Management of Asthma in Children

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The prevalence of asthma in children has increased 160 percent since 1980, and the disease currently affects nearly 5 million children in the United States. The National Asthma Education and Prevention Program provides guidelines for improved asthma care. The goals of this program are to limit the frequency, severity and costliness of asthma exacerbations through extensive education of physicians, children and caregivers. The four components of asthma management include regular assessment and monitoring, control of factors that contribute to or aggravate symptoms, pharmacologic therapy and education of children and their caregivers. The guidelines recommend a stepwise approach to pharmacologic treatment, starting with aggressive therapy to achieve control and followed by a "step down" to the minimal therapy that will maintain control. Quick relief of symptoms can be achieved preferentially by the use of short-acting beta$_2$ agonists. Medications for long-term control should be considered for use in children with persistent symptoms. Inhaled corticosteroids are the most potent long-term anti-inflammatory medications. Other options include long-acting beta$_2$ agonists, cromolyn sodium and nedocromil, antileukotriene agents and theophylline. All have advantages and disadvantages in individual situations. (Am Fam Physician 2001;63:1341-8,1353-4.)

O *A patient information handout on asthma, written by the authors of this article, is provided on page 1353.*

ACE *This article exemplifies the AAFP 2001 Annual Clinical Focus on allergies and asthma.*

Asthma currently affects nearly 5 million children in the United States—more than 5 percent of the population younger than 18 years.[1] In children four years or younger, the prevalence increased 160 percent from 1980 to 1994, and from 1980 to 1993, the death rate from asthma nearly doubled among persons five to 24 years.[1] Asthma is 26 percent more prevalent and results in more severe disability and more frequent hospitalizations in black children than in white children, and black children are four to six times more likely to die of asthma.[2,3] In children younger than 15 years, asthma accounts for 3 million physician visits, 570,000 emergency department visits, 164,000 hospital stays, 8.7 million prescriptions and 10 million missed school days per year.[4,5]

These statistics highlight the need to aggressively manage this disease and its symptoms. Unfortunately, anti-inflammatory agents such as inhaled corticosteroids are not yet prescribed for all patients with persistent asthma[6] and, even when these medications are prescribed, they may be underutilized because parents fear the possibility of adverse side effects or children have difficulty using metered-dose inhalers (MDIs). New therapeutic options are available and with aggressive, appropriate therapy, physicians can prescribe an asthma management regimen to ameliorate symptoms, control disease and allow normal activity even in children as young as one to two years.

Pathophysiology

Asthma is a chronic inflammatory disorder that produces airway hyperresponsiveness, airflow limitation and persistent respiratory symptoms, such as wheezing, coughing, chest tightness and shortness of breath.[7] Airflow limitation is produced by acute bronchoconstriction, airway edema, mucous plug formation and airway remodeling.[8]

Asthma has immediate and delayed inflammatory responses. During the early phase, mast cells release mediators (e.g., histamine, leukotrienes, prostaglandins and thromboxanes) that lead to vasodilation, edema and bronchoconstriction.[9] Leukotrienes, recently recognized as key culprits in asthma, are approximately 1,000 times more potent than histamines

in mediating an inflammatory response. Their powerful chemotactic effect on neutrophils, monocytes and lymphocytes enhances the inflammatory response.[10]

During the late phase, cytokines are released that prolong inflammation and activate eosinophils, basophils, lymphocytes and mast cells. Chronic inflammation may result in smooth muscle hyperplasia, bronchial hyper-responsiveness and increased collagen deposition beneath the basement membrane, which further narrows the airway.[11]

Diagnosis

Fifty to 80 percent of children with asthma develop symptoms before five years of age.[12] Asthma symptoms vary widely and may mimic other childhood diseases (e.g., upper respiratory infections). When parents report episodic or persistent coughing, wheezing, shortness of breath, rapid breathing or chest tightness, and if these symptoms are worse during the evening or early morning hours, or are associated with triggers (e.g., exercise, allergen exposure), the physician should suspect asthma.

Alternative diagnoses should be excluded. Wheezing is not present in all patients with asthma and is not a sign exclusive to asthma. Wheezing may be caused by respiratory infections, rhinitis, sinusitis or vocal cord dysfunction. Before a definitive diagnosis of asthma is reached, consideration should be given to other factors, such as foreign body aspiration, or to other diseases, such as cystic fibrosis or heart disease, that may be causing the patient's symptoms.

Obtaining a medical history is essential to establishing the diagnosis of asthma. Factors associated with the onset of asthma symptoms include allergy, family history of asthma or allergy, perinatal exposure to tobacco smoke, viral respiratory infections, male gender and low birth weight.[13] Young children who develop persistent asthma are likely to have increased serum IgE levels at nine months of age, atopic dermatitis and rhinitis (unrelated to upper respiratory infection) during their first year, severe lower respiratory infections requiring hospitalization and diminished airway function by six years of age.[13]

Identification of symptom patterns, severity of symptoms and precipitating factors will support the diagnosis of asthma: "How often and when do episodes occur?" "What is their duration?" "Do symptoms occur or worsen during the night, with exercise or with an infection?" "Are they precipitated or aggravated by specific triggers?" "Do they interfere with sleep or daily activities, or require emergency department or hospital visits?" "How often are short-acting bronchodilators used?" "Are symptoms temporarily relieved by bronchodilators?"[14]

Pulmonary function tests should be, and allergy tests may be conducted to confirm the diagnosis.[15] Spirometry performed before and 15 to 20 minutes after the child inhales a short-acting bronchodilator assesses airflow obstruction and determines its reversibility. Pulmonary function results consistent with asthma include variable airflow obstruction (20 percent or more) with serial spirometry or peak expiratory flow (PEF) measurements, and an increase in forced expiratory volume in one second (FEV_1) of 12 percent or more after bronchodilator therapy. Unfortunately, routine pulmonary function testing is unreliable in infants and many preschool children. These tests may be a more reliable indicator in children who are three to four years of age, but considerable variation

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exists because of poor technique and the use of adult-sized equipment. In most children, the primary diagnostic tool is clinical assessment.[16] However, pulmonary function tests should be performed as soon as possible.

A significant percentage of patients (75 to 85 percent) with asthma have positive immediate hypersensitivity skin tests (IgE), indicating the vital role that allergy plays in pediatric asthma. Atopy is the strongest predictor for wheezing progressing to asthma; therefore, a history of allergies is significant.[17]

Treatment

Treatment should include patient education, trigger avoidance and drug therapy regimens that enable patients to function without limitations from asthma symptoms. *Table 1*[18] summarizes the standard diagnosis and treatment parameters and provides a list of commonly used medications.

EDUCATION

Education for patients and caregivers should focus on the identification and avoidance of triggers, understanding the uses of prescribed medications and the importance of compliance and monitoring, as well as the proper use of inhalation devices.[19] Daily self-management plans provide guidance for patients in peak flow monitoring, medication usage and symptom reporting. Emergency action plans help identify an exacerbation and delineate the actions to take. These plans should be developed in consultation with caregivers and patients, and provided to them in writing. Excellent examples of these plans are provided in the asthma guidelines from the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute.[20] (The guidelines are available on the Web at: http://www.nhlbisupport.com/asthma/index.html).

TRIGGERS AND ENVIRONMENTAL CONTROL

Asthma triggers include allergens from dust mites or mold spores, animal dander, cockroaches, pollen, indoor and outdoor pollutants, irritants (e.g., tobacco smoke, smoke from wood-burning stoves or fireplaces, perfumes, cleaning agents), pharmacologic triggers (e.g., aspirin or other nonsteroidal anti-inflammatory drugs, beta blockers and sulfites), physical triggers (e.g., exercise, hyperventilation, cold air) and physiologic factors (e.g., stress, gastroesophageal reflux, respiratory infection [viral, bacterial] and rhinitis).

Environmental control measures include removing carpets from the patient's bedroom and living areas, weekly washing of bedding and clothing in water hotter than 55°C (130°F), the use of specially designed mattress and pillow covers, removing stuffed animals and similar objects that are likely to harbor allergens, keeping pets outdoors and using special furnace filters to remove airborne allergens. The Web site of the American Academy of Allergy, Asthma and Immunology (http://www.aaaai.org) is an excellent source of valuable, scientifically based information and specialized products for persons with asthma.

Up to 80 percent of asthmatic children have allergic rhinitis. If specific IgE hypersensitivity has been identified by radioallergosorbent test (RAST) or skin testing, the triggers to be avoided can be specified.[21] Consultation with an allergist can define the optimal regimen to reduce sensitivity to specific allergens. Because exposure to tobacco smoke is a major cause of respiratory problems in children who are predisposed to or already have asthma, exposure should be strictly avoided.[22]

COMPLIANCE

Poor compliance is a major problem in pediatric asthma management, and several factors play a role in this. These include the route of administration (oral therapy is preferred to inhaled medication),[23] frequency of dosing (once- or twice-daily regimens are preferred),[24] medication effects (a slow onset of action and long duration on discontinuance have poor adherence rates) and the risk or concern of side effects.

TABLE 1

Stepwise Approach for Managing Infants and Young Children (< 5 Years of Age) with Acute or Chronic Asthma Symptoms

Asthma diagnosis	*Quick relief**	*Long-term control*	*Medication*	*Price†*
Step 4; severe, persistent	Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, using either: • Inhaled short-acting beta$_2$ agonist by nebulizer or spacer/holding chamber and face mask *or* • Oral beta$_2$ agonist	Daily anti-inflammatory medications: • High-dose inhaled corticosteroid with spacer/holding chamber and face mask *and* • If needed, add systemic corticosteroids (0.25 to 2 mg per kg per day) and reduce to lowest daily or alternate-day dosage that stabilizes symptoms.‡	Oral corticosteroids • Methylprednisone (Medrol), 2-mg tablet • Prednisolone (Prelone syrup), 5 mg per 5 mL (Pediapred liquid), 5 mg per 5 mL • Prednisone 5-mg tablet (Deltasone), 5-mg tablet (Intensol), 5 mg per mL liquid	 $ 44.00 for 100 tablets 15.50 per 120 mL 20.50 per 120 mL 3.50 to 6.50 for 100 tablets 4.50 31.00
Step 3; moderate, persistent	Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, using either: • Inhaled, short-acting beta$_2$ agonist by nebulizer or spacer/holding chamber and face mask *or* • Oral beta$_2$ agonist	Daily anti-inflammatory medications, either: • Medium-dose inhaled corticosteroid with spacer/holding chamber and face mask *or, once control is established* • Low- to medium-dose inhaled corticosteroid and nedocrimil (Tilade) *or* • Low- to medium-dose inhaled corticosteroid and long-acting bronchodilator (e.g., either long-acting, inhaled beta$_2$ agonist or theophylline SR)	Long-acting beta$_2$ agonist • Salmeterol (Serevent MDI) (Serevent Diskus DPI) • Albuterol SR (Volmax tablet) (Proventil Repetabs), 4-mg tablet • Salmeterol/Fluticasone (Advair diskus) 100 µg/50 µg 250 µg/50 µg 500 µg/50 µg	 42.00 43.50 83.00 for 100 tablets 77.50 for 100 tablets 104.00 130.00 177.00
Step 2; Mild, persistent	Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, either: • Inhaled, short-acting beta$_2$ agonist by nebulizer or spacer/holding chamber and face mask *or* • Oral beta$_2$ agonist	Daily anti-inflammatory medications: • Cromolyn (nebulizer preferred, or MDI) or nedocromil (MDI), 3 to 4 times daily *or* • Low-dose inhaled corticosteroid with spacer/holding chamber and face mask	Cromolyn (Intal) inhaler Nedocromil (Tilade) inhaler Inhaled corticosteroids • Beclomethasone (Beclovent MDI), 42 µg per puff (Vanceril DS MDI), 84 µg per puff • Budesonide (Pulmicort Turbuhaler DPI), 200 µg per puff • Pulmicort Respules, 0.25 mg, 0.5 mg • Flunisolide (AeroBid MDI), 250 µg per puff • Fluticasone (Flovent), 44 µg per puff (Flovent) 220 µg per puff • Triamcinolone (Azmacort MDI), 100 µg per puff • Theophylline 200 mg 300 mg (SR) 450 mg (TR) Antileukotrienes • Zafirlukast (Accolate), 10-mg tablet • Montelukast (Singulair), 10-mg tablet 4- or 5-mg chewable tablet • Zileuton (Zyflo Filmtab), 600-mg tablet	47.00 36.00 45.00 42.00 19.00 126.00 for 30 tablets, either strength 63.00 47.00 (13-g canister) 95.50 (13-g canister) 53.00 5.50 to 10.50 for 30 tablets 7.50 to 12.50 for 30 tablets 8.50 for 30 tablets 62.00 for 100 tablets 71.00 for 30 tablets 73.00 to 83.00 for 30 tablets 91.00 for 120 tablets

Table continues

TABLE 1 *Continued*

Asthma diagnosis	*Quick relief**	*Long-term control*	*Medication*	*Price†*
Step 1; mild, intermittent	Short-acting bronchodilator as needed for symptoms < 2 times per week. Intensity of treatment depends on severity of exacerbation, using either: • Inhaled, short-acting beta$_2$ agonist by nebulizer or spacer/ holding chamber and face mask *or* • Oral beta$_2$ agonist	No daily medication	Short-acting inhaled beta$_2$ agonist • Albuterol (Airet nebulizer), 2.5 mg per 3 mL (Proventil-HFA MDI), 90 µg per puff (Ventolin Rotacaps DPI), 200 µg per puff • Bitolterol (Tornalate MDI), 0.37 µg per puff • Levalbuterol (Xopenex nebulizer), 1.25 mg per 3 mL • Pirbuterol (Maxair MDI), 0.2 µg per puff	 $49.50 41.00 32.00 46.00 (15-mL canister) 47.50 13.00 (2.8-g inhaler); 43.00 (25.6-g inhaler)

DPI = dry powder inhaler; MDI = metered-dose inhaler; SR = sustained release; TR = timed release; DS = double strength.

**—Daily or increasing use of short-acting inhaled beta$_2$ agonists may indicate the need for additional long-term controller therapy; may try step-up therapy.*
†— Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2000. Cost to the patient will be higher, depending on prescription filling fee.
‡—Ipratropium (Atrovent) may be added to control exacerbations.

NOTE: *Treatment should be reviewed every one to six months; a gradual stepwise reduction in treatment may be possible. By contrast, if control is not maintained, consider step-up therapy; first review patient medication technique, adherence and environmental control (avoidance of allergens or other factors that contribute to asthma severity).*

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Many children cannot master proper MDI use even after repeated training, and when children succeed in mastering the proper MDI technique, only 10 to 15 percent of the medication reaches the lungs.[24] Spacers make MDIs easier to use and are essential in many children younger than six years. MDIs with face-masks or nebulizers may be necessary in children up to five years, particularly during an asthma emergency. Dry powder inhalers (DPIs) can be used by children if they can demonstrate adequate inhalation velocity using a training whistle.[25]

PHARMACOLOGIC THERAPY

Asthma is classified into four levels according to its severity: mild intermittent, mild persistent, moderate persistent or severe persistent. Treatment is based on the frequency and severity of exacerbations and the degree of lung function impairment, generally assessed by the variability in such objective measurements as FEV_1 and PEF, as shown in *Table 2*.[18]

The National Asthma Education and Prevention Program guidelines[20] recommend a stepwise approach to pharmacologic treatment starting with the most aggressive therapy necessary to achieve control, followed by a "step down" to the minimal therapy that will maintain control. The goals of pharmacologic therapy are to minimize daytime and nocturnal symptoms, the number of asthma episodes and the use of short-acting beta agonists, to improve PEF to 80 percent or more of personal best and to allow the child to maintain normal activities without producing adverse medication side effects.

QUICK-RELIEF MEDICATIONS

These drugs, including short-acting inhaled or oral beta$_2$ agonists, short-course oral corticosteroids or ipratropium (Atrovent), are taken as needed for immediate relief of

Treatment of children with asthma should begin with the most aggressive therapy necessary to achieve control, followed by "stepping down" to the minimal therapy that will maintain control.

acute symptoms and before exercise to prevent exercise-induced bronchospasm.

Short-acting beta$_2$ agonists rapidly relax bronchial smooth muscle and are the therapy of choice to relieve acute symptoms and prevent exercise-induced bronchospasm. Beta$_2$ agonists relieve symptoms but do not affect the underlying disease. These agents have a good safety record but are subject to overuse because they provide rapid relief and have a short duration of effect. Overuse reduces their efficacy and has been associated with increased bronchial hyperreactivity, central nervous system overstimulation, worsening asthma and death.

Overuse indicates that asthma is not controlled and requires increased anti-inflammatory treatment. Therefore, refills of reliever medications should be closely monitored. Most MDIs hold 120 two-spray doses and should last one month if used four times daily. With well-controlled asthma, one inhaler ideally should last for one year.[26]

Oral corticosteroids have broad anti-inflammatory effects and may be used in a limited, short course (three to 10 days) to gain initial control of the asthma and speed resolution of moderate-persistent or severe-persistent exacerbations.[26]

The anticholinergic drug ipratropium (in the orally inhaled formulation) is not approved by the U.S. Food and Drug Administration for the treatment of asthma in children 12 years or younger. However, it has been prescribed for off-label use in children with asthma and may be helpful in those rare children who do not tolerate inhaled beta$_2$ agonists, or it may be added to a beta$_2$ agonist such as albuterol (Ventolin) to treat acute asthma exacerbations.

TABLE 2
Diagnosis of Asthma

Asthma diagnosis	*Days with symptoms**	*Nights with symptoms*	*PEF (% personal best) or FEV$_1$ (% predicted best)*
Step 4; severe persistent	Continual	Frequent	≤60
Step 3; moderate persistent	Daily	≥5 times per month	>60 to <80
Step 2; mild persistent	>2 times per week	3 to 4 times per month	≥80
Step 1; mild intermittent	≤2 times per week	<2 per month	≥80

FEV$_1$ = forced expiatory volume in one second; PEF = peak expiratory flow.

**—Standard symptoms are wheezing, coughing, dyspnea and chest tightness.*

Adapted with permission from Rachelefsky GS, Shapiro GG, Bergman D, Blessing-Moore J. Pediatric asthma: promoting best practice. Guide for Managing Asthma in Children. Rochester, N.Y.: American Academy of Allergy, Asthma & Immunology, 1999.

LONG-TERM CONTROL MEDICATIONS

Medications for long-term control should be taken daily to maintain control of asthma and prevent exacerbations. Inhaled corticosteroids are the most potent and effective long-term anti-inflammatory medications. They reduce inflammation in airways, improve pulmonary function to a greater degree than any other medication, reduce bronchial hyperresponsiveness and may reduce some aspects of airway remodeling, thus modifying disease progression. Some corticosteroids are effective in once- or twice-daily dosing regimens and may be used in all patient groups and for all levels of disease severity.[26] The FDA recently approved budesonide inhalation suspension (Pulmicort Respules), the only nebulizable corticosteroid for children one to eight years. It is available in unit doses of 0.25 mg and 0.50 mg for once- or twice-daily dosing.

Nonetheless, the improper use of inhaled corticosteroids does raise some concerns. Long-term use at high doses may inhibit growth velocity; therefore, children's growth should be monitored regularly, and the dosage should not exceed the recommended level unless other options, such as the addition of an antileukotriene agent or a long-acting beta$_2$ agonist, have proved unsuccessful. Furthermore, inhaled corticosteroids do not provide immediate relief, and some patients

may overuse bronchodilators and omit their anti-inflammatory therapy.[18]

Fear of adverse side effects (e.g., oropharyngeal candidiasis or inhibited growth) resulting from inhaled corticosteroids may discourage compliance.[27] Patient education is essential to relieve these fears, and alternate therapies should be available for use in patients who are resistant to inhaled corticosteroids and those who cannot master the proper use of inhaler devices. A summary of comparative daily doses of inhaled corticosteroids can be accessed at http://www.nhlbi.nih.gov/health/prof/lung/asthma/practgde/adult.pdf.

Long-acting beta$_2$ agonists are not as effective as inhaled corticosteroids in reducing airway hyper-responsiveness or controlling the inflammation of asthma. However, long-acting beta$_2$ agonists are effective bronchodilators and may be used as add-on therapy with inhaled corticosteroids to reduce nocturnal asthma symptoms and prevent exercise-induced bronchospasm.[26] They are not a substitute for anti-inflammatory medications and should not be used to treat patients with acute symptoms or exacerbations. The FDA approved a long-acting beta$_2$ agonist, salmeterol (Serevent), for treatment of asthma in children 12 years and older. It may provide 24-hour bronchodilation with twice-daily dosing and may reduce nocturnal asthma symptoms and prevent exercise-induced bronchospasm.[28] There is evidence that long-acting beta$_2$ agonists used with inhaled corticosteroids have additive effects. In August of 2000, the FDA approved a combination of almeterol and fluticasone (Advair diskus) that should be released in the United States in April of 2001 in a formulation for children 12 years and older. The dosage is one inhalation twice daily.

Theophylline produces mild-to-moderate bronchodilation and may be used as add-on therapy with anti-inflammatory medications.[26] However, theophylline has a narrow therapeutic index, variable clearance rates, drug interactions and serious side effects; therefore, monitoring of blood levels is required. Theophylline is reserved for the treatment of patients with severe asthma, when polypharmacy is necessary.

Poor compliance is a major problem in pediatric asthma management.

Cromolyn sodium (Intal) and nedocromil (Tilade) are first-line, daily anti-inflammatory inhaled agents that inhibit early- and late-phase bronchoconstriction, with virtually no serious side effects and no known drug interactions.[26] These medications are available in MDI and nebulizer formulations; however, frequent administration is required (up to four doses daily), which may discourage compliance.[24] Furthermore, these agents are less effective than corticosteroids in many patients. Nedocromil's bitter taste may discourage compliance in some children.

Antileukotriene agents were developed to inhibit the effects of leukotrienes. This class of drugs represents the first new approach to asthma therapy in 25 years. The leukotriene receptor antagonists montelukast (Singulair) and zafirlukast (Accolate), and the 5-lipoxygenase inhibitor zileuton (Zyflo) are unique in their ability to target specific components of asthmatic inflammation.[29] Montelukast is available for the treatment of children with asthma who are six to 14 years of age, at a dosage of 5 mg once daily at bedtime. A 10-mg tablet is approved for use in children older than 15 years,[30] and the FDA recently approved a 4- or 5-mg chewable tablet for children two to five years. Zafirlukast is also FDA-labeled for the treatment of children with asthma who are older than seven years, at a dosage of 10 mg twice daily.[31] Although zileuton is FDA-labeled for pediatric treatment, it is prescribed infrequently because it has a four-times daily dosing regimen and a risk of hepatotoxicity that requires monitoring.

Although the role of these drugs continues to evolve, the antileukotrienes have demonstrated

efficacy against exercise- and allergen-induced bronchoconstriction, and an additive benefit in the treatment of patients with symptomatic, moderate asthma who are taking maintenance inhaled corticosteroids.[32,33] They reduce the need for rescue medication in patients with mild asthma and are appropriate as long-term therapy in patients who require more than an occasional treatment with beta$_2$-agonist bronchodilators. Data on the safety of montelukast and zafirlukast are excellent, with an adverse event profile similar to that of placebo.[31,32] Churg-Strauss syndrome (an eosinophil-associated vasculitis) has reportedly been associated (rarely) with corticosteroid withdrawal and may represent an unmasking of a previously unrecognized condition.[34]

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