Chapter 6
Asthma

Abbreviations ABPA: allergic bronchopulmonary aspergillosis; AERD: aspirin-exacerbating respiratory disease; ANCA: antineutrophilic cytoplasmic antibody; BAL: bronchoalveolar lavage; CBC: complete blood count; COPD: chronic obstructive pulmonary disease; COX: cyclooxygenase; CT: computed tomography; DLCO: diffusing capacity for carbon monoxide; DPI: dry powder inhaler; ECP: eosinophilic cationic protein; EDN: eosinophil-driven neurotoxin; EPO: eosinophil peroxidase; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GERD: gastroesophageal reflux disease; GM-CSF: granulocyte-macrophage colony-stimulating factor; ICAM: intercellular adhesion molecule; IFN: interferon; IL: interleukin; MBP: major basic protein; MDI: metered dose inhaler; MRI: magnetic resonance imaging; NAEPP: National Asthma Education and Prevention Program; NSAIDs: nonsteroidal anti-inflammatory drugs; p-ANCA: perinuclear anti-neutrophilic cytoplasmic antibody; PEFR: peak expiratory flow rate; PGD_2: prostaglandin D_2; PGE_2: prostaglandin E_2; PGF_{2a}: prostaglandin F_{2a}; RADS: reactive airways dysfunction syndrome; RANTES: regulated on activation, T-cell expressed and secreted; RSV: respiratory syncytial virus; STAT: signal transducer and activator of transcription; TGF: transforming growth factor; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule.

6.1 Overview

Asthma is a complex genetic disorder characterized by airway inflammation and reversible airflow obstruction resulting in a symptom complex of wheezing, dyspnea, or cough (or some combination of these). It is characterized further by multiple phenotypes that may differ on the basis of the age at onset, triggering factors, response to treatment, and variable patterns of reversibility both during acute exacerbations and with long-standing disease.

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6.2 Epidemiology

Asthma is a common disease that is increasing in prevalence worldwide, with the highest prevalence in industrialized countries. It is estimated that nearly 300 million people in the world have asthma. In the United States, more than 20 million people report symptoms consistent with the diagnosis of asthma, including 5 million younger than 18 years, and nearly 5,000 people die each year with asthma reported as the underlying cause of death. People who have asthma account for nearly 500,000 hospitalizations annually. Because the prevalence and morbidity of asthma have been increasing worldwide, there is concern that asthma patients are not always readily identified and may not receive optimal treatment for their disease.

6.3 Pathophysiology

6.3.1 Genetics

As commonly observed clinically, atopic diseases such as allergic rhinitis, atopic dermatitis, and asthma occur in families. Subsequent familial aggregation, twin, and gene linkage studies have provided evidence to support this. Studies of twins allow comparisons between monozygotic twins who share 100% of their genes and dizygotic twins who share approximately 50% of their genes. The greater occurrence of asthma in monozygotic twins, even those raised in different environments, is evidence for a genetic component. In family studies, asthma is more common in children of allergic asthmatic parents than in those of nonallergic asthmatic parents, underscoring the importance of atopy. Asthma occurs less frequently in the children of parents who are nonasthmatic and nonallergic. Applying a specific risk ratio for a given family is difficult because of the different environmental variables that can contribute to the development of asthma and also the differences in the population prevalence of asthma. Generally, in the United States, if one parent has allergic asthma, the child has approximately a 20% chance of developing asthma, and if both parents have allergic asthma, the child has approximately a 40% chance.

The inheritance pattern of asthma is a “complex genetic disorder” similar to hypertension and diabetes mellitus. Asthma cannot be classified as simply having an autosomal dominant, recessive, or sex-linked mode of inheritance. It is polygenic. Several gene linkages have been shown with asthma. These are summarized in Table 6.1. The primary chromosomes and regions that have been identified include chromosome band 5q31 (total IgE and eosinophils, interleukin [IL]-4, IL-5, IL-13, CD14), chromosome 6 (major histocompatibility complex, tumor necrosis factor [TNF]), chromosome band 11q13 (β-chain of the high-affinity IgE receptor), chromosome 12q (interferon [IFN]-γ, nitric oxide synthetase, leukotriene A_4 hydrolase, signal transducer and activator of transcription [STAT]-6), and chromosome 13q (cysteinyl leukotriene 2 receptor). Recently, the *ADAM33* gene on chromosome 20,

Table 6.1 Genetic linkages associated with asthma

Chromosome	Candidate genes or products
1p	Interleukin (IL)-12 receptor
5q23-25	IL-3, IL-4, IL-5, IL-9, IL-13, granulocyte macrophage colony-stimulating factor (GM-CSF)
	LTC4S
	GM-CSF receptor
	β_2-Adrenergic receptor
	Glucocorticosteroid receptor
6p21-23	Major histocompatibility complex
	Tumor necrosis factor
	Transporters involved in antigen processing and presentation (TAP1 and TAP2)
7q11-14	T-cell receptor γ chain, IL-6
11q13	High-affinity IgE receptor (FcεRI) β chain
	Fibroblast growth factor 3
12q14-24	Interferon-γ
	Stem cell factor
	Nitric oxide synthetase (constitutive)
	Leukotriene A_4 hydrolase
13q21-24	Cysteinyl leukotriene 2 receptor
14q11-13	T-cell receptor α and δ chains
	Nuclear factor κβ inhibitor
16p11-12	IL-4 receptor
17p12-17	CC chemokine cluster
19q13	CD22, transforming growth factor β_1
20p13	*ADAM33*

Modified from Steinke, J. W., Borish, L., and Rosenwasser, L. J. (2003) Genetics of hypersensitivity. J. Allergy Clin. Immunol. 111, S495–S501. Erratum in: J. Allergy Clin. Immunol. 112, 267. Used with permission

which encodes a protein-processing enzyme (a metalloprotease) that is expressed in lung fibroblasts, myofibroblasts, and smooth muscle cells, has been found to be commonly associated with asthma. In addition to the effect of the gene itself, the interaction between the gene and the environment may also have a role. Once specific sequences are identified for genetic susceptibility, the gene–environment interaction will need to be studied to help understand the importance of the relationship of the gene and the environment on the overall asthma process.

Pharmacogenetics is another key area in the gene–asthma relationship. Pharmacogenetics uses the variation in drug response in different individuals as a result of genetic differences. Genetic variations in drug target genes can be used to predict clinical responses to treatment. In asthma, alterations in the β_2-adrenoceptor, cysteinyl leukotriene synthesis, the glucocorticoid receptor, muscarinic receptors, and phosphodiesterases may all affect the response to treatment with different classes of drugs.

The gene for the β_2-adrenoceptor has received extensive attention as a candidate gene for asthma risk and severity and response to treatment with β-agonists. Two important coding variants at position 16 and position 27 appear to be functionally

important. Because of linkage disequilibrium, however, individuals with polymorphisms at one genetic locus may or may not have changes at another position. Therefore, a "bad" polymorphism at one site may be countered by a "good" polymorphism at another site. At this point, however, it appears that chromosome 5 arg16/arg16 homozygous asthma patients have an increase in asthmatic exacerbations and decrease in peak expiratory flow when taking albuterol regularly. If these results are confirmed, they could have a significant effect on how one-sixth of asthma patients in the United States with the arg16/arg16 phenotype are treated. Another example of this is the lipoxygenase pathway, which results in the synthesis of the cysteinyl leukotrienes. The promoter region of 5-lipoxygenase has variants labeled "wild type" and "non-wild type." The wild type variant is the more common and more effective enzyme and, thus, produces more leukotrienes. Because of less effective enzymatic activity, the non-wild type produces fewer leukotrienes. Consequently, blockage of the leukotriene pathway would be expected to result in better clinical outcomes in the wild type than in the non-wild type. This was borne out when the use of leukotriene inhibitors was found to increase forced expiratory volume in 1 s (FEV_1) in the wild-type asthma patients compared with the non-wild type. Clinical screening for these and other polymorphisms are in their infancy. In the near future, it is likely that genetic testing will help guide therapy.

6.3.2 Airway Obstruction

6.3.2.1 Inflammation

Airway inflammation is the characteristic feature of asthma and contributes to many hallmarks of the disease, including airflow obstruction, bronchial hyperresponsiveness, and the initiation of remodeling. The classic microscopic features include infiltration of the airways by inflammatory cells, hypertrophy of the smooth muscle, and thickening of the lamina reticularis just below the basement membrane. Persistent airway inflammation is considered the characteristic feature of severe, mild, and even asymptomatic asthma. The pattern of inflammation varies with the severity and the chronicity of the disease and may also determine the responsiveness of the patient to treatment. Many inflammatory cells, cytokines, chemokines, and adhesion proteins contribute to airway inflammation in asthma.

One mechanism that initiates airway inflammation is antigen exposure in sensitized individuals. This results in the activation of the resident cells of the airways (mast cells) and the recruitment of inflammatory cells (lymphocytes, neutrophils, and eosinophils) into the airways (Fig. 6.1). The antigen binds with specific IgE antibody bound to mast cells. This binding activates mast cells to release preformed histamine and newly generated leukotrienes and prostaglandins along with transcription of numerous cytokines. Histamine and prostaglandin D_2 (PGD_2) and leukotriene C_4 induce bronchoconstriction, mucus secretion, and mucosal edema. The key proinflammatory cytokines include IL-4, IL-5, and IL-13. They regulate

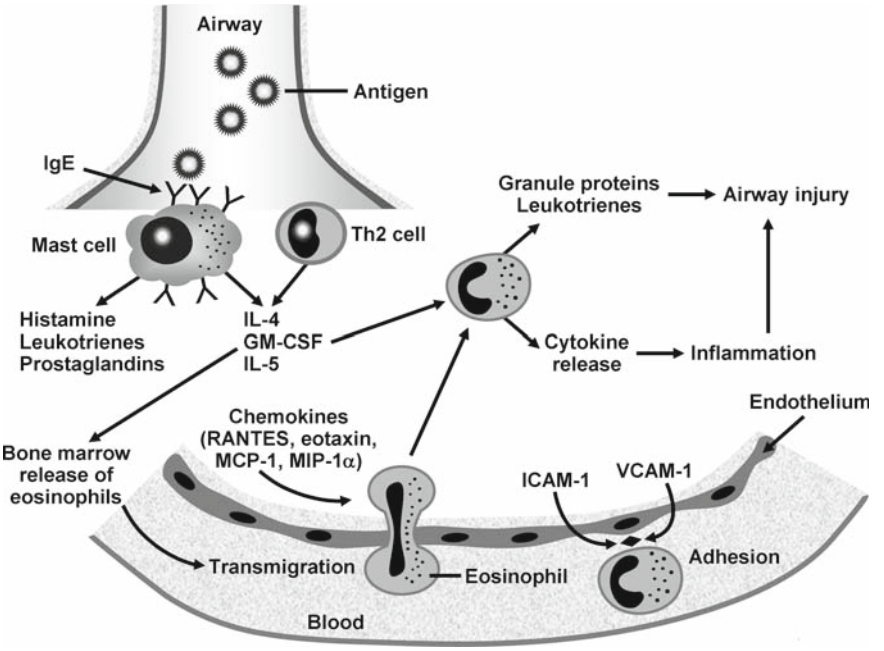

Fig. 6.1 Pathogenesis of allergic asthma. Antigen binds with mast cell-bound IgE, resulting in release of histamine, leukotrienes, prostaglandins, and cytokines. The cytokines induce the influx of inflammatory cells and their activation through the upregulation of chemokines, adhesion molecules, and bone marrow release. Inflammatory cells in the airway release granule proteins, leukotrienes, and cytokines, causing airway injury. *GM-CSF* granulocyte-macrophage colony-stimulating factor; *ICAM* intercellular adhesion molecule; *IL* interleukin; *MCP* monocyte chemotactic protein; *MIP* macrophage inflammatory protein; *RANTES* regulated on activation, T-cell expressed and secreted; *VCAM* vascular cell adhesion molecule. Modified from Busse, W. W. and Lemanske, R. F. (2001) Asthma. N. Engl. J. Med. 344, 344–362. Used with permission

IgE synthesis, Th2 lymphocyte differentiation, and the development of eosinophilic inflammation. The mast cell also produces other cytokines and proteases including TNF-α, transforming growth factor (TGF)-β, fibroblast growth factor, tryptase, and chymase, which may contribute to remodeling of the airway wall by activating myofibroblasts. T-lymphocytes are the primary effector cells in asthma by coordinating many of the actions of other inflammatory cells in the airways through the release of cytokines. Also, lymphocytes and epithelial cells generate chemokines, including RANTES and eotaxin, which enable the recruitment of eosinophils to the airway.

Another critical step in this process is the activation of endothelial adhesion proteins, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. These proteins combine with specific receptors on neutrophils, eosinophils, and lymphocytes to reduce the flow of these cells in blood vessels and to assist in cell movement from the vessels into the airway. Once in the

airway, the inflammatory cells release various enzymes and proteins that damage the airway epithelium and contribute to the inflammation.

Eosinophils are considered the predominant and most characteristic cells in asthma, as observed with both bronchoalveolar lavage (BAL) and bronchial biopsy. The eosinophils contain several granules that are toxic to the airway. The four principal basic proteins are major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-driven neurotoxin (EDN). These proteins are associated with the desquamated epithelium in asthmatic airways and enhancement of vagally mediated bronchoconstriction. Eosinophils also produce inflammatory cytokines, growth factors, and chemokines. Neutrophils likely have a role in certain subsets of asthma. Neutrophils can become activated and release myeloperoxidase, which is toxic to the respiratory epithelium. Neutrophil accumulation is a hallmark of patients who die suddenly of asthma and of patients with severe, corticosteroid-dependent asthma.

Cytokines are glycoproteins that are synthesized and released by many cell types after activation. Cytokines include interleukins, interferons, and growth factors. Their primary effect on inflammation includes regulation of IgE synthesis, mediation of eosinophil activation, and induction of cellular adhesion molecules that mediate the transendothelial migration of leukocytes. The primary cytokine airway profile in asthma patients includes IL-3, IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). In patients with allergic asthma, IL-4 and IL-5 are increased, whereas in those with nonallergic asthma, primarily IL-5 is increased. The lack of increase in IL-4 in nonallergic asthma is likely due to lack of an IgE-mediated response, whereas both groups have eosinophil involvement, which is regulated by IL-5. Chemokines are another group of molecules that contribute to asthma inflammation through chemotactic activity. Chemokines are divided into two main families: A chemokines, which recruit neutrophils, and B chemokines, which recruit eosinophils and mononuclear cells. The latter includes RANTES and eotaxin, which work in conjunction with IL-5 by causing local tissue migration of eosinophils after they are released into the circulation. The relative contributions of A and B chemokines will emerge with the development of specific antagonists and their effect in various asthma models.

6.3.2.2 Airway Mucosal Edema

The thickness of the airway wall is increased in asthma and related to disease severity. The increase in thickness results from an increase in most tissue compartments, including the smooth muscle, epithelium, submucosa, adventitia, and mucosal glands. Inflammatory edema involves the entire airway, particularly the submucosal layer, with marked hypertrophy and hyperplasia of the submucosal glands and hyperplasia of goblet cells. Also, many of the same mediators that lead to contraction of bronchial smooth muscle, such as histamine and leukotrienes, can increase the permeability of the capillary membrane to cause mucosal edema. These changes combine to contribute to the obstruction of airway flow.

6.3.2.3 Mucus Hypersecretion

One of the characteristic features of severe asthma is the overproduction of mucus. Mucus can mechanically narrow the airway lumen and cause obstruction. In severe asthma, tenacious mucus plugs can cause airway obstruction that leads to ventilation-perfusion mismatch and hypoxemia. Mucus plugs are composed of mucus, serum proteins, inflammatory cells, and cellular debris, including desquamated epithelial cells and macrophages arranged in a spiral pattern (Curschmann's spirals). The development of mucus plugging occurs in severe, prolonged attacks of asthma or in patients with chronic disease. The end result is compromise of the airway lumen and impairment of mucociliary clearance.

6.3.2.4 Remodeling

Some patients with asthma develop irreversible airflow obstruction. This process has been labeled *airway remodeling* and represents an injury-repair process of the airway tissue. The remodeling occurs from a dysregulated attempt at tissue repair. Several components of airway remodeling have been identified, including hypertrophy of airway smooth muscle, hyperplasia of mucus glands and goblet cells, angiogenesis (vascular hyperplasia), and collagen deposition (fibrosis) in the airway. These features appear to be permanent and are not reversed by treatment. The processes that lead to this development have not been fully defined nor has the question been answered about why this process occurs in some asthma patients and not others. The process appears to be under the control of mediators distinct from those involved in the acute inflammatory response. The generation and presence of growth factors appear more critical and lead to structural changes in the airway tissue. The airway epithelium is likely a key regulator of the remodeling process. Bidirectional communication has been demonstrated between the epithelial and mesenchymal cells. In this system, damage to the epithelial layer stimulates a myofibroblast proliferative response associated with an increased level of growth factors. Overall, the transition to remodeling from inflammation suggests a new group of mediators with actions on smooth muscle growth, collagen deposition, blood vessel proliferation, and mucus gland hyperplasia. Although it has been theorized that adequate control of inflammation results in less remodeling, this has not been proved clinically and is currently a high-priority research subject.

6.3.3 Airway Hyperresponsiveness

Airway hyperresponsiveness is increased airway narrowing after exposure to constrictor-inducing agents. In asthma patients, it occurs with exposure to chemical and physical stimuli and allergens. Chemical stimuli include cholinergic agonists

such as methacholine and carbachol and also histamine, leukotrienes C_4 and D_4, PGD_2, prostaglandin F_{2a} (PGF_{2a}), and adenosine. Physical stimuli include exercise, hyperventilation of cold dry air, and both hypotonic and hypertonic nebulized solutions. Airway hyperresponsiveness can be demonstrated in nearly all patients who have symptomatic asthma. Sometimes a specific trigger is needed to demonstrate it. Some subjects with normal methacholine responsiveness can still develop symptomatic asthma when exposed to appropriate stimuli such as specific allergens and occupational chemical exposures.

Airway hyperresponsiveness has been correlated directly with airway inflammation in asthma. Airway hyperresponsiveness improves in most children and adults with asthma treated with inhaled corticosteroids, which decrease inflammation. It appears that airway hyperresponsiveness is caused by inflammatory and structural changes in the airway, although the particular cells and mediators have not been fully identified. Structural changes associated with airway hyperresponsiveness include patchy desquamated epithelium, thickening of the reticular collagen layer of the basement membrane, and hypertrophy and hyperplasia of airway smooth muscle. Airway hyperresponsiveness itself, however, is not unique to asthma. A positive methacholine challenge test is diagnostic for airway hyperresponsiveness, which also can be seen in atopic disease, cystic fibrosis, rhinitis, and smokers and even in normal individuals for a few weeks after a viral respiratory infection.

6.3.4 Fatal Asthma

The pathologic changes seen in fatal asthma are generally similar to those seen in severe asthma but to a more significant extent. Multiple factors cause excessive airway narrowing in fatal asthma, including increased production of mucus, increased shortening of airway smooth muscle, alterations in the mechanics of the airway wall, loss of inflammatory inhibitory factors, and increased permeability from epithelial damage. One of the most common and characteristic findings is the occlusion of the bronchial lumen by mucus plugs. This occurs in airways of all sizes. Of interest, it has been calculated that the contents of the submucus glands alone cannot cause excessive narrowing; therefore, it is the accumulation of the mucus and the additional effects of smooth muscle shortening that cause excessive narrowing of the airway. The goblet cell hyperplasia that leads to excessive mucus production likely represents a reparative response to epithelial damage in an attempt to restore the normal protective barrier. The epithelial damage appears to have several sources. The inflammatory milieu results in the production of proteins, proteases, and chemicals toxic to the epithelium. Concomitant viral infections, often seen in fatal asthma, damage the epithelium. In addition to stimulating goblet cell hyperplasia, damaged epithelium results in easier access of irritants to nerve endings, enhanced penetration of allergen particles, loss of inactivation of proinflammatory peptides, and reduced mucociliary clearance.

The inflammatory pattern in fatal asthma is variable, with eosinophils and T-lymphocytes as the predominant cell types. Neutrophils have also been implicated in having a major role in a subset of patients with fatal asthma. Edema of the airway is regarded as an important feature of fatal asthma, but it is difficult to quantify. Edema contributes to the increased wall thickness in fatal asthma, causing a more pronounced decrease in the diameter of the airway lumen with the contraction of smooth muscle. Similarly, one of the hallmarks of severe and fatal asthma, the thickening of the subepithelial basement membrane zone with dense deposition of collagen fibrils, exponentially reduces airway diameter with smooth muscle contraction. Further studies of the clinical characteristics, with the histopathologic findings, will provide a better understanding of the mechanisms underlying the different clinical forms of asthma.

6.4 Clinical Presentation and Differential Diagnosis

Asthma can be manifested in several different ways. In some instances, it appears to be isolated, occurring only in the setting of upper respiratory infection, allergen exposure, or exercise. In others, particularly children, asthma may occur primarily as isolated chronic cough. More traditionally, asthma is manifested as repeated episodes of wheezing, cough, or dyspnea with varying levels of severity. The onset of asthma often occurs in childhood and has strong associations with other diseases, such as atopic dermatitis and allergic rhinitis. Asthma may also commence in adulthood in association with allergic disease or in the absence of allergic sensitization.

When obtaining a history, it is important to inquire specifically about what type of respiratory symptoms the patient is having. The patient or parent may not know what "wheeze" means and may use the term incorrectly to describe noisy breathing, snoring, or stridor. It is also important to quantify the frequency and duration of the asthma symptoms because the physician's interpretation of the history can significantly overestimate or underestimate the symptoms. Specific clues can be found in the timing, activities involved, and the environment in which symptoms occur; for example, symptoms triggered primarily at nighttime or by exercise, tobacco smoke, strong emotional expression, weather changes, aerosolized irritants, or cold air exposures are particularly helpful in establishing the diagnosis of asthma. There may be specific allergen triggers such as exposure to pollens, molds, dust mites, cockroaches, or pets. A frequent trigger for many asthma patients is a viral upper respiratory tract infection that can lead to an exacerbation of asthma and an increase in asthma symptoms that can persist for weeks after the infection has resolved. Because of the reversibility seen in asthma, the patient may be asymptomatic when evaluated, particularly if the asthma is mild. Key issues to globally address are the following:

1. Specific description of the respiratory difficulty
2. Details about the frequency of respiratory symptoms

- Length of time that symptoms persist (minutes, hours, days)
- Episodic or persistent
- Seasonal or perennial
- Time of day

3. Relationship to environment – home, work, indoors, outdoors, animals, temperature
4. Relationship to activity – exercise

On physical examination, the classic sign is expiratory wheezing or a prolonged expiratory phase. *Wheeze* is defined as a continuous musical sound heard during chest auscultation that lasts longer than 250 ms. Wheezes can originate from airways of any size and can be high or low pitched. In asthma, wheezes may vary in character as the degree of airway narrowing varies from place to place in the lung. Auscultation allows identification of the characteristics and location of the wheezing as well as variations in air entry among different lung regions. Wheezing requires sufficient airflow to produce the sound; hence, an asthma patient with a severely tight airway may not have a wheeze. Close attention should be paid to the chest examination. Findings that can suggest another process include a hyperexpanded chest, cyanosis, stridor, decreased inspiratory-to-expiratory ratio, and rhonchi. Crackles or other adventitious breath sounds suggest pulmonary parenchymal disease or pulmonary edema. The neck examination should include palpation for supratracheal lymphadenopathy or tracheal deviation. The cardiac examination should focus on the identification of congenital heart disease in children and congestive heart failure in adults. Nasal and skin evaluations are also helpful. The presence of pale, boggy nasal turbinates with clearish discharge is suggestive of allergic rhinitis, which likely contributes to allergic asthma. Nasal polyps are associated typically with a more severe underlying asthma and, in children, can be a clue to underlying cystic fibrosis. Skin findings of atopic dermatitis are consistent with an atopic diathesis, which often can include chronic rhinitis and asthma. The digits should be inspected for the presence of cyanosis or clubbing. The presence of these features suggests a process other than asthma.

In an acute attack, physical examination findings depend on the severity and may include an increased respiratory rate, use of accessory muscles, wheezing, tachycardia, and pulsus paradoxus. In an acute severe attack with pending respiratory arrest, the patient may appear drowsy or confused, the respiratory rate is often greater than 30 min^{-1}, wheezing is heard throughout inhalation and exhalation or may be absent if air movement is limited, and the initial tachycardia may revert to a bradycardia.

A definitive diagnostic test for asthma does not exist. The diagnosis of asthma requires the documentation of episodic airway obstruction and the reversibility of that obstruction. In older children and adults, spirometry is very helpful in quantifying the amount of airway obstruction and the presence of reversibility. In children younger than 5 years, repeat clinical evaluations are required. Testing performed in the diagnosis and assessment of asthma is outlined below in the chapter.

Wheezing is a common symptom in children. Up to 10–15% of infants wheeze during their first year of life, and up to 25% of children younger than 5 years

wheeze. Most infants and children with recurrent wheezing are likely to have asthma; however, a wide variety of congenital and acquired conditions can have similar features. Several aspects of the medical history can raise questions about whether asthma is the correct or only diagnosis. These clinical features include the following:

- A history of persistent expiratory wheezing since birth suggests a congenital abnormality.
- Symptoms that vary with change in position may be caused by tracheomalacia or vascular rings.
- Failure to thrive and recurrent sinopulmonary infections suggest cystic fibrosis or immunodeficiency.
- Occurrence of wheezing with feeding can be associated with tracheoesophageal fistula or gastroesophageal reflux.
- Sudden onset of wheeze, followed by persistent wheeze, is consistent with foreign body aspiration.

These entities need to be considered particularly in patients who do not have a response to standard asthma treatment (Table 6.2).

Table 6.2 Differential diagnosis of asthma–airway diseases

Children
Upper and middle respiratory tract
Foreign body
Laryngeal webs
Tracheomalacia
Tracheoesophageal fistula
Vascular rings
Vocal cord dysfunction
Lower respiratory tract
Bronchiolitis
Cystic fibrosis
Bronchiectasis
Bronchopulmonary dysplasia
Bronchiolitis obliterans
Adults
Upper and middle respiratory tract
Vocal cord dysfunction
Vocal cord paralysis
Laryngeal or subglottic stenosis
Laryngotracheomalacia
Foreign body
Lower respiratory tract
Chronic obstructive pulmonary disease
Tumors
Cystic fibrosis or immunodeficiency

6.4.1 Differential Diagnosis in Children

6.4.1.1 Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease with a frequency of one in approximately 2,500 births. Common presenting symptoms and signs include persistent sinopulmonary infections, pancreatic insufficiency, and failure to thrive. Respiratory symptoms include a persistent, productive cough; hyperinflation of the lung fields; and pulmonary function tests consistent with an obstructive airway disease. However, many patients demonstrate mild or atypical symptoms, including wheezing, and clinicians should remain alert to the possibility of cystic fibrosis even when only a few of the usual features are present. Particularly, the presence of nasal polyps in a child should alert the physician of the possibility of cystic fibrosis. The sweat chloride test can be performed to exclude cystic fibrosis. Even with the slightest suspicion of disease, this test should be performed because the diagnosis of cystic fibrosis has major implications for the patient.

6.4.1.2 Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a chronic lung disease that occurs in premature infants and is characterized by impaired alveologenesis that leads to a global decrease in the number of alveoli and in gas-exchange surface area. It occurs infrequently in infants of more than 30 weeks' gestational age or birth weight more than 1,250 g. Most infants with bronchopulmonary dysplasia are ventilator-dependent from birth, with respiratory distress syndrome requiring surfactant therapy. However, bronchopulmonary dysplasia can develop in situations in which respiratory distress syndrome is mild or absent. The physical examination findings vary. The common findings are tachypnea, retractions, and, depending on the amount of atelectasis or pulmonary edema (or both), crackles. Expiratory wheezing may or may not be present. Chest radiographs can show various findings, including normal to low lung volumes, diffuse haziness due to inflammation or pulmonary edema (or both), atelectasis, and air trapping and hyperinflation. Most infants gradually improve over the first 4 months after initial instability during the first 6 weeks. Oxygen supplementation is gradually weaned until the infant can maintain adequate oxygenation on room air.

6.4.1.3 Foreign Body

Foreign body aspiration should be suspected in any patient who presents with sudden onset of wheezing, particularly if there is no previous history of wheezing. Approximately 80% of cases of pediatric foreign body aspiration occur in children younger than 3 years, with the peak incidence between 1 and 2 years of age. Commonly aspirated foreign bodies in children include peanuts, other nuts, seeds,

hardware, and pieces of toys. The signs and symptoms of foreign body aspiration vary according to the location of the foreign body and the elapsed time since the event. In a severe acute event, the child presents with severe respiratory distress, stridor, hoarseness, and cyanosis. In this emergency situation, the object is usually lodged in the larynx or trachea. More commonly, the foreign body is located in the bronchi (right lung > left lung), and the situation is less emergent. Physical examination findings can include generalized wheezing or localized findings such as focal wheeze or decreased breath sounds. The classic triad of wheeze, cough, and diminished breath sounds are present in 50–60% of cases. Patients may also present days to weeks after the initial aspiration. In this situation, they often present with nonspecific symptoms of dyspnea, wheeze, chronic cough, or recurrent pneumonia. A careful history is required to inquire about an initial choking episode that may have been forgotten. A history of choking, when specifically sought, is found in approximately 80–90% of confirmed cases.

A plain chest radiograph is sometimes helpful in foreign body aspiration. Its usefulness depends on the degree of airway obstruction and whether the object is radiopaque. Most aspirated foreign bodies are radiolucent, such as foods, which limits the usefulness of radiographs. In bronchial foreign body aspiration, the most common radiographic findings are hyperinflated lung, atelectasis, mediastinal shift, and pneumonia. These findings are seen in approximately 1/3 of cases. In children who have a suggestive history and normal chest radiograph, expiratory chest radiography or fluoroscopy may be helpful. Computed tomography (CT) scans and magnetic resonance imaging (MRI) appear to be of limited use.

Rigid bronchoscopy should be performed if a foreign body is suspected. Although flexible bronchoscopy is also used for this purpose, rigid bronchoscopy is currently considered the procedure of choice for removal of aspirated foreign bodies in children.

6.4.1.4 Tracheoesophageal Fistula

Tracheoesophageal fistula is a common congenital anomaly, occurring in approximately 1 in 3,500 births. It typically occurs with esophageal atresia and occurs alone (H-type fistula) in only 5% of cases. In infants with tracheoesophageal fistula and esophageal atresia, symptoms develop immediately after birth, with excessive secretions, choking, drooling, respiratory distress, and inability to feed. Patients with the H-type fistula present with coughing and choking associated with feeding. Depending on the size of the fistula, the diagnosis can be delayed for months to years. With small fistulas, patients have a history of mild respiratory distress associated with feeding or recurrent episodes of pneumonia.

The diagnosis of tracheoesophageal fistula with esophageal atresia can be made by attempting to pass a catheter into the stomach and confirm coiling with a chest radiograph. Diagnosis of isolated tracheoesophageal fistula is more difficult. This sometimes can be confirmed with an upper gastrointestinal series, with use of a thickened water contrast material, but often esophageal endoscopy and bronchoscopy

are required. Treatment is surgical ligation of the fistula and anastomosis of the esophageal segments. The prognosis is generally good, but close follow-up is required because esophageal stricture and tracheomalacia are reported complications.

6.4.1.5 Tracheomalacia

Tracheomalacia is characterized by a dynamic collapse of the trachea during respiration that results in airway obstruction. Most of the lesions are intrathoracic, causing airway collapse during expiration. Extrathoracic lesions are rare and lead to collapse during inspiration. There are three types of tracheomalacia. Type 1 is due to an intrinsic defect in the cartilaginous portion of the trachea that results in an increased proportion of membranous trachea and resultant airway collapse. Type 2 tracheomalacia is caused by extrinsic tracheal compression. This can be congenital or acquired and is associated with compression by cardiovascular structures, tumors, lymph nodes, or other masses. Type 3 lesions result from prolonged positive pressure ventilation or an inflammatory process that weakens the cartilaginous support of the trachea.

The signs and symptoms depend on the location and extent of the tracheal abnormality. Patients with intrathoracic tracheomalacia typically present with noisy breathing, a recurrent harsh, barking, or crouplike cough; in comparison, extrathoracic lesions cause inspiratory stridor. Symptoms may increase when the infant is supine. Wheezing can be present at birth but usually becomes apparent in the first 2–3 months of life. The wheezing becomes more prominent with upper respiratory tract infections and activity. Although chest radiographs are often normal, they are helpful in assessing for mediastinal masses and cardiomegaly. Changes in airway caliber during fluoroscopy can sometimes establish the diagnosis. Definitive diagnosis is usually made with bronchoscopy, with the observation of tracheal collapse with expiration. CT or MRI may help define the extent of the lesion. Most affected infants have spontaneous improvement by 12 months of age; however, patients can remain symptomatic into adulthood. Exercise intolerance may be seen in adults. In severe instances, treatment includes positive pressure ventilatory support, tracheal surgery, or placement of a tracheal stent.

6.4.1.6 Laryngeal Web

Laryngeal webs are a rare congenital abnormality caused by failure of resorption of the epithelial layer that covers the laryngeal opening. With failure of resorption, the vocal folds are incompletely separated, causing obstruction. Webs can occur anywhere along the anterior or posterior larynx and can also occur from trauma to the airway, as with intubation or injury. Patients with laryngeal webs usually present in infancy with respiratory distress and an unusual cry. In milder disease, symptoms may occur later and include a hoarse or weak voice, breathiness, and varying

degrees of dyspnea and stridor, depending on the extent of the obstruction. Diagnosis is made with visualization of the web. The extent of surgical treatment required depends on the area of the lesion, and it can range from simple lysis of the web to laryngeal reconstruction.

6.4.1.7 Bronchiolitis

Bronchiolitis is a general term used to describe the presence of a nonspecific inflammatory response in the small airways. The term is confusing because it describes both a clinical syndrome and a constellation of histologic abnormalities that may occur from a number of various processes. In the published reports on bronchiolitis, there often is no tissue confirmation of the disease, which explains the many uncertainties about the epidemiology, pathophysiology, and therapy of the condition. The clinical syndromes associated with bronchiolitis include inhalation injury, drug-induced reactions, associations with connective tissue disease, idiopathic, and, most commonly, infections. In children, bronchiolitis has been referred to as "infectious asthma" and "wheezy bronchitis."

The diagnosis of bronchiolitis is based on a typical history and results of the physical examination. The key findings in infectious bronchiolitis include intermittent fever, runny nose, cough, tachypnea, abdominal pain, and crackles or wheezing. The presence or the severity of these findings has not been shown to distinguish reliably among viral, bacterial, or atypical organisms. Respiratory syncytial virus (RSV) is the most common viral cause of bronchiolitis in children younger than 2 years. Laboratory testing, including chest radiography, rapid viral panels or cultures, and complete blood count (CBC) are considered to have low utility in the evaluation of children who have mild airway disease. Reports are not clear about the benefits of the tests for children who have moderate to severe airway disease. Chest radiographs may be normal, although in some instances hyperinflation with peribronchial thickening or atelectasis may be present.

Although asthma and bronchiolitis share clinical manifestations and possible pathogeneses, it is important to try to distinguish between them on the basis of the past history and current presentation. Many children with bronchiolitis do not develop asthma and may be inappropriately labeled, particularly with the first episode. Risk factors identified for wheezing during viral infections in infancy and early childhood include maternal smoking, maternal history of asthma, and elevated IgE levels. Environmental history and overall review of systems can help distinguish between these entities and, thus, allow for implementation of avoidance techniques to prevent future exacerbations. Also, for a wheezing child younger than 3 years, risk for asthma is increased if one major criterion and two minor criteria are met:

- Major criteria – parental asthma, eczema
- Minor criteria – allergic rhinitis, eosinophilia, wheezing apart from viral upper respiratory tract illness

Children younger than 2 years frequently do not respond vigorously to inhaled or injected bronchodilators in a purely infectious setting, although there is a subset that does show improvement and a therapeutic trial should be considered.

6.4.1.8 Congenital Vascular Ring

Vascular ring abnormalities are caused by developmental failure of parts of the paired aortic arches during embryonic life. This may result in compression of the trachea or esophagus or both. Symptomatic vascular rings usually are diagnosed in early life, but the delay between the first appearance of symptoms and the time to diagnosis is significant. The diagnosis usually is made during the first year of life. Inspiratory stridor, wheezing, and dyspnea are prominent in cases of vascular ring, but other respiratory symptoms such as recurrent respiratory tract infections and cough may be associated with a vascular ring. Persistence of these symptoms should raise the question of a possible vascular ring.

Clues to a vascular ring on chest radiography include a right-sided aortic arch or tracheal compression or both. However, these findings often are absent. Esophography is more sensitive and shows a double esophageal impression on the frontal view associated with a posterior notch on the side view. Other studies that can be performed to better define the anatomy include bronchoscopy, CT, MRI, and angiography. The treatment for symptomatic vascular rings is surgical correction.

6.4.1.9 Immunodeficiency

Immunodeficiency can present in myriad ways. Conditions that may be confused with asthma, particularly in the earlier stages, are humoral immune deficiencies. These result from impaired antibody production because of an intrinsic B-cell defect or dysfunctional interaction between B- and T-cells. Although T-cell defects underlie some of these diseases, cellular immunity is largely intact. The resultant antibody deficiency in humoral immune deficiencies leads to recurrent upper and lower respiratory tract infections with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. The most common humoral primary immunodeficiencies are IgA deficiency, X-linked agammaglobulinemia, and common variable immunodeficiency. Most IgA-deficient individuals (nearly 90%) are asymptomatic. Those who are symptomatic often have a concurrent immunodeficiency. X-linked agammaglobulinemia and common variable immunodeficiency can be manifested in childhood or adulthood, although X-linked agammaglobulinemia typically becomes manifest between 6 and 18 months of age. The evaluation of patients with recurrent sinopulmonary infections should include IgA, IgM, and IgG immunoglobulin levels. IgG is markedly decreased in X-linked agammaglobulinemia and common variable immunodeficiency. For these conditions, treatment consists of immunoglobulin replacement. There is no immunoglobulin replacement therapy for IgA deficiency. These patients often have anti-IgA antibody and are at risk for an anaphylactic reaction when receiving blood products.

6.4.1.10 Bronchiolitis Obliterans

Bronchiolitis obliterans is a rare disease caused by epithelial injury to the lower respiratory tract that results in obstruction of the lower airways. It can be idiopathic or occur after infectious, chemical, or immunologic injury. Patients usually present with tachypnea, dyspnea, cough, and wheeze unresponsive to bronchodilator therapy. Physical examination shows diffuse wheezing and crackles. Chest radiographs typically show diffuse interstitial infiltrates and atelectasis. Pulmonary function testing shows airway obstruction without a response to bronchodilators.

6.4.2 Differential Diagnosis in Adults

The differential diagnosis of asthma in adults differs from that in children because congenital defects of the upper airway, heart, and lungs are rare. In adults, the primary distinctions need to be made between new-onset and acquired diseases of the upper airway, heart, and lungs (Table 6.2). Of primary importance is the distinction between upper and lower airway disease. Physical examination and pulmonary function testing can be helpful in this regard. Baughman and Loudon compared recorded sounds from the neck and chest in patients with upper airway obstruction, patients with asthma, and extubated patients with no airway obstruction. They found that the sound signal associated with asthma had a frequency similar to that of stridor. The musical sound in patients with stridor occurred during inspiration, but the sounds in those with asthma occurred predominantly during expiration. In addition, the signal was more intense over the neck than over the chest in those with stridor; for asthma patients, the reverse was true. Therefore, the major difference between upper respiratory airway obstruction and asthma was the inspiratory timing of the sound and the prominence of the sound over the neck. The differences in pulmonary function testing of these entities are reviewed below in the section on testing.

6.4.2.1 Obstructive Lung Disease

Chronic obstructive pulmonary disease (COPD) is characterized by air-flow limitation that (as opposed to typical asthma) is not fully reversible. The air-flow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. The diagnosis of COPD should be considered for any patient who has cough, sputum production, or dyspnea or a history of exposure to risk factors, primarily smoking, for the disease. The diagnosis requires spirometry; a decreased FEV_1-to-forced vital capacity (FVC) ratio establishes an obstructive process. This alone though is not definitive, because the same pattern can be seen in asthma. The key differentiating features are the clinical presentation, lack of reversibility with treatment, exposure (primarily smoking) history, and the diffusing capacity for carbon monoxide (D_{LCO}) with pulmonary function testing (Table 6.3). D_{LCO} is normal or increased

Table 6.3 Differentiating asthma from chronic obstructive pulmonary disease (COPD)

Feature	Asthma	COPD
Age at onset	Child or adult	Fifth decade
Family history	Often positive	Noncontributory
Smoking role	Less significant	Highly significant
Respiratory symptoms	Vary daily	Slow, progressive decline
Inflammation	Th2 phenotype Eosinophils	Interleukin-8, tumor necrosis factor-α Neutrophils
Response to corticosteroids	Highly responsive	Slightly responsive

in asthma and decreased in COPD. Some patients with asthma cannot be distinguished from those with COPD, and a subset of patients may have both asthma and COPD. The management of these patients should be similar to that of those with asthma. The primary treatment for COPD consists of bronchodilators, glucocorticoids, and oxygen therapy. The bronchodilators most commonly used are β-agonists, anticholinergic drugs, and, less commonly, methylxanthines. These medications can be used in combination in both short- and long-acting forms. For example, a patient with stage 2 COPD may use a long-acting anticholinergic agent in conjunction with a long-acting β-agonist agent daily, adding a short-acting anticholinergic or β-agonist as needed. The effect of glucocorticoids in COPD is less dramatic than in asthma. In some studies, inhaled corticosteroids cause a small increase in FEV_1, a small reduction in bronchial reactivity in stable COPD, and a reduction in COPD exacerbations. In other studies, no significant changes were noted. Currently, a trial of inhaled corticosteroids can be instituted in those with stage 3 COPD and continued if clinical improvement is noted over a 6-month period and withdrawn if no clinical improvement is noted.

Although neither chronic bronchitis nor emphysema is required in the definition of COPD, the terms are often used in describing patients with COPD. Chronic bronchitis, traditionally labeled as "blue bloater," is a clinical diagnosis defined by the presence of chronic productive cough for 3 months in each of two successive years. Emphysema, traditionally labeled as "pink puffer," is a pathology term that describes abnormal permanent dilatation of airspaces distal to the terminal bronchioles, which results in poor oxygen diffusion into the pulmonary vasculature. Patients can have COPD without falling into these two categories. Because obstruction is the primary manifestation, treatment for these groups is essentially the same as for COPD.

6.4.2.2 Mechanical Obstruction

Vocal Cord Paralysis

Vocal cord paralysis can cause respiratory symptoms that vary with the extent of the paralysis (paresis versus complete paralysis), exact location of the affected cord, and whether it is unilateral or bilateral. Unilateral vocal cord paralysis can be associated with breathy voice, ineffective cough, dysphagia, and aspiration. These

signs and symptoms should be sought, particularly if there is any voice component to the symptoms. The paralysis is caused primarily by injury or inflammation of the vagus or recurrent laryngeal nerve. Common causes include surgery or procedures involving the thyroid gland, carotid artery, neck, chest, and base of the skull. Other causes include tumor, trauma, aneurysm, and neural disorders. However, bilateral vocal cord paralysis often is associated with preserved voice but more respiratory and aspiration signs. Bilateral vocal cord paralysis is usually caused by bilateral thyroid surgery but can also be caused by neurologic events.

Laryngeal and Subglottic Stenosis

Postintubation tracheal lesions are a common cause of upper airway obstruction and represent the principal indication for tracheal resection and reconstructive surgery in patients with subglottic stenosis. These injuries are caused by cuff-induced pressure necrosis, with subsequent formation of granulomas and fibrotic tissue. The main risk factor for development of the lesion is prolonged intubation. The obstruction can become manifest days to years after intubation. Therefore, if upper airway obstruction is suspected, it is imperative to inquire about a previous intubation history.

Several systemic diseases have been shown to cause upper airway obstruction. Wegener's granulomatosis is classically characterized by necrotizing granulomatous vasculitis of the upper and lower airway and, in most cases, involvement of the kidney. In a National Institutes of Health study of 158 patients with Wegener's granulomatosis, 16% had tracheal stenosis, with 2% presenting with this manifestation. Tracheal stenosis has also been reported in sarcoidosis and amyloidosis.

Idiopathic subglottic stenosis is a diagnosis of exclusion. It is not clear whether this group represents a distinctly separate group or a collection of different systemic illnesses that have not been identified. In general, there appears to be two groups of patients: those with mild disease that responds well to laser incision and dilatation, and those with more dense and complex scars that require resection and reconstruction. A disproportionate number of females are afflicted, the significance of which is unclear. The normal tracheal diameter ranges from 10–25 mm. With narrowing of the upper airway, dyspnea on exertion is typically the first symptom and becomes manifest when the airway diameter is narrowed to 8 mm. Symptoms at rest and decreased peak flow readings occur at 5 mm. Pulmonary function testing classically shows flattening of both the inspiratory and expiratory loop with a fixed upper airway obstruction.

Laryngotracheomalacia with Relapsing Polychondritis

Relapsing polychondritis can present in various ways depending on the severity and organ system involved. Auricular involvement is the most common feature, eventually appearing in approximately 85% of patients. Other areas that can be involved

include the eye, nose, airways, cardiovascular system, skin, joints, kidney, and nervous system. The primary airway manifestations of relapsing polychondritis include glottic, subglottic, laryngeal, or tracheobronchial inflammation with luminal encroachment; fibrosis-induced luminal contracture; and loss of structural cartilaginous support resulting in laryngeal collapse during forced inspiration or tracheal collapse (or both) during expiration. Symptoms include hoarseness, aphonia, wheezing, inspiratory stridor, nonproductive cough, and dyspnea. Onset is most likely in the fifth and sixth decades, although all age groups can be affected. Relapsing polychondritis may coexist with various vasculitides or other autoimmune illnesses. Physical examination findings depend on the organs involved. Classic findings include a diffuse violaceous erythematous appearance to the cartilage-containing areas of the auricle and a saddle-nose nasal deformity. No test is diagnostically specific for relapsing polychondritis. The diagnosis is established by clinical findings, supportive laboratory data, and biopsy of an involved cartilaginous site. Pulmonary function testing may show varying degrees of inspiratory or expiratory obstruction (or both). Marked expiratory obstruction correlates well with bronchoscopic abnormalities in the upper airway.

Foreign Body Aspiration

Foreign body aspiration is more common in children than adults; approximately only 20% of recognized cases occur in patients older than 15 years. In adults, the nature of the foreign body is highly variable. Neurologic disorders, syncope, and alcohol or sedative abuse predispose to foreign body aspiration. Acute presentation in adults is rare. In a subacute or chronic presentation, the initial choking episode is often not recalled. Coughing is seen in approximately 80% of cases. Other associated symptoms include fever, hemoptysis, chest pain, or wheeze. Dyspnea is present only 25% of the time. The diagnosis is frequently overlooked unless the patient reports or is queried about a choking episode. Radiographically, a radiopaque foreign body can be seen on routine imaging. Unilateral hyperinflation can occur but is more common in the pediatric than in the adult population. Fiberoptic bronchoscopy is the diagnostic procedure of choice in adults, although rigid bronchoscopy may be required for extraction.

6.4.2.3 Cardiac Disorders

Atrial Myxoma

Myxomas are the most common primary cardiac tumor. The clinical manifestations depend on the anatomic location of the tumor. Approximately 80% of myxomas originate in the left atrium, and the majority of others are found in the right atrium. The tumors vary widely in size (range, 1–15 cm in diameter). The common respiratory symptoms are dyspnea and cough. Associated cardiovascular signs and symptoms

often include orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, edema, and fatigue. Symptoms may worsen in certain body positions because of the location of the tumor in the atrium. Physical examination findings, in addition to evidence of right heart and left heart dysfunction, include diastolic murmur or evidence of embolization. Echocardiography is the test of choice for the initial evaluation; cardiac MRI or CT can also be performed to help distinguish the type of tumor. These studies provide the background regarding the need and type of surgical intervention.

Mitral Valve Prolapse

Mitral valve prolapse is a common disorder, occurring in 2–3% of the population. The cause of primary mitral valve prolapse is unknown. The classic auscultatory features are a midsystolic click or multiple clicks, sometimes followed by a midsystolic to late systolic murmur at the apex. Several nonspecific symptoms have been associated with mitral valve prolapse and termed the *mitral valve syndrome*. These include dyspnea, exercise intolerance, panic, anxiety, palpitations, and numbness. Controlled clinical studies suggest that patients with mitral valve prolapse and control subjects are equally symptomatic, although autonomic and neuroendocrine dysfunction may underlie some of the symptoms associated with mitral valve prolapse.

Congestive Heart Failure

Congestive heart failure may be manifested by symptoms similar to those of asthma: wheezing and worsening of respiratory symptoms at night and with physical activity. The main point is to be aware of the possibility of congestive heart failure, because the physical examination often provides the diagnosis. The major findings include an elevated jugular venous pulse, crackles on lung examination, and lower extremity edema. The cardiac examination may also show an abnormal rhythm, soft heart sounds, or murmur.

6.4.2.4 Vocal Cord Dysfunction

Vocal cord dysfunction, also known as functional upper airway obstruction, episodic paroxysmal laryngospasm, and paradoxic vocal cord movement, is an entity without a specific organic cause that may mimic asthma or organic upper airway obstruction. Normally during the respiratory cycle, the vocal cords are abducted during inspiration and expiration, allowing for maximal airflow. In vocal cord dysfunction, the vocal cords are inappropriately adducted on inspiration. This functional airway obstruction results in a marked inspiratory stridor that can be mistaken for asthmatic wheezing. During an attack, laryngoscopy shows a paradoxic inspiratory adduction of the anterior vocal cords with a posterior

diamond-shaped glottic gap. At this time, spirometry demonstrates a flattened inspiratory flow-volume loop with a normal expiratory flow-volume loop. However, when the patient is asymptomatic, the results of laryngoscopy and spirometry are typically normal.

Vocal cord dysfunction appears to be psychogenic in nature. Patients are not considered to be malingering, because they do not intentionally produce their symptoms. Currently, it is thought to represent a conversion disorder associated with other conditions such as depression. Patients may present with significant respiratory distress and dramatic inspiratory stridor. On physical examination, harsh breath sounds are loudest above the sternal notch and less audible through the chest wall. Because of the suspicion of asthma, patients typically receive treatment with high-dose glucocorticoids and β-adrenergic agonists, which fail to relieve symptoms. The condition of these patients is often labeled as *refractory asthma*. Arterial blood gases are normal when the patient is symptomatic and asymptomatic. It is important to note that vocal cord dysfunction can coexist with true asthma. Up to 20% of asthma patients may have some degree of vocal cord dysfunction. Clues to help distinguish vocal cord dysfunction from asthma include the following:

- Minimal response to aggressive asthma treatment
- Flattened inspiratory flow-volume loop when symptomatic
- Stridor on physical examination when symptomatic
- Normal arterial blood gas measurements during a “severe” attack

Vocal cord dysfunction is difficult to treat. In most cases, the diagnosis is often delayed and it is difficult to taper or discontinue long-standing medications. It is difficult for patients to accept the diagnosis of a nonorganic disorder. There is no well-defined treatment protocol. No studies have been published on the effectiveness of psychodynamic or psychopharmacologic treatment. Some success has been reported with speech therapy, which uses breathing techniques and voice and neck relaxation exercises to eliminate the symptoms at their onset. These patients often have postnasal drainage and gastroesophageal reflux disease (GERD) that contribute to vocal cord dysfunction, and management of these disorders helps decrease the dysfunction.

6.4.2.5 Systemic Disorders

Cystic Fibrosis

Although cystic fibrosis is commonly thought of as a childhood disease, it is not uncommon for the initial diagnosis to be made during the adult years. The respiratory manifestations include a persistent productive cough, hyperinflation of the lungs seen on a chest film, pulmonary function tests consistent with an obstructive process, and concomitant sinus disease. With advancement of the disease, bronchiectasis appears. The sweat chloride test is the initial test of choice, but in adults, the results can sometimes be equivocal. Molecular diagnosis is usually made by

direct mutation analysis of specific known mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Carcinoid

Bronchial carcinoid tumors are rare, comprising less than 5% of the primary tumors of the lung. They can occur at any age, but the mean age is between 43 and 60 years. The clinical presentation usually consists of recurrent pneumonitis, cough, and hemoptysis. Of interest, dyspnea and the typical symptoms associated with carcinoid syndrome (flush and diarrhea) are rare. Fiberoptic bronchoscopy and tumor biopsy are the usual diagnostic procedures. The 10-year survival rate is 80–90%.

6.4.3 Testing

6.4.3.1 Spirometry

Pulmonary function testing can be used to detect airway expiratory flow obstruction and airway hyperresponsiveness. Pulmonary function testing has two components: spirometry and plethysmography. All patients who have asthma or are being evaluated for asthma should have spirometry. Spirometry measures the maximal volume of air forcibly exhaled from the point of maximal inhalation, the FVC, and the volume of air exhaled during the first second of this maneuver, FEV_1. A flow-volume curve is generated by plotting the flow rate (L s^{-1} on the *y*-axis) versus lung volume (L on the *x*-axis). Expiratory flow obstruction is indicated by decreased FEV_1 and decreased FEV_1/FVC ratio compared with the predicted values based on age, height, sex, and race. In symptomatic asthma, FEV_1 typically is decreased, whereas FVC remains relatively normal. Airway obstruction results in a characteristic appearance of the flow-volume loop – a scooped appearance of the expiratory loop (Fig. 6.2).

These changes, however, are not specific for asthma, because they are also seen in COPD. Spirometry is generally performed in children older than 5 years, although many children cannot perform the maneuver until after age 7 years. In younger children, management decisions about initiating and adjusting treatment should be based primarily on the frequency and severity of past exacerbations and symptom presentation, with spirometry used as a guide in the assessment and response to treatment.

Another component of spirometry is the determination of reversibility as indicated by a bronchodilator response to a β-adrenergic agonist such as albuterol. After a bronchodilator is administered, the FEV_1 often improves. A significant improvement in FEV_1 after a bronchodilator is administered is defined by the American Thoracic Society as a 12% increase in FEV_1, which represents at least a 200-mL increase in

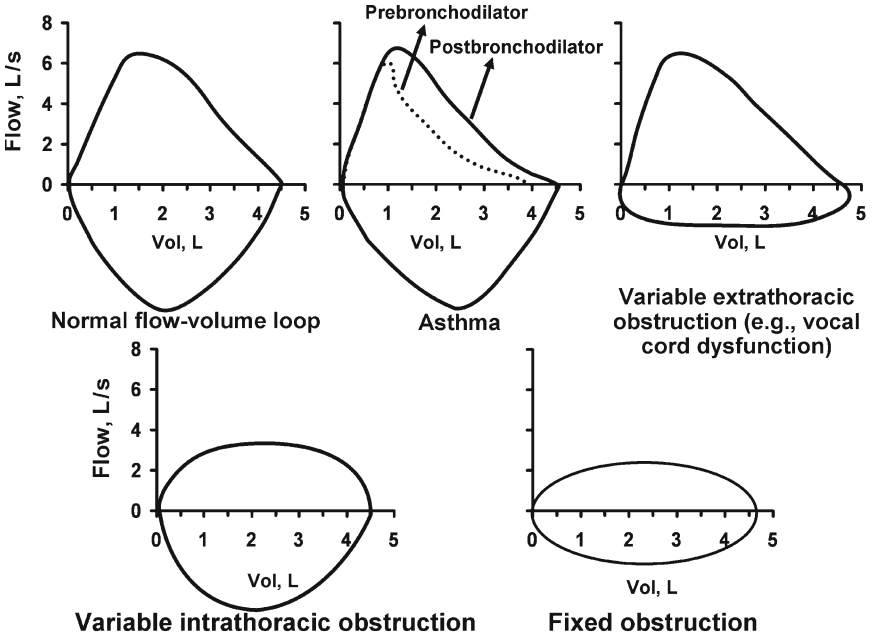

Fig. 6.2 Pulmonary function testing. Flow-volume loops

volume. Such a response is suggestive of a diagnosis of asthma. Some patients with asthma do not exhibit a significant bronchodilator response because of marked underlying inflammation. These patients often have a low baseline FEV_1 and may require anti-inflammatory treatment to demonstrate reversibility.

Methacholine bronchoprovocation testing can be performed to measure airway hyperresponsiveness. Methacholine is a cholinergic agonist that stimulates muscarinic receptors on airway smooth muscle and produces bronchoconstriction. In patients who have asthma, the airway smooth muscle is more sensitive to methacholine, resulting in bronchoconstriction at lower dosages, thus differentiating patients with asthma from those without asthma. Although different protocols are used for methacholine challenge, the results are often presented as the provocative concentration that results in a 20% decrease in FEV_1. One method for performing methacholine challenge uses a 0.25-mg mL^{-1} methacholine solution for inhalation. Two milliliters of this solution is placed in the nebulizer, and the patient is instructed to take one deep inhalation, followed by repeat spirometry. If FEV_1 has decreased less than 15%, four more breaths of methacholine are administered. If FEV_1 decreases 20% or more, the test is positive. A short-acting β-agonist should then be administered to ensure that FEV_1 returns toward the baseline value. This type of testing should not be performed in a patient known to have asthma, because some patients are very sensitive and can develop severe bronchospasm. This testing

should be performed only if the patient has a normal baseline spirometry (FEV_1) and the diagnosis of asthma is in question. False-positive methacholine challenges can be seen in allergic rhinitis, cystic fibrosis, COPD, congestive heart failure, tobacco use, and upper respiratory tract infection.

Pulmonary function testing is also useful for diagnosing upper airway obstruction. The pattern of obstruction caused by upper airway lesions is determined by the level of the airway at which the obstruction occurs. Physiologically, the laryngotracheal airway can be divided into two levels: intrathoracic and extrathoracic. The intrathoracic airway is surrounded by pleural pressure and the extrathoracic airway, by atmospheric pressure. When the obstruction caused by a lesion changes with the respiratory cycle it is called a *variable lesion*. Variable extrathoracic obstruction, as with vocal cord paralysis and vocal cord dysfunction, is characterized by increased obstruction with inspiration. This increase is due to the negative pressure within the airway compared with the positive atmospheric pressure around the airway during inspiration. During expiration, however, the marked positive pressure within the airway decreases the obstruction so that the expiratory curve may be normal (Fig. 6.2). Conversely, variable intrathoracic obstruction, which is usually due to tumor, causes increased obstruction during expiration. This occurs because the positive pleural pressure during expiration causes compression of the airway at the site of the lesion. During inspiration, the negative pleural pressure lessens the obstruction, allowing a normal inspiratory loop (Fig. 6.2). In fixed obstruction, the airway diameter does not change with inspiration or expiration. Decreased airflow through the site of obstruction represented by a plateau will be seen in the expiratory and inspiratory curves (Fig. 6.2).

DLCO measures the ability of the lungs to transfer gas from the inhaled air to the red blood cells in the pulmonary capillaries, and this is helpful in distinguishing between asthma and emphysema, particularly in patients at risk for both illnesses, such as smokers and older patients. In asthma, DLCO is typically normal or increased, whereas in emphysema and other pulmonary parenchymal diseases in which gas exchange at the alveolar–capillary membrane is impaired, DLCO is decreased. Smokers with airway obstruction but normal DLCO values usually have chronic obstructive bronchitis, but not emphysema.

6.4.3.2 Peak Flow Measurement

Peak flow measurement is a simple and inexpensive way to monitor airflow in the office and at home. In this maneuver, patients expire forcefully into the peak flow meter, a hollow tube, which measures the peak expiratory flow rate (PEFR) in liters per second. Although PEFR is not as accurate as spirometry, it correlates well with the presence of bronchospasm and is a good estimate of the severity of asthma. It is particularly helpful in those with moderate-to-severe persistent asthma and with decreased awareness of asthma symptoms. A baseline measure should be obtained with which to compare future readings. The baseline value should be obtained when the patient is feeling well after a period of maximal asthma therapy; this represents

the "personal best." Further monitoring can be performed on a scheduled or as needed basis depending on the patient's asthma history. The clinician should provide clear instructions for the patient to follow when the PEFR begins to decrease. This is outlined for the patient in the asthma action plan. An example of an asthma action plan and approximately normal values for PEFR are provided in Tables 6.4 and 6.5, respectively.

6.4.3.3 Sputum Eosinophils

Examination of the sputum for eosinophils is a noninvasive way to measure airway inflammation. Different induction and processing techniques can be used, but patients typically have sputum induction with aerosolized 3% hypertonic saline by way of a nebulizer. The patient then coughs sputum into a sterile container, which is processed and stained to obtain a total cell count and a differential cell count. The analysis of sputum eosinophils has provided results comparable to an analysis of specimens obtained with bronchoscopy. In mild and severe asthma, sputum eosinophils increase during exacerbations and increased baseline sputum eosinophil counts predict exacerbation with withdrawal of corticosteroid therapy. A recent study used sputum eosinophil counts to regulate the dosage of anti-inflammatory agents in patients with moderate to severe asthma. This approach resulted in significantly fewer exacerbations and fewer hospital admissions than in the guideline-based (clinical symptoms and spirometry) group at similar corticosteroid doses. This suggests that the measurement of sputum eosinophils is beneficial in selecting the appropriate amount of anti-inflammatory medication required to control asthma. Currently, this procedure is not widely available, but it is considered safe if performed in a controlled environment. Also, it potentially can be important in diagnosing and monitoring asthma.

6.4.3.4 Exhaled Nitric Oxide

Exhaled nitric oxide has been studied as another noninvasive measure of airway inflammation that increases with an acute exacerbation or loss of asthma control. The fraction of nitric oxide in the exhaled air increases in proportion to inflammation of the bronchial wall, induced sputum eosinophilia, and airway hyperresponsiveness. Increases in exhaled nitric oxide are associated with a deterioration in asthma control, and exhaled nitric oxide levels are decreased in a dose-dependent manner with anti-inflammatory treatment. Initial studies have shown that the use of exhaled nitric oxide measurements performed regularly in patients with moderate asthma resulted in a lower maintenance dose of inhaled corticosteroid needed to control asthma as compared with the use of a dose-adjustment strategy based on conventional guidelines. Exhaled nitric oxide has been proposed as a diagnostic tool for asthma, but the baseline levels of exhaled nitric oxide can vary significantly with age, sex, smoking, infection, allergic rhinitis, and genetic polymorphisms in the

Table 6.4 Asthma action plan

Name_____	Date_____
Physician's name_____ Phone number_____	Emergency phone number_____
Personal best peak flow_____	
Green zone	Peak flow between_____ to_____ (80–100% of personal best) Symptoms: no cough, wheeze, or shortness of breath during day or night Treatment plan: long-term controller medications – used daily 1._____ 2._____ 3._____ : rescue medication 1._____
Yellow zone	Peak flow between_____ to _____(50–80% of personal best) Symptoms: cough, wheeze, shortness of breath, or waking at nighttime due to asthma Treatment plan: adjustment of long-term controller medications 1._____ 2._____ 3._____ : rescue medication 1._____ 2 or 4 puffs or nebulizer every 20min up to 1h : if symptoms and peak flow do not return to green zone after 1h of treatment: Add____ mg of _____ (oral steroid) Call physician
Red zone (Medical alert)	Peak flow <50% of personal best Symptoms: very short of breath or cannot do usual activities • Rescue medication 4 puffs or nebulizer •_____ mg prednisone • Seek emergent care

Table 6.5 Approximate normal peak flow rate values[a]

Children and adolescents

Height, inches	Males, L min^{-1}	Females, L min^{-1}	Height, inches	Males, L min^{-1}	Females, L min^{-1}
40	115	114	55	316	315
41	128	127	56	329	328
42	141	141	57	343	342
43	155	154	58	356	355
44	166	168	59	370	369
45	182	181	60	383	382
46	195	194	61	397	395
47	209	208	62	410	409
48	222	221	63	423	422
49	235	235	64	437	436
50	249	248	65	450	449
51	262	261	66	464	462
52	276	275	67	477	476
53	289	288	68	491	489
54	303	302	69	504	503

Males, L min^{-1}

	Height, inches				
Age, year	60	65	70	75	80
15	511	531	548	564	578
20	554	604	624	681	740
25	580	608	636	682	730
30	584	617	627	660	703
35	599	622	643	661	677
40	597	620	641	659	675
45	591	613	633	651	668
50	580	602	622	640	656
55	566	588	608	625	640
60	551	572	591	607	622
65	533	554	572	588	603
70	515	535	552	568	582
75	496	515	532	547	560

Females, L min^{-1}

	Height, inches				
Age, year	60	65	70	75	80
15	423	438	451	463	473
20	444	460	474	486	497
25	455	471	485	497	509
30	458	475	489	502	513
35	458	474	488	501	512
40	453	469	483	496	507
45	446	462	476	488	499
50	437	453	466	478	489
55	427	442	455	467	477
60	415	430	443	454	464
65	403	417	430	441	451
70	390	404	416	427	436
75	377	391	402	413	422

(Continued)

nitric oxide synthetase genes. Therefore, the usefulness of exhaled nitric oxide may be in monitoring asthma control, guiding therapy, and predicting response to corticosteroid therapy as opposed to making the diagnosis.

6.5 Classification of Asthma

6.5.1 Types

Asthma can be divided into various subtypes on the basis of the pathophysiologic mechanism of asthma. The two primary subtypes are allergic asthma and nonallergic asthma. Aspirin-induced asthma is another subtype.

6.5.1.1 Allergic Asthma

Allergic asthma is caused by the inhalation of a specific airborne allergen that triggers an IgE-mediated reaction. Allergic asthma implies a temporal relationship between allergen exposure and subsequent respiratory symptoms. The respiratory symptoms develop within minutes or up to an hour after allergen exposure. Allergic asthma occurs most commonly from ages 4–40 years but is also present in the older population. It is estimated that 75% of patients with persistent asthma have some component of allergic asthma.

Common allergens associated with allergic asthma include tree, grass, and weed pollens; molds; dust mites; animal dander; and cockroach. The diagnosis of allergic asthma should be suspected when the signs and symptoms of asthma correlate closely with the local patterns of pollen and mold release. When perennial symptoms of asthma are present, the temporal relationship may not be obvious because of continuous allergen exposure. Potential causes of perennial allergic asthma include animal dander, dust mite, cockroach, and, depending on the climate, pollens and molds.

6.5.1.2 Nonallergic Asthma

In nonallergic asthma, IgE-mediated sensitivity is not present. Nonallergic asthma occurs at any age but is more likely to occur in patients younger than 4 years and older than 50 years. The results of skin prick testing and in vitro allergen testing are

Table 6.5 (continued)

Data from National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

[a]These figures are a guideline only. The range of "normal" functions depends on many factors that cannot all be included in a table. These values represent average normal values with 100L min^{-1}

negative. Allergens do not trigger worsening of symptoms; the major triggers seem to be upper respiratory tract infections, GERD, and irritants. In addition, the underlying inflammation can wax and wane without obvious triggers. The respiratory inflammation is not IgE mediated, but it is still primarily eosinophilic. Nonallergic asthma generally appears to have a more severe and progressive course than allergic asthma, particularly if onset is late in life and requires more aggressive treatment.

The term *mixed asthma* refers to the presence of both allergic and nonallergic asthma. This likely represents the majority of asthma patients. A typical example is a patient with allergic asthma due to tree pollens who has a flare of asthma in the winter because of an upper respiratory tract infection. Other examples include patients with daily persistent asthma and positive skin tests that do not correlate with perennial asthma symptoms (skin tests positive only to tree and negative to dust mites, dog, cat, and molds).

6.5.1.3 Aspirin-Induced Asthma

Aspirin-induced asthma represents a small subset of asthma patients. These patients with underlying asthma, nasal polyposis, and chronic rhinosinusitis develop respiratory signs and symptoms with the use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). This reaction is a class effect with the same respiratory symptoms produced with the use of any of the cyclooxygenase (COX)-1 inhibitors, including aspirin, ibuprofen, and naproxen. The respiratory reaction, consisting of rhinorrhea, nasal congestion, dyspnea, and wheezing, typically occurs within minutes and up to 3 hours after ingestion. Of interest, these patients typically have nonallergic asthma. This group is discussed in more detail in the medication-exacerbating asthma section and the chapter on rhinosinusitis (Chap. 4).

6.5.2 Initial Evaluation of Chronic Asthma Severity

The severity of asthma generally is considered a function of the intensity of the disease. However, it is difficult to easily define asthma severity because it can vary over time. The two primary measures used to define asthma severity are current impairment and future risk. These two measures do not correlate perfectly with each other, and both need to be considered to adequately address disease severity. Compounding the variables used in trying to define asthma severity are the measures used to define asthma control and the responsiveness of the asthma to treatment. Also, studies suggest that measures of health care use are an important addition to the traditional measures of asthma severity. Considering all this, the American Thoracic Society sponsored an expert workshop to develop a consensus definition for severe asthma that would apply not just to the initial evaluation but also to patients receiving treatment for asthma. The definition of the American Thoracic Society is based on a combination of major and minor criteria that aim to

Table 6.6 American Thoracic Society workshop consensus for definition of severe/refractory asthma[a,b]

Major characteristics
1. Treatment with continuous or near continuous (≥50% of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids
Minor characteristics
1. Requirement for additional daily treatment with a controller medication (e.g., long-acting β-agonist, theophylline, or leukotriene antagonist)
2. Asthma symptoms requiring short-acting β-agonist use on a daily or near-daily basis
3. Persistent airway obstruction (FEV_1 < 80% predicted, diurnal peak expiratory flow variability 20%)
4. One or more urgent care visits for asthma per year
5. Three or more oral corticosteroid bursts per year
6. Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose
7. Near-fatal asthma event in the past

From Moore, W. C. and Peters, S. P. (2006) Severe asthma: an overview. J. Allergy Clin. Immunol. 117, 487–494. Used with permission

[a]Definition requires one or both major criteria and two minor criteria

[b]Requires that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant

identify subjects with inadequate control despite treatment with corticosteroids. According to this definition, subjects with severe asthma must meet one of two major criteria: (1) the use of high-dose inhaled corticosteroids or (2) the requirement for very frequent oral corticosteroid use (>50% of the year). Also, two of seven minor criteria must be met: (1) the use of additional controller medications besides inhaled corticosteroids, (2) the presence of daily symptoms requiring rescue inhaler, (3) reduced lung function (FEV_1 < 80% of predicted and diurnal PEF variability >20%), (4) one or more urgent care asthma visits per year, (5) recurrent (≥3) exacerbations requiring oral corticosteroids per year, (6) clinical deterioration with corticosteroid withdrawal, and (7) a history of a near-fatal asthma event (Table 6.6).

The "current impairment" in asthma is an evaluation of the frequency and intensity of symptoms and functional limitations the patient is experiencing. The goal is to achieve minimal or no chronic symptoms, including nocturnal awakenings; minimal or no need for acute rescue therapy, such as inhaled β_2-agonists; establishment of a normal lifestyle with no limitations on activities, including exercise; and normalization of pulmonary function. In 1997 and 2002, the National Asthma Education and Prevention Program (NAEPP) sponsored by the National Institutes of Health published comprehensive guidelines that classify asthma severity as mild intermittent or mild, moderate, or severe persistent asthma on the basis of symptoms and pulmonary function findings. Patients with mild intermittent asthma experience symptoms once or twice weekly and have normal or near-normal spirometry and PEFRs. Patients with symptoms 3 days of the week or more are classified as having persistent asthma. The degree of the asthma (mild, moderate, severe) then depends

on daily symptoms, nighttime symptoms, frequency of exacerbations, and peak flow rates and spirometry readings. With the release of new information and the development of new therapies, an update of the NAEPP guidelines was released to the public for comment in February 2007, and the completed update was released in late 2007. One significant new concept is differentiating asthma "severity" from "control" and the incorporation of these areas as they relate to risk and impairment. Severity assessment is performed to initiate therapy, and control assessment is performed to adjust therapy. Separating the two concepts dispels the common misperception that well-controlled asthma is synonymous with mild asthma and poorly controlled asthma is synonymous with severe asthma. The classification of asthma according to severity for children ages 0–4, children ages 5–12, and for those older than 12 years according to the new guideline is shown in Tables 6.7, 6.8, and 6.9. Characterization of the severity is critical for outlining the initial treatment plan (see below). This is particularly important when separating patients with mild intermittent asthma from those with mild persistent asthma. For mild persistent asthma, a daily antiinflammatory medication is recommended, whereas mild intermittent asthma requires primarily a short-acting β-agonist to be used as needed.

Future risk is also critical in defining asthma severity and, thus, in outlining an overall management plan. Future risk considers the likelihood of future asthma exacerbations. This is important because exacerbations account for loss of time at work or school, decreased quality of life, and much of the cost of asthma care. The other primary future risk involved in asthma is the progressive loss of pulmonary function. Contrary to previous belief, asthma is not always a totally reversible process. Severe and irreversible airflow obstruction, accelerated loss of pulmonary function, and remodeling of all the tissue elements of the airway wall can be found in chronic "never smoker" asthma patients.

Of the future risks, the one that has been best assessed is asthma exacerbations. The strongest predictor of this risk is the history of previous exacerbations that resulted in emergency department visits, hospitalizations, or intubations. Also, assessment of the current severity with regard to increased day and nighttime symptoms, functional impairment, and frequent use of rescue therapy indicates an increased risk of exacerbations in the future. However, some patients with minimal symptoms for long periods can be prone to sudden and severe attacks. Therefore, a patient who currently has minimal symptoms but a past history of severe exacerbations would be considered to have a more severe form of asthma than a patient without a history of severe exacerbations.

Identifying possible markers for risk of exacerbations has been studied intensely. A decreased FEV_1 has been shown to be related to an increased risk of exacerbations. Measurement of bronchial reactivity, for example, to methacholine, has also been shown to be predictive of exacerbations. Patients receiving treatment with inhaled corticosteroids dosed to reduce bronchial reactivity were found to have fewer asthma exacerbations than those treated regularly. Markers of airway inflammation such as sputum eosinophils and exhaled nitric oxide have also been measured and used as the primary parameter for changing dosage of inhaled corticosteroids. Treatment in this fashion has shown a decrease in asthma exacerbations.

Table 6.7 Classifying asthma severity in children ages 0–4 years[a]

	Classification of asthma severity (ages 0–4 years)[b]			
		Persistent		
Components of severity	Intermittent	Mild	Moderate	Severe
Impairment				
Symptoms	≤2 days per week	>2 days per week but <1 time per day	Daily	Throughout the day
Nighttime awakenings	0	1–2 times per month	3–4 times per month	>1 time per week
Risk				
Exacerbations (requiring oral systemic corticosteroids)	0–1 per year	2–3 per year	4–5 per year	>5 per year
	Frequency and severity may fluctuate over time			
	Exacerbations of any severity may occur in patients in any severity category			
Recommended step for initiating treatment	Step 1	Step 2	Step 3	Step 3
				and consider short course of oral systemic corticosteroids
	In 2–4 weeks, evaluate level of asthma control that is achieved, and adjust treatment accordingly			

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

[a] Assessing severity and initiating therapy in children who are not currently taking long-term-control medication

[b] Level of severity is determined by both impairment and risk

Table 6.8 Classifying asthma severity and initiating treatment in children ages 5–11 years

	Classification of asthma severity (ages 5–11 years)			
		Persistent		
Components of severity	Intermittent	Mild	Moderate	Severe
Impairment				
Symptoms	≤2 days per week	>2 days per week but not daily	Daily	Throughout the day
Nighttime awakenings	≤2 days per month	3–4 per month	>1 per week but not nightly	Often 7 per week
Short-acting β_2-agonist use for symptom control (not prevention of exercise-induced bronchospasm)	≤2 days per week	>2 days per week but not daily	Daily	Several times daily
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal FEV_1 between exacerbations			
	FEV_1 > 80% predicted	FEV_1 > 80% predicted	FEV_1 = 60–80% predicted	FEV_1 < 60% predicted
	FEV_1/FVC > 85%	FEV_1/FVC > 80%	FEV_1/FVC = 75–80%	FEV_1/FVC < 75%
Risk				
Exacerbations (requiring oral corticosteroids)	0–1 per year	≥2 per year ⟶ Frequency and severity may fluctuate over time for patients in any severity category Relative annual risk of exacerbations may be related to FEV_1		
Recommended step for initiating treatment	Step 1	Step 2	Step 3 medium-dose ICS option and consider short course of systemic oral corticosteroids	Step 3 medium-dose ICS option or Step 4 and consider short course of systemic oral corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust treatment accordingly		

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

FEV_1 forced expiratory volume in 1s; *FVC* forced vital capacity; *ICS* inhaled corticosteroid

Table 6.9 Classifying asthma severity and initiating treatment in adults and youths age ≥12 years

Components of severity		Classification of asthma severity (Age ≥12 years)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days per week	>2 days per week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2 per month	3–4 per month	>1 per week but not nightly	Often 7 per week
Normal FEV_1/FVC: 8–19 years 85% 20–39 years 80% 40–59 years 75% 60–80 years 70%	Short-acting β_2-agonist use for symptom control (not prevention of exercise-induced bronchospasm)	≤2 days per week	>2 days per week but not >1 per day	Daily	Several times daily
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1 > 80% predicted	FEV_1 > 80% predicted	FEV_1 > 60 but <80% predicted	FEV_1 < 60% predicted
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced > 5%
Risk					
Exacerbations (requiring oral corticosteroids)		0–1 per year	≥ 2 per year →		
			Frequency and severity may fluctuate over time for patients in any severity category		
			Relative annual risk of exacerbations may be related to FEV_1		
Recommended step for initiating treatment		Step 1	Step 2	Step 3 and consider short course of systemic oral corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust treatment accordingly			

Modified from the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

FEV_1 forced expiratory volume in 1s; *FVC* forced vital capacity

However, the effect of inhaled corticosteroids dosed by various means to prevent the progressive loss of pulmonary function is not clear. Currently, no prospective study has shown that early treatment with an inhaled corticosteroid, despite preventing exacerbations, prevents the progression of asthma to a more severe form. Possibly, the ultimate answer to the question, "do inhaled corticosteroids alter the natural course of asthma?" will not be answered. Despite this lack of clarity, it is imperative to prescribe the most effective treatment and to prescribe it early. Recently, O'Byrne et al. have shown that daily low-dose anti-inflammatory treatment in patients with recent onset of persistent asthma decreased the loss of lung function over time, corroborating the earlier work of Agertoft and Pederson and Haahtela. Perhaps markers of inflammation or novel markers of remodeling will be helpful in the future to further assess this risk and, thus, help define the severity of the disease.

Clearly, the patient's current symptoms are not the only measurement of severity. Simple methods for assessing current impairment are available. Future risk, history of exacerbations, spirometry, and the amount of medication required to control the symptoms also contribute significantly. These areas need to be addressed during the initial evaluation. Because the severity of asthma fluctuates over time, repeated assessments are required. To summarize, the following information should be obtained on the initial evaluation. Positive answers on the risk assessment portion point to increased severity:

1. Current impairment
   - Symptoms
   - Nighttime awakenings
   - Need for rescue medication
   - Number of work/school days missed
   - Ability to participate in desired activities
   - Lung function: spirometry, peak flow
2. Risk Assessment
   - Amount of severe airflow obstruction on spirometry
   - Amount of persistent airflow obstruction despite maximal pharmacotherapy
   - History of two or more emergency department visits or hospitalizations for asthma in the past year
   - History of intubation or intensive care unit admission for asthma

6.6 Evaluation of Factors Contributing to Asthma Severity

Factors that exacerbate asthma should be identified and managed in all asthma patients, particularly in those with moderate or severe persistent asthma. Management of these factors results in better asthma control and the need for less pharmacotherapy to treat the asthma. In this chapter, the exacerbators of asthma are divided into

Table 6.10 Common exacerbators of and contributors to asthma

Common exacerbators of an acute asthma attack
Infections
Exercise
Vocal cord dysfunction
Allergens
Medications
Common contributors to chronic asthma (airsmog)[a]
*A*llergens
*I*rritants/pollutants
*R*hinitis/sinusitis
*S*moking
*M*edications
*O*ccupational/obstructive sleep apnea
*G*astroesophageal reflux

[a]These conditions should be assessed for and optimally managed in all patients with asthma

two groups: those that typically initiate an acute attack and those that contribute to ongoing chronic asthma. Although these groups overlap, the acute instigators most often include infections, allergens, exercise, vocal cord dysfunction, and medications. The chronic contributors can be remembered with the mnemonic "airsmog" (*a*llergens, *i*rritants/pollutants, *r*hinitis/sinusitis, *s*moking, *m*edications, *o*ccupational exposures, *o*bstructive sleep apnea, and *g*astroesophageal reflux) (Table 6.10).

6.6.1 Allergens

Allergen exposure can affect asthma in two critical ways: as a common precipitant of asthmatic symptoms and the inception of asthma through chronic airway inflammation. The airborne allergens (dust mites, pets, molds, trees, grasses, and weeds), as opposed to food allergens, contribute importantly to chronic asthma. The formation of IgE antibody to the airborne allergens does not usually occur until age 2–3 years. Therefore, aeroallergen-induced asthma is uncommon until that time. Allergens have the highest prevalence of involvement in asthma during later childhood and adolescence and peaks in the second decade of life. Airborne allergen-induced asthma can occur throughout adulthood; however, the prevalence decreases with increasing age.

Indoor allergens, particularly cockroach, cat, and dust mite, clearly have a role in asthma provocation, and they appear to have a role in asthma inception. Decreasing the constant exposure to these allergens through environmental modifications diminishes the primary trigger for the chronic allergic and inflammatory response. This may result in marked relief from the symptoms of asthma and rhinitis and a reduction in airway hyperreactivity over time.

The same aeroallergens important in allergic rhinitis also contribute to asthma exacerbations. One aeroallergen in particular that appears to trigger severe asthma exacerbations is *Alternaria alternata*. *Alternaria* has been implicated as a risk factor for sudden respiratory arrest in adolescents and young adults with asthma. Tree, grass, and weed pollens can also trigger a seasonal asthma pattern. This is often associated with upper respiratory tract symptoms. Although food allergies can trigger bronchospasm, it is quite unusual for food to trigger bronchospasm without other concomitant symptoms. Typically, skin and gastrointestinal manifestations are present. This occurs within 1 hours after eating the food allergen.

6.6.2 Infections

Like allergens, infections can affect asthma by being a precipitant of an acute attack or having a role in asthma inception. Viruses, *Chlamydia* spp., and *Mycoplasma* spp. have been implicated in the pathogenesis of asthma. Viruses, particularly RSV, have been associated with the inception of the asthma phenotype. Because this virus is ubiquitous (nearly 100% of children are infected by age 2 years), additional genetic, environmental, sequential, or developmental factors must contribute to its linkage with asthma. Children who have persistent symptoms of asthma or develop asthma after an RSV infection usually have other risk factors such as a maternal history of asthma and increased IgE levels. Precisely how RSV infections pathogenically induce asthma has not been established. *Chlamydia* and *Mycoplasma* spp. are atypical bacteria associated with ciliary dysfunction and epithelial damage in airway cells. Their presence in the airway has been associated with chronic asthma. Although their presence does not provide a causal link to asthma, macrolide treatment of patients with chronic asthma, both with and without the presence of the bacteria, produced improvement only in those with the bacteria. Larger definitive studies are needed to determine whether antibiotic treatment in patients with chronic asthma and known infection with *Chlamydia* or *Mycoplasma* spp. alters the course of the disease.

In patients with established asthma, viral upper respiratory tract infections are important in producing acute exacerbations of airway obstruction. The increases in airway hyperreactivity that follow a respiratory viral infection usually occur within 48 hours after the cold symptoms and persist for at least 2 weeks. Possible mechanisms include direct epithelial damage, the production of virus-specific IgE antibodies, increased production of IgE antibodies specific for other antigens, and upregulation of inflammatory mediator release. Rhinovirus, the common cold virus, is the most frequent cause of exacerbations, but other viruses, including metapneumovirus, parainfluenza, RSV, influenza, and coronavirus, have also been implicated. The symptoms can include marked wheezing and shortness of breath or a prolonged cough, typically spasmodic, that is worse at night. Viral upper respiratory tract infections are the most common provocateur of asthma in children, particularly during the winter months. These asthma flares are at times resistant to

standard therapy of inhaled β-agonist and inhaled corticosteroids. Oral corticosteroids may be required and have been shown to decrease hospitalizations in viral-induced asthma exacerbations.

Mycoplasma pneumoniae and *Chlamydia pneumoniae* are commonly associated with severe exacerbations. These microbes can be causative in up to 20% of children with asthma exacerbations who require hospitalization.

However, infections may have the potential to actually prevent the development of respiratory tract diseases, including asthma. The hygiene hypothesis purports that an increased number of infections, particularly during early childhood, may decrease the development of allergic sensitization or asthma. This is based on the findings that lower rates of asthma and allergic diseases have been found in children who are raised on farms, attend day care in the first 6 months of life, or have older siblings. It is thought that the higher exposure to infectious agents or endotoxins skews the immune system toward a vigorous Th1 system and a suppressed Th2 response to allergens. This hypothesis continues to be studied.

6.6.3 Exercise

Exercise is a common precipitant of asthma. The symptoms of exercise-induced bronchospasm can include wheezing, coughing, shortness of breath, and, in children, chest pain or discomfort. The onset of symptoms is typically 10–15 min after exercise begins or 5–15 min after exercise is completed. Sports most commonly associated with precipitating the symptoms of asthma are aerobic in nature, such as running or cross-country skiing, as compared with those that do not require a high ventilatory rate, such as weight lifting or diving. The symptoms are most intense for 5–10 min and usually resolve within 15–30 minutes. The degree of bronchoconstriction is rarely severe enough to be life threatening. If severe, there is often a component of poorly controlled underlying disease or concomitant allergen or irritant exposure.

Exercise-induced bronchospasm can be confirmed with spirometry by showing more than a 15% decrease in FEV_1 after exercise. In addition, peak flow readings can be performed before and after exercise to document decreased airflow. The diagnosis can also be suspected with alleviation of symptoms with use of a prophylactic medication, such as a β_2-agonist before exercise. This phenomenon is discussed in detail below in Sect. 6.7.7. Special Groups.

6.6.4 Vocal Cord Dysfunction

Vocal cord dysfunction, particularly diagnosis and management, is discussed above in the section on Differential Diagnosis. Although vocal cord dysfunction can present as an asthma masquerader, it is common for asthma and vocal cord

dysfunction to coexist. As many as 50% of patients with a diagnosis of vocal cord dysfunction also have airway hyperresponsiveness. It is estimated that 10–20% of asthma patients may have some component of vocal cord dysfunction. Of interest, other comorbidities for asthma are also associated with vocal cord dysfunction, including rhinitis and GERD. Rhinitis and GERD should be treated to minimize their contribution to irritation of the vocal cords. Coexisting vocal cord dysfunction should be considered in patients with known asthma that has become difficult to control, particularly if the clinical pattern features sudden onset and resolution of symptoms, a minimal response to increased asthma therapy, or symptoms localized to the vocal cords.

6.6.5 Irritants and Pollutants

Persons with asthma are more sensitive than those without asthma to air pollutants and irritants such as environmental cigarette smoke, traffic emissions, and photochemical smog components. Increased pollution levels, including particulates (<10 μm), sulfur dioxide, and nitric oxide, increase asthma symptoms. Ozone exposure and proximity to major roadways are associated with an increased incidence of the disease. Recently, complex organic molecules from diesel exhaust particles have been associated with worsening asthma and may also act, as other pollutants do, as allergic adjuvants through airway inflammation, which enhance the severity of immune-mediated lung disease.

Of the irritants and pollutants, cigarette smoke has been the most studied because it is likely the most important indoor pollutant that is harmful to human health. Tobacco smoke contains more than 4,000 chemical substances, many of which are carcinogenic, mutagenic, irritating, or toxic. Postnatal exposure to environmental tobacco smoke shows a causal link with the development of asthma in childhood. This is dose dependent, with the strongest effect detected in the youngest children. There is also evidence that environmental tobacco smoke exposure is related to an increased risk of adult-onset asthma, with the risk often most strongly related to workplace environmental tobacco smoke exposure as opposed to home exposure. There is evidence of a dose–response relationship. Although extensive evidence shows that ambient air pollution exacerbates existing asthma, the link with the development of asthma is less established, but it has been suggested. There are approximately 300 occupational asthmagens. Because exposures in the industrial workplace are often identifiable, the offending agent can usually be isolated. Occupational asthma has been prevented successfully through the identification and reduction of workplace exposure to enzymes in the detergent industry and the use of powdered natural rubber latex gloves in the health care industry.

It is important to inquire about the exposure to pollutants and irritants in both the home and work environment, particularly environmental cigarette smoke. Parents should be educated and encouraged not to smoke, or to quit if they are already smokers, to reduce childhood exposure. Once an asthmagen is recognized

in the workplace, issues with respect to exposure, dose–response, and avoidance need to be addressed. Additional studies linking irritants and pollutants with asthma are needed to help determine the most effective way for individuals to be protected.

6.6.6 Rhinosinusitis (United Airway Hypothesis)

The link between upper airway and lower airway disease has long been of interest to clinicians. Recently, epidemiologic, immunologic, and therapeutic links have been established among rhinitis, sinusitis, and asthma. This has led to the concept of *united airways disease*, or *allergic rhinobronchitis*. The existence of the "united airways" was first deduced from epidemiologic studies. Several cross-sectional studies have shown the association between rhinitis and asthma: up to 50% of patients with rhinitis have asthma, and rhinitis occurs in up to 80% of patients with asthma. Longitudinal studies have confirmed this link and have shown that rhinitis usually precedes and is a risk factor for asthma, even independently of atopic status.

From the physiologic and immunologic standpoint, several studies have shown that the upper and lower respiratory airways behave as a single entity. It has been shown that a high percentage of patients with perennial allergic rhinitis alone without a clinical diagnosis of asthma have bronchial hyperreactivity and obstructive spirometric impairments. A direct correlation between the degree of nonspecific bronchial responsiveness (methacholine challenge) and the degree of nonspecific nasal responsiveness (histamine challenge) has been shown in patients with asthma and rhinitis. Bronchial mucosal inflammation mirrors changes seen in the nose with allergen challenge. These changes are bidirectional, whereby nasal challenge results in both nose and bronchial inflammation, and bronchial challenge also results in both nose and bronchial inflammation. This mechanism for the "cross-talk" between the nose and the lungs has not been clarified completely, but it has been hypothesized that these systemic events are mediated by a neurohumoral mechanism and the effect of cytokine release on the bone marrow.

The link between rhinitis and asthma has also been shown by the effect of medications on the nose and lung. Treatment of rhinitis with intranasal corticosteroids has a favorable effect on bronchial symptoms. Other studies have shown that correct treatment of rhinitis significantly reduces the rate of hospital admissions and emergency department visits for asthma exacerbation. Antihistamines have been shown to reduce asthma symptoms and bronchodilator use in patients with allergic rhinitis and asthma. Allergen immunotherapy has been shown to decrease the symptoms of asthma and to help prevent the development of asthma in adults and children who have seasonal or perennial rhinitis.

All asthma patients should be assessed carefully for rhinitis by environmental history, symptoms, and physical examination. Appropriate treatment of the rhinitis allows for better management of the asthma and may also favorably alter its course.

6.6.7 Smoking

In developed countries, approximately 25% of adults with asthma are current smokers and another 25% are former smokers. Asthma patients who smoke have worse symptom control, greater need for rescue medication, accelerated decrease in lung function, increased mortality rate at 6 years after a near-fatal asthma attack, alterations in the airway inflammatory cell milieu, and a decreased therapeutic response to corticosteroids.

There are numerous inflammatory changes in asthma patients who smoke compared with asthma patients who do not smoke. Of interest, the number of eosinophils is increased in sputum samples of asthma patients who smoke. In smokers, proinflammatory cytokines are increased, including IL-4, IL-8 and TNF-α, and anti-inflammatory cytokines, IL-10 and IL-18, are decreased. Exhaled nitric oxide levels are decreased in steroid-naïve smokers with mild asthma compared with those who are nonsmokers. Cigarette smoke may decrease exhaled nitric oxide by inhibiting inducible nitric oxide synthetase. In normal smokers, exhaled nitric oxide levels then increase after smoking cessation. Currently, it is not clear which of these effects is most important in causing asthma difficulty.

Cigarette smoking and asthma combine to accelerate lung function decline to a greater degree than either variable alone. The Copenhagen City Heart Study, performed over a 15-year period, found that the average annual decline in FEV_1 for asthma patients who were nonsmokers was 33 mL, whereas for asthma patients who smoked, it was 58 mL for males 40–59 years old. Perhaps most important for the long term is the reduced effectiveness of corticosteroids in asthma patients who smoke. In studies ranging from 3 weeks to 9 months, asthma patients who did not smoke had a significant increase in morning peak expiratory flow, mean FEV_1, and the mean provocative concentration required to elicit a 20% decrease in FEV_1 with methacholine compared with placebo, whereas no change was noted in asthma patients who smoked. Even oral prednisolone failed to provide a significant improvement in FEV_1, morning PEF, and asthma control score in asthma patients who smoked, whereas these parameters were improved in asthma patients who did not smoke.

The best treatment for smokers with asthma is smoking cessation. Former smokers, as opposed to current smokers, show improvement in morning PEF values after oral corticosteroid treatment. Smoking cessation in nonasthma subjects reduces respiratory symptoms and the frequency of respiratory infections. Over time, the rate of decline of lung function returns to that of never smokers. Few data are available of direct study of asthma patients who smoked but have quit. Nicotine replacement therapy or a medication such as bupropion in the setting of a structured smoking cessation program is most likely to be effective in smoking cessation. Smokers with asthma who are unable to stop may require alternative treatment or treatment in addition to corticosteroids. Cigarette smoke induces the CYP family of the cytochrome P-450 enzymes, which increases the clearance of theophylline. There is almost a twofold decrease in the half-life in smokers as compared with nonsmokers. Little information is available about the effects of other antiasthma drugs such as leukotriene antagonists or β_2-agonists. Theoretically, leukotriene antagonists may

be of benefit for asthma patients who smoke because cigarette smoking induces higher levels of urinary leukotriene E_4.

6.6.8 Medications

Medications have the potential to exacerbate asthma. The most common medications implicated in exacerbating asthma are β-adrenergic blockers (β-blockers) and aspirin and other NSAIDs.

β-Blockers are useful in the treatment of numerous disease states, including hypertension, congestive heart failure, coronary artery disease, glaucoma, and migraine headache. They can be divided into multiple groupings, but the most practical classification is selective and nonselective β-blockers. Selective β-blockers are β_1 selective or cardioselective, preferentially blocking β_1-receptors in the heart. Common selective β_1-blockers include atenolol (Tenormin), metoprolol (Toprol), betaxolol (Kerlone), and bisoprolol (Zebeta). At higher doses, however, β_2 blockade also begins to occur and becomes more pronounced as the dosage is increased. Nonselective β-blockers block β_1 receptors in the heart as well as the β_2 receptors on bronchial smooth muscle cells. The commonly used nonselective β-agonists include propranolol (Inderal), sotalol (Betapace), timolol (Blocadren) and nadolol (Corgard). Timolol and betaxolol (Betoptic) are topical eye drop β-blockers used to treat glaucoma. Even though they are used topically, they have been reported to cause severe exacerbations of asthma. Patients often do not know the name of the eye drops they use; β-blockers usually have a yellow or blue cap on the bottle. Generally, nonselective β-adrenergic antagonists are more likely to induce bronchospasm in patients with known asthma than the selective β_1-blockers. However, severe exacerbations of asthma have been reported in both groups, with the exacerbations occurring in patients with mild, moderate, or severe asthma. The actual incidence of a severe asthma exacerbation with the use of a cardioselective or nonselective β-agonist is unknown. Certainly, some asthma patients are able to tolerate the use of cardioselective β-blockers without difficulty. According to a recent systematic review, a single dose of a cardioselective β-blocker produced a 7.46% reduction in FEV_1, whereas treatment for 3–28 days produced no change in FEV_1.

In determining the use of a β-blocker in treating an asthma patient, the benefit-to-risk ratio requires review. For strictly migraine prophylaxis, hypertension, or glaucoma, other medication options should likely be considered for asthma patients. For patients with severe angina, coronary artery disease, or congestive heart failure, for which β-blockers have been shown to decrease morbidity and mortality, a cardioselective β-blocker can be considered, particularly for a patient with mild, well-controlled asthma. However, there is no test or clinical pattern that predicts an asthma flare with the use of a β-blocker. If a cardioselective β-blocker is to be used, the patient should be counseled on the possibility of an asthma exacerbation and appropriate measures should be instituted to manage a possible exacerbation. Nonselective β-blockers should be avoided.

Aspirin and other NSAIDs can induce rhinorrhea and bronchospasm in a subset of patients with underlying rhinosinusitis, nasal polyps, and asthma. Various terms have been used to describe this phenomenon, including aspirin intolerance, aspirin sensitivity, aspirin-induced asthma, and aspirin idiosyncrasy. Currently, it is called *aspirin-exacerbating respiratory disease* (AERD). Aspirin and other NSAIDs that inhibit COX-1 cause this reaction. Because these reactions are dose dependent, small doses may not induce the reaction, but large doses may. Although aspirin and NSAID exposure trigger a respiratory reaction, sometimes very severe, the underlying asthma and rhinosinusitis continue in the absence of exposure to aspirin or NSAIDs. Except for sensitivity to aspirin and NSAIDs, these patients cannot be differentiated from other patients with asthma and sinus disease. The prevalence of aspirin and NSAID sensitivity among asthma patients with associated rhinosinusitis and nasal polyps is approximately 30–40%. In asthma patients without nasal polyposis, aspirin and NSAID sensitivity is approximately 10%. There is no skin test or in vitro test to identify these patients because the reaction is not IgE mediated. The reaction is mediated by COX-1 inhibition, which results in a decrease in the protective prostaglandin E_2 (PGE_2) and an increase in the production of inflammatory leukotrienes and prostaglandins. All the NSAIDs that inhibit COX-1 cross-react with aspirin, inducing the respiratory reaction. These include the most commonly used NSAIDs such as indomethacin, ibuprofen, and naproxen. Weak inhibitors of COX-1 such as acetaminophen and salsalate can produce respiratory reactions in patients with AERD, but this typically occurs only with large doses and only in a small proportion of these patients. Selective COX-2 inhibitors such as celecoxib and rofecoxib do not appear to cross-react with aspirin and appear to be safe for patients with AERD.

For patients with AERD for whom aspirin or NSAID therapy is critical, such as patients with coronary artery disease who need aspirin prophylaxis, patients with severe arthritis unresponsive to other treatments, or patients with AERD with intractable nasal polyp formation and rhinosinusitis, aspirin can be given through a supervised, graded, desensitization protocol. This protocol is outlined in the chapter on rhinosinusitis. The pathogenesis of aspirin desensitization is largely unknown, but it results in aspirin and NSAID tolerance when continued daily and, over time, down-regulation of leukotriene production.

6.6.9 Occupational

Occupational asthma, an often overlooked cause for asthma, is reviewed at the end of this chapter in the section Special Groups.

6.6.10 Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by intermittent partial or total (or both) airway occlusion during sleep and is associated with serious health consequences, including insulin resistance, hypertension, cardiovascular diseases, and worsening

of asthma control. It is estimated that 20% of adults have mild obstructive sleep apnea, and in nearly 7%, it is moderate to severe. The majority of patients, 50–90%, with nighttime asthma symptoms or severe asthma, have obstructive sleep apnea. Treatment with continuous positive airway pressure significantly improves nighttime symptom control but little change in baseline spirometry.

6.6.11 Gastroesophageal Reflux Disease

The true incidence of GERD in asthma and as a causative factor in asthma severity has not been fully established. It has been estimated that 45–65% of asthma patients have GERD. Epidemiologic evidence has established an association between GERD and asthma, and some evidence supports a causative role. The proposed mechanisms by which GERD may affect asthma include microaspiration of gastric refluxate or a vagally mediated esophagobronchial reflex mechanism with subsequent bronchospasm. Although no unique clinical identifiers establish whether GERD is contributing to asthma, it should be considered in difficult-to-control asthma, nonallergic asthma, asthma with moderate to severe GERD, and nocturnal asthma. Clinical suspicion is a critical component in the diagnosis of GERD-induced asthma. In patients with a history suggestive of the condition, an empiric trial of a high-dose proton pump inhibitor for 3–6 months is a reasonable strategy. Appreciable changes in spirometry in the short term are not typically seen. Esophageal pH monitoring should be performed in asthma patients with GERD symptoms that do not respond to an empiric trial of proton pump inhibitors and in patients in whom asymptomatic GERD (silent GERD) may have a role. Silent GERD may be present in up to one-third of asthma patients. Surgical therapy for GERD-triggered asthma may hold promise. Thus far, data consist mainly of uncontrolled studies. Additional large randomized studies in subgroups of patients with asthma treated with proton pump inhibitors or surgical intervention will help clarify the role of GERD treatment in asthma.

6.7 Treatment

The overall treatment of asthma is multifactorial, with the general goal of disease control. The key components to obtaining asthma control are patient education, evaluation, and management of all the asthma-exacerbating factors and the use of appropriate pharmacotherapy. All these components – not just pharmacotherapy – are integral to patient management.

6.7.1 Patient Education

In asthma as in other chronic diseases, education serves as the foundation to be built upon to obtain disease control. Key points that should be emphasized in asthma education include understanding (1) the basics of asthma, (2) the rationale for the

use of the different medications, (3) the importance of compliance with the medications, (4) the correct use of the various inhalers and peak flow meters, (5) environmental modification of triggers of asthma, (6) recognizing and responding to asthma symptoms, and (7) knowing when to call a physician or to seek emergency department care. These seem to be self-evident; however, if they are not addressed with the patient repeatedly, as with other chronic diseases, compliance becomes poor, resulting in poor disease control.

Asthma education is not a one-time experience. To be effective, asthma education needs to be an ongoing experience that builds over time. This requires time and dedication by the health care team. Communication with the patient is needed to establish treatment goals that result in the patient living a normal lifestyle with minimal to no symptoms and reduce the risk of asthma exacerbations.

6.7.2 Pharmacologic Therapy

Medications for asthma can be divided into two major categories: medications for as-needed use, termed *quick-relief medications*, and medications for daily use, termed *long-term control* or *maintenance medications*. All patients with asthma should have a short-acting bronchodilator for as-needed use. All patients with persistent asthma, whether mild, moderate, or severe, should be using at least one long-term daily asthma controller medication with anti-inflammatory properties. Even though long-acting β-agonists such as salmeterol and formoterol are considered long-term control medications, they should only be prescribed in conjunction with a daily anti-inflammatory agent. The usual dosages for long-term control medications are listed in Table 6.11 and the dosages for the quick-relief medications, in Table 6.12. Although asthma medications are available in multiple forms, they are administered primarily by the inhalation route.

6.7.2.1 Inhalation Devices

The inhalation of therapeutic aerosols is an effective method of drug delivery in the management of asthma. Three principal types of devices are used to generate aerosols: metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. All three use different mechanisms to generate aerosols, and the differences among them are important for discerning the most appropriate device for drug delivery, depending on characteristics of the patient and the therapeutic agent used.

Metered Dose Inhaler

Most inhaled medications currently used for asthma are available as MDIs. MDI technology has used primarily chlorofluorocarbons as propellants. Chlorofluorocarbons

Table 6.11 Usual dosages for long-term control medications

Medication	Dosage form	Adult dose	Child dose
Systemic corticosteroids			
Methyl prednisolone	2-, 4-, 8-, 16-, 32-mg tablets	7.5–60 mg per day in single dose in am or qod as needed for control	0.25–2 mg kg^{-1} daily in single dose in am or qod as needed for control
Prednisolone	5-mg tablets, 5 mg per 5 mL, 15 mg per 5 mL	Short-course "burst" to achieve control: 40–60 mg per day as single or 2 divided doses for 3–10 days	Short-course "burst": 1–2 mg kg^{-1} per day, maximum 60mg per day for 3–10 days
Prednisone	1-, 2.5-, 5-, 10-, 20-, 50-mg tablets, 5 mg mL^{-1}, 5 mg per 5 mL		
Long-acting inhaled β_2 agonists[a]			
Salmeterol	MDI 21 μg per puff	2 puffs q12h	1–2 puffs q12h
	DPI 50 μg per blister	1 blister q12h	1 blister q12h
Formoterol	DPI 12 μg per single-use capsule	1 capsule q12h	1 capsule q12h
Combined medication			
Fluticasone-salmeterol	DPI 100, 250, or 500 μg per 50 μg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma
	MDI 45, 115, or 230 μg per 21 μg	2 puffs bid; dose depends on severity of asthma	2 puffs bid; dose depends on severity of asthma
Budesonide-formoterol	MDI 80 or 160 μg per 4.5 μg	2 puffs bid; dose depends on severity of asthma	2 puffs bid; dose depends on severity of asthma
Cromolyn and nedocromil			
Cromolyn	MDI 0.8 mg per puff	2–4 puffs tid–qid	1–2 puffs tid–qid
	Nebulizer 20 mg per ampule	1 ampule tid–qid	1 ampule tid–qid
Nedocromil	MDI 1.75 mg per puff	2–4 puffs bid–qid	1–2 puffs bid–qid
Leukotriene modifiers			
Montelukast	4- or 5-mg chewable tablet 4-mg granule packets 10-mg tablet	10 mg qhs	4 mg qhs (1–5 years) 5 mg qhs (6–14 years) 10 mg qhs (>14 years)

(Continued)

Table 6.11 (Continued)

Medication	Dosage form	Adult dose	Child dose
Zafirlukast[b]	10- or 20-mg tablet	40 mg daily (20-mg tablet bid)	20 mg daily (7–11 years) (10-mg tablet bid)
Zileuton[b]	300- or 600-mg tablet	2,400 mg daily (give tablets qid)	
Methylxanthines[c]			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg kg^{-1} per day; usual max 800 mg per day	Starting dose 10 mg kg^{-1} per day; usual max: <1 year of age: 0.2 (age in weeks) + 5 = mg kg^{-1} per day ≥1 year of age: 16 mg kg^{-1} per day

From the National Asthma Education and Prevention Program, Expert Panel Report (2002) Guidelines for the management and diagnosis of asthma – update on selected topics 2002. NIH Publication No. 02-5075. Bethesda, MD: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute and from the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

bid twice daily; *DPI* dry powder inhaler; *MDI* metered-dose inhaler; *max* maximum; *q12h* every 12h; *qhs* at bedtime; *qid* 4 times daily; *qod* every other day; *tid* 3 times daily

[a]Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids

[b]Monitor liver function tests

[c]Serum monitoring is important (serum concentration of 5–15 μg mL^{-1} at steady state)

Table 6.12 Usual dosages for quick-relief medications

Medication	Dosage form	Adult/adolescent dose	Child dose	Comments
Short-acting inhaled β_2-agonists				
	MDI			
Albuterol Albuterol HFA Pirbuterol Levalbuterol HFA	90 μg per puff 90 μg per puff 200 μg per puff 45 μg per puff	2 puffs q4h as needed and 15 min before exercise (applies to all four medications)	1–2 puffs q4h as needed and 15 min before exercise (applies to albuterol and levalbuterol for ages 5–11 years and albuterol for ages <5 years)	An increasing use or lack of expected effect indicates diminihed control of asthma; not generally recommended for daily long-term treatment Use for symptom relief >2 times weekly indicates need for additional therapy Differences in potency exist so that all products are essentially equipotent on a per-puff basis May double usual dose for significant exacerbations Nonselective agents (e.g., epinephrine, isoproterenol, metaproterenol) are not recommended
	DPI			
Albuterol Rotahaler	200 μg per capsule	1–2 capsules q4–6h as needed and before exercise	1 capsule q4–6h as needed and before exercise	
	Nebulizer solution			
Albuterol	5 mg mL^{-1} (0.5%) multi-dose vial 2.5 mg per 3 mL (0.83%) unit-dose vial 0.63 mg per 3 mL and 1.25 mg per 3 mL	1.25–5 mg (0.25–1 mL) in 2–3 mL of saline q4-6h 1 vial q4-6h	0.1–0.2 mg kg^{-1} (minimum 1.25 mg, max, 2.5 mg) in 2–3 mL 1/2–1 vial q4–6h	May mix with cromolyn or ipratropium nebulizer solutions or saline q4–6h May double dose for significant exacerbations
Levalbuterol	0.31 mg, 0.63 mg, or 1.25 mg per 3 mL	0.63–1.25 mg q6–8h	0.31–0.63 mg q6–8h (ages 5–11 years) 0.31–1.25 mg q4–6h (age <5 years)	

(Continued)

Table 6.12 (Continued)

Medication	Dosage form	Adult/adolescent dose	Child dose	Comments
Anticholinergics				
	MDI			
Ipratropium	18 μg per puff	2–3 puffs q6h	1–2 puffs q6h	Evidence is lacking for producing added benefit to β_2-agonists in long-term asthma therapy
Ipratropium with albuterol	18 μg per puff of ipratropium bromide and 90 μg per puff of albuterol	2–3 puffs q6h	…	
	Nebulizer solution			
Ipratropium	0.25 mg mL^{-1} (0.02%)	0.25–0.5 mg q6–8h	0.25 mg q6–8h	
Ipratropium with albuterol	0.5 mg per 3 mL ipratropium bromide and 2.5 mg per 3 mL albuterol	3 mL q4–6h	1.5 mL q4–6h	
Systemic corticosteroids Methylprednisolone	2-, 4-, 8-, 16-, 32-mg tablets	Short-course "burst"; 40–60 mg per day as single or 2 divided doses for 3–10 days	Short-course "burst"; 1–2 mg kg^{-1} per day, maximum 60 mg per day, for 3–10 days	Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. Burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. Usually achieved in 3–10 days, may require longer treatment periods. No evidence that tapering the dose after improvement prevents relapse
Prednisolone	5-mg tablets, 5 mg per 5 mL, 15 mg per 5 mL			
Prednisone	1-, 2.5-, 5-, 10-, 20-, 25-, 50-mg tablets; 5 mg mL^{-1}, 15 mg per 5 mL solutions			

Modified from the National Asthma Education and Prevention Program, Expert Panel Report (2002) Guidelines for the management and diagnosis of asthma – update on selected topics 2002. NIH Publication No. 02-5075. Bethesda, MD: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute and the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

DPI dry powder inhaler; *HFA* hydroxyfluoroalkane; *max* maximum; *MDI* metered-dose inhaler; *q4h* every 4h; *q4–q6h* every 4–6h; *PEF* peak expiratory flow

constitute approximately 95% of the formulation released from an MDI. However, they have been found to deplete the stratospheric ozone, and, following adoption of the Montreal protocol, an international agreement has been placed to ban chlorofluorocarbons. The alternatives include MDIs with other propellants, such as hydrofluoroalkane and the DPIs. The U.S. Food and Drug Administration (FDA) approval process for new inhalers requires that the replacement products demonstrate comparability with the corresponding chlorofluorocarbon-containing inhalers so that clinicians and patients can anticipate similar effectiveness and safety with the new products. Currently, fluticasone, levalbuterol, and albuterol are available in hydrofluoroalkane formulations.

Spacers and valved holding chambers are accessory devices that reduce oropharyngeal deposition of the drug, enhance lung delivery, and minimize the importance of the hand–breath coordination. A spacer device is an open-ended tube that allows the MDI plume to slow down and the propellant to evaporate before inhalation. A valved holding chamber incorporates a one-way valve that traps the plume and allows the aerosol to be delivered from the chamber only during inspiration. A valved holding chamber can incorporate a mask for patients who are unable to use a mouthpiece because of age, poor coordination, or impaired mental status. The accessory devices should be washed with dishwashing detergent and allowed to air dry to remove residue from the medication and to eliminate static charge.

Dry Powder Inhaler

DPIs function by drawing air through a dose of powdered medication. This requires an inspiration at relatively high inspiratory flow rates. Larger carrier particles impact in the oropharynx, giving the patient the sensation of having inhaled the dose. However, this impaction is less than with an MDI, and patients may feel that they are not receiving any medication. DPIs are breath actuated; thus, coordination between manual inhaler actuation and inspiration is not required. However, because the magnitude and duration of the patient's inspiratory effort influence the aerosol generation from the DPI, these devices should be used cautiously in the very young, elderly, and those with neuromuscular weakness. Some DPIs require manual manipulation to load the dose, and this may be difficult for patients with limited dexterity. DPIs do not require the use of spacing devices.

Nebulization

Nebulization requires a pressurized gas supply that allows liquid atomization of the medication. Several factors contribute to the efficiency of the nebulization, including the respirable dose, nebulization time, dead volume, and patient interface. The respirable dose is a function of the total output of the nebulizer and the size of the particles produced. Droplet size should be 2–5 μm for airway deposition and 1–2 μm for parenchymal deposition. The nebulization time is an important determinant

of patient compliance in the outpatient setting. This is a function of the volume of drug to be delivered and the flow rate of the driving gas. The treatment is complete when the nebulizer begins sputtering. Although nebulizers typically are used intermittently, continuous nebulizations can be administered in the emergency department or during hospital treatment of acute asthma. The volume of the medication trapped inside the nebulizer is referred to as the dead volume of the device. This volume is typically in the range of 1–3 mL. Increasing the fill volume helps to decrease the proportion of the dose lost as dead volume. This maneuver increases nebulization time. Considering these factors, a nebulizer fill volume of 4–6 mL is generally recommended. During nebulization, the solution within the nebulizer becomes increasingly concentrated as water evaporates from the solution; therefore, per breath, more medication is delivered late in the course of treatment. Nebulized aerosols can be administered with a mouthpiece or face mask. Because significant facial and eye deposition can occur when a face mask is used, a mouth piece is usually favored. Generally, for home use, MDIs or DPIs are recommended, and nebulizations are reserved for severe acute exacerbations. For patients unable to tolerate MDIs or DPIs, a nebulizer is an option.

6.7.2.2 Inhaled Corticosteroids

Corticosteroids are the most potent and effective long-term control medications for asthma. Their anti-inflammatory properties include the suppression of airway eosinophil recruitment, the suppression of cytokine production, and the suppression of inflammatory mediator release. Their clinical effects include reduction in the severity of symptoms, improvement in PEFR and spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and possibly the prevention of airway remodeling. Inhaled corticosteroids should be considered a first-line treatment for patients with mild, moderate, or severe persistent asthma. As a single agent, inhaled corticosteroids are more effective than theophylline, salmeterol, nedocromil, and leukotriene modifiers in the management of asthma.

The choice of a specific inhaled corticosteroid depends on the potency of the corticosteroid required and the delivery device. There is a significant difference in the potency among the various inhaled corticosteroids (Table 6.13). Realization of these differences is important in initiating or adjusting therapy. For example, for a patient with moderate-to-severe persistent asthma, a more potent corticosteroid such as budesonide or fluticasone (220 μg) would be used instead of triamcinolone or beclomethasone in an effort to minimize puffs. In contrast, for a patient with mild persistent asthma, lower potency corticosteroids could be prescribed, such as fluticasone (44 μg), triamcinolone, or beclomethasone. In principle, each patient should receive the lowest effective dose required to achieve good asthma control. On the basis of an evaluation of symptoms, supplemental bronchodilator use, exacerbations, peak flow, spirometry, and possibly sputum eosinophils and exhaled nitric oxide, the dose of inhaled corticosteroid can be adjusted so that the lowest effective dose is used.

Table 6.13 Estimated comparative daily dosages for inhaled corticosteroids

	Low daily dose		Medium daily dose		High daily dose	
Drug	Adult	Child[a]	Adult	Child[a]	Adult	Child[a]
Beclomethasone CFC 42 or 84 μg per puff	168–504 μg	84–336 μg	504–840 μg	336–672 μg	>840 μg	>672 μg
Beclomethasone HFA 40 or 80 μg per puff	80–240 μg	80–160 μg	240–480 μg	160–320 μg	>480 μg	>320 μg
Budesonide DPI 90, 180, or 200 μg per inhalation	180–600 μg	180–400 μg	600–1,200 μg	400–800 μg	>1,200 μg	>800 μg
Inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Flunisolide 250 μg per puff	500–1,000 μg	500–750 μg	1,000–2,000 μg	1,000–1,250 μg	>2,000 μg	>1,250 μg
Flunisolide HFA 80 μg per puff	320 μg	160 μg	320 –640 μg	320 μg	>640 μg	≥640 μg
Fluticasone						
MDI: 44, 110, or 220 μg per puff	88–264 μg	88–176 μg	264–440 μg	176–352 μg	>440 μg	>352 μg
DPI: 50, 100, or 250 μg per inhalation	100–300 μg	100–200 μg	300–500 μg	200–400 μg	>500 μg	>400 μg
Triamcinolone acetonide 75 μg per puff	300–750 μg	300–600 μg	750–1,500 μg	600–900 μg	>1,500 μg	>900 μg
Mometasone DPI 200 μg per puff	200 μg	NA	400 μg	NA	>400 μg	NA

From the National Asthma Education and Prevention Program, Expert Panel Report (2002) Guidelines for the management and diagnosis of asthma – update on selected topics 2002. NIH Publication No. 02-5075. Bethesda, MD: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute and the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

CFC chlorofluorocarbon; *DPI* dry powder inhaler; *HFA* hydroxyfluoroalkane; *MDI* metered-dose inhaler; *NA* no data available

[a] Children ≤12 years old

The safety of inhaled corticosteroids has been studied extensively. Systemic effects have been identified, particularly at high doses, but their clinical significance is unclear. There may be interindividual variations in dose–response effects. In general, the potential for adverse effects must be weighed against the risk of uncontrolled asthma; to date, the evidence supports the use of inhaled corticosteroids.

The most common side effects from inhaled corticosteroids are local adverse effects: oral candidiasis (thrush) and dysphonia. Oral candidiasis is more frequent in adults than children. It typically is seen when high doses of inhaled corticosteroids are used. To significantly decrease the risk of oral candidiasis developing, a spacer device should be used with the MDI formulations and, with all methods of inhalation, the mouth should be rinsed after inhaler use. Dysphonia is seen primarily with high doses of inhaled corticosteroids. This can be prevented and treated by rinsing the mouth after inhalation, using a spacer device, reducing the dosage, and resting the voice.

The most studied systemic side effects of inhaled corticosteroids include linear growth, bone metabolism and osteoporosis, hypothalamic-pituitary axis function, and cataracts. The effect of inhaled corticosteroids on growth in children is difficult to study because of multiple confounding factors on growth, including the concomitant use of systemic corticosteroids, concomitant atopy, and asthma itself. A few studies of children with asthma treated with inhaled corticosteroids have identified some growth delay, but others have not shown a difference. Even with growth delay, it appears that the expected height is still attained or decreased by 1 cm. Low-to-medium doses of inhaled corticosteroids appear to have no serious adverse effects on bone mineral density in children. A small, dose-dependent decrease in bone mineral density may be found in adults, but the clinical significance is not clear. In children, low-to-medium dose of inhaled corticosteroid therapy has no significant effect on the incidence of subcapsular cataracts or glaucoma. In adults, high lifetime exposure to inhaled corticosteroids may increase the prevalence of cataracts. An association between glaucoma and long-term high-dose inhaled corticosteroids may be seen in those with a family history of glaucoma.

6.7.2.3 Leukotriene-Modifying Agents

Leukotrienes are inflammatory mediators that are released from mast cells, eosinophils, and basophils. They are products of arachadonic acid metabolism. Leukotrienes cause the contraction of airway smooth muscle, increase vascular permeability, increase mucus secretions, and recruit inflammatory cells into the airways. Leukotriene-modifying agents are divided into two groups: the 5-lipoxygenase inhibitor (zileuton) and the leukotriene-receptor antagonists (zafirlukast and montelukast). Zileuton inhibits the formation of leukotrienes B_4, C_4, D_4, and E_4. Zafirlukast and montelukast inhibit the binding of the cysteinyl leukotrienes C_4, D_4, and E_4 to the leukotriene receptor. The leukotriene modifiers are indicated as monotherapy for the treatment of mild persistent asthma. They should be considered for these patients who prefer an oral agent or who are unable or unwilling to use

inhaled corticosteroids. When comparing the overall effectiveness of leukotriene modifiers with inhaled corticosteroids, most outcome measures significantly favor inhaled corticosteroids. Leukotriene modifiers can be used in combination with an inhaled corticosteroid for moderate or severe persistent asthma. The leukotriene modifiers can help reduce symptoms of allergic rhinitis. This may be a consideration for patients with coexisting asthma and allergic rhinitis.

Zileuton may increase liver transaminases, and follow-up with liver transaminase testing is recommended monthly for 3 months, then every 2–3 months for the rest of the first year and periodically thereafter for long-term therapy. No specific recommendation has been made for monitoring liver transaminases in conjunction with zafirlukast or montelukast therapy. Leukotriene modifiers have been linked to cases of Churg–Strauss vasculitis. Some observers have suggested that these cases were primary eosinophilic disorders that were unmasked as systemic corticosteroids were tapered with leukotriene-modifier therapy. However, eosinophilic disorders have been associated with leukotriene modifier treatment even in the absence of previous corticosteroid therapy. If this association is true, it appears to be very rare.

Zileuton is approved for children older than 12 years and for adults. The dosage is 600 mg four times daily. Montelukast, 4 mg daily, is administered in granules or chewable tablet form to children 12 months to 5 years old. The dosage for ages 6–14 years is 5 mg daily and for those 15 years and older, 10 mg daily. For zafirlukast, the dosage is 10 mg twice daily for ages 5–11 years and 20 mg twice daily for those 12 years and older. Concomitant use of warfarin results in higher warfarin levels and subsequently higher prothrombin time levels; thus, close monitoring and adjustment are advised.

6.7.2.4 Chromones

Nedocromil and cromolyn are mild anti-inflammatory agents that inhibit the release of mast cell mediators. They inhibit the early and late phase responses to allergen challenge and are bronchoprotective for exercise. They are second-line agents that may be used to treat mild persistent asthma or as prophylaxis for exercise-induced asthma and allergen-induced asthma. The effectiveness of nedocromil and cromolyn are similar to that of leukotriene antagonists and theophylline. They are less effective than inhaled corticosteroids. Cromolyn is available as an MDI or DPI or in solution for nebulization. Nedocromil is available as an MDI. The usual dosing is two puffs four times daily, although nedocromil may be given twice daily. Both have very few significant adverse effects. About 20% of patients find the taste of nedocromil unpleasant. Nedocromil and cromolyn are not recommended for moderate or severe persistent asthma.

6.7.2.5 Methylxanthines

Theophylline functions as a nonselective inhibitor of cyclic adenosine monophosphate phosphodiesterases in airway smooth muscle, resulting in bronchodilatation.

Theophylline inhibits the activation of inflammatory cells in vitro; however, the clinical importance of the anti-inflammatory effect appears to be small. Theophylline is a second- or third-line agent for the daily treatment of persistent asthma. Sustained-release theophylline is effective for nocturnal asthma. For moderate or severe persistent asthma, theophylline can be given in combination with an inhaled corticosteroid.

Theophylline use is limited by its side effect profile. Adverse effects include nausea, headache, insomnia, diarrhea, irritability, and tremors. The recommended therapeutic range is 5–15 μg mL^{-1}. Lower doses, providing a serum level of 5–10 μg mL^{-1}, usually are tolerated better than higher doses. Because theophylline is metabolized through cytochrome P-450, it has significant drug interactions. Medicines that decrease the clearance of theophylline and, thus, increase theophylline levels include macrolide antibiotics, fluoroquinolone antibiotics, propranolol, diltiazem, verapamil, disulfiram, and oral contraceptives. Medications that increase theophylline clearance and decrease theophylline levels include phenytoin, phenobarbital, and cimetidine. If patients have been treated for several years with theophylline, care must be taken when discontinuing the medication. The abrupt withdrawal of theophylline can cause an exacerbation of asthma. If theophylline treatment is being discontinued, it is recommended that the theophylline be tapered slowly and the patient be aware of the possibility of asthma being exacerbated.

6.7.2.6 Long-Acting β_2-Agonists

In November 2005, the FDA issued an advisory on the use of long-acting β-agonists for asthma, requesting manufacturers to include warnings on the labels that these agents may worsen asthma exacerbations and increase the risk of death. This was based primarily on the Salmeterol Multicenter Asthma Research Trial (SMART). In this 28-week, randomized, double-blind placebo-controlled observational study, there was a small but statistically significant increase in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in the total population that received salmeterol. The risk appeared to be greater in African Americans than in Caucasians. The effect of concomitant inhaled corticosteroid use was not able to be interpreted in this study because of the design and lack of control of multiple variables. The interpretation of the results of this study and the subsequent FDA warning have engendered significant controversy, with some experts favoring the warning and others thinking it is overreaching. There is general agreement that in mild-to-moderate persistent asthma, inhaled corticosteroids should be administered in sufficient amounts to control symptoms, whereas for patients with more severe disease and who still require daily administration of albuterol in addition to adequate doses of inhaled corticosteroids, long-acting β-agonists may be added to relieve symptoms.

Long-acting β-agonists have extended hydrophobic side chains that interact with the lipid bilayer of the cell membrane, leading to a prolonged duration of action. Bronchodilatation begins approximately 10 min after inhalation of salmeterol, and the peak response is reached after several hours. Bronchodilatation begins in only 3 min after inhalation of formoterol, with peak bronchodilatation in about 1 hours. The duration of action of both salmeterol and formoterol is approximately 12 hours. Salmeterol is available in both MDI and DPI forms and formoterol is available in a DPI form.

The primary adverse effects of long-acting β-agonists are similar to those of short-acting β-agonists, namely, tremor and increased heart rate. Continuous use of salmeterol can decrease the bronchoprotective effect of salmeterol against exercise or bronchial challenge. Inhaled long-acting β-agonists should not be used for rescue or quick relief of asthma symptoms. As a controller agent, long-acting β-agonists should not be used as a single agent because they lack an anti-inflammatory effect.

Long-acting β-agonists are most effective as an adjunct to inhaled corticosteroids in the treatment of moderate-to-severe persistent asthma. They are particularly effective in the treatment of nocturnal asthma. The recommended dose of an inhaled long-acting β-agonist is two puffs twice daily for salmeterol MDI and one puff twice daily for salmeterol or formoterol DPI.

6.7.2.7 Short-Acting β_2-Agonists

Inhaled short-acting β_2-agonists are indicated for the immediate, as-needed control of asthma symptoms. This is often described as a "rescue" therapy. Also, short-acting β_2-agonists are used for prophylaxis of exercise-induced asthma and asthma provoked by allergic triggers. Short-acting β_2-agonists are selective β_2-agonists that act on bronchodilators through the relaxation of bronchial smooth muscle. Because β_2 receptors are also found in the heart, β_2-agonists can cause sympathomimetic side effects such as tachycardia, palpitations, and tremor.

Short-acting β_2-agonists can be given in nebulized, MDI, or oral forms. The primary β-agonists used are albuterol, pirbuterol, and levalbuterol. Levalbuterol is the R-isomer of racemic albuterol. Because it only contains the R-isomer, less albuterol can be used to achieve the same amount of bronchodilation. For short-acting β-agonists, the onset of bronchodilation occurs within minutes, peaks at about 15 min, and has a duration of action of about 4–6 hours.

Overuse of β-agonists has been linked to increased asthma morbidity and mortality. Most authors believe that β-agonists themselves are not the cause of the morbidity or mortality but rather their overuse is a marker for severe undertreated asthma. If a patient is using a canister of short-acting β_2-agonist monthly, the entire treatment program should be reviewed because this amount represents a warning for overall poorly controlled asthma. Short-acting β_2-agonists should be taken on an as-needed basis. Regular, daily treatment with short-acting β_2-agonists has no advantage.

6.7.2.8 Oral Corticosteroids

Systemic oral corticosteroids are indicated for the treatment of acute asthma and for severe persistent asthma of patients whose asthma is not well controlled by high-dose inhaled corticosteroids and long-acting β-agonists. Many oral corticosteroid products are available. Prednisone is the best studied and least expensive oral corticosteroid commonly used to treat asthma. The adverse effects of prolonged use of oral corticosteroids include hyperglycemia, growth suppression, osteoporosis, posterior subcapsular cataracts, fat redistribution, skin thinning and bruising, mood changes, and suppression of the hypothalamic-pituitary axis. In hospitalized patients without risk for impending ventilatory failure, oral prednisone appears to be as effective as intravenous corticosteroids. Prednisone, 40–80 mg per day or 1–2 mg kg^{-1} daily for children, may be given in divided doses. For patients with mild asthma that is typically well controlled, an exacerbation of asthma generally resolves with a 3- to 10-day course of prednisone. For patients who require long-term prednisone treatment, the dose should be titrated to the lowest effective dose. Prednisone can be administered daily or on alternate days. The alternate-day regimen may help reduce systemic adverse effects. Control of asthma should be assessed periodically by the evaluation of symptoms, supplemental bronchodilator use, exacerbations, peak flow, and spirometry to adjust the dose to the lowest effective dose. For patients receiving continuous dosing, blood pressure, height, weight, glucose, bone density, and cataracts should be assessed periodically. Adults may benefit from a preventive approach with calcium (1,200–1,500 mg per day) and vitamin D (age 51–70 years, 400 IU per day and >70 years, 800 IU per day) supplementation.

6.7.2.9 Anticholinergic Agents

Anticholinergic medications do not carry an approved indication for use in asthma, although they may be a useful alternative for people who are intolerant to the side effects of β-agonists. Anticholinergic medications are a first-line bronchodilator in patients with COPD. Patients with a combination of asthma and COPD are most likely to benefit from this medication. Anticholinergic agents block muscarinic receptors that regulate airway tone and mucus production, resulting in bronchodilation.

Anticholinergic agents are available in a short-acting form, ipratropium bromide (Atrovent), and a long-acting form, tiotropium bromide (Spiriva). Ipratropium can be given in nebulized form or by MDI. The bronchodilation peaks approximately 1 hours after inhalation and lasts for 4 hours. Ipratropium is also available in a combination form with albuterol (Combivent) that is available in both MDI and nebulized forms. Tiotropium is available as a DPI through a HandiHaler device. It is dosed as one inhalation once daily, with bronchodilation occurring over a 24-hours period. The main side effects from anticholinergic agents are dry mouth and occasional cough. They may potentially worsen symptoms associated with narrow-angle

glaucoma, prostatic hyperplasia, or bladder neck obstruction and should be prescribed with caution in patients with these conditions.

6.7.2.10 Anti-Immunoglobulin E Antibody

Omalizumab is a humanized anti-IgE monoclonal antibody. This drug binds to the Fc portion of IgE, preventing the IgE from binding to the IgE receptor on mast cells. Omalizumab decreases the serum levels of IgE by at least 95% and disrupts type I IgE-mediated hypersensitivity reactions. Therefore, omalizumab is used in the treatment of allergic asthma. The current FDA-approved indication for omalizumab is for moderate-to-severe persistent allergic asthma. The medication is given subcutaneously either every 2 weeks or every 4 weeks, depending on the dosage required. Dosing is based on the patient's weight and total IgE level. Allergen testing is required to establish allergic sensitivity. This can be performed with allergen skin prick testing or in vitro studies of IgE binding to the pertinent aeroallergens. In clinical studies, omalizumab, in both children older than 12 years and adults, resulted in improved symptoms, fewer disease exacerbations, and decreased use of other asthma medications such as corticosteroids. However, only minimal changes in measured airflow and airway hyperreactivity have been shown with omalizumab. No published clinical studies have compared the safety and effectiveness of omalizumab with corticosteroids. Currently, omalizumab appears to be an effective anti-inflammatory agent, primarily in severe allergic asthma; its precise role in the management of allergic asthma has not been defined fully. In 2007, a boxed warning was added to the product label of omalizumab (Xolair). This addresses the risk of anaphylaxis, which is estimated to be at least 0.2% in postmarketing studies. Because of the risk of anaphylaxis, it is recommended that omalizumab be administered under medical supervision by providers who are able to treat anaphylaxis. Anaphylaxis can occur after any dose of the drug, and its onset can be delayed after administration.

6.7.2.11 Allergen Immunotherapy

Allergen immunotherapy consists of injections of allergen extracts to which the patient is allergic to induce an immunologic tolerance. In asthma, the airborne allergens, that is, animal dander, dust mites, mold, and tree, grass, and weed pollens, are injected to neutralize the allergic triggers of asthma in sensitive patients. There appear to be multiple mechanisms by which allergen immunotherapy is able to induce tolerance, including an increase in IgG blocking antibodies, the generation of suppressor T-cells, deviation from a Th2 to a Th1 cytokine release profile, and the production of T-cell tolerance.

Several studies have documented improvement of asthma symptoms of patients receiving immunotherapy; however, not all controlled studies have been consistently positive. A 1995 meta-analysis found an odds ratio of symptomatic improvement with immunotherapy of 3.2 (95% CI, 2.2–4.9). A revision of this meta-analysis by the same authors in 2003 incorporated 20 new studies and again showed highly

significant improvement in symptoms, nonspecific bronchial hyperreactivity, and risk of symptom deterioration in the immunotherapy groups.

Patients who have persistent or seasonal allergic nasal symptoms as well as asthma appear to benefit the most. The National Asthma Education and Prevention Program Expert Panel Report recommends that allergen immunotherapy be considered if there is clear evidence of a relation between symptoms and exposure to an unavoidable allergen, symptoms occur during a major portion of or through the entire year, or symptoms are difficult to control with pharmacologic management. An evaluation of the airborne allergens is required to establish allergic sensitivity. This can be performed with allergen skin prick testing or in vitro studies of IgE binding.

In the United States, standard practice of allergen immunotherapy starts with dilutions of 1:1,000 or 1:10,000 of the maintenance concentrate. Various protocols can be used, but the dose is typically increased at intervals of every 3–10 days during the "build-up" phase until the maintenance dose is achieved. Once the maintenance dose is achieved, the injections are given every 2 or 4 weeks. The length of treatment with immunotherapy is not well defined, although 3–5 years is considered a normal course of treatment. The initial response to treatment requires approximately 3–12 months. Among the patients who improve with immunotherapy, the majority continue to have improvement after a 3- to 5-year course of treatment ends. Approximately 25% have a return of symptoms soon after treatment. No method predicts which patients will have prolonged improvement or recurrence of their allergies.

The main risk of allergen immunotherapy is the development of a severe allergic reaction or asthma exacerbation to the immunotherapy injection. Severe reactions to immunotherapy are rare, with fatalities occurring in fewer than one per million injections. To reduce the risk of reactions, patients should be selected appropriately and educated about warning symptoms. Patients who have brittle or unstable asthma or a baseline $FEV_1 < 70\%$ are at increased risk for a reaction and should be excluded from immunotherapy. For asthma patients, peak flow rates should be measured before the injections and injections should be postponed if there is clinical or peak flow evidence of an exacerbation. Patients should be observed for 30 min after an immunotherapy injection, and the injections should only be given by personnel who are trained and equipped to use epinephrine, parental glucocorticoids, intravenous fluids, intubation equipment, and nebulizers.

6.7.3 Treatment of an Acute Asthmatic Attack

Physical findings in patients with exacerbations do not always correlate well with the degree of airflow obstruction. Although diffuse expiratory wheezing is a common finding, patients with the most severe impairment may have decreased breath sounds that limit auscultatory wheezing. Once treatment is initiated, the wheezing may become manifest. Symptoms of an acute asthma attack include a sensation of air hunger, chest tightness, cough, fatigue, or inability to lie flat. Signs of an acute

exacerbation include the use of accessory muscles during respiration, wheezing, diaphoresis, and inability to complete sentences. Altered mental status is an ominous sign and necessitates immediate emergency care or hospitalization. Physical examination should include close monitoring of vital signs: blood pressure, pulse, and respiratory rate and a detailed examination of the nose, throat, and chest. Patients with a severe exacerbation usually have increased pulse and respiratory rates and abnormal pulsus paradoxus. Pulsus paradoxus is the difference in systolic blood pressure taken between inspiration and expiration. Pulsus paradoxus of 10–20 mmHg occurs with moderate obstruction and one more than 25 mmHg, with severe obstruction. Peak expiratory flow readings and spirometry can further quantify the obstruction. Spirometry may be difficult to perform in the setting of a severe exacerbation. A peak flow reading <50% of predicted or personal best is consistent with a severe exacerbation; 50–80% is consistent with a moderate exacerbation and >80%, with a mild exacerbation.

Treatment is based on clinical findings, both subjective and objective, peak flow readings, and previous underlying disease and treatment. The approach is different for a patient with mild asthma who has a seasonal pollen-induced exacerbation than for one who has moderate-to-severe persistent asthma and a respiratory infection who has already been using nebulized albuterol at home. The latter patient usually requires more aggressive management. β-Agonists and corticosteroids form the cornerstone of initial treatment. Oxygen is also recommended for all except mild acute exacerbations. An overview of the management of acute asthma is given in Fig. 6.3.

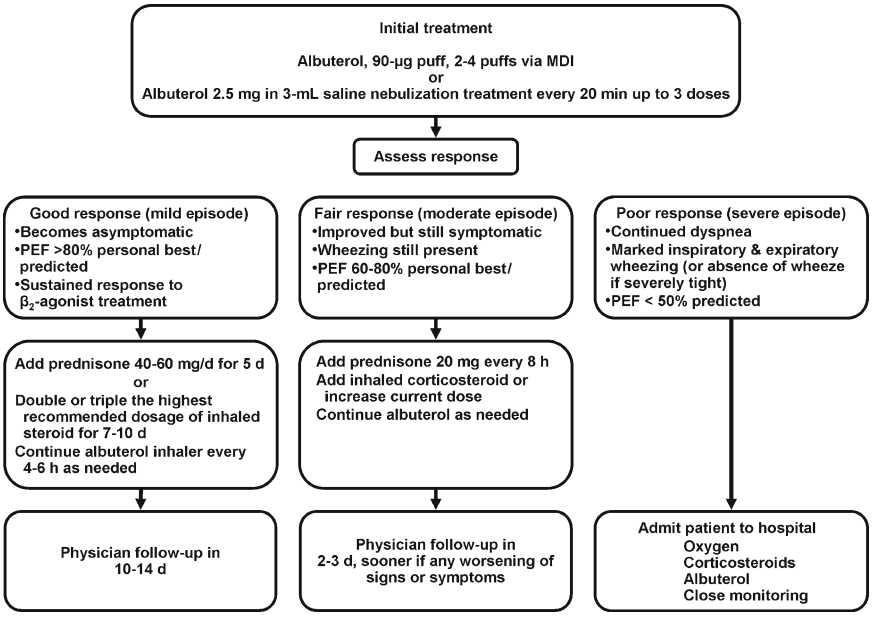

Fig. 6.3 Management of acute asthma. *PEF* peak expiratory flow

Approximately 50% of patients achieve maximal bronchodilation after one unit dose, or 2.5 mg of albuterol nebulized in 2.5–3.0 mL of normal saline. This therapy can be repeated every 15–20 min until the patient's condition is stable or the decision has been made to hospitalize the patient. Approximately 90% of patients achieve this response after three doses or 7.5 mg of inhaled albuterol. Therefore, the patient's clinical status after 3–4 doses of albuterol is often a better indicator rather than the initial presentation of whether inpatient care is required. Levalbuterol, a third-generation β-agonist, consists of the *R*-enantiomer of albuterol, which is responsible for the bronchodilatory effect. It is approved for ages 12 years and older. The usual starting dose is 0.63 mg in 3-mL unit dosages and, thus, has fewer systemic β-agonist side effects than albuterol 2.5 mg. The highest levalbuterol dose recommended is 1.25 mg in a 3-mL solution. It is approved for use every 6–8 hours, but likely can be given repeatedly, like albuterol. Because of conflicting study results, there is no clear-cut benefit when levalbuterol is compared with albuterol.

Corticosteroids are helpful in the treatment of acute asthma. Even though they do not have a rapid onset of action that immediately reverses the process, the anti-inflammatory properties can help prevent the exacerbation from escalating further and can shorten the time of the exacerbation. In addition to treatment with β-agonists, many patients with a mild exacerbation of asthma can be treated successfully with a higher-than-recommended dose of inhaled corticosteroid. For example, the dose of inhaled fluticasone may be increased to 220 μg, two puffs four times daily, instead of the usual top dose of 220 μg, two puffs twice daily for a 10-day period. Other inhaled corticosteroids can be used similarly by doubling or tripling the highest recommended dose. However, this strategy is less likely to work in patients who have a moderate or severe exacerbation, who overuse a β-agonist, or who have a severe upper respiratory infection exacerbating their asthma. Short courses of prednisone or other systemic corticosteroid are usually effective for establishing control of an exacerbation of asthma. These medications are most effective when given early in the exacerbation. For children, a common "steroid burst" is 1–2 mg kg^{-1} daily for 5 days, and for adults, prednisone 45–60 mg daily for 5 days. Most patients have considerable improvement in 5 days. Tapering the dose of systemic corticosteroids is not required after a short course (<1 week). When systemic corticosteroid treatment is longer than 10 days, it is advisable to taper the medication to help lessen the side effects of steroid withdrawal, including fatigue, depression, myalgias, and arthralgias. In essentially all exacerbations of asthma, corticosteroid treatment should be implemented or increased and continued for 5–10 days after the exacerbation to ensure stabilization. For example, a mild or moderate exacerbation that improves considerably with two treatments of nebulized albuterol is often followed by a relapse if corticosteroids, either inhaled or systemic, are not also started or increased. Corticosteroids can also be given intravenously or intramuscularly. There is no evidence that intravenous or intramuscular corticosteroids have a faster onset of action than oral corticosteroids. In hospitalized patients, a common approach is to administer intravenous methylprednisolone at 60 mg three times daily for the first 48 hours, with further dosage adjustment depending on the patient's response. Intravenous corticosteroids are advisable in the setting of severe

dyspnea or nausea and vomiting associated with the asthma exacerbation. For asthma patients who present at the emergency department, the early use of corticosteroids results in fewer hospitalizations.

6.7.4 Status Asthmaticus Treatment

Status asthmaticus is defined as a severe exacerbation of asthma that does not respond to aggressive bronchodilator therapy. Patients in status asthmaticus are on the verge of acute respiratory failure and are at risk for intubation and mechanical ventilatory support. Common signs are tachypnea, tachycardia, and the use of the accessory muscles of respiration despite aggressive bronchodilator treatment. Status asthmaticus is treated with oxygen, intravenous corticosteroids, and nebulized β-agonist on a frequent (every 1–2 hours) or continuous basis. Patients are weaned from the β-agonist as their condition improves. Treatment includes close observation in an intensive care unit, especially during the first 6–12 hours, to monitor for progression to respiratory failure. Correction of acid-base imbalances helps in therapy. If respiratory failure occurs despite intensive medical management, artificial mechanical ventilation is indicated.

6.7.5 General Approach

6.7.5.1 Initial Therapy Based on Level of Severity and Subsequent Step-Wise Management

Previously, guidelines for asthma management outlined treatment recommendations on the basis of the assessment of asthma severity. These guidelines provided algorithms for increasing the dosages of medications and for adding other treatments. The practical application of these recommendations can be challenging because of the variable nature of asthma, the minimization of symptoms by patients, and poor compliance with the medications and home-based measurements. For patients who are already taking control medications, asthma severity can be assessed by their response, or lack of it, to treatment. Asthma severity and therapeutic response, however, are not always strictly correlated. To help circumvent these issues, the 2007 NAEPP guidelines recommend evaluating asthma severity to guide the choice of appropriate medication and other therapeutic interventions in only patients with newly diagnosed, untreated asthma. Once therapy is initiated, the evaluation of patients with asthma should shift to assessing the level of asthma control to guide decisions to adjust therapy.

Asthma control is assessed by several parameters, including symptoms, nighttime awakenings, interference with normal activity, β-agonist use, spirometry, validated questionnaires, and exacerbations. After asthma is controlled, the goal is to reduce

the anti-inflammatory medication to the lowest effective dose. Currently, the level and duration of control required before a downward titration is undertaken and the strategy by which such adjustments should be accomplished are not known. A general rule is to consider stepping down treatment if the asthma has been well controlled for at least 3 months. Biologic markers of inflammation, such as eosinophil sputum counts and exhaled nitric oxide levels, may help in this process after they have been refined for application to the clinical setting.

6.7.5.2 Initial Therapy: Pediatric Asthma

The classification of asthma severity, which takes into account both the impairment and the risk, provides a guide for initiating asthma therapy. Initial therapy based on severity is outlined in Tables 6.7 and 6.14 for ages 0–4 years and in Tables 6.8 and 6.15 for ages 5–12 years. Once therapy is selected, the patient's response to treatment guides decisions about adjusting the therapy based on control of the impairment and risk factors. Although each asthma patient requires individualized care, some general rules are helpful in guiding therapy decisions.

For children with persistent asthma, whether mild, moderate, or severe, a daily long-term controller medication is indicated. Inhaled corticosteroids are the preferred therapy for initiating long-term control therapy. For children with mild asthma, recognition of the appropriate long-term controller therapy can be difficult, because children are often asymptomatic between episodes. Indications for the use or consideration of a long-term controller medication for the 0–4-year-old age group also includes the following:

- More than three episodes of wheezing that lasted longer than 1 day within the past year and risk factors for developing asthma, including (1) atopic dermatitis, (2) sensitization to aeroallergens, or (3) parental history of asthma or two of the following: food allergy, more than 4% blood eosinophilia, or wheezing in the absence of a viral respiratory infection
- Requires symptomatic treatment 3 days or more weekly for more than 4 weeks
- Required systemic corticosteroids for severe exacerbation of asthma two or more times within the last 6 months

In these situations, treatment with a daily low-dose inhaled corticosteroid can help reduce exacerbations and decrease symptoms but does not appear to alter the future course of asthma severity. Another option to consider is the use of daily controller therapy only during periods of higher risk, such as the fall and winter months, when the incidence of viral upper respiratory tract infections is higher. This approach has not been evaluated systematically; however, theoretically, it should help reduce symptoms and exacerbations in patients with mild asthma whose symptoms are confined to these times.

Alternative anti-inflammatory long-term controller options include leukotriene receptor antagonists or cromolyn. These are less potent than inhaled corticosteroids.

Table 6.14 Stepwise approach for managing asthma in children ages 0–4 years

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	↑
Inhaled short-acting β_2-agonists PRN	Low-dose ICS[a] *or* (in order of preference) montelukast or cromolyn	Medium-dose ICS[a]	Medium-dose ICS[a] *and* Either montelukast or LABA	High-dose ICS[a] *and* Either montelukast or LABA	High-dose ICS[a] *and* Either montelukast or LABA *and* Oral corticosteroids	Step up if needed (first, check adherence and environmental control)
						Assess control
						Step down if possible
						↓
Intermittent asthma	Persistent asthma: daily medication					
	Consult with asthma specialist if step 3 care or higher is required					
	Consider consultation at step 2					

Patient education and environmental control at each step

Quick-relief medication for all patients

- β_2-Agonist as needed for symptoms. Intensity of treatment depends on severity of symptoms
- With viral respiratory infection: β_2-agonist q4–6h up to 24h (longer with physician consult). If treatment needs to be repeated more than once every 6 weeks, consider starting daily long-term-control therapy (step 2). Consider short course of systemic oral corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations
- *Caution*: Increasing use of β_2-agonist or use of >2 days per week for symptom control (not prevention of exercise-induced bronchoconstriction) indicates inadequate control and the need to step up treatment

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

ICS inhaled corticosteroid; *LABA* inhaled long-acting β_2-agonist

[a]Preferred treatment

Note: If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up

Table 6.15 Stepwise approach for managing asthma in children ages 5–11 years

Intermittent asthma	Persistent asthma: daily medication					
Consult with asthma specialist if step 4 care or higher is required						
Consider allergen immunotherapy in steps 2–4 for patients who have persistent, allergic asthma						
Consider consultation at step 3						↑
Step 1 *Preferred*: SABA prn	Step 2 *Preferred*: Low-dose ICS *Alternative*: LTRA, cromolyn, nedocromil, or theophylline	Step 3 *Preferred*: Medium-dose ICS *or* Low-dose ICS+either LABA, LTRA, or theophylline	Step 4 *Preferred*: Medium-dose ICS+LABA *Alternative*: Medium-dose ICS+either LTRA or theophylline	Step 5 *Preferred*: High-dose ICS+LABA *Alternative*: High-dose ICS+either LTRA or theophylline	Step 6 *Preferred*: High-dose ICS+LABA+oral corticosteroid *Alternative*: High-dose ICS+either LTRA or theophylline+oral corticosteroid	Step up if needed (first, check adherence, environmental control, and comorbid conditions) *Assess control* Step down if possible (and asthma is well controlled for at least 3 months) ↓

Patient education and environmental control at each step

Quick-relief medication for all patients:

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to three treatments at 20-min intervals, as needed. Short course of systemic oral corticosteroids may be needed
- *Caution*: increasing use of β_2-agonist or use >2 times per week for symptoms control (not prevention of exercise-induced bronchoconstriction) indicates inadequate control and the need to step up treatment

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ICS inhaled corticosteroid; *LABA* inhaled long-acting β_2-agonist; *LTRA* leukotriene receptor antagonist; *prn* as needed; *SABA* inhaled short-acting β_2-agonist

Considerations for the initial treatment in addition to treatment effectiveness include mode of delivery of the medication, history of previous response to therapy, and anticipated compliance with the treatment regimen. The following are the FDA-approved age indications for the controller medications:

1. Inhaled corticosteroids
   - Budesonide nebulizer solution (children >1 year)
   - Fluticasone DPI (children ≥4 years)
2. Leukotriene antagonist
   - Montelukast (children >1 year)
3. Chromones
   - Cromolyn nebulizer solution (children ≥2 years)

6.7.5.3 Initial Therapy: Adult Asthma

As for the initial therapy of pediatric asthma, the classification of asthma based on impairment and risk provides a guide for initiating therapy for adults (Tables 6.9 and 6.16). For adults, spirometry helps to clarify further the current impairment. Inhaled corticosteroids are the preferred treatment for persistent asthma that requires a long-term controller medication. Alternatives include cromolyn, leukotriene receptor antagonists, and sustained-release theophylline. The effectiveness of these alternatives is less than that of inhaled corticosteroids.

6.7.5.4 Stepwise Management of Therapy Based on Severity and Control

The aim of asthma therapy is to maintain long-term control of asthma with the least amount of medication. To achieve this, a stepwise approach to therapy has been implemented in which the number of medications and the amount of the medications are increased as necessary and decreased when possible to maintain control. The emphasis on control is a new key concept of the 2007 NAEPP report. An overview of the critical components of control and recommended actions to maintain control are shown in Tables 6.17–6.19 for the respective age groups of 0–4, 5–12 and ≥12 years.

Key issues in the stepwise approach include what to add when. Specific therapy should be tailored to the needs and circumstances of the individual patient. Short-acting inhaled β-agonists taken as needed are the primary treatment for intermittent asthma. If a β-agonist is required for quick-relief treatment more than twice weekly, then therapy should be increased to the persistent asthma regimen. Patients with persistent asthma should receive daily long-term control medication that has anti-inflammatory effects. Overall, inhaled corticosteroids are the most effective single agents. In addition, quick-relief medication should be made available to all patients

Table 6.16 Stepwise approach for managing asthma in adults and youths ages ≥12 years

Persistent asthma: daily medication
Consult with asthma specialist if step 4 care or higher is required

Consider allergen immunotherapy in steps 2–4 for patients who have persistent, allergic asthma

Intermittent asthma	Consider consultation at step 3					↑
Step 1 *Preferred*: SABA prn	Step 2 *Preferred*: Low-dose ICS *Alternative*: Cromolyn, nedocromil, LTRA, or theophylline	Step 3 *Preferred*: Medium-dose ICS *or* Low-dose ICS+LABA *Alternative*: Low-dose ICS+either LTRA, theophylline, or zileuton	Step 4 *Preferred*: Medium-dose ICS+LABA *Alternative*: Medium-dose ICS+either LTRA, theophylline, or zileuton	Step 5 *Preferred*: High-dose ICS+LABA *and* Consider omalizumab for patients who have allergies	Step 6 *Preferred*: High-dose ICS+LABA+oral corticosteroid *and* Consider omalizumab for patients who have allergies	Step up if needed (first, check adherence, environmental control, and comorbid conditions) *Assess control* Step down if possible (and asthma is well controlled for at least 3 months) ↓

Patient education and environmental control at each step

Quick-relief medication for all patients:

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to three treatments at 20-min intervals, as needed. Short course of systemic oral corticosteroids may be needed
- Use of a β_2-agonist >2 days per week for symptom control (not prevention of exercise-induced bronchoconstriction) indicates inadequate control and the need to step up treatment

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute
ICS inhaled corticosteroid; *LABA* inhaled long-acting β_2-agonist; *LTRA* leukotriene receptor antagonist; *prn* as needed; *SABA* inhaled short-acting β_2-agonist.

Table 6.17 Assessing asthma control and adjusting therapy in children ages 0–4 years

	Classification of asthma control (ages 0–4 years)[a]		
Components of control	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days per week	>2 days per week	Throughout the day
Nighttime awakenings	≤1 per month	>1 time per month	>1 time per week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting β_2-agonist use for symptom control (not prevention of exercise-induced bronchoconstriction)	≤2 days per week	>2 days per week	Several times per day
Risk			
Exacerbations (requiring oral corticosteroids)	0–1 per year	2–3 per year	>3 per year
Recommended action for treatment	• Maintain current treatment • Attempt step down if well controlled for at least 3 months	• Step up 1 step and • Reevaluate in 2–4 week • For side effects, consider alternative treatment options	• Consider short course of systemic oral corticosteroids • Step up 1–2 steps, and • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

[a]The level of control or impairment is based on the most severe impairment category

who have persistent asthma. If the asthma is not controlled with a low-dose inhaled corticosteroid despite excellent compliance, inhaler technique, and lack of triggers or coexisting conditions, then the therapeutic options include increasing the inhaled corticosteroid dose to the medium-dose range or adding a long-acting β-agonist to a low dose of inhaled corticosteroid. These are considered essentially equal options based on risk and benefit. Alternative options include adding a leukotriene antagonist or theophylline to the low-dose inhaled corticosteroid. The next step in treatment combines a medium-dose inhaled corticosteroid and long-acting β-agonist. Alternatives to this include a leukotriene antagonist or theophylline in addition to the medium-dose inhaled corticosteroid. If further control is required, then high-dose inhaled corticosteroids and a long-acting β-agonist are recommended. No

Table 6.18 Assessing asthma control and adjusting therapy in children ages 5–11 years

	Classification of asthma control (ages 5–11 years)[a]		
Components of control	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days per week but not more than once on each day	>2 days per week or multiple times on ≤2 days per week	Throughout the day
Nighttime awakenings	≤1 time per month	≥2 times per month	≥2 times per week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting β_2-agonist use for symptom control (not prevention of exercise-induced bronchoconstriction)	≤2 days per week	>2 days per week	Several times per day
Lung function	FEV_1 or peak flow >80% predicted $FEV_1/FVC > 80\%$	FEV_1 or peak flow = 60–80% predicted $FEV_1/FVC = 75–80\%$	FEV_1 or peak flow <60% predicted $FEV_1/FVC < 75\%$
Risk			
Exacerbations (requiring oral corticosteroids)	0–1 per year	2–3 per year	>3 per year
Recommended action for treatment	• Maintain current step • Attempt step down if well controlled for at least 3 months	• Step up at least 1 step and • Reevaluate in 2–4 weeks • For side effects: consider alternative treatment options	• Consider short course of systemic oral corticosteroids • Step up 1–2 steps, and • Reevaluate in 2 weeks • For side effects: consider alternative treatment options

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute

FEV_1 forced expiratory volume in 1s; *FVC* forced vital capacity

[a]The level of control or impairment is based on the most severe impairment category

long-term studies have assessed the efficacy of adding a leukotriene antagonist to this regimen. Omalizumab could be considered at this juncture for patients who have IgE-mediated asthma and sensitization to the pertinent perennial allergens. Allergen immunotherapy should be considered for patients with persistent asthma

Table 6.19 Assessing asthma control in adults and youths ages ≥12 years

	Classification of asthma control in patients ages ≥12 years[a]		
Components of control	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days per week	>2 days per week	Throughout the day
Nighttime awakenings	≤2 per month	1–3 per week	≥4 per week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting β_2-agonist use for symptom control (not prevention of exercise-induced bronchoconstriction)	≤2 days per week	>2 days per week	Several times daily
FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/personal best
Validated questionnaires			
ATAQ	0	1–2	3–4
ACQ	≤0.75	≥1.5	Not applicable
ACT	≥20	16–19	≤15
Risk			
Exacerbations	0–1 per year	2–3 per year	>3 per year
Progressive loss of lung function	Evaluation requires long-term follow-up care		
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate with specific levels of control but should be considered in the overall assessment of risk		
Recommended action for treatment	• Maintain current step • Consider step down if well controlled for at least 3 months	• Step up 1 step • Reevaluate in 2–6 weeks • For side effects, consider alternative treatment options	• Consider short course of systemic oral corticosteroids • Step up 1–2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

From the National Asthma Education and Prevention Program: Expert Panel Report 3. (2007) Guidelines for the diagnosis and management of asthma. NIH publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute
ACQ asthma control questionnaire; *ACT* asthma control test; *ATAQ* asthma therapy assessment questionnaire; *FEV_1* forced expiratory volume in 1s
[a]The level of control or impairment is based on the most severe impairment category

when there is a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Asthma can be highly variable over time, and the treatment should be adjusted accordingly. Reassessment is critical in determining asthma control. Key areas that should be monitored include the following:

1. Impairment
   - Symptoms
   - Nighttime awakenings
   - Interference with normal activity
   - Short-acting β-agonist use
   - Spirometry or peak flow
   - Validated questionnaires
2. Risk
   - Exacerbations
   - Loss of lung function
   - Treatment-related adverse effects

These factors help in determining the level of treatment required to maintain control and in preventing exacerbations. Once well-controlled asthma is achieved and maintained for at least 3 months, a reduction in pharmacologic therapy should be considered. This will allow for using the minimal therapy for well-controlled asthma. If well-controlled asthma is not achieved and maintained, secondary causes should be assessed. These include patient compliance and technique in using the medications and the presence of a coexisting condition or a provocateur.

An asthma action plan should be reviewed for essentially all patients who have asthma. Even patients with mild intermittent asthma may experience sudden, severe exacerbations of asthma. It is essential that the exacerbations be recognized early so treatment can be implemented. The action plan should include symptoms of worsening asthma, peak flow meter reading guidelines, and recommendations for using β-agonist rescue therapy, increasing the use of controller medications, administration of systemic corticosteroids, and seeking medical care. An example of an asthma action plan is shown in Table 6.4.

6.7.6 Treatment of Persistent Severe or Intractable Asthma

Severe asthma represents <10% of all cases of asthma, but these patients account for a disproportionate share of the health costs and morbidity associated with the disease. Several severe asthma phenotypes have been described on the basis of the age of the patients, age at disease onset, corticosteroid resistance, chronic airflow obstruction, and evidence for eosinophilic airway inflammation on biopsy. In this group of patients, it is particularly important that the diagnosis of asthma is confirmed, that correct use and compliance with medications are confirmed, and that all possible

exacerbating factors (airsmog) are optimally managed. The mainstay of pharmacotherapy are high-dose inhaled corticosteroids and long-acting β-agonists. Possible adjunctive long-acting controller medications include leukotriene antagonists, theophylline, omalizumab, and anticholinergic agents. Systemic corticosteroids are used for exacerbations and may be required for maintenance therapy. The goal is to use as little systemic corticosteroid as possible to maintain stable airway function. For some patients, the asthma can be controlled with an every-other-day corticosteroid regimen. Patients who require systemic corticosteroids need monitoring and treatment for side effects, particularly increased glucose levels in those with diabetes mellitus, posterior subcapsular cataracts, and osteopenia or osteoporosis. Monitoring and corticosteroid dosage based on inflammatory markers such as sputum eosinophils and nitric oxide hold promise for the future as a way to prescribe as little systemic corticosteroid as possible. Various immunomodulating steroid-sparing agents have been attempted over the years, but generally the experience with methotrexate, troleandomycin, gold, and intravenous gamma globulin have been disappointing. Patients with severe asthma require specialist management of their condition.

6.7.7 Special Groups

6.7.7.1 Occupational Asthma

Occupational asthma is a disease characterized by variable outflow obstruction and hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not due to stimuli encountered outside the workplace. It has been estimated that 5–10% of all cases of asthma in industrialized nations are occupationally related. Occupational asthma can be separated into two main subtypes: immunologic and nonimmunologic. The immunologic subtype can be subdivided further into immunologically mediated asthma and hypersensitivity pneumonitis. The nonimmunologic subtype is due to an irritant type of reaction, usually with large exposure to the offending substance, and is termed *reactive airways dysfunction syndrome* (RADS). RADS is characterized by a high level of exposure to the offending agent, acute onset of asthma symptoms, persistence of asthma symptoms for 3 months, and development of airway hyperreactivity with subsequent irritant exposure (exercise, cold air, fumes, etc.). These subtypes can overlap. Many reactive chemicals can cause disease by inducing immunologic asthma or RADS. With other substances, for example, Western red cedar, the pulmonary response is not well delineated as being either immunologically mediated or an irritant response.

Most agents that cause occupational asthma are high-molecular-weight proteins of plant, animal, or bacteria origin. Low-molecular-weight chemicals act as irritants and can aggravate underlying asthma or produce RADS. Low-molecular-weight chemicals can also form an immunologically mediated reaction by haptenizing proteins in the respiratory tract, enabling binding by IgE. Common causes of occupational asthma are listed in Table 6.20.

Table 6.20 Major causes of occupational asthma

High-molecular-weight agents	Workers at risk
Plant proteins (wheat, grains, coffee beans, cotton, etc.)	Farmers, bakers, textile workers, food processors, millers
Animal proteins (domestic animals, birds, mice, etc.)	Farmers, veterinarians, laboratory workers, animal handlers
Latex	Healthcare workers, laboratory workers, rubber manufacturers
Enzymes (Bacillus subtilis, trypsin, papain, etc.)	Detergent manufacturers, pharmaceutical workers
Seafood	Seafood processors
Gums	Carpet makers, pharmaceutical workers
Low-molecular-weight agents	**Workers at risk**
Isocyanates (toluene diisocyanate, diphenylmethane diisocyanate, naphthalene diisocyanate)	Spray painters; insulation installers; polyurethane workers; plastics, rubber, and foam workers
Anhydrides (trimellitic anhydrate, phthalic anhydride)	Paint, plastic, and epoxy resin manufacturers
Metals (nickel, platinum, etc.)	Platers, welders, metal and chemical workers
Wood dusts (Western red cedar)	Forest workers, carpenters, woodworkers
Fluxes (colophony, etc.)	Solderers, electrical workers
Dyes (carmine, henna extract, etc.)	Textile workers, fur dyers, beauticians
Acrylate (methacrylate, cyanoacrylate)	Health professionals, body shop workers
Drugs (psyllium, antibiotics, etc.)	Pharmaceutical workers, health professionals

All asthma subjects should be questioned not only about their occupation, but also about their work environment. The work environment history should include details about the building they work in, the agents or chemicals they work with directly, and the other processes ongoing in their work area. Typically, the symptoms of occupational asthma occur only at work and improve when a person is away from the work environment. With progression of the disease, however, the relation between the work environment and the symptoms become less clear-cut. This is particularly true for workers with underlying asthma whose symptoms are made worse by nonspecific irritants at work or those with poorly controlled asthma. Also, workers may not be exposed to the offending agent every day, and intermittent exposures can be hard to identify. The latency period between the onset of exposure and the onset of symptoms is highly variable. Generally, the latency period is shorter with exposure to low-molecular-weight agents than to high-molecular-weight agents.

The initial evaluation of the patient should first confirm whether the patient indeed has asthma. Pulmonary function testing is indicated to obtain baseline pulmonary function and to determine the presence of asthma. Asthma can be confirmed by an increase of 12% or more in FEV_1 after administration of a bronchodilator or a decrease of 20% or more in FEV_1 after bronchoprovocation, for example, as with methacholine. Establishing that asthma is occupational can be difficult. The underlying principle is to identify the offending substance and show sensitivity with skin or in vitro testing or to detect an objective change in pulmonary

function with work exposure. Skin and in vitro testing to substances present in the work environment, when positive, suggest a causal relation. In many instances, however, reagents for skin or in vitro testing are not available. Also, in RADS, skin and in vitro testing will be negative. Often, it is necessary to reproduce the symptoms by challenge. The challenge may be conducted by natural exposure of the patient to the work environment or by controlled bronchoprovocation to the suspected substance in the laboratory. When the challenge consists of normal work environment exposure, serial measurement of the PEFRs is helpful. With one method of monitoring, the patient records the PEFR four times daily for 2 weeks at work and for a similar period away from work. This approach has several potential problems, including reproducibility of the readings, compliance and honesty of the patients, and interpretation of the results. Similarly, spirometry can be performed, with measurements of FEV_1 in the workplace compared with measurements made on a nonwork day. This may need to be done repeatedly, because measurement of a single FEV_1 when the patient is at work instead of at home does not have sufficient sensitivity to detect a relation between work and asthma. Another method to determine the effect of the work environment is induced sputum measurement for eosinophils. An increase of 1% or more of sputum eosinophils obtained after 2 weeks of work exposure compared with a sample obtained after 2 weeks with no work exposure increases the sensitivity and specificity of occupational asthma diagnosis compared with PEFR monitoring alone.

Many workers with occupational asthma do not recover completely, even after they leave the work environment. Early diagnosis and removal from the work environment are critical for the goal of complete recovery. Sometimes, changes can be made in the work environment to eliminate or significantly decrease exposure. However, levels of exposure below the legal limit that are based on toxicity may still precipitate an IgE-mediated reaction. Consultation with an industrial hygienist may be helpful in measuring the exposure. Although no preemployment screening test has been effective in predicting the development of occupational asthma, effort should be made to educate workers and managers in high-risk industries so that affected workers can be recognized early.

6.7.7.2 Asthma in Pregnancy

The prevalence of asthma in pregnancy is approximately 7%. Managing asthma during pregnancy is unique because of the effect of pregnancy on asthma and the effect of asthma and the treatment of asthma on the developing fetus and mother. The primary goal is to optimize both fetal and maternal health.

During pregnancy, about one-third of patients with asthma experience improvement in symptoms, one-third experience worsening of symptoms, and one-third remain the same. The first trimester is generally well tolerated by asthma patients. An increase in symptoms and exacerbations have been reported to occur most commonly between weeks 17 and 36 of gestation, but there are fewer symptoms and exacerbations during weeks 37–40. Asthma generally remains controlled during

labor and delivery. Overall, the first trimester and last month of pregnancy appear to be relatively free of asthma exacerbations, and the second and early third trimester have more potential for an increase in symptoms. The course of the asthma is often consistent in a woman during successive pregnancies. The mechanisms responsible for the changes in the course of asthma during pregnancy are not known; however, the changes do not appear to be due to random fluctuations in the disease. Possibilities include the physiologic changes during pregnancy, stress, underuse of medication, infection, immunologic response to the fetus, and atopic changes.

The general principles of asthma management during pregnancy do not differ substantially from those of nonpregnant asthma patients. The primary concern is the control of asthma, not the avoidance of asthma medications. The patient needs to be educated about the potential adverse effects of uncontrolled asthma on the well-being of the fetus and needs to understand that treating asthma with medications is safer than an increase in asthma symptoms that may lead to maternal and fetal hypoxia. The goal is to have no limitation of activity, no exacerbations, normal pulmonary function, minimal chronic symptoms, and minimal adverse effects of medications.

Objective assessments and monitoring should be performed on pregnant asthma patients. Patients with an $FEV_1 < 80\%$ of predicted are at increased risk for asthma morbidity and pregnancy complications. Because asthma has been associated with decreased fetal growth and preterm birth, accurate dating is helpful. There should be open lines of communication with the patient's obstetrician, and the obstetrician should be involved in the management of the patient's asthma and obtain information about the asthma status during prenatal visits.

Avoidance of asthma triggers, such as fumes, tobacco smoke, pollutants, and allergens, should be reviewed. Allergen immunotherapy can be continued during pregnancy in patients who tolerate the immunotherapy well without systemic reactions and are at a maintenance dose and do not require escalation of the dose. Immunotherapy should not be started during pregnancy because of the risk of a systemic reaction during the build-up phase and the latency of the immunotherapy effect.

Pharmacologic management of pregnant women with asthma has been updated recently in the document "NAEPP Working Group Report on Managing Asthma during Pregnancy: Recommendations of Pharmacologic Treatment – Update 2004." This update supercedes the initial report from 1993 and the 2002 update. The primary recommendations include the use of inhaled corticosteroids as the preferred controller therapy for mild, moderate, or persistent asthma. In addition, for moderate persistent asthma, the combination of a low-dose inhaled corticosteroid plus a long-acting β-agonist or medium-dose inhaled corticosteroid were considered equal treatment options. In 1979, the FDA established five categories to describe a drug's potential for causing adverse effects during pregnancy (Table 6.21). These categories are based on human data, animal studies, and consideration of whether the benefit of the drug's use during pregnancy outweighs the risk. No asthma or allergy medication meets the requirements for category A.

There do not appear to be clear-cut recommendations for the choice of specific medications in each medication category. In 1993, the Working Group on Asthma and Pregnancy recognized as treatment options during pregnancy the inhaled

Table 6.21 U.S. Food and Drug classification scheme for medications in pregnancy[a]

Category	Animal studies	Human studies
A	Negative	Negative
B	Negative	Not done
B	Positive	Negative
C	Positive	Not done
C	Not done	Not done
D	Positive or negative	Positive
X[b]	Positive	Positive

[a]Negative = no teratogenicity demonstrated; positive = teratogenicity demonstrated
[b]Drug contraindicated in pregnancy

corticosteroids used at that time, namely, beclomethasone dipropionate, triamcinolone, and flunisolide. Because most of the experience was with beclomethasone, it was considered the inhaled corticosteroid of choice. Since then, reports have supported the overall safety of inhaled corticosteroids in pregnancy. Currently, most of the available safety data are for budesonide, which is considered the preferred inhaled corticosteroid in pregnancy. There have not been data to suggest that other corticosteroids are less safe in pregnancy; therefore, if a pregnant woman with asthma is using an alternative inhaled corticosteroid and doing well, then it is reasonable to continue with the medication. Data about the use of systemic corticosteroids during pregnancy have raised some concern. Although there is no definite increased risk of total congenital malformations, a statistically significant increased risk of oral clefts in infants of mothers treated with oral corticosteroids during the first trimester has been shown. Other adverse outcomes associated with systemic corticosteroid use include preeclampsia, low birth weight, and preterm delivery. However, it is difficult to determine if these outcomes are due to the corticosteroids or the underlying asthma. The current recommendations support the use of oral corticosteroids when indicated for long-term management of severe asthma or for severe exacerbations during pregnancy.

The initial guidelines did not make a recommendation about a specific short- or long-acting β-agonist. On the basis of current data, albuterol is recommended as the inhaled short-acting β-agonist of choice. Few data have been published about the safety of salmeterol and formoterol. Because salmeterol has been available for a longer time, it is considered the long-acting β-agonist of choice. Other medications recommended during pregnancy as alternative choices for mild persistent asthma include cromolyn, theophylline, zafirlukast, and montelukast. Theophylline, zafirlukast, and montelukast can also be used as add-on therapy to inhaled corticosteroids. Serum theophylline levels need to be monitored closely, with maintenance serum levels targeted at 5–12 μg mL^{-1}.

Practitioners should be aware of the potential side effects that commonly used labor medications may have on asthma. Prostaglandin $F_{2\alpha}$, ergonovine, and methylergonovine, which are used for postpartum hemorrhage, can induce bronchospasm.

Transcervical or intra-amniotic prostaglandin E_2 used for cervical ripening can also induce bronchospasm. Intravaginal or intracervical prostaglandin E_2 gel, prostaglandin E_2 suppositories, magnesium sulfate, and calcium channel blockers can be safely administered to asthma patients. For patients receiving regular systemic corticosteroid therapy or who have received frequent bursts during pregnancy, supplemental corticosteroids are recommended for the stress of labor and delivery. A typical stress dose is 100 mg hydrocortisone intravenously at admission and repeated every 8 hours for 24 hours.

6.7.7.3 Exercise-Induced Asthma

Exercise-induced asthma is the term often used to describe bronchoconstriction that follows exercise in asthma patients and produces the symptoms of cough, wheeze, dyspnea, or chest tightness (or some combination of these). This has also been termed, more accurately, *exercise-induced bronchoconstriction*, because exercise does not induce asthma, but rather exacerbates underlying asthma. Exercise-induced asthma occurs in 80–90% of patients with asthma and occurs with equal frequency in children and adults. The prevalence of exercise-induced asthma in the general population is approximately 6–13%, and approximately 10% of patients with this condition have no history of asthma or allergic disease. The magnitude of exercise-induced asthma is correlated with the underlying degree of airway hyperresponsiveness; therefore, in many patients with mild, episodic asthma, even strenuous exercise does not cause clinically significant bronchoconstriction.

The underlying pathophysiologic mechanism of exercise-induced asthma is not entirely clear. Under normal breathing conditions, the majority of the warming and humidification of inspired air is done by the nasal mucosa. During vigorous exercise, the large airways are recruited to provide the extra heat and humidity to condition the inspired air. As a person exercises, minute ventilation increases and, thus, respiratory water and heat loss increase. There is disagreement about the relative contributions of airway water loss versus airway cooling versus airway rewarming (after exercise). It is difficult to separate the roles of these potential triggers of exercise-induced asthma, but it has been shown that experimental inhalation of hot dry air can produce this condition but that it is attenuated when the inspired gas is humified and closer to body temperature, implying that water loss is the principal trigger. An interesting observation is that approximately 50% of patients who have exercise-induced asthma are refractory to exercise-induced symptoms if they exercise again within 60 min after the first exercise session. However, if the second exercise challenge is more than 3 hours after the first, the refractory period is lost and the symptoms are similar to those after the first exercise session. The refractory period does not occur if the patient is pretreated with indomethacin, suggesting that prostaglandins help provide protection during the refractory period. Other observations in exercise-induced asthma include an increase in inflammatory mediators, including histamine and leukotrienes C_4 and D_4, activation of peripheral Th2-type lymphocytes, and eosinophil influx and activation. In contrast, exhaled nitric oxide

levels do not appear to correlate well with the development or severity of exercise-induced asthma.

The primary symptoms associated with exercise-induced asthma include any combination of cough, dyspnea, chest tightness, chest discomfort, and wheeze. The symptoms may occur during exercise, usually 10–15 min into the exercise or 5–15 min after the completion of the exercise. The symptoms typically clear within 60 min after the exercise is completed. As noted above, there is a refractory period of up to 3 hours after the initial exercise. If the exercise is resumed within this time, little or no bronchoconstriction occurs. Symptoms are usually more pronounced with aerobic exercise such as with bicycling, running, and cross-country skiing, which involve a significant increase in the ventilatory rate. Activities that are less aerobic, such as weight lifting, diving, or yoga, are less likely to trigger exercise-induced asthma. Patients usually note that symptoms are increased when exercising in cold dry air compared with warm moist air.

Conventionally, exercise-induced asthma testing is performed in the laboratory, with 6–8 min of treadmill exercise sufficient to increase the heart rate to 85% of the predicted maximum. Spirometry is performed before the exercise and should be at least 75% of the patient's predicted value. Spirometry is then repeated immediately upon completion of the exercise and repeated 5–10 min after exercise stops. The lowest postexercise value is obtained and compared with the preexercise level. A decrease in the FEV_1 of 15% or more is considered a positive test. If spirometry is not available, peak expiratory flow rates can also be used. These should also be obtained before exercise and repeated upon completion of the exercise and at 3, 5, and 10 min after exercise. The initial peak flow reading should be 75% or more of the personal best. A decrease of 15% is considered a positive test.

If the diagnosis is unclear despite attempts to measure pulmonary function, further evaluation is required. The primary differential diagnosis for exercise-induced respiratory symptoms includes normal physiologic exercise limitation, upper airway obstruction, vocal cord dysfunction, parenchymal pulmonary disease, and cardiac disorders. Further evaluation may require formal exercise testing in a referral center that uses pulmonary function testing with lung volumes, diffusion capacity, and oxygen saturation.

Several nonpharmacologic therapeutic modalities are available to aid in the treatment of exercise-induced asthma. Patients should be advised to have a warm-up period before more strenuous exercise. This should consist of 5–10 min of stretching and mild exercise. This warm-up may help decrease the severity of exercise-induced asthma. The patient should be encouraged to increase cardiovascular fitness. Improvement in overall fitness lowers the minute ventilation required for a given level of exercise, thereby decreasing one of the primary stimuli for bronchoconstriction. Because breathing warm and humidified air is helpful, nasal breathing should be recommended. Similarly, patients should be instructed to breathe through a loosely fitting scarf or mask when exercising in cold, dry conditions to further humidify the air.

The pharmacotherapy of exercise-induced asthma varies with the clinical setting. Generally, if exercise-induced asthma occurs in poorly controlled asthma, the

most important strategy is to improve the overall control of the underlying asthma. Once the underlying asthma is well controlled, the treatment strategy is the same as for those in whom the exercised-induced symptoms are the only provocateur of airway hyperreactivity. The inhaled short-acting β-agonists are the primary prophylactic treatment for exercise-induced asthma. They significantly reduce or eliminate the condition in 85–90% of patients. A typical dose is two puffs of albuterol taken 15–45 min before exercise. This protects from exercise-induced asthma for approximately 2 hours, although the duration of bronchodilation is nearly 4 hours.

Another approach is the use of chromones. Inhaled cromolyn or nedocromil may be considered for patients in whom short-acting β-agonists are not fully effective. The dosage can range from 2 to 6 puffs 20 min before exercise. In addition, they may have a synergistic effect when used in combination with β-agonists. Long-acting β-agonists have also been shown to be effective in prophylaxis of exercise-induced asthma. The advantage of these medications is that they may be taken hours before exercise. There has been concern about the development of tolerance to the drug over time. Leukotriene receptor antagonists have also shown benefit in exercise-induced asthma. The long half-life of these agents allows for protection from exercise-induced asthma for up to 12 hours after ingestion. Inhaled corticosteroids do not prevent exercise-induced asthma in the short term. With long-term use, however, they improve airway hyperresponsiveness and decrease the bronchoconstriction associated with exertion.

If patients experience acute breakthrough symptoms despite prophylactic treatment or in the absence of prophylactic treatment, the primary treatment is a short-acting β-agonist. Other prophylactic measures, such as chromones and leukotriene antagonists, are not effective for acute treatment of exercise-induced asthma.

6.7.7.4 Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction to the antigens of *Aspergillus fumigatus*, a ubiquitous airborne fungus. This reaction occurs primarily in patients with asthma or cystic fibrosis. The aspergillus spores within the bronchial tree activate the immune system to cause tissue inflammation that results in proximal bronchiectasis and bronchiolitis obliterans. ABPA occurs in 1–2% of patients with persistent asthma and in 2–15% of those with cystic fibrosis. ABPA can occur in asthma of any severity, but it is more common in patients with moderate or severe persistent asthma.

The pathogenesis of ABPA is incompletely understood. T-cells likely have an important role by generating cytokines such as IL-4, IL-5, and IL-13 that contribute to the eosinophilia and elevated IgE seen in ABPA. In addition to the Th-2-mediated eosinophilic inflammation, enzymes and toxins released from the fungi and neutrophilic-mediated inflammation likely contribute to airway damage and central bronchiectasis. Besides the histologic features of asthma, ABPA is characterized by mucoid impaction of the bronchi and bronchocentric granulomatosis. The fungi do not invade the mucosa, but instead serve as the instigator of the immune response.

The clinical presentation of ABPA is characterized by persistent asthma complicated by recurrent episodes of bronchial obstruction, expectoration of brownish mucous plugs, and difficult-to-control asthma. No single test confirms the diagnosis of ABPA. Because of the marked inflammatory response, several laboratory abnormalities are typically noted. The diagnostic criteria for ABPA include the following:

1. History of asthma
2. Positive skin prick test or in vitro test to *A. fumigatus*
3. Elevated serum levels of IgG and IgE to *A. fumigatus*
4. Elevated total serum IgE (>1,000 ng mL^{-1})
5. Eosinophilia (>500 μL^{-1})
6. Pulmonary infiltrates on chest X-ray or chest CT
7. Central bronchiectasis

To make the diagnosis of ABPA, both a history of asthma (or cystic fibrosis) and a positive skin prick test or in vitro test to *A. fumigatus* should be documented (criteria 1 and 2 above). However, asthma patients can have IgE sensitivity to *A. fumigatus* without having ABPA. Approximately 20–30% of asthma patients have positive immediate skin prick testing to *A. fumigatus*. The diagnosis of ABPA-S (seropositive) is made when the first four criteria are met. The diagnosis of ABPA-CB (central bronchiectasis) is made when criteria 1–4 and 7 are met. A staging system has also been devised for ABPA.

- Stage 1 (acute): patient first appears with ABPA-S
- Stage 2 (remission): IgE level has decreased to 50–75% of the peak IgE
- Stage 3 (exacerbation): new radiographic infiltrates; IgE doubles
- Stage 4 (corticosteroid dependent): prednisone cannot be tapered without worsening asthma symptoms; increase in IgE level or development of radiographic infiltrates
- Stage 5 (fibrosis): lungs are fibrotic; pulmonary function testing shows restrictive defect with irreversible obstruction

The treatment of ABPA is designed to control the episodes of acute inflammation and to prevent the development of progressive lung injury and fibrosis. An acute flare of ABPA (stage 1 or 3) is treated with 0.5–1.0 mg kg^{-1} of prednisone for 14 days, followed by reduction to every-other-day dosing and tapering over 2–4 months. The total serum IgE is an excellent marker of disease and should be monitored at 4 weeks and then monthly or bimonthly for 1 year. Clinical improvement is generally accompanied by a 35% decrease in serum IgE. If serum IgE does not decrease, one should consider medicine noncompliance, a continuing ABPA exacerbation, or another diagnosis. If patients are treated early and aggressively, few will have the disease progress to stage 5. Corticosteroids do not appear to benefit stage 5 disease. Itraconazole has also been studied in ABPA, and it should not be administered in place of corticosteroids for ABPA. Itraconazole may provide additional benefit to corticosteroid treatment. It should be considered for patients with a slow or poor response to corticosteroids or stage 4 disease. The daily dose should

not exceed 400 mg. Typical duration of therapy is 3–6 months. With itraconazole therapy, liver function tests should be monitored monthly.

6.7.7.5 Churg–Strauss Syndrome

Churg–Strauss syndrome is a systemic small-vessel vasculitis that occurs in patients with severe asthma and sinusitis. Four different definitions of the diagnosis of Churg–Strauss syndrome have been developed: the pathologic criteria of Churg and Strauss, the clinical criteria of Lanham and colleagues, the clinical criteria from the American College of Rheumatology, and the criteria from the Chapel Hill Concensus Conference (Table 6.22). This syndrome is a systemic disease that develops in patients with a history of upper airway disease and sinusitis. Involvement of other organs varies but typically includes the heart, gastrointestinal tract, cerebral vessels, joints, muscles, skin, and nerves. There is no single confirmatory laboratory test for Churg–Strauss syndrome. The diagnosis depends on the clinical presentation of the disease, with its histologic hallmarks. Tissue eosinophilia is essential, and blood eosinophilia in an untreated patient is almost always present. Although perinuclear anti-neutrophilic cytoplasmic antibody (p-ANCA) is usually detectable, its absence does not rule out the syndrome.

Churg–Strauss syndrome should be considered in a patient with moderate to severe asthma who has any of the following features: new-onset footdrop (mononeuritis

Table 6.22 Definitions of Churg–Strauss syndrome

Churg and Strauss 1951 (autopsy pathologic material)
History of asthma
Tissue eosinophilia
Systemic vasculitis
Extravascular granulomas
Fibrinoid necrosis of connective tissue
Lanham et al. (1984) (clinical with or without pathologic condition)
Asthma
Eosinophilia, $>1.5 \times 10^9\ L^{-1}$
Evidence of vasculitis that involves at least two organs
American College of Rheumatology 1990 (Masi, A. T. et al.) (clinical with or without pathologic condition; diagnosis likely when four of the six criteria are present)
Asthma
Eosinophilia, >10%
Neuropathy, mononeuropathy, or polyneuropathy
Pulmonary infiltrates
Paranasal sinus abnormality
Extravascular eosinophil infiltration on biopsy
Chapel Hill Consensus Conference 1994 (Jennette, J. C. et al.) (pathologic/clinical)
"Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels and associated with asthma and eosinophilia"

From Lilly, C. M., Churg, A., Lazarovich, M., et al. (2002) Asthma therapies and Churg–Strauss syndrome. J. Allergy Clin. Immunol. 109, S1–S19. Used with permission

multiplex); palpable purpura, bruising, or chronic urticarial-type lesions (small-vessel vasculitis of dermal blood vessels); migratory pulmonary infiltrates (eosinophilic infiltration of the lung); or cardiac enlargement with or without failure. Other associated symptoms include decreased appetite, paresthesias, headache, arthralgias, abdominal pain, proteinuria or hematuria, or worsening sinusitis. The differential diagnosis includes hypereosinophilic syndrome, the vasculitides, ABPA, hyperplastic rhinosinusitis with nasal polyposis, eosinophilic pneumonia, parasitic disease, and drug allergy.

Laboratory evaluation includes a complete blood count with differential cell count, ANCA studies, erythrocyte sedimentation rate, urinalysis, chest radiography, aspergillus skin testing, total IgE, stool examination for ova and parasites, and biopsy. Diagnostic biopsy should be performed on the most accessible affected tissue. Biopsy of sites that are not affected clinically is of limited value and therefore discouraged. Helpful biopsy sites include the sural nerve or affected muscle of patients with footdrop, skin biopsy of those with purpura, and lung biopsy of those with migratory pulmonary infiltrates.

The clinical course of Churg–Strauss syndrome varies, and there are no proven markers of disease activity. Nevertheless, monitoring of blood eosinophil counts and acute phase reactants are generally recommended for monitoring disease activity. Elevations in these may presage clinical exacerbation and help the physician in guiding medical management. For most patients with evidence of active vasculitis, corticosteroids and immunosuppressive agents are considered first-line therapy. Treatment for Churg–Strauss syndrome requires high doses of corticosteroids, with adjustment of the dose based on disease response. When corticosteroid therapy does not induce remission, the primary immunosuppressive agents used are cyclophosphamide and α-interferon.

6.8 Clinical Vignettes

6.8.1 Vignette 1

A 70-year-old man presented with continued cough, dyspnea, and wheeze. He had no previous history of respiratory problems until 1 year ago when concomitant sinusitis and cough, dyspnea, and wheeze developed. At that time, evaluation showed the following: normal chest radiograph; pulmonary function testing with a markedly decreased FEV_1/FVC ratio and an FEV_1 of 0.91 L, 28% predicted, and normal DLCO; coronal sinus CT with chronic pansinusitis and nasal polyps; negative ANCA studies; normal IgE; and negative allergen skin prick testing to common aeroallergens, including *Aspergillus*. He subsequently had functional endoscopic sinus surgery, after which his sinus symptoms improved significantly. However, over the course of the year, he continued to have cough, dyspnea, and wheeze essentially daily. He states that he does not have nighttime symptoms. He states that he has no other health problems, specifically no skin rash, weakness, or kidney problems.

Currently, he reports taking a combination of fluticasone and salmeterol (Advair) 250/50 one puff twice daily, prednisone 20 mg per day, montelukast (Singulair) 10 mg per day, pantoprazole (Protonix) 20 mg per day, and albuterol inhaler approximately once daily. Physical examination showed normal vital signs and normal skin. Ears, nose, and throat examination was normal. The cardiac examination was unremarkable. Lung examination was notable for scattered mild expiratory wheeze. There were no increased breath sounds over the sternal notch or inspiratory breath sounds. Currently, spirometry showed a decreased FEV_1/FVC ratio with an FEV_1 of 1.64 L, 51% predicted. Inspiratory loop was normal. Peripheral blood eosinophils were undetectable. Chest radiographic findings were unremarkable.

Comment: This situation represents a difficult process. The patient is currently symptomatic despite prednisone therapy and an intensive asthma management program. Always in severe asthma or steroid-dependent asthma, one must ensure that asthma is the correct diagnosis. In this case, the patient's clinical symptoms and pulmonary function testing are compatible with asthma. Other considerations that have been assessed include special subsets of asthma; ABPA (unlikely given the negative *Aspergillus* skin test and normal IgE) and Churg–Strauss syndrome (unlikely given the lack of peripheral eosinophilia, negative ANCA studies, and lack of skin or neurologic symptoms). Other conditions, including cardiac conditions, upper airway disorders, and other pulmonary conditions should also be assessed. On the basis of the above studies and thorough physical examination, these other conditions do not appear to be involved at this point. The next step is to consider all the factors that can contribute to asthma. The main issues to address are compliance, technique, and evaluation of exacerbators, using the mnemonic "air-smog," which includes *a*llergens, *i*rritants, *r*hinosinusitis, *s*moking, *m*edications, *o*ccupational history, and *g*astroesophageal reflux.

These issues were reviewed with the patient. Compliance did not appear to be an issue. Both he and his wife were quite clear in confirming his medication schedule. Technique was an issue. It was noted he was using the fluticasone/salmeterol inhaler incorrectly. He was given instruction and observed using the medication until it was mastered. Possible exacerbators of his asthma were reviewed. Allergens were thought not likely to be a factor based on negative skin prick testing to the common aeroallergens. He did not have exposure to irritants at his home. The rhinosinusitis had been stable since his surgery. He received maintenance treatment with intranasal corticosteroid and saline irrigations. He was a nonsmoker. He was not taking any β-blocker medication, in either pill or eye drop form. He was retired but continued to haul fertilizer by truck (occupation) and would occasionally note increased symptoms when loading and unloading the truck. He often forgot to wear a mask when loading and unloading. Although he had a history of gastroesophageal reflux, it was well controlled with pantoprazole.

Comment: Further review uncovered areas for improvement. The main areas were improved inhaler technique and the use of a mask when loading and unloading the fertilizer. Also, to maximize his inhaler regimen, fluticasone/salmeterol was increased to a high dose 500/50 one puff twice daily, with plans for a slow prednisone taper.

At follow-up 2 months later, the patient noted significant improvement, although he still required prednisone 5 mg per day to maintain good symptom control. He did not develop any other symptoms. He continued his inhaler regimen and his rhinosinusitis treatment. Further evaluation showed peripheral eosinophils 200 μL^{-1} (normal, <500), sputum eosinophils of 8% (normal, <3%), and exhaled nitric oxide 50 parts per billion (normal, <30). His FEV_1 increased to 70% predicted.

Comment: This patient would be considered to have severe asthma on the basis of the medications required to keep his symptoms controlled. He appears to have the late-onset, eosinophilic inflammation phenotype. In this phenotype, it is not uncommon to have concomitant sinus disease. This phenotype is typically difficult to treat. The patient will require close follow-up and should have preventive measures placed and close monitoring for corticosteroid adverse effects, particularly for posterior subcapsular cataracts and osteoporosis. Compliance, technique, and exacerbating factors (airsmog) need to be assessed routinely. The development of Churg–Strauss syndrome should be kept in mind. The goal is to decrease the corticosteroid dose whenever possible based on symptoms, pulmonary function, and inflammatory parameters.

6.8.2 Vignette 2

A 26-year-old female nurse with a history of anxiety presents for evaluation of asthma symptoms that have developed over the past 8 months. Despite the use of daily high-dose inhaled corticosteroids, long-acting β-agonist, and frequent use of albuterol, she continues to have symptoms of dyspnea. No cough is associated with this, but at times she feels that she wheezes. She states that she has no symptoms of rhinitis or gastroesophageal reflux. Her respiratory symptoms occur either randomly or sometimes with exposures to strong odors. There is not a strong association with exercise. She does feel it is worse when she is under increased stress. She has been treated with oral corticosteroids three times over the past 8 months. Currently, she is asymptomatic, and physical examination findings, with close attention paid to the ears, nose, and throat; heart; and lung examinations, are completely normal. Previous evaluations have included chest radiography, spirometry, electrocardiography, and echocardiography, and the results were normal.

Comment: She already has had many tests performed that have been nonrevealing. It is extremely important to obtain a good description of her dyspnea and wheeze.

The patient describes the dyspnea as typically occurring suddenly. Within minutes, she will quickly go from feeling fine to feeling that she is short of breath or cannot get a deep breath. Sometimes, the symptoms last up to 30 min and other times for days. In between episodes, she is asymptomatic. The albuterol does not seem to help when she uses it. She is not sure if the prednisone made any difference in her symptoms. She describes the wheeze as “loud breathing,” typically more pronounced during inspiration.

Comment: The details of her symptoms are helpful. The sudden onset of symptoms can be seen in asthma, but asthma is generally slower in onset. The lack of benefit from albuterol and prednisone is highly suggestive of a process other than asthma. The noisy breathing during inspiration may be more consistent with stridor than with wheeze. Stridor can be a sign of an upper airway obstruction. In fixed upper airway obstruction, symptoms typically are precipitated initially by exertion and may progress to the point of occurring at rest. Currently, she is asymptomatic; it would be most helpful to evaluate her at a time she is symptomatic.

The patient returns when she is symptomatic. She appears dyspneic, with a respiratory rate of 24 breaths per minute and has audible stridor. Pulse oximetry is normal at 98% oxygen saturation. The lung examination shows increased breath sounds over the sternal notch with inspiration. The chest is clear.

Comment: The physical examination findings are not typical for asthma. An upper airway process is suggested by stridor and increased breath sounds over the sternal notch. Evaluation of the upper airway is needed.

While the patient was symptomatic, rhinolaryngoscopy was performed and showed paradoxical vocal cord adduction during inspiration.

Comment: This finding is diagnostic of vocal cord dysfunction. Unfortunately, it is often difficult to perform rhinolaryngoscopy when the patient is symptomatic. An inspiratory loop performed when the patient is symptomatic can be helpful, because it would show a flattened inspiratory loop and normal expiratory loop. Management of vocal cord dysfunction includes speech therapy and treatment of possible exacerbating factors, such as anxiety, depression, gastroesophageal reflux, and rhinitis.

6.8.3 Vignette 3

A 27-year-old woman presents during her first trimester of pregnancy for evaluation of her asthma. She describes a history of mild asthma dating back to childhood. She has never been hospitalized for asthma but did require an emergency department visit 7 months ago. She believed her asthma worsened with her previous pregnancy 3 years ago. Currently, she describes daily symptoms of wheeze and shortness of breath and nighttime symptoms once or twice weekly. She is using her albuterol inhaler three times daily. She was prescribed an inhaled corticosteroid 7 months ago, but discontinued it 3 months ago when she discovered she was pregnant. She has intermittent rhinitis symptoms but says she has no gastroesophageal reflux. She thinks her asthma is worse when cleaning the house. She has had a cat in the home for the last year. She does not smoke cigarettes. Physical examination showed scattered end-expiratory wheezes. Spirometry showed a decreased FEV_1/FVC ratio and an FEV_1 of 75% predicted. This improved to 85% predicted after two puffs of inhaled albuterol.

Comment: This patient has mild-to-moderate persistent asthma that is not optimally controlled. In an effort to improve her asthma, education should be undertaken to explain the management of asthma in pregnancy. It should be emphasized that the main

risk to her and her baby is not the common medications used to treat asthma, but rather poorly controlled asthma. Allergy testing, particularly to dust mite and cat, would be helpful to assess possible exacerbators of her asthma. She is at risk for worsening asthma during this pregnancy because it occurred with her last pregnancy.

Allergy skin testing was strongly positive to dust mite, but negative to cat.

Comment: A comprehensive asthma management plan should be outlined that includes the following: (1) education about asthma and pregnancy, (2) environmental measures to decrease dust mite exposure, primarily by encasing the mattress and pillows with allergen-impermeable covers and washing the bedding in hot water weekly, (3) institution of low-dose inhaled corticosteroid, with instruction on inhaler technique, (4) peak flow rate instruction and development of a peak flow-based asthma action plan, and (5) follow-up in 2–4 weeks and scheduled visits thereafter, with easy availability for any problems between scheduled visits.

6.8.4 Vignette 4

A 42-year-old woman presents for evaluation of a 6-month history of chest tightness, nonproductive cough, and dyspnea. The patient reports a long-standing history of mild allergic rhinitis, with symptoms primarily in the spring and fall; however, these symptoms have been rather constant over the past year. She does not recall respiratory problems or asthma being diagnosed when she was a child. The patient has never smoked, and there have not been any changes in the home environment over the past decade. She says she does not take any prescription or over-the-counter medications or have symptoms of gastroesophageal reflux. Overall, she was in good general health. Her vital signs were normal. Nasal examination was notable for boggy edema of the inferior turbinates, with a small amount of clearish discharge. The heart examination was normal. The lung examination showed scattered expiratory wheezes. Spirometry showed a slightly decreased FEV_1/FVC ratio and an FEV_1 of 80% of predicted. This improved to 94% of predicted after two puffs of albuterol.

Comment: The patient's history, physical examination findings, and spirometry are consistent with rhinitis and asthma. Although she has a history of seasonal allergies, it is not clear why persistent rhinitis and asthma have developed. More information is required about her home and work environment to search for clues to why this may have progressed.

The patient relates she has lived in the same home for the past 12 years. No major remodeling has been done, and there has not been any dampness or water damage. She does not have any pets. However, she reports that she changed jobs approximately 1 year ago. She previously had worked as a cashier and now works in a bakery for a local supermarket. Her primary jobs are cake decoration and baking. On further questioning, she thought her symptoms were worse on days she baked cakes and better on days when she was not at work. She did not have a history of food allergies.

Comment: Possibilities for her increasing symptoms include a new sensitivity to dust mite or occupational exposure. The patient's report of increased symptoms at work raises the question of occupational asthma. In a bakery, wheat flour is the most common allergen, followed by soy flour. The role of an occupational exposure can be measured by having the patient stay off work for 1 week, then remeasuring the FEV_1, or performing serial peak flows before and after work exposure.

The patient stayed home from work for 1 week, treating her respiratory symptoms with inhaled albuterol. Her symptoms were well controlled with albuterol. Albuterol was discontinued 24 hours before her follow-up visit at the end of the week. On the follow-up visit, her lungs were clear to auscultation. Spirometry showed a baseline FEV_1 of 95% predicted and a normal FEV_1/FVC ratio. Allergen skin prick testing was markedly positive to wheat flour and was negative to soy flour and dust mite.

Comment: The findings are consistent with allergy to inhaled wheat flour, or "bakers' asthma," resulting in allergic rhinitis and asthma. Ideally, she should be moved to an area with limited exposure to wheat flour. Continued exposure to wheat flour would result in persistent rhinitis and asthma symptoms. It is important to treat the rhinitis as part of the asthma management. Masking and aggressive pharmacologic measures, including intranasal corticosteroid, H_1-blocker, inhaled corticosteroid, and inhaled β-agonist (as needed), should be used if the patient remains on the job. However, this would not be ideal.

6.8.5 Vignette 5

A 36-year-old female day care worker has a history of mild persistent asthma. She developed a persistent cough, maxillary discomfort, and purulent nasal secretions 7 days after contracting an upper respiratory tract infection. Her asthma had worsened, and she reported only partial relief with the use of inhaled albuterol. The physical examination was notable for a low-grade temperature of 100.4°F, right maxillary tenderness, purulent nasal secretions, and scattered end-expiratory wheezes. The peak expiratory flow was 330 L min^{-1}, 70% of predicted. Initial treatment included amoxicillin-clavulanate (Augmentin), 875 mg twice daily; increasing the daily inhaled steroid budesonide 200 μg from one puff twice daily to two puffs twice daily, and albuterol MDI, two puffs as needed every 4 hours.

Comment: The patient has had an upper respiratory tract infection, and now she has sinusitis and worsening asthma. Upper respiratory tract infections are the most common trigger for acute worsening of asthma. Increasing the inhaled corticosteroid may help improve the asthma exacerbation. This is likely most effective when done earlier in the course. The sinusitis is being treated appropriately with amoxicillin-clavulanate.

The patient returns 2 days later with increasing shortness of breath, chest tightness, and cough. She has been using her albuterol inhaler 4 times daily with only

mild improvement in symptoms. On physical examination, she is afebrile with frequent coughing and a respiratory rate of 20 breaths per minute. The lung examination shows scattered expiratory wheezes throughout all lung fields. There are no crackles. Peak flow is 220 L min^{-1}, 50% of predicted. She was given albuterol, 0.5 mg in 3 mL of saline by nebulization × 3 and prednisone 40 mg by mouth. Following the nebulizations, the lung examination showed a decrease in the expiratory wheezes, with good air movement. The peak flow rate improved to 360 L min^{-1}, and, subjectively, the patient felt better. She was prescribed prednisone 40 mg per day for 5 days and albuterol inhaler two puffs every 4 hours, with continuation of budesonide 200 μg, two puffs twice daily. Plans were made for follow-up in 5 days, or sooner if her symptoms worsened.

Comment: Patients, even with mild asthma, can have severe exacerbations in conjunction with respiratory infections. These require aggressive treatment. The earlier use of high-dose inhaled corticosteroid or oral prednisone may have prevented the severe exacerbation.

At follow-up 5 days later, the lung examination showed only rare expiratory wheeze, and peak flow increased to 410 L min^{-1}. She was asked to continue the budesonide at two puffs twice daily for 6 weeks, with probable resumption to one puff twice daily at that time.

Comment: The patient had significant improvement with the use of oral prednisone. Even though her condition was clinically improved, the asthma, particularly from an inflammatory viewpoint, has not returned to baseline. To help prevent relapse and to hasten recovery to preexacerbation levels, she will continue the higher dose of inhaled corticosteroid for 6 weeks. At that time, she should have a follow-up examination and a review of her peak flow measurements to aid in reestablishing her management program.

Suggested Reading

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