THE PEDIATRIC CLINICS OF NORTH AMERICA

Pediatr Clin N Am 50 (2003) 631–654

Treating the wheezing infant

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The care for infants and small children with wheezing episodes is a challenging endeavor because of the multiple issues involved in identification of patients who need interventions, age-specific methods of administration of medications, use of appropriate medications, and lack of objective measures to diagnose or assess disease control. Two fundamental questions need to be addressed in the treatment of young children with wheezing. The first is whether the young child with wheezing has a diagnosis of asthma or is a child with transient wheezing. This distinction is important because the response to medication is different in the two conditions. An approach to distinguish these two populations is discussed in the article on the natural history of asthma. The second fundamental question, asked once the diagnosis of persistent asthma is made, is considers when is it appropriate to start controller therapy.

The decision to treat an acutely wheezing child with asthma is usually not difficult, because bronchodilator medications, supplemental oxygen if needed, and systemic glucocorticoids are readily accepted therapy, and response is usually rapid with minimal adverse effects expected. The treatment of the infant or young child with acute wheezing, in the absence of a definitive diagnosis of asthma, is less clear. Studies of the pharmacologic treatment of acute wheezing in infants seem to be confounded by the heterogeneous population included in the investigations. Whether to use bronchodilators, systemic or inhaled corticosteroids, or leukotriene modifiers during these acute episodes is poorly defined.

The other challenging decisions relate to administration of controller therapy. Why should special considerations be made to treat wheezing in young children? First, asthma in young children affords a significant burden on health care use. The prevalence of asthma in children has increased from 3.6% in 1980 to 8.7% in

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doi:10.1016/S0031-3955(03)00051-8

2001. There are approximately 6.3 million children with asthma. Admission rates for children younger than 4 years of age with asthma are greater than those of all other age groups, and they account for a significant proportion of the high annual rate in asthma mortality [1]. In addition, younger children with asthma are more likely to have multiple admissions to the hospital for acute exacerbations [2]. Furthermore, in a retrospective analysis of 49 asthmatic children whose mean age was 5.2 years (range, 2 months to 16 years) admitted to a community-based pediatric intensive care unit over a 10-year period, 75% were 6 years of age and younger [3]. A significant number of parental missed workdays are incurred while caring for acutely ill children.

Another important reason why controller therapy for wheezy infants and younger children has gained recent favor is the growing interest in determining whether intervention at the earliest stages of asthma will alter the long-term outcome of the disease, given that most asthmatics have onset of the disease in the first 4 years of life. Epidemiologic studies suggest that the cumulative prevalence of asthma is as high as 22% by the age of 4 years [4,5].

Recently published clinical practice guidelines have attempted to address special issues in the management of asthma in young children [6,7]. The diagnosis of wheezing in young children is based largely on clinical judgment (ie, an assessment of symptoms and physical findings), because lung function measurements in infants and small children are not available clinically. In differentiating transient wheeze from persistent asthma in infants and toddlers, one must frequently rely on family history as a risk factor, because the young child's allergic status is often not known. The first practical consideration in approaching the wheezing child is to ascertain that an alternative diagnosis is not being overlooked. The differential diagnosis of wheezing in infants and toddlers includes foreign body aspiration, congenital airway and heart anomalies, abnormalities of the great vessels, cystic fibrosis, recurrent aspiration, immunodeficiency, pulmonary infections, ciliary dyskinesia, and mediastinal masses. The correct diagnosis is essential because the treatments for these conditions can vary substantially. A practical approach that can be considered for a young child in whom asthma is strongly suspected is an empiric trial of asthma controller therapy while other evaluations are still being pursued.

Because recurrent wheezing in young children represents a heterogeneous group of disorders with different risk factors and prognoses, it can be difficult to make a definitive diagnosis of asthma in this age group. As a result, many young children at risk for asthma are not treated with appropriate controller medications. At present, atopy seems to be the only consistent risk factor for the subsequent development of asthma. The young child with a diagnosis of eczema or a confirmed history of allergic rhinitis seems to be at greater risk for persistent asthma. Unfortunately for the infant and toddler, the diagnosis of allergic reactivity may be unclear.

A landmark study from the Tucson Children's Respiratory Group has shown that there are several subtypes of recurrent wheezers. The investigators enrolled more than 1000 newborns served by a large health maintenance organization to

evaluate for factors involved in early-onset wheezing and its relation to persistent wheezing at 6 years of life [8]. Nearly one third of the cohort had at least one episode of wheezing by 3 years of age. Only 40% of these early wheezers had persistent wheeze at 6 years of age, representing 14% of the entire cohort with wheezing both before 3 years and at 6 years of age. Those children who had early-onset wheezing that persisted at 6 years of life were more likely to have a positive maternal history of asthma, elevated IgE levels with normal lung function at 1 year, and low lung function with elevated IgE levels at 6 years. Twenty percent of the total group had at least one episode of wheezing associated with a respiratory tract infection during the first 3 years of life but had no wheezing at 6 years. Those children who had early-onset transient wheezing were more likely to have diminished airway function in infancy and a history of maternal smoking and were less likely to be atopic. Fifteen percent of the children did not wheeze during the first 3 years of life but had wheezing at 6 years. The percentage of atopic children was similar in late-onset and persistent wheezers, and atopic late wheezers were also likely to have mothers with asthma. Hence, a similar genetic predisposition for the asthma phenotype seems to characterize persistent and late-onset wheezers. It is still not certain whether the late-onset wheezers are a distinct group from the persistent wheezers. One must also remember that this study addressed the risk of persistent asthma in the population; for an individual young child with wheezing, this variable might be difficult to assess. Further, lung function and measures of IgE are frequently not available when the infant appears in the emergency department with the first or even a third episode of wheezing with a viral illness.

Who then should be treated with controller therapy? The recently published executive summary from the National Asthma Education and Prevention Program (NAEPP) expert panel report [6] considers initiation of a controller therapy in young children who require symptomatic treatment more than twice a week or presence of severe exacerbations less than 6 weeks apart. In addition, controller therapy is recommended for "infants and young children who have had more than 3 episodes of wheezing in the past year that lasted more than 1 day and affected sleep and who have risk factors for the development of asthma (parental history of asthma or physician-diagnosed atopic dermatitis or 2 of the following: MD-diagnosed allergic rhinitis, wheezing apart from colds, and peripheral blood eosinophilia)." This set of criteria is based largely on the asthma predictive index using the stringent criteria proposed in another important study from the Tucson Respiratory Study Group [9].

Adult and pediatric studies have demonstrated the beneficial effects of introduction of inhaled glucocorticoids closer to the time of asthma diagnosis or onset of symptoms, suggesting an amelioration of the disease process is possible [10,11]. It is imperative that a careful selection be made of children who would likely benefit from a treatment strategy, with the hope that the natural history of asthma can be altered. Whether early intervention with any therapy can alter the subsequent outcome of recurrent wheezers in infancy remains an unresolved issue. Reijonen et al [12] sought to determine if early anti-inflam-

matory therapy would protect against subsequent development of asthma. Eighty-nine children 2 years old or younger who were hospitalized for infection associated with wheezing were enrolled to receive 4 months of budesonide, cromolyn, or no treatment and were followed for 3 years. The investigators found that a 4-month course of anti-inflammatory therapy did not change the occurrence of asthma 3 years later, with approximately half of the children in the cromolyn, budesonide, and control groups having current asthma.

The fact that a 4-month course of anti-inflammatory did not prevent the development of repeated wheezing episodes is not at all surprising. A 4-month course of anti-inflammatory therapy is unlikely to provide sufficient time to have disease-modifying effects. A large multicenter trial, the Prevention of Early Asthma in Kids (PEAK) study, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Research and Education Network, will attempt to determine whether long-term therapy can alter the outcome of young children predisposed to the development of asthma. Almost 300 children 24 to 48 months of age with recurrent wheezing identified as predisposed to develop asthma using a modified asthma predictive index have been enrolled to receive a 2-year course of inhaled glucocorticoid or matching placebo two times per day. The primary outcome variable is the prevalence of active asthma in the year after study medications are discontinued. This study should provide critical information regarding the role of an anti-inflammatory agent administered soon after the onset of the disease.

Controller therapy for small children with recurrent wheezing

Asthma management using a step-wise approach is advocated in the recently released NHLBI/NAEPP executive summary [6] update on clinical guidelines for the diagnosis and management of asthma (Table 1). The choice of controller therapy for young children (< 6 years of age) is still largely dependent on the frequency of daily and nighttime symptoms, with a classification system similar to that used for older children and adults except for the exclusion of lung function tests, because these children cannot perform those maneuvers. Inhaled glucocorticoid therapy administered either by the nebulizer or by pressurized metered dose inhaler (pMDI), with holding chamber with or without a face mask, or by dry powder inhaler (DPI) is now recommended for all levels of asthma severity except for the mild intermittent category. Cromolyn, leukotriene-receptor antagonists (LTRAs), and nedocromil are listed alphabetically (the expert panel determined that there were no perceived differences among therapies) as alternative medications for young children with mild persistent asthma. For infants and younger children under 5 years of age, the use of a low-dose inhaled corticosteroid plus a long-acting bronchodilator or a medium-dose inhaled glucocorticoid by itself is considered a preferred treatment for moderate persistent asthma. This recommendation is based predominantly on extrapolation from studies of older children and on expert opinion in the absence of higher quality evidence.

Table 1
Stepwise approach for managing infants and young children (5 years of age and younger) with acute or chronic asthma

Classify severity Clinical features before treatment or adequate control Symptoms/day (symptoms/night)	Medications required to Maintain long-term control
Step 4 Severe persistent Continual (frequent)	Preferred treatment • High-dose inhaled glucocorticoids and long-acting inhaled β_2-agonists and, if needed, • Glucocorticoid tablets or syrup long-term (2 mg/kg/day; generally do not exceed 60 mg/day). Make repeat attempts to reduce systemic corticoisteroids and establish control with high-dose inhaled corticoisteroids
Step 3 Moderate persistent Daily (> 1 night/week)	Preferred treatment • Low-dose inhaled glucocorticoids and long-acting inhaled β_2-agonists or • Medium-dose inhaled glucocorticoids Alternative treatment • Low-dose inhaled glucocorticoids and either leukotriene-receptor antagonist or theophylline If needed (particularly in patients with recurring severe exacerbations) Preferred treatment • Medium-dose inhaled glucocorticoids and long-acting inhaled β_2-agonists Alternative treatment • Medium-dose inhaled glucocorticoids and either leukotriene-receptor antagonist or theophylline
Step 2 Mild persistent >2/week but < 1/day (> 2 nights/month)	Preferred treatment • Low-dose inhaled glucocorticoid (with nebulizer or MDI with holding chamber with or without face mask or DPI) Alternative treatment (listed alphabetically): • Cromolyn (nebulizer is preferred or MDI with holding chamber) • Leukotriene receptor antagonist
Step 1 Mild intermittent $\leq$ 2 days/week ($\leq$ 2 nights/month)	No daily medication needed

Abbreviations: MDI, metered dose inhaler; DPI, dry powder inhaler.

The alternative treatment for children younger than 5 years of age is a low-dose inhaled glucocorticoid with a leukotriene modifier or theophylline.

The updated GINA guidelines were released in May of 2002 [7]. A treatment algorithm similar to that used in school children is recommended for preschool children and infants because there is no specific section devoted to asthma management for this age group. Similar recommendations in the updated Global Initiative for Asthma (GINA) guidelines and the recent NHLBI/NAEPP guidelines include (1) inhaled glucocorticoids should be used as first-line therapy in

children with all levels of persistent asthma; (2) alternatives to inhaled glucocorticoids include the cromones, theophylline, and perhaps LTRAs for mild persistent asthma. There are a few differences between the GINA and the NHLBI NAEPP guidelines. First, the GINA guidelines do not advocate LTRAs as monotherapy in patients with mild persistent asthma because there are not enough data to justify their use in children with mild persistent asthma. Second, the GINA guidelines recommend add-on controller medications such as theophylline, long-acting β-agonists (LABAs), or LTRAs for both moderate and severe persistent asthma.

Glucocorticoids

In 2002 the NAEPP and GINA have both published guidelines based on an evidence-based review that recommend inhaled corticosteroids as the primary maintenance treatment for children with persistent asthma. In the young infant or toddler for whom the diagnosis of asthma is still inconclusive, what is the role of glucocorticoids in the acute management of the wheezing illness and in the prevention of further episodes? The role of inhaled glucocorticoids in the infant and toddler with recurrent wheezing secondary to viral infections is another unresolved issue. Good data support the guideline recommendation for the use of inhaled glucocorticoids in the child with a diagnosis of persistent asthma and stepping up to inhaled corticosteroids and long-acting bronchodilators, as described in the two guidelines documents, if symptoms are not controlled. The Childhood Asthma Management Program (CAMP) trial demonstrated significant reductions in exacerbations for children treated with inhaled budesonide as a daily controller. Because a large proportion of exacerbations in children are caused by acute viral illnesses, one may extrapolate that acute wheezing is modified by this therapy during acute viral illness in children with a diagnosis of persistent asthma. Doull [13] has reviewed the topic of controller therapy for the prevention of viral-induced asthma. He was unable to find data that supported treatment of children with intermittent viral-induced asthma. This population differs from the children in the CAMP study.

Inhaled glucocorticoids are recommended as the preferred initial controller therapy for all infants and toddlers with persistent asthma. Most studies on the efficacy of inhaled glucocorticoid therapy in young children have used nebulized budesonide, the only medication approved by the Food and Drug Administration (FDA) for use children as young as 1 year of age. The initial studies with nebulized budesonide enrolled relatively small numbers of young children with moderate to severe persistent asthma and uniformly found nebulized budesonide to be superior to placebo in improving symptoms, reducing prednisone use, or improving overall asthma control [14,15]. Recent studies with greater numbers of study participants evaluated the efficacy and safety of nebulized budesonide in children with mild to moderate persistent asthma. Shapiro et al [16] studied three doses of budesonide (0.25 mg, 0.5 mg, and 1 mg) administered two times per day over a 12-week period in a double-blind, randomized, placebo-controlled study of 178 children, 4 to 8 years old, receiving chronic inhaled glucocorticoid therapy.

In another study, Kemp et al [17] investigated the efficacy of nebulized budesonide (0.25, 0.5, or 1.0 mg) administered one time per day in a 12-week randomized, double-blind, placebo-controlled study of 359 children aged 6 months to 8 years (mean age 4.7 years) with mild persistent asthma not receiving inhaled glucocorticoid therapy. In both studies, all doses of budesonide were superior to placebo in reducing both day- and nighttime symptoms. In addition, budesonide resulted in significant improvements in morning peak expiratory flow rates in patients who could adequately perform the procedure. Kemp et al [17] reported fewer days of rescue β-agonist use in children treated with budesonide than in children treated with placebo. Shapiro et al [16] found significantly fewer withdrawals from the study because of poorly controlled asthma in the active treatment group (9% versus 36% for budesonide and placebo, respectively). Although it was a short-term study, budesonide therapy did not result in any linear growth suppression, nor was it associated with basal or corticotropin-stimulated cortisol suppression. All doses of budesonide were found to be equally effective based on the parameters studied. These results suggest that in mild to moderate childhood asthma, nebulized budesonide, 0.5 mg per day, seems to be an effective and safe starting dose with subsequent dose adjustments based on clinical need and assessment of response.

In a larger study, Baker et al [18] studied several budesonide doses (0.25 mg or 1 mg administered one time per day or 0.25 mg or 0.5 mg administered two times per day) versus placebo in 480 children aged 6 months to 8 years (mean age 4.6 years) over a 12-week period. Improvement in symptom scores occurred as early as 2 weeks after budesonide treatment was initiated. As noted in the Shapiro [16] and Kemp [17] studies, no dose-dependent effects were apparent. The investigators suggested that a dose of 0.25 mg per day may be sufficient to control mild asthma, whereas patients with moderate asthma should be treated with 0.5 to 1.0 mg per day, and those with severe oral steroid–dependent asthma should be treated with 1 to 2 mg per day. No differences in basal cortisol levels were noted during the treatment period for any group, nor were differences in corticotropin-stimulated cortisol levels found between any of the active treatment groups and placebo.

The package insert for nebulized budesonide recommends that it be delivered with a jet nebulizer and a mouthpiece or by a suitable mouthpiece [19]. Blow-by administration has not been demonstrated to be effective, and the package insert warns against exposing the eyes to the nebulized budesonide. There are no data at present on the simultaneous delivery of budesonide and an inhaled β-agonist.

The efficacy of glucocorticoid therapy delivered by a pressurized chamber with a spacer and face mask in small children with asthma has been demonstrated in only a few studies. In an earlier randomized, double-blind study from Denmark, Bisgaard et al [20] compared high-dose budesonide (400 μg two times per day) or placebo from a pressurized aerosol with a Nebuhaler (Astra Zeneca) and face mask for 12 weeks in 77 children (aged 11–36 months) with recurrent wheezing. Active treatment afforded a 75% reduction in wheezing severity; improvement was not noted in the placebo group. In addition, there were fewer severe exacerbations

and fewer days of prednisolone therapy for the budesonide-treated group. The investigators further noted that the effect of treatment was evident after 6 to 8 weeks. In another double-blind, parallel-group, randomized, placebo-controlled trial, these investigators showed improvements in lung function measurements and bronchial hyperresponsiveness in moderately to severely asthmatic children (aged 35–71 months) treated for 8 weeks with budesonide (400 μg two times per day) administered by a pMDI with a spacer and face mask. [21] Lung function was measured using the Jaeger system as the specific airway resistance (sRaw) using whole-body plethysmography, as resistance by the interrupter technique (Rint), and as resistance and reactance at 5 Hz (Rrs5 and Xrs5) by the impulse oscillation technique. Bronchial reactivity was assessed using cold, dry air and methacholine challenge tests. Improvement in lung function was seen with budesonide treatment. A significant reduction in bronchial responsiveness to cold air, but not methacholine, was also found after 8 weeks of high-dose budesonide treatment. In addition, budesonide-treated patients (n = 19) had significant improvement in nighttime symptoms and daytime use of rescue medication compared with patients receiving placebo (n = 19). There were also significant differences in the improvement in asthma symptom-free days and total 24-hour symptom-free periods between the budesonide- and placebo-treated groups.

Bisgaard et al [22] have also studied the effect of fluticasone propionate delivered by a pMDI with a large-volume spacer in a placebo-controlled study. Children (n = 237) with a mean age of 28 months were enrolled to receive fluticasone (50 or 100 μg, two times per day) or placebo for 12 weeks following a 4-week run-in phase. Fluticasone resulted in a dose-related improvement in asthma symptoms with fluticasone, 200 μg per day, more effective than placebo in 8 out of 10 diary card parameters (including wheezing, cough, and breathlessness), whereas fluticasone, 100 μg per day, resulted in significant improvements in 5 parameters. In addition, fewer children receiving fluticasone experienced asthma exacerbations, and fewer still required a prednisolone burst. The authors suggested that fluticasone delivered by a holding chamber and mask may be effective in this population of small children because of its high potency and its long retention time within the lung. These properties, which are present to lesser degrees with the other inhaled glucocorticoids, may explain why so few published studies in this age group demonstrate efficacy with the other inhaled glucocorticoids.

The best means of delivering an inhaled glucocorticoid to an infant or young child still needs resolution. Further studies are required that compare the use of nebulizers and MDIs with spacers and masks to determine the preferred delivery system. Measures of efficacy and adverse effects need to be compared. Costs of these alternative systems may vary significantly, as do child and family compliance and time needed for medication delivery. No inhaled corticosteroid is licensed in the United States for use with a spacer and mask.

Who then are likely to respond to inhaled glucocorticoid therapy? A recent study by Roorda et al [23] using data from two large placebo-controlled studies provides valuable information about which preschool children are likely to respond to an inhaled glucocorticoid. They evaluated the clinical features of

preschool children likely to respond to fluticasone administered by a pMDI with holding chamber and face mask. The investigators identified two clinical features that predicted a positive response to inhaled glucocorticoid therapy: presence of frequent symptoms (≥ 3 days per week) and a family history of asthma. The presence of rhinitis or eczema in the child and the number of previous exacerbations were not associated with response to fluticasone. The presence of eczema clearly predisposes a child with recurrent wheezing to subsequent asthma [10] but does not seem to predict response to inhaled glucocorticoid therapy. A lack of response over a short course of treatment (12 weeks) does not necessarily mean that a response would not be seen over a much longer period of time. In any case, this study is an important first step in understanding which children with recurrent wheezing are likely to respond to controller therapy.

Inhaled glucocorticoids and growth in small children

Although recent studies evaluating the safety of long-term inhaled glucocorticoid therapy in school-aged children with asthma have not shown inhaled glucocorticoid therapy to be associated with significant growth suppression [24,25], no such studies exist evaluating the long-term effect of inhaled glucocorticoids on the linear growth of preschool children. Reid et al [26], in an open-label study, measured linear growth velocity in 40 children (mean age 1.4 years) before and during treatment with nebulized budesonide. Before entry into the study, all of the children had troublesome asthma despite treatment with an inhaled glucocorticoid administered with a pMDI with spacer and mask or nebulized cromolyn. They were then administered nebulized budesonide, 1 to 4 mg per day, depending on the level of asthma severity. The median intervals of time for linear growth determinations during the run-in period and nebulized budesonide treatments were 6 months and 1 year, respectively. The height standard deviation scores (SDS) for the group were -0.21 during the run-in period, -0.46 at baseline, and -0.17 after at least 6 months of nebulized budesonide. Note that a SDS of less than zero denotes impaired growth velocity. Thus, the subjects were growing at an impaired rate before nebulized budesonide therapy, and the institution of nebulized budesonide did not result in further growth suppression. In fact, there was a trend toward improved growth velocity during nebulized budesonide.

Skoner et al [28] recently evaluated the growth of children enrolled in 52-week open-label extension studies of the three efficacy studies of budesonide by Drs. Shapiro [16], Kemp [17], and Baker [18]. Following participation in the 12-week efficacy studies, the study participants were invited to continue in a 52-week open-label extension study in which 670 children were randomly assigned in a 2:1 ratio to receive nebulized budesonide or conventional asthma therapy. The dose of budesonide was 0.5 mg, either one or two times per day, with a taper to the lowest tolerated dose; conventional asthma therapy consisted of any available therapy, including inhaled glucocorticoids in two of the studies. The investigators found a modest impairment in growth in only one of the three extension studies. The

extension study in which a decline in growth was noted consisted primarily of young children with milder asthma who had not been taking inhaled glucocorticoids before entry into the initial study. In contrast, the two extension studies that did not find growth impairment consisted of children with more severe disease and had allowed for inhaled glucocorticoid use as part of the conventional asthma therapy algorithm. The Skoner study [27] suggests that modest growth suppression can occur in young children receiving nebulized budesonide who have not required inhaled glucocorticoid therapy in the past, and that children with milder asthma may be at greater risk for growth suppression secondary to increased intrapulmonary deposition. Alternatively, the findings may be attributable to the fact that more than twice as many children assigned to the conventional asthma therapy arm withdrew from the study because of poor asthma control. This withdrawal may have exaggerated the growth of children randomly assigned to conventional asthma therapy, because a greater number of poorly controlled asthmatics, who probably had the poorest growth, were not included in the final growth analysis.

That poor asthma control can negatively impact growth is a well-known but often overlooked phenomenon. A study by Ninan and Russell [28] demonstrates this finding. The growth of 58 children with asthma (mean age 3.5 years for boys, 4.4 years for girls) was followed over a 5-year period. Each child's asthma was classified as being in good, moderate, or poor control according to asthma symptoms during a 2-year observational period before the institution of inhaled glucocorticoid therapy. The group as a whole had diminished growth velocity at the start of the study, with a mean height velocity standard deviation (HVSD) score of − 0.51. Children whose asthma was in good control had the least evidence of growth suppression before beginning inhaled glucocorticoid therapy and continued to grow at the same rate while receiving therapy (HVSD score − 0.01 before treatment versus − 0.07 during treatment). In contrast, the children whose asthma was poorly controlled grew poorly before and after institution of inhaled glucocorticoid therapy (HVSD score − 1.50 before treatment versus − 1.55 during treatment). Those with moderately controlled asthma demonstrated improved growth velocity during inhaled glucocorticoid therapy, with the HVSD score increasing from − 0.83 to − 0.49. The investigators concluded that poor asthma control adversely affected linear growth to a greater extent than did inhaled glucocorticoid therapy.

Little is known about the systemic activity of inhaled glucocorticoids delivered by the pMDI and spacer in young children. In a randomized, double-blind, double-dummy, three-way crossover study, 40 children (mean age 2.4 years) received in randomized fashion 4 weeks of treatment with budesonide, 200 μg two times per day, pMDI and NebuChamber (Astra Zeneca, Lund, Sweden), fluticasone, 200 μg two times per day pMDI and Babyhaler (GlaxoSmithKline, Greenford, UK), or placebo two times per day, with measurements of lower-leg length using knemometry [29]. There was a significant reduction of the growth rate with either glucocorticoid treatment, compared with placebo, with no significant difference in growth rate between the two glucocorticoids. The budesonide, fluticasone, and

placebo treatment groups had an adjusted short-term lower-leg growth rates of 45, 34, and 85 μm per day, respectively. Although the authors emphasized that this is a short-term study in young children of the systemic activity of two potent inhaled glucocorticoids at 400 μg per day using a very sensitive measure of linear growth, they warn of the urgent need to address the long-term safety of such therapy in future clinical trials. The study also illustrates the need to use the lowest effective dose of the inhaled glucocorticoid. In this trial fluticasone was prescribed at twice the dose recommended for young children in the United States. Whether long-term use of inhaled glucocorticoids when instituted in the preschool-aged child will be associated with suppression of linear growth and impairment of bone growth and development remains an open question.

Alternative or adjunct medications

Cromolyn and nedocromil

Cromolyn and nedocromil are related compounds that have similar effects on inhibiting mediator release from mast cells. They are now considered non-preferred alternative monotherapy for children with mild persistent asthma [6]. A few studies have shown no added benefit with the use of cromolyn over placebo in young children with more severe disease [30–32]. These medications have few if any significant adverse effects, and, as a result, these compounds are still used by many pediatricians. They must be administered frequently (three to four times per day) to be effective. Several efficacy studies which found cromolyn to have beneficial effects were short-term trials and employed small numbers of young children [33,34].

Leukotriene-modifying agents

Leukotrienes are potent proinflammatory mediators that induce bronchospasm, mucus secretion, and airway edema. In addition, they may be involved in eosinophil recruitment into the asthmatic airway [35]. Two classes of leukotriene modifiers have been developed– synthesis inhibitors that inhibit the production of leukotrienes, and receptor antagonists that block the binding of leukotrienes to their receptors. The recent NHLBI/NAEPP update [6] and the GINA guidelines [7] have positioned the LTRAs as nonpreferred alternative monotherapy for children with mild persistent asthma and as alternative adjunct therapy to low- and medium-dose inhaled glucocorticoids for patients with moderate persistent asthma. The GINA guidelines also recommend LTRAs as a supplemental therapy to high-dose inhaled glucocorticoids for severe persistent asthma. Leukotriene modifiers have been shown to reduce asthma symptoms and supplemental β-agonist use while improving baseline pulmonary function in both children and adults [36–39]. Zafirlukast and montelukast are LTRAs and are the only leukotriene modifiers currently approved for use in children less than 12 years old. Zafirlukast is administered two times per day and is approved for children 7 years and older, whereas montelukast is approved for children 2 years of age and older.

In a randomized, double-blind, multicenter, placebo-controlled trial, the efficacy and safety of a 4-mg chewable montelukast tablet were evaluated in children with asthma [40]. More than 600 children 2 to 5 years of age were enrolled to receive montelukast or placebo for 12 weeks in double-blind, multicenter, multinational study at 93 centers worldwide. Montelukast was well tolerated and was not associated with any significant adverse effects. Montelukast was found to be superior to placebo in reducing daytime symptoms, including improvements in cough, wheeze, difficulty breathing, and activity level, and it effectively reduced nighttime cough. In addition, montelukast therapy was associated with a reduction in rescue β-agonist use and reduced need for prednisone for acute severe exacerbations.

Few studies address the effects of medications on objective outcome parameters in young children because of the lack of availability of reliable lung function measurements. Bisgaard and Nielsen [41] evaluated the effect of montelukast, 5 mg per day for 2 days, on the bronchoconstrictor response to cold air challenge (measured as changes in specific airway resistance in a whole-body plethysmography [sRaw]), in a randomized, placebo-controlled, cross-over two-period study with a washout of at least 1 week between periods, in 16 asthmatic children (age range, 3.1 to 5.7 years). Eight of these children were receiving inhaled glucocorticoid therapy. With cold air challenge, airway resistance increased only by 17% after montelukast treatment compared to 46% increase after placebo treatment ($P < 0.01$). The bronchoprotection provided by montelukast was found to be reproducible and seemed to be independent of concurrent steroid treatment. Based on the results of these limited studies, montelukast seems to be a safe and effective therapy for use in young children with asthma.

Long-acting inhaled β_2-agonists

The current NHLBI/NAEPP update summary [6] has placed inhaled LABAs (such as salmeterol and formoterol) as the preferred add-on therapy for children and adults with moderate and severe persistent asthma. In a double-blind, randomized, parallel, multinational study in 286 children aged 4 to 17 years previously treated with inhaled glucocorticoid therapy, the combination of budesonide (160 μg) and formoterol (9 μg), two times per day, in a single inhaler for 12 weeks was found to be more efficacious than budesonide alone (200 μg, two times per day) in terms of improvement in peak expiratory flow rates and forced expiratory volume in 1 second (FEV_1) [42]. The randomized, double-blind, parallel study conducted by Verberne et al [43] in children 6 to 16 years old comparing the addition of salmeterol with increasing the dose of beclomethasone failed to show any further benefit in FEV_1, airway responsiveness, symptom scores, or exacerbation rates after 1 year of treatment. These results are in marked contrast to several studies in adults [44–46] with all levels of asthma severity in which the addition of a LABA was superior to increasing the dose of inhaled glucocorticoid in patients inadequately controlled by an inhaled glucocorticoid alone. No studies in younger children have evaluated the efficacy of LABAs as add-on therapy.

Salmeterol delivered using the Diskus (GlaxoSmithKline, Research Triangle Park, NC) device is approved by the FDA for use in children as young as 4 years of age (using a 50-μg blister every 12 hours), whereas formoterol delivered using the Aerolizer (Novartis Pharma AG, Bassell, Switzerland) is approved for use in children 6 years of age and older (using a 12-μg capsule every 12 hours). The LABAs are not viewed as rescue medications for acute episodes of bronchospasm, nor are they meant to replace inhaled anti-inflammatory agents. Salmeterol has a longer onset of action, with maximal bronchodilation approximately 1 hour following administration; formoterol has an onset of effect within minutes. Because these medications have a prolonged duration of action of at least 12 hours, they are especially well suited for patients with nocturnal asthma [47] and for individuals who require frequent use of short-acting β-agonist inhalations during the day to prevent exercise-induced asthma [48].

At the present time, the efficacy of LABAs in preschool-aged children has not been extensively evaluated. Preschool-aged children may deserve an extended bronchodilatory coverage during exercise, because they are constantly active. One study evaluated the bronchoprotective effects of a single dose of salmeterol given through a Babyhaler spacer device using a methacholine provocation challenge in children less than 4 years old with recurrent episodes of wheezing. Originally, 42 preschool children (age range, 8–45 months) received a 25-, 50-, or 100-μg dose of salmeterol and a placebo dose 2 to 7 days apart in a double-blind, randomized, cross over, fashion, but only 33 completed the study. Methacholine challenge by auscultation and pulse oximetry monitoring one hour after the dose was done. All the subjects had reactivity to methacholine at or below 8 mg/mL on both visits. The investigators found a dose-dependent bronchoprotective effect of salmeterol measured by treatment/placebo methacholine dose ratios. Significant improvements from placebo were only found for the 50-μg (2.5-fold) and 100-μg (fourfold) doses [49].

Nielsen and Bisgaard [50] compared the bronchodilatory and bronchoprotective effects of formoterol (9 μg), salmeterol (200 μg), and placebo delivered in a new device, which is a mechanically actuated DPI with spacer. Twelve 2- to 5-year-old children completed this randomized, double-blind, placebo-controlled, cross-over study. Bronchodilation as early as 3 minutes after the dose was measured as sRaw done during tidal breathing using a constant volume whole-body plethysmography. Bronchoprotection, on the other hand, was determined by measuring changes in sRaw after a cold, dry air challenge. Although in this study improvement in sRaw was seen as early as 3 minutes after dosing with single doses of both formoterol and salmeterol, the effect of formoterol was sustained through 8 hours, compared with only 4 hours of bronchodilatory effect afforded by salmeterol. Formoterol provided significant bronchoprotection against cold, dry air–induced bronchoconstriction compared with either salmeterol or placebo at 4 and 8 hours after dosing. Formoterol and salmeterol provided 80% and 50% bronchoprotective effects, respectively, compared with placebo, at the 15-minute cold, dry air challenge. This study demonstrates the potential of LABAs, specifically formoterol, to provide extended or sustained bronchodilatory and

bronchoprotective effects for up to 8 hours in small children who are constantly active. This device is not commercially available in the Unites States, however, and this class of medications has yet to be approved for use in children younger than 4 years of age.

Theophylline

Theophylline is an effective medication in children with asthma [51,52]. Recently published studies using bronchial biopsy specimens from adults with asthma have suggested that the modest anti-inflammatory effects from of low doses of theophylline are associated with clinical response [53,54]. Despite the recent evidence suggesting that theophylline may display anti-inflammatory properties, it is rarely used in the United States in young children because of concerns regarding the difficulty in titrating doses, its narrow therapeutic window, and potential toxicity. The NHLBI/NAEPP 2002 guidelines [6] mention theophylline only as an alternative add-on treatment to low- and medium-dose inhaled glucocorticoid for small children with moderate asthma. The GINA guidelines [7] extend its use as an add-on medication for severe persistent asthma and an alternative monotherapy for mild persistent asthma in children. The NHLBI expert panel report II guidelines state that ''theophylline may have particular risks of adverse side effects in infants, and theophylline should only be considered if serum concentration levels will be carefully monitored'' [55]. Theophylline has a narrow therapeutic window and a variable metabolism from infancy through childhood; hence, levels need to be routinely monitored, and frequent dose adjustments are necessary, especially with ongoing fever or concurrent medication known to delay theophylline clearance, such as macrolide antibiotics (erythromycin, and clarithromycin), cimetidine, antifungals, and ciprofloxacin [56]. Lastly, sustained-release theophylline can be erratically absorbed [57].

Medications for acute wheezing episodes

Short-acting β-agonists

The NAEPP guidelines recommend the use of short-acting β_2-agonists for all patients with intermittent and persistent asthma of all disease severities. This class of medication is used only as a reliever or before exercise or as bronchoprotection before unavoidable allergen exposure. Two areas that require further discussion are whether the young child with transient asthma would benefit from this class of medications during the acute illness, and, if so, the best technique to deliver these medications to the acutely wheezing child.

The Cochrane Database of Systemic Reviews [58] addressed the first of these questions. Three parameters were assessed: clinical symptom scores, oximetry, and duration of hospitalization. The odds ratio of demonstrating an improvement in clinical score was 0.29 (confidence interval [CI] 0.19–0.45). Children treated with bronchodilators did not demonstrate a significant improvement in oximetry

or in duration of hospitalization. The significance of the lack of clinical improvement may have been confounded by recurrent wheezing episodes in some of the children. This difficulty in distinguishing the study population is also a common problem for clinicians in treating these young infants and toddlers who are not clearly defined at the time of illness as being transient wheezers or asthmatics. The lack of improvement in oximetry may have resulted because the studies were performed in patients with mild disease that might not have much room for improvement. The significance of this meta-analysis is that the issue is still not completely resolved after many years of study and probably relates to the heterogeneous young wheezer population. Because these were placebo-controlled trials, children with severe disease were more likely to be excluded, and some of these findings are difficult to generalize.

At present the use of inhaled β_2-agonists in infants with wheezing but without a confirmed diagnosis of asthma is recommended if the history supports a history of persistent asthma and in more severe acute episodes. Continued treatment of responders may be confounded with the placebo effect of any treatment. When considering discontinuing treatment in a possible nonresponder, one must remember that one definition of status asthmaticus is failure to respond to inhaled short-acting β_2-agonists.

The efficacy and safety of short-acting β_2-agonists have been documented even in children less than 2 years of age with recurrent wheezing [60]. Because of their rapid onset of action and fairly long duration of action (4–6 hours), these medications are the treatment of choice for significant asthma exacerbations and acute episodes of bronchospasm. Beta-agonists are now considered rescue medications and should only be used by symptomatic patients. Although the NHLBI expert panel report II does not offer specific dosage recommendations for younger children, it recommends 0.05 mg/kg with a minimum dose of 1.25 mg and a maximum of 2.5 mg in 2 to 3 ml saline for use in older children [55]. The Third International Pediatric Consensus Statement on the Management of Childhood Asthma recommends a fixed dose of albuterol, 2.5 to 5 mg, by a nebulizer for children 5 years of age or younger [61].

Penna et al [62] found young children to have lower plasma albuterol/salbutamol concentrations following multiple nebulized treatments despite having received a greater amount of albuterol (178.8 versus 137 μg/kg) than children older than 5 years. This finding was independent of severity of the initial attack. The authors concluded that the lower serum albuterol levels in the younger children who had received greater doses was secondary to either enhanced clearance of the drug or less efficient delivery of the drug in this age group. These data would suggest that smaller children actually require a larger amount of albuterol per kilogram, and that albuterol toxicity is less likely to occur. Detailed pharmacokinetic studies would be required to answer this question fully.

The question of how best to deliver an inhaled short-acting β_2-agonist may be less controversial. One study from an emergency department investigating 168 children aged 2 to 24 months attempted to address this clinical question [59]. The infants and toddlers were treated in a blinded fashion with a MDI and spacer with

mask or a nebulizer. One delivery system provided active therapy, and the alternative system delivered placebo. The primary outcome was admission rate. For 26% to 30% of the study population, this was the first wheezing episode. The admission rate for the patients treated with a nebulizer was three times greater (odds ratio, 3.22, $P = 0.05$) than for children treated with MDI even after correction for initial higher pulmonary index in the nebulizer group. In addition there was less adverse effect on heart rate with the MDI. These findings are supported by other studies in the literature. Metered dose inhalers are an appropriate alternative for delivering reliever medications to acutely wheezing infants and are a more cost-effective method.

Anticholinergic agents

The anticholinergic agent ipratropium bromide is now available for nebulizer administration. Its use as an adjunct therapy for acute exacerbations in childhood asthma has increased. Schuh et al [63] were among the first to demonstrate the additive effect of nebulized ipratropium bromide combined with albuterol on lung function in children presenting to the emergency room for acute asthma. Several subsequent studies that involved children younger than 5 years of age have confirmed and extended their results [64]. Quareshi et al [65], in a large randomized, double-blind, placebo-controlled study, sought to determine whether the addition of ipratropium bromide to standard emergency department therapy for acute asthma in children 2 to 18 years of age would reduce hospitalization rates. More than 400 children were randomly assigned to receive nebulized albuterol every 20 minutes for 1 hour or nebulized albuterol three times plus the addition of ipratropium bromide with the second and third albuterol treatments, plus prednisone. The overall rate of hospitalization was lower in the ipratropium group than in the control group (27.4% versus 36.5%, $P = 0.05$). Although no difference in hospitalization rates was observed for patients with moderate exacerbations, patients with severe exacerbations (peak expiratory flow rate $< 50\%$) who received ipratropium were less likely to be hospitalized than the control group (37.5% versus 52.6%; $P = 0.02$). Ipratropium was also effective at reducing the asthma symptom score and in mildly improving the oxygen saturation but had no effect on improving peak expiratory flow rates. This reduction in hospitalization is of significant importance. The investigators stated that for every seven patients with severe acute asthma treated with ipratropium, one hospitalization could be prevented. In contrast, a more recent study by Zorc et al [66] failed to confirm that the use of ipratropium resulted in fewer asthma hospitalizations. These investigators studied 427 children over 12 months of age (11% were < 2 years old) with mild to severe attacks and found no difference in the rates of hospital admission between the two treatment groups (22% in the control group and 18% in the treatment group, $P = 0.33$). Of those discharged from the emergency room, however, those treated with ipratropium had shorter time to discharge by about 30 minutes ($P = 0.001$), with the effect most marked in children younger than 5 years old. Also, fewer albuterol doses were delivered to the treatment group.

Although no studies are available that address the use of this medication specifically in children younger than 5 years old, several of the studies that included children as young as 2 years old demonstrate that ipratropium bromide seems to be an effective adjunct therapy in acute childhood asthma. Whether it is effective in reducing hospitalization rates for acute asthma remains to be more fully elucidated.

Short-course glucocorticoid therapy

Several studies have demonstrated clinical efficacy of glucocorticoid therapy in the treatment of acute childhood asthma. Efficacy has been demonstrated in studies evaluating single doses of oral and parenteral glucocorticoid administered in the emergency room [67,68], short-courses of oral glucocorticoid in the clinic setting [69], and both oral and intravenous glucocorticoid therapy for children hospitalized with acute exacerbations of asthma [70–73].

Studies have also demonstrated orally administered glucocorticoids to be as effective as intravenous glucocorticoids for most children admitted to the hospital with an acute asthma exacerbation. Because orally administered liquid steroid preparations are absorbed rapidly (within 30 minutes to 1 hour) and are usually as effective as intravenous glucocorticoid in the management of acute asthma in young children, oral therapy can be used in many cases [74]. Hospitalized children who are in severe distress or who require high-flow rates of oxygen to treat hypoxemia adequately are candidates for intravenous glucocorticoid therapy. The NHLBI guidelines for acute severe asthma recommend administering intravenous methylprednisolone at a dosage of 1 mg/kg every 6 hours for 48 hours with a taper to 1 to 2 mg/kg/day (maximum 60 mg/day) in two divided doses until the patient's peak expiratory flow rate reaches 70% of predicted or personal best [55].

Dosing strategies and duration of oral glucocorticoid therapy for children with acute asthma exacerbations are still arbitrary. In a randomized, double-blind study, 98 children aged 1 to 15 years admitted to the hospital were randomly assigned to receive prednisolone, 0.5, 1.0, or 2.0 mg/kg per day, administered as a single daily dose [75]. Clinical measures of efficacy such as symptom scores, oxygen saturation, heart rate, number of albuterol treatments required, and duration of hospitalization were compared among the three groups. The investigators found no difference in any of the clinical parameters studied among the three groups. Combined cough and wheeze score and use of rescue bronchodilators within 2 weeks of discharge were also comparable among the groups. This study suggests that low-dose prednisolone is as effective as high-dose prednisolone and is one of many studies that have failed to demonstrate a dose-response effect for systemically administered glucocorticoids. With increased awareness of the potential for adverse effects with glucocorticoid therapy in general, it makes sense to use the lowest effective dose, especially in children with moderately severe asthma who often require frequent short courses of prednisone for acute asthma exacerbations. These children will often also be receiving moderate doses

of inhaled glucocorticoid therapy, and additive adverse effects may occur with the combined use of intermittent oral and inhaled glucocorticoids. The NHBLI expert panel report II guidelines [55] suggest 1 to 2 mg/kg/day (maximum 60 mg/day) of prednisone or methylprednisolone in a single or in two divided doses for 3 to 10 days; the British guidelines [76] recommend initiating a short course of prednisolone for 1 to 3 days (1 to 2 mg/kg/day for children younger than 1 year and 20 mg/day for children aged 1–5 years) for children with mild or moderate episodes requiring 3 to 4 hourly bronchodilator treatments after 12 hours for outpatient management of acute exacerbations. For most children inhaled corticosteroids, as well as other controller medications, should be continued during oral and parental administration of glucocorticoids.

Garrison and colleagues performed a meta-analysis of the use of systemic corticosteroids for the management of acute bronchiolitis [77]. Their literature review revealed six relevant articles that used two main outcomes: length of stay or duration of symptoms and clinical scores. For the infants receiving systemic corticosteroids, there was a significant reduction in the first two measures of 0.43 days ($P = 0.03$). In addition children receiving systemic corticosteroids had significantly better clinical scores. Although the authors of this analysis describe some of the limitations of this study, including publication bias and heterogeneous population, this review provides useful data supporting the use of systemic glucocorticoids during acute wheezing episodes in infants with or without a confirmed diagnosis of asthma.

Inhaled glucocorticoids for acute wheezing

A few studies are now available that demonstrate the efficacy of inhaled glucocorticoid therapy for acute episodes of wheezing in young children. Inhaled glucocorticoid therapy (budesonide Turbuhaler, 200 μg, four times per day) has been shown to be as effective as oral prednisolone (2 mg/kg/day) in the treatment of older children presenting to the emergency room with moderately severe acute asthma exacerbations. After a week of treatment and after corticotropin stimulation, however, inhaled glucocorticoid therapy has been associated with higher serum cortisol concentration compared with oral glucocorticoid therapy [78]. Studies comparing nebulized versus systemic glucocorticoids in preschool children with acute episodic wheeze are still unavailable.

The use of high-dose inhaled corticosteroids for the management of early exacerbations in young children with prior episodic wheezing episodes has the potential to modify the severity of symptoms, as demonstrated in certain studies using double-blind intrasubject comparisons (treatment pair design). High-dose inhaled corticosteroids did not offer an advantage over placebo in reducing admission rates or need for systemic steroids, however [79,80], probably because the studies employed a small sample size to detect a difference or the dose/delivery of the inhaled steroids by pMDI and spacer was not sufficient.

Recently, Sano et al [81] assigned children aged 3 to 24 months admitted to the hospital for severe wheezing and respiratory distress to receive either

nebulized budesonide (0.25 mg, four times per day) (n = 39) or ipratropium bromide (0.1 mg, four times day) (n = 32), administered with inhaled fenoterol treatments. All received inhaled fenoterol (0.083 mg/kg every 4 hours), intravenous hydrocortisone (40 mg/kg/day), and oxygen as needed. Children receiving antibiotic therapy or requiring an intensive care admission were excluded. The clinical response, demonstrated by a significantly greater reduction in clinical score (based on the severity of wheezing and retractions) after 12 hours and respiratory rates after 24 hours, was faster in the budesonide/fenoterol group than in the ipratropium/fenoterol group. In addition, the length of hospital stay was almost 30% shorter in the budesonide/fenoterol group than in the ipratropium/fenoterol group (66 versus 93 hours, respectively, $P < 0.01$). Finally, after 3 days, about half of the children treated with budesonide/fenoterol had been discharged, whereas 84% of children treated with ipratropium/fenoterol still remained in the hospital. The results of this study suggest that inhaled glucocorticoid treatment offers an additive effect to systemic steroid and bronchodilator therapy for small children with severe wheezing and dyspnea, possibly by exerting a more efficient and direct action on airway inflammation.

Whether nebulized glucocorticoid therapy is beneficial in treating acute bronchiolitis or in preventing postbronchiolitis wheezing was addressed by Richter and Seddon [82]. In a randomized, double-blind, placebo-controlled trial, 40 infants with bronchiolitis (83% respiratory syncytial virus–positive by immunofluorescence or culture) with no previous history of wheezing were enrolled to receive either nebulized budesonide suspension (1 mg every 12 hours the first 5 days, then 500 μg every 12 hours for the remainder of the 6-week treatment period) (n = 20) or placebo (0.9% saline every 12 hours for 6 weeks) (n = 19). These infants were followed for a total of 6 months. Fifteen infants receiving budesonide and 12 infants receiving placebo required hospitalization for at least 48 hours. There were no significant differences in oxygen requirement, length of hospital stay, and clinical scores between the budesonide- and placebo-treated groups for infants hospitalized for at least 48 hours. During the 6-week treatment period and even during the 6-month follow-up period, there were no differences in symptom scores and bronchodilator requirements between active treatment and placebo groups. Surprisingly, more patients in the budesonide-treated group were eventually readmitted for respiratory problems during the 6-month follow-up period.

In patients with bronchiolitis, inhaled glucocorticoids do not necessarily alter the acute and chronic course. This finding emphasizes the heterogeneous origins of wheezing in young children, with airway inflammation playing a significant role in only a fraction of these cases. Alternatively, this finding also raises the question of whether an inhaled anti-inflammatory medication is adequately delivered in an acutely wheezing infant.

Theophylline in acute asthma

The routine use of theophylline in acute asthma has significantly declined during the past several years, mainly because of a series of studies that show

theophylline provides no additive effect to frequently administered β-agonists in most cases. A study by Strauss et al [83] illustrates this point in children. These investigators found intravenous theophylline offered no additional benefit to frequently used inhaled β-agonists and parenteral glucocorticoids in 31 children, aged 5 to 18 years, hospitalized with acute asthma. Theophylline was no more effective than placebo in improving pulmonary function, decreasing need for inhaled β-agonists, or shortening the length of hospitalization. Theophylline was even associated with a greater incidence of headache, nausea, emesis, abdominal pain, and palpitations compared with placebo. These children, however, had moderate asthma exacerbations, with none requiring admission to the intensive care unit.

Theophylline may still play an important role in acute, life-threatening asthma, as demonstrated in a recent study by Yung et al [84]. These investigators in a randomized, double-blind, placebo-controlled trial of 163 children (1 to 19 years old) with an acute severe asthma exacerbation found intravenous theophylline to be an effective therapy. Those receiving theophylline showed greater improvement in lung function after 6 hours and in oxygen saturation in the first 30 hours compared with those receiving placebo. In addition, fewer patients receiving theophylline required treatment with intravenous albuterol. All five patients who required intubation for respiratory failure had been randomly assigned to the placebo group. This finding suggests that intravenous theophylline can be an important adjunctive therapy in young children with acute, life-threatening severe asthma requiring admission to the intensive care unit.

Summary

The management of infants and small children with asthma is a challenging task because of the many issues unique to this age group that deserve special consideration. The diagnosis of asthma is limited by inherent difficulties in obtaining objective measures of lung function and airway inflammation. In persistently symptomatic patients, the decision to initiate controller therapy is not as great an issue as it is in infants and young children with recurrent episodic wheeze in whom early intervention may allow a window of opportunity potentially to alter the course of the disease. The reality is that even if atopy has been consistently implicated in the development of persistent asthma, there is not a well-established set of criteria by which patients who are likely to benefit from early intervention controller therapy can be identified. Hence, large prospective studies need to be performed evaluating the impact of early pharmacologic intervention on the natural history of infantile asthma. Many areas needing investigation involve what medications to use, how best to deliver the medications, and how to monitor the response to treatment. Only a few medications have been approved for use in this population. Long-term studies evaluating available drugs such as inhaled glucocorticoids, LABAs, and the leukotriene-modifying agents in young children still need to be performed.

Acknowledgment

The authors thank Jan Manzanares for assistance in the preparation of the manuscript.

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