

Anti-Inflammatory Pharmacotherapy for Wheezing in Preschool Children

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Summary. Accumulating evidence indicates that there are at least two phenotypes of wheezing in preschool years with distinct natural history. Frequent wheezing in the first 3 years of life with risk factors for asthma (e.g., eczema, maternal asthma) predicts symptoms in older age, while infrequent viral-associated wheezing without risk factors for asthma has a benign prognosis. This systematic review summarizes evidence on the use of anti-inflammatory medications in preschool children with wheezing. Literature search was performed using Medline and the Cochrane Library. Retrieved articles were critically appraised. Episodic use of high-dose inhaled corticosteroids (>1,600 mcg/day of beclomethasone) may ameliorate severity of intermittent viral-associated wheezing. Maintenance inhaled corticosteroids can control symptoms in children with frequent wheezing associated with risk factors for asthma. Inhaled corticosteroids do not alter the natural history of wheezing even when started early in life and could have a negative impact on linear growth rate. Short courses of oral corticosteroids have been proposed as an effective measure to control exacerbations of symptoms although there is little evidence supporting their use. Some studies support the administration of non-steroidal anti-inflammatory medications (leukotriene pathway modifiers, cromones, methylxanthines) for mild frequent wheezing. Maintenance inhaled corticosteroids is the most effective measure for controlling frequent wheezing in preschool children, especially when accompanied by risk factors for asthma. This treatment does not affect the natural history of wheezing, although deceleration of linear growth rate is the most commonly recognized systemic adverse effect. **Pediatr Pulmonol.** © 2007 Wiley-Liss, Inc.

Key words: anti-inflammatory medications; asthma; cromolyn; inhaled corticosteroids; leukotriene modifiers.

INTRODUCTION

In an article published in *Pediatric Pulmonology* a few years ago, evidence on the administration of anti-inflammatory medications to preschool children for recurrent wheezing was critically reviewed.¹ Since then, important new data have been added to the literature regarding the prognosis and treatment of episodes of lower airway obstruction in the first 5 years of life.^{2–6} Nebulized corticosteroids are now available in the USA for use in children younger than 6 years, while at least 3 well-designed studies have addressed the potential benefits associated with intermittent or long-term administration of this class of medications.^{3,4,6} In addition, cromones are less frequently prescribed by pediatricians compared to the past, whereas leukotriene receptor antagonists are more frequently used and more extensively studied in clinical trials.^{5,7}

Thus, the aims of the present article are: (i) to summarize recently published data related to management of wheezing in the first 5 years of life; (ii) to attempt interpretation of the reported efficacy or lack of efficacy of the available anti-inflammatory medications; and (iii) to

propose indications for prescribing anti-inflammatory medications to preschool children with intermittent or persistent symptoms of lower airway obstruction.

METHODS

To assess efficacy of anti-inflammatory medications, randomized clinical trials, systematic reviews, nonrandomized or uncontrolled clinical trials, observational

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studies, consensus statements, narrative reviews, commentaries and letters to medical journals expressing expert opinions were retrieved and analyzed. The literature search covered English-language articles published in the period from January 1966 to September 2006, and was performed using MEDLINE (www.ncbi.nlm.nih.gov) and the Cochrane Library (www.update.cochrane.co.uk).

The search criteria used were the following: (i) (“wheezing” or “wheeze” or “asthma”) and (“infants” or “toddlers” or “children”) and (“corticosteroids” or “methylprednisolone” or “prednisolone” or “prednisone” or “dexamethasone” or “beclomethasone” or “budesonide” or “fluticasone”); (ii) (“wheezing” or “wheeze” or “asthma”) and (“infants” or “toddlers” or “children”) and (“leukotriene pathway modifiers” or “leukotriene receptor antagonists” or “montelukast”); (iii) (“wheezing” or “wheeze” or “asthma”) and (“infants” or “toddlers” or “children”) and (“cromolyn” or “sodium cromoglycate” or “nedocromil sodium”); (iv) (“wheezing” or “wheeze” or “asthma”) and (“infants” or “toddlers” or “children”) and (“methylxanthines” or “theophylline”); and (v) (“wheezing” or “wheeze” or “asthma”) and (“infants” or “toddlers” or “children”) and (“ketotifen” or “cetirizine”).

Retrieved abstracts were reviewed and the full text of relevant articles was read. The bibliographies of all selected articles were also examined manually.

Relevant articles were then critically appraised based on principles described previously.^{8–11} After the critical review process was completed, the articles were classified into four levels of evidence as was proposed in the Global Initiative for Asthma (GINA) Report and in the National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma-2002 Update.^{12,13} *Level A* included well-designed, randomized, double-blind, placebo-controlled, clinical trials with substantial number of participants (at least 200). *Level B* referred to randomized trials with limited number of patients (fewer than 200) and posthoc or subgroup analyses of large clinical trials; also meta-analyses of a number of studies were classified in this category. *Level C* incorporated results from uncontrolled, nonrandomized trials or from observational studies. *Level D* referred to expert opinion that was based on clinical experience and not on published evidence.

PROGNOSIS OF WHEEZING IN PRESCHOOL CHILDREN AND THE ROLE OF ANTI-INFLAMMATORY MEDICATIONS

Definitions

Asthma is an inflammatory disease characterized by recurrent episodes of lower airway obstruction and bronchial hyperresponsiveness to various stimuli.^{12,14} Symptoms accompanying lower airway obstruction

include cough, wheezing and dyspnea that may be triggered by exercise, viral respiratory infections or exposure to cold air or allergens. Airway obstruction is reversible, either spontaneously or following treatment.

In many clinical trials of anti-inflammatory medications given to preschool children with lower airway obstruction, frequency of “wheezing reported by parents” was one of the outcome measures used. In epidemiology studies the term describes an expiratory sound originating from narrowed large- and medium-diameter lower airways.¹⁵ In contrast to investigators, parents describe as “wheeze” not only the presence of a sound heard from the child’s chest but also other symptoms such as cough, difficulty breathing or “being unwell.”¹⁵ Moreover, parents have difficulty recognizing wheeze in children who have wheezing.¹⁶

A number of different terms have been used in the literature to describe frequency of symptoms consistent with lower airway obstruction. Both the GINA Report¹² and the NHLBI Guidelines-2002 Update¹³ classify asthmatic symptoms as *mild intermittent*, or *mild, moderate and severe persistent* and therefore similar terms can be used in young children. In the everyday clinical practice, pediatricians usually deal with two clinical presentations of lower airway obstruction affecting preschool children: (i) *intermittent (or episodic) wheezing* associated with viral respiratory infections and no symptoms between attacks;^{17,18} and (ii) *persistent wheezing* lasting several weeks with frequent recurrences. Persistent wheezing can be defined as:³ (i) daily symptoms lasting for at least 4 weeks; or (ii) five exacerbations of symptoms associated with lower airway obstruction within a period of 6 months. Intermittent or persistent wheezing during the first 5 years of life can be mild, moderate or severe in intensity.

It should be noted that the term “persistent” has also been used in the pediatric literature to characterize persistence of episodes of wheezing at 6 years of age when the initial episode presented prior to 3 years of age.¹⁹ In the present article, “persistent” refers to continuous or semi-continuous symptoms. Untreated preschool children experiencing intermittent viral-associated wheezing usually have 2–3 episodes per year mostly outside the summer period.⁵ Only a minority of preschool children experience persistent wheezing.²⁰

Which Preschool Children will Develop Asthma?

Because asthma frequently begins in early childhood,²¹ it is tempting for the physician to treat preschool children presenting with intermittent or persistent symptoms related to lower airway obstruction using antiasthmatic medications.

To maximize the efficacy of treatment with anti-inflammatory medications and to minimize the possibility of side effects, physicians need to have clear answers to the

following questions: (i) which preschool children with wheezing will develop asthma? (ii) which phenotypes of wheezing are responsive to anti-inflammatory medications? (iii) which subjects are at risk for developing persistent deficits in expiratory flow function? and (iv) what is the possibility of side effects from inhaled corticosteroids in relation to dosage and duration of treatment?

Interesting data on the different phenotypes and prognosis of wheezing during preschool years have been published recently. In a population-based birth cohort in Tucson (Arizona) over 800 children were followed up till the age of 16 years.^{2,19} History of wheezing at the age of 6 years was correlated with high risk for wheeze between ages 8 and 16 years. If the first episode of wheezing occurred prior to 3 years of age and wheeze episodes persisted at age 6 years, deterioration in expiratory flow function was identified during the first 6 years of life. Those children who wheezed prior to age 3 years but did not wheeze at 6 years of life had decreased expiratory flow function in early infancy probably related to congenitally small airways. Such children were at low risk for reported respiratory symptoms between 8 and 16 years of age.

Using data from the Tucson cohort, Castro-Rodriguez et al.²² identified factors present during the first 3 years of life that were associated with high risk for wheezing in the subsequent years (Tucson criteria). Modified Tucson criteria are summarized in Figure 1.

Potential Benefits From Anti-Inflammatory Treatment

The NHLBI Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 2) have defined as anti-inflammatory those medications (corticosteroids, leukotriene pathway modifiers, cromones, and methylxanthines) that can reduce markers of inflammation in airway tissues or secretions (i.e., inflammatory cells or mediators) as well as decrease airway hyper-

responsiveness.¹⁴ Corticosteroids reverse a range of inflammatory responses in contrast to other agents that block certain pathways of inflammation.

Potential benefits from the administration of anti-inflammatory medications to preschool children with symptoms of lower airway obstruction include: (i) reduction of severity of symptoms at rest or during exercise; (ii) decreased frequency of symptom recurrences, emergency department visits and hospitalizations and consequently improved quality of life; and (iii) prevention of deficits in lung function growth.^{12,14,23} A few studies have indicated a negative correlation between lung function level and duration of asthmatic symptoms prior to initiation of treatment.^{24,25} Based on these findings, it has been proposed that early introduction of inhaled corticosteroids may prevent development of persistent deficits in expiratory flow function.¹²⁻¹⁴ It has been speculated that lung function deficits are related to thickening of the airway epithelial reticular basement membrane.²⁶

Some important arguments against the early in life treatment strategy are the following: (i) many subjects with episodes of wheezing during the first 3 years of age do not have asthmatic symptoms later in life;² (ii) no consistent correlation has been found between reticular basement membrane thickness and duration of symptoms, level of expiratory flow function, or degree of mucosal eosinophilic inflammation;²⁶⁻³⁰ (iii) none of four well-designed clinical trials that have recruited preschool or school-age children with intermittent or persistent wheezing have revealed a sustained positive effect on lung function following long-term administration of inhaled corticosteroids compared to treatment with placebo;^{3,4,6,31} (iv) although prolonged treatment with inhaled corticosteroid initiated early in life controls frequent wheezing, symptoms recur after discontinuation of the medication⁴ and (v) at the present time there is not enough evidence indicating that prolonged treatment with inhaled

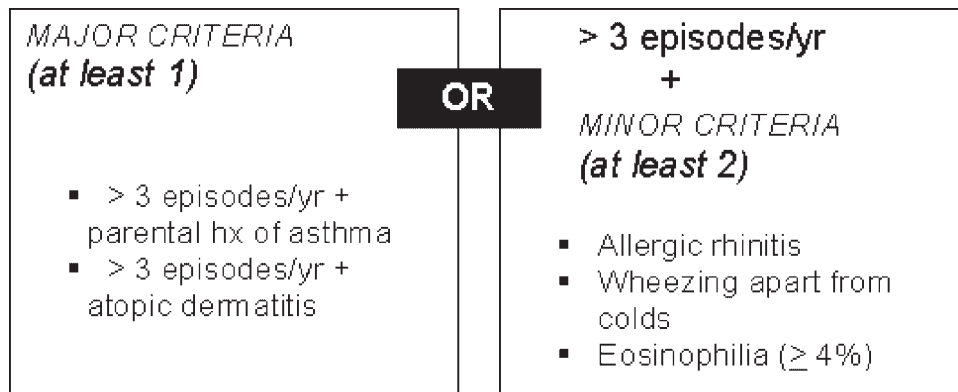


Fig. 1. Modified Tucson criteria for children aged less than 3 years who are at high risk for wheezing after 6 years of age according to Castro-Rodriguez and colleagues²² (modified according to the NHLBI Guidelines for the Diagnosis and Management of Asthma-2002 Update).¹³

corticosteroids is completely devoid of adverse effects. Three clinical trials studying the efficacy of prolonged administration of inhaled corticosteroids demonstrated a negative effect on the rate of linear growth.^{4,6,31} It is possible that there are other systemic adverse effects which have not yet been identified.

Studies Assessing the Efficacy of Anti-Inflammatory Treatment for Intermittent or Persistent Wheezing in Preschool Children: Methodologic Considerations

Appreciating the efficacy of anti-inflammatory medications in infants and young children with wheezing is a very difficult task. At least three issues are of particular importance when evaluating the efficacy of anti-inflammatory medications: (i) inclusion criteria for participation to the clinical trial (especially definition of study groups and severity of illness); (ii) type of interventions; and (iii) outcome variables that were selected to evaluate efficacy of medications.

Published studies have recruited preschool children with various phenotypes of wheezing: viral-associated wheezing,⁵ persistent symptoms of lower airway obstruction³² or wheezing accompanied by risk factors for the development of asthma.^{4,33} Interventions have also been very heterogeneous among the various investigations. In some trials, inhaled corticosteroids have been used³⁴ although in other studies participants have received cromolyn,³⁵ nedocromil,³¹ or leukotriene pathway modifiers.^{5,7} Some investigators have administered high doses of inhaled corticosteroids,³⁴ although others have chosen to give low doses of corticosteroids.^{3,36} Methods of administration of inhaled anti-inflammatory medications vary considerably: in many trials participants have received inhaled agents by an inhaler/spacer combination,³⁷ but in some studies a nebulizer has been used.³²

Outcome variables (efficacy end-points) in published trials have not been consistent. Some of the primary efficacy end-points have been the following: number of symptom-free days, daytime and nighttime symptom scores, need for bronchodilators, number of courses of systemic corticosteroids, number of hospitalizations or emergency department visits.³⁸ In a few studies, numerous efficacy measures have been selected and multiple comparisons among study groups have been carried out.^{39,40} The active medication has been found to be efficacious for some of the selected clinical parameters but not for others.

Measurement of expiratory flow function can be very useful especially in infants with persistent wheezing and history of atopy or maternal asthma.^{19,41} It is possible that infants with persistent symptoms are at risk for lung function growth deficits. Nevertheless, in the vast majority

of clinical trials, pulmonary function testing has not been selected as an outcome measure.

In summary, clinical trials of anti-inflammatory medications administered to preschool children with episodes of lower airway obstruction have been very heterogeneous regarding phenotypes of wheezing studied, types of interventions applied and primary efficacy end-points used. Methodologic heterogeneity among studies contributes to our uncertainty about the best therapeutic approach for preschool children with recurrent wheezing. At the minimum, children with viral-associated wheezing and without risk factors for asthma should be studied separately from subjects with persistent wheezing who fulfill the Tucson criteria (Fig. 1).

SYSTEMIC CORTICOSTEROIDS

A short course of oral corticosteroids has been proposed as an effective measure to improve symptoms, prevent emergency room visits and hospitalizations and decrease length of hospital stay in young children with severe wheezing or symptoms of upper respiratory tract infection and a history of severe viral-associated exacerbations (*Evidence D*).^{12,13,23,42} This expert opinion is supported by some but not all studies.

In a blinded study, 74 patients aged 7–54 months who presented to the emergency department with acute wheezing, were treated with either a single dose of intramuscular methylprednisolone (4 mg/kg) or normal saline as placebo.⁴³ Corticosteroid treatment significantly reduced the hospital admission rate (*Evidence B*). In an open trial of 32 children younger than 6 years with a history of severe wheezing associated with viral respiratory infections,⁴⁴ 16 of 32 children received prednisone (1 mg/kg/day) in addition to bronchodilators with the first sign of upper respiratory tract infection, while the remainder 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 double-blind, placebo-controlled and partial cross-over trial, 38 children aged less than 18 months with history of previous hospitalization for wheezing received either oral prednisolone (2 mg/kg/day) or placebo for 5 days during acute exacerbations of respiratory symptoms.⁴⁵ Daily symptom scores were similar between the two study groups during treatment (*Evidence B*). Another placebo-controlled trial assessed the effect of 20 mg of prednisolone given daily for 5 days to preschool children (1–5 years old) with history of viral wheeze during an episode of acute wheezing.⁴⁶ A total of 120 children were studied and no difference was found among the prednisolone and the placebo-treated groups regarding mean symptom score during a period of 7 days (*Evidence B*).

A number of methodologic weaknesses of the previous trial⁴⁶ should be mentioned. Administration of the study drug was initiated by parents irrespective to the severity of wheezing; parents also evaluated the child for the primary outcome measure of the trial (symptom score). Most participants had probably symptoms of mild severity; for example, the mean daytime respiratory symptom score for the placebo-treated group was 0.95 in a scale ranging from 0 to 3. Only 3% of subjects treated with placebo required hospitalization. It is possible that the modest number of participants did not allow identification of small differences in symptom score favoring prednisolone among children with mild symptoms. Clinical trials with larger number of subjects and more severe symptoms will probably have adequate power to clarify whether systemic corticosteroids ameliorate severity of acute wheezing in preschool children.

In conclusion, there is no strong evidence supporting the efficacy of systemic corticosteroids when administered to preschool children with previous history of severe lower respiratory symptoms at the first sign of viral respiratory infection in order to prevent an exacerbation. Administration of systemic corticosteroids may be considered in preschool children presenting with moderate to severe acute wheezing in an attempt to decrease severity of symptoms (*Evidence D*).^{12,13,23}

INHALED CORTICOSTEROIDS

Intermittent Viral-Associated Wheezing

As discussed previously, the term viral-associated wheezing has been introduced to describe a history of episodic symptoms related to upper respiratory tract infections and no findings between attacks.^{17,18} Viral upper respiratory tract infections are associated in time with asthma exacerbations leading to hospital admissions in both children and adults.⁴⁷ They have been identified in 80–85% of asthma exacerbations in school-age children in the community.⁴⁸ Furthermore, the majority of wheezing episodes in infants occur concomitantly with a viral respiratory infection.⁴⁹ 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.

A systematic review in the Cochrane Library evaluated inhaled corticosteroid treatment given intermittently or daily to children younger than 17 years of age with recurrent mild episodes of wheezing related to viral upper respiratory tract infections.¹⁷ Some of the reviewed studies included preschool children with viral-induced wheezing who received either high-dose inhaled corticosteroid at the onset of an upper respiratory tract infection,^{50–52} or continuous treatment with a low-dose of inhaled corticosteroid.³⁶ Results of the review showed

that intermittent use of high-dose inhaled corticosteroid (1,600–3,200 mcg/day of beclomethasone dipropionate or budesonide) decreased the severity of symptoms (*Evidence B*). There was also a trend for reduced requirement for oral corticosteroids. No benefit in the severity of symptoms, or the need for systemic corticosteroids and hospital admission was identified with low-dose inhaled corticosteroid (400 mcg/day of budesonide for 4 months). This last conclusion was based on two randomized, double-blind, placebo-controlled trials of which only one included preschool children.³⁶

At least 1 more study appeared in the literature after the Cochrane review was published. In the Prevention of Asthma in Childhood (PAC) study, 294 infants received randomly a 2-week course of inhaled budesonide (400 mcg/day) or placebo for episodes of wheezing occurring between 1 month and 3 years of age.³ All recruited infants had a maternal history of asthma. Randomization was performed after the first episode of wheezing and for each episode the medication was initiated after the third day of symptoms. Number of symptom-free days, number of episodes of wheezing, time from randomization to study discontinuation due to development of persistent wheezing and average duration of each exacerbation were some of the selected outcome measures. Over the almost 3 years of the investigation, there were no differences among the two study groups regarding the selected efficacy measures (*Evidence A*). At the age of 3 years, the two groups had similar specific airway resistance. Initiation of treatment 3 days after the onset of symptoms,⁵³ and the low dose of budesonide (400 mcg/day) used may have been potential reasons for the lack of efficacy of the active medication in ameliorating intensity of symptoms.

Persistent Wheezing

Persistent wheezing during preschool years may be the initial clinical presentation of bronchial asthma.²¹ A systematic review addressed the efficacy of prophylactic inhaled corticosteroid in childhood asthma.⁵⁴ Ten of 24 trials included in the review, involved preschool children with persistent wheezing (377 subjects) who received placebo, beclomethasone dipropionate (150–400 mcg/day), or budesonide (300–2,000 mcg/day) for 4–24 weeks. Compared to placebo, inhaled corticosteroids decreased the mean total symptom score and mean concomitant β_2 -agonist and oral steroid use, and increased mean peak expiratory flow rate in asthmatic children (*Evidence B*). There was no statistically significant difference in the rate of hospital admissions; however only 3 of 10 trials with preschool children used this outcome variable.

In the NHLBI Guidelines for the Diagnosis and Management of Asthma-2002 Update¹³ indications for

long-term administration of inhaled corticosteroids to children of preschool age are summarized as follows:

- (1) Symptomatic treatment required more than twice a week.
- (2) Severe exacerbations of wheezing less than 6 weeks apart.
- (3) More than three episodes of wheezing in the past year, lasting more than 1 day and affecting sleep provided that the Tucson criteria are fulfilled (Fig. 1).

The Prevention of Early Asthma in Kids (PEAK) study was a multicenter, double-blind, placebo-controlled trial that recruited 2- to 3-year-old children at high risk for asthma according to the Tucson criteria.⁴ All children had at least four episodes of wheezing during the year prior to enrolment to the study and an indication for prophylactic treatment according to the NHLBI Guidelines.¹³ Two hundred and eighty-five participants received inhaled fluticasone propionate (176 mcg/day) or placebo for 2 years. While children were receiving inhaled corticosteroids, they had significantly higher mean proportion of episode-free days (93.2% vs. 88.4%), less need for systemic corticosteroids, better lung function but similar number of hospitalizations compared to subjects receiving placebo (*Evidence A*). However, during the observation year following the 2-year intervention period, the two groups were similar in the proportion of episode-free days (primary efficacy measure), number of exacerbations, use of systemic corticosteroids, number of hospitalizations or lung function (impulse oscillometry). Thus, in children at high risk for asthma prolonged treatment with inhaled corticosteroids that was initiated early in life did not prevent development of asthma-like symptoms after discontinuation of the medication (*Evidence A*).

In the Inhaled Fluticasone in Wheezy Infants (IFWIN) study,⁶ 200 young children (age range 0.5–4.9 years) with parental history of atopy were randomized to receive either inhaled fluticasone propionate (200 mcg/day) or placebo if they had two episodes of wheezing or persistent wheezing lasting more than 1 month. The dose of the study drug was tapered every 3 months according to control of symptoms. By the third month of treatment, children in the fluticasone group had significantly lower symptom score, fewer unscheduled visits for wheeze and similar number of exacerbations compared to subjects in the placebo group (*Evidence A*). Nevertheless, at the age of 5 years the fluticasone group was similar to the placebo group in the proportion of participants with current wheeze, physician-diagnosed asthma, use of asthma medication, lung function and airway reactivity (eucapnic voluntary hyperventilation challenge; *Evidence A*).

Nine additional randomized, double-blind, placebo-controlled trials published after the meta-analysis are summarized in Table 1.^{32,33,39–41,55–58} Results of these

trials are in accordance with findings of the systematic review.⁵⁴

In summary, continuous treatment with inhaled corticosteroids decreases the number of days with symptoms in children with persistent wheezing without preventing the need for hospitalization. Using as an example the PEAK study,⁴ it can be stated that children treated with a low dose of inhaled fluticasone have an average of 5% fewer days with symptoms (or 18 days per year) than children receiving placebo. It is arguable whether this increase in symptom-free days is clinically significant. The “cost” for this beneficial effect is a negative impact of the medication on linear growth and possibly other-yet unrecognized-systemic adverse effects (see “Systemic effects of inhaled corticosteroids”). Therefore, it could be proposed that only selected children with troublesome symptoms and frequent need for systemic glucocorticosteroids should receive inhaled corticosteroids as maintenance treatment.

Systemic Effects of Inhaled Corticosteroids

Inhaled corticosteroids reach the systemic circulation and possibly cause side effects via three routes:^{12,14,59} (i) 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.^{60,61} (ii) 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%.⁵⁹ (iii) Medication deposited in the mouth and not swallowed may be systemically absorbed without undergoing first pass metabolism in the liver.¹²

It is possible that long-term use of inhaled corticosteroids can affect function of the hypothalamic-pituitary-adrenal axis, linear growth and bone metabolism or possibly result in cataracts or glaucoma. There are few data supporting the occurrence of such adverse effects in preschool children treated with either short-term or long-term inhaled corticosteroids. Interpretation of the published literature is complicated by the fact that various studies have used different methods to assess function of the hypothalamic-pituitary-adrenal axis.^{62,63}

Level A Evidence

The short-term safety of budesonide inhalation suspension was assessed in a multicenter, 12-week, double-blind, placebo-controlled trial of 1,017 infants and children (6 months to 8 years old) with persistent asthma who were

TABLE 1—Studies Assessing the Role of Inhaled Corticosteroids to Preschool Children With Persistent Wheezing not Included in the Meta-Analysis by Calpin et al.⁶¹

First author (year)	Type of study—evidence level	Number of subjects completing study—age range—Atopic status	Active medication (mcg/day)	Outcomes	Favorable outcome for ICS
Baker et al. (1999) ³²	Randomized Double-blind Placebo-controlled A	386 BUD 95 placebo 6 months to 8 years	BUD (250–1,000) for 12 weeks	Daytime symptom score Nighttime symptom score	Yes (BUD 500–1,000) Yes (BUD 500–1,000)
Bisgaard et al. (1999) ⁵⁵	Randomized Double-blind Placebo-controlled A	80 FP-100 mcg 76 FP-200 mcg 81 placebo 12–47 months	FP (100–200) for 12 weeks	Cough-free days Wheeze-free days Cough-free nights ¹ Wheeze-free days ¹ Number of exacerbations ¹	Yes (FP-200) Yes Yes Yes Yes (FP-200)
Nielsen and Bisgaard (2000) ⁴⁰	Randomized Double-blind Placebo-controlled B	19 BUD 19 placebo 35–71 months	BUD (800) for 8 weeks	Daytime symptom score Nighttime symptom score Symptom-free days Symptom-free nights Daytime rescue medication Nighttime rescue medication Number of exacerbations	No Yes Yes No Yes No Yes
Chavasse et al. (2001) ⁵⁶	Randomized Double-blind Placebo-controlled B	19 FP 18 placebo 3–12 months Atopic	FP (300) for 12 weeks	SR _{aw} ¹ R _{int} ¹ R _{rs} ⁵ ¹ X _{rs} ⁵ ¹ CACH ¹ MCh ¹ Symptom score Symptom-free days	No Yes Yes Yes Yes No Yes Yes
Roorda et al. (2001) ³⁹	Randomized Double-blind Placebo-controlled A	152 FP 153 placebo 12–47 months 169 children with frequent wheezing	FP (200) for 12 weeks	Symptom-free days and nights Bronchodilator use ¹	Yes (frequent symptoms subgroup) Yes (frequent symptoms subgroup)
Pao and McKenzie (2002) ⁵⁷	Randomized Double-blind Placebo-controlled Cross-over B	61 2–5 years Atopic/non-atopic	FP (200) for 6 weeks	R _{int} BDR Symptom score	Yes (atopic subgroup) Yes (atopic subgroup) No
Teper et al. (2004) ³³	Randomized Double-blind Placebo-controlled B	10 FP-100 mcg 10 FP-250 mcg 10 placebo 6–24 months	FP (100–250) for 6 months	Number of exacerbations Bronchodilator use	Yes Yes

(Continued)

TABLE 1—(Continued)

First author (year)	Type of study-evidence level	Number of subjects completing study-age range-Atopic status	Active medication (mcg/day)	Outcomes	Favorable outcome for ICS
Teper et al. (2005) ⁴¹	Randomized Double-blind Placebo-controlled B	14 FP 12 placebo 7.5–20 months	FP (250) for 6 months	V'_{maxFRC} Symptom-free days Number of exacerbations Bronchodilator use	Yes No Yes Yes
Hofhuis et al. (2005) ⁵⁸	Randomized Double-blind Placebo-controlled B	40 FP 22 placebo 4–24 months Atopic/non-atopic	FP (200) for 13 weeks FRC_{1p} R_{int1} Symptom score ¹ Symptom free days ¹ Bronchodilator use ¹	V'_{maxFRC} FRC_{1p} R_{int1} Symptom score ¹ Symptom free days ¹ Bronchodilator use ¹	No No No Yes at 6 weeks Yes at 6 weeks No

BDR, bronchodilator responsiveness; CACh, cold air challenge; FP, fluticasone propionate; FRC_{pr} , functional residual capacity by plethysmography; ICS, inhaled corticosteroid; MCh, metacholine challenge; R_{int} , interrupter resistance; R_{rs} , airway resistance at 5 Hz by impulse oscillation technique; SR_{aw} , specific airway resistance; V'_{maxFRC} , maximum forced expiratory flow at functional residual capacity by rapid thoracoabdominal compression technique; X_{rs5} , airway reactance at 5 Hz by impulse oscillation technique.
¹Secondary outcome measure.

allocated randomly to one of the following treatment groups: placebo, or budesonide 250 mcg/day, 500 mcg/day, 1,000 mcg/day, or 2,000 mcg/day.⁶⁴ There were no significant differences between the placebo and the budesonide study groups in basal or ACTH-stimulated cortisol levels.

In the PEAK study,⁴ when 2- to 3-year-old children who received fluticasone propionate (176 mcg/day) were compared to the placebo-treated group, they had a mean difference of -1.1 cm at the end of the 2-year treatment period and -0.7 cm at 1 year later. At the end of the observation period (1 year after treatment), the average height percentile for the fluticasone group was 54.4 and for the placebo group 56.4. Therefore, the steroid-treated group had acceleration in linear growth rate after discontinuation of the medication, and it is possible that height would become similar in the two treatment groups over time.

In the IFWIN study,⁶ those children (0.5–4.9 years old) who were randomized to receive inhaled fluticasone propionate (200 mcg/day) had a significant decrease in height Z score after 6 months of treatment relative to subjects who received placebo. Dose of the study medication was decreased or discontinued according to control of symptoms. At the 5th birthday both the active medication and the placebo groups had similar change in height Z score comparatively to the pre-treatment Z score (Evidence A). All fluticasone-treated children received the medication for at least 9 months.

Some further long-term data on the effect of inhaled budesonide, administered intermittently were provided by the PAC study.³ After 3 years in the trial, budesonide-treated and placebo-treated infants did not have a difference in standing height or bone mineral density. No information was presented about any changes in height Z score or position in percentile curves of individual subjects in relation to number of budesonide courses received by each participant over the duration of the study.

Level B and C Evidence

Three studies with level B evidence^{33,65,66} and six studies with level C evidence^{67–73} on the systemic effects of inhaled corticosteroids are summarized in Table 2. Three of nine studies revealed a suppressive effect of inhaled budesonide on the hypothalamic-pituitary-adrenal axis or on linear growth.

Systemic glyocorticosteroids administered during the first 2 weeks of life to rats have an adverse effect on alveolar development.⁷⁴ More specifically, excessive glyocorticosteroid during a critical time of early lung development in the rat induces alveolar wall thinning and microvascular maturation and it suppresses outgrowth of new interalveolar septa.⁷⁵ These are signs of precocious maturation of the developing lung. The effect of nebulized

TABLE 2—Adverse Effects of Inhaled Corticosteroids in Preschool Children (Evidence B and C)

First author (year)	Evidence level	Age-number of treated patients	Steroid (mcg/day) duration of therapy	On adrenal function	On bone metabolism	On linear growth
Bisgaard (1993) ⁶⁵	B	13–36 months 18	BUD (200) BUD (400) Placebo 4 weeks of each treatment	NR	NR	Yes
Anhoj et al. (2002) ⁶⁶	B	1–3 years 40	BUD (400) FP (400) Placebo 4 weeks of each treatment	NR	NR	Yes
Teper et al. (2004) ³³	B	6–24 months 30	FP (100) or FP (250) or Placebo for 6 months	No	NR	No
Gleeson and Price (1988) ⁶⁷	C	2–6 years 28	BUD (400) for 6 weeks	No	NR	NR
Varsano et al. (1990) ⁶⁸	C	3.5–7 years 16	BUD (200) for 12 months	No	NR	No
Volovitz et al. (1993) ⁶⁹	C	2–7 years 15	BUD (200) for 3–5 years	No	NR	No
Le Bourgeois et al. (1995) ⁷⁰	C	9–53 months 11	BDP (500–860) for 4.5–7.5 months	NR	No	NR
Wennergren et al. (1996) ⁷¹	C	5–47 months 102	BUD (500–2,000) for 18 weeks	Yes	NR	NR
Reid et al. (1996) ⁷²	C	0.3–3 years 40	BUD (1,000–4,000) for 0.5–1.5 years	NR	NR	No
Bisgaard et al. (2004) ⁷³	C	1–3 years 625	FP (200) or Cromolyn(20 mg)	No	NR	No

BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate; NR, not reported.

budesonide was recently studied in rabbits with ages 1–5 weeks.⁷⁶ Treatment with inhaled corticosteroid was related to decreased lung volume, peripheral airway wall thickness and number of alveolar attachments to the airways. These data from animal studies have raised concerns that inhaled corticosteroids given during the first 5 years of life may adversely affect lung growth.⁷⁷ At the present time, there is no evidence from human studies supporting this concept.

Rare adverse effects of inhaled corticosteroids, like acute adrenal insufficiency and tongue hypertrophy, have been reported. A 21-month-old asthmatic boy had a hypoglycemic seizure during a proven acute adrenal crisis secondary to high-dose nebulized budesonide treatment (up to 8,000 mcg/day for 14 months).⁷⁸ 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.⁷⁹ This adverse effect appeared 2–4 weeks following initiation of treatment, and disappeared gradually after discontinuation of therapy.

In summary, inhaled corticosteroids administered to preschool children with wheezing may affect linear growth or the function of the hypothalamic-pituitary-adrenal axis as indicated by relevant tests. The clinical significance of the above findings is currently

unknown and further investigation of this area is necessary.

NON-STEROIDAL ANTI-INFLAMMATORY MEDICATIONS

Leukotriene Pathway Modifiers

Two classes of medications are classified under the term leukotriene pathway modifiers: (i) leukotriene synthesis inhibitors (zileuton); and (ii) cysteinyl leukotriene receptor antagonists (Cys-LTRAs; montelukast, pranlukast, zafirlukast). In three trials evaluating the use of montelukast in asthmatic children, a decrease in the concentration of exhaled nitric oxide was noted after 2–4 weeks of treatment.^{80–82} In an observational study, asthmatic children who were treated with montelukast had lower cysteinyl leukotriene levels in exhaled breath condensate than those who were not.⁸³

Montelukast is the main Cys-LTRA studied in preschool children. Over the last 5 years, data from two well-designed clinical trials on the use of montelukast in preschool children have been reported. In a multicenter, double-blind, placebo-controlled trial, 689 subjects aged 2–5 years and with physician-diagnosed asthma were treated with montelukast (4 mg daily) or placebo for 12 weeks.⁷ Children had at least three episodes of

symptoms during the previous year and a predefined level of daytime asthma symptoms. Participants in the montelukast study group improved significantly more than patients treated with placebo, in several clinical parameters related to asthma: daytime and nighttime asthma symptoms, percentage of days without symptoms, need for β_2 -agonist or oral corticosteroid, and physician global evaluation⁷ (*Evidence A*).

In a second randomized, multicenter, double-blind, parallel-group study, 549 2- to 5-year-old children with history of asthma exacerbations associated with respiratory infections and minimal symptoms between episodes were recruited.⁵ Participants received either montelukast 4–5 mg/day or placebo for 48 weeks. The average yearly exacerbation rate (primary efficacy end-point) was significantly lower in children receiving montelukast (1.6 episodes; 95% confidence interval: 1.35–1.88) than in subjects receiving placebo (2.34; 1.97–2.79; *Evidence A*). Oral corticosteroids use and number of hospitalizations were similar among the two study groups, although montelukast did not affect the average duration and severity of exacerbations.

Of note, children with viral-associated wheezing receiving placebo had a low average yearly rate of exacerbations (2.34 episodes).⁵ Montelukast decreased the average frequency of exacerbations by about one episode per year without affecting the severity of symptoms and the number of hospitalizations. Intermittent use of orally administered and/or high-dose inhaled corticosteroids may be a more effective measure in reducing the morbidity from viral-associated wheezing than chronic administration of leukotriene pathway modifiers.

Cromolyn and Nedocromil

The safety of long-term treatment of young children with cromones is supported by the lack of serious adverse effects in multiple studies. There are only rare reports of adverse incidents such as urticaria, angioedema, bronchospasm, anaphylaxis, and pulmonary infiltrates with eosinophilia, which have been summarized in a review article.⁸⁴ When airway biopsies were taken from adult asthmatic patients treated with sodium cromoglycate, decreased numbers of eosinophils, lymphocytes and mast cells infiltrating the bronchial mucosa were found compared to placebo-treated subjects.⁸⁵

A Cochrane review summarized results of 15 trials of inhaled nedocromil administered to children with asthma (a total of 1,422 children).⁸⁶ Short-term studies included in the meta-analysis showed that nedocromil improved symptom scores and spirometry indices in comparison to placebo. In contrast, long-term (>6 months) studies in which the outcome measure was symptom-free days provided conflicting results (*Evidence B*).

Another Cochrane Review of 24 randomized, placebo-controlled trials of cromolyn that involved more than

1,000 subjects assessed a variety of outcomes to evaluate the efficacy of the medication.⁸⁷ There was no difference between children treated with placebo and those who received cromolyn regarding symptom-free days (primary outcome measure). For day wheeze score, overall symptom/severity score and use of bronchodilators, the difference between cromolyn and placebo favored the former. Cromolyn and placebo were similar in day cough score, steroid use and hospital admission rate. The meta-analysis concluded that there is insufficient evidence to support the superiority of cromolyn over placebo in children with asthma (*Evidence B*).

In the GINA Report-2005 Update and the NHLBI Guidelines-2002 Update, cromones are proposed as an alternative anti-inflammatory medication to inhaled corticosteroids for preschool children with mild persistent symptoms.^{12,13} The British Thoracic Society Guideline on the Management of Asthma has evaluated the evidence of benefits of cromolyn in childhood as contentious and for this reason the medication is not recommended for use in preschool children.²³

Although there is clear evidence that inhaled corticosteroids are superior to cromones in asthma control (lower symptom scores, fewer exacerbations, better lung function, less need for bronchodilators),⁸⁸ no randomized, double-blind trials have directly compared cromolyn to leukotriene pathway modifiers. Some indirect comparisons of the two classes of medications can be made using published data. The additional decrease in mean overall symptom score with cromolyn over placebo as calculated in the Cochrane meta-analysis was -0.19 (95% confidence interval -0.07 to -0.32).⁸⁷ The relative decrease in symptom score related to the administration of montelukast to preschool children with persistent wheezing was similar: -0.12 (-0.2 to -0.04).⁷ Furthermore, the decrease in daytime wheeze score was -0.11 (-0.19 to -0.03) with cromolyn⁸⁷ and -0.09 (-0.17 to 0.00) with montelukast.⁷

In summary, studies with better methodology comparing cromones administered to preschool children with wheezing to leukotriene pathway modifiers or placebo are necessary. These trials should study children with intermittent viral-associated wheezing separately from subjects with persistent wheezing.

Methylxanthines

In the NHLBI Guidelines-2002 Update,¹³ addition of theophylline to low-dose inhaled corticosteroid is recommended as an alternative treatment to medium-dose inhaled corticosteroid for the treatment of moderate persistent symptoms (*Evidence D*). Theophylline acts as a bronchodilator in preschool children.⁸⁹ Airway biopsies in adult asthmatic patients who received long-term treatment with theophylline showed that the medication has also immunomodulatory effects.⁹⁰

A Cochrane review analyzed 34 randomized trials in children with asthma (18 months to 18 years old) that compared administration of methylxanthines with placebo, short-acting bronchodilators, inhaled corticosteroids, or cromolyn for at least 4 weeks.⁹¹ The studies recruited a total of 2,734 children. Inhaled corticosteroids were superior to methylxanthines in terms of decreasing number of exacerbations and intensity of symptoms, but methylxanthines were better than placebo in increasing symptom-free days. There were no differences in symptoms or use of rescue medication between theophylline and regular administration of bronchodilators or cromolyn (*Evidence B*). Evidence on the addition of methylxanthines to inhaled corticosteroids was inconclusive.

The most frequent side effects of theophylline are headache, nausea, vomiting, and anorexia.⁹² In a systematic review of 12 pediatric studies, no behavioral or cognitive adverse effects of theophylline were identified (*Evidence B*).⁹³

Ketotifen and Cetirizine

Ketotifen is an antihistamine that has been used for years in European and other countries as an orally administered agent for the control of mild asthma. A Cochrane review summarized 26 studies involving 1,826 subjects aged 4 months to 18 years.⁹⁴ The medication was administered at a dose of no less than 1 mg daily for at least 8 weeks. The meta-analysis concluded that ketotifen was superior to placebo in reducing the asthma symptom score, the frequency of asthma exacerbations, the need for bronchodilators and the use of oral corticosteroids (*Evidence B*).

Cetirizine is another antihistamine that has been tested as a prophylactic agent for asthma in young children. In the Early Treatment of the Atopic Child (ETAC) study,⁹⁵ cetirizine (0.25 mg/kg) or placebo were given to infants with atopic dermatitis for 18 months to assess whether the active medication can suppress or delay the onset of asthma. A total of 549 children had follow-up for a period of 18 months after completion of treatment. Over the 36 months of the study, no difference was identified in cumulative prevalence of asthma among the cetirizine and the placebo study groups (*Evidence A*). In subgroup analysis, over the duration of the study and among subjects sensitized to grass pollen, there was decreased prevalence of asthma in the cetirizine-treated group compared to the placebo-treated group.

CONCLUSIONS

- Our knowledge about the natural history of wheezing in preschool children has improved.

Children with wheezing in the first 3 years of life are at high risk for asthma in late childhood and

adolescence if the Tucson criteria are fulfilled (Fig. 1). Presence of wheezing at the age of 6 years is associated with high risk for asthma in subsequent years. Intermittent, viral-associated wheeze in the first 3 years of life without risk factors for asthma has usually a benign prognosis.

- Short courses of systemic corticosteroids may be administered in an effort to ameliorate severity of moderate-to-severe acute wheezing.

Published evidence supporting this statement is limited. Episodic use of high-dose inhaled corticosteroid (>1,600 mcg/day of beclomethasone dipropionate or equivalent) may decrease severity of intermittent viral-associated wheezing.

- NHLBI Guidelines for the Diagnosis and Management of Asthma-2002 Update¹³ summarize indications for long-term administration of anti-inflammatory medications to children of preschool age.

Long-term controller therapy is recommended for children who: (i) require administration of bronchodilators for more than 2 days per week or (ii) have severe exacerbations of symptoms more frequently than every 6 weeks; or (iii) have more than three episodes of wheezing in the past year, which last more than 1 day and affect sleep provided that the Tucson criteria are fulfilled (high risk for asthma; Fig. 1).

- Inhaled corticosteroids are suggested as the preferred maintenance anti-inflammatory treatment in the NHLBI Guidelines.¹³

Inhaled corticosteroids control symptoms but do not seem to alter the natural history of wheezing. Leukotriene receptor antagonists, cromolyn or methylxanthines are suggested as alternative medications in young children with mild persistent symptoms. There are no studies assessing the relative efficacy of cromones and leukotriene receptor antagonists in controlling symptoms and preventing recurrences.

- Inhaled corticosteroids are systemically absorbed.

Deceleration in linear growth rate is the most frequent recognized systemic adverse effect of maintenance treatment with inhaled corticosteroids.

FUTURE RESEARCH

- Published studies on the efficacy of anti-inflammatory medications when administered to preschool

children with wheezing are very heterogeneous regarding phenotypes of wheezing studied, interventions applied and outcome measures used. Future national and international consensus statements on asthma should set research goals for the diagnosis and treatment of wheezing in preschool children and suggest the most appropriate methodology to achieve these goals.

- Children with persistent wheezing treated with inhaled corticosteroids do not have better lung function as a group in the long term when compared to untreated patients. However, one cannot exclude the possibility that there are individual children with severe symptoms and progressive lower airway obstruction who will get a benefit in expiratory flow function from inhaled corticosteroids.⁹⁶ Criteria to recognize such patients should be developed.
- It is uncertain whether deceleration in linear growth rate related to maintenance treatment with inhaled corticosteroids is fully reversible after discontinuation of the medication. More studies are required to exclude the possibility of other unrecognized systemic adverse effects.
- It would be useful to evaluate the efficacy of cromolyn and nedocromil in comparison to leukotriene pathway modifiers in well-designed clinical trials. It is still unknown whether substitution of non-steroidal medications for inhaled corticosteroids, as symptoms improve, is efficacious and decreases the risk for potential side effects.

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