Management of Asthma in Children

James P. Kemp, M.D., University of California School of Medicine, San Diego, California
Judith A. Kemp, D.O., San Diego, California

Asthma currently affects nearly 5 million children in the United States—more than 5 percent of the population younger than 18 years. 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. 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. 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.

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 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. Airflow limitation is produced by acute bronchoconstriction, airway edema, mucous plug formation and airway remodeling.

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. 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 (FEV1) 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

The Authors
JAMES P. KEMP, M.D., is clinical professor of pediatrics in the Division of Immunology and Allergy at the University of California School of Medicine, San Diego, and immediate past president of the American Academy of Allergy/Asthma and Immunology. Dr. Kemp earned his medical degree from the University of Virginia School of Medicine, Charlottesville, and completed a residency in pediatrics at Emory University School of Medicine, Atlanta. Dr. Kemp completed a fellowship in pediatric allergy and immunology at the University of California, San Francisco, School of Medicine.

JUDITH A. KEMP, D.O., is in private practice in San Diego. She earned her medical degree from the College of Osteopathic Medicine of the Pacific (now Western Health Sciences University), Pomona, Calif., and completed a residency in family practice at Sharp/Grossmont Hospital, San Diego.

Address correspondence to James P. Kemp, M.D., Allergy and Asthma Medical Group and Research Center, 9610 Granite Ridge Dr., Ste. B, San Diego, CA 92123 (e-mail: JPK3355@aol.com). Reprints are not available from the authors.
exists because of poor technique and the use of adult-sized equipment. In most children, the primary diagnostic tool is clinical assessment. 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.

Treatment

Treatment should include patient education, trigger avoidance and drug therapy regimens that enable patients to function without limitations from asthma symptoms. Table 1 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. 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. (The guidelines are available on the Web at: http://www.nhlbi.nih.gov/guidelines/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. 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.

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), frequency of dosing (once- or twice-daily regimens are preferred), medication effects (a slow onset of action and long duration on discontinuance have poor adherence rates) and the risk or concern of side effects.
### Stepwise Approach for Managing Infants and Young Children (< 5 Years of Age) with Acute or Chronic Asthma Symptoms

<table>
<thead>
<tr>
<th>Asthma diagnosis</th>
<th>Quick relief*</th>
<th>Long-term control</th>
<th>Medication</th>
<th>Price†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 4; severe, persistent</strong></td>
<td>Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, using either:</td>
<td>Daily anti-inflammatory medications:</td>
<td>Oral corticosteroids</td>
<td>$44.00 for 100 tablets</td>
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<td></td>
<td>• Inhaled short-acting β₂ agonist by nebulizer or spacer/holding chamber and face mask or • Oral β₂ agonist</td>
<td>• 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.</td>
<td>• Methylprednisolone (Medrol), 2-mg tablet</td>
<td>15.50 per 120 mL</td>
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<td>• Prednisolone (Pediapred liquid), 5 mg per 5 mL</td>
<td>20.50 per 120 mL</td>
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<td></td>
<td></td>
<td>• Prednisone 5-mg tablet</td>
<td>3.50 to 6.50 for 100 tablets</td>
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<td></td>
<td></td>
<td></td>
<td>• Deltasone, 5-mg tablet (Intensol), 5 mg per mL</td>
<td>4.50</td>
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<tr>
<td><strong>Step 3; moderate, persistent</strong></td>
<td>Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, using either:</td>
<td>Daily anti-inflammatory medications, either:</td>
<td>Long-acting β₂ agonist</td>
<td>42.00</td>
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<td></td>
<td>• Inhaled, short-acting β₂ agonist by nebulizer or spacer/holding chamber and face mask or • Oral β₂ agonist</td>
<td>• Medium-dose inhaled corticosteroid with spacer/holding chamber and face mask or, once control is established • Low- to medium-dose inhaled corticosteroid and nedocromil (Tilade)</td>
<td>• Salmeterol (Serevent MDI)</td>
<td>43.50</td>
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<td></td>
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<td>• Inhaled, short-acting β₂ agonist by nebulizer or spacer/holding chamber and face mask or • Oral β₂ agonist</td>
<td>or • Low- to medium-dose inhaled corticosteroid and long-acting bronchodilator (e.g., either long-acting, inhaled β₂ agonist or theophylline SR)</td>
<td>• Albuterol SR (Volmax tablet)</td>
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<td></td>
<td>• Salmeterol/Fluticasone (Advair diskus) 100 µg /50 µg</td>
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<td>250 µg /50 µg</td>
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<td>500 µg /50 µg</td>
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<td>177.00</td>
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<td><strong>Step 2; Mild, persistent</strong></td>
<td>Short-acting bronchodilator as needed for symptoms. Intensity of treatment depends on severity of exacerbation, either:</td>
<td>Daily anti-inflammatory medications:</td>
<td>Cromolyn (Intal) inhaler Nedocromil (Tilade) inhaler Inhaled corticosteroids</td>
<td>47.00</td>
</tr>
<tr>
<td></td>
<td>• Inhaled, short-acting β₂ agonist by nebulizer or spacer/holding chamber and face mask or • Oral β₂ agonist</td>
<td>• 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</td>
<td>• Beclomethasone (Beclovent MDI), 42 µg per puff</td>
<td>45.00</td>
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<td></td>
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<td>• Vanceril DS MDI), 84 µg per puff</td>
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<td>• Budesonide (Pulmicort Turbuhaler DPI), 200 µg per puff</td>
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<td>• Pulmicort Respules, 0.25 mg, 0.5 mg</td>
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<td>• Flunisolide (AeroBid MDI), 250 µg per puff</td>
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<td>• Fluticasone (Flovent), 44 µg per puff (Flovent) 220 µg per puff</td>
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<td></td>
<td>• Triamcinolone (Azmacort MDI), 100 µg per puff</td>
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<td>• Theophylline 200 mg</td>
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<td>300 mg (SR)</td>
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<td>450 mg (TR)</td>
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<td></td>
<td>Antileukotrienes</td>
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<td></td>
<td></td>
<td></td>
<td>• Zafirlukast (Accolate), 10-mg tablet</td>
<td>62.00 for 100 tablets</td>
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<td></td>
<td></td>
<td></td>
<td>• Montelukast (Singulair), 10-mg tablet</td>
<td>71.00 for 30 tablets</td>
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<td></td>
<td></td>
<td></td>
<td>• Methylprednisolone (Medrol), 10-mg tablet</td>
<td>73.00 to 83.00 for 30 tablets</td>
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<td></td>
<td></td>
<td></td>
<td>• Fluticasone (Flovent), 44 µg per puff</td>
<td>91.00 for 120 tablets</td>
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</tbody>
</table>

Table continues
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 FEV₁ and PEF, as shown in Table 2.38

The National Asthma Education and Prevention Program guidelines29 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 beta₂ agonists, short-course oral corticosteroids or ipratropium (Atrovent), are taken as needed for immediate relief of symptoms. 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 beta₂ agonists rapidly relax bronchial smooth muscle and are the therapy of choice to relieve acute symptoms and prevent exercise-induced bronchospasm. Beta₂ 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 hyper-reactivity, 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 beta₂ agonists, or it may be added to a beta₂ agonist such as albuterol (Ventolin) to treat acute asthma exacerbations.

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 hyper-reactivity 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 beta₂ agonist, have proved unsuccessful. Furthermore, inhaled corticosteroids do not provide immediate relief, and some patients

| TABLE 2
<table>
<thead>
<tr>
<th>Diagnosis of Asthma</th>
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<tr>
<td>Asthma diagnosis</td>
</tr>
<tr>
<td>Step 4; severe persistent</td>
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<tr>
<td>Step 3; moderate persistent</td>
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<tr>
<td>Step 2; mild persistent</td>
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<tr>
<td>Step 1; mild intermittent</td>
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</tbody>
</table>

FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.

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

Poor compliance is a major problem in pediatric asthma management.
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 beta2-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

REFERENCES

17. von Mutius E. Progression of allergy and asthma through childhood to adolescence. Thorax 1996; 51(suppl 1):S3-6.