

Asthma in Infants and Children

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Asthma is the most common chronic illness in childhood and represents a significant burden to health care and educational systems. Between one quarter and two thirds of childhood asthma cases persist into adulthood. Childhood asthma may be particularly difficult to diagnose because of the high prevalence of episodic wheezing and cough in childhood illnesses such as upper respiratory tract infections.

National and worldwide guidelines for the management of asthma in children are continually being updated. These guidelines recommend first establishing a diagnosis and assessing the severity of disease, initiating pharmacologic therapy based on symptoms and lung function, and adjusting doses and agents as required based on the level of asthma control. Inhaled corticosteroids are the cornerstone of long-term asthma management in children of all ages. Recent research efforts have focused on ways to improve inhalant drug delivery to the lungs and minimize oral and systemic bioavailability so as to improve the therapeutic benefit:risk ratio. (*Clinical Cornerstone*. 2007;8[4]:44–61) © 2008 Excerpta Medica Inc. All rights reserved.

Asthma is the most common chronic childhood illness in the United States, with more than 6.2 million children affected in 2004.¹ In 2004, the highest prevalence of asthma was seen in children 5 to 17 years of age, with a rate of 95.5 per 1000 population. Childhood asthma represents a significant burden to the health care and educational systems—38% of the 497,000 hospital discharges due to asthma were for children under the age of 15 years, and childhood asthma accounted for an estimated 14 million lost school days in 2004.¹

The prevalence of childhood asthma in the United States is characterized by significant racial and geographical disparity. Among children <18 years of age, black children were significantly more likely to have a diagnosis of asthma, an episode or attack in the past year, and an asthma-related emergency room visit, even after controlling for measurable child and family characteristics such as income, birth weight, maternal health, and access to health insurance.² Increases in asthma rates have been greatest in urbanized areas, where there may be greater and prolonged exposure to indoor allergens such as dust mite, cockroach, cat, and fungi.³

Asthma usually begins in early childhood as a pattern of persistent atopic wheezing that is exacerbated with allergen exposure and viral respiratory infections. Those children with persistent wheeze up to age 5 years who do not experience atopic sensitization will typically become

asymptomatic after age 5 years, and nearly all will be free of symptoms by age 13 years.⁴ Among children with atopic wheezing, however, symptoms will typically increase after age 5 years and then plateau. Ongoing experience of asthma symptoms and a detrimental effect on lung function are also more likely to occur in children with early (≤ 5 years) sensitization to perennial allergens, and more likely still when the exposure to perennial allergens is more intensive and occurs during the first 3 years of life.⁴ In contrast, later sensitization to allergens, sensitization to seasonal allergens, and early sensitization to food allergens are not associated with an effect on lung function between the ages of 5 and 13 years.

The severity of asthma symptoms and reduced lung function do not usually deteriorate in childhood and may even improve during adolescence.⁵ Although an estimated 30% to 50% of childhood asthma cases “resolve” at puberty, the condition often resurfaces in adulthood. Approximately one quarter to two thirds of childhood asthma cases persist into adulthood.⁶ Children with severe asthma symptoms are more likely to have persistent asthma as adults. Diminished lung function (ie, diminished airflow and airway obstruction) in childhood is associated with poorer prognosis and outcomes during adulthood.⁷ A high blood eosinophil count, an indirect marker of airway inflammation, is predictive for the persistence of symptoms and the presence of airway hyper-

responsiveness in adulthood.⁷ An Asthma Predictive Index (discussed later in this article) has been developed that has been shown to be highly predictive for asthma development in children ages 6, 8, 11, and 13 years.⁸

There is growing evidence that early recognition and intervention in childhood asthma can improve symptom control and reduce the frequency of asthma exacerbations, thereby reducing childhood morbidity and health care resource utilization. Moreover, early intervention may help slow the progression of airway remodeling in children with asthma. Although this is controversial, most of the asthma-related deficits in lung function occur by age 6 years in children whose symptoms begin before the age of 3 years.⁹ Indeed, reduced airway function in 2-month-old infants has been correlated with a reduction in lung function when these patients reach young adulthood.¹⁰ This subgroup of children, then, should be the focus of early intervention efforts.

KEY POINT

Most of the asthma-related deficits in lung function occur by age 6 years in children whose symptoms begin before the age of 3 years. This subgroup of children, then, should be the focus of early intervention efforts.

However, this subset of children may be difficult to distinguish from transient wheezers who eventually outgrow their symptoms by age 3 years. Moreover, asthma treatment may be particularly problematic in this age group because of the difficulties associated with the use of inhaler devices, the lack of clinical data in very young children, and the increased risk of medication-related side effects in very young children.

In recent years, there has been a heightened interest in developing effective and safer asthma treatments for young children. Newer formulations and delivery systems are making it easier for clinicians to treat their youngest patients, with the goal of attenuating the underlying inflammatory process and improving lung function early in the disease course. This paper discusses the diagnostic and disease management strategies in child-

hood asthma, with a focus on new developments in the treatment of asthma in very young children.

PATHOGENESIS OF ASTHMA IN CHILDREN

Both genetic and environmental factors play a role in the pathogenesis of childhood asthma, and the interaction of these factors may determine whether asthma persists or resolves in later childhood. For example, children may develop persistent airway inflammation with repeated viral infections and exposure to irritants such as tobacco smoke. However, all children exposed to these agents do not go on to develop asthma. Host responses to chronic inflammation are also important. Asthmatic children have a propensity for inappropriate immunoglobulin E (IgE) allergen sensitization (T-helper type 2 [Th2] response) as well as poorly regulated local responses that lead to airway inflammation and abnormal tissue repair (airway remodeling).¹¹ The propensity for Th2-type responses often precedes allergen sensitization and may be genetically determined.

On the other hand, it may be exposure to the viral infection or noxious agent that increases the propensity for a Th2-type response. Severe respiratory infection is associated with the appearance of mature dendritic cells in infant airways, which are normally free of dendritic cells in the absence of inflammation.¹¹ Age-related immaturity in dendritic cell function may render these cells incapable of producing adequate T-helper type 1 (Th1) responses, increasing the propensity for Th2 responses.¹¹

In addition, viral infection can damage the airway epithelium, increasing airway exposure to antigens and allergens.^{12,13} Disruption of the airway epithelium is also associated with increased expression of proinflammatory cytokines and growth factors.¹² This can contribute to airway remodeling with subepithelial fibrosis and abnormal vascularization and significant effects on lung function. Bacterial infections can also elicit an IgE-mediated response and may play a role in asthma exacerbations.¹⁴ Even in the absence of infection, airway epithelial damage is associated with neutrophil activation and mobilization in children with acute exacerbations of asthma.¹⁵

While these data suggest a possible causative role for viral infection in the pathogenesis of asthma, other evidence points to a protective effect of frequent upper respiratory infection. It is thought that early exposure to infectious agents may confer some protection against development of asthma, a theory known as the *hygiene*

hypothesis.¹⁶ Increased family size and early exposure to daycare, which are surrogate markers of infectious load, are inversely correlated with the later development of allergy and asthma. This may also explain why asthma prevalence is higher in industrialized, developed nations, where the exposure to common infectious agents is less prevalent.¹⁶

Several studies have shown that while frequent upper respiratory infection in early childhood may protect against development of asthma, lower respiratory infections appear to be positively associated with atopy development.¹³ Repeated infection may perpetuate inflammation and airway hyperresponsiveness in children with atopy.

RISK FACTORS FOR CHILDHOOD ASTHMA

Several host and environmental risk factors may predispose children to asthma (Table I).¹⁷

Host Risk Factors

Atopy leads to allergen sensitization early in life. Children who undergo allergic sensitization during the first 3 years of life are more likely to develop asthma than those who are sensitized later in life. Atopy is usually co-inherited with airway hyperresponsiveness, a tendency for the airway to narrow excessively and too quickly in response to stimuli.¹⁷

Children who develop asthma appear to have a genetic propensity for a Th2-polarized immune pathway. At birth, there is a normal Th2-biased response to environmental allergens. This system needs certain stimuli to shift it in

favor of a Th1-type response.¹⁸ Upper respiratory infections and exposure to certain allergens or stimuli may help achieve this shift. This supports the hygiene hypothesis and explains why the rates of asthma are greater in Westernized, developed nations. There may also be genetic mutations within the immune system that predispose to asthma. For example, mutations in the gene for glutathione S-transferase may lead to impaired detoxification of endotoxin from tobacco smoke, house dust, or microbes.¹⁹

Among young children, asthma is more prevalent in boys than girls. This is likely a result of narrower airways and increased airway tone among boys.¹⁷ The observed racial differences in the prevalence of asthma (eg, a higher rate among African Americans in the United States) are primarily due to socioeconomic and environmental factors rather than racial predisposition.¹⁷

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In young children, asthma is more prevalent among boys than girls. This is likely a result of narrower airways and increased airway tone among boys.

Low birth weight was found to be a strong independent predictor of an asthma diagnosis at age 3 years among young urban children. In an urban population-based sample, children who were of low birth weight were almost twice as likely to develop asthma by age 3 years compared with those of normal birth weight (34% vs 18%). In this sample, very little of the association between low birth weight and asthma diagnosis could be explained by demographic, socioeconomic, medical, behavioral, and neighborhood characteristics included in the analysis.²⁰

Environmental Risk Factors

The most important environmental risk factors for asthma are exposure to indoor allergens (eg, domestic mites, cat and dog dander, cockroach allergen, and fungi), outdoor allergens (eg, pollen), tobacco smoke, and occupational sensitizers.¹⁷ The dose-response relationships between allergen exposure and sensitization differ between allergens and between geographic areas. With respect to house dust mites, local environmental factors

TABLE I. RISK FACTORS FOR DEVELOPING ASTHMA IN CHILDREN.¹⁷

| |
|------------------------------|
| Host factors |
| Airway hyperresponsiveness |
| Atopy |
| Gender |
| Genetic predisposition |
| Race/ethnicity |
| Low birth weight |
| Environmental factors |
| Indoor/outdoor allergens |
| Tobacco smoke |
| Air pollution |
| Respiratory infections |
| Parasitic infections |
| Socioeconomic status |
| Family size |
| Diet and drugs |
| Obesity |

may modulate the relationship between exposure to this allergen and specific sensitization.²¹

Both the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) guidelines have issued recommendations to minimize exposure to indoor and outdoor allergens (Table II)^{22,23} as a key step in the management of asthma.

Acute viral respiratory infections during early childhood are associated with asthma exacerbations.¹⁷ About 80% of documented influenza A infections precipitate asthma exacerbations in known asthmatics.²⁴ For this reason, the American Academy of Pediatrics and the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends annual influenza vaccination for all children with asthma.^{24,25} Rhinovirus infection has also

been shown to be a significant predictor of wheezing in infants at elevated risk for developing allergic respiratory diseases. Data from a recent study suggest that rhinovirus among infants (≤ 1 year) is, in fact, a stronger predictor of wheezing in the third year of life than passive smoke exposure, sensitization to foods, or respiratory syncytial virus.^{26,27}

DIAGNOSIS OF ASTHMA IN CHILDREN

Childhood asthma may be particularly difficult to diagnose because of the high prevalence of episodic wheezing and cough in childhood illnesses such as upper respiratory tract infections. Three patterns of wheezing are common in children 5 years and younger. *Transient early wheezing* is associated with inadequate lung maturation and maternal smoking. It generally resolves by age 3 years as the lungs mature. *Persistent early-onset wheezing* occurs in association with viral respiratory infections and may persist into late childhood. However, there is generally no family history of atopy or evidence of atopy. *Late-onset wheezing*, which usually begins after 1 year of age, persists throughout childhood and develops into asthma. Children with late-onset wheezing generally have evidence of atopy (eg, food allergies, eczema) and airway pathology characteristic of asthma.^{17,28}

A new phenotype of wheezing in preschool children has recently been described, although it has not, at present, been included in national asthma guidelines. This new category, "severe intermittent wheezing," describes

KEY POINT

The American Academy of Pediatrics and the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends annual influenza vaccination for all children with asthma.

TABLE II. SOURCES OF ALLERGEN EXPOSURE AND ACTIONS TO TAKE.^{22,23}

| Sources | Actions |
|---------------------------------|---|
| Allergens from animals with fur | Remove animals from the home/sleeping area. |
| Cockroach allergen | Clean the home thoroughly and often. Use pesticide spray but make sure the child is not at home when spraying occurs. |
| Domestic dust mite allergens | Wash bed linens/blankets weekly in hot water. Dry in a hot dryer/sun. Encase pillows/mattresses in airtight covers. Replace carpets with linoleum/wood flooring, especially in sleeping rooms. Use vinyl/leather/plain wooden furniture instead of fabric-upholstered furniture. If possible, use vacuum cleaners with filters. |
| Drugs | Do not take β -blockers/aspirin or NSAIDs if these medicines cause asthma symptoms. |
| Indoor mold | Reduce dampness in the home; clean damp areas frequently. |
| Outdoor pollens and mold | Close windows/doors. Remain indoors when pollen/mold counts are highest. |
| Physical activity | Do not avoid physical activity. Exercise symptoms can be prevented/diminished by taking a rapid-acting inhaled β_2 -agonist, or cromone, before strenuous exercise. Furthermore, continuous treatment with inhaled glucocorticosteroids markedly reduces the occurrence of exercise-induced asthma. |
| Tobacco smoke | Stay away from tobacco smoke. Children and their families should not smoke. |

children, age 12 to 59 months, who experience severe wheezing episodes associated with atopic features and significant illness-related morbidity, occurring over otherwise extended periods of wellness.²⁹

A clinical index based on the presence of wheeze before age 3 years and a history of atopy (family history of asthma or eczema), or 2 of 3 minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis) have been shown to predict the presence of asthma in later childhood.^{8,30} A clinical index (referred to as the Asthma Predictive Index) to define asthma risk may be seen in **Table III**.⁸ Symptoms such as frequent wheezing (>3 times a year), activity-induced cough or wheezing, cough particularly at night and early morning, absence of seasonal variation in wheeze, and persistence of symptoms after age 3 years usually warrant a diagnosis of asthma. However, in very young children, alternative causes may explain such symptoms.²² Neonatal onset of symptoms, failure to thrive, vomiting, and focal lung and cardiovascular signs suggest a diagnosis other than asthma. A sweat test (to exclude cystic fibrosis), measurements of immune function, chest radiography, and reflux studies can help rule out these other possible causes of asthma.^{6,31}

Because airway and lung function inflammation measurements are difficult to make in young children, diagnosis of asthma is usually made based on clinical signs and symptoms. The majority of young children who wheeze in infancy do not wheeze after the age of 3 years—the wheezing is transient and benign. One way to distinguish transient wheezing from persistent atopic wheezing is to take a detailed history to determine risk factors, triggers, age of onset, temporal pattern of

symptoms, and concomitant symptoms. Children with persistent atopic wheezing will usually begin wheezing after the first year of life, have discrete attacks with symptom-free periods, frequent symptoms that are exacerbated at night, and a family history of asthma. A history of atopy (eg, food allergies or eczema) is also common. Laboratory tests may reveal elevated serum IgE and peripheral blood eosinophilia.²⁸

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ASTHMA MANAGEMENT IN CHILDREN

The goals of asthma management in children are to control asthma symptoms, maintain normal activity levels, maintain pulmonary function, and prevent asthma exacerbations. The chronic inflammation of the airways associated with asthma may, over time, lead to airway remodeling and loss of pulmonary function that may not be entirely reversible with medication. Airway damage and remodeling, manifested as thickening of the reticular basement membrane, may occur even before symptoms appear or a diagnosis of asthma is made. This underscores the importance of early intervention and treatment.²⁸

Childhood asthma management guidelines are continually being updated based on emerging evidence from clinical trials. Recently, updates were made to the guidelines of NAEPP coordinated by the National Heart, Lung, and Blood Institute of the National Institutes of Health, as well as GINA, to reflect these developments. The 2007 NAEPP guidelines provide separate recommendations for very young children (age 0–4 years), young children (5–11 years), and youths (12 years and older).²³ Asthma management in children comprises several facets, including educating children and their parents about simple asthma management skills, identifying and reducing exposure to allergens (avoidance of triggers), assessing severity of asthma and administering appropriate therapy based on the current level of control, monitoring asthma

TABLE III. A CLINICAL INDEX TO DEFINE ASTHMA RISK.*

| Major Criteria | Minor Criteria |
|------------------------------------|--------------------------------------|
| 1. Parental MD asthma [†] | 1. MD allergic rhinitis [§] |
| 2. MD eczema [‡] | 2. Wheezing apart from colds |
| | 3. Eosinophilia (≥4%) |

*Loose index for the prediction of asthma: History of early recurrent wheezing plus at least 1 of 2 major criteria or 2 of 3 minor criteria.

[†]History of a physician diagnosis of asthma.

[‡]Physician diagnosis of atopic dermatitis.

[§]Physician diagnosis of allergic rhinitis.

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control and adjusting therapy as required, and managing asthma exacerbations.³¹

In children, pharmacologic management of asthma involves a stepwise approach in which therapy is based on severity and on the current level of asthma control and current treatment (**Figures 1 and 2**).^{23,31} For example, if asthma is not controlled (based on symptoms, lung function parameters, and use of rescue medication), therapy is intensified. If symptoms are well controlled for several months, therapy can be stepped down so that minimum effective doses of medication can be used to maintain control.

Very Young Children (0–4 Years of Age)

For very young children with intermittent asthma (ie, occasional symptoms of short duration that do not interfere with daily activities or sleep), daily medication is not required—these patients can take short-acting β -agonist reliever medication as needed.^{23,31} It should be noted, however, that a significant proportion of pediatric patients who present to the emergency department with asthma exacerbations are classified as having intermittent disease.³²

For treatment-naïve patients with mild persistent asthma, therapy is usually started at step 2, where the preferred daily treatment is low-dose inhaled corticosteroids (ICSs); the leukotriene modifier, montelukast, or cromolyn may be used as an alternative therapy. If adequate control is not achieved with these agents, increasing low-dose ICSs to medium-dose ICSs is the preferred treatment (step 3) for children 0 to 4 years of age.³¹ If asthma is still uncontrolled with this regimen, therapy is intensified further to step 4, where the preferred treatment is medium-dose ICSs plus either a long-acting β_2 -agonist (LABA) or montelukast (although it should be noted that no clinical trial data are currently available for the use of LABA in this age group).²³ Asthma that is still not controlled with these medications may require high-dose ICSs plus LABA or montelukast (step 5). Oral corticosteroid therapy in combination with a high-dose ICS and either LABA or montelukast may be given if warranted (step 6).²³

Young Children (5–11 Years of Age)

In young children (defined as 5–11 years of age) with mild persistent asthma, initial therapy again consists of low-dose ICSs. A leukotriene antagonist (eg, montelukast), cromolyn, nedocromil, or theophylline may also be used in lieu of ICS therapy, although these medica-

tions should normally be regarded as nonpreferred. For young patients who are not controlled on these medications or patients who have moderate persistent asthma, therapy is intensified to step 3, where either low-dose ICSs or medium-dose ICSs, plus a second agent (LABA, leukotriene modifier, or sustained-release theophylline) is administered. In step 4, medium-dose ICSs used in combination with LABA are the preferred treatment; medium-dose ICSs plus leukotriene receptor antagonist or theophylline are an alternative.²³ In step 5, high-dose ICSs plus LABA is the preferred treatment, with high-dose ICSs plus either a leukotriene modifier or theophylline as an alternative.²³ (As with the 0–4-year age group, no clinical trial data are available for the use of LABA in children 5–11 years of age.) In step 6, the preferred treatment is to add an oral corticosteroid to high-dose ICSs plus a LABA omalizumab; the alternative is to use high-dose ICSs plus either a leukotriene modifier or theophylline plus an oral corticosteroid.²³

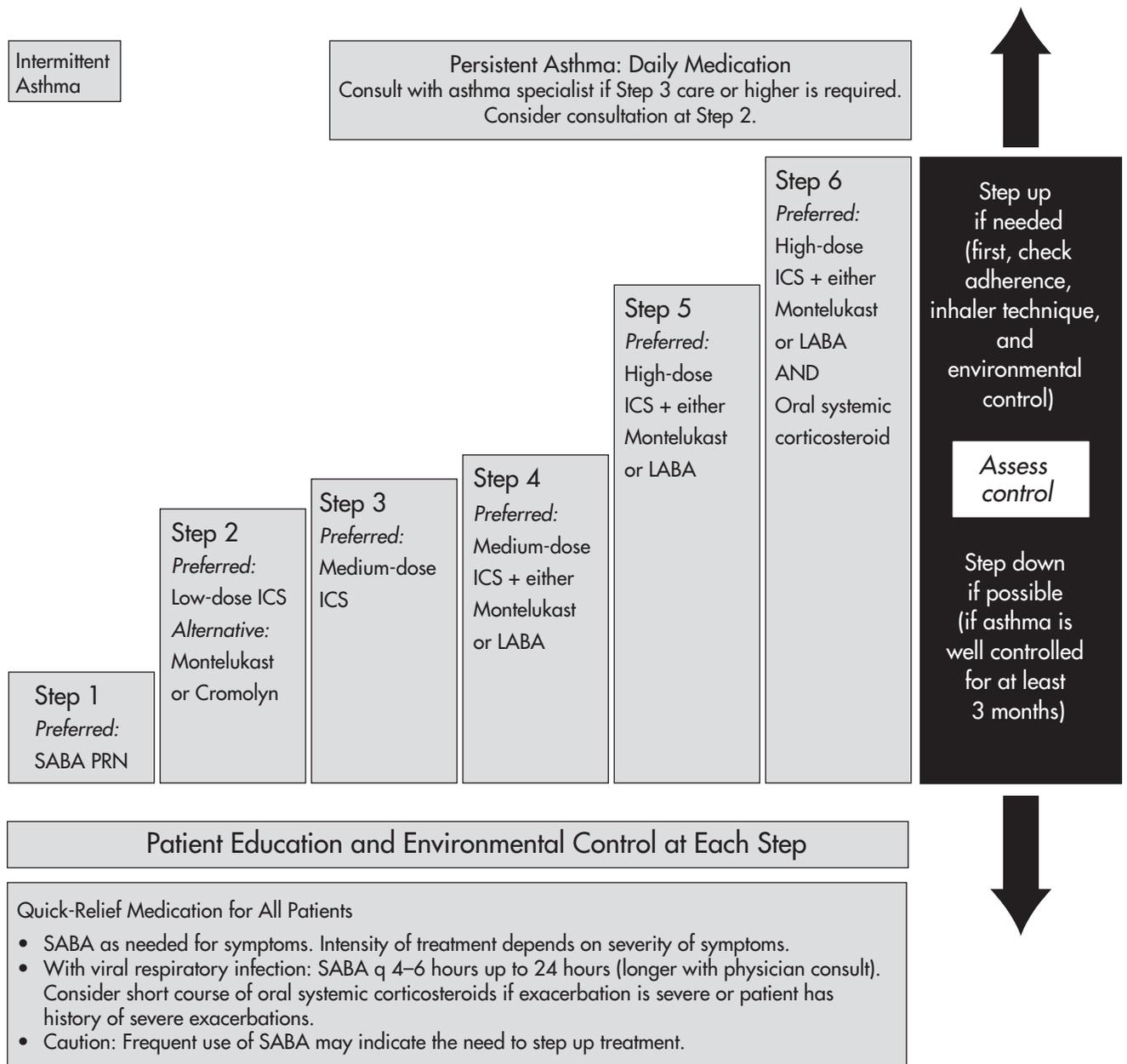
Delivery Devices

The choice of delivery device depends on the age of the child, efficacy of drug delivery, ease of use, safety, and cost-effectiveness. In children younger than 4 years, a pressurized metered-dose inhaler (MDI) with a spacer and face mask or a nebulizer with a face mask (younger children) or mouthpiece (older children) is recommended. In children age 4 to 6 years, an MDI with a dedicated spacer and mouthpiece is preferred. For older children, a dry powder inhaler, breath-actuated pressurized MDI, or pressurized MDI with spacer and mouthpiece are all viable options. It is important that the inhalation delivery system be matched to the patient's needs and developmental level, and it is vital that a child's inhalation technique be checked to ensure safe and effective medication delivery.

ICSs are the cornerstone of long-term asthma management in children of all ages. In children older than

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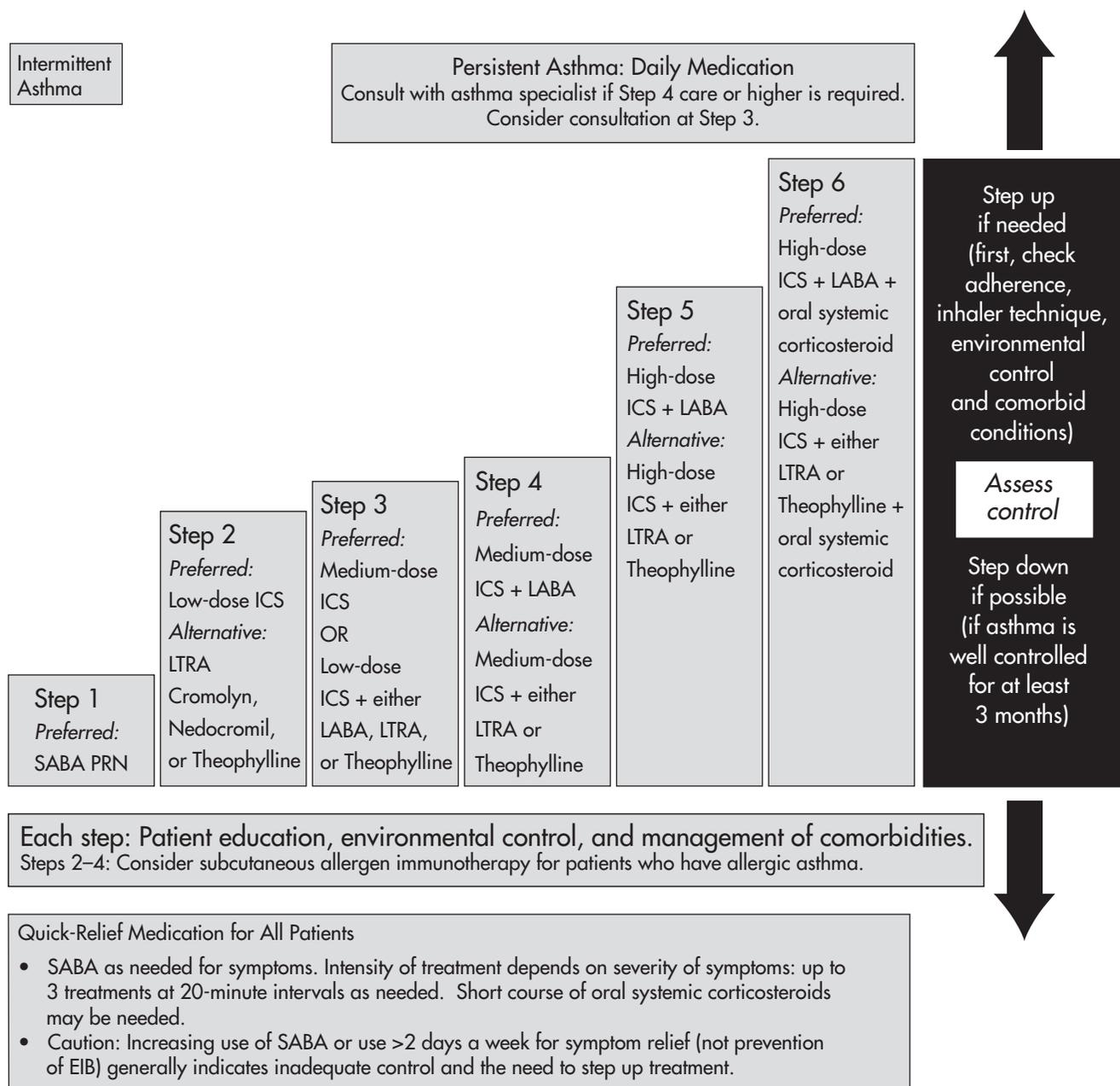


SABA = inhaled short-acting β_2 -agonist; ICS = inhaled corticosteroid; LABA = inhaled long-acting β_2 -agonist.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4 to 6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0 to 4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

Figure 1. Stepwise approach for managing asthma in very young children (0–4 years of age).²³



SABA = inhaled short-acting β_2 -agonist; ICS = inhaled corticosteroid; LABA = inhaled long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist, EIB = exercise-induced bronchospasm.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS and ICS + LABA are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

Figure 2. Stepwise approach for managing asthma in young children (5–11 years of age).²³

5 years, even low doses of ICSs result in marked and rapid clinical improvements in symptoms and lung function. Mild disease can be well controlled with ICS monotherapy. Maintenance treatment with ICSs controls asthma symptoms; reduces the frequency of acute exacerbations and hospital admissions; improves quality of life, lung function, and bronchial hyperresponsiveness; and reduces exercise-induced bronchospasm.⁹ For these reasons, ICS therapy is recommended as first-line treatment for the long-term management of asthma in children older than 5 years as well as very young children (0–4 years of age).

KEY POINT

Inhaled corticosteroids are the cornerstone of long-term asthma management in children of all ages.

Leukotriene antagonist monotherapy can provide improvement in children >5 years of age. In children 2 to 5 years of age with intermittent asthma, leukotriene antagonists may reduce viral-induced asthma exacerbations.³¹ For children whose asthma is not sufficiently controlled by low doses of ICSs, add-on leukotriene antagonist therapy may improve asthma symptoms and reduce exacerbations.³¹

An LABA is generally used as add-on therapy to ICSs in a fixed combination (ie, single inhaler) and may be used in children >5 years of age whose asthma is not sufficiently controlled by low or medium doses of ICSs, although clinical data regarding this approach in young children are limited.³¹ Combination therapy in teenagers and adults has been shown to improve peak flow and lung function measurements and can also reduce the frequency of exacerbations.³³ Monotherapy with LABAs should be avoided. The effect of LABAs, alone or in combination with ICSs, has not been studied sufficiently in children <5 years of age.³¹

Theophylline, as monotherapy or as add-on therapy to inhaled or oral corticosteroids, has been shown to be effective in controlling day and nocturnal asthma symptoms and improving lung function. However, theophylline therapy can be associated with significant side effects and, therefore, it is rarely used in children at the current time.

Sodium cromoglycate and nedocromil sodium have a limited role in the long-term management of asthma in children. Use of oral LABAs is not recommended in children due to side effects such as muscular tremor and cardiovascular stimulation. Systemic (ie, oral) corticosteroids should be used only for the treatment of acute exacerbations and for the rare child with the highest level of chronic asthma severity needing other therapy.³¹

For the acute management of asthma episodes, rapid-acting inhaled β_2 -agonist therapy (eg, albuterol inhaler) is the preferred treatment in children of all ages. These agents result in rapid bronchodilation and offer protection against exercise-induced bronchoconstriction for 0.5 to 2 hours.³¹

ASSESSING ASTHMA CONTROL IN CHILDREN

Once pharmacologic therapy has been initiated, the level of asthma control should be monitored so that adjustments to therapy can be made as early as possible. The primary approach to assessing asthma control is through patient and/or parental reports of daytime and nocturnal symptom severity and frequency, functional limitations (eg, exercise-induced bronchoconstriction), lung function (as measured by forced expiratory volume in the first second [FEV₁]), use of and need for rescue medication, and exacerbations, if any.³¹ Recommendations from the 2007 NAEPP guidelines for assessing asthma control and adjusting treatment may be seen in **Tables IV** and **V**.²³

Several questionnaires have been developed to assess asthma control, and their utility and validity have been evaluated in children. The Asthma Therapy Assessment Questionnaire measures asthma control using 7 questions about recent and chronic asthma symptoms and their consequences. Scores on this assessment are correlated with validated measures of child health status, asthma impact, and health care utilization. The Asthma Control Test is a simple 5-item self-administered questionnaire designed for use by children 12 years and older. Scores on this instrument range from 5 (poor control) to 25 (complete control), with scores of 19 or less indicating less than adequate asthma control.³⁴

Exercise-induced bronchoconstriction is a symptom of uncontrolled asthma and may be used to guide treatment. This aspect about asthma control is usually determined based on the clinical history since an exercise test

TABLE IV. ASSESSMENT OF ASTHMA CONTROL AND TREATMENT ADJUSTMENT IN CHILDREN 0 TO 4 YEARS OF AGE.²³

| Components of Control | | Classification of Asthma Control (0–4 Years of Age) | | |
|---|--|---|---|--|
| | | Well Controlled | Not Well Controlled | Very Poorly Controlled |
| Impairment | Symptoms | ≤2 Days/week | >2 Days/week | Throughout the day |
| | Nighttime awakenings | ≤1×/month | >1×/month | >1×/week |
| | Interference with normal activity | None | Some limitation | Extremely limited |
| | Short-acting β ₂ -agonist use for symptom control (not prevention of EIB) | ≤2 Days/week | >2 Days/week | Several times per day |
| Risk | Exacerbations requiring oral systemic corticosteroids | 0–1/year | 2–3/year | >3/year |
| | | Consider severity and interval since last exacerbation | | |
| | Treatment-related adverse effects | Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate with specific levels of control but should be considered in the overall assessment risk. | | |
| Recommended Action for Treatment | | <ul style="list-style-type: none"> • Maintain current treatment. • Regular follow-up every 1–6 months. • Consider step down if well controlled for at least 3 months. | <ul style="list-style-type: none"> • Step up (1 step) and • Reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options. | <ul style="list-style-type: none"> • Consider short course of oral systemic corticosteroids. • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative options. |

EIB = exercise-induced bronchospasm.

is time-consuming. Measurement of fractional concentration of exhaled nitric oxide (FeNO) is a relatively new noninvasive procedure that can be used to determine asthma control in children, since it is felt to be a marker of airway inflammation. FeNO determinations for purposes of asthma management is still in its infancy, and is presently limited due to the cost of doing the procedure, but it may someday be a routine test done in almost all children with asthma.³⁵

Persistence of symptoms and overuse of rescue medication may signal the need for more intense therapy—this may be achieved by increasing the dose of ICSs or adding a LABA. In children who are inadequately controlled with low to medium doses of ICSs, the addition of an LABA improves lung function and asthma control and reduces asthma exacerbations. Resolution of symptoms may require a reassessment of severity and appropriate step-down therapy. For example, children whose asthma is well controlled with medium doses of ICSs may be able to

reduce their daily dose. However, a reduction in therapy should only be initiated after the patient has experienced 3 months of stability, and should not occur during the season when the patient is normally symptomatic.

ADVANCES IN ASTHMA THERAPY IN CHILDREN

Limitations of Current Asthma Treatment for Children

ICS therapy with or without the addition of an LABA is a highly effective approach to asthma management in children. However, both physicians and parents may be reluctant to prescribe or use ICS therapy for fear of systemic side effects such as adrenal suppression and growth suppression.

The presence of exogenous corticosteroids in the circulation can reduce endogenous cortisol production and suppress the hypothalamic-pituitary-adrenal (HPA) axis. However, clinical experience with ICSs has demonstrated

TABLE V. ASSESSMENT OF ASTHMA CONTROL AND TREATMENT ADJUSTMENT IN CHILDREN 5 TO 11 YEARS OF AGE.²³

| Components of Control | | Classification of Asthma Control (5–11 Years of Age) | | |
|---|--|---|--|--|
| | | Well Controlled | Not Well Controlled | Very Poorly Controlled |
| Impairment | Symptoms | ≤2 Days/week but not more than once on each day | >2 Days/week | Throughout the day |
| | Nighttime awakenings | ≤1×/month | ≥2×/month | ≥2×/week |
| | Interference with normal activity | None | Some limitation | Extremely limited |
| | Short-acting β ₂ -agonist use for symptom control (not prevention of EIB) | ≤2 Days/week | >2 Days/week | Several times per day |
| Lung function | | | | |
| | • FEV ₁ or peak flow | >80% Predicted/ personal best | 60%–80% Predicted/ personal best | <60% Predicted/ personal best |
| | • FEV ₁ /FVC | >80% | 75%–80% | <75% |
| Risk | Exacerbations requiring oral systemic corticosteroids | 0–1/year | ≥2/year | |
| | | Consider severity and interval since last exacerbation | | |
| | Reduction in lung growth | Evaluation requires long-term follow-up. | | |
| | Treatment-related adverse effects | Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate with specific levels of control but should be considered in the overall assessment risk. | | |
| Recommended Action for Treatment | | <ul style="list-style-type: none"> • Maintain current treatment. • Regular follow-up every 1–6 months. • Consider step down if well controlled for at least 3 months. | <ul style="list-style-type: none"> • Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options. | <ul style="list-style-type: none"> • Consider short course of oral systemic corticosteroids, • Step up at 1–2 steps and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options. |

EIB = exercise-induced bronchospasm; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.

that the risk of HPA suppression and adrenal insufficiency is very low, particularly when the agents are used in recommended doses. Children with severe asthma who are taking high doses of ICSs or receiving additional topical corticosteroids may be at increased risk for HPA suppression and should have plasma cortisol levels monitored.³⁶

The potential for ICSs to suppress growth is of particular concern to parents of children with asthma. Although oral corticosteroids are potent inhibitors of linear growth in children, ICSs are associated with a much lower risk of growth suppression. Studies have found that although moderate-dose ICS therapy does result in mild detectable slowing of 1-year growth in prepubertal children, effects on adult height are not

detectable—thus, children treated with ICSs reach normal adult height.³⁶ ICS formulations with more efficient first-pass hepatic inactivation of swallowed drug may reduce the risk of growth suppression. Children aged 4 to 10 years are more susceptible to the growth-suppressing effects of ICSs than adolescents.

ICSs are also associated with local side effects in the oropharyngeal cavity such as oral candidiasis and voice changes, a result of deposition of active drug in the mouth and pharynx after inhalation.³⁷

Despite the efficacy of ICSs and the relatively favorable safety profile of ICSs compared with oral corticosteroids, there is overriding concern about the adverse effects of these agents, which leads to suboptimal medication ad-

herence. Moreover, proper administration of inhaled therapy requires training on the part of parents (in the case of very young children) as well as young children. Incorrect use of an inhaler device can lead to suboptimal dosing and inadequate control of asthma symptoms. These drawbacks have prompted the development of novel formulations and delivery systems that improve drug delivery to the airways, minimize local and systemic side effects, and facilitate administration in young children.³⁸

Pharmacologic and Medical Advances

Omalizumab is a recombinant human monoclonal antibody directed at IgE. It is approved for use in adults and is now being studied in pediatric patients. IgE plays a fundamental role in the pathogenesis of asthma. IgE antibodies bind to high-affinity IgE receptors on the surface of mast cells. Cross-linking of receptor-bound IgE antibodies by the allergen results in degranulation of mast cells and the release of various proinflammatory mediators, resulting in airway smooth muscle constriction, edema, and increased airway mucous secretion; this in turn leads to airflow limitation and asthma symptoms such as wheezing, cough, and shortness of breath. Given the significant role of IgE in the allergic response, agents that inhibit IgE synthesis or activity may be of value in the management of asthma.³⁹

Omalizumab forms a small inactive complex with free IgE, preventing its interaction with effector cells and subsequent mast-cell degranulation. A single injection of omalizumab has been shown to significantly reduce serum concentrations of free IgE, attenuate early and late asthmatic responses after allergen inhalation, and improve asthma symptom control. Omalizumab therapy also has a steroid-sparing effect and has been shown to be effective in reducing asthma exacerbations when used with ICSs and during steroid tapering phases of therapy. Omalizumab also has tolerability comparable to placebo, with the exception of injection-site reactions and rare anaphylaxis.³⁹

Also in development are novel ICS agents that address the safety concerns of currently available ICSs without compromising efficacy. The major factors that influence the clinical efficacy of ICSs are drug deposition in the airways, receptor binding affinity, and the time the drug is available at the site of action.

The higher the proportion of drug deposited in the lungs, the higher the efficacy of the ICSs. The degree of drug deposition in the airways is dependent on the deliv-

ery device, formulation used, and particle size. The aerosol propellant used in the MDI can affect drug deposition—MDIs that use hydrofluoroalkane as a propellant and are a solution rather than a suspension, may be more effective in delivering drug to the airways than those that use chlorofluorocarbons.⁴⁰ Particle size should be small enough so that the inhaled particles can reach the smallest airways, which have a diameter of ~2 μm . Particles between 2 and 5 μm will deposit in the bronchi and bronchioles, and those between 1 and 2 μm will deposit in the peripheral lung. Deposition in both areas of the lung would exert the optimal therapeutic effect.⁴⁰ Suspension formulations have larger particle sizes than solution formulations; thus, solution formulations have greater intrapulmonary deposition than suspension formulations.^{37,40}

A higher binding affinity for the glucocorticoid receptor suggests higher potency; however, it may also mean more side effects since adverse effects are mediated through the same receptor. Receptor binding affinity is measured relative to that of dexamethasone, arbitrarily set at 100. Of the currently available ICSs, fluticasone propionate has a relative receptor binding affinity of 1800.⁴⁰

The local and systemic side effects of ICSs, to a great extent, depend on the potency of the agent, the delivery system, and the absorption characteristics of the steroidal agent. For example, MDIs deposit about 10% of the administered dose in the airways and 80% into the mouth and oropharynx, from where it is swallowed and absorbed systemically. A spacer device can increase the proportion of the dose deposited in the airways to about 20%.³⁶ Differences in the pharmacokinetic properties of ICSs also affect their propensity to cause side effects. The amount of drug available systemically after oral administration is <1% for fluticasone propionate, 10.6% for triamcinolone acetonide, 11% for budesonide, and 41% for beclomethasone dipropionate.³⁶

Safety of an ICS can be enhanced by reducing oral and systemic bioavailability. Oral bioavailability may be reduced by using small particles to enhance respiration and delivery to the lungs or by ensuring that drug deposited in the oral cavity is inactive. Systemic bioavailability of an ICS depends on the amount absorbed into the circulation from the oral cavity, deposition of drug in the lung, as well as the pharmacokinetic and pharmacodynamic properties of the ICS, including half-life, clearance, degree of protein binding, and absorption. Properties of an

ideal ICS are a half-life that balances efficacy and safety, a high clearance rate to reduce the time that the drug is available systemically, and increased serum protein binding to minimize the levels of free drug in the circulation.⁴⁰

Ciclesonide is a novel ICS with pharmacokinetic and pharmacodynamic properties that reduce oral and systemic availability, thereby improving the safety profile. Ciclesonide, the parent drug, is inactive when administered by inhalation, but is converted in the lungs to the active metabolite desisobutyryl-ciclesonide, which has potent anti-inflammatory effects. Thus, ciclesonide provides local (ie, pulmonary) anti-inflammatory activity with less potential oral and systemic side effects.³⁷ Ciclesonide itself has low affinity for the glucocorticoid receptor whereas the active metabolite has a relative binding affinity (1200) comparable to that of other potent ICSs.³⁷ The oral bioavailability of both ciclesonide and the active metabolite is <1%; the small fraction that is absorbed orally undergoes extensive first-pass metabolism in the liver; thus, systemic exposure is very low after oral ingestion of ciclesonide, suggesting a low potential for systemic side effects.³⁷

Ciclesonide has high distribution in the lung (52%) and a low rate of distribution in the oropharyngeal cavity, reducing the potential for local side effects.³⁷ Ciclesonide is highly bound to plasma proteins and, as a result, only about 1% of circulating ciclesonide and the active metabolite is unbound.³⁷ This may explain ciclesonide's low potential for cortisol suppression. Ciclesonide also has a short half-life and is eliminated rapidly after reaching the general circulation, further reducing systemic exposure after inhalation.³⁷

The efficacy and safety of ciclesonide in children age 4 to 11 years have been evaluated in 2 identical, 12-week, double-blind, placebo-controlled, parallel-group trials.⁴¹ In these trials, a total of 1031 children were randomly assigned to receive placebo or ciclesonide (40, 80, or 160 µg) once daily. No other medications were administered except an albuterol hydrofluoroalkane MDI as rescue medication. The primary outcome was the change in FEV₁; secondary end points included asthma symptom scores, daily albuterol use, and HPA function. At the end of the study, pulmonary function (as measured by FEV₁) and asthma symptom scores improved and rescue medication use decreased in all ciclesonide groups; the improvements in the 80- and 160-µg groups were statistically significant versus placebo. HPA-axis function was within the normal range, with no clinically significant changes

reported. The incidence of treatment-emergent adverse events was comparable in the 4 treatment groups.⁴¹

In a noninferiority trial, ciclesonide was shown to be comparable to fluticasone propionate in terms of an increase in FEV₁ and peak expiratory flow, improvements in asthma symptoms, reduction in rescue medication use, and asthma symptom-free days in 556 children age 6 to 15 years with persistent asthma. However, ciclesonide appeared to be associated with fewer systemic effects on the HPA axis than fluticasone propionate.⁴²

In a double-blind, placebo-controlled 4-period crossover study of 24 children with asthma, ciclesonide 160 µg/day was comparable to placebo with respect to effects on lower-leg growth and urinary cortisol secretion, confirming its low potential for systemic side effects and cortisol suppression at maximally effective doses.⁴³

Advance in Behavioral Intervention

Disease management programs are of particular benefit in pediatric patients with asthma. Self-management programs and asthma camps that teach children how to recognize asthma symptoms, use an inhaler and peak flow meter, manage asthma episodes and exacerbations, and monitor response to therapy have been shown to improve asthma control, reduce school absenteeism, and reduce health care utilization.⁴⁴

SUMMARY

Asthma, the most common chronic illness in childhood, represents a major cause of preventable morbidity and health care resource utilization. National and worldwide guidelines have been issued for the management of asthma in children. These guidelines recommend first establishing a diagnosis and assessing the severity of disease, initiating pharmacologic therapy based on symptoms and lung function, and adjusting doses and agents as required based on the level of asthma control. The cornerstone of therapy for persistent asthma in children are ICSs. These agents control asthma symptoms, reduce asthma exacerbations, and improve pulmonary function. However, there is a reluctance on the part of physicians as well as parents to use ICSs, primarily due to fear of adverse effects on adrenal function and growth. The systemic adverse effects of ICSs and other inhaled therapy depend on the oral and systemic bioavailability of the particular agent, which in turn depends on the delivery device and the pharmacokinetic and pharmacodynamic properties

of the agent itself. Recent research efforts have focused on ways to improve inhalant drug delivery to the lungs and minimize oral and systemic bioavailability so as to improve the therapeutic benefit:risk ratio. Ciclesonide is a novel ICS prodrug whose properties allow for targeted delivery to the lungs and low oral and systemic bioavailability, which in turn results in fewer systemic side effects and an improved safety profile.

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Dialogue Box

EDITORIAL BOARD

What contributing factors should be considered in patients with childhood asthma whose condition continues into adulthood?

CHIPPS

Allergic comorbidities play a major role, especially in nonsmokers. Patients with an early onset of allergic rhinitis (particularly those sensitized to aeroallergens, such as house dust mites, dog or cat dander, with a high level of exposure), a history of eczema, or a strong family history of asthma—these are the patients much more likely to have persistence of asthma into adulthood.

EDITORIAL BOARD

In patients with a family history of asthma, would aggressive treatment of allergic rhinitis reduce the risk for developing asthma?

CHIPPS

Yes. This was well demonstrated in the Preventive Allergy Treatment study, which found in a group of patients with allergic rhinitis and a family history of asthma that treating with immunotherapy for 3 years produced a 2.4-fold relative risk reduction of developing asthma and a little >3-fold reduction in the risk for developing asthma at 10 years out. Those were the long-lasting effects of just 3 years of immunotherapy.

EDITORIAL BOARD

Does menstruation impact asthma?

CHIPPS

Absolutely, menses-related asthma can be a very significant problem. It's a well-documented fact that exacerbations occur during menstruation in 10% to 20% of young female adult asthmatics. Indeed, some have very striking exacerbations just prior to withdrawal bleeding. Fluctuating levels of female hormones appear responsible.

EDITORIAL BOARD

Do oral contraceptives impact this?

CHIPPS

Yes. It gets better. It particularly gets better using the very low-dose birth control pills producing periods once every 60 to 90 days. In addition, an improvement in asthma has been seen in women on intramuscular injections of depot medroxyprogesterone acetate.

EDITORIAL BOARD

What level of eosinophilia would be a significant predictor of asthma?

CHIPPS

An absolute eosinophil count >400/mm³. It is the absolute count that is predictive, not the percentage on the differential.

EDITORIAL BOARD

When would you consider ordering pulmonary function tests (PFTs) in a young child with recurrent wheezing?

CHIPPS

Following the second or third episode of wheezing, especially in a patient who has a positive asthma predictive index (API). For a patient with a positive API and a third episode of wheezing, the chances of asthma with persistence of symptoms is way north of 75%.

EDITORIAL BOARD

Do you require confirmation of the diagnosis on PFTs prior to starting a child on a long-term controller medication for asthma?

CHIPPS

No. Recognize that it's rare for a patient <5 or 6 years of age to be able to do good PFTs. In a patient <5 or 6 years of age, I would generally initiate therapy with a positive API following the third episode of wheezing.

Dialogue Box

EDITORIAL BOARD

Does early initiation of inhaled corticosteroids (ICSs) impact the natural history of the disease?

CHIPPS

No. There are at least 4 recent studies which demonstrated that the natural history of the disease is not impacted. What is accomplished is control of the burden of the illness and improvement of lung function. Bronchial hyperreactivity is improved while the patient is receiving treatment, but within 3 to 4 months of stopping treatment, the beneficial effects are gone.

EDITORIAL BOARD

Are all ICS agents approved for use in asthma patients <5 years of age?

CHIPPS

No. The 3 ICSs that are approved are budesonide (Pulmicort Respules[®] [AstraZeneca LP, Wilmington, Delaware]), which is approved down to 1 year of age; fluticasone (Flovent[®], and also a component of Advair[®] HFA [GlaxoSmithKline, Triangle Park, North Carolina]), which is approved down to 4 years of age; and ciclesonide (Alvesco[®] [Nycomed US, Inc., Florham Park, New Jersey]), which is approved down to 12 years of age.

EDITORIAL BOARD

Is there a difference between them and the ICSs not approved by the US Food and Drug Administration?

CHIPPS

Not really. When an inhaled steroid is reformulated into a hydrofluoroalkane solution, this may potentially have a greater effect on linear growth.

EDITORIAL BOARD

Do you have concerns with the use of ICSs and suppression of the hypothalamic-pituitary-adrenal (HPA) axis?

CHIPPS

Not really. You've got to be on a medium or high dose for that to occur. Usually only very high doses of ICS

cause a clinically significant suppression of the HPA axis.

EDITORIAL BOARD

In a patient on high-dose ICSs, how would you assess whether suppression of the HPA had occurred?

CHIPPS

Although a rough screening test, I usually measure a morning plasma cortisol level. If <5, I'd refer the patient for endocrinology consultation.

EDITORIAL BOARD

What is the cause of intermittent wheezing in young children who don't have an atopic basis?

CHIPPS

They have viral-induced airway reactivity with mucus plugging. They have bronchial hyperresponsiveness as a result of their small airway caliber and very poorly developed β -receptors that cause them to be somewhat bronchodilator unresponsive. These patients tend to have morbidity only at the time of illness. Once their illness abates, their airways go back to normal and they're back at baseline. They have a >65% chance of not being symptomatic once they get past the third or fourth grade and move toward puberty.

EDITORIAL BOARD

How common is the triad of asthma, nasal polyps, and aspirin sensitivity?

CHIPPS

It occurs in about 3% to 5% of asthmatics.

EDITORIAL BOARD

Can patients have 2 components of the triad without having the third?

CHIPPS

Yes, I regularly see patients who have chronic sinus disease and nasal polyps who are aspirin-sensitive

Dialogue Box

and who have hives but don't have asthma. However, at least half to two thirds of them will also have asthma.

EDITORIAL BOARD

Please comment further on the prerequisites for stopping ICSs in a patient with asthma.

CHIPPS

First, you need to make sure that asthma stability and control are present for at least 3 months. Second, you need to make sure that the patient is out of their at-season risk. For example, even if you have a young child who has been stable during the 3 months of summer, you'd be in leave of your senses to stop their medicine knowing that you're entering into the fall illness season. Furthermore, for a patient with a significant allergic diathesis, it makes no sense to me to stop their medicines before their allergy season even though they've been stable for 3 months. The point of all this is to use your head and confirm that, even if control is achieved and stability has been gained for 3 months or more, you're stepping down therapy at a time when you would not expect them to have significant risk of exacerbation.

EDITORIAL BOARD

Do you have any concerns with reducing bone mineral density in a teenage female on ICSs?

CHIPPS

Yes, if they're on a medium dose or above. I emphasize to such patients the importance of taking at least 1200 milligrams of calcium plus vitamin D daily.

EDITORIAL BOARD

ICSs are regarded as the preferred therapy at nearly all treatment steps in the new guidelines. In a patient who does not respond at a given step, do you ever try an alternative drug at that same step as opposed to moving to a higher step?

CHIPPS

Since up to 20% to 25% of asthmatic patients may not respond appropriately to inhaled steroids, it would be very reasonable to question whether an ICS is the right drug in a patient who does not seem to respond to a low dose (and surely the low end of a medium dose) of an ICS. In light of this, I would almost always try an alternative agent prior to moving up a step in treatment.