonide.<sup>91</sup> The study was multicenter and double-blind, with a cross-over design (4 weeks of montelukast and 4 weeks of placebo in random order) (*Evidence A*). A recent Cochrane review evaluated the few published studies on the efficacy of leukotriene pathway modifiers compared to inhaled corticosteroids. The reviewers concluded that inhaled corticosteroids appear more effective than leukotriene receptor antagonists, but more trials are necessary to confirm this finding.<sup>92</sup> Superior efficacy of inhaled corticosteroids was noted in improving lung function and quality of life, and in reducing symptoms and use of bronchodilators. The number of exacerbations was similar in patients with mild to moderate asthma who received leukotriene receptor antagonists or inhaled corticosteroids in doses equivalent to 0.25–0.4 mg/day of beclomethasone dipropionate (*Evidence B*).

No significant differences in the frequency of adverse effects between montelukast and placebo have been noted.<sup>90</sup> However, a 9-year-old child treated for asthma with zafirlukast developed symptoms of drug-induced lupus, which resolved after discontinuation of the medication.<sup>93</sup> In addition, a 7-year-old asthmatic child who received pranlukast had laboratory and histologic findings consistent with acute allergic tubulointerstitial nephritis.<sup>94</sup>

There is not enough information on the efficacy of leukotriene pathway modifiers compared to or in combination with chromones. No difference was found in the efficacy of zafirlukast in comparison to cromolyn when they were administered to asthmatic adults with mild disease.<sup>95</sup> Consideration of alternatives suggests that the four-times-a-day regimen of chromones will be probably associated with a higher rate of patient noncompliance relative to once- or twice-a-day oral administration of a competitive leukotriene receptor antagonist.<sup>96</sup>

### **Theophylline: Efficacy Data and Adverse Effects**

In both the 2002 GINA report<sup>23</sup> and the 2002 update of the NHLBI *Guidelines for Diagnosis and Management of Asthma* ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)), theophylline is one of the medications that may be added to inhaled corticosteroids to improve control of moderate persistent symptoms. Theophylline acts as a bronchodilator in preschool children with asthma symptoms<sup>97,98</sup> (*Evidence C*). Airway biopsies in adult asthmatic patients who received long-term treatment with theophylline showed that the medication also has immunomodulatory effects.<sup>99</sup> The additive effect of the medication in school-age children with steroid-dependent asthma (oral or inhaled) was shown in a small double-blind, cross-over study<sup>100</sup> (*Evidence B*).

The most frequent side effects of theophylline are headache, nausea, vomiting, and anorexia.<sup>101</sup> In a systematic review of 12 pediatric studies, no behavioral or cognitive adverse effects of theophylline were identified.<sup>102</sup>

## CONCLUDING COMMENTS

### Administration of Anti-Inflammatory Medications: Two Different Approaches

There are different approaches in the literature regarding the administration of anti-inflammatory medications to children with recurrent wheezing. Many pediatric respiratory specialists recommend early introduction of inhaled corticosteroids to the treatment regimen in the hope that controlling inflammation will prevent airway remodeling and development of nonreversible airway obstruction. They also believe that inhaled corticosteroids are safe agents, and that the benefits from their use outweigh the potential risks. Other physicians view the problem from a different perspective: asthma begins in childhood, but the majority of preschool children with recurrent wheezing (especially those with viral-induced symptoms) do not have asthma symptoms when they reach school age; the risk for complications related to the long-term use of inhaled corticosteroids, such as growth retardation, cataracts, or osteoporosis, has not yet been completely defined.

There are not enough large randomized, double-blind, controlled trials on the efficacy and safety of anti-inflammatory medications for preschool children with wheezing. Some observational studies have given conflicting results. Therefore, it is very difficult to suggest the best treatment approach to recurrent wheezing in preschool children with certainty. At least part of the problem is due to the coexistence of wheezy infants who will continue having asthma symptoms later in life, with another group of preschool children who have recurrent wheezing, but whose symptoms remit as they grow older.<sup>13</sup> The differences in pathophysiologic mechanisms of wheezing in preschool years which persists in late childhood vs. those of wheezing of infancy and early childhood which remits later in life are not clear at present.

### Indications for Administration of Anti-Inflammatory Medications

The beneficial effects of anti-inflammatory agents can be classified as short-term (control of symptoms) and long-term (prevention of airway remodeling). Currently, there are insufficient data to support the hypothesis that early introduction of anti-inflammatory treatment for recurrent wheezing in preschool children prevents the development of irreversible airway obstruction.<sup>18,103,104</sup> To improve quality of life, infants and young children who consistently require symptomatic treatment more than

twice a week or those who experience severe exacerbations less than 6 weeks apart should probably be given daily anti-inflammatory medication.<sup>1</sup> Inhaled corticosteroids may control symptoms in many preschool children, especially those with persistent wheezing.<sup>38–42</sup> In both the 2002 GINA report<sup>23</sup> and the 2002 update of the NHLBI *Guidelines for the Diagnosis and Management of Asthma* (www.nhlbi.nih.gov), maintenance inhaled corticosteroids are the preferred anti-inflammatory medication for mild, moderate, or severe persistent symptoms.

For a subpopulation of young patients with viral-induced symptoms, low-dose inhaled corticosteroids do not prevent exacerbations.<sup>24,34</sup> In such cases, early administration of a short course of an oral corticosteroid soon after the appearance of respiratory symptoms may prevent emergency room visits and hospitalizations.<sup>35–37</sup> In the 2002 GINA report, maintenance inhaled corticosteroids are recommended for children with severe episodic symptoms in doses equal to those administered for moderate persistent symptoms<sup>23</sup>) (*Evidence D*). Similarly, in the 2002 update of the NHLBI *Guidelines for the Diagnosis and Management of Asthma* (www.nhlbi.nih.gov) inhaled corticosteroids are recommended for infants and young children with more than three episodes of wheezing affecting sleep over the past year, when certain risk factors for the development of asthma are present (*Evidence D*).

### Safety of Long-Term Treatment With Inhaled Corticosteroids

Most studies on the safety of inhaled corticosteroids in pediatrics have recruited patients older than 5 years of age, and only a few of them included preschool children. Clinical trials with infants and young children have lasted less than a year and have studied mostly HPA axis effects (Table 2). From the limited available data, it appears that low doses of corticosteroids (less than 0.4 mg/day of beclomethasone dipropionate) do not usually suppress the HPA axis. Recent studies in school-age children show that growth rate is reduced to a small degree during the first year of administration of inhaled corticosteroids, but this reduction is not sustained with continued treatment. More trials in both preschool and school-age children are required to confirm these findings. It should be emphasized that the effect of inhaled corticosteroids on linear growth and ultimate height may be different in early childhood due to the rapid somatic growth during this period of human development. Isolated cases of adverse events have been described even with low doses of corticosteroids (0.3 mg/day),<sup>51</sup> confirming the suspicion that inhaled medications may have clinically important systemic actions.

The critical question is whether any unrecognized, cumulative, and nonreversible changes (e.g., decrease in bone mass, development of cataracts, or a negative impact on organ development<sup>105</sup>) occur in young children with

recurrent wheezing who receive inhaled corticosteroids for years. In view of the accumulating concerns in the literature, the Food and Drug Administration now requires labeling of inhaled corticosteroids with a warning about the possibility of reduced growth velocity from their use in pediatric patients.<sup>106</sup>

### Alternatives to Inhaled Corticosteroids

Low-dose corticosteroids or medications with a better safety profile such as leukotriene pathway modifiers and chromones should be considered for symptoms of mild severity. In many cases, an inhaled corticosteroid is the only anti-inflammatory medication able to control moderate or severe persistent lower airway symptoms, but recent evidence on the efficacy and safety of leukotriene pathway modifiers in preschool children with persistent symptoms is encouraging. Addition of a leukotriene pathway modifier or theophylline to an inhaled corticosteroid is one of the suggested treatment regimens for preschool children with moderate persistent symptoms (2002 GINA report and 2002 update of the NHLBI *Guidelines for the Diagnosis and Management of Asthma*). An orally administered agent may offer better patient compliance compared to an inhaled chromone given four times a day.

Future prospective studies, evaluating the efficacy of anti-inflammatory medications in preschool children with recurrent wheezing, should attempt to form patient study groups on the basis of common pathophysiologic mechanisms of wheezing. Important research questions have yet to be answered: which preschool children with recurrent wheezing are at risk for development of nonreversible airway obstruction? Does early introduction of inhaled corticosteroids prevent airway remodeling? What are the side effects of inhaled corticosteroids when they are started at a very young age and continued for several years? Does the addition of leukotriene pathway modifiers have a steroid-sparing effect? As a child's clinical status improves, may chromones or leukotriene pathway modifiers be substituted for inhaled corticosteroids? These and other questions should be considered and investigated before a regimen of anti-inflammatory therapy in preschool children with recurrent or persistent wheezing can be proposed with certainty.

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