

The only effective measure for evading animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed to lower the pollen exposure. HEPA filters reduce the counts of airborne mold spores.

Oral antihistamines administered as needed are suitable pharmacotherapy for the patient with mild, intermittent symptoms. Antihistamines relieve sneezing and rhinorrhea. The 2nd-generation antihistamines are preferred because they cause less sedation. Four are currently available: cetirizine (2–5 yr: 2.5 mg PO once daily; ≥6 yr: 5–10 mg PO once daily), loratadine (2–5 yr: 5 mg PO once daily; ≥6 yr: 10 mg PO once daily), fexofenadine (6–11 yr: 30 mg PO bid; ≥12 yr: 60 mg PO bid or 180 mg PO qd), and azelastine nasal spray (5–11 yr: 1 spray/nostril bid; ≥12 yr: 2 sprays/nostril bid). Pseudoephedrine (available without prescription; 2–6 yr: 15 mg PO q6h; 6–12 yr: 30 mg PO q6h; >12 yr: 60 mg PO q6h), an oral vasoconstrictor that can be associated with irritability and insomnia, may be used for nasal congestion, and the anticholinergic nasal spray ipratropium bromide (2 sprays/nostril bid or tid, use 0.03% preparation) can be used for serous rhinorrhea. Intranasal decongestants may be used for less than 5 days, not to be repeated more than once a month. Sodium cromoglycate (available without prescription) is effective but requires frequent administration (every 4 hr). Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage.

Patients with more persistent, severe symptoms require treatment with intranasal corticosteroids. These agents are effective for all symptoms of AR with eosinophilic inflammation but not for rhinitis associated with neutrophils or free of inflammation. The older drugs beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract as well as from the respiratory tract. Fluticasone (>4 yr: 1–2 sprays/nostril once daily), mometasone (3–11 yr: 1 spray per nostril once daily; >11 yr: 2 sprays/nostril once daily), and budesonide (>6 yr: 1–2 sprays/nostril once daily) have lower bioavailability and a better safety profile.

A consultation with an allergist is recommended for patients with AR who do not respond to treatment. The allergist may propose more effective avoidance measures and/or immunotherapy. Allergen immunotherapy interferes with IgE production and allergen-induced allergic symptoms and has been found to be effective in the treatment of AR.

**Complications.** Chronic sinusitis is a frequent complication of AR, most often associated with purulent infection, but a proportion of patients develop marked mucosal thickening, sinus opacification, and nasal polyposis with inflammation but negative cultures. The inflammatory process is characterized by marked eosinophilia. Allergens may be the inciting agents. The sinusitis of **triad asthma** (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often shows poor response to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Approximately 60% of patients with AR have asthma and even those who do not may manifest bronchial hyperresponsiveness. In patients who have both disorders, the aggravation of AR coincides with exacerbation of asthma and the treatment of nasal inflammation often reduces bronchospasm. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of tonsils and adenoids; the former may be associated with obstructive sleep apnea and the latter with eustachian tube obstruction, serous effusion, and otitis media.

Children with AR experience frustration over their appearance; some have a cognitive impairment. Pediatric Rhinoconjunctivitis Quality of Life measures in these children have documented

anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, interferes with sleep, and leads to school absenteeism.

Bousquet J, Van Cauwenberge P, Khaltaev NL: Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147–334.

Milgrom H: Attainments in atopy: Special aspects of allergy and IgE. *Adv Pediatr* 2002;49:273–97.

New perspectives on pediatric allergic rhinitis. Proceedings of a workshop. Barcelona, Spain. *J Allergy Clin Immunol* 2001;108:S1–64.

Sly RM: Changing prevalence of allergic rhinitis and asthma. *Ann Allergy Asthma Immunol* 1999;82:233–48.

## Chapter 134

# Childhood Asthma

Andrew H. Liu, Joseph D. Spahn, and  
Donald Y. M. Leung

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the “twitchiness” of the airways—airways hyper-responsiveness—to provocative exposures. Other associated histopathologic abnormalities of the airways characteristic of asthma include epithelial damage, subepithelial collagen deposition with basement membrane thickening, and mucus gland and smooth muscle hypertrophy. These pathologic changes, linked to persistent airways inflammation and hyperresponsiveness, form the chronic basis of this disease.

Clinical manifestations of asthma are intermittent. Dry coughing, expiratory wheezing, chest tightness, and dyspnea are commonly provoked by physical exertion and airways irritants (e.g., cold and dry air, environmental tobacco smoke). Asthma symptoms are usually associated with widespread but variable airflow obstruction that is generally reversible either spontaneously or with treatment. Asthma exacerbations for prolonged periods (i.e., from days to weeks) are induced by common respiratory viral infections and by inhaled allergen exposure in sensitized asthmatics. These exacerbations are characteristically worse at night and can progress to severe airflow obstruction, shortness of breath, and respiratory distress and insufficiency. Rarely, severe sequelae such as hypoxic seizures, respiratory failure, and death can occur.

Current asthma management is aimed at reducing airways inflammation by using daily “controller” anti-inflammatory medications, minimizing proinflammatory environmental exposures, and controlling co-morbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, including less need for “quick-reliever” asthma medication (i.e., β-agonist bronchodilators) and fewer exacerbations. Exacerbations can, nevertheless, still occur. Early intervention with systemic glucocorticoids can greatly reduce the severity of such episodes. Thus, in contrast to past images of debilitated and frail asthmatic children, recent improvements in asthma management and especially pharmacotherapy enable all but the rare child with severe asthma to live normally. With good asthma management, almost all children with asthma can (1) attend school regularly, (2) participate fully in the sport of their choice, (3) sleep well without disturbance due to asthma, (4) experience little to no adverse effects from asthma pharmacotherapy, and (5) with early intervention, stay safe by keeping asthma exacerbations from becoming severe.

**Etiology.** Although the cause of childhood asthma has not been pinpointed, contemporary research implicates an interplay between genetic and environmental factors. The strong associa-

tion of common childhood asthma with concomitant allergies suggests that environmental factors influence immune development toward the asthmatic phenotype in susceptible individuals.

**GENETICS.** Twin studies have revealed a 0.74 concordance of asthma between monozygotic twins and a 0.35 concordance between dizygotic twins, implicating a genetic contribution to asthma development. More than 22 loci on 15 autosomal chromosomes have been linked to asthma. Although the genetic linkages to asthma have sometimes differed between cohorts, asthma has been consistently linked with loci containing proallergic, proinflammatory genes (e.g., the IL-4 gene cluster on chromosome 5). Genetic variation in receptors for different asthma medications is associated with variation in biologic response to these medications (e.g., polymorphisms in the glucocorticoid,  $\beta$ -adrenergic, and leukotriene receptors). Accordingly, asthma pharmacogenomics should optimize asthma pharmacotherapy in the future by genotyping patients to predict their response to different asthma medication options.

**ENVIRONMENT.** Common viral infections of the respiratory tract, such as with respiratory syncytial virus (RSV), can induce small airways bronchiolitis. RSV is a common cause of severe bronchiolitis and/or pneumonia in the first 2 yr of life. It is also a common precipitant of asthma exacerbations at any age. Interestingly, whereas nearly all children by age 2 yr have immunologic evidence of previous RSV infection, only 12–40% of those infected report bronchiolitis symptoms. This implies that host features affect the extent of airways injury from viral pathogens. Likewise, injurious viral infections of the airways (i.e., manifesting as pneumonia and/or bronchiolitis requiring hospitalization) are risk factors for persistent asthma in childhood.

Some airways exposures besides viral infections can exacerbate ongoing airways inflammation and increase disease severity. Allergen exposure, in sensitized individuals, can initiate airways inflammation and hypersensitivity to other irritant exposures as well. Indeed, perennial allergen exposure in sensitized asthmatics is a major contributor to disease severity. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes “cure” asthma. Environmental tobacco smoke, endotoxin, and air pollutants (e.g., ozone, sulfur dioxide) aggravate airways inflammation and increase asthma severity. Cold dry air and strong odors can trigger bronchoconstriction when airways are irritated but do not worsen airways inflammation or hyperresponsiveness.

**Epidemiology.** Asthma is a common chronic disease, causing considerable morbidity. Based on information collected by the United States National Center for Health Statistics in 1998, 8.65 million children (12.1%) were reported to have physician- or health care professional–diagnosed asthma in their lifetime, and 3.8 million children (5.3%) had experienced an asthma episode in the preceding 12 mo. Childhood asthma in the United States is the most common cause of childhood emergency department visits, hospitalizations, and missed school days, accounting annually for 867,000 emergency department visits, 166,000 hospitalizations, and 10.1 million school days lost. Although death due to asthma is relatively uncommon in children (0.3 deaths per 100,000 population per year), asthma was responsible for 164 deaths of children in the United States in 1998. Many of these asthma deaths could probably have been avoided. Indeed, asthma is generally an underdiagnosed and undertreated condition.

In the United States, asthma morbidity and mortality are particularly high in African-American children. Asthma hospitalization and death rates are more than three times higher in black versus white Americans. A combination of biologic, environmental, economic, and psychosocial risk factors is believed to increase the likelihood of severe asthma exacerbations for

ethnic minority asthmatics living in U.S. “inner-city” low-income communities. Although asthma prevalence is slightly higher in black versus white U.S. children (i.e., in 1998, 16.1% vs. 13.2%, respectively), asthma prevalence is not believed to differ significantly with either ethnicity or income status. Therefore, asthma morbidity and mortality is linked with ethnic minority and low-income status whereas asthma prevalence is primarily associated with urban living.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. For example, in the United States from 1982 to 1994, childhood asthma prevalence increased 72%. Numerous studies conducted in different countries have reported a similar increase in asthma prevalence of about 50% per decade. Of further interest, childhood asthma prevalence varies widely in different locales. A large international study of childhood asthma prevalence (by report) in 56 countries (International Study of Asthma and Allergies in Childhood) found about a 20-fold variation in asthma prevalence (range, 1.6–36.8%). Furthermore, asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence ( $R = 0.75$  and  $0.74$ , respectively;  $p < .0001$ ). Childhood asthma seems particularly common in modern metropolitan locales and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries (e.g., rural Africa, China, India) and farming communities (e.g., in Germany, Austria, Switzerland, Finland, Quebec) are less likely to have asthma and allergy. This striking variation in childhood asthma prevalence has led to investigations of potential environmental and lifestyle factors that may explain these differences as well as the recent rise in asthma (see Chapter 130).

Approximately 80% of asthmatics report disease onset before 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority will go on to have persistent asthma in later childhood. Several risk factors for persistent asthma have been identified (Box 134–1). Allergy in these young wheezers has emerged as a major risk factor for persistent childhood asthma and may be evident in the early childhood years as clinical conditions (atopic dermatitis, allergic rhinitis, food allergies).

There are two main types of childhood asthma: (1) recurrent wheezing in early childhood, primarily triggered by common viral infections of the respiratory tract, and (2) chronic asthma associated with allergy that persists into later childhood and often adulthood. A third emerging type of childhood asthma typically occurs in females who develop obesity and early-onset puberty (by 11 years of age). Although asthma mediated by “occupational” exposures is often not considered, some children are raised in settings, on farms or with farm-type animals in the home, where occupational-type exposures can mediate a fourth type of childhood asthma. **Triad asthma**, characteristically

#### BOX 134–1. Early Childhood Risk Factors for Persistent Asthma

- Parental asthma
- Allergy
  - Atopic dermatitis
  - Allergic rhinitis
  - Food allergy
  - Inhalant allergen sensitization
  - Food allergen sensitization
- Severe lower respiratory tract infection
  - Pneumonia
  - Bronchiolitis requiring hospitalization
- Wheezing apart from colds
- Male gender
- Low birth weight
- Environmental tobacco smoke exposure

associated with hyperplastic sinusitis/nasal polyposis and hypersensitivity to aspirin and nonsteroidal anti-inflammatory medications (e.g., ibuprofen), rarely has its onset in childhood. Current evidence suggests that, of these different types of childhood asthma, the most common form is that associated with allergy. Additionally, allergen sensitization and exposure is associated with more severe asthma.

**Pathogenesis.** The pathologic changes linked to persistent airways inflammation and hyperresponsiveness underlie the chronic basis of asthma.

**AIRWAYS OBSTRUCTION.** Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airways lumens; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes), can fill the airways and induce epithelial damage and desquamation into the airways lumen. Excess production of mucus into the airways and edema of the surrounding tissues also contribute to blockage of airways.

**AIRWAYS INFLAMMATION, HYPERRESPONSIVENESS, AND REMODELING.** Asthmatic airways tissues have increased numbers of mast cells, activated eosinophils, and activated helper T lymphocytes (see Chapter 130). Helper T lymphocytes that produce proallergic, proinflammatory cytokines (e.g., IL-4, IL-5, IL-13) and chemokines (e.g., RANTES, eotaxin) mediate this inflammatory process. Other immune cells (e.g., cytotoxic T lymphocytes, NK cells, eosinophils, mast cells, basophils) can produce these proallergic, proinflammatory cytokines and chemokines as well. Airways inflammation is strongly linked to hypersensitivity of airways smooth muscle (**airways hyperresponsiveness**) to irritant exposures, such as cold air, dry air, strong odors, and particulate matter in smoke.

Airways inflammation is also linked to less reversible airways changes, such as basement membrane thickening, subepithelial collagen deposition, and smooth muscle and mucus gland hypertrophy and hyperplasia. These airways “remodeling” abnormalities resemble an aberrant tissue repair process in response to persistent tissue injury. Therefore, persistent airways inflammation and remodeling are believed to underlie the chronic functional and pathologic abnormalities as well as the intermittent and episodic clinical manifestations of asthma.

Inhaled allergen challenge studies have revealed two distinct phases of airflow obstructive processes in asthma: (1) an **early phase** (within 15–30 min) consisting of bronchoconstriction and (2) a **late phase** (4–12 hr after allergen exposure) of tissue inflammation and immune cellular infiltration into the airways, in addition to airways edema and excess mucus production. The late phase is also associated with airways hyperresponsiveness that can persist for several weeks. The early phase can be prevented with inhaled  $\beta$ -agonist bronchodilator pretreatment; in contrast, the late phase can be prevented with anti-inflammatory agents (e.g., glucocorticoids) but not  $\beta$ -agonists. Therefore, a quick recovery after an acute allergen-induced exacerbation does not mean that the episode is over; on the contrary, a more serious and sustained late-phase episode can occur hours later.

**PROGRESSION OF SEVERE ASTHMA EXACERBATIONS.** Airflow obstruction during asthma exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen at night (i.e., between midnight to 8 AM), when airways inflammation and hyperresponsiveness are at their peak. Complications that can occur during severe exacerbations include atelectasis and air leaks in the chest (pneumomediastinum or pneumothorax).

Importantly, the first-line pharmacotherapy,  $\beta$ -agonists, can increase pulmonary blood flow through obstructed, unoxxygenated areas of the lungs, causing ventilation-perfusion mis-

matching, and precipitating hypoxemia. Hypoxia perpetuates bronchoconstriction, which further worsens the condition. Severe and progressing asthma exacerbations clearly need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy.

**Clinical Manifestations and Diagnosis.** Chronic symptoms are a key aspect of asthma. The medical history typically provides key information in diagnosing asthma. Intermittent dry coughing and/or expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults will report associated shortness of breath and chest tightness; younger children are more likely to report intermittent, nonfocal chest “pain.” Respiratory symptoms are characteristically worse at night, especially during prolonged exacerbations triggered by respiratory infections or inhaled allergens. Other asthma symptoms in children can be subtle and include decreased physical activity, general fatigue (possibly due to sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (i.e., bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms are typically provoked by numerous common events or exposures: physical exertion and hyperventilation (e.g., laughing), cold or dry air, and airways irritants (Box 134–2). Exposures that induce airways inflammation, such as viral infections and inhaled allergens, also increase airways hyperresponsiveness to irritant exposures. Numerous occupational exposures incite asthma in some adults. Similarly, some children might be chronically exposed to these same airways sensitizers in their home or school environments, leading to “occupational” asthma in children. Accordingly, an environmental history is essential to optimal asthma diagnosis (see Chapter 131) and management.

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic der-

### BOX 134–2. Asthma Triggers

- Common viral infections of the respiratory tract
- Aeroallergens in sensitized asthmatics
  - Animal dander
  - Indoor allergens:
    - Dust mites
    - Cockroaches
    - Molds
  - Seasonal aeroallergens:
    - Pollens (trees, grasses, weeds)
    - Seasonal molds
- Environmental tobacco smoke
- Air pollutants
  - Ozone
  - Sulfur dioxide
  - Particulate matter
  - Wood- or coal-burning smoke
  - Endotoxin, mycotoxins
  - Dust
- Strong or noxious odors or fumes
  - Perfumes, hairsprays
  - Cleaning agents
- Occupational exposures
  - Farm and barn exposures
  - Formaldehydes, cedar, paint fumes
- Cold air, dry air
- Exercise
- Crying, laughter, hyperventilation
- Co-morbid conditions
  - Rhinitis
  - Sinusitis
  - Gastroesophageal reflux

matitis, and food allergies), parental asthma, and/or asthma symptoms apart from colds, supports the diagnosis of asthma. Because numerous conditions can mimic asthma, the process of excluding common asthma masqueraders such as chronic rhinosinusitis and gastroesophageal reflux should begin in the medical history.

During routine clinic visits, children with asthma commonly present without abnormal signs. Some may exhibit a dry, persistent cough. By auscultation, the chest examination is also often normal. When breath sounds are abnormal, expiratory high-pitched polyphonic wheezing is typically heard by auscultation and is sometimes even audible without a stethoscope. Deeper breaths can sometimes elicit otherwise undetectable wheezing. The physical examination in asthmatics is also helpful in identifying co-morbid conditions (e.g., allergic rhinoconjunctivitis, rhinosinusitis, atopic dermatitis) and abnormalities consistent with other asthma-masquerading conditions (Box 134–3).

During asthma exacerbations, expiratory wheezing and a prolonged expiratory phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior, are consistent with regional hypoventilation owing to airways obstruction. Crackles, or rales, and rhonchi can also be heard resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate

acute asthma management. In severe exacerbations, the greater degree of airways obstruction causes increased work of breathing and respiratory distress manifested as inspiratory and expiratory wheezing, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use.

**DIFFERENTIAL DIAGNOSIS.** Many childhood respiratory conditions can present as symptoms and signs similar to asthma (see Box 134–3). Besides asthma, other common causes of chronic, intermittent coughing and/or wheezing include rhinosinusitis and gastroesophageal reflux (GER). Both GER and chronic sinusitis can be challenging to diagnose in children. GER is often clinically silent in children, and children with chronic sinusitis typically do not report sinusitis-specific symptoms such as localized sinus pressure or tenderness. In addition, both GER and rhinosinusitis are often co-morbid conditions with childhood asthma.

In early life, chronic coughing and wheezing can indicate a congenital anatomic abnormality of the airways, foreign body aspiration, recurrent aspiration, cystic fibrosis, or bronchopulmonary dysplasia. In adolescents, vocal cord dysfunction (VCD) can present as intermittent daytime wheezing. In this condition, the vocal cords close inappropriately, during inspiration and sometimes expiration, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most VCD cases, spirometric lung function testing will reveal “truncated” and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. However, VCD can also co-exist with asthma. Flexible rhinolaryngoscopy in the symptomatic VCD patient can reveal paradoxical vocal cord movements, with anatomically normal vocal cords. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., GER/aspiration, rhinosinusitis, and asthma) can improve VCD. During acute VCD exacerbations, inhalation of heliox (a mixture of 70% helium with 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

In some locales, hypersensitivity pneumonitis (e.g., farming communities, homes of bird owners), pulmonary parasitic infestations (e.g., rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare asthma-masquerading conditions at any childhood age include bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi, and medication-induced coughing and/or wheezing as an adverse effect.

**Laboratory Findings.** Lung or pulmonary function tests including bronchoprovocation challenges are the basis of documenting the presence of asthma and the severity of acute exacerbations.

**LUNG FUNCTION TESTING.** Measures of expiratory airflow are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in asthmatics who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction has become severe.

**Spirometry** measures airflow and lung volumes during a forced expiratory maneuver and is considered the gold standard measure of airflow in asthma. Its helpfulness as an objective measure in the initial evaluation and management of asthmatics has led to recommendations for its standard use in the U.S. National Asthma Education and Prevention Program (NAEPP) guidelines sponsored by the U.S. National Institutes of Health. In asthma, airways blockage results in reduced airflow and smaller partial-expiratory lung volumes (Fig. 134–1). Of these measures, normative values for FEV<sub>1</sub> (forced expiratory volume

### BOX 134–3. Differential Diagnosis of Childhood Asthma

#### UPPER RESPIRATORY TRACT CONDITIONS

Allergic rhinitis\*  
Chronic rhinitis\*  
Sinusitis\*  
Adenoidal or tonsillar hypertrophy  
Nasal foreign body

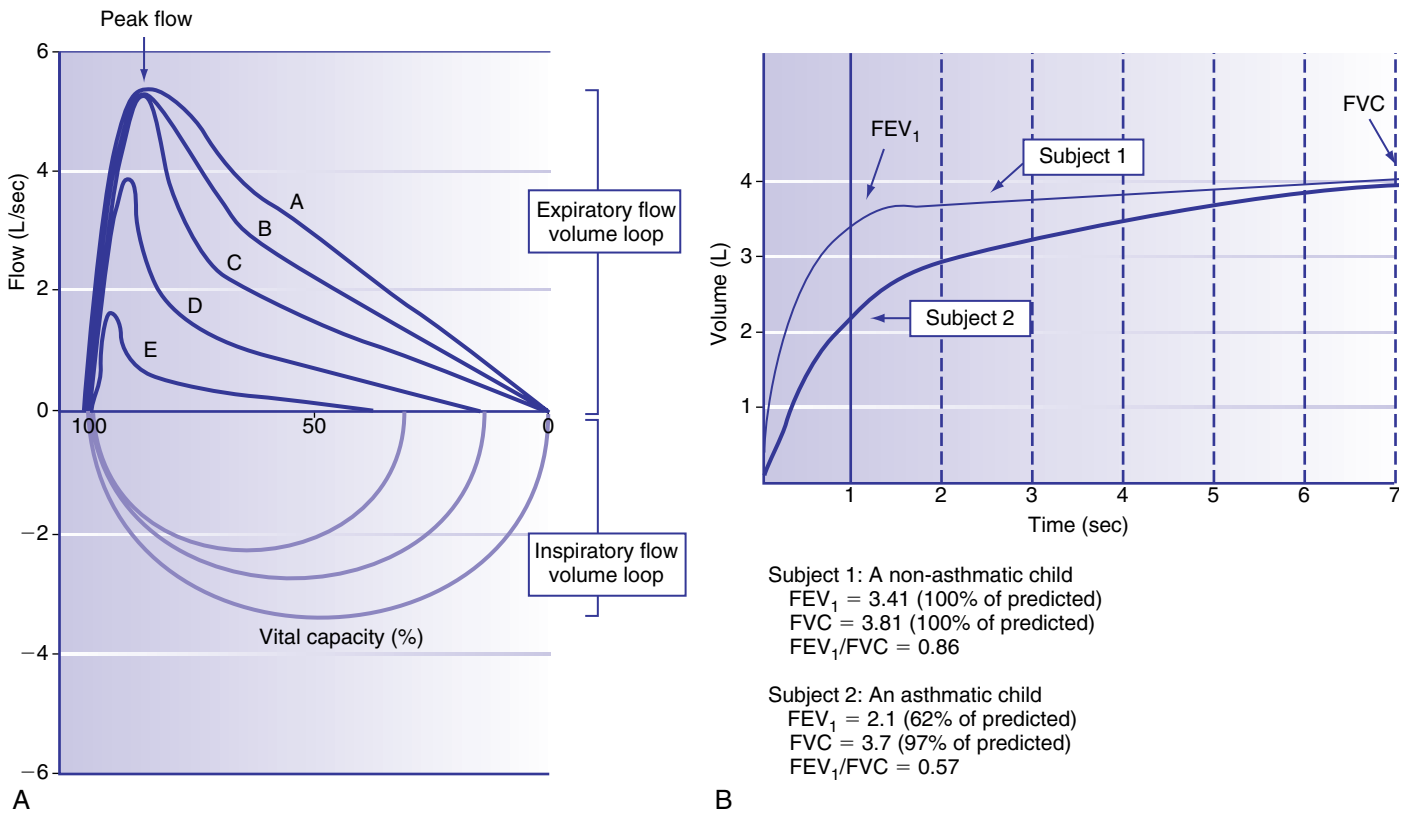
#### MIDDLE RESPIRATORY TRACT CONDITIONS

Laryngotracheobronchomalacia\*  
Laryngotracheobronchitis (e.g., pertussis)\*  
Laryngeal web, cyst or stenosis  
Vocal cord dysfunction\*  
Vocal cord paralysis  
Tracheoesophageal fistula  
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)  
Foreign body aspiration\*  
Chronic bronchitis from environmental tobacco smoke exposure\*  
Toxic inhalations

#### LOWER RESPIRATORY TRACT CONDITIONS

Bronchopulmonary dysplasia or chronic lung disease of preterm infants  
Viral bronchiolitis\*  
Gastroesophageal reflux\*  
Causes of bronchiectasis:  
Cystic fibrosis  
Immune deficiency  
Allergic bronchopulmonary mycoses (e.g., aspergillosis)  
Chronic aspiration  
Immotile cilia syndrome, primary ciliary dyskinesia  
Bronchiolitis obliterans  
Interstitial lung diseases  
Hypersensitivity pneumonitis  
Pulmonary eosinophilia, Churg-Strauss vasculitis  
Pulmonary hemosiderosis  
Tuberculosis  
Pneumonia  
Pulmonary edema (e.g., congestive heart failure)  
Medications associated with chronic cough  
Acetylcholinesterase inhibitors  
β-Adrenergic antagonists

\*More common asthma masqueraders.



**FIGURE 134-1.** Spirometry. *A*, Spirometric flow-volume loops. *A* is an expiratory flow-volume loop of a nonasthmatic, without airflow limitation. *B* through *E* are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (*B* is mild; *E* is severe). Note the “scooped” or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater “scooping.” *B*, Spirometric volume-time curves. Subject 1 is a nonasthmatic; subject 2 is an asthmatic. Note how the FEV<sub>1</sub> and FVC lung volumes are obtained. The FEV<sub>1</sub> is the volume of air exhaled in the 1st second of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort. Note that subject 2’s FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio are smaller than subject 1’s, demonstrating airflow obstruction. Also, subject 2’s FVC is very close to what is expected.

in 1 sec) have been standardized for children, based on height, gender, and ethnicity. The reductions in FEV<sub>1</sub> as a percentage of predicted is one of four criteria used to determine asthma severity in the NAEP guidelines. Because asthmatics are typically hyperinflated, often profoundly, FEV<sub>1</sub> can be simply adjusted for full expiratory lung volume, the forced vital capacity (FVC), with an FEV<sub>1</sub>/FVC ratio. Generally, an FEV<sub>1</sub>/FVC ratio less than 0.8 indicates significant airflow obstruction (Box 134-4). Such measures of airflow alone, however, are not diagnostic of asthma, because numerous other conditions can cause airflow reduction. Bronchodilator response to inhaled  $\beta$ -agonist medication (i.e., albuterol by nebulizer) is greater in asthmatics vs. nonasthmatics—an improvement in FEV<sub>1</sub> greater than 12% is consistent with asthma. Importantly, valid spirometric measures are dependent on a patient’s ability to properly execute a full, forced, and prolonged expiratory maneuver, typically feasible in children older than 6 yr of age (with some younger exceptions). Reproducible spirometric efforts are an indicator of test validity. If, on three consecutive attempts, the FEV<sub>1</sub> is within 5%, then the best FEV<sub>1</sub> effort of the three is used.

**Bronchoprovocation challenges** can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, histamine, and cold or dry air. The degree of airways hyperresponsiveness to these exposures correlates with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in a general practice setting. **Exercise challenges**

(i.e., aerobic exertion or “running” for 6–8 min) can also help to identify the child with **exercise-induced bronchospasm**. Although the airflow response of nonasthmatics to exercise is to increase functional lung volumes and improve FEV<sub>1</sub> slightly (5–10%), exercise typically induces airflow obstruction in untreated asthmatics. Accordingly, in asthmatics, FEV<sub>1</sub> typically decreases during or after exercise by more than 15% (see Box 134-4). The onset of exercise-induced bronchospasm is usually within 15 min after a vigorous exercise challenge and can spontaneously resolve within 60 min. Studies of U.S. school-age children using such exercise challenges typically identify about 10% with exercise-induced bronchospasm but previously undiagnosed asthma, in addition to the known asthmatics with exercise-induced bronchospasm. Exercise challenges can induce

#### BOX 134-4. Lung Function Abnormalities in Asthma

##### Spirometry

##### Airflow limitation

Low FEV<sub>1</sub> (relative to percentage of predicted norms)

FEV<sub>1</sub>/FVC ratio < 0.8

##### Bronchodilator response (to inhaled $\beta_2$ -agonist)

Improvement in FEV<sub>1</sub>  $\geq$  12%\*

##### Exercise challenge

Worsening in FEV<sub>1</sub>  $\geq$  15%\*

Peak flow morning-to-afternoon variation  $\geq$  20%\*

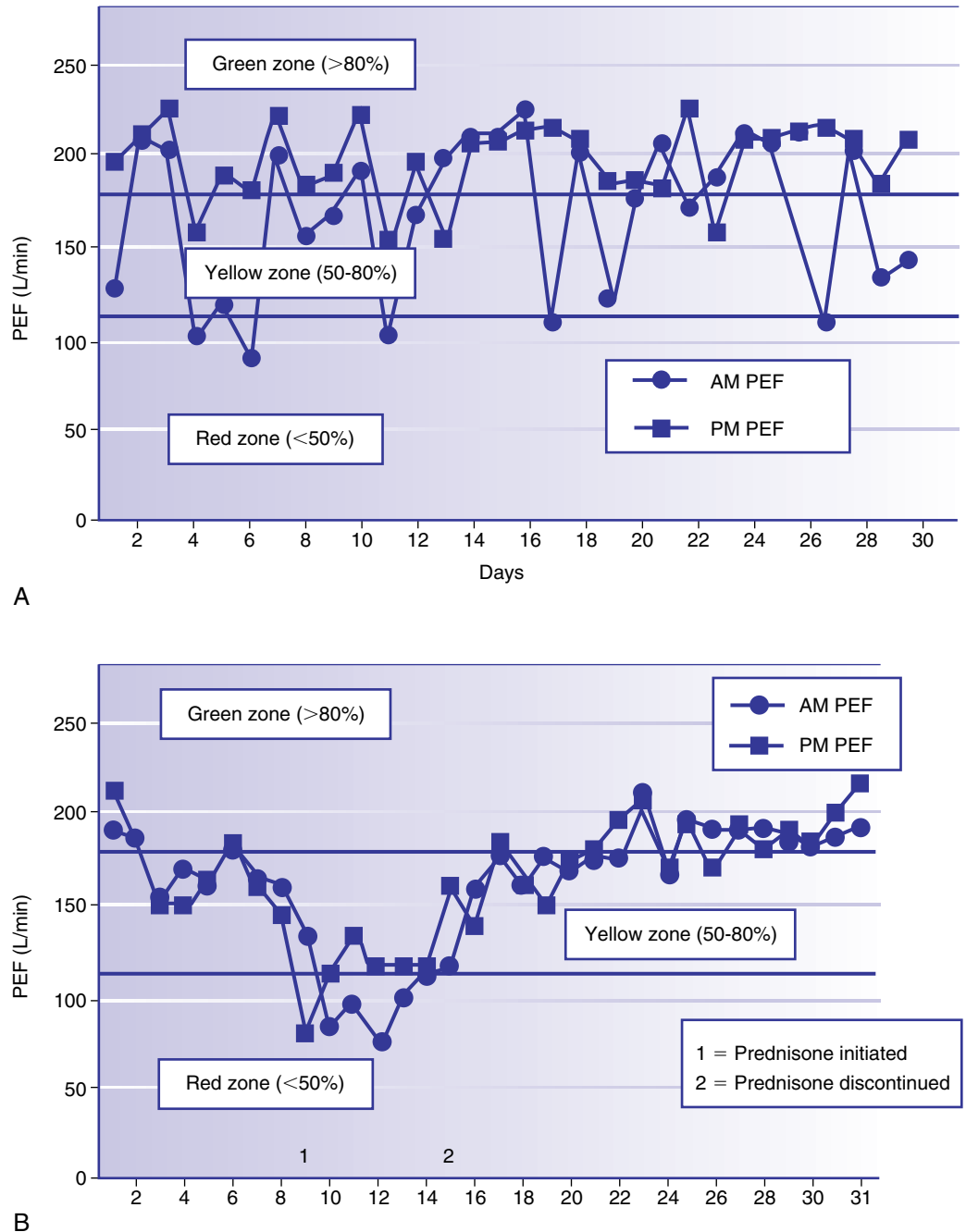
\*Main criteria consistent with asthma.

severe asthma exacerbations in at-risk patients; therefore, careful patient selection for exercise challenges, and preparedness for severe asthma exacerbations, is required.

**Peak expiratory flow (PEF) monitoring** devices provide a simple and inexpensive home-use tool to measure airflow and can be particularly helpful in many circumstances. PEFs vary in their ability to detect airflow obstruction, and, in some patients, PEF declines only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of three consecutive attempts) for several weeks for patients to practice the technique, to determine a “personal best,” and to correlate PEF values with symptoms (and ideally spirometry). PEF morning-to-evening variation greater than 20% is consistent with asthma (Fig. 134–2 and see Box 134–4).

**RADIOLOGY.** Chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening. Chest radiographs are helpful in identifying abnormalities that are hallmarks of asthma masqueraders (e.g., aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans), and complications during asthma exacerbations (e.g., atelectasis, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. For example, bronchiectasis is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan and implicates asthma masqueraders such as cystic fibrosis, allergic bronchopulmonary mycoses (e.g., aspergillosis), ciliary dyskinesias, or immune deficiencies.

**FIGURE 134–2.** Peak flow monitoring. *A*, Peak expiratory flows (PEFs) performed and recorded twice daily, in the morning (AM) and evening (PM), over 1 mo in an asthmatic child. This child’s “personal best” PEF is 220 L/min; therefore, *green zone* (>80–100% of best) is 175–220 L/min; *yellow zone* (50–80%) is 110–175 L/min; and *red zone* (<50%) is less than 110 L/min. Note that this child’s PM PEFs are almost always in the green zone, whereas his AM PEFs are often in the yellow or red zone. This illustrates the typical diurnal AM-to-PM variation of inadequately controlled asthma. *B*, PEFs performed twice daily, in the morning (AM) and evening (PM), over 1 mo in an asthmatic child who developed a viral respiratory tract infection. Note that the child’s PEF values were initially in the green zone. A viral respiratory tract infection led to asthma worsening, with a decline in PEF to the yellow zone that continued to worsen until PEFs were in the red zone. At that point, a 4-day prednisone course was administered, followed by improvement in PEF back to the green zone.



Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5–12 yr old asthmatic children (Childhood Asthma Management Program [CAMP]), 88% had inhalant allergen sensitization by allergy prick skin testing.

**Treatment.** The goals of childhood asthma management for children can be simply stated (Box 134–5). The NAEPP guidelines have been adapted for childhood asthma in a joint publication of the American Academy of Allergy, Asthma & Immunology and the U.S. National Institutes of Health’s National Heart, Lung and Blood Institute and the American Academy of Pediatrics entitled *Pediatric Asthma: Promoting Best Practice*. These guidelines describe four components to optimal asthma management (Box 134–6).

**REGULAR ASSESSMENT AND MONITORING.** Asthma management can be optimized through regular clinic visits every 2–4 wk until good asthma control is achieved. Two to four regular annual asthma check-ups are recommended to maintain good asthma control. During these visits, asthma control can be assessed by asking about (1) the frequency of asthma symptoms during the day, at night, and with physical exercise; (2) the frequency of “rescue” short-acting  $\beta$ -agonist medication use and refills; (3) the number and severity of asthma exacerbations since the last visit; and (4) participation in school, sports, and other preferred activities. Lung function testing (i.e., spirometry) is recommended annually, and more often if asthma is inadequately controlled. PEF monitoring at home can be especially helpful when assessing asthmatic children with poor symptom perception, other causes of chronic coughing in addition to asthma, moderate-to-severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr old and who are able to master this skill. Use of a “stoplight” zone system, preferably tailored to each child’s best PEFs, can optimize effectiveness and interest (see Fig. 134–2): the green zone (80–100% of predicted or the child’s best) indicates good control, the yellow zone (50–80%) indicates less than optimal control and necessitates increased awareness and treatment, whereas the red zone (<50%) indicates poor control requiring immediate intervention. The NAEPP guidelines recommend once-daily PEF monitoring, preferably in the morning.

**CONTROL OF FACTORS CONTRIBUTING TO ASTHMA SEVERITY.** Controllable factors that can significantly worsen asthma can be generally grouped as (1) environmental exposures and (2) co-morbid conditions (Box 134–7).

**Eliminate or Reduce Problematic Environmental Exposures.** The majority of children with asthma have an allergic component to their disease. Because of this, steps should be taken to investigate and minimize allergen exposures in sensitized asthmatics. Several studies have shown that, in sensitized asthmatics, reduced exposure to allergens can decrease asthma symptoms, the need for medications, and airways hyperresponsiveness.

Asthmatic children who are sensitized to indoor allergens in particular can experience greater asthma severity due to year-round exposure and can benefit from measures to minimize

#### BOX 134–5. Goals of Childhood Asthma Management

- Maintain normal activity
- Regular school or daycare attendance
- Full participation in physical exercise, athletics, and other recreational activities
- Prevent sleep disturbance
- Prevent chronic asthma symptoms
- Keep asthma exacerbations from becoming severe
- Maintain normal lung function
- Experience little to no adverse effects of treatment

#### BOX 134–6. Four Components of Optimal Asthma Management

##### REGULAR ASSESSMENT AND MONITORING

- Asthma check-ups
  - Every 2–4 wk until good control is achieved
  - 2–4 per year to maintain good control
- Lung function monitoring

##### CONTROL OF FACTORS CONTRIBUTING TO ASTHMA SEVERITY

- Eliminate or reduce problematic environmental exposures
- Treat co-morbid conditions: rhinitis, sinusitis, gastroesophageal reflux

##### ASTHMA PHARMACOTHERAPY

- Long-term-control versus quick-relief medications
- Classification of asthma severity for anti-inflammatory pharmacotherapy
- Step-up, step-down approach
- Asthma exacerbation management

##### PATIENT EDUCATION

- Provide a two-part care plan
  - Daily management
  - Action plan for asthma exacerbations

#### BOX 134–7. Control of Factors Contributing to Asthma Severity

##### ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES

- Environmental tobacco smoke elimination or reduction
  - In home and automobiles
- Allergen exposure elimination or reduction in sensitized asthmatics
  - Animal danders
    - Pets (cats, dogs, rodents, birds)
    - Pests (mice, rats)
  - Dust mites
  - Cockroaches
  - Molds
- Other airway irritants
  - Wood- or coal-burning smoke
  - Strong chemical odors and perfumes (e.g., household cleaners)
  - Dusts

##### TREAT CO-MORBID CONDITIONS

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

##### GET ANNUAL INFLUENZA VACCINATION (UNLESS EGG-ALLERGIC)

allergen exposure in the home. Common perennial allergen exposures include furred or feathered animals as pets or as pests and occult indoor allergens such as dust mites, molds, and cockroaches. Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood, and coal smoke, dusts, and strong or noxious odors and fumes can all aggravate asthma. At the very least, these airways irritants should be eliminated or reduced from the homes and automobiles used by asthmatic children. School classrooms and daycare centers can also be sites of asthma-worsening environmental exposures. Eliminating or minimizing these exposures can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Common viral infections of the respiratory tract are difficult to avoid; annual influenza vaccination is recommended for all asthmatic children (except for those with egg allergy).

**Treat Co-morbid Conditions.** Rhinitis, sinusitis, and gastroesophageal reflux commonly accompany asthma and can worsen disease severity. Indeed, these conditions are also common causes of chronic coughing. Effective management of these co-morbid conditions can often improve asthma symptoms and

disease severity, so that less medication is needed to achieve good asthma control.

Gastroesophageal reflux (GER) is commonly noted in asthmatics, with a reported incidence of up to 64%. GER may worsen asthma through two postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macroaspiration) and (2) reflex bronchospasm. GER should be suspected in all individuals with difficult-to-control asthma, especially patients with prominent symptoms while eating or sleeping (i.e., in a horizontal position). GER can be confirmed by demonstration of reflux of barium into the esophagus during a barium swallow procedure or by esophageal pH monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal pH monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated 6 in) and antacid medications such as H<sub>2</sub>-receptor antagonists (e.g., cimetidine, ranitidine) or proton pump inhibitors (e.g., omeprazole, lansoprazole), and possibly prokinetic pharmacotherapy, administered for a 6–8 wk period.

Radiographic evidence for sinus disease is also common in patients with asthma. Several case series have reported significant improvement in asthma control in patients diagnosed and treated for occult sinus disease. A screening CT scan of the sinuses is the current gold standard test for sinus disease. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations and intranasal glucocorticoids should be instituted, and a 3 wk course of antibiotics administered.

**PRINCIPLES OF ASTHMA PHARMACOTHERAPY.** The NAEPP guidelines classify asthma severity before treatment using four parameters: (1) frequency of daytime or (2) nighttime symptoms, (3) degree of airflow obstruction by spirometry, and/or (4) PEF variability (Table 134–1). Asthmatics can be categorized in four disease severity groups, as “mild intermittent” or “persistent” disease that is “mild,” “moderate,” or “severe.” A major objective of this approach is to identify and treat all “persistent” asthma with anti-inflammatory controller medication. The “3 Strikes” rule is a handy memory aid for determining if an asthmatic child should receive controller therapy based on the NAEPP guidelines. Simply put, if an asthmatic child has asthma symptoms or requires quick-relief medication more than three times per week, awakens at night due to asthma more than three times per month, or requires a refill for a quick-relief inhaler prescription more than three times per year, then that patient should receive daily controller therapy. Low-dose inhaled glucocorticoids, leukotriene pathway modifiers, or cromolyn/nedocromil are the recommended controllers for mild persistent asthmatics; sustained-release theophylline is an alternative. The recommended controller medication for moderate persistent asthmatics is medium-dose inhaled glucocorticoids or low-dose inhaled glucocorticoids in combination with a long-acting  $\beta$ -agonist or a leukotriene pathway modifier; sustained release theophylline or long-acting oral  $\beta$ -agonists are alternatives. Severe persistent asthmatics should receive high-dose inhaled glucocorticoids, a long-acting bronchodilator, and routine oral glucocorticoids if needed. “Mild intermittent asthma” is the only level of asthma severity where daily controller therapy

**TABLE 134–1. Stepwise Approach for Managing Asthma: Severity Classification and Management\***

Asthma Severity	Days with Symptoms	Nights with Symptoms	Lung Function	Long-Term-Control Medication	Quick-Relief Medication	Education
<b>Step 1:</b> <i>Mild Intermittent</i>	<3 per wk	<3 per mo	FEV <sub>1</sub> or PEF $\geq$ 80% of predicted; PEF variability <20%	No daily medication needed	<b>Short-acting <math>\beta</math>-agonist</b> as needed and before exercise; Use $\geq$ 3 times per wk may indicate need to initiate long-term-control therapy	Asthma facts, MDI and spacer technique, role of medications, action plan, environmental control measures
<b>Step 2:</b> <i>Mild Persistent</i>	$\geq$ 3 per wk	3–4 per mo	FEV <sub>1</sub> or PEF $\geq$ 80% of predicted; PEF variability 20–30%	<b>Anti-inflammatory:</b> either low-dose <b>inhaled glucocorticoid, cromolyn, nedocromil, or leukotriene modifier.</b> Sustained-release theophylline is an alternative.	<b>Short-acting <math>\beta</math>-agonist</b> as needed and before exercise; daily use or increasing use may indicate need for additional long-term-control therapy	Step 1 actions plus: self-monitoring, group education, review and update self-management plan
<b>Step 3:</b> <i>Moderate Persistent</i>	Daily symptoms, daily use of short-acting $\beta$ -agonists	>1 time per wk	FEV <sub>1</sub> or PEF >60 and $\leq$ 80% predicted; PEF variability >30%	<b>Anti-inflammatory:</b> <b>inhaled glucocorticoids</b> (medium-dose) or inhaled glucocorticoids (low-dose) and either <b>long-acting <math>\beta</math>-agonist (LABA), leukotriene modifier,</b> sustained-release theophylline, or LABA tablets.	<b>Short-acting <math>\beta</math>-agonist</b> as needed and before exercise; daily use or increasing use may indicate need for additional long-term-control therapy	Step 1 actions plus: self-monitoring, group education, review and update self-management plan
<b>Step 4:</b> <i>Severe Persistent</i>	Continual symptoms, limited physical activity, frequent exacerbations	Frequent	FEV <sub>1</sub> or PEF $\leq$ 60% of predicted; PEF variability >30%	<b>Anti-inflammatory:</b> <b>inhaled glucocorticoids</b> (high-dose) and long-acting bronchodilator: either <b>LABA, leukotriene modifier,</b> sustained-release theophylline, and/or LABA tablets. Oral glucocorticoid if needed.	<b>Short-acting <math>\beta</math>-agonist</b> as needed and before exercise; daily use or increasing use may indicate need for additional long-term-control therapy	Step 2 and 3 actions plus: referral for individual education/counseling

\*Based on clinical features before treatment; classification is determined by the patient's most severe feature; bold print indicates preferred medication; asthmatics with “persistent” disease of any severity should be treated with a “long-term-control” anti-inflammatory medication.

Modified from the National Asthma Education & Prevention Program: Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD, National Institutes of Health, National Heart, Lung, and Blood Institute, 1997.

is not recommended. In these subjects, short-acting inhaled  $\beta$ -agonists are recommended as needed for symptoms and for exercise pre-treatment for those with exercise-induced bronchospasm. Short-acting  $\beta$ -agonists are the recommended reliever medication for all asthma severity levels. They are to be used as needed for acute symptoms.

**“Step-Up, Step-Down” Approach.** The NAEPP guidelines outline a stepwise approach to asthma therapy that emphasizes initiating higher-level controller therapy at the outset to establish prompt control, with measures to “step-down” therapy once good asthma control is achieved.

**Inhalation Technique.** Optimal inhalation technique for each puff of metered-dose inhaler (MDI)-delivered medication is a slow (5 sec) inhalation, then a 5–10 sec breath hold. No waiting time between puffs of medication is needed. Spacer devices for the delivery of all medications from MDIs should be used universally in all children with asthma. **Spacer devices** are simple and inexpensive tools that serve three major functions: (1) they decrease the amount of coordination required to use MDIs, especially in young children; (2) they improve the delivery of inhaled drug to the lower airways, which in turn improves medication efficacy; and (3) they minimize the risk of systemic absorption of inhaled glucocorticoids, thus minimizing potential adverse effects of this class of medications. Mouth rinsing is recommended after inhaled glucocorticoid use to rinse out inhaled glucocorticoids deposited on the oral mucosa.

**Combination Pharmacotherapy.** Most children will have their asthma well controlled on a single controller medication. In children who continue to be symptomatic on low to moderate doses of inhaled glucocorticoid therapy, studies have shown a superior outcome when a long-acting  $\beta$ -agonist or leukotriene pathway modifier is added to the original dose of inhaled glucocorticoids rather than doubling the dose of the inhaled glucocorticoid. Thus, lung function and asthma control can be optimized without increasing the potential for systemic effects from inhaled glucocorticoids.

**Adherence.** Asthma is a chronic condition that is often best managed with daily controller medication. However, adherence with a daily regimen can be suboptimal. A study that evaluated adherence of asthmatic children to routine inhaled glucocorticoids found that they were underused 60% of the time. In addition, individuals who required an oral glucocorticoid burst due to an asthma exacerbation had used their inhaled glucocorticoids the least (<15% of the time). Other studies have found that adherence is poorer when prescribed frequency of medication administration is greater (i.e., 3–4 times/24 hr). Therefore, treatment strategies should be designed to minimize the frequency with which medications are administered (i.e., once or twice daily).

**QUICK-RELIEF OR RELIEVER MEDICATIONS.** Asthma medications are used as quick-relief, or “reliever” or “rescue,” medications, or long-term-control, or “controller,” medications (Table 134–2). Quick-relief medications (inhaled  $\beta_2$ -agonists, inhaled anticholinergics, and short-course systemic glucocorticoids) are used in the management of acute episodes of bronchospasm.

**Short-Acting  $\beta_2$ -Agonists.** Given their rapid onset of action, effectiveness, and 4–6 hr duration of action, inhaled short-acting  $\beta$ -agonists (e.g., albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute episodes of bronchospasm (i.e., “rescue” medications) and for preventing exercise-induced bronchospasm.  $\beta$ -Agonists bronchodilate by inducing airway smooth muscle relaxation, reducing vascular permeability airways edema, and improving mucociliary clearance. Studies have reported that overuse of  $\beta$ -agonists is associated with increased death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on short-acting  $\beta$ -agonists as a “quick fix” for their asthma, rather than using controller medications in a preventive man-

**TABLE 134–2. Asthma Medications by Category**

Category	Examples of Medications	
<b>Quick-relief medications (“relievers”)</b>	Short-acting inhaled $\beta$ -agonists: Albuterol (Ventolin, Proventil) Levalbuterol (Xopenex) Terbutaline (Brethaire) Pirbuterol (Maxair) Metaproterenol (Alupent)	
	Inhaled anticholinergics: Ipratropium (Atrovent) Atropine	
	Short-course systemic glucocorticoids: Prednisone (Deltasone) Methylprednisolone (Medrol) Methylprednisolone Sodium Succinate (Solu-Medrol)	
	<b>Long-term-control medications (“controllers”)</b>	Nonsteroidal anti-inflammatory agents: Cromolyn (Intal) Nedocromil (Tilade)
		Inhaled glucocorticoids: Beclomethasone (Vancril, Beclovent, Qvar) Flunisolide (Aerobid) Budesonide (Pulmicort) Fluticasone (Flovent) Triamcinolone (Azmacort) Mometasone (Asmanex)
		Sustained-release theophylline (Slobid, Theodur, Uniphyll)
		Long-acting inhaled $\beta$ -agonists: Salmeterol (Serevent) Formoterol (Foradil)
		Leukotriene modifiers: Montelukast (Singulair) Zafirlukast (Accolate) Zileuton (Zyflo)
		Oral glucocorticoids (prednisone, methylprednisolone)

ner. It is helpful to monitor the frequency of inhaled  $\beta$ -agonist use, in that use of >1 canister/mo (200 inhalations/mo) indicates inadequate asthma control and necessitates initiating or intensifying controller therapy.

**Anticholinergic Agents.** As bronchodilators, the anticholinergic agents (e.g., ipratropium bromide) are much less potent than the  $\beta$ -agonists. Inhaled ipratropium is primarily used in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium has been shown to significantly improve lung function and to reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium bromide is the anticholinergic drug of choice because it has few central nervous system adverse effects, and it is available in both MDI and nebulizable formulations. Although widely used in children with asthma exacerbations of all ages, it is approved by the U.S. Food and Drug Administration (FDA) for use in children >12 yr of age.

**Systemic Glucocorticoid Therapy.** Short-course, systemic glucocorticoid therapy is recommended for use in moderate-to-severe asthma exacerbations, both to hasten recovery and prevent recurrence of symptoms. The efficacy of glucocorticoid therapy for asthma exacerbations in children is firmly established. Studies evaluating single doses of glucocorticoids administered in the emergency department, short courses of oral glucocorticoids in the clinic setting, and both oral and intravenous formulations in hospitalized children have all demonstrated effectiveness. Studies in children hospitalized with acute asthma have found glucocorticoids administered orally to be as effective as intravenous glucocorticoids. Accordingly, oral glucocorticoid therapy can often be used, although children in respiratory distress who require high flow rates of oxygen to adequately treat hypoxemia are obvious candidates for intravenous glucocorticoid therapy. For hospitalized children, the NAEPP guidelines recommend administering methylprednisolone at 1 mg/kg/dose every 6 hr for 48 hr, with a taper to 1–2 mg/kg/24 hr (maximum 60 mg/24 hr) in two divided doses until the patient’s PEFs reach 70% of predicted or personal best. For outpatient

management of acute asthma, the NAEPP guidelines suggest 1–2 mg/kg/24 hr (maximum 60 mg/24 hr) of prednisone or methylprednisolone in a single or two divided doses for 3–10 days.

**LONG-TERM-CONTROL OR CONTROLLER MEDICATIONS.** Mild to moderate persistent asthma should be treated with long-term-control medications, which include nonsteroidal anti-inflammatory agents, inhaled glucocorticoids, sustained-release theophylline, long-acting inhaled  $\beta$ -agonists, and leukotriene modifiers.

**Nonsteroidal Anti-inflammatory Agents.** Cromolyn and nedocromil are “nonsteroidal” anti-inflammatory agents that can inhibit both the early and late phase components of allergen-induced asthmatic responses and can inhibit exercise-induced bronchospasm. Both drugs are indicated for mild to moderate asthma and are considered first-line anti-inflammatory drugs for children with mild persistent asthma according to the NAEPP guidelines. Although largely devoid of adverse effects, these medications must be administered frequently (two to four times/24 hr) and are not nearly as effective as the other two major controller classes of medications, namely, the inhaled glucocorticoids and leukotriene-modifying agents. As a result, they should now be considered alternative agents. Because they inhibit exercise-induced bronchospasm, they can be used in place of short-acting  $\beta$ -agonists, especially in children who develop unwanted adverse effects with  $\beta$ -agonist therapy (e.g., tremor and elevated heart rate). They can also be used in combination with short-acting  $\beta$ -agonists in patients who continue to experience exercise-induced bronchospasm despite short-acting  $\beta$ -agonist pretreatment.

**Glucocorticoids.** Glucocorticoids are available in inhaled, oral, and parenteral forms. Glucocorticoids are the most potent and effective medications used to treat both the acute (administered systemically) and chronic (administered topically) manifestations of asthma.

**Inhaled Glucocorticoid Therapy.** The development of inhalation devices, which effectively deliver potent glucocorticoids into the airways, have made inhaled glucocorticoid therapy the treatment of choice for patients with persistent asthma (see Table 134–1). Inhaled glucocorticoid therapy has been shown to reduce asthma symptoms, improve baseline pulmonary function, and reduce bronchial hyperresponsiveness. In addition, inhaled glucocorticoid therapy in children with mild to moderate persistent asthma results in less need for “rescue” short-acting  $\beta$ -agonists use and less need for prednisone and can reduce,

by up to 50%, urgent care visits and hospitalizations for acute asthma. Lastly, large epidemiologic studies have now demonstrated low-dose inhaled glucocorticoid therapy to “protect” against asthma death. Inhaled glucocorticoids achieve all of the goals of asthma therapy and as a result have become the gold standard treatment for asthma.

The NAEPP guidelines recommend low-dose inhaled glucocorticoid therapy for all patients with persistent asthma. Whether inhaled glucocorticoids should be first-line therapy in children with mild persistent asthma is controversial. Advocates for inhaled glucocorticoid therapy argue that because this medication reduces airways inflammation, bronchial hyperresponsiveness, and asthma morbidity and mortality, it should be used in all patients with persistent asthma. In contrast, others argue that since inhaled glucocorticoid therapy is not without the potential for adverse effects, its use should be reserved for those with moderate to severe persistent asthma. A few studies have suggested that delay in initiation of inhaled glucocorticoid therapy leads to a diminished therapeutic response. The implication of these studies is that asthma is a progressive condition that requires anti-inflammatory therapy to prevent airway remodeling and subsequent loss of therapeutic response.

There are currently five FDA-approved inhaled glucocorticoids, with a sixth product likely to be approved in 2002 (see Table 134–3). Inhaled glucocorticoids are available for use in MDIs with ozone-friendly propellants, as dry powder inhalers (DPIs), or in suspension for nebulization. All of the available inhaled glucocorticoids are effective in asthma. Fluticasone propionate, mometasone furoate, and, to a lesser extent, budesonide are thought to be “second generation” inhaled glucocorticoids in that they display greater topical to systemic potency compared with other available inhaled glucocorticoids, resulting in a better therapeutic index. Second-generation inhaled glucocorticoids display both increased anti-inflammatory potency and reduced systemic bioavailability, owing to extensive first-pass hepatic metabolism, making these compounds well suited for patients with severe asthma. The NAEPP guidelines recommend starting with higher inhaled glucocorticoid doses and “stepping down” the dose as asthma control improves. Many studies have shown that a fraction of the initial glucocorticoid dose is often sufficient once asthma control is achieved. The ideal inhaled glucocorticoid dose should be large enough to control asthma symptoms yet small enough to avoid the potential for adverse systemic effects (see Table 134–3). Inhaled

**TABLE 134–3. Inhaled Glucocorticoids Daily Dosage Guidelines\***

Glucocorticoid	Low Dose	Medium Dose	High Dose
<b>Beclomethasone</b> 42, 84 $\mu$ g/puff (40 $\mu$ g/puff HFA–propellant)	84–336 $\mu$ g (2–8 puffs of 42 $\mu$ g/puff or 1–4 puffs of 84 $\mu$ g/puff)	336–672 $\mu$ g (8–16 puffs of 42 $\mu$ g/puff or 4–8 puffs of 84 $\mu$ g/puff)	>672 $\mu$ g (> 16 puffs of 42 $\mu$ g/puff or > 8 puffs of 84 $\mu$ g/puff)
<b>Budesonide</b> Turbuhaler (DPI) 200 $\mu$ g/inhalation Respules (nebulizer) 250, 500 $\mu$ g/vial	200–400 $\mu$ g (1–2 inhalations) 500 $\mu$ g QD	400–800 $\mu$ g (2–4 inhalations) 1000 $\mu$ g	> 800 $\mu$ g (>4 inhalations) 2000 $\mu$ g
<b>Flunisolide</b> 250 $\mu$ g/puff (MDI)	500–750 $\mu$ g (2–3 puffs)	1000–1250 $\mu$ g (4–5 puffs)	> 1250 $\mu$ g (>5 puffs)
<b>Fluticasone</b> 44, 110, 220 $\mu$ g/puff (MDI)	88–176 $\mu$ g (2–4 puffs of 44 $\mu$ g/puff)	176–440 $\mu$ g (4–10 puffs of 44 $\mu$ g/puff or 2–4 puffs of 110 $\mu$ g/puff or 1–2 puffs of 220 $\mu$ g/puff)	> 440 $\mu$ g (>4 puffs of 110 $\mu$ g/puff or > 2 puffs of 220 $\mu$ g/puff)
<b>Triamcinolone</b> 100 $\mu$ g/puff (MDI with spacer)	400–800 $\mu$ g (4–8 puffs)	800–1200 $\mu$ g (8–12 puffs)	>1200 $\mu$ g (> 12 puffs)

\*Estimated comparative daily doses for children  $\leq$  12 yr of age.

Modified from the National Asthma Education & Prevention Program Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. Bethesda, MD, National Institutes of Health, National Heart, Lung, and Blood Institute, 2002.

glucocorticoids can be effective when administered once or twice daily.

Although inhaled glucocorticoids have been widely used in adults with persistent asthma, their use in children has been lagging. The reluctance to use inhaled glucocorticoids in childhood asthma has come primarily from their potential for adverse effects with chronic use. Generally, clinically significant adverse effects that occur with chronic systemic glucocorticoid therapy (Box 134–8) have not been seen or have been only rarely reported in children receiving inhaled glucocorticoid therapy in recommended doses. The risk of adverse effects from inhaled glucocorticoid therapy is related to the dose and frequency with which inhaled glucocorticoids are given. High doses (1,000 µg/24 hr in children) administered frequently (e.g., four times/24 hr) have an increased risk for local and systemic adverse effects.

The most commonly encountered adverse effects from inhaled glucocorticoid therapy are local and consist of oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush is thought to occur as a result of local immunosuppression. Dysphonia occurs as a result of vocal cord myopathy. These effects are dose dependent and are most common in individuals on high-dose inhaled and/or oral glucocorticoid therapy. The incidence of these local effects can be greatly minimized by using a holding chamber or “spacer” when using inhaled glucocorticoids delivered via a MDI because these devices effectively

reduce the oropharyngeal deposition of the drug. Mouth rinsing using a “swish and spit” technique after inhaled glucocorticoid inhalation is also recommended after administration of any inhaled glucocorticoid.

The potential for growth suppression with long-term inhaled glucocorticoids has long been a concern among health care professionals caring for asthmatic children. Complicating this issue is the long known, but often overlooked observation that asthma, especially poorly controlled asthma, can adversely affect growth. In the long term, prospective Childhood Asthma Management Program (CAMP) study, after a mean of 4.3 yr of therapy, children with mild to moderate asthma randomized to budesonide (400 µg/24 hr) had grown 22.7 cm, whereas those randomized to placebo had grown 23.8 cm—a 1.1 cm difference. Of importance, this 1.1 cm difference occurred primarily in the first year of therapy, indicating that the growth suppression was a transient, not progressive phenomenon. Agertoft and Pedersen, in an open-label, controlled study, found no difference in the measured versus the expected adult heights in a cohort of asthmatics who had received inhaled budesonide (400 µg/24 hr) for longer than 9 yr. They also noted transient growth suppression in the first few years of therapy, with eventual catch-up growth and no adverse effect on final adult height. These two long-term studies support the contention that inhaled glucocorticoid therapy results in a modest and transient effect on growth that is unlikely to have a significant adverse effect on adult height.

Two large pediatric studies that have evaluated the effect of long-term inhaled glucocorticoids on bone mineral density failed to find a relationship between inhaled glucocorticoids use and diminished bone mineral density. Although these studies cannot predict a significant effect of inhaled glucocorticoid therapy on osteoporosis in later adulthood (i.e., after 30 yr of use), improved asthma control may result in less glucocorticoid therapy needed over time. In summary, current evidence suggests that long-term inhaled glucocorticoid therapy has no significant effect on adult attained height or on bone mineral density. These findings were with budesonide at doses of roughly 400 µg/24 hr; higher doses of inhaled glucocorticoids will have a greater potential for adverse effects.

**Systemic Glucocorticoid Therapy.** Inhaled glucocorticoid therapy has allowed the majority of patients with asthma to maintain good control of their disease. Indeed, inhaled glucocorticoid therapy has allowed many patients with severe asthma to reduce or even discontinue maintenance oral glucocorticoids. Thus, oral glucocorticoid therapy is now used primarily to treat asthma exacerbations and in rare patients with severe disease who remain symptomatic despite optimal use of other asthma medications. In these severe asthmatics, every attempt should be made to exclude any co-morbid conditions and to keep the oral glucocorticoid dose at ≤20 mg administered on alternate days. Doses exceeding this amount are associated with numerous adverse effects (see Box 134–8). To determine the need for continued oral glucocorticoid therapy, a gradual taper of the oral glucocorticoid dose should be considered, with close monitoring of the patient’s symptoms and lung function.

When administered orally, prednisone, prednisolone, and methylprednisolone are rapidly and nearly completely absorbed, with peak plasma concentrations occurring within 1–2 hr. Of interest, prednisone is an inactive pro-drug that requires biotransformation via first pass hepatic metabolism to prednisolone, its active form. Glucocorticoids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of glucocorticoids and can result in diminished therapeutic effect. Other medications

### **BOX 134–8. Adverse Effects Associated with Chronic Systemic Glucocorticoid Use**

#### **METABOLIC/ENDOCRINOLOGIC EFFECTS**

Hypokalemia  
Hyperglycemia  
Hyperlipidemia  
Adrenal suppression  
Growth suppression  
Delayed sexual maturation (delayed puberty)  
Weight gain  
Cushingoid habitus (central obesity with wasting of the extremities)  
Diabetes mellitus

#### **MUSCULOSKELETAL EFFECTS**

Osteoporosis/vertebral compression fractures  
Aseptic necrosis of bone (hips, shoulders, knees)  
Myopathy (acute and chronic forms)

#### **DERMATOLOGIC EFFECTS**

Dermal thinning and striae  
Increased skin fragility  
Acne  
Hirsutism

#### **OPHTHALMOLOGIC EFFECTS**

Cataracts  
Glaucoma

#### **IMMUNOLOGIC EFFECTS**

Diminished IgG levels  
Loss of delayed-type hypersensitivity  
Potential for increased risk of opportunistic infection, reactivation of latent tuberculosis, or severe varicella infection

#### **HEMATOLOGIC EFFECTS**

Lymphopenia  
Neutrophilia

#### **CARDIOVASCULAR EFFECTS**

Hypertension  
Atherosclerosis

#### **PSYCHOLOGIC/NEUROLOGIC EFFECTS**

Mood swings  
Steroid withdrawal syndrome  
Pseudotumor cerebri  
Psychosis

(e.g., ketoconazole, oral contraceptives) can significantly delay glucocorticoid metabolism. Macrolide antibiotics (e.g., erythromycin, clarithromycin) can also delay glucocorticoid clearance; however, this effect is limited to methylprednisolone.

Children who require chronically administered oral glucocorticoids are at risk of developing steroid-induced adverse effects over time (see Box 134–8). Essentially all major organ systems can be adversely affected by chronically administered oral glucocorticoid therapy. These effects can occur immediately (i.e., metabolic effects) or can develop insidiously over several months to years (e.g., growth suppression, osteoporosis, cataracts). Most adverse effects depend on the duration of treatment and occur in a cumulative dose-dependent manner.

**Theophylline.** Theophylline is rarely used in pediatric asthma because of its potential toxicity. Theophylline, when used chronically, can reduce asthma symptoms and need for supplemental  $\beta$ -agonist use. Because theophylline may have some glucocorticoid-sparing effects in individuals with oral glucocorticoid-dependent asthma, it is still sometimes used in this group of asthmatic children. Theophylline has a narrow therapeutic window; therefore, serum theophylline levels need to be routinely monitored, especially if the patient has a viral illness associated with a fever or is placed on a medication known to delay theophylline clearance, such as macrolide antibiotics, cimetidine, oral antifungals, oral contraceptives, and ciprofloxacin. Elevated theophylline levels have been associated with headaches, vomiting, cardiac arrhythmias, seizures, and death.

**Long-Acting Inhaled  $\beta$ -Agonists.** Salmeterol and formoterol are long-acting inhaled  $\beta$ -agonists (LABAs), considered as controller medications. Neither is intended for use as a “rescue” medication for acute episodes of bronchospasm or asthma exacerbations, nor recommended as monotherapy for persistent asthma. Salmeterol has a prolonged onset of action, with maximal bronchodilation about 1 hr after administration, whereas formoterol has an onset of action within 5–10 min. Both medications have a prolonged duration of effect of at least 12 hr. Given their long duration of action, they are well suited for patients with nocturnal asthma and for individuals who require frequent use of short-acting  $\beta$ -agonist inhalations during the day to prevent exercise-induced bronchospasm. Their major role is as “add-on” agents in patients who are suboptimally controlled on inhaled glucocorticoid therapy alone. Several studies have found the addition of an LABA to an inhaled glucocorticoid to be superior to doubling the dose of the inhaled glucocorticoid in subjects whose asthma is inadequately controlled on an inhaled glucocorticoid alone. These results suggest that LABAs have some inhaled glucocorticoid-sparing effects. Both LABAs are FDA approved for use in children (salmeterol: > age 4 yr; formoterol: > age 6 yr).

**Leukotriene-Modifying Agents.** Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and leukotriene receptor antagonists. Zileuton, currently the only leukotriene synthesis inhibitor, is not approved for use in children < 12 yr of age. Because zileuton is administered four times daily, can result in elevated liver function enzymes in 2–4% of patients, and interacts with medications metabolized via the cytochrome-P450 system, it is rarely prescribed for children with asthma.

Leukotriene receptor antagonists (LTRAs) have bronchodilator and targeted anti-inflammatory properties and block exercise-, aspirin-, and allergen-induced bronchoconstriction. Two LTRAs are approved for use in children: zafirlukast and montelukast. Both medications improve asthma symptoms, decrease need for supplemental  $\beta$ -agonist use, and improve pulmonary function in patients with asthma. Montelukast is administered once daily (10 mg for children  $\geq$  15 yr; 5 mg for children 6–14 yr;

4 mg for children 2–5 yr). Zafirlukast is FDA approved for use in children 7 yr and older and is administered twice daily (10 mg twice daily in children 7–11 yr; 20 mg twice daily in children > 12 yr). Although incompletely studied in children with asthma, LTRAs appear to be less effective than inhaled glucocorticoids in patients with moderate persistent asthma. In general, studies have found inhaled glucocorticoids improve baseline lung function by 10–15%, whereas LTRAs improve baseline lung function by 5–7.5%. These drugs are not thought to have significant adverse effects, although recent case reports described a Churg-Strauss–like syndrome of pulmonary infiltrates, eosinophilia, and cardiomyopathy in adults with glucocorticoid-dependent asthma treated with zafirlukast. It remains to be determined whether these patients had a primary eosinophilic vasculitis masquerading as asthma, which was “unmasked” as their oral glucocorticoid dose was tapered, or whether the disease was a rare adverse effect of the drug.

**ASTHMA EXACERBATION MANAGEMENT.** Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms associated with expiratory airflow obstruction. It is important to consider asthma severity based on the frequency and severity of previous asthma exacerbations and to identify asthmatics at increased risk for life-threatening exacerbations. Asthma exacerbation severity can be quantified by the number of emergency department visits, hospitalizations, and systemic glucocorticoid courses for asthma exacerbations. Previous severe asthma exacerbations, resulting in respiratory distress, hypoxia, or respiratory failure are probably the best predictors of a future life-threatening exacerbation or fatal asthma episode. Biologic, environmental, economic, and psychosocial risk factors for increased asthma morbidity and mortality have been identified (Box 134–9).

**Home Management of Asthma Exacerbations.** All asthmatics should have a written action plan that can help guide them in recognizing and assessing their overall asthma control and the severity of acute asthma exacerbations. Recognizing symptoms early and intensifying treatment soon after symptoms worsen

#### BOX 134–9. Risk Factors for Asthma Morbidity and Mortality

##### BIOLOGIC

- Previous severe asthma exacerbation
- Severe airflow obstruction
- History of rapidly occurring attacks
- Severe airways hyperresponsiveness
- Increasing and large diurnal variation in peak flows
- Decreased chemosensitivity and perception of dyspnea
- Poor response to systemic glucocorticoid therapy
- Male gender
- Low birth weight
- Nonwhite (especially black) ethnicity

##### ENVIRONMENTAL

- Allergen exposure
- Environmental tobacco smoke exposure
- Air pollution exposure
- Urban environment

##### ECONOMIC/PSYCHOSOCIAL

- Poverty
- Crowding
- Mother <20 yr old
- Mother with less than high school education
- Inadequate medical care
  - Inaccessible
  - Unaffordable
  - No regular medical care (only emergent)
  - No care sought for chronic asthma symptoms
  - Delay in care of asthma exacerbations
  - Inadequate hospital care for asthma exacerbation
- Psychopathology in the parent or child
- Family problems
- Alcohol or substance abuse

can often prevent further worsening and can keep exacerbations from becoming severe. One study found that having a written home action plan was associated with a 70% reduction in the risk of asthma death associated with an acute exacerbation. Clinical signs and symptoms characteristic of an acute episode include cough, shortness of breath, wheezing, chest tightness, use of accessory muscles, and suprasternal retractions. The NAEPP guidelines recommend immediate treatment with "rescue" medication (i.e., inhaled short-acting  $\beta$ -agonist, up to three treatments in 1 hr). A good response is characterized by resolution of symptoms within an hour, no further symptoms over the next 4 hr, and improvement in PEF of 80% predicted or personal best. The child's physician should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24–48 hr. If the child has an incomplete response to initial treatment with rescue medication (i.e., persistent symptoms and/or a PEF of 60–80% of predicted or personal best), a short course of oral glucocorticoid therapy (e.g., prednisone 1–2 mg/kg/24 hr for 4 days) in addition to inhaled  $\beta$ -agonist therapy should be instituted. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or presence of risk factors for asthma morbidity or mortality. Patients should have medications such as inhaled short-acting  $\beta$ -agonists, oral glucocorticoids, and equipment for treating exacerbations at home.

**Emergency Department Management of Asthma Exacerbations.** The primary goals of asthma management in the emergency department setting include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Treatment is based on clinical severity on arrival, response to initial therapy, and presence of risk factors that are associated with asthma death. Initial treatment includes close monitoring of clinical status, treatment with supplemental oxygen, inhaled  $\beta$ -agonist every 20 min for 1 hr, and if necessary, systemic glucocorticoids (2 mg/kg/day) given either orally or intravenously. Inhaled ipratropium may be added to the  $\beta$ -agonist treatment if no significant response is seen with the first inhaled  $\beta$ -agonist treatment. A *subcutaneous* injection of epinephrine or other  $\beta$ -agonist may be administered in severe cases. The patient may be discharged to home if there is sustained improvement in symptoms, normal physical findings, PEF greater than 70% of predicted or personal best, and an oxygen saturation greater than 92% on room air for 4 hr. Discharge medications include administration of an inhaled  $\beta$ -agonist up to every 3–4 hr plus a 3–7 day course of oral glucocorticoids.

**Hospital Management of Asthma Exacerbations.** For patients with a moderate to severe asthma exacerbation that does not significantly improve within 1–2 hr after the initial treatment, associated with PEFs less than 70% or oxygen saturations less than 90–92%, admission to the hospital is warranted. Other indications for hospital admission include prolonged symptoms before the emergency department visit, inadequate access to medical care and medications, difficult psychosocial conditions, or difficulty in obtaining transportation to the hospital in event of further deterioration. Admission to an intensive care unit is indicated for patients with poor response to therapy, persistent severe respiratory distress, or evidence of impending respiratory arrest.

Supplemental oxygen, frequently administered inhaled  $\beta$ -agonists, and systemic glucocorticoid therapy are the treatments of choice for children admitted to the hospital for acute asthma. Supplemental oxygen is administered because many children hospitalized with acute asthma will have hypoxemia, especially at night. Short-acting  $\beta$ -agonists can be delivered frequently and, if needed, continuously. When administered

continuously, significant systemic absorption of  $\beta$ -agonist occurs and, as a result, continuous nebulization can obviate the need for intravenous  $\beta$ -agonist therapy. Adverse effects of frequently administered  $\beta$ -agonist therapy include tremor, irritability, tachycardia, and hypokalemia. Patients requiring frequent or continuous nebulized  $\beta$ -agonist therapy should have continuous cardiac monitoring. Because frequent  $\beta$ -agonist therapy can cause ventilation-perfusion mismatch and precipitate hypoxemia, oximetry is indicated with supplemental oxygen. Ipratropium is often added to albuterol every 6 hr, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled  $\beta$ -agonist therapy and systemic glucocorticoids. Patients with persistent severe dyspnea and high-flow oxygen requirements will often require intravenously administered fluids. In this situation, administration of fluids at or slightly below maintenance fluid requirements is recommended, owing to increased antidiuretic hormone (ADH) secretion associated with status asthmaticus.

Despite intensive therapy, some asthmatic children will remain critically ill and at risk for intubation and mechanical ventilation. Complications related to asthma exacerbations increase with intubation and assisted ventilation; therefore, every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including intravenous  $\beta$ -agonists, intravenous theophylline, heliox, and intravenous magnesium sulfate have some demonstrated benefit as adjunctive therapies in severe status asthmaticus.

**Intravenous Theophylline.** Although several recent studies have failed to demonstrate the effectiveness of intravenous theophylline in hospitalized children receiving frequent inhaled  $\beta$ -agonist and systemic glucocorticoid therapy, theophylline may still have a role in the treatment of children with severe, life-threatening asthma exacerbations. In a recent study of children with acute severe asthma (mean FEV<sub>1</sub> 37% at baseline), intravenous theophylline resulted in a rapid and sustained increase in oxygen saturation and lung function compared with placebo. In addition, fewer patients on intravenous theophylline required intravenous albuterol; in those who did, intravenous albuterol was required for a shorter duration of time. Lastly, all study patients requiring intubation were in the placebo-treated group. This study suggests that intravenous theophylline can be an important adjunctive therapy in acute severe childhood asthma. If a child responds poorly to intensive therapy with nebulized albuterol, ipratropium, and parenteral glucocorticoids, then adding intravenous theophylline should be considered. Because theophylline use is associated with adverse effects, with overdose resulting in dire consequences, the proper loading and maintenance doses should be used according to the child's age and weight, with serum theophylline level monitoring to ensure values within the therapeutic and nontoxic range.

**Heliox.** Inhaled heliox (a 70:30 helium:oxygen mixture) has been shown, in several small studies, to be effective in the treatment of acute severe asthma. Because heliox has a density about one-third that of room air, inhalation of this gas mixture can result in decreased airways resistance and clinical improvement within 20 min, even in patients already receiving intensive inhaled  $\beta$ -agonist and intravenous glucocorticoid therapy. Thus, heliox treatment early in the course of status asthmaticus may provide a period with reduced respiratory distress until  $\beta$ -agonist and glucocorticoid therapy can relieve bronchoconstriction and airway narrowing. In severe cases when high-content supplemental oxygen is needed, heliox's 30% oxygen content may limit its use.

**Intravenous Magnesium Sulfate.** Based on its smooth muscle relaxant properties, many studies have evaluated the effect of magnesium sulfate in acute asthma, but at present it remains controversial whether magnesium is effective in acute asthma. A small controlled study in children who presented to the emer-

gency department with acute asthma found magnesium sulfate (25 mg/kg, maximum dose 2 g) to improve lung function and result in fewer admissions to the hospital when compared with placebo. If magnesium sulfate is to be used, blood pressure should be monitored every 10–15 min during the infusion and for up to 90 min after the infusion, because hypotension is a known adverse effect. Magnesium levels before and 30 min after the infusion should also be obtained.

**Mechanical Ventilation.** Rarely, a severe asthma exacerbation in children results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction, while reducing hyperinflation, air trapping, and the likelihood of barotrauma (i.e., pneumothorax, pneumomediastinum). To minimize the likelihood of such complications, mechanical ventilation should be anticipated and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric intensive care setting. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to moderate hypercapnia (i.e.,  $P_{CO_2}$  40–60 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10–15 mL/kg tidal volume, 8–15 breaths/min, peak pressures less than 60 cm  $H_2O$ , and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve plugs of mucus in the chest, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. Considering the nature of asthma exacerbations leading to respiratory failure, those of rapid or abrupt onset tend to resolve quickly (i.e., hours to 2 days); in contrast, severe asthma exacerbations that progress gradually to respiratory failure can take days to weeks for airways obstruction to improve enough to allow for cessation of mechanical ventilation. Such prolonged cases are further complicated by muscle atrophy and, when combined with corticosteroid-induced myopathy, profound muscle weakness requiring prolonged rehabilitation.

Management of severe childhood asthma exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, childhood asthma deaths rarely occur in medical centers; most asthma deaths occur at home or in community settings, before lifesaving medical care can be administered. This highlights the importance of home and community management of asthma exacerbations, emphasizing early intervention measures to keep exacerbations from becoming severe and steps to reduce asthma severity.

**MANAGEMENT OF INFANTS AND YOUNG CHILDREN WITH ASTHMA.** Not every infant and small child who wheezes in the first few years of life will go on to develop asthma. Nevertheless, young children with recurrent wheezing problems can benefit from conventional reliever and controller asthma medications. As well, with wheezing exacerbations (typically triggered by viral respiratory tract infections), nebulized albuterol, and short courses of oral glucocorticoids mitigate exacerbation progression and can keep them from becoming severe.

There are three FDA-approved controller-class medications for use in young children: nebulized cromolyn, nebulized budesonide, and montelukast. Cromolyn has been widely used in infants and young children because it is available for administration by nebulization and is devoid of serious adverse effects. Unfortunately, it is not a potent medication, and administration four times daily for several weeks is necessary to achieve effective action. Nebulized budesonide is FDA approved for use in children as young as 1 yr of age. It has been extensively studied in infants and young children with recurrent wheezing and is both safe and effective. It is available for use in two concentra-

tions (0.25 mg and 0.50 mg/vial) and can be administered once or twice daily, depending on disease severity. Montelukast is FDA approved for use in children as young as 2 yr of age (recommended dose is 4 mg once daily). Both nebulized budesonide and montelukast appear to be more effective than cromolyn. Nebulized budesonide would be indicated in young children with moderate to severe persistent asthma symptoms and in those who have failed to respond to cromolyn and montelukast. An oral medication such as montelukast that can be administered once daily offers some advantages over nebulized medications in terms of ease of use and convenience.

Treating the infant and young child with asthma with aerosol therapy presents unique challenges. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants markedly increases the difficulty of drug targeting to the lung airways. Young children are incapable of reliably performing the maneuvers specified for optimal delivery of aerosol therapy delivered via an MDI or DPI. For these reasons, medication delivery devices suitable for young children are limited to those that require minimal cooperation. There are currently two types of delivery systems for inhaled medications for this age group: the nebulizer and the MDI with spacing/holding chamber and face mask. The NAEPP guidelines recommend the nebulizer for the delivery of cromolyn and high-dose short-acting  $\beta$ -agonist. Inhaled glucocorticoid delivered using a MDI with spacing/holding device and face mask is considered acceptable, although perhaps not the preferred means of administering inhaled glucocorticoids to young children and infants, owing to a current paucity of published information or FDA approval.

Nebulizers have been the mainstay of aerosol treatment and remain the first choice of delivery systems for infants and young children. A major advantage of the nebulizer is the simple technique required of relaxed tidal breathing. Multiple studies have demonstrated the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. Disadvantages of nebulizers include expense, need for a power source, inconvenience in that treatments take about 5 min, and potential for bacterial contamination.

Studies in young children comparing the delivery of short-acting  $\beta$ -agonists via MDI versus nebulizer have shown both devices to be effective in most cases, including the emergency department setting when comparable doses of medication are administered. Studies with radiolabeled albuterol given by MDI with a spacer and face mask to children younger than 5 yr old reveal less than 2% dose delivery to the lower airways. Fluticasone administered via a spacer device and face mask was clinically effective in a European study of infants and young children with recurrent wheezing.

**PATIENT EDUCATION.** Specific elements in the clinical care of children with asthma, centered around education, are believed to make an important difference in the home management and adherence of families to an optimal plan of care (Box 134–10). With education, the child and family become partners in the asthma management process. In initial patient visits, a basic understanding of the pathogenesis of asthma can help asthmatic children and their parents to understand the importance of recommendations aimed at reducing airways inflammation. Good asthma control in children should be specified so that the expectations of optimal asthma management are made clear (see Box 134–5). Explaining the importance of steps to reduce airways inflammation to achieve good asthma control and addressing concerns about potential adverse effects of asthma pharmacotherapy, and especially their risks relative to their benefits, can be essential to achieve long-term adherence with asthma pharmacotherapy and environmental control measures.

All asthmatic children and their families can benefit from a written asthma management plan with two main components:

**BOX 134–10. Key Elements of Productive Clinic Visits for Asthma**

Specify goals of asthma management  
 Explain basic facts about asthma  
 Contrast normal versus asthmatic airways  
 Link airways inflammation, “twitchiness,” and bronchoconstriction  
 Long-term-control and quick-relief medications  
 Address concerns about potential adverse effects of asthma pharmacotherapy  
 Teach, demonstrate, and have patient show proper technique for:  
 Inhaled medication use (spacer use with MDI)  
 Peak flow measures  
 Investigate and manage factors that contribute to asthma severity  
 Environmental exposures  
 Co-morbid conditions  
 Written two-part asthma management plan  
 Daily management  
 Action plan for asthma exacerbations  
 Regular follow-up visits  
 Twice yearly (more often if not well controlled)  
 Monitor lung function annually

(1) a **daily management plan** describing regular asthma medication use and other measures to keep asthma under good control and (2) an **action plan for asthma exacerbations**, describing actions to take when asthma worsens, including what medications to take and when to contact the regular physician and/or obtain emergent or urgent medical care.

Regular follow-up visits can help to maintain optimal asthma control. In addition to the assessment and monitoring of disease severity, follow-up visits should evaluate adherence and concerns with asthma management recommendations, and especially the daily administration of controller medications when prescribed. Reassessment during each visit of the role of different medications in asthma management and the technique used with inhaled medication use can be insightful and lead to important teaching opportunities. Indeed, inhaled medication (and spacer) use and PEF monitoring are important skills for asthmatics to learn and improve with practice and review at each visit. Encouraging open communication of concerns about asthma management recommendations (e.g., daily controller medication use) can be insightful and improve adherence with a management plan that might not have been adequately or properly implemented.

**REFERRAL FOR CONSULTATION.** NAEPP guidelines recommend referral of asthmatics to an asthma specialist, a board-certified allergist, or pulmonologist for consultation. Asthma specialists can typically provide lung function testing, allergen sensitization assessment and testing, detailed evaluation for asthma masqueraders (e.g., flexible rhinolaryngoscopy or bronchoscopy), bronchoprovocation challenges, environmental assessment and modification recommendations, extensive patient and parent education, and management support of complex or severe asthmatics. Asthmatics with upper airways conditions may require referral to an otolaryngologist. Asthmatics with psychosocial risk factors for asthma morbidity or mortality may benefit from referral to a mental health professional.

**Prevention.** Currently, asthma prevention strategies are in their infancy. With recent evidence that chronic airways inflammation may result in pathologic remodeling changes, early intervention with anti-inflammatory medications in young children with recurrent wheezing and persistent asthma risk factors may halt disease progression. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immune modulatory intervention might prevent asthma development. A “hygiene hypothesis” purports that microbial exposures in early life might drive early immune development away from allergen sensitization and allergic inflammation. Accordingly, early life microbial exposures have

been associated with a lower likelihood of allergen sensitization and atopic dermatitis in infants and a lower likelihood of asthma and bronchial hyperresponsiveness in later childhood. If these microbial exposures truly have an asthma-protective effect, then these findings may foster new strategies for asthma prevention.

Current evidence also suggests that several other nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breast-feeding (greater than 4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of developing asthma; therefore, all standard childhood immunizations are recommended for asthmatic children, including varicella and annual influenza vaccines.

- American Academy of Allergy, Asthma & Immunology: *Pediatric Asthma: Promoting Best Practice*. AAAAI, Milwaukee, WI, 1999, pp 1–139. ([www.aaaai.org](http://www.aaaai.org))  
 Beasley R, Crane J, Lai CK, et al: Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000;105:5466–72.  
 Busse WW, Lemanske RF Jr: Asthma. *N Engl J Med* 2001;344:350–62.  
 Childhood Asthma Management Program Research Group: Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054–63.  
 Martinez FD, Wright AL, Taussig LM, et al: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133–38.  
 Milgrom H, Taussig LM: Keeping children with exercise-induced asthma active. *Pediatrics* 1999;104:e38.  
 National Institutes of Health, National Heart, Lung & Blood Institute, National Asthma Education & Prevention Program: *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*. Washington DC, 1997, pp 1–86; and *Update on Selected Topics 2002*. Washington, DC, 2002, pp 1–6.. ([www.nhlbi.nih.gov/guidelines/asthma](http://www.nhlbi.nih.gov/guidelines/asthma))  
 Szefler SJ, Leung DYM (editors): *Severe Asthma: A Multidisciplinary Approach*, 2nd ed. In Lenfant C (series editor): *Lung Biology in Health and Disease Series*. New York, Marcel Dekker, 2001, pp 1–635.

**Chapter 135****Atopic Dermatitis (Atopic Eczema)** *Donald Y. M. Leung*

Atopic dermatitis (AD) is a highly pruritic skin disease that affects more than 10% of children. It is frequently associated with elevated serum IgE levels, and nearly 80% of patients with AD develop allergic rhinitis and/or asthma.

**Pathogenesis.** Complex interactions between genetic, environmental, and immunologic factors contribute to the pathogenesis of AD. Current therapies in AD have evolved from an understanding of the pathobiology of this disease.

**SYSTEMIC IMMUNE RESPONSE.** Most patients with AD have peripheral blood eosinophilia and increased serum IgE levels. Peripheral blood T cells from AD patients produce decreased amounts of interferon-gamma (IFN- $\gamma$ ), an inhibitor of T helper type 2 (Th2) cell function. IFN- $\gamma$  generation *ex vivo* is inversely correlated with serum IgE concentrations in AD. An increased frequency of allergen-specific T cells producing increased interleukin (IL)-4, IL-5, and IL-13 in the peripheral blood of patients with AD contributes to the eosinophilia and increased IgE levels in AD.

**SKIN IMMUNOPATHOLOGY.** Clinically *unaffected* skin of AD patients is not normal but reveals mild epidermal hyperplasia and a sparse perivascular T-cell infiltrate. Acute skin lesions are characterized by **spongiosis**, or marked intercellular edema, of the epidermis. The dendritic antigen-presenting cells (APCs) in the skin, Langerhans cells (LCs), in lesional and, to a lesser extent, nonlesional skin of AD exhibit surface-bound IgE