II  ASTHMA

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Definition

Asthma is characterized by narrowing of the airways in response to various stimuli and the presence of airway inflammation of varying degree. Unlike the more fixed or permanent airflow obstruction typical of chronic bronchitis, emphysema, cystic fibrosis, bronchiectasis, and bronchiolitis, the airflow obstruction associated with asthma may be completely reversible [see 14:III Chronic Obstructive Diseases of the Lung]. Asthma is a chronic disease, yet the degree of airflow obstruction can vary widely over time and change within minutes or over a period of days to weeks. Increased responsiveness of the airways to various stimuli is seen even in asymptomatic asthma patients who have normal lung function.

Increased responsiveness of the airways and reversible airflow obstruction are not unique to asthma. Many patients with chronic obstructive lung disease (e.g., chronic bronchitis or cystic fibrosis) exhibit nonspecific hyperresponsiveness, although obstruction is not completely reversible and some degree of obstruction is always present. In particular, some current or past cigarette smokers with chronic bronchitis and airflow obstruction exhibit episodic wheezing and shortness of breath that closely mimic asthma. There is no consensus on how such patients should be classified, but we prefer to consider their ailment not as asthma but as asthmatic bronchitis, a subcategory of chronic bronchitis that has features in common with asthma [see 14:III Chronic Obstructive Diseases of the Lung]. This distinction is important in studies of the prevalence and mortality of asthma.

There is no single pathognomonic feature by which asthma may be recognized, nor is there a definitive diagnostic test for asthma. Many clinical settings, such as wheezing in association with childhood respiratory tract infections and long-standing asthma in adults with irreversible obstruction, defy straightforward classification. Fortunately, in clinical practice, asthma is generally far easier to recognize than it is to define.

Epidemiology

The prevalence of self-reported asthma was 7.2% in 2000, an increase of 130% from 1982.1 The incidence of new cases of asthma was highest in persons younger than 5 years. In persons older than 10 years, the incidence remained at approximately 0.2 to 0.4 new cases per 100 person-years at risk. The prevalence of asthma was higher for boys than for girls and higher in Hispanic and African-American children than in white children, though the difference has decreased in recent years.2 In a population survey, obesity was found to be associated with an increased prevalence of asthma.3 In persons older than 40 years who were newly diagnosed as having asthma, approximately one half had a history of cigarette smoking and had been previously diagnosed as having chronic bronchitis or emphysema; these patients would have been more accurately diagnosed as having asthmatic bronchitis. Still, the number of cases of asthma that develop in persons who have never smoked cigarettes is sufficiently large to make true adult-onset asthma common.

The reported prevalence of asthma in the United States is higher than in Japanese and in Eskimo populations but lower than in New Zealand. It is not known whether these differences reflect genetic or environmental factors or result from variable diagnostic criteria. Data suggest that there are genetic markers on multiple chromosomes that relate to bronchial hyperresponsiveness and atopy.4 Childhood exposure to antigen-rich environments, such as a farm, is associated with a reduced incidence of asthma and allergy, suggesting changes in the maturation process of the immune system.5

In patients with chronic asthma, Mycoplasma and Chlamydia species have been identified in lung specimens, suggesting a possible role for infection in the pathogenesis.6

The prevalence of bronchial hyperreactivity far exceeds that of clinically manifest asthma. In large population surveys, many of the persons with hyperresponsive test results were free of respiratory symptoms. In the general population, bronchial responsiveness occurs in a normal pattern of distribution, with a skew toward increased reactivity. Some persons with hyperreactive airways do not have asthma [see Figure 1] but may develop asthma later in life. In patients with asthma, there is a direct relation between heightened bronchial responsiveness and annual decline in lung function.7

Complete remission of asthma is relatively common in children; as many as 25% remain asymptomatic from adolescence onward. Infrequent symptoms and normal pulmonary function are favorable prognostic factors. In adults, prolonged remission of asthmatic symptoms is considerably less common. Patients older than 65 years tend to have severe asthma that infrequently goes into remission; in these patients, asthma is less reversible.

Asthma was once thought to cause considerable morbidity but not mortality. It is now clear that severe attacks of asthma can end fatally. In the United States in 1999, the annual mortality from asthma in persons 15 to 34 years of age was 0.59 per 100,000 population, an incidence about twice that in 1980.1 In some areas of the United States, this increase occurred despite a decrease in

![Figure 1](image-url)
air pollution. Mortality was more than twice as high among African Americans as among whites and was greatest in patients with eosinophilia and in those who experienced major responses to inhaled bronchodilators. Most deaths occur in places other than the hospital and are most likely the result of asphyxiation caused by pulmonary obstruction. Rapid progression to respiratory failure (hyperacute attacks) characterizes near-fatal episodes. Some sudden deaths in asthmatic patients may be caused by cardiac injury incurred as a result of the disease or of toxicity from the drugs used to treat it. Many of the patients who die during an attack previously had a life-threatening attack, suggesting that some of the patients at greatest risk can be identified and potentially managed differently. Elderly patients may be at particular risk for undertreatment because they are less aware of bronchoconstriction than younger patients.

Pathogenesis

The pathologic features of asthma are airway wall inflammation associated with infiltration by various inflammatory cells, luminal obstruction of airways by inflammatory cells, mucus and shed epithelial cells, and bronchial wall edema secondary to increased vascular permeability.1 Characteristic of but not unique to asthma are thickening of the epithelial basement membrane, eosinophilic infiltration, and hypertrophy and hyperplasia of airway smooth muscle. Pulmonary arteries adjacent to occluded, inflamed airways also show inflammation.

Cellular and biochemical mechanisms have been sought for three important features of the disease: chronic airway inflammation, reversible airflow obstruction, and bronchial hyperreactivity. The allergen immunologic model is an important contribution to our current understanding of the pathogenesis of asthma [see Allergen Model, below, and 6:VII Allergy].

ALLERGEN MODEL

In atopic persons, repeated antigen exposure leads to the synthesis and secretion by plasma cells of specific IgE antibodies [see Figure 2]. Presentation of sensitizing antigen by mucosal dendritic cells to Th2 CD4+ T cells results in the production of interleukin-4 (IL-4) and IL-13, which stimulate B cells to produce IgE. Antigen-specific IgE becomes fixed to mast cells as well as to basophils and certain other cell types. Antigens can cross-link adjacent IgE molecules, triggering a series of biochemical reactions that cause the explosive release of vasoactive, bronchoactive, and chemotactic agents from mast cell granules into the extracellular milieu; these agents have an important role in airway inflammation, contraction, and hyperresponsiveness. Chemical mediators of airway inflammation released after stimulation of mast cells include (1) preformed mediators contained within granules, such as histamine, and several cytokines, such as IL-4, IL-5, granulocyte-macrophage colony-stimulating factor [GM-CSF], and tumor necrosis factor-α (TNF-α), and (2) newly synthesized phospholipid derivatives, including leukotrienes (sulfidopeptide leukotrienes C₄, D₄, and E₄), prostaglandins, and platelet-activating factor (PAF). These mediators cause the contraction of bronchial smooth muscle, stimulation of intraepithelial sensory nerve endings (leading to reflex bronchoconstriction via vagal cholinergic efferent pathways), increased microvascular permeability (facilitating the formation of airway edema), stimulation of secretion of mucus, and the production in the bone marrow of inflammatory cells, including eosinophils, and their subsequent migration into the airways. Eosinophils infiltrate the airways during the hours after an allergen exposure and may contribute to the pathogenesis of asthma in several ways [see Figure 2].1 Eosinophils preferentially synthesize leukotriene C₄ from arachidonic acid, releasing additional amounts of this potent mediator. They also stimulate histamine release from mast cells and basophils, providing a positive feedback loop. In addition, eosinophils release major basic protein, a granule-derived protein that has potent toxic effects on the respiratory epithelium.

When the thickness of an airway wall increases as a result of edema and cellular infiltration, any degree of smooth muscle contraction will cause a corresponding increase in airflow obstruction, thereby resulting in hyperresponsiveness.

A subgroup of patients with asthma develop irreversible airflow obstruction,2 thought to be the result of permanent remodeling of the airway. Pathologically, airway remodeling is characterized by bronchial wall thickening caused by an increase in the thickness of the lamina reticularis, an increase in the number and size of smooth muscle cells, and an increase in mucous glands and blood vessels; these changes correlate with disease severity. Substances generated by inflammatory cells, such as transforming growth factor–β (TGF-β), probably mediate these changes.3

Many questions remain unanswered by the allergen model of the pathogenesis of asthma. For example, persons with asthma often have no evident sensitivity to allergens, no excess of circulating IgE antibodies, and no increase in the number of mast cells retrievable on lavage of the lung. Furthermore, the asthma in such patients is clinically indistinguishable in its major features from allergen-triggered asthma in patients with atopy; shared characteristics include the presence of cytokines suggestive of Th2 lymphocyte participation4 and increased numbers of high-affinity IgE receptors.5 There may be differences in the degrees of airway inflammation and remodeling between the two types, and there may be a greater number of neutrophils, as compared with eosinophils, in the nonatopic group.6 Although mast cells may be activated by events other than antigen-specific IgE cross-linking on the cell surface, such as binding of complement components C3a and C5a, it is difficult to assign the mast cell a pivotal role in patients with non–allergen-triggered asthma.

ABNORMAL NEURAL REGULATION MODEL

An alternative hypothesis implicates abnormalities in the autonomic neural regulation of airway function.7 Administration of a beta-adrenergic blocking agent such as propranolol uniformly induces airflow obstruction in persons with asthma; this suggests that an imbalance between excitatory (i.e., bronchoconstrictor) and inhibitory (i.e., bronchodilator) neural input may be present. Autonomic dysfunction that would favor the development of bronchoconstriction in patients with asthma might include increased stimulation of the afferent limb of the parasympathetic reflex, a deficiency in the number or the function of beta-adrenergic receptors, an increase in alpha-adrenergic receptor responsiveness, and a deficiency in inhibitory innervation.8 Peptide transmitters contained within sensory nerve endings are extremely potent bronchoconstrictors. Their release after retrograde conduction down a sensory nerve axon may be another important mechanism leading to airflow obstruction in patients with asthma.

COMBINATION MODELS

It is likely that chemical mediators released from inflammatory cells interact with the autonomic nervous system. Many me-
Leukotrienes produce bronchospasm and airway edema. Released chemotactic factors, along with factors from the Th2 CD4+ T cells, cell to degranulate, which in turn leads to the release of mediators of the immediate response and the late response. Histamine and the IL-4, IL-6, and IL-13 from Th2 CD4+ T cells to produce IgE, which binds to mast cells. Inhaled antigen binds to IgE, stimulating the mast cell to degranulate, which in turn leads to the release of mediators of the immediate response and the late response. Histamine and the leukotrienes produce bronchospasm and airway edema. Released chemotactic factors, along with factors from the Th2 CD4+ T cells, facilitate eosinophil traffic from the bone marrow to the airway walls. These late responses lead to excessive mucus production, airway wall inflammation, injury, and hyperresponsiveness. (GM-CSF—granulocyte-macrophage colony-stimulating factor; IL—interleukin)

Pathogenesis of allergic asthma. Inhaled antigen is processed by dendritic cells and presented to Th0 CD4+ T cells. This results in the generation of either Th1 or Th2 CD4+ T cells, with Th2 CD4+ T cells predominating in asthma. B cells are stimulated by interleukins IL-4, IL-5, and IL-13 from Th2 CD4+ T cells to produce IgE, which binds to mast cells. Inhaled antigen binds to IgE, stimulating the mast cell to degranulate, which in turn leads to the release of mediators of the immediate response and the late response. Histamine and the leukotrienes produce bronchospasm and airway edema. Released chemotactic factors, along with factors from the Th2 CD4+ T cells, facilitate eosinophil traffic from the bone marrow to the airway walls. These late responses lead to excessive mucus production, airway wall inflammation, injury, and hyperresponsiveness. (GM-CSF—granulocyte-macrophage colony-stimulating factor; IL—interleukin)

Pathophysiology

The severity of airflow obstruction in patients with asthma ranges from being virtually nonexistent to being very severe, with associated respiratory failure. During an attack of asthma, spirometric indices are those typical of an obstructive ventilatory defect [see 14/1 Functional Assessment of the Lung and Diagnostic Techniques]. The forced vital capacity may remain within the normal range during mild obstruction but may be reduced during a severe attack to 50% of normal or lower because of airway closure with gas trapping. The forced expiratory volume in 1 second (FEV1) and the peak expiratory flow (PEF) provide objective measurements for assessing the severity of airflow obstruction and for monitoring the course of an exacerbation of asthma. Although there is considerable variability, on average, a patient requiring emergency treatment has an FEV1 or PEF that is 30% to 35% of normal. Residual volume increases as airflow obstruction worsens and may exceed values of four times normal. In moderate to severe attacks of asthma, functional residual capacity (FRC) may increase by as much as 1 to 2 L above normal. In part, contraction of inspiratory muscles during the expiratory phase of the respiratory cycle, when inspiratory muscles are normally at rest, may...
serve to maintain this hyperinflated FRC. Except in cases involving severe airflow obstruction, total lung capacity (TLC) remains within the normal range.

Residual abnormalities in lung function may persist even after complete symptomatic resolution of acute episodes of asthma. Typically, decreases in maximal flow rates and increases in residual volume may persist for days to weeks after an acute attack and may represent persistent low-grade airway inflammation.

The transfer factor for carbon monoxide may be elevated in some patients, possibly because of greater recruitment of capillaries from higher pulmonary arterial pressure. Because of ventilation-perfusion mismatching, an elevation in the alveolar-arterial oxygen difference (A-aDO₂) is common, but severe hypoxemia is rare. The severity of hypoxemia cannot be accurately determined from the degree of airflow obstruction—an observation that has led to the idea that hypoxemia may be related more to peripheral airway obstruction than to central obstruction.

The tachypnea and alveolar hyperventilation that are observed during an asthmatic exacerbation result not from chemoreceptor stimulation but from neural reflexes within the lungs. Hypocapnia and respiratory alkalosis are the most common findings on arterial blood gas analysis. Metabolic (lactic) acidosis may also be seen if there is severe hypoxemia in combination with the increased work of breathing. When airflow obstruction becomes very severe (FEV₁ < 25% of normal), dead space ventilation increases, whereas total ventilation can increase no further; this results in an increase in carbon dioxide tension (Pco₂) back to normal levels. Ultimately, despite an increase in CO₂ production, total minute ventilation begins to fall; as a result, alveolar ventilation decreases still further and hypocapnia ensues. Respiratory muscle fatigue has been postulated as a potential cause of hypercapnic respiratory failure in patients with asthma.

**Dyspnea**

Dyspnea tends to vary greatly over time, depending on the severity of airflow obstruction. At times, airflow obstruction prevents any significant physical exertion; at other times, strenuous exercise is possible but may trigger wheezing and shortness of breath [see Exercise-Induced Asthma, below]. During a severe attack, a desperate hunger for air is the overwhelming symptom. Chest tightness commonly occurs with dyspnea and may be confused with angina pectoris. Most patients associate their chest tightness with the sensation of being unable to take in a full and satisfying breath. Older patients are less aware of airflow obstruction.

Bronchoconstriction can be triggered by a variety of stimuli that have little or no impact on the airways of nonasthmatic persons; these responses can be helpful diagnostically. The stimulus need not be a specific allergen or chemical in the workplace; a nonspecific (i.e., nonantigenic) stimulus, such as strenuous exercise, especially while breathing dry air, may trigger the response.

**STIMULI THAT TRIGGER ATTACKS**

The stimuli that trigger attacks vary among persons. For many patients, attacks of asthma are triggered by allergens such as ragweed or animal dander, house dust containing antigens from dust mites and cockroaches, strong odors or fumes, and ingested substances such as certain foods, sulfiting agents, aspirin, and tartrazine [see Specific Forms and Complications of Asthma, below]. Emotional upset and stress may trigger symptoms in some patients, but the precise role of the central nervous system in regulating airway function is difficult to quantitate. Reflux of gastric acid into the lower esophagus may exacerbate asthmatic symptoms, presumably through vagally mediated parasympathetic nervous reflexes, but the role of gastroesophageal reflux in asthma remains controversial.

Persistent posterior drainage of nasal mucus may also be an aggravating factor. Indirect evidence indicates that nasal and sinus disease increases airway responsiveness and thereby exacerbates asthma. This inference is based on changes in responsiveness and clinical severity after nasal administration of steroids. Other stimuli are virtually universal precipitants of asthma. Such stimuli include strenuous exercise, particularly if it is performed in cold air; respiratory illnesses, usually viral in origin; inhaled irritants such as ozone, sulfur dioxide, and smoke; and beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and ethanol (in Asian patients).

Specific antigen responsiveness may be more severe after exposure to environmental pollutants. Some women with asthma have been noted to have a significant increase in exacerbations during the preovulatory and perimenstrual periods.

Persons whose asthma is triggered by identifiable inhaled antigens (aeroallergens) usually have atopic disease. Exceptions include cases of asthma caused by certain sensitizing antigens encountered in the workplace that may not elicit an IgE antibody response [see Occupational Asthma, below]. Certain laboratory test results support a diagnosis of atopic disease: peripheral blood eosinophilia; increased total serum IgE levels; increased specific IgE levels, determined by a radioallergosorbent test (RAST) directed at a particular antigen; and positive wheal-and-flare reactions to antigens pricked or injected into the skin.

A distinction is often made between persons with asthma who have known allergic precipitants of their bronchoconstriction (extrinsic asthma) and those who do not (intrinsic asthma). Patients who show evidence of an atopic contribution to their asthma may have a greater rate of decline of lung function than...
those who do not. However, this distinction has probably been overemphasized and may be misleading, because it implies a differentiation of etiology or pathogenesis that is not supported by current data. Categorization into extrinsic or intrinsic asthma groups is difficult: allergic precipitants may not be recognized, symptoms of other atopic diseases may create ambiguity, and laboratory test results may be intermediate or falsely positive. Fortunately, the management of asthmatic patients is not dependent on the distinction between extrinsic and intrinsic types.

**LABORATORY TESTS**

No single laboratory test can establish a diagnosis of asthma, but a test for bronchodilator responsiveness can provide supportive evidence when asthma is suspected on clinical grounds. In patients with baseline airflow obstruction, a large (>15%) increase in airflow after inhalation of a bronchodilator suggests asthma. Unfortunately, as a diagnostic test, bronchodilator responsiveness lacks both sensitivity and specificity. False negative results are likely in asthmatic patients who have near-normal baseline lung function, in patients who are tested shortly after self-administration of a bronchodilator, and in patients with severe airflow obstruction resulting from airway inflammation and luminal obstruction by secretions. False positive bronchodilator responses may be observed in some patients with chronic bronchitis, emphysema, or other diseases associated with chronic airflow obstruction. A false positive response is especially likely when the baseline FEV₁ is very low, in which case even a small absolute increment in expiratory flow represents a relatively large percentage increase.

Because asthma is episodic, a diagnosis of asthma may be suspected on the basis of recurrent symptoms, even if there is normal pulmonary function. Bronchoprovocation may be a useful diagnostic test in this setting. In bronchial challenge testing, a non-specific stimulus is administered, and pulmonary function is then measured. It is anticipated that asthmatic patients will experience airflow obstruction in response to the provocative stimulus. Stimuli used for bronchoprovocation include exercise, eucapnic hyperventilation, and aerosolized methacholine, histamine, or adenosine 5'-monophosphate. Although bronchoprovocation tests are very sensitive, they are not specific for asthma [see Figure 1]. An alternative is demonstration of lability by use of a self-operated peak flowmeter; a diurnal variation in PEF of 15% or more is highly suggestive of asthma.

In an adult with new onset of asthmatic symptoms, a chest radiograph is warranted to exclude alternative diagnoses. In patients with asthma, the chest radiograph is usually normal; occasionally, subtle changes indicative of bronchial wall thickening are detected, and during an episode of severe airflow obstruction, radiographic signs of hyperinflation may be present. Chest radiographs of patients treated for exacerbations reveal unsuspected pulmonary infiltrates, atelectasis, pneumothorax, or pneumomediastinum only 2% of the time.

**Differential Diagnosis**

Viral tracheobronchitis, which can be caused by several pathogens (e.g., adenovirus, rhinovirus, influenza virus, herpes simplex virus), can constitute an acute respiratory illness associated with wheezing [see 7:XXV Respiratory Viral Infections]. Churg-Strauss syndrome [see 14:IV Focal and Multifocal Lung Disease] is a form of vasculitis characterized by asthmalike airflow obstruction and wheezing.

Many diseases associated with chronic airflow obstruction [see 14:III Chronic Obstructive Diseases of the Lung] cause episodic wheezing. Some diseases affect the airway in a manner that can be mistaken for asthma. For example, sarcoidosis may cause endobronchial granuloma formation with resultant airflow limitation, cough, wheezing, and dyspnea that are refractory to the usual bronchodilator medications. In addition, rheumatoid arthritis may be associated with bronchiolitis, producing findings that mimic refractory asthma.

Congestive heart failure and pulmonary embolism cause dyspnea and wheezing. Wheezing in association with interstitial pulmonary edema is common enough to have been designated cardiac asthma. Improvement after administration of an inhaled bronchodilator does not exclude cardiac asthma as the cause of wheezing. Wheezing is a rare manifestation of pulmonary embolism. Although in the acute setting, either pulmonary edema or pulmonary embolism may be mistaken for asthma, a detailed evaluation of the patient and the clinical course should clarify the diagnosis.

The conditions most likely to be confused with asthma over a more protracted period are those that cause partial upper airway obstruction [see Table 1]. In this context, the term upper airway refers to the single lumen airway from the carina upward. Dyspnea and wheezing associated with upper airway obstruction may be continuous and fail to respond to bronchodilators—a pattern that suggests focal anatomic obstruction. However, in other cases, signs and symptoms may be intermittent and may be brought on by exercise (because of the increased airflow across the narrowed orifice) or by certain postures. Epinephrine

<table>
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<th>Table 1 Causes of Upper Airway Obstruction</th>
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**EXTRINSIC COMPRESSION**
- Mediastinal neoplasm
- Retrosternal goiter
- Retropharyngeal abscess
- Fibrosing mediastinitis
- Thoracic aortic aneurysm

**INTRALUMINAL OBSTRUCTION**
- Foreign-body aspiration

**INTRINSIC STRUCTURAL ABNORMALITY**

**Infectious Disorders**
- Epiglottitis
- Croup
- Leprosy
- Syphilis
- Diphtheria

**Neoplastic Disorders**
- Oropharyngeal, laryngeal, or tracheal tumors

**Inflammatory and Degenerative Disorders**
- Enlarged tonsils and adenoids
- Laryngeal or tracheal granulation tissue
- Cricothyroiditis arthritis
- Tracheobronchial amyloidosis
- Sarcoidosis
- Laryngomalacia
- Tracheomalacia
- Tracheal or laryngeal stenosis

**Neurologic Disorders**
- Bilateral vocal cord paralysis
- Functional laryngospasm
Exercise-induced asthma is distinct from exercise limitation caused by other forms of cardiopulmonary disease in which breathlessness develops after a certain level of exercise and gradually resolves with rest. In contrast, an asymptomatic person with asthma and normal or near-normal lung function may exercise for several minutes without experiencing any symptoms. After exercise, pulmonary obstruction develops (often accompanied by wheezing, shortness of breath, and chest tightness); the magnitude of obstruction is directly related to the length of the exercise and the coolness and dryness of the inspired air. The obstruction spontaneously resolves 30 to 60 minutes after onset.

The crucial determinants of exercise-induced asthma are the level of ventilation during exercise and the temperature and relative humidity of the inspired air. The higher the minute ventilation during exercise and the colder and drier the inspired air, the greater the airflow obstruction that develops after exercise. The intrathoracic airways become cooled and lose water as they conduct large volumes of inspired air. The fall in airway temperature and evaporative drying of the mucosa have been postulated as the initiating stimuli for bronchoconstriction. The classic pattern is adduction of the anterior two thirds of the vocal cords with a posterior diamond-shaped chink. This occurs during inspiration but can be present during the entire respiratory cycle.

Specific Forms and Complications of Asthma

**EXERCISE-INDUCED ASThma**

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**NOCTURNAL ASTHMA**

During periods of heightened disease activity, it is common for patients with asthma to experience symptoms at night. They may awaken at 2:00 to 4:00 A.M. with typical symptoms. Measurements of pulmonary function before and after sleep usually document a significant worsening of obstruction in the morning, a phenomenon referred to as morning dipping. This phenomenon may contribute to the observed clustering of asthmatic deaths in the hours between midnight and 8:00 A.M.

Many causal factors have been invoked: sleep-related changes in airway tone, lung volumes, and airway inflammation; circadian variations in circulating histamine, cortisol, and epinephrine levels; prolonged exposure to allergens or irritants in the bedroom; late asthmatic reactions to daytime allergens or other inciting stimuli; gastroesophageal reflux related to the supine posture; retained airway secretions resulting from depressed cough reflex; and an increase in the intervals between antiasthmatic medication use.

**NEAR-FATAL AND HYPERACUTE ASTHMA**

There are data to suggest that patients at risk for near-fatal or fatal asthma differ histologically and pathophysiologically from other patients with asthma. Advanced age, greater airway reactivity, previous use of mechanical ventilation, and long-term steroid therapy are important risk factors for mortality. Additional risk factors are previous hospitalizations for asthma, problems with compliance, major psychiatric diagnoses, use of major tranquilizers, reduced chemosensitivity to hypoxemia, and perception of dyspnea. Patients with hyperacute attacks are at the greatest risk for mortality.

Histologically, patients who die less than 1 hour after the onset of symptoms have a larger proportion of neutrophils and fewer eosinophils than patients who die more than 2.5 hours after the onset of an attack, suggesting that pathogenesis may be different in those who have hyperacute attacks; such hyperacute attacks may possibly represent infection. The central airways of asthmatic patients who die during an attack have greater amounts of smooth muscle and submucosal glands than the central airways of patients in nonfatal cases and may be more responsive to bronchoconstrictive stimuli and less responsive to bronchodilators.

In some studies, regular use of beta agonists seemed to be associated with an unfavorable outcome in asthma patients. However, observations of patients with near-fatal asthma have shown that severe asphyxia and not cardiac arrhythmias may be the cause of near-fatal episodes, suggesting that undertreatment rather than overtreatment is the problem.

**ASTHMA CAUSED BY ASPIRIN, SULFITES, OR TARTRAZINE**

Perhaps 10% to 20% of patients with asthma exhibit an idiosyncratic reaction to ingested acetylsalicylic acid (aspirin). Within 15 minutes to 4 hours after ingestion of as little as 10 mg of aspirin, patients may experience significant worsening of airflow obstruction and nasal or ocular symptoms (e.g., nasal congestion, rhinorrhea, and conjunctival injection). Nasal polyps are common in aspirin-sensitive asthmatic patients; the term aspirin triad has been used to describe the combination of asthma, nasal polyps, and idiosyncratic reactions to aspirin.

It is thought that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger bronchoconstriction in susceptible asthmatic patients by blocking the cyclooxygenase-mediated conversion of arachidonic acid to prostaglandins (particu-
larly prostaglandin E2 [PGE$_2$], a potent anti-inflammatory prostaglandin). This causes shunting of arachidonic acid toward the lipoxygenase pathway, where, possibly on the basis of genetic polymorphisms, there is increased expression of LTC4 synthetase. This in turn facilitates the formation of this bronchoconstrictor and proinflammatory leukotriene. The hypothesis does not account for the idiosyncratic nature of the reaction in only a minority of asthmatic persons or for the peculiar finding that, in rare cases, a patient with asthma actually exhibits improvement in lung function after administration of aspirin.

A history of asthmatic worsening or nasal or conjunctival symptoms after aspirin ingestion is usually sufficient to identify aspirin-sensitive patients. Such patients should avoid any product containing aspirin or other NSAIDs that inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Acetaminophen and salicylate are weak COX-1 inhibitors, but with high doses, reactions can occur in a minority of aspirin-sensitive patients. Sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphene do not inhibit COX enzymes and can be used safely. The recently released COX-2 inhibitor rofecoxib has been shown to be safe in aspirin-sensitive patients; rofecoxib is a more powerful anti-inflammatory and analgesic agent than the agents previously available.

Sulfiting agents, including sodium and potassium bisulfite and metabisulfite, are used in the food-processing industry as sanitizing agents, preservatives, and antioxidants. They are also in a great number of medications, including some bronchodilator solutions. Restaurant food, almost all wines and certain beers, fresh and dried fruits, peeled potatoes, avocado dip, and shrimp and other shellfish are common sources of sulfites. The asthmatic reactions may be severe and life threatening, but they usually respond rapidly to bronchodilator therapy. An estimated 5% of persons with asthma are thought to have sulfite sensitivity.

Tartrazine, a food dye approved by the Food and Drug Administration, is a coal tar derivative widely used in prepared foods and drinks, medications, and mouth care products. Worsening of airflow obstruction in asthmatic patients has been reported in double-blind, placebo-controlled oral challenges with tartrazine. In most instances, positive responses occurred only in aspirin-sensitive asthmatic patients. Other reports have called into question the existence of tartrazine sensitivity. Tartrazine-free diets are so restrictive that careful documentation of sensitivity in a controlled fashion should always precede the imposition of such a diet on a patient.

ASTHMA IN PREGNANCY

Asthma is a potentially serious medical problem during pregnancy. Pregnant women with asthma have higher rates of complications of pregnancy, such as hypertension gravidarum, uterine hemorrhage, preeclampsia, placenta previa, and need for cesarian section; these complications are especially prevalent in patients with severe asthma. There is little evidence for increased maternal mortality associated with asthma. Prematurity and intrauterine growth retardation of the fetus are associated with poor asthma control in the mother. Improved control of asthma is associated with improvement in fetal outcome.

Of pregnant patients with asthma, one third will experience improvement in their asthma, one third will remain stable, and one third will experience a worsening of their asthma. Those with more severe asthma are at greater risk of their asthma worsening.

OCCUPATIONAL ASTHMA

Persons with asthma are susceptible to exacerbations of their disease when exposed to irritant dusts or fumes in the work environment. Occupational asthma, however, refers to asthma of new onset that is caused by prolonged exposure to a specific inhaled substance in the workplace. Occupational exposures may be involved in the development or worsening of as much as 10% of asthma cases. The particular gas, dust, or vapor seems to sensitize the airways; continued exposure causes reversible airway narrowing and the development of nonspecific bronchial hyperreactivity.

A typical history is that of a worker who after a few months (but sometimes up to several years) at a job notices cough, wheezing, and chest tightness shortly after arriving at the workplace, especially after a brief absence (so-called Monday morning asthma). Symptoms persist while the patient is at work but often abate after the patient returns home. Continued occupational exposure may lead to more persistent symptoms, more continuous airflow obstruction, and susceptibility to the typical spectrum of precipitants of asthma in addition to the offending agents encountered in the work environment. Some persons with occupational asthma report a delayed onset of asthmatic symptoms: symptoms begin hours after the patient leaves the workplace, making recognition of an association with the offending agent more difficult. Occasionally, workers experience recurrent nocturnal asthmatic symptoms for several nights after a work-related exposure.

More than 200 substances have been linked to occupational asthma, and the list continues to grow [see Table 2]. Major categories of offending agents include laboratory animals, birds, insects, and various animal products; plants and wood dust; biologic enzymes; isocyanates; anhydrides; metals; fluxes; latex; and drugs and other chemicals. For some of these agents, an immunologic mechanism involving the immediate hypersensitivity reaction has been demonstrated; for other substances, atopy does not predispose persons to the development of disease, and evidence for an IgE-mediated pathogenesis is lacking. Genetic factors also probably play a role in susceptibility among workers. The prevalence of disease varies with the sensitizing agent. For example, asthma develops in approximately 5% to 10% of workers exposed to toluene diisocyanate, in an estimated 20% of bakers exposed to wheat flour or rye flour, and in as many as 50% of those who work with platinum salts or proteolytic enzymes. Reducing concentrations of offending agents by better control of dust lowers the incidence of asthma exacerbations and may decrease sensitization.

Exposure to irritant gases can range from contact with pure chlorine gas in industrial or environmental spills to inhalation of smoke (which contains several toxic gases as well as particulate matter and carbon monoxide). Such exposure can result in a wide spectrum of syndromes, ranging from acute tracheobronchitis to diffuse alveolar damage that results in acute respiratory distress syndrome. An intermediate response, termed reactive airway dysfunction syndrome (RADS), is a severe and persistent asthmatic state that can be difficult to treat and may result in long-term impairment of function. Preexisting lung disease and chronic cigarette smoking are risk factors for more severe reactions.

Variations in lung function related to occupational exposures can be confirmed by the use of simple portable devices for recording PEF. Definitive diagnosis entails isolating the offending agent and having the patient inhale carefully controlled concentrations of it while pulmonary function is sequentially recorded.
Late reactions are important to our basic understanding of asthma, because often the clinical manifestations of asthma, particularly during subacute exacerbations, more closely mimic late asthmatic reactions than early reactions in terms of both timing and responsiveness to medications. Evidence from bronchoalveolar lavage specimens indicates that the late response correlates temporally with an influx of eosinophils and neutrophils into the airways. Release of spasmogens and chemotactic factors from mast cells may account for the immediate response and for the subsequent cellular infiltration. A secondary wave of mediator release, together with airway inflammation, accounts for the delayed development of obstruction. In animal models of the late asthmatic reaction, the development of bronchial hyperreactivity is coincident with the late response and is prevented by its inhibition.

**Allergic Bronchopulmonary Aspergillosis**

Allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity reaction to colonization of the airways by *Aspergillus* species, rarely occurs except in patients with asthma. This disorder typically develops in patients with atopy and long-term asthma and is marked by fever, flulike symptoms, myalgias, and lassitude. The chest radiograph reveals pulmonary infiltrates, often with associated atelectasis of the involved segments or lobes because of tenacious mucous plugs that occlude the proximal airways. Although this entity is frequently mistaken for bacterial pneumonia, sputum cultures are negative for pathogenic bacteria. Clues to the proper diagnosis include the presence of sputum and blood eosinophilia, the volume loss that accompanies the pulmonary infiltrates, and failure of the infiltrates to respond to antibiotics.

**Table 2** Causes of Occupational Asthma

<table>
<thead>
<tr>
<th>Potential Hazard</th>
<th>Persons at Risk</th>
<th>Sensitizing Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory animals, birds, insects, other animal</td>
<td>Laboratory workers, animal handlers,</td>
<td>Rats, mice, rabbits, guinea pigs</td>
</tr>
<tr>
<td>products</td>
<td>veterinarians</td>
<td>Pigeons, chickens, budgerigars (shell parakeets)</td>
</tr>
<tr>
<td></td>
<td>Pigeon breeders, poultry workers, bird fanciers</td>
<td>Grain mites</td>
</tr>
<tr>
<td></td>
<td>Grain workers</td>
<td>Moths and butterflies</td>
</tr>
<tr>
<td></td>
<td>Entomologists</td>
<td>Crabs and prawns</td>
</tr>
<tr>
<td></td>
<td>Crab and prawn processors</td>
<td></td>
</tr>
<tr>
<td>Plants, wood dust</td>
<td>Bakers</td>
<td>Wheat flour, rye flour</td>
</tr>
<tr>
<td></td>
<td>Food processors</td>
<td>Coffee beans, castor beans</td>
</tr>
<tr>
<td></td>
<td>Tea workers</td>
<td>Tea leaves</td>
</tr>
<tr>
<td></td>
<td>Tobacco manufacturers</td>
<td>Tobacco leaves</td>
</tr>
<tr>
<td></td>
<td>Carpenters, sawmill operators, cabinetmakers</td>
<td>Wood dust, including western red cedar dust</td>
</tr>
<tr>
<td>Biologic enzymes</td>
<td>Detergent industry workers</td>
<td><em>Bacillus subtilis</em></td>
</tr>
<tr>
<td></td>
<td>Pharmaceutical industry workers, biomedical researchers</td>
<td>Pepsin, trypsin, bromelain</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>Workers with polyurethane, plastics, and</td>
<td>Toluene diisocyanate</td>
</tr>
<tr>
<td></td>
<td>varnish</td>
<td>Hexamethylene diisocyanate</td>
</tr>
<tr>
<td>Anhydrides</td>
<td>Workers with epoxy resins and plastics</td>
<td>Phthalic, trimellitic, and other anhydrides</td>
</tr>
<tr>
<td>Metals</td>
<td>Tanners</td>
<td>Chromium</td>
</tr>
<tr>
<td></td>
<td>Platinum refiners</td>
<td>Platinum</td>
</tr>
<tr>
<td></td>
<td>Metal platers</td>
<td>Nickel</td>
</tr>
<tr>
<td>Fluxes</td>
<td>Aluminum solderers</td>
<td>Aminoethylhexanolamine</td>
</tr>
<tr>
<td></td>
<td>Electronics workers</td>
<td>Colophony</td>
</tr>
<tr>
<td>Drugs, other chemicals</td>
<td>Pharmaceutical workers</td>
<td>Penicillins, cephalosporins, methyldopa, spiramycin, tetracycline</td>
</tr>
<tr>
<td></td>
<td>Workers with plastics and rubbers</td>
<td>Azodicarbonamide</td>
</tr>
<tr>
<td></td>
<td>Insulators</td>
<td>Urea, formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Refrigeration workers</td>
<td>Freon</td>
</tr>
<tr>
<td></td>
<td>Hairdressers</td>
<td>Persulfate salts, henna</td>
</tr>
</tbody>
</table>

for several hours. Skin testing with the appropriate soluble extracts and RAST tests for specific IgE antibody assess only the presence of sensitization to the agent. Many workers exhibit positive skin-test or RAST results but have no evidence of asthma.
necrosis in the walls of central bronchi lead to bronchiectasis and large mucous plugs (mucoid impaction). At times, a granulomatous response leads to the replacement of bronchial and peribronchial tissue (bronchocentric granulomatosis). An eosinophilic pneumonia commonly affects the surrounding lung tissue.

The pulmonary infiltrates may resolve spontaneously but commonly recur, leading to the radiographic appearance of migratory pulmonary infiltrates [see Figure 4]. Chronic disease commonly involves the upper lobes; typical features include bronchiectasis (usually involving central airways) and fibrosis with retraction. Chronic ABPA may be readily mistaken for tuberculosis, especially because hemoptysis occurs in one third to one half of cases. ABPA can occur in patients with cystic fibrosis, and a minority of patients with ABPA have mutations in the gene that regulates cystic fibrosis transmembrane conductance.

The diagnosis of allergic bronchopulmonary aspergillosis can be confirmed by the following test results: (1) repeated isolation of Aspergillus organisms from the sputum, (2) positive immediate skin-test reaction to Aspergillus antigen, (3) elevated total serum IgE level (usually > 1,000 ng/ml in patients not receiving corticosteroids), and (4) elevated levels of specific IgE and IgG antibodies against Aspergillus (levels are usually twice those of allergic asthmatic control subjects who do not have allergic bronchopulmonary aspergillosis).

Management

In the United States, the total cost incurred because of asthma, including the direct costs of care and the indirect costs from lost productivity, is estimated to be $5.8 billion a year. More than half the costs arise from hospital care; 80% of the costs are incurred by 20% of the patients.

Studies of patients hospitalized for exacerbations of asthma have documented deficiencies in the care that patients had been receiving before admission, which suggests that published guidelines are not understood and are not being used by primary care physicians. Additionally, many patients are not satisfied with their asthma treatment. Education of the patient is a key and often neglected aspect of care that has the potential to improve outcomes. Self-monitoring with the use of inexpensive peak flowmeters may improve a patient’s ability to judge disease severity and reduce morbidity.

A specialist can provide more therapeutically effective and more cost-effective treatment and should be involved in the care of all patients with moderate to severe asthma.

ANTIASTHMATIC MEDICATIONS

Medications used to treat asthma can be classified into two groups according to their principal actions. Drugs that act primarily as relaxants of tracheobronchial smooth muscle (i.e., bronchodilators) include beta-adrenergic agonists, theophylline and its derivatives, and anticholinergics; those that act mainly as inhibitors of inflammation include corticosteroids, Cromolyn sodium, nedocromil, leukotriene inhibitors, and other anti-inflammatory medications [see Table 3]. [For treatment of specific presentations, see Management Strategies, below.]

Beta-Adrenergic Agonists

Beta-adrenergic agonists function as bronchodilators by stimulating the beta receptors on tracheobronchial smooth muscle, with the consequent activation of adenylate cyclase and a rise in intracellular cyclic adenosine monophosphate (cAMP) concentration. Epinephrine is short acting (30 to 60 minutes) when inhaled and activates both alpha-adrenergic and beta-adrenergic receptors. Beta-adrenergic stimulation predominates in the airways, resulting in bronchodilatation, but dominant peripheral alpha-adrenergic stimulation results in vasoconstriction and may cause a rise in blood pressure. In clinical practice, epinephr-
rined is given primarily as a subcutaneous injection for acute relief of severe airflow obstruction. It is also sold without prescription as an inhalant in metered-dose canisters.

Isoproterenol, a powerful nonselective beta-adrenergic agonist, has a short duration of action. Although it is available as an inhalant for the treatment of asthma, it has largely been replaced by newer, more selective beta2-adrenergic agonists.

Selective beta2-adrenergic agonists have structural modifications that make them effective by oral administration as well as by inhalation. The duration of action of these compounds is 4 to 6 hours. Examples are metaproterenol, terbutaline, and albuterol [see Table 4]. Bitolterol has a slightly extended duration of action of 6 to 8 hours; it is currently available only in a metered-dose delivery system. A preparation that contains only the R isomers of albuterol (levalbuterol) has recently been marketed with minimal anticorticoid effect.51 However, the effects are small, and the magnitude of the dilator response to high doses of beta agonists in an emergency situation is not diminished in those patients who use these agents regularly. Regular use of inhaled steroids may prevent some of these adverse effects associated with routine use of beta2-adrenergic agonists.51

Over the years, beta2-adrenergic agonists given by inhalation have been the mainstay of treatment for asthma because of their rapid onset of action, their effectiveness, and their convenience. In the mid-1980s, an increase in asthma deaths occurred after the introduction of a newer beta2-adrenergic agonist, fenoterol, in New Zealand. A study based in Saskatchewan, Canada, however, suggested that all beta2-adrenergic agonists, especially if used heavily, are associated with an increased risk of fatal and near-fatal asthmatic episodes, but a meta-analysis has suggested that the risk is very small and may be confined to beta2-adrenergic agents given by nebulizer.55 The most obvious question concerning these studies is whether the increased mortality occurred because of administration of excessive amounts of the therapeutic agent or because of the severity of illness in those patients given the drug. Further studies, however, have suggested a mildly increased degree of airway responsiveness to allergens with regular use of beta2-adrenergic agonists. These observations must be added to the list of potentially negative effects associated with regular use of these drugs. These concerns have been the subject of much debate, and as yet, no clear consensus has emerged. One recent study suggested that there is no benefit from regular use of albuterol as opposed to as-needed dosing in mildly asthmatic patients.56 Another study found no deterioration in asthma control in patients with moderate to severe asthma as a result of regular use of albuterol.57

When patients begin to feel the need for more frequent use and increased doses of inhaled beta agonists, they should be seen by a physician and evaluated for additional aggravating factors, and the addition of other treatments should be considered. There are not sufficient data available to justify removing inhaled beta agonists from the market or even to justify significantly changing the way in which they are used. Nonetheless, excessive reliance on inhaled bronchodilators, without sufficient attention to the underlying inflammatory component of the disease, continues to be a problem in the way asthma is managed. Inhaled corticosteroids, rather than scheduled doses of beta agonists, should be considered as first-line therapy for asthmatic patients with daily symptoms. Daily use of inhaled corticosteroids, supplemented by inhaled beta agonists only as needed, provides better long-term control of asthma than scheduled doses of beta agonists.

Theophylline

Theophylline is a methylxanthine closely related in structure to caffeine.5 It was thought that theophylline acted by increasing

Figure 4  This posteroanterior chest radiograph shows an asthmatic patient with allergic bronchopulmonary aspergillosis. Characteristic radiographic findings include the migratory nature of the infiltrates, the predominant upper lobe involvement, and the associated atelectasis. The minor fissure forms the lower border of the upper right lobe infiltrate; the minor fissure is displaced cephalad, indicating loss of volume in the right upper lobe.
cAMP levels by inhibiting the activity of phosphodiesterase, an enzyme that facilitates the conversion of cAMP to the noncyclic 5′-AMP. Other modes of action for theophylline have been explored, including antagonism of adenosine at its receptor. Theophylline may also have anti-inflammatory effects that include reduction of inflammatory cell numbers, expression of cytokines, and acceleration of neutrophil apoptosis.\textsuperscript{56,57}

Theophylline is almost completely absorbed from the gastrointestinal tract. The rate of absorption, however, can vary greatly, depending on the formulation. A rapid onset of action can be achieved with the elixir of theophylline (peak effect at approximately 60 minutes), whereas a long duration of action results from slow-release preparations (peak effect at 6 to 8 hours), making once- or twice-daily dosing schedules possible. Aminophylline (the ethylenediamine salt of theophylline) and oxtriphylline (the choline salt of theophylline) are more water soluble than theophylline. Aminophylline is the preparation used for I.V. administration; its bronchodilator activity is solely attributable to theophylline, which by weight constitutes 85% of aminophylline.

Oxidation and demethylation of theophylline take place in the liver; hepatic metabolites, along with a small amount of unaltered theophylline, are excreted in the urine. The average serum
half-life of theophylline in nonsmoking adults is approximately 7 to 9 hours, but differences in metabolic rates among people and in the same person over time lead to considerable variability in theophylline serum concentrations after a given dose. Clearance of theophylline is accelerated in children, in cigarette smokers, and in persons receiving phenytoin; its clearance is delayed by numerous influences, such as primary liver disease, right ventricular failure, and the use of several drugs, including cimetidine, erythromycin, ciprofloxacin, and oral contraceptives.

In mild to moderate asthma, the bronchodilator response varies directly with the theophylline serum concentration. Significant bronchodilatation occurs at theophylline concentrations as low as 5 to 8 mg/L; at concentrations exceeding 20 mg/L, side effects become increasingly common. Thus, a therapeutic range of 10 to 20 mg/L has been recommended. However, recent evidence suggests that lower levels may be effective among inhaled short-acting beta2 agonists. First-line agents may lead to sinus tachycardia, extrasystoles, and atrial arrhythmias. In cases of severe theophylline toxicity caused by overdosage (theophylline concentration > 40 mg/L and especially at levels > 60 mg/L), clearance of theophylline can be accelerated by administration of activated charcoal, either orally or by nasogastric tube; this will remove any theophylline remaining in the stomach or intestine. On rare occasions, charcoal hemoperfusion is necessary to reduce theophylline concentrations rapidly. This relatively narrow therapeutic index, along with highly variable clearance rates, has necessitated measurement of serum theophylline concentrations in many clinical circumstances—especially in patients with severe airflow obstruction, in whom maximal bronchodilator effect is desired.

Side effects are common with theophylline and may occur at serum concentrations at or even below the target therapeutic range. GI complaints include nausea and vomiting, abdominal pain, and diarrhea. Headache, nervousness, insomnia, and tremors are the most common neurologic side effects. Cardiac stimulation may lead to sinus tachycardia, extrasystoles, and atrial arrhythmias. In cases of severe theophylline toxicity caused by overdosage (theophylline concentration > 40 mg/L and especially at levels > 60 mg/L), clearance of theophylline can be accelerated by administration of activated charcoal, either orally or by nasogastric tube; this will remove any theophylline remaining in the stomach or intestine. On rare occasions, charcoal hemoperfusion is necessary to reduce theophylline concentrations rapidly.
The risk of life-threatening toxicity depends not only on the drug level but also on whether intoxication is acute or chronic. A theophylline level between 40 and 50 mg/L in an acutely intoxicated patient carries a very low risk of seizures; however, the same level in a patient receiving long-term theophylline therapy whose ability to clear the drug is impaired represents a potentially life-threatening intoxication and carries a significant risk of seizures. Moreover, when a toxic level is attributable to reduced clearance rather than to acute intoxication, the duration of risk is greater because of theophylline’s long half-life.

Because of the multiple side effects, need to monitor blood levels of the drug, potential severity of toxicity, and availability of several newer classes of drugs that can be substituted, theophylline is used far less than before.

**Anticholinergic Agents**

Anticholinergic agents have been used as bronchodilators for hundreds of years in the form of atropine and stramonium, alkaloid derivatives of the datura plant. Because atropine is well absorbed into the blood across the respiratory tract mucosa, it causes significant systemic side effects, even when administered by inhalation. The atropinic congeners ipratropium bromide and methylatropine nitrate are poorly absorbed into the circulation when inhaled and therefore have limited side effects. Atropine and its derivatives compete with acetylcholine at its receptors, which are adjacent to the parasympathetic, postganglionic (muscarinic) nerve endings.

Ipratropium bromide requires a slightly longer time than inhaled beta-adrenergic agonists to reach peak effect (60 minutes), but it lasts 4 to 6 hours. It has a somewhat smaller bronchodilatory effect in patients with asthma. Potential advantages are (1) its minimal cardiac stimulatory effects, making it particularly desirable for use in patients with coronary artery disease or cardiac arrhythmias, and (2) its additive bronchodilatory effect when used in combination with submaximal doses of beta-adrenergic agonists. No benefit is gained by adding ipratropium bromide to a regimen of beta-adrenergic agonists given at maximal doses in long-term therapy. There is a modest benefit for patients with acute asthma exacerbations. The primary indication for anticholinergic agents is chronic obstructive pulmonary disease.

**Systemic Corticosteroids**

Corticosteroids do not relax tracheobronchial smooth muscle directly. Nevertheless, in patients who have severe airflow obstruction that is refractory to bronchodilator therapy, corticosteroids are the most potent antiasthmatic medication available. Although the precise mechanism of action of corticosteroids in the treatment of asthma is unknown, it is widely believed that their anti-inflammatory actions are important in the relief of airflow obstruction. One possible anti-inflammatory mechanism is the modulation of the release of cytokines from inflammatory cells. Other potential mechanisms of action are increased synthesis of an inhibitor of phospholipase A2, which would suppress the release of arachidonic acid from cell membrane phospholipids, and up-regulation of beta-adrenergic receptors, which would potentiate the bronchodilator response to beta-adrenergic agonists.

The optimal dosage, dosage schedule, preparation, and duration of therapy for treatment of asthma with corticosteroids are uncertain; as a result, physicians have widely varying practice preferences. Data suggest that lower dosages of I.V. hydrocortisone (200 mg/day) are as effective as higher dosages (2,000 mg/day) in hospitalized patients and that a prolonged taper of oral prednisone may not be necessary to prevent late exacerbations of asthma.

Systemic corticosteroids are commonly employed for short courses (e.g., 1 to 3 weeks) to treat exacerbations of asthma refractory to bronchodilator therapy. Prednisolone and prednisone, which is metabolized to prednisolone in the liver, are the most widely used oral preparations in the treatment of asthma; the two agents are equally effective in patients who do not have severe liver disease. Long-term maintenance therapy should be avoided because of the well-known side effects of extended steroid use. In those few cases in which relief of symptomatic airflow obstruction cannot be achieved by other means, orally administered corticosteroids are given at the lowest effective dose. Alternate-day administration minimizes side effects and hypothalamic-pituitary-adrenal axis inhibition and may provide sufficient control of chronic symptoms.

**Inhaled Corticosteroids**

Inhaled corticosteroids are not bronchodilators and do not promote the immediate relief of airflow obstruction. Their role is as long-term maintenance therapy aimed at preventing recurrent exacerbations of asthma. Regular use of inhaled corticosteroids, even in low doses, has been shown to largely prevent a major portion of asthma hospitalizations and deaths. These benefits are realized, however, only when the proper dose is prescribed and the patient takes the medication regularly using proper technique.

Five steroid preparations that are poorly absorbed into the blood after inhalation are available in the United States: beclomethasone, triamcinolone, flunisolide, fluticasone, and budesonide [see Table 5]. New formulations using the propellant hydrofluoroalkane (HFA) instead of the chlorofluorocarbons (CFCs), which harm the ozone layer, are now available. Because these inhalers generate smaller aerosol particles, more of the inhaled steroids are delivered into the small airways, resulting in improved therapeutic response. They inhibit the late-phase response even when given after antigen challenge and, if taken long term, reduce airway inflammation and remodeling. If given in the afternoon, inhaled corticosteroids can be taken once a day. After a period of days to weeks of regular use of inhaled corticosteroids, many patients experience decreased airflow hyperreactivity. High doses of inhaled corticosteroids may be as effective as moderate doses of prednisone in the treatment of exacerbations. Long-term oral corticosteroid therapy can be discontinued in some patients, and the frequency of bronchodilator administration can often be reduced. Inhaled corticosteroids are often particularly effective during periods of increased exposure to aeroallergens. Local side effects include glossitis, sore throat, hoarseness, dysphonia, and oral candidiasis. Oral candidiasis occurs in 5% to 15% of patients who use inhaled corticosteroids; the incidence can be reduced by rinsing the mouth with water after each use, by the use of spacer devices, or both. Despite extended use of inhaled steroid preparations, histologic changes in the bronchial mucosa and alterations in oropharyngeal flora do not occur. Potential systemic side effects in adults, usually seen only with high doses of inhaled corticosteroids, include skin atrophy, reduction in bone density, cataracts, and suppression of the hypothalamic-pituitary-adrenal axis.

**Cromolyn Sodium and Nedocromil**

Cromolyn sodium is unique among the antiasthmatic medications. It is not a bronchodilator, does not antagonize the action
of inflammatory mediators, and does not directly reverse established inflammation. It acts as an inhibitor of inflammation, apparently by preventing the release of chemical mediators from mast cells, even in the presence of cell-bound IgE antibody and appropriate antigen. The mechanism of action is unknown. Two effective delivery systems are available: a cromolyn sodium solution for nebulization and an aerosol delivered by metered-dose pressurized canister.

Controlled trials have shown that cromolyn sodium is beneficial for atopic asthmatic patients during allergy season (the drug is preferably started 1 week before allergen exposure), for patients who experience exercise-induced asthma (the drug is taken 10 to 20 minutes before exercise), for patients who have asthma induced by exposure to animals, and for those with certain forms of occupational asthma. Like inhaled corticosteroids, cromolyn sodium may be effective in reducing the need for systemic corticosteroids and decreasing use of multiple bronchodilators in patients who must take such medications frequently. Adverse reactions occur infrequently and include rash, myositis, headache, and GI upset. Inhaled corticosteroids have a greater steroid-sparing effect than cromolyn.

The efficacy of nedocromil is similar to that of cromolyn sodium.

**Leukotriene Inhibitors**

A group of new drugs that inhibit the bronchospastic and proinflammatory effects of the leukotrienes have recently been approved for the treatment of asthma. Leukotrienes play a significant role in the treatment of asthma induced by exercise, aspirin, and allergens. The leukotrienes, now known to be the active substances in what was formerly called slow-reacting substance of anaphylaxis, are formed in mast cells and eosinophils from arachidonic acid by the complex of 5-lipoxygenase and the 5-lipoxygenase–activating protein. Through a series of further enzymatic steps, the active compound, leukotriene D$_4$ (LTD$_4$), is produced. LTD$_4$ produces bronchospasm and airway inflammation through a specific receptor, cysteinyl leukotriene receptor type 1 (CysLT1).

Drugs that inhibit two steps in this pathway have been developed: zileuton inhibits 5-lipoxygenase activating protein (FLAP), and montelukast and zafirlukast inhibit CysLT1. The specific indications for these drugs in the treatment of asthma are still being established. Patients with aspirin-induced and exercise-induced asthma respond well to either a FLAP or CysLT1 inhibitor. Leukotriene inhibitors are effective in approximately 50% of patients with mild, persistent asthma or moderate asthma and may be added to or substituted for inhaled or oral anti-inflammatory drugs, but they are not as effective as long-acting beta agonists or inhaled corticosteroids.

**Other Anti-inflammatory Agents**

Antihistamines have not been recommended as part of the usual treatment of asthma. Newer-generation drugs, however, are more potent inhibitors of in vivo histamine effects and show some promise, possibly in combination with other mediator blockers such as the leukotriene inhibitors.

A small group of asthmatic patients either are unresponsive to corticosteroids or require persistent high doses of steroids for adequate control. These patients may have abnormalities of the intracellular mechanisms of steroid action, some of which may be the effects of cytokines and may be reversed by high-dose steroid therapy. Some of these patients, however, require the use of other anti-inflammatory therapy.

Methotrexate may have a steroid-sparing effect in steroid-dependent asthmatic patients, but the data are conflicting. Many patients referred to specialists for methotrexate therapy can be managed with higher doses of inhaled steroids, theophylline administered at therapeutic levels, and inhaled anticholinergics along with elimination of precipitating problems such as rhinosinusitis and gastroesophageal reflux.

One study found that auranofin, an oral gold preparation, had steroid-sparing effects in asthmatic patients. Cyclosporine,
an inhibitor of T cell activation, has been shown to have efficacy in some patients with severe asthma.90 Other treatments that have been found to possibly benefit these patients include hydroxychloroquine,91 kelimab (a chimeric monoclonal antibody to CD4),92 high-dose I.V. immunoglobulin,94 and monoclonal anti-IgE antibody.95

** MANAGEMENT STRATEGIES **

**Outpatient Care**

In newly diagnosed asthma patients, the identification of avoidable precipitants of airway obstruction should be sought by history, and whenever possible, precipitants should be removed from the environment.96 Common sources of allergens and irritants in the home include pets, insects, mites, cigarette smoke, dust and mold, feather pillows, down comforters, and shag rugs.

Because patients with a history of asthma can often identify allergens from experience, skin testing is rarely necessary or useful except in demonstrating hypersensitivity to a suspected allergen when the history is not conclusive. Exposure to allergens may not always cause immediate symptoms but rather may induce a state of enhanced bronchial hyperreactivity to many nonspecific stimuli. The relation between allergen exposure and worsening of asthma may not be immediately apparent.

An air filter or air conditioner may be helpful during periods of heavy outside air contamination. Beta-blocking drugs, including ophthalmic solutions, should be avoided; if such a drug is absolutely necessary, a selective beta-blocking agent should be given in the lowest possible dosage. Treatment of postnasal drip or esophageal reflex of gastric acid may ease symptoms in some patients. Weight loss in obese patients with asthma may also improve symptoms and lung function.97

Immunotherapy is controversial.88,89 Administration of an allergen in gradually increasing amounts theoretically leads to desensitization through induction of IgG antibodies that block antigen-IgE binding. Immunotherapy may be effective in some patients with specific types of allergic asthma, but the role of immunotherapy in the majority of patients with asthma has not been determined.

Several new types of devices have been developed to directly deliver medication to the airways.87 Breath-actuated metered-dose inhalers, dry-powder inhalers, and metered-dose inhalers with new, nonchlorofluorocarbon (hydrofluoroalkane) propellants are now on the market. The dry-powder inhalers seem to be easier than the other types of delivery devices for patients to use, because no coordination of hand action and breathing is required. However, most patients who use the new types of delivery devices still require a metered-dose inhaler as part of their regimen.

Some patients have difficulty using metered-dose aerosol systems, either because of lack of coordination or because of a physical handicap. Spacer devices or reservoir bags (into which the medication is sprayed from the metered-dose canister and from which the patient then inhales) may greatly assist patients with poor coordination; an adapter is available for patients with arthritic hands. Use of a spacer results in greater delivery of the drug to the airway88 and a reduction in complications because of improved coordination of actuation. The principal mechanisms underlying these effects are a settling out of larger particles that would otherwise adhere to the posterior pharynx and a slowing of the rate of inhalation (most devices have warning signals when inspiration is too fast), allowing the intermediate-sized particles to make the turn from the mouth into the airway.

**Mild asthma** Patients with very mild asthma need only intermittent bronchodilator therapy for occasional symptoms. Short-acting beta-adrenergic agonists delivered by metered-dose inhalers are preferred on the basis of rapid onset, potent bronchodilator effect, and few side effects.

**Moderate to severe asthma** Because airway inflammation is the primary problem in moderate to severe asthma, the fundamental therapy is corticosteroids, mainly by inhalation.98 Studies of patients with asthma have demonstrated a slowing of the decline in lung function after the addition of inhaled corticosteroids to a regimen of inhaled bronchodilators. Use of bronchial hyperreactivity as an additional indicator of the need for anti-inflammatory therapy has been reported to result in more aggressive treatment and improved outcomes.92

Patients with daily symptoms and persistent airflow obstruction should use inhaled steroids regularly. Inhaled beta-adrenergic agonists should continue to be used on an as-needed basis. In patients receiving low-dose inhaled steroids, the addition of a regular dose of a long-acting selective beta-2-adrenergic agonist may provide improved control.99 Although long-acting selective beta-2-adrenergic agonists should not be used in place of low-dose inhaled steroids, their use can often lead to a reduction in the dosage of inhaled steroids.90

Theophylline preparations are sometimes used as first-line therapy. The advantages of theophylline are the convenience of a once- or twice-daily dosing schedule, lower medication costs, avoidance of the drug-delivery problems encountered with inhaled medications, the long duration of action of slow-release preparations, and a potential anti-inflammatory action. The major disadvantages include frequent noxious side effects and the fact that serum levels of theophylline must be measured often, because levels cannot be accurately determined on the basis of dose and body weight alone. Theophylline is less effective than a long-acting inhaled beta-2-adrenergic agonist and inhaled corticosteroids.89

When inhaled corticosteroids in combination with a beta-adrenergic agonist or theophylline do not adequately control symptoms, the two bronchodilators can be combined or a leukotriene modifier can be added.100 Inhaled ipratropium bromide can be given to patients who require additional bronchodilatation. Because it has minimal cardiac effects, it can be used for patients with angina pectoris or cardiac arrhythmias. A metered-dose inhaler containing both albuterol and ipratropium is available and is convenient when the two drugs are required.

In patients who remain symptomatic despite use of inhaled corticosteroids and a combination of inhaled beta-adrenergic agonist, theophylline, and possibly ipratropium bromide, two therapeutic approaches can be taken. Milder, more chronic symptoms can sometimes be managed by an increase in the dosage of inhaled corticosteroids or by the addition of inhaled cromolyn sodium or nedocromil. More severe and acute symptoms often warrant a short course of oral corticosteroids. Often, patients show dramatic improvement with oral corticosteroids but experience a relapse of symptoms shortly after the medication is discontinued. Such relapses can be managed by reinstituting the oral corticosteroids and tapering to alternate-day therapy at the minimal dosage necessary to maintain the patient's symptoms at an acceptable level.
Nocturnal asthma  Nocturnal asthma and the associated disruption in sleep are a significant component of morbidity in some patients with asthma. Attempts to alleviate the problem include removal of potentially offending stimuli from the environment and administration of long-acting bronchodilators as late in the evening as possible without interfering with the patient’s ability to fall asleep. Salmeterol, which remains active for 10 to 12 hours, is useful therapy for this aspect of the asthmatic diathesis.99 Prednisone administered at 3:00 P.M. can enhance the effects of oral steroids on nocturnal symptoms. In rare instances, it is necessary for patients to awaken at a scheduled time during the night to take medications and expectorate secretions to avert an exacerbation. In general, as the asthma abates overall, nocturnal symptoms also resolve.

Exercise-induced asthma  Exercise-induced asthma can be a significant source of morbidity in asthmatic patients, particularly in those who are physically active. Inhaled beta-adrenergic agonists and cromolyn sodium are both active as prophylactic agents. Inhalation of beta2 agonists has been found to be safe in pregnancy, should be considered. Use of a long-acting beta2 agonist in this situation should only occur after considering the risk.

If asthma is still not controlled or if a severe exacerbation occurs, use of systemic corticosteroids may be necessary. Prednisone and prednisolone have been found to be safe for the fetus in the vast majority of studies. There may, however, be an increased risk of the maternal complications of pregnancy associated with systemic corticosteroid usage.

Once control is established, the doses of corticosteroids should be gradually lowered.

Occupational asthma  Treatment of the milder airway responses may include inhaled corticosteroids, bronchodilators, and, if the airways are infected, antibiotics.

In most cases, occupational asthma is cured by removal of the offending agent or transfer of the patient from the site of the offending agent. Transfer of the patient to a job that merely reduces rather than eliminates exposure does not effectively relieve symptoms. In a few cases, asthma continues for years after the patient has left the workplace.

Allergic bronchopulmonary aspergillosis  Systemic corticosteroids are used in treatment. Although antifungal therapy and inhaled corticosteroids have not been thought to be helpful, evaluations of itraconazole—an antifungal with enhanced activity against Aspergillus species102—and high-dose inhaled beclomethasone105 indicate that use of these modalities in combination may be useful. Besides symptomatic and radiographic evidence of a response to therapy, the total serum IgE concentration has been used to follow the course of the disease; in some instances, an increase in IgE concentration heralds an exacerbation.

Emergency Therapy

On arrival of the patient in the emergency department, oxygenation should immediately be assessed by pulse oximetry, and controlled doses of oxygen should be provided to increase the O2 saturation to greater than 90%.104 An arterial blood gas measurement should be obtained as soon as practical. Patients with severe hypoxemia should be rapidly evaluated for hypercapnia, pneumothorax, atelectasis, or pneumonia, because most patients with uncomplicated asthma do not have hypoxemia.

The most effective emergency treatment is repeated administration of a shorter-acting beta-adrenergic agonist by inhalation. There is no advantage to giving beta agonists systemically, and the inhaled route is preferred for initial therapy, even in severe exacerbations. Administration of a beta-adrenergic agonist by metered-dose inhaler and a spacer device is as effective as administration by nebulization and requires less time with a respiratory therapist, making this approach potentially more cost-effective. In patients younger than 45 years, beta-adrenergic agonists can be administered every 15 to 20 minutes for up to three or four doses without adverse hemodynamic consequences, though unpleasant side effects from adrenergic overstimulation are universal. The addition of inhaled ipratropium to the inhaled beta-adrenergic agonist therapy may provide additional, though modest, benefit.9 Intravenous aminophylline has been found to be only a weak bronchodilator in this setting and adds little benefit. Intravenous corticosteroids should be given early for severe attacks because the steroids will not take effect for as long as 12 hours.106 High doses are no more effective than routine doses of hydrocortisone or methylprednisolone.105

Evaluation of lung function through spirometry or measurement of peak expiratory flow is useful in assessing the severity of the asthmatic attack and the response to treatment. Patients whose FEV1 or PEF is decreased to 25% of normal or lower are at risk for hypercapnia, and their arterial blood gas values should be obtained. Patients who have hypercapnia despite initial bronchodilator therapy should receive further treatment in an intensive care unit. Hypercapnia signals very severe and potentially life-threatening airway obstruction; fortunately, most hypercapnia...
chronic asthmatic patients can be treated with intubation and mechanical ventilation [see 14:VIII Respiratory Failure]. Some patients respond rapidly to an intensive bronchodilator regimen and can be discharged from the emergency department promptly. Because some degree of persistent airflow obstruction is likely to remain in such patients despite the resolution of their dyspnea and wheezing, most patients should be placed in an intensified home treatment program at the time of release; for most patients, this program should include a brief course of corticosteroids. The routine use of oral corticosteroids for 1 week after discharge from the emergency department reduces the rate of relapse in patients treated for an acute asthma exacerbation.108 Other patients experience only slight, gradual improvement despite repeated administration of potent bronchodilators. Such obstruction is caused by edema and inflammation of the airways and by secretions.

In-Hospital Therapy

Failure of emergency therapy to resolve signs and symptoms of obstruction after 3 to 4 hours is the most common indication for hospitalization. Respiratory failure with hypercapnia severe enough to require endotracheal intubation or the presence of significant barotrauma requires immediate hospitalization. In-hospital therapy for asthma to a large extent is simply a continuation of the measures that were begun in the emergency department. Development of protocols for hospital care have resulted in improved outcomes.107

Inhaled bronchodilators continue to be the mainstay of therapy. In severe, life-threatening attacks of asthma, short-acting inhaled beta-adrenergic agonists can be given as often as every 1 to 2 hours if necessary. As the obstruction resolves, administration can be less frequent. A long-acting beta-agonist may be useful in reducing the need for frequent inhaled short-acting beta-adrenergic agonists.109 The role of aminophylline in the hospital management of acute asthma is uncertain.110 Corticosteroids are indicated in virtually all patients admitted for severe asthma. Two regimens commonly employed for the treatment of such patients are (1) hydrocortisone, 2 mg/kg by I.V. bolus, followed by 0.5 mg/kg/hr by continuous infusion, and (2) methylprednisolone, 60 to 125 mg by I.V. bolus every 6 hours. The optimal dosage and route of administration remain uncertain. Most patients will improve with treatment, though progress may require several days. Serial determinations of pulmonary function are useful for monitoring the response to therapy. When the FEV1 or PEF reaches 50% to 60% of normal, patients usually have minimal or no symptoms, and the wide fluctuations in airflow that often characterize a patient’s initial course abate. The frequency and intensity of the bronchodilator regimen can then be decreased, I.V. medications can be switched to oral preparations, and the patient can be started on a program that can be continued after hospital discharge.

Occasionally, a patient deteriorates despite appropriate therapy. In this situation, it is necessary to monitor arterial blood gases closely. Intubation and mechanically assisted ventilation are needed in cases involving progressive hypercapnia and significant respiratory acidosis. All intubated patients should have their lung function assessed by recording the airway pressure required to deliver a tidal volume (tidal volume divided by plateau pressure [compliance]), flow resistive pressure (peak pressure minus plateau pressure), and the presence and degree of intrinsic positive end-expiratory pressure (dynamic hyperinflation). Baseline measurements can be compared to subsequent values as a means to assess response to therapy or need for accelerated treatment. If initial values reflect only modest obstruction in a hypercapnic asthmatic patient, a substantial contribution of respiratory muscle fatigue or weakness to the respiratory failure is likely [see 14:VIII Respiratory Failure]. Extreme measures, such as I.V. administration of isoproterenol, bronchial lavage to remove mucous plugs, and general anesthesia, are potentially dangerous and rarely indicated.

Ancillary measures include use of controlled supplemental oxygen for patients with arterial oxygen desaturation (O2 saturation < 90%) and empirical broad-spectrum antibiotic therapy (e.g., ampicillin, tetracycline, erythromycin, or trimethoprim-sulfamethoxazole) for patients with fever and sputum purulence that is not caused by eosinophils. There is at best only marginal benefit from vigorous hydration, inhaled saline mists, mucolytic therapy (e.g., acetylcysteine), and chest physiotherapy.

Additional Information

Additional information on asthma can be obtained from the National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov/health/prof/lung/asthma/practgde.htm), the American Lung Association (www.lungusa.org), and the American Thoracic Society (www.thoracic.org). Information on occupational asthma can be obtained at the Health, Environment, and Work Web site (http://www.agius.com/health/resource/ocasthma.htm).

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References


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Figure 2  Seward Hung.