Management of Asthma in Children: Translating Patient-Oriented Evidence into Practice

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Asthma is the most common medical diagnosis among hospitalized children. In the United States, it accounts for approximately 15% of nonsurgical hospital admissions in the pediatric age-group. Asthma is a leading cause for emergency care requirements and for missed school as well as a cause for considerable morbidity, disability, and occasional mortality at all ages.[1]

Despite these discouraging statistics, convincing data indicate that this failure of asthma management is not the result of inadequate therapeutic potential but instead represents ineffective delivery of medical care.[2,3] Unfortunately, the most widely distributed guidelines for asthma management have been complex and not readily applicable in the primary care setting for pediatric asthma.[4,5] Guidelines proposed by the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health were first published in 1991 with major revisions in 1997 and 2002 and a further revision anticipated later in 2007.[4,5] Each of the previous versions has had well over 100 pages with multiple complex diagrams. The latest revision submitted for review prior to final editing and distribution had over 600 pages in draft form. While there was an attempt to apply the principles of evidence-based medicine in the latest update of the guidelines, their length and consequent complexity distract from the goal of providing guidance to primary care physicians.

This article reviews NHLBI guideline[4,5] recommendations that we regard as evidence-based, low-intensity measures that provide the highest yield in providing a favorable outcome for asthma management. These measures focus on making the correct diagnosis, characterizing the clinical pattern, prescribing therapy appropriate for the clinical pattern, providing effective patient/parent education, advising elimination of exposure to environmental irritants, and providing effective monitoring and follow-up. Consistent with the most recent version of the NHLBI guidelines, the focus is on attaining control of asthma.

TAKE HOME POINTS

- Diagnose critically—do not underdiagnose or overdiagnose asthma.
- Characterize the clinical pattern as intermittent, chronic, or seasonal allergic.
- Viral respiratory infection–induced asthma is very common in young children and will not respond to or be prevented by maintenance medication, including inhaled corticosteroids.
- Patients and their parents should be provided with intervention measures (ie, an inhaled β_2-agonist [albuterol or pirbuterol] and an oral corticosteroid) along with verbal and written instructions regarding use for an acute exacerbation.
- Provide maintenance medication for chronic or seasonal allergic asthma.
- Eliminate exposure to tobacco smoke and other lung irritants.
- Determine whether allergens contribute to symptoms and minimize exposure, if possible.
- Monitor the clinical course with regularly scheduled visits; assess adherence to the medical regimen by checking pharmacy records if control is not attained.
- Settle for nothing less that control of asthma based on specified criteria.

DIAGNOSIS OF ASTHMA

Asthma is a disease characterized by hyperresponsiveness of the airways to various stimuli, resulting in

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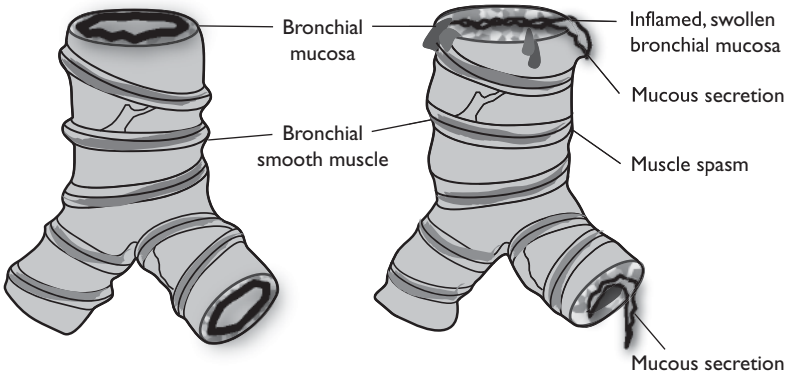

Figure 1. Artist's rendition of the 2 components of airway obstruction in asthma. Bronchospasm and inflammation with mucosal edema and mucous secretions are illustrated on the right. The normal airway is illustrated on the left.

airway obstruction that is reversible to a substantial degree either spontaneously or with treatment. The airway obstruction is caused by varying degrees of bronchospasm and inflammation. Inflammation results in mucosal edema and mucous secretion (**Figure 1**).

Asthma should be considered when patients present with the following symptoms: recurrent or chronic wheezing most prominent on expiration; recurrent or chronic coughing; repeated diagnoses of bronchitis; or repeated diagnoses of pneumonia not clinically consistent with pyogenic infection. The diagnosis of asthma is most efficiently confirmed by demonstrating the complete response of symptoms or reversibility of airway obstruction measured with spirometry following administration of an inhaled β_2-adrenergic-receptor agonist or a 5- to 10-day course of high-dose oral corticosteroids (**Table 1**). Patients clearly not made asymptomatic or not having substantial reversibility of airway obstruction with these measures should be referred to an appropriate subspecialist for further evaluation for other inflammatory disorders or occasionally functional disorders that can cause similar symptoms, such as cystic fibrosis, primary ciliary dyskinesia,[9] tracheal or bronchial malacia,[10] foreign body aspiration, vocal cord dysfunction,[11] hyperventilation,[12] or habit cough syndrome.[13,14]

Although the diagnosis of asthma has no lower age limit, making this diagnosis in young children has been associated with controversy.[15] In young children, symptoms resulting from airway inflammation associated with asthma all too frequently have been misdiagnosed as pneumonia and bronchitis,[16] or alternative diagnostic terminology, such as "reactive airway disease,"[17] has been used. Calling acute asthma exacerbations bronchitis or pneumonia results in ineffective and unnecessary use of antibiotics.[18,19] However, asthma is also overdiagnosed, which results in unnecessary use of medication and ineffective treatment.[12,14,20,21]

Table 1. Doses of Prednisone or Prednisolone to Obtain Maximal Effect on Asthmatic Airways

Age	Dose*
Infant	15 mg twice daily
1–3 yr	20 mg twice daily
4–13 yr	30 mg twice daily
> 13 yr	40 mg twice daily

Note: Because there are insufficient dose-response data to support recommendations based on weight or body size, these are empirical doses solely based on our experience that lower doses less reliably provide complete cessation of symptoms with the goal of a 5- to 10-day course. Lower doses almost certainly will be adequate for some patients, and minor side effects require limiting dosage in some patients to once daily in the morning only. There is no reason to taper short courses of corticosteroids.[6–8]

*Reduce dose to morning only if irritability or insomnia is problematic after the initial 1 or 2 days of treatment.

CLINICAL CHARACTERIZATION OF ASTHMA

Phenotypical Patterns

Because of the heterogeneous nature of asthma, making the diagnosis is not sufficient for the development of the most appropriate treatment plan. Planning effective and efficient strategies for managing asthma requires identification of the clinical pattern of disease in the patient to be treated. These clinical patterns generally can be determined by a brief history that addresses the questions shown in **Table 2**.

Intermittent. The intermittent asthma pattern is characterized by episodic symptoms. The most common phenotype is asthma that is solely triggered by viral respiratory infections, with periods between the infections being free of symptoms. Typically, parents of children with this pattern will say, "Every time he/she gets a cold, it goes into his/her chest." Generally, this pattern of asthma begins in the first 1 or 2 years of life. The typical course is the onset of coryza from a

Table 2. Questions for Determining Patterns in Pediatric Asthma

At what age did onset of lower respiratory symptoms occur?
Are symptoms only associated with a viral respiratory infection?
Are there extended periods between episodes of respiratory symptoms where there is no cough or wheeze?
Is there a seasonal variation in symptoms, and does the season match that of inhalant allergens or the season of increased viral respiratory infections?
Are respiratory symptoms related to specific environmental exposures?
Are lower respiratory symptoms occurring daily for extended periods?

common cold virus followed by cough, wheezing, and respiratory distress of varying severity that progresses over the next 1 to 2 days. The duration of symptoms without effective intervention can be days, weeks, or months. During asymptomatic periods between colds, these patients have no evidence of airway inflammation when examined by bronchoalveolar lavage.[22] This is the most common type of asthma seen in preschool-aged children, and many of these children continue to have asthma with viral respiratory infections throughout life.

The frequency of colds in preschool-aged children is increased for those in day care or those with an older sibling in school. The seasonal pattern for the intermittent asthma phenotype parallels the seasonal pattern of cold viruses that begin with the onset of the school year and continues throughout the fall, winter, and spring.[23] Because children experience an average of 7 colds per year, with 15% of children experiencing 12 or more,[24] the symptoms can appear to be continuous for a period of time; summer time generally is a period free of symptoms in children with asthma limited to exacerbations from viral respiratory infection. Distinguishing this common intermittent pattern of asthma from a chronic or seasonal allergic pattern is important because, unlike the latter, the most effective maintenance therapies will not prevent the viral respiratory infection–induced asthma that characterizes it.[25]

The absence of specific IgE in an infant or toddler with a pattern of intermittent viral respiratory infection–induced asthma is generally predictive of a future associated with a greatly reduced frequency of symptoms or remission over time. While most infants and toddlers with asthma have this intermittent pattern, allergy testing is effective in identifying those who have an allergic component currently contributing to their disease or those who are at risk for more persistent symptoms in the future.[26] Contrary to the belief of some, there is no age limit for allergy testing (**Figure 2**).

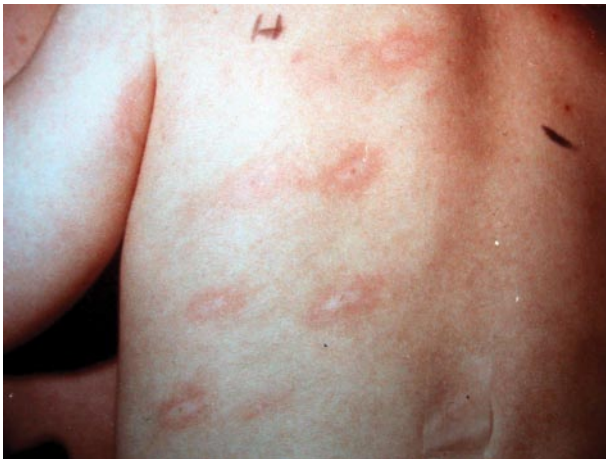

Figure 2. This 11-month-old infant was hospitalized at age 9 months with severe acute asthma preceded by rhinoconjunctivitis during the peak of the grass pollen season in a Northern California valley area where grass pollen is a major inhalant allergen. The typical wheal and flare of the multiple related species of grass pollen native to that area are seen on the left side of the infant's back. They are much larger than the histamine control (H), and there was no reactivity to the diluent control (C). Skin tests on the right side using other common inhalant allergens were all negative. While immunotherapy using injections of allergenic extracts rarely is indicated at this age, this infant illustrates a striking exception where benefit reasonably could be expected.

Chronic. Patients with chronic asthma experience virtually daily year-round symptoms and, in the absence of effective maintenance therapy, do not have extended symptom-free periods. These children may have begun with the viral respiratory infection–induced intermittent pattern of symptoms with subsequent evolution to persistent daily symptoms. Most, but not all, have an allergic component to their asthma.

Seasonal allergic. These patients experience daily symptoms during an inhalant allergy season. Allergens and seasonal patterns will vary with the geographic region. In the north central United States, the most common allergens are outdoor molds that grow on decaying vegetation from early spring through late fall, with peaks particularly in the spring and fall. In other parts of the world, seasonal symptoms may occur in reaction to molds, pollens, or a combination of both.

It is important to note that these clinical patterns may overlap. For example, patients with chronic disease often have intermittent exacerbations from viral respiratory illness and may have seasonal allergic exacerbations. Nonetheless, identification of the clinical pattern contributes to the determination of a therapeutic strategy.

Severity

All of the above clinical patterns can vary in severity from trivial to life-threatening. Questions to assess severity include:

- Do respiratory symptoms interfere with sleep?
- Do respiratory symptoms interfere with activity?
- How frequently is rescue medication (bronchodilator and systemic corticosteroids) used?
- How frequently is urgent care required (at a physician's office or emergency department [ED])?
- How frequently is hospitalization required?
- Has intensive care been required?
- Has ventilatory assistance been required?
- Have acute life-threatening events occurred?

Environmental Risk Factors

An assessment of the environment and its role in contributing to the patient's symptoms is necessary in characterizing asthma. The following questions can quickly identify the presence of relevant allergens and irritants:

- Is the patient's home located in an urban or rural area?
- What is the age of the home?
- Does the home have a basement, and are there dampness or water leakage problems?
- Is there a forced air heating system or central air conditioning?
- Are there pets in the home?
- Are there smokers in the home?
- Is there a nearby industrial or agricultural source of air pollution?

Patients living in rural homes, especially those on a farm, can have more intense exposure to outdoor molds during activities that stir up decaying vegetation, as in harvesting. Very old homes may be plagued by indoor mold, especially if there is a basement with dampness or water leakage. Forced air heating can distribute aeroallergens throughout the home but also provides an opportunity to utilize a high-efficiency air filter to minimize aeroallergens in the indoor environment. Pets are a common contributing factor to asthma, but these members of the family should not be blamed for symptoms without demonstrating specific IgE to the dog or cat and obtaining a convincing history that exposure contributes to morbidity. Cigarette smoke and other causes of burning vegetation, indoor fireplaces, and outdoor bonfires or leaf burning are important nonallergenic irritants that contribute to asthmatic symptoms.

Common and Uncommon Comorbidities

Atopic dermatitis and allergic rhinitis are commonly associated with asthma. The presence of atopic dermatitis in infants increases the likelihood that the child will develop allergic asthma and allergic rhinitis. Allergens that contribute to asthma symptoms also frequently are etiologic factors for allergic rhinitis. While the association of sinusitis and gastroesophageal reflux with asthma is well established, the claim by some that they have an etiologic role or contribute to the pathologic process of asthma is not supported by convincing evidence.[27,28]

An uncommon comorbidity in asthma is allergic bronchopulmonary aspergillosis (ABPA). ABPA is essentially an allergic pneumonia that occurs only in association with asthma or cystic fibrosis. It involves both antigen-specific IgE to *Aspergillus*, a common household mold, and antigen-specific IgG to *Aspergillus* antigens. The classic clinical presentation involves transient low-grade fevers associated with equally transient pulmonary infiltrates. Eosinophil-laden mucous plugs can develop, resulting in localized atelectasis. Airway damage eventually can occur, resulting in a pattern of proximal bronchiectasis characteristic of prolonged ABPA. If *Aspergillus*-specific IgE is present and the clinical pattern is consistent with ABPA, the presence of precipitating IgG antibodies to *Aspergillus* identified by double-gel diffusion confirms the diagnosis.[29] Treatment requires a sustained period of alternate morning prednisolone, the addition of itraconazole, and minimization of exposure to *Aspergillus*.

THERAPEUTIC STRATEGIES

The treatment of asthma can be divided into 2 therapeutic strategies: intervention measures for acute symptoms and maintenance measures for prevention of future symptoms. All patients require the ready availability of intervention measures. Patients with chronic asthma manifested by persistent year-round symptoms or with periods of seasonal allergic asthma also require maintenance medication, either continuously or seasonally, depending on their clinical pattern. However, convincing data have demonstrated that maintenance medication does not prevent exacerbations of recurrent asthma from viral respiratory infections, the most common pattern of asthma in young children.[30–32]

The following sections discuss the medications and interventions that comprise these strategies, with a review of evidence supporting their use and discussion of how to apply them in practice. A systematic approach to medication selection permits optimal management that meets established and generally attainable criteria for control (**Table 3**).

Table 3. Criteria for Control of Asthma

Absence of hospitalization
Absence of urgent care requirements
Absence of interference with sleep
Absence of interference with activity
Infrequent use of inhaled β_2-agonists for acute symptoms
Infrequent use of oral corticosteroids
Normal or near normal pulmonary function by spirometry

Treatment of Acute Asthma Symptoms

The most appropriate place to treat acute symptoms of asthma is where they occur—at home, at school, or at play. Treatment in the doctor's office, ED, or hospital generally should be considered as damage control for manifestations of treatment failure. The most effective measures for treating acute asthma exacerbations are inhaled and oral medications. These measures are more effective when used prior to the need for urgent medical care.

Inhaled short-acting β_2-agonists. Inhaled β_2-agonists are the most effective bronchodilators, and an inhaled β_2-agonist, such as albuterol or pirbuterol, is typically the initial intervention measure for acute symptoms. All patients with asthma symptoms should receive a short-acting bronchodilator. These agents provide rapid onset of bronchodilatation but do not alter the inflammatory component of asthma that contributes to airway obstruction.

Albuterol is the most common β_2-agonist for relief of acute symptoms and is available in formulations for nebulizer and for metered-dose inhaler (MDI). Older children generally can use a MDI successfully, but albuterol is commonly administered by nebulizer in young children and in EDs. Recent data have demonstrated that use of a MDI with a valved holding chamber in young children can provide equal or better efficacy in the emergency care setting.[33,34] The simplicity, more rapid administration, lower cost, and greater portability of the MDI with a valved holding chamber has made this the method of choice for aerosol administration in children with asthma who are younger than 6 years.

Whether a nebulizer or MDI with a valved holding chamber is used, proper instruction and a tight-fitting mask for patients too young to seal their mouths on a mouthpiece are essential. Additionally, it is important to realize that a crying child gets little medication by either method of delivery.[35] A useful device for patients aged 6 years and older who are unable to reliably coordinate actuation of the albuterol (or levalbuterol) MDI with inhalation is a breath-activated aerosol inhaler (Maxair Autohaler) that delivers pirbuterol, a β_2-agonist therapeutically equivalent to albuterol, upon initiation of inhalation. (See illustrations of devices for inhalation and their use at www.uihealthcare.com/allerpulm.)

Marketing of the active optical isomer of albuterol, levalbuterol, has focused on the potential for the traditional racemic preparation of albuterol to have adverse effects that are not present with levalbuterol. However, clinical studies have not supported this claim,[36,37] and levalbuterol should be considered therapeutically equivalent to the racemic preparation when given in a dosage equivalent to the levalbuterol component of racemic albuterol (ie, since half of racemic albuterol is levalbuterol and the other half is clinically inert, any milligram dose of racemic albuterol is therapeutically equivalent to half that dose of levalbuterol).[38] The one study suggesting a therapeutic advantage of levalbuterol over racemic albuterol for children with acute asthma seen in an ED[39] was not supported in 2 subsequent studies.[40,41]

Systemic corticosteroids. It is the inflammatory component of airway obstruction in asthma that results in hospitalization, respiratory failure, and occasional fatalities. The β_2-agonists do not alter the inflammatory component of airway obstruction, and inhaled corticosteroids, even in high doses, have been shown to be only minimally effective for acute exacerbations of asthma,[42] most of which are caused by viral respiratory infections.[43] Systemic corticosteroids effectively reverse the inflammatory component of asthma and are as effective orally as when given parenterally. In contrast to an inhaled β_2-agonist, which acts in minutes, the onset of action of systemic corticosteroids is slow. The earliest documented effect that can be detected is at 3 to 4 hours,[44,45] but typically 12 to 24 hours are required for a major degree of effect to be apparent.

When oral corticosteroids are given early in the course of an asthma exacerbation, emergency care and hospitalization can be prevented (**Table 4**).[46,47] Several studies have demonstrated that early aggressive use of systemic steroids in children having an acute exacerbation of asthma provides clinical benefit.[44–48] Storr and colleagues[48] examined the effect of oral prednisolone in children hospitalized with acute asthma in a randomized, double-blind, placebo-controlled trial in which 67 children (mean age, 5 yr) received prednisolone and 73 received placebo shortly after admission. Those younger than 5 years old received 30 mg of prednisolone and those 5 years or older received 60 mg. At a 5-hour decision time, approximately 20% of patients who received prednisolone could be discharged compared with only approximately 2%

Table 4. Dosage and Decisions for Usual Treatment of Acute Symptoms of Asthma

Medication	Dosage	When to Use
Albuterol, levalbuterol, or pirbuterol by MDI or nebulizer	Usually 2–4 inhalations from an MDI, but up to 6 inhalations can be used (1 at a time), which is equivalent to the most common dosage by nebulizer	As needed for cough, wheezing, or labored breathing Scheduled use has no advantage over as-needed use and may be deleterious for some patients Repeated requirements for bronchodilator use during an exacerbation generally warrant a short course of an oral corticosteroid
Prednisone, prednisolone, methylprednisolone, dexamethasone as tablets; liquid formulations and oral disintegrating tablets of prednisolone are available for young children; parenteral forms are indicated only when there is concern about oral retention	*See* Table 1 for dosage of prednisone or prednisolone	When bronchodilator subresponsiveness is identified by incomplete resolution of symptoms and signs from even repeat use of the bronchodilator Continue until asymptomatic; reevaluate if not improving within 5 days or asymptomatic within 10 days; there is no need to taper[6–8]
Ipratropium aerosol	0.5 mg with 2.5–5 mg albuterol by nebulizer	Indicated for severe acute asthma in the ED or hospital when response to a β_2-agonist is inadequate for relief of respiratory distress

ED = emergency department; MDI = metered-dose inhaler.

of patients who received placebo. Among those not discharged at 5 hours, more rapid improvement and earlier discharge occurred in the prednisolone-treated patients than in the placebo-treated patients.

Tal and colleagues[44] conducted a double-blind, placebo-controlled trial to examine the value of systemic corticosteroids in children ranging from 0.5 to 5 years of age who presented to an ED for acute asthma. Using 4 mg/kg of intramuscular methylprednisolone or normal saline, the decision to admit the patients to the hospital at 3 hours after medication administration was higher in the 35 patients given placebo (> 40%) than in the 39 patients given methylprednisolone (20%). Scarfone and colleagues[45] examined the effect of oral prednisone in children (mean age, 5 yr) seen in an ED for acute asthma. In that randomized, double-blind trial, 36 patients received 2 mg/kg of prednisone and 39 received placebo. No differences were seen in a mock decision to admit at 2 hours, but at 4 hours, approximately 50% of the placebo-treated children were admitted compared with only 30% of the prednisone-treated children. The differences were substantially larger for a subgroup judged most sick in which over 70% of the placebo-treated children were admitted compared with less than half that number among the prednisone-treated children.

Harris et al[46] examined the value of early administration of oral corticosteroids in ambulatory children (median age, 12 yr) with occasional acute exacerbations despite being on maintenance medication that controlled daily symptoms. Oral prednisone (30 mg twice daily for patients under age 13 yr and 40 mg twice daily for those over age 13 yr) or placebo was started at the onset of an exacerbation defined as symptoms incompletely responding to an inhaled bronchodilator. All of the 22 prednisone-treated patients subsequently improved, returning to baseline clinical status and normal pulmonary function within 7 days, while 8 of the 19 placebo-treated patients required further acute intervention because of deteriorating status.

Brunette and colleagues[47] examined the value of oral corticosteroids in preventing exacerbations of asthma in a group of 32 children younger than 6 years of age who had an average of 7 hospitalizations in a year for acute viral respiratory infection–induced asthma. During the subsequent year, half were given prednisone 1 mg/kg/day at the onset of a viral respiratory infection. This intervention was associated with a 90% reduction in hospitalizations among the treated group, whereas no reduction in hospitalization occurred in patients who were not treated in this manner.

These studies demonstrate that early administration of systemic corticosteroids for acute asthma permitted earlier discharge from the hospital, decreased the likelihood of admission in patients presenting for emergency care of asthma, and prevented progression of exacerbations of asthma in ambulatory patients at risk for requiring urgent care. Additionally, the study by Brunette and colleagues,[47] although not a blinded placebo-controlled trial like the others described above, suggests a high degree of efficacy for early administration of oral corticosteroids in preventing the early symptoms of a viral respiratory infection from progressing to severe acute asthma in children at high risk for requiring hospitalization. Despite previous controversies regarding the use of oral corticosteroids,[49] these data support

Table 5. Initial Dosage and Decisions for Treatment of Persistent Symptoms of Chronic or Seasonal Allergic Asthma

Medication	Dosage	When to Use	Comments
Inhaled corticosteroid	Fluticasone (110 µg HFA MDI) 1 inhalation twice daily Beclomethasone (80 µg HFA MDI) 1 inhalation twice daily Budesonide inhalation powder (oral breath-activated inhaler) 1 inhalation twice daily	First-line medication for persistent symptoms	Use the fluticasone or beclomethasone MDI with a valved holding chamber and mask for infants and toddlers; most can use a chamber without a mask by age 4 yr; the budesonide breath-activated inhaler can be used effectively in most by age 6 yr
Montelukast	4 mg sprinkle, 4 or 5 mg chewable, or 10 mg tablets (similar blood levels for each) once daily	As an alternative to an inhaled corticosteroid for mild persistent symptoms	Provides modest additional benefit as add-on to inhaled corticosteroids
Long-acting β_2-agonist	Fluticasone 100 µg/salmeterol 50 µg inhalation powder 1 inhalation twice daily Budesonide 160 µg/formoterol 4.5 µg inhalation powder 1 inhalation twice daily	When a conventional dose of inhaled corticosteroid does not maintain control	It is essential to monitor for the occasional patient made worse from the addition of a long-acting β_2-agonist
Slow-release theophylline	Begin with 10 mg/kg/day divided twice daily to a maximum of 150 mg twice daily; increase in increments to 16 mg/kg/day to a maximum of 300 mg twice daily; monitor serum theophylline concentrations to attain peak serum concentrations of 10–15 µg/mL[55]	As an additive agent to an inhaled corticosteroid for the occasional patient where a long-acting β_2-agonist worsens rather than improves asthma control	Awareness of drug interactions (eg, antiseizure medications, macrolide antibiotics, and ciprofloxacin) and effect of fever on theophylline levels (ie, prolonged half-life) is essential for safety[55]

Note: Acute exacerbations, especially when induced by a viral respiratory infection, require the intervention measures in Table 4.

HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

early administration of systemic corticosteroids as the standard of care for acute exacerbations of asthma.[50] Concerns regarding the sometimes repeated requirements for short courses of oral corticosteroids for viral respiratory infection–induced exacerbations that young children frequently experience have been examined, and sustained adverse effects appear not to occur.[51]

Emergency care interventions. When care is required in the emergency care setting, ipratropium, an anticholinergic aerosol, added to inhaled albuterol has been of value for severe acute asthma not fully responsive to albuterol alone.[52] However, it has no documented clinical role in ambulatory patients. Intravenous magnesium may have some value for severe acute asthma, although routine use is not indicated.[53,54] Oxygen is also indicated to correct hypoxemia. Measurement of pH and P_{CO_2} is indicated when hypoxemia is present. Early in the course of acute asthma, ventilation-perfusion mismatching causes hypoxemia. As airway obstruction progresses, P_{CO_2} gradually increases, which constitutes respiratory failure. While ventilation-perfusion mismatching requires only continued oxygen and pharmacologic intervention measures, respiratory failure requires admission to an intensive care setting where assisted ventilation is available if sufficiently rapid reversal of the airway obstruction does not occur.

Treatment of Persistent Symptoms of Chronic or Seasonal Allergic Asthma: Maintenance Measures

Maintenance medication is designed to prevent future symptoms by the use of acceptably safe daily medication that effectively suppresses asthma symptoms and maintains normal lung function. Maintenance medication is indicated for patients with chronic asthma and for those with prolonged seasonal allergic asthma. Rational medication selection and careful monitoring of the patient with regularly scheduled return visits permit optimal management for meeting criteria for control (Table 3) with the least medication (**Table 5**).

Inhaled corticosteroids. Inhaled corticosteroids are the maintenance medication with the greatest degree of efficacy and are the usual first choice for patients with persistent symptoms. In preschool-aged children with persistent asthma, these agents can be delivered effectively by both MDI via a valved holding chamber and by nebulizer with efficacy in decreasing asthma symptoms.[56–58] There is no evidence that the nebulizer solution offers any therapeutic advantage over the simpler use of a pressurized MDI with a valved holding chamber. Whichever inhaled corticosteroid preparation is used, careful attention to individualized instruction is essential for efficacy. Appropriate delivery technique is even more critical for inhaled corticosteroids than for

bronchodilator aerosol since there is no immediate effect that is clinically apparent. For infants and toddlers, a tight-fitting mask[59] and quiet breathing are essential since a crying child gets little delivery of aerosolized medication to the lungs.[60] Although there is evidence for dose-related systemic effects,[61] conventional low doses of corticosteroids have an established safety record.[62,63] A minimal degree of hypothalamic-pituitary axis suppression and a small degree of transient growth suppression is detectable at modest doses, but neither clinically detectable adverse effects nor a sustained effect on growth are apparent, except at higher doses.[64]

Long-acting inhaled β_2-agonists (LABAs) and theophylline. While higher doses of an inhaled corticosteroid are beneficial for some patients whose asthma symptoms are not controlled by the conventional dose, studies in adults have shown that adding a LABA (salmeterol or formoterol)[65,66] or theophylline[55] provides, on average, greater clinical benefit than increasing the dose of the inhaled corticosteroid. However, similar studies have not shown such benefit in younger children. Nonetheless, the use of products that combine an inhaled corticosteroid and a LABA would be a rational option for asthma not controlled with conventional doses of an inhaled corticosteroid alone. However, a subset of patients are affected adversely by LABAs, and theophylline is a better choice for additive therapy for these patients (Table 5). A report of 2 patients who had life-threatening symptoms poorly responsive to β_2-agonist bronchodilators while receiving salmeterol with dramatic clinical response to stopping the salmeterol[67] was consistent with studies showing that certain genetic polymorphisms of the β_2 receptor were associated with down-regulation of that receptor during regular administration of β_2-adrenergic agents.[68,69] Although such adverse events are uncommon, monitoring is necessary to ensure that benefit actually occurs from the use of the corticosteroid-LABA combination products and that responsiveness to albuterol or equivalent for symptom relief and blocking of exercise-induced bronchospasm is not decreased. In discussing the safety of LABAs, Martinez[70] argued for caution and close medical monitoring in patients with sufficiently severe asthma to justify the addition of a LABA to maintenance inhaled corticosteroids.

Leukotriene modifiers. Leukotriene modifiers either act as competitive inhibitors of leukotriene, one of the mediators of inflammation for asthma, or decrease the production of leukotrienes. The leukotriene receptor antagonist montelukast has potential benefit for some patients with milder manifestations of asthma. An example of the clinical applicability of montelukast is in the young child with daily cough and wheeze that disturbs sleep and limits activity somewhat but rarely results in the need for urgent medical care. An oral medication such as montelukast is particularly useful where an inhaled medication is more problematic to provide on a regular twice daily basis, as in young children.[71] Montelukast also has some additive effect with inhaled corticosteroids.[72] However, the additive effect of montelukast does not appear to be as great as that seen with a LABA or theophylline.[72] Although montelukast may be justified as a therapeutic trial, failure to meet criteria for control (Table 3) requires the utilization of inhaled corticosteroids. The merits of montelukast relate primarily to its simplicity of administration and complete lack of adverse effects, not to a high level of clinical efficacy.

Other leukotriene modifiers marketed in the United States include zafirlukast, a competitive receptor antagonist similar in action and efficacy to montelukast, and zileuton. However, zafirlukast requires twice daily administration in contrast to the once daily administration of montelukast and has some drug interaction potential not present with montelukast. Zileuton is a specific inhibitor of 5-lipoxygenase, an enzyme that results in the formation of leukotrienes from arachidonic acid. While having a degree of efficacy, zileuton requires 4 times daily administration and has drug interaction potential.

Patient/parent education. The best decision-making by the physician will fail unless the family and/or patient are adequately educated about the benefits and risks, if any, of each medication and the implementation of the treatment plan.[73] Especially important is having a simple written action plan that deals with periods of increased symptoms and exacerbations. There is no advantage to complex plans with stop light illustrations.[74] Seasonal allergic increases in symptoms may warrant an increase or additional maintenance medication. Viral respiratory infection–induced symptoms are likely to require a short course of oral corticosteroids.

Treating comorbidities. Treating comorbidities may benefit the control of chronic asthma. It has been suggested that treating chronic rhinitis with topical nasal steroids has a beneficial effect on asthma,[75] although the validity of this report has been questioned.[76] There is a great deal of controversy regarding the role of sinusitis and gastroesophageal reflux as comorbidities that contribute to asthma. While both sinusitis and gastroesophageal reflux are associated with asthma, the evidence that treating them benefits asthma is anecdotal only.[27,28,77] While chronic rhinitis should be treated with topical nasal steroids in patients experiencing discomfort from nasal congestion and gastroesophageal

reflux should be treated in those experiencing the substernal discomfort associated with that disorder, there is little reason to expect clinically important benefit for the asthma itself. As for sinusitis, symptoms attributed to that disorder are predominantly those of rhinitis, and there is little correlation between radiologic evidence of sinusitis and clinical symptomatology.[27,78]

Environmental control measures. Environmental factors that adversely affect asthma include aero-irritants and aero-allergens. Tobacco smoke, fireplaces, wood burning stoves, and strong odors are all potential triggers of the sensitive airways of the patient with asthma. Cigarette smoke is a major irritant that increases the frequency and severity of acute and chronic asthmatic symptoms.[3] In a study that evaluated the impact of a specialty care program on control of asthma in children (criteria defined in Table 3) over a 1-year period of observation among those exposed (n = 44) or not exposed to cigarette smoke (n = 75), cigarette smoke exposure was associated with a significantly lower likelihood of meeting criteria for control despite receiving care at the same specialty clinic (50% versus 89%; $P < 0.001$).[3] Clinically important aero-allergens vary by region and include pollens, outdoor and indoor molds, animal dander, cockroach, and dust mites. Environmental control measures can contribute to control of asthma. Measures to minimize specific aero-allergen exposure should be guided by knowledge of specific IgE to allergens in the patient and the aerobiology of the patient's environment and a careful history that permits a reasoned judgment regarding the extent to which the exposures contribute to symptoms.

Immunotherapy (allergy shots) can provide benefit for asthma in highly selected cases where the symptoms can be convincingly related to a limited number of well-defined inhalant allergens for which immunotherapy has been shown to be effective.[79,80] Another measure of potential benefit for the allergic component of asthma is the monoclonal anti-IgE preparation omalizumab. Although quite costly, severely symptomatic asthma that has a major allergic component may benefit substantially from this medication.[81]

Monitoring the Clinical Course of the Patient

Successful management of asthma does not stop with writing the prescriptions. Patients should rarely need to be seen during acute symptoms, since the patient or family should have been taught successful management by use of the inhaled bronchodilator for symptom relief and early intervention with a short course of systemic corticosteroid for an exacerbation that does not respond to the inhaled β_2-agonist. However, scheduled return visits are essential to review adherence to the treatment plan, check inhaler technique, assess if the patient meets criteria for control, and adjust treatment when appropriate to meet those criteria with the least amount of medication.

While the peak flow meter is recommended by some as a useful means of monitoring patients with asthma, the weight of evidence indicates that symptom monitoring (and consequent need for intervention with an inhaled β_2-agonist) is generally equal to[82,83] or better[84,85] than peak flow monitoring in providing early warning of an exacerbation that requires intervention. The only patients for whom a home peak flow meter might be useful are the occasional underperceiver, usually with very severe chronic asthma, who does not recognize worsening airway obstruction, or the overperceiver, who identifies anxiety or hyperventilation attacks as asthma.

There is interest in using exhaled nitric oxide as a marker of asthmatic inflammation.[86,87] Although the commercial device available to measure exhaled nitric oxide may have some clinical usefulness, troublesome asthmatic inflammation is generally adequately detectable by the presence of active symptoms and the measurement of the extent to which pulmonary function does not fully reverse with a bronchodilator.

General medical care for asthma should include routine immunizations. Of these, the varicella vaccine is particularly important because of the small but serious risk of disseminated varicella that has been reported when the infection is incubating during a course of high-dose systemic corticosteroids.[88] A yearly influenza vaccine is now a general recommendation for children and is especially appropriate for children with asthma.[89] A small risk from influenza vaccine is present for those with allergy to egg. However, clinically important adverse effects appear to be unlikely to occur.[90]

Evaluating and Managing Difficult Asthma

Difficult asthma is that which does not meet criteria for control despite appropriate therapy. The reason for such poor control varies: in some cases, the asthma is poorly responsive to usual measures, but more often the poor control results from poor adherence to the medical regimen. When poorly controlled symptoms of asthma are present despite appropriately prescribed medication, adherence can be verified by asking for a record of medication refills from the patient's pharmacy. A month's supply of medication that lasted 6 months can readily explain inadequate control. The technique of using inhaled medication also can be an issue. Observing technique during a routine office visit

can be revealing and provide an opportunity for appropriate education. In some cases, there is apparent poor control because the patient does not have asthma at all but has a condition with symptoms that mimic those of asthma[14] (*see* Diagnosis of Asthma section). Placing the patient with difficult asthma in a hospital for a period of around-the-clock observation may be necessary in some cases to sort out these various confounding problems.

NATURAL HISTORY

A question frequently asked by parents is, "Will my child outgrow the asthma?" The long-term clinical course of asthma in young children has been examined in a prospective study with repeated evaluations over 35 years.[91] In 1963, all second grade children aged 6 to 7 years in Melbourne, Australia, had a medical examination at school that included a short questionnaire and interview that asked parents if their child had experienced episodes of wheezing or asthma and whether such episodes had been associated with symptoms of a viral respiratory infection. Based on this survey, an overall community prevalence for asthma symptoms in childhood was estimated to be about 20%, a rate similar to that described more recently in the United States.[92,93] A stratified sample was then randomly selected the following year from the approximately 30,000 7-year-old children in the survey, including 105 second graders who had never wheezed to serve as controls, 75 with less than 5 episodes of previous wheezing with viral respiratory infections, 104 with 5 or more episodes of previous wheezing with viral respiratory infections, and 113 with recurrent wheezing not limited to association with viral respiratory infections. The investigators also entered 83 children from the same population who had severe chronic asthma since before age 3 years with persistent symptoms, barrel chest deformity, and/or forced expiratory volume that was 50% or less than the forced vital capacity. The children were reevaluated at ages 14, 21, 28, 35, and 42 years.[94–97]

Seventy-five percent of the sample followed longitudinally had infrequent episodes, while 25% had frequent episodes. Of the children who initially had asthma, 40% were free of respiratory symptoms by age 10 years, and 50% were asymptomatic by age 14 years. In the remainder, symptoms continued into adult life but were frequently not troublesome, present only with viral respiratory infections or exercise for many. However, 10% who had ceased wheezing in childhood had recurrences as young adults, some with troublesome symptoms. The group with severe chronic asthma had growth failure and delayed puberty but eventually attained normal adult height. Although 50% of the group with severe chronic asthma improved considerably at puberty, only 5% became totally asymptomatic.

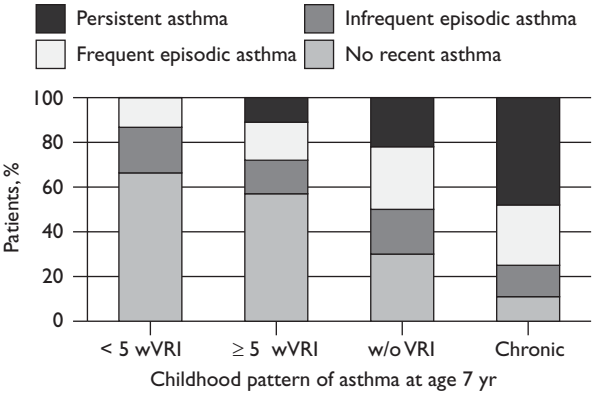

Figure 3. Clinical expression of childhood asthma at age 42 years in those with < 5 episodes of wheezing with viral respiratory infection (wVRI), ≥ 5 episodes of wVRI, recurrent wheezing not limited to VRI (w/o VRI), and severe chronic asthma at age 7 years. (Adapted from Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. J Allergy Clin Immunol 2002;109:189–94. Copyright 2002, with permission from Elsevier.)

When the children were examined at age 42 years, a correlation between the nature of the symptoms in childhood and the subsequent outcome was apparent (**Figure 3**). Over half of those with symptoms of asthma limited to an association with viral respiratory infection prior to age 7 years were asymptomatic at age 42 years. Others were still having episodic asthma, and a few had developed persistent asthma. The frequency of all patterns of active asthma at age 42 years was greater among those in whom wheezing without viral respiratory infections had been reported in childhood. Approximately half of those with severe chronic asthma as children continued to have persistent symptoms at age 42 years, with only 11% of that group reporting no recent asthma.

There has been speculation that early treatment with inhaled corticosteroids could modify the course of subsequent asthma. The hypothesis that inhaled steroids given for episodic wheeze might alter the subsequent course of asthma was examined in a randomized double-blind study of infants; it showed no benefit either for acute symptoms or the frequency of recurrent episodes.[98] This hypothesis also has been tested in a group of 2- and 3-year-old children randomly assigned to receive fluticasone aerosol or placebo over a 1-year period. While symptoms were significantly less in the inhaled corticosteroid–treated group, the frequency of asthmatic symptoms became identical to the placebo-treated group once the inhaled corticosteroids

were stopped, indicating the absence of any sustained effect on the disease.[99]

SUMMARY

Asthma is a common cause of morbidity in children that is both underdiagnosed and overdiagnosed. Key points for successful asthma management are as follows: make an accurate diagnosis (avoid under or overdiagnosis); characterize the clinical pattern as intermittent, chronic, or seasonal allergic; realize that viral respiratory infections are the most common cause of acute exacerbations and will not be prevented by maintenance medications; educate the patient/parents regarding the indication for both intervention and maintenance medication; provide the means for early effective intervention with an inhaled β_2-agonist as well as an oral corticosteroid for acute exacerbations that do not respond to bronchodilators; and advise elimination of exposure to environmental irritants, particularly tobacco smoke. The goal of controlling asthma includes elimination of acute care visits and hospitalization, elimination of nocturnal symptoms and interference with activity, and minimal use of intervention measures other than for viral respiratory infection–induced exacerbations. In advising parents about the future for their children with asthma, those with only intermittent viral respiratory infection–induced asthma and no allergic component contributing to symptoms are likely to either eventually remit or have fewer symptoms. However, those with more persistent symptoms have a greater likelihood of continuing to have asthma as adults. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 17.

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