CHAPTER 34

Asthma

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OUTLINE

OBJECTIVES

1. Define asthma.
2. Discuss the epidemiology of asthma.
3. Discuss the pathophysiology of asthma.
4. List the risk factors for asthma.
5. Describe the clinical features of nocturnal asthma, exercise-induced asthma, and occupational asthma.
6. Describe the disease severity classification proposed by the National Asthma Education and Prevention Program.
7. Discuss the role of peak flow monitoring in the management of asthma.
8. Compare the role of controller medication and quick-relief medication in the management of asthma.
9. Compare the use of nebulizers, metered dose inhalers, and dry powder inhalers in the delivery of aerosols to the patient with asthma.
10. Discuss the role of alternative treatment modalities in the management of asthma.
11. List the goals of mechanical ventilation of the patient with asthma.
12. Discuss the role of education in the disease management of asthma.

KEY TERMS

airway hyperresponsiveness
airway inflammation
allergen
asthma
asthma education program
asthma trigger
bronchial challenge testing
controller medication
exercise-induced asthma (EIA)
exhaled nitric oxide (eNO)
extrinsic asthma
heliox
intermittent asthma
intrinsic asthma
mild persistent asthma
moderate persistent asthma
National Asthma Education and Prevention Program (NAEPP)
nocturnal asthma
peak flow meter
quick-relief medication
severe persistent asthma

INTRODUCTION

Asthma is one of the most common chronic diseases of the pulmonary system. The third expert panel report (EPR) from the **National Asthma Education and Prevention Program (NAEPP)** of the National Institutes of Health issued this working definition of **asthma**, which remains unchanged from previous EPR guidelines:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli; reversibility of airflow limitation may be incomplete in some patients with asthma.[1]

This chapter presents issues related to the respiratory care of patients with asthma.

Epidemiology

Asthma is a common chronic disease that is increasing in prevalence and severity. The asthma literature frequently mentions epidemiology, prevalence, and incidence. Webster's ninth *New Collegiate Dictionary* defines *epidemiology* as a branch of medical science that deals with the incidence, distribution, and control of disease in a population. *Prevalence* refers to the number of individuals with a diagnosis at any given time (e.g., in 2010), whereas *incidence* refers specifically to the number of newly diagnosed cases that occur within a specific period of time (e.g., the past century).

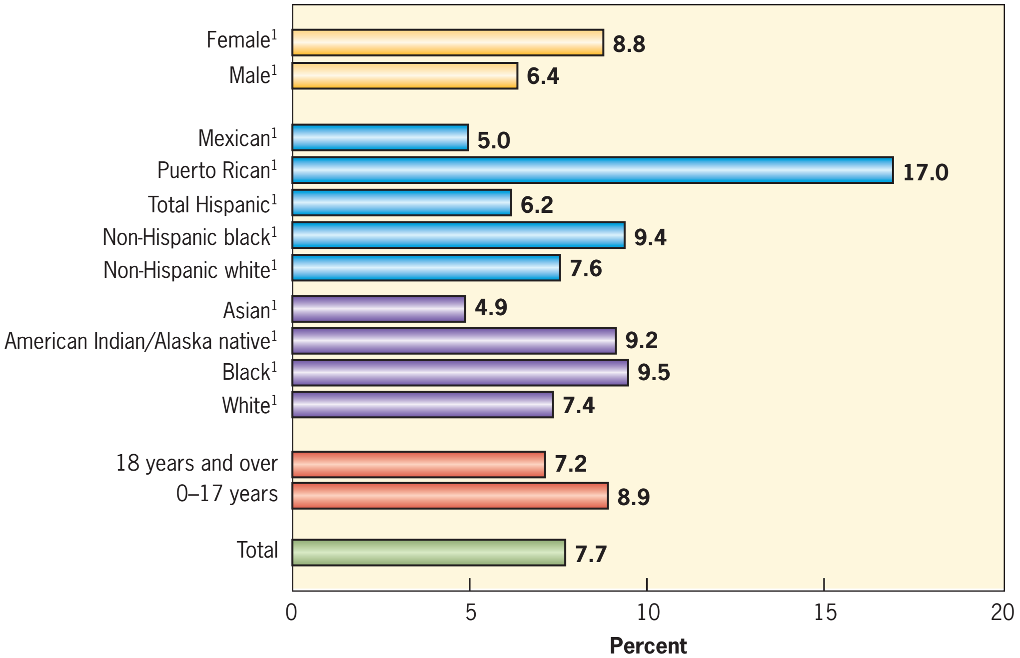

FIGURE 34–1 Asthma prevalence in the United States in 2005. [1]Age adjusted to 2000 U.S. standard population. From National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma03-05/asthma03-05.htm.

The prevalence and incidence of asthma are difficult to estimate because of the inherent problems with surveys and the varying definitions for asthma. Asthma is prevalent in approximately 10% to 12% of the population in different countries. This represents an estimated 300 million cases globally, 22 million of which are in the United States (**Figure 34–1**).[2,3]

Despite recent advances in both pharmacologic and nonpharmacologic management strategies, the prevalence of asthma is increasing, particularly in developing and developed nations. Presently, prevalence in the United States is monitored in terms of prevalence of attacks per year. This increased in the period from 1999 to 2005. Likewise, outpatient and physician office visits increased, but fortunately emergency department visits and deaths decreased (**Table 34–1**).[3]

TABLE 34–1 Changes in Rate (per 100,000) of Attack in the Past Year, Outpatient, Emergency Department Visits, and Deaths Due to Asthma, 1999–2005

	1999	2005
Prevalence	40,700	42,000
Outpatient visits	40,000	50,800
Emergency department visits	7500	6400
Deaths	20	14

Data from Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma—United States, 1980–1999. *MMWR.* 2002;51(SS01):1–13; and Akinbami L. Asthma prevalence, health care use and mortality: United States, 2003–2005. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma03-05/asthma03-05.htm#fig2.

Although asthma is more prevalent in males, it tends to be more severe in females. African Americans, especially those residing in urban areas, are three times more likely to be diagnosed with asthma in the United States. In the United States, asthma is the third leading cause of preventable hospitalization and resulted in 4055 deaths in 2003.[3]

People with asthma who are Puerto Rican have death rates that are four times higher than those of Caucasians (**Figure 34–2**).[3] Patients who have had frequent hospital admissions or previous life-threatening asthma are the most susceptible to asthma mortality.

Patients classified as having life-threatening asthma have been subgrouped into the following three classes:

- The typical case, a patient who presents with a gradual deterioration over time and experiences a life-threatening episode
- The patient with relatively mild, asymptomatic chronic asthma who suffers an acute episode in a relatively short time frame (referred to as *acute asphyxia asthma*)
- The patient who is a combination of the previous two classes

Misdiagnosis and inadequate treatment by disease severity are significant factors contributing to the increased incidence and prevalence of asthma.

The severity of acute episodes may vary from mild to life threatening within a given patient over the course of the disease or within a given year. In 2003, people with asthma lost 22.9 million school and work days because of their disease.[3] Likewise, there were 497,000 hospitalizations for asthma in 2004.[1]

Along with the increasing prevalence of asthma

AGE-SPECIFIC ANGLE

Death rates are greatest for people with asthma aged 18 years and older.

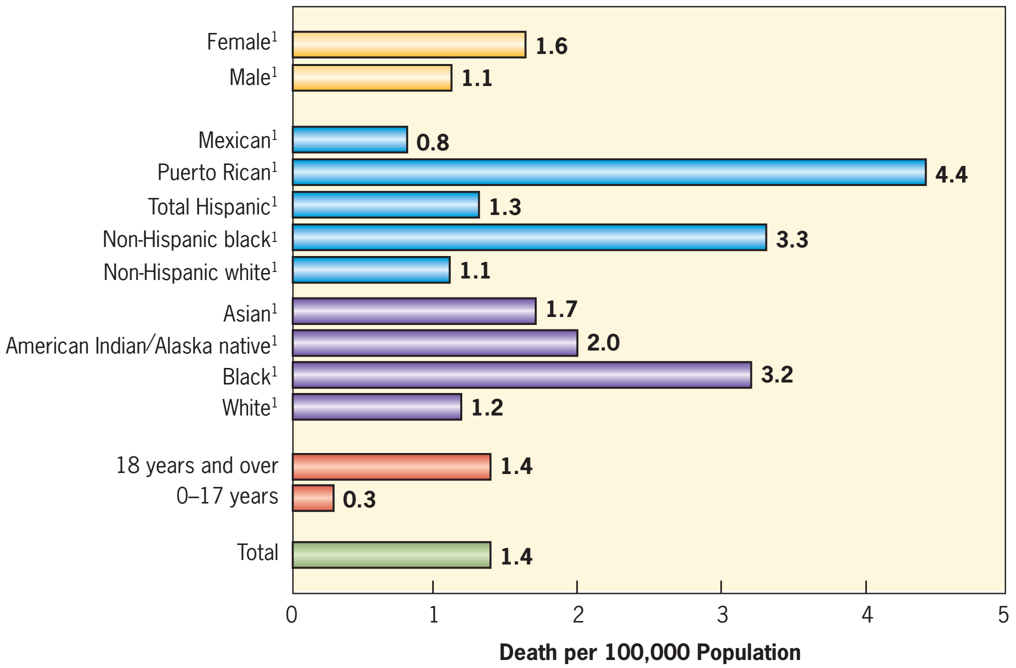

FIGURE 34–2 Asthma deaths per 100,000 population in the United States in 2005. [1]Age adjusted to 2000 U.S. standard population. From National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma03-05/asthma03-05.htm.

is the economic burden that comes with this chronic condition. In the early 1990s, the cost to treat asthma was estimated to be approximately $6 billion per year, with 43% of the cost associated with hospitalizations, emergency department (ED) visits, and death. The cost of ED therapy for asthma in the same year was $270 million, which represented 8% of the total direct cost of caring for asthma.[4] The fastest-growing age segment with asthma is children, a fact that has been reported to have had a staggering impact on the cost to treat asthma. A recent study suggests that the hospitalization costs for children younger than 5 years with asthma reach approximately 74% of their total healthcare costs.[5] The same study reported that the highest sector in the adult population for cost is also associated with hospitalizations (54%). Medications resulted in 16.5% of the total cost to treat asthma in adults, compared with 5.4% in children younger than 5 years.

> **AGE-SPECIFIC ANGLE**
>
> Asthma is increasing at the fastest rate in children younger than 5 years.

The high cost associated with acute care treatment of asthma has led to the implementation of disease management programs.[6–8] Because of the high volume of asthma visits and admissions in most urban areas, disease management programs or clinical practice guidelines can reduce cost by eliminating practice variation in the emergency department or hospital in the treatment of asthma. Eliminating acute treatment that adds cost without degrading the overall quality of care can be an effective tool in the management of asthma.[9,10]

Although asthma is not a curable disease, it can be managed effectively. Asthma mortality, and to a lesser degree morbidity, is largely preventable. Appropriate medications based on disease severity, and patient or caregiver adherence to a written asthma action plan can result in highly effective disease management. Patient education and awareness and control of environmental triggers also play a significant role in the overall management of the disease. Even with overall effective management from an educational, medical, and adherence standpoint, some patients develop severe persistent asthma with frequent exacerbations that may result in ED visits or hospitalizations.

Pathophysiology

The exact underlying cause of asthma is still unknown. Asthma is a multifactorial disease that has been associated with allergenic, hereditary, psychosocial, socioeconomic, environmental, and infectious causes. Asthma is not the only cause of wheezing. **Box 34–1** lists other potential causes or diagnoses associated with wheezing.

Even if the underlying cause of asthma is known in an individual, the trigger stimuli of an exacerbation may change over time. The pathophysiology of the disease is largely related to inflammation, hyperresponsiveness, and obstruction. **Figure 34–3** demonstrates the interrelationship of these three factors in the underlying mechanism of the disease.

> **RESPIRATORY RECAP**
>
> **Pathophysiology of Asthma**
> - Airway inflammation
> - Airway hyperresponsiveness
> - Airway obstruction

Airway Inflammation

Regardless of the trigger mechanism or the underlying cause of asthma, **airway inflammation** plays an important role. Acute and chronic inflammation affects airway caliber, airflow, and underlying bronchial hyperresponsiveness, which enhances susceptibility to bronchospasm. Chronic inflammation may be associated with a

BOX 34–1

Differential Diagnosis of Wheezing

Small and Large Airway Obstruction

- Asthma
- Airway tumors
- Bronchiolitis (in children)
- Cardiogenic pulmonary edema
- Cystic fibrosis
- Pneumonia; aspiration
- Bronchopulmonary dysplasia

Large Airway Obstruction

- Airway and esophageal foreign bodies
- Pulmonary emboli
- Tumors
- Vascular rings
- Focal pneumonia
- Laryngeal webs or malacia
- Tracheal stenosis
- Lymphadenopathies
- Vocal cord dysfunction

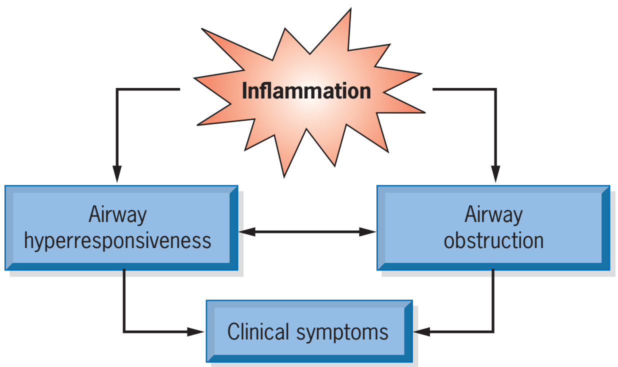

FIGURE 34–3 The interplay and interaction between airway inflammation and the clinical symptoms and pathophysiology of asthma. Modified from National Asthma Education Program, National Heart, Lung and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007*. Bethesda, MD: National Institutes of Health; 2007. NIH Publication 08-4051.

permanent alteration in airway structure, know as *remodeling*. Once remodeling occurs, the patient's asthma is not responsive to current treatment. Therefore, the control of inflammation is a central feature of asthma therapy.

Inflammatory cells that appear to be the most significant are lymphocytes, dendritic cells, mast cells, eosinophils, macrophages, epithelial cells, and T helper 2 cells. Among the mediators of inflammation are chemokines, nitric oxide, IgE, interleukins, cytokines, histamine, granulocyte macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-α (TNF-α). The release of inflammatory mediators results in recurrent exacerbations that manifest as wheezing, progressive shortness of breath, chest tightness, and coughing that may be more persistent nocturnally or in the early mornings.[11] In most patients, these exacerbations are usually self-limiting or resolve rapidly to appropriate asthma treatment.

Airway Hyperresponsiveness

A marker associated with asthma is the increased sensitivity, or **airway hyperresponsiveness**, to both specific and nonspecific factors. These factors have little or no effect on people with normal airways. The Lung Health Study showed that the majority of women and half the men diagnosed with chronic obstructive pulmonary disease (COPD) also have a component of hyperresponsiveness.

Airway hyperresponsiveness is a mechanism in which the airways constrict too easily and frequently, an exaggerated bronchoconstrictor response to a wide variety of stimuli. Factors associated with hyperresponsive airways include environmental factors (both indoor and outdoor), exercise, allergens, and viral infections. The degree or level of airway hyperresponsiveness usually correlates with the clinical severity of the disease.[1] Control of inflammation can reduce airway hyperresponsiveness and improve asthma control.[1]

Bronchial challenge testing with methacholine serves as a measure of responsiveness to general stimuli. Asthma is characterized by the reversibility of airflow obstruction. These challenge tests are usually administered in a pulmonary function laboratory. The methacholine challenge test begins with spirometry. The patient then inhales five breaths of increasing concentrations of methacholine, each time followed by performance of spirometry. The methacholine concentration at which a 20% decrease in FEV_1 (forced expiratory volume in 1 second) occurs ($PC_{20\%}$) is the end point. $PC_{20\%}$ is reached sooner and with a lower dose of methacholine in patients with asthma than in subjects without asthma. The test is followed (usually within 15 minutes) by administration of a short-acting β_2-agonist that should result in a 12% to 15% increase in FEV_1.

Airway Obstruction

The final component in the definition of asthma is airway obstruction, or the limitation of airflow through the airways. Airflow limitation is most commonly caused by the IgE-mediated release of inflammatory mediators into the airways, which come into contact with airway smooth muscles. More specifically, the mediators usually associated with an IgE response include histamine, tryptase, prostaglandin, and leukotrienes. However, when the airways are hyperresponsive, several stimuli can exacerbate bronchoconstriction (**Box 34–2**).

BOX 34–2

Changes That Lead to Airway Obstruction

Acute bronchoconstriction
Chronic mucous plug formation
Airway edema
Airway remodeling

In most patients, the airflow limitation or bronchoconstriction will spontaneously resolve with the administration of a short-acting β_2-agonist. Patients who have persistent disease or who have had asthma for a number of years may develop an incomplete response as a result of airway remodeling. These patients are difficult to separate from the COPD population. Patients who continue to have airway obstruction after initiation of conventional therapy are considered to be in status asthmaticus.

Pathogenesis

The factor that initiates the inflammatory process in the first place is unknown. It is known that the origins of asthma occur early in life, with the interplay of genetic and environmental factors as the immune system develops. This field of study, which emerged after the release of the second EPR, focuses on what has become known as the hygiene hypothesis.[1] Two types of T helper (Th) lymphocytes exist: Th1 and Th2. Th1 lymphocytes produce interleukin-2 and interferon-γ, which are important in response to infection. Th2 lymphocytes generate cytokines that mediate inflammation. At birth, Th2 is favored, and exposure to environmental stimuli such as infections will activate Th1 responses and balance Th1 and Th2. The imbalance in or favoring of Th2 favors the development of asthma. The favoring of Th2 is associated with the Western lifestyle: widespread use of antibiotics, an urban environment, diet, and sensitization to house-dust mites and cockroaches. The favoring of Th1 occurs when the child is exposed to other children or siblings, viral infection, and a rural environment. Thus, our Western obsession with cleaning everything and eliminating microorganisms from the environment may not be doing our children any favors (the hygiene hypothesis). A review can be found elsewhere.[12]

Other factors affecting pathogenesis are genetics (asthma has an inheritable component), gender (asthma predominates in boys until puberty), environmental factors (which are important in the development, persistence, and severity of asthma), allergens (sensitivity and exposure to allergens are important to the development of asthma in children), respiratory infections (see the earlier discussion of the hygiene hypothesis), and other environmental exposures (especially tobacco). This interaction of host and environmental exposures early in life is related to development of asthma.

Risk Factors

The strongest identifiable predisposing factor for the development of asthma is atopy. Atopy is the familial or genetic predisposition to develop an IgE-mediated response to common allergens in the environment. Asthma in childhood is normally linked to atopic factors. Among the many phenotypes of asthma, this is called *atopic*, *pediatric*, or *allergic asthma*. A study of 6- to 34-year-olds in Tucson, Arizona, found a strong, direct correlation between serum IgE levels and the development or presence of asthma, and a weaker correlation between positive skin test reactions and the development or presence of asthma.

Atopic asthma is diagnosed by skin-prick testing, in which a multitude of known allergens are introduced to the patient's immune system through small pricks in the arms. The most common method of skin testing is a radioallergosorbent test (RAST) that measures antigen-specific IgE. A study of children in eight metropolitan areas indicated that the highest risk factors for atopic asthma in inner-city children were cockroach antigen, animal dander, and dust mites.[13]

RESPIRATORY RECAP

Risk Factors for Asthma

» Allergens
» Pollution
» Food and drug additives
» Viral agents

Factors that may contribute to or enhance the development of asthma include environmental pollution, low birth weight, tobacco smoke, diet, and viral infections. Asthma has also been associated with sinusitis and gastrointestinal reflux.

Allergens

The majority of asthmatics suffer attacks exacerbated by inhalation of an **allergen**. Many allergens, both indoor (e.g., mold, animal dander, cockroach antigen, dust mites) and outdoor (e.g., grass and tree pollens), may trigger an exacerbation. Other allergens are found in certain foods such as dairy products, shellfish, nuts, mushrooms, and preservatives.

An allergic asthma exacerbation usually has two phases. The first phase is the acute phase. The presence of an **asthma trigger** on a hypersensitive airway causes rupture and degranulation of mast cells. Airway mast cells release mediators (leukotrienes, eosinophil chemotactic factor of anaphylaxis [ECF-A], prostaglandins, and histamine) into the tracheobronchial tree. These mediators all interact with the airway smooth muscle, resulting in bronchoconstriction, edema, vasodilation, and eosinophil release, and also may cause increased secretion production.

The second phase of an asthma attack is the inflammatory phase, occurring several hours after the first phase has resolved. Inflammatory mediators are released into the airway. Evidence suggests that airway inflammation is caused not by one particular type of inflammatory mediator but by an intricate cycle of complex interactions that develop between multiple mediators, inflammatory cells, and other cells and tissues commonly found in the airways. The inflammatory response usually results in the migration of these various inflammatory cells and mediators into the airways, where they cause direct injuries, such as alterations in epithelial integrity, abnormalities in autonomic neural control of airway tone, mucus hypersecretion, change in mucociliary function, and an increase in airway smooth muscle responsiveness.[1] The presence of the second phase of an asthma exacerbation is why a patient should be monitored for 4 to 8 hours after the initial phase has resolved, and why oral corticosteroids are considered for rapid relief in the emergency department for treatment of exacerbation. Oral corticosteroids help to control the severity of the second phase.

Allergens from indoor sources consist mainly of cockroach antigen, domestic dust mites, animal dander, and mold (*Alternaria*) or fungi. Indoor allergens appear to be a main trigger in industrialized, developed countries. In developed countries, insulated housing that has been heated, humidified, cooled, and carpeted is prone to increased levels of indoor allergenic sources.

Dust mites appear to be the major cause of asthma worldwide, especially when infants are exposed to high concentrations in the first 3 to 6 months of life. The predominant domestic mite is *Dermatophagoides* species. The allergens are located in the inhaled microscopic fecal pellets. Dust mites are found in common household products but are especially prominent in bedding, carpet, stuffed animals, and soft furnishings. Dust mites grow best in humid air at temperatures of 22° to 26° C (71.6° to 78.8° F). The best method for eradicating mites is to wash potential breeding material in hot water (>54.4° C [>130° F]). One study indicated cockroach antigen as the leading allergenic cause of inner-city asthma.[14] Cockroach antigen is found in the microscopic excrement and powdered dried bodies of cockroaches and is inhaled by the sensitized patient.

AGE-SPECIFIC ANGLE

Dust mites are a major cause of asthma when infants are exposed to high concentrations in their first 3 to 6 months of life.

Cats are highly allergenic. The principal source of allergen is found in cat excrement. Cat saliva has also been identified as a source of cat antigen. Dog sensitivity is not as well documented but has been found to contribute to allergenic sources.

Fungi and molds also have been identified as allergenic risks in specific individuals with moderate to severe asthma. Fungi are most commonly found to grow extremely well in areas used for heating, cooling, or humidification. Home humidifiers provide a special risk for indoor fungal growth and air contamination.

Outdoor allergen sources are primarily pollens. The sources of these pollens include grasses, trees, flowers, weeds, and fungi. Each season particular outdoor allergen sources appear as major contributing factors for initiating asthma exacerbations. In the early spring, trees are the prominent trigger in pollen-associated asthma attacks. As the temperatures warm in the late spring and early summer, grasses and flowers reign as the initiators. In early fall, weeds play an important role in eliciting asthma exacerbations. The fall season also initiates the mold-induced exacerbations, predominately from *Alternaria* and *Cladosporium* species.

Pollution and Environmental Irritants

The role of indoor and outdoor air pollution in the development or initiation of an asthma attack remains unproved and controversial. Air pollution often has been accused of being a viable source for the increase in prevalence of asthma, but research has failed to produce a direct link to air pollution and asthma. Outdoor types of pollution are mainly associated with industrialized nations that have a large amount of industrial or photochemical smog.

Indoor air pollutants have had a higher association with the development of respiratory symptoms. Maternal smoking during pregnancy results in harmful in utero exposure of the fetus and increases the risk of the child's developing recurrent wheezing in the first 5 years of life. It is well established that exposure to environmental tobacco smoke increases the severity of asthma, increases the risk of asthma-related ED visits and hospitalizations, and decreases the quality of life in both children and adults.[1] Other potential sources of indoor air pollution include nitric oxide, carbon dioxide, carbon monoxides, nitrogen oxides, sulfur dioxides, formaldehydes, cleaning chemicals, solvents and paint, perfumes or aerosol sprays, and biologic sources such as endotoxins.

Temperature changes often have been associated with eliciting asthma exacerbations. Although this appears to be largely unfounded, the roles of humidity in the summer months and cold air during winter months are still a mystery.

Food and Drug Additives

Many patients with asthma who have allergies to specific foods increase their potential to develop exacerbations from intake of these foods. Foods that contain salicylates, some food-coloring agents, food preservatives (e.g., sulfites), and monosodium glutamate are substances known to be associated with asthma exacerbations.

Drugs may be associated with an increased likelihood of exacerbation. The primary risk is with nonsteroidal anti-inflammatory agents and aspirin. Patients who have sensitivity to aspirin have an increased risk of developing asthma later in life.

Viruses

Viral illness seasons (October through December and February through April) coincide with the most prevalent hospitalization periods for asthma in both children and adults. It has been reported that 37% of adult patients with acute asthma admitted over a 12-month period had evidence of recent respiratory tract infection.[15] This phenotype of asthma has been called **intrinsic asthma**, in contrast to **extrinsic asthma**. The inflammatory responses to viral infections (especially in the lower respiratory tract) may start the cascade of symptomatic wheezing from inflammatory debris or excessive mucus production in the airways.

Induced sputum[16] has been used as a marker of the effects of natural colds and influenza on the airways of the lungs. Natural colds (by day 4) cause neutrophilic lower airway inflammation that is greater in people with asthma than in healthy subjects. The greater inflammatory response in people with asthma may be due to the changes associated with trivial eosinophilia or to the different viruses involved. As was stated earlier, exposure to viral infections early in life influences the development of the immune system, promoting a protective function.

The most prominent of these viral infections is respiratory syncytial virus (RSV). The population at highest risk for severe cases of RSV and other lower respiratory tract infections, namely, the indigent inner-city population, also is at high risk for asthma. Infants with RSV early in life who developed high titers of RSV IgE were three times more likely to have recurrent wheezing after 48 months.

AGE-SPECIFIC ANGLE

A relationship exists between respiratory viral infections in early childhood and the development of asthma.

The exact role that early childhood respiratory tract infections play in the development of asthma is unclear. However, respiratory tract infections are a significant risk factor for the initiation of an asthma exacerbation that may or may not result in an individual seeking acute care. Infections should be identified to the patient with asthma as a trigger. Furthermore, written asthma treatment plans should include a component for increasing or stepping up therapy at the onset of symptoms. There is an advantage of hospitalization prevention when families of children with asthma had a written treatment plan that could initiate more aggressive outpatient management with the onset of coldlike symptoms.[17]

Other Asthma Phenotypes

Nocturnal Asthma

Nocturnal symptoms are quite common in people of all ages with asthma and even in patients who have intermittent or mild persistent asthma. Although **nocturnal asthma** is prevalent in up to 75% of all patients with asthma,[18] many do not correlate these nighttime symptoms with asthma. The presence of nocturnal asthma is a marker for uncontrolled or more severe asthma.[19–21]

A variety of mechanisms are interactive when nocturnal asthma is present.[22] The mechanisms seem to revolve around circadian alterations of body temperature, vagal tone, mediators, inflammation, epinephrine, and β_2-receptor function.[23,24] Other variables considered to be potential causes include gastroesophageal reflux, inhalation of cooler or drier air by mouth while sleeping, aspiration, sinusitis, increased mucus production, sleep apnea, and the normal decrease in lung function while sleeping.

An extensive amount of research has been undertaken in an attempt to optimize the treatment of nocturnal asthma. Treatment of nocturnal asthma requires therapy that uses a chronopharmacologic approach, that is, use of medications on a schedule that decreases nocturnal asthma symptoms.[22] An optimal therapeutic regimen should include some or multiple components of sustained-release theophylline, long-acting β-adrenergics, and/or inhaled corticosteroids. Comorbid conditions (e.g., obstructive sleep apnea, gastroesophageal reflux) must also be treated. Nighttime awakenings are a sign of persistence of asthma and loss of control, and are not to be tolerated.

Exercise-Induced Asthma

Exercise-induced asthma (EIA) is characterized by transient airway obstruction, typically occurring 5 to 15 minutes after strenuous exertion. EIA is prevalent in 90% of individuals with asthma. The prevalence of EIA among athletes is estimated to range between 3% and 11%.

There are cases of undiagnosed asthma that suddenly appears in competitive high school athletes.[25] Diagnosis of EIA may be made based on a history of symptoms (cough, wheeze, and chest tightness with exercise challenge testing). More traditionally or for definitive diagnosis, a fall of 10% or more in the FEV_1 or in peak expiratory flow (PEF) rate after exercise is diagnostic. Vocal cord dysfunction is commonly confused with EIA.[1]

The exact etiology of EIA is unclear. Theories range from temperature-related causes to inflammatory mediator release (**Box 34–3**). EIA symptoms typically appear during or after exercise, peak at 8 to 15 minutes after exercise, and eventually spontaneously resolve in about 20 to 30 minutes. Frequently, a refractory period (of up to 3 hours) occurs after initial recovery, during which repeat exercise causes less bronchospasm.

BOX 34–3

Etiologic Theories for Exercise-Induced Asthma

- Respiratory heat or water loss (or both) from the bronchial mucosa
- Mucosal drying and increased osmolarity stimulating mast cell degranulation
- Rapid airway rewarming after exercise, causing vascular congestion, increased permeability, and edema leading to obstruction
- Hyperventilation, causing discharge of bronchospastic chemical mediators

Appropriate treatment with anti-inflammatory medication (evidence grade A) reduces airway hyperresponsiveness and is associated with a reduction in the frequency and severity of EIA.[1] Other therapy for EIA includes the use of a short-acting β_2 agonist (SABA) 15 to 20 minutes before exercise; although a long-acting β_2 agonist (LABA) is also appropriate, frequent use may mask poorly controlled persistent asthma. Leukotriene receptor antagonists (LTRAs) can help in 50% of cases of EIA. Cromolyn may be effective but is not as good as SABAs. A warm-up period before exercise and cool-down afterward may help attenuate EIA, as will a mask or scarf over the mouth and nose in cold weather. Coaches should be made aware of EIA in any student so a SABA can be used prior to exercise classes. Although prevention is the main objective in managing EIA, education regarding its nature and management is important.

Occupational Asthma

Occupational asthma is characterized by variable airway hyperresponsiveness in the workplace. The patient typically reports increased symptoms while at work or within several hours of the completion of a shift, with improvement on weekends or during vacations. In addition, the presence of sensitizing agents and the presence of similar symptoms in coworkers are suggestive of occupational asthma. The diagnosis can be made by monitoring peak flows for 2 weeks in the workplace and 1 week away. Both new-onset asthma and exacerbations of preexistent asthma may occur as a result of occupational exposures. Occupational asthma is the most common occupational lung disease in developed countries.

Isocyanates are the most common etiologic agents. Inciting agents are divided into two broad categories: low-molecular-weight chemicals (e.g., trimellitic anhydride, formaldehyde), which require combination of the chemical, which is an incomplete antigen (i.e., a hapten), with a protein conjugate to produce a sensitizing neoantigen; and high-molecular-weight organic materials (e.g., grain dust, avian proteins), which may serve as complete antigens. Cigarette smoking is also an important risk factor for occupational asthma. The asthma educator may work with the onsite healthcare providers to discuss avoidance, ventilation, respiratory protection, and provision of a tobacco smoke-free environment.

Disease Severity Classification

Asthma is classified in terms of severity and control. *Severity* is defined as the intrinsic intensity of the disease process, wherein the patient's frequency and intensity of symptoms is evaluated. *Control* refers to the degree to which the manifestations of asthma are minimized and the goals of therapy are met. Both severity and control include the domains of current impairment (symptoms) and future risk (based on history of exacerbation and use of oral corticosteroids). Preferably, the patient's asthma should be classified before beginning controller therapy. Once classification has occurred, therapy is started based on a stepwise approach, to include recommended SABAs, LABAs, and inhaled corticosteroids. Once a patient has been on the recommended regimen and efforts have been made to control environmental factors, the patient is reevaluated for asthma control.

RESPIRATORY RECAP

Asthma Disease Severity Classification

» Intermittent
» Mild persistent
» Moderate persistent
» Severe persistent

Patients are divided into three age categories by the EPR-3: children aged 0 to 4 years, children aged 5 to 11 years, and children aged 12 and older to adults. For the child 0 to 4 years of age, upon presentation, the child is evaluated for frequency of symptoms, nighttime awakenings, use of SABAs, and interference with normal activity (the elements of impairment) and risk (i.e., the number of exacerbations requiring oral corticosteroids in the past year and the frequency of exacerbations).[1] For the child aged 5 to 11 years, the same factors are used to assess impairment, plus spirometry is added, with particular attention to FEV_1 and the ratio of FEV_1 to percent forced vital capacity (FEV_1/FVC%).[1] The same criteria are used for risk. In all patients older than 12 years, the same criteria are used to assess impairment, with age-specific ranges for FEV_1/FVC%. The same criteria are used for risk as with children.[1]

The NAEPP expert panel has developed a four-tiered system to classify chronic disease severity.[1] The four categories are intermittent, mild persistent, moderate persistent, and severe persistent asthma. A patient may have a higher severity in one area versus another. When classifying the patient's asthma, the level of severity corresponds to the worst level of the patient's impairment or risk. For example, the patient may have symptoms on more than 2 days per week, but not daily, but has an FEV_1 less than 60% of predicted. This patient would be classified as having severe persistent asthma, and treated accordingly.

Therapy is a stepwise approach, according to level of severity. Once the level of severity is established, the clinician selects a therapeutic step (steps 1 through 6, with step 6 being reserved for the most severe cases).

Intermittent

Intermittent asthma is the least severe of the four classes of disease severity. People with asthma in this category experience symptoms two or more times per week. These patients generally are expected to experience nocturnal symptoms of coughing, wheezing, or breathlessness no more than two times per month. They require SABAs no more than twice per week. There is no interference with normal activity. These patients have normal pulmonary function tests between exacerbations, although their exacerbations are generally brief (from a few hours to a few days). They have required zero to one course of oral corticosteroids in the past year.

Routine management of these patients (regardless of age) generally consists of as-needed SABAs. Although these patients may have the chronic component of their disease classified as intermittent, the periodic exacerbations that occur may vary in their intensity. Sometimes, although rarely, these exacerbations result in this class of patients needing to seek ED treatment or resulting occasionally in hospitalization.

Mild Persistent

People with **mild persistent asthma** experience symptoms of coughing or wheezing more than twice per week but less than once per day. These patients generally experience nocturnal symptoms of coughing, wheezing, or breathlessness more than two times per month. These patients may use their SABA more than twice per week, but not daily. These patients have symptoms that cause a minor limitation to normal activities of daily living. Pulmonary function is normal. Exacerbations may be more frequent.

Routine management of these patients generally consists of step 2 therapy: as-needed short-acting β_2-agonist with the addition of a controller medication. In all patients, the recommended controller medication is an inhaled corticosteroid (ICS), whereas in children aged 0 to 4 the options of cromolyn sodium or montelukast are indicated as a potential substitute for inhaled corticosteroids. In children aged 5 to 11, alternatives include cromolyn, montelukast, theophylline, or nedocromil. The alternatives are only used if there is a contraindication to ICS, since the ICS is actually controlling inflammation. The same therapy is used for those aged 12 years and older.

Although these patients may have the chronic component of their disease classified as mild persistent, the periodic exacerbations that occur also vary in their intensity. These exacerbations periodically result in this class of patients needing to seek ED treatment or occasionally result in hospitalization.

Moderate Persistent

People with **moderate persistent asthma** experience symptoms of coughing or wheezing on a daily basis. Moderate persistent asthma patients generally experience nocturnal symptoms of coughing, wheezing, or breathlessness more than once per week. SABA use is daily. These patients have symptoms that cause some interference with normal activities of daily living. Spirometry results show an FEV_1 above 60% but less than 80% of predicted, and $FEV_1/FVC\%$ is reduced by 5%.

Management of patients aged 0 to 4 years consists of step 3 or 4 therapy: SABA for exacerbations and medium-dose inhaled corticosteroid (step 3) in addition to LABA or montelukast (step 4) daily. In older children, step 3 therapy consists of low-dose ICS and either LABA, LRTA, or theophylline, or medium-dose ICS. Step 4 therapy is medium-dose ICS with a LABA or medium-dose ICS and either LRTA or theophylline. For those aged 12 and older, step 3 therapy is low-dose ICS and the addition of a LABA, or low-dose ICS with an LRTA or theophylline. Step 4 therapy is medium-dose ICS with a LABA or medium-dose ICS with either LRTA or theophylline. These patients may routinely need to seek ED treatment or require hospitalization secondary to the chronic inflammatory component of their asthma.

Severe Persistent

This category is the highest level of the four classes of disease severity. Patients with **severe persistent asthma** experience symptoms of coughing or wheezing almost continually. Severe persistent asthma patients experience nocturnal symptoms of coughing, wheezing, or breathlessness almost every night. These patients may use their SABA several times daily, a dangerous practice that correlates with an increased incidence of death. These patients have symptoms that cause extremely limited activities of daily living. Spirometry results show an FEV_1 less than 60% of predicted and an $FEV_1/FVC\%$ reduced more than 5%.

Management of these patients consists of step 5 or 6 therapy: short-acting β_2-agonist for exacerbations for all age groups. Controller drugs for the 0- to 4-year age group are high-dose ICS in addition to either LABA or montelukast (step 5), or high-dose ICS with LABA or montelukast or oral corticosteroids (step 6). Step 5 therapy for the 5- to 11-year age group consists of high-dose ICS with a LABA, or high-dose ICS and LRTA or theophylline. Step 6 is high-dose ICS and LABA with consideration of oral corticosteroid, or high-dose ICS and LRTA or theophylline plus an oral corticosteroid. For those 12 and older, step 5 therapy is high-dose ICS in combination with a LABA and consideration of omalizumab for those with allergies. In step 6, an oral corticosteroid is added to step 5 therapy and omalizumab is considered. These patients may frequently seek ED treatment and require hospitalization secondary to the chronic inflammatory component of their asthma.

Although patients may be classified in any of the four categories, periodic review of chronic symptoms and adherence is necessary. Quite often asthma is controlled with appropriate medications, and compliance and treatment can be decreased to a lower severity class with a decrease in symptoms. From the opposite perspective, with increasing symptomatic data, it may be necessary to intensify the treatment regimen to address the increase in symptoms.

Assessing Control of Asthma

After initiating therapy according to the stepwise scheme, patients should be evaluated for control of asthma. Just as when initiating therapy, the practitioner evaluates the patient in the domains of impairment and risk, using the same criteria: frequency of symptoms, nighttime awakenings, interference with normal activity, SABA use, lung function (age 5 and older), validated questionnaires about quality of life (adults), number of exacerbations requiring oral corticosteroids, and treatment-related adverse effects.

Asthma is classified as well controlled, not well controlled, or very poorly controlled, according to the worst symptom or finding. If a patient's asthma is well controlled for at least 3 months, consideration is given to stepping therapy down one step. If the asthma is not well controlled, patient adherence is checked and consideration is given to stepping up one step, with reevaluation in 6 weeks. If asthma is very poorly controlled, a short course of oral corticosteroids is considered, as is stepping up one to two steps, in addition to checking adherence and evaluating side effects. In either case, alternative treatment options are considered in the presence of adverse effects.

Status Asthmaticus

Severe attacks of asthma poorly responsive to adrenergic agents and associated with signs or symptoms of potential respiratory failure are referred to as *status asthmaticus*. The mechanisms of airflow obstruction and the principles of treatment for status asthmaticus are similar to those in which the asthma responds promptly to treatment. Although this term has been used for years when referring to a refractory asthma exacerbation, it is not used anywhere in the EPR-3, other than in a few references. Perhaps it is time to refer to this condition as a severe exacerbation or an exacerbation requiring admission to an intensive care unit.

Objective Measurements

One of the primary goals of asthma management and control is to maintain normal (or near normal) lung function. Objective assessment of the degree of variable airflow obstruction, hyperresponsiveness, and airflow reversibility is a fundamental component in the diagnosis of asthma. The precise measurement of airflow changes is important to evaluate the effectiveness of therapeutic maintenance or interventions.

The most familiar ways to diagnose and monitor airflow are pulmonary function testing (spirometry) and peak flow meters. In 1994 the American Thoracic Society (ATS) differentiated between diagnostic and monitoring devices.[26] Diagnostic evaluation by pulmonary function testing includes bronchial challenge, spirometry, lung volumes, and airway resistance. A relatively new diagnostic tool for the inflammatory component of asthma is measurement of exhaled nitric oxide levels.

RESPIRATORY RECAP

Objective Measurements in Asthma

- » Spirometry
- » Lung volumes and airways resistance
- » Peak flow
- » Exhaled nitric oxide

Spirometry

Studies have demonstrated that children as young as 3 years of age can perform spirometry approximately 20% of the time. The NAEPP recommends diagnostic spirometry at initial diagnosis and at least yearly after initial diagnosis, at the age of 5 or later. The airflow obstructive component of asthma is caused primarily by a decrease in expiratory flows and/or a high airway resistance. The spirometry data of a patient with asthma with airflow obstruction show a normal or slightly decreased FVC, a decreased or normal FEV_1, a decreased or normal PEF, and a decreased percentage of FEV_1/FVC. The ATS has recommended a diagnosis of asthma when airflow reversibility achieves an increase in FEV_1 of 200 mL and 12%.[26] Pre- and postbronchodilator testing is the hallmark intervention to decipher airflow reversibility. Normal spirometry with a suspected history of asthma symptoms may be an indication for bronchial challenge testing. During periods of acute exacerbations, people with asthma may have significant amounts of hyperinflation and air trapping that will suggest a restrictive disease and require the measurement of lung volumes for accurate diagnosis.

Lung Volumes and Airways Resistance

Body plethysmography is the diagnostic tool that is used to achieve measurements of airways resistance (Raw), airway conductance (Gaw), and static lung volumes.

Static lung volumes are the primary test that differentiates restrictive diseases from obstructive diseases. Static lung volumes are useful also to detect the presence of hyperinflation. Raw may be normal in asymptomatic asthma, although Gaw may be decreased. Normally during acute exacerbations, Raw is increased. Bronchodilator effectiveness is accurately evaluated with measurements of Raw during acute exacerbations.

Peak Flow Meters

Peak flow meters (**Figure 34–4**) have been classified by the ATS as monitoring devices for the management of asthma.[26] The EPR-3 recommends that written asthma action plans be based on either symptoms or peak flow measurements.[1] Peak flow monitoring should be considered for patients who have moderate or severe persistent

FIGURE 34–4 Commercially available peak flow meters.

asthma, those classified as "poor perceivers," or those with worsening asthma, an unexplained response to environmental or occupational exposures, and others at the discretion of the clinician and the patient. The patient's "personal best" peak flow should be known. The personal best is the highest peak flow of three successive measurements, taken during an asymptomatic period.

The accuracy and reliability of different peak flow meters have been questioned. Variation occurs even within a manufactured brand of peak flow meter. For this reason, a patient should use a specific device for consistent readings. When analyzing peak flow data, one must realize the limitations of the measurements. Peak flow readings are extremely effort dependent and are an indicator of large airway obstruction. Often the mistake is made to attribute all low measurements to poor effort or lack of cooperation when there is airway obstruction present. Sometimes the clinician cannot differentiate between poor data or airway obstruction.

Consensus opinion from the NAEPP committee established a traditional three-zone approach to the management of acute asthma exacerbations: green (>80% of personal best), yellow (50% to 79% of personal best), and red (<50% of personal best) (**Box 34–4**). Most of the predicted normal values or nomograms for peak flow values are based on sex and height in healthy subjects. Most people with moderate to severe asthma could not achieve these predicted values on their best days. This is the rationale to develop a personal best reading for peak flows on an individual-by-individual basis.

Exhaled Nitric Oxide

In 1993, Jorgens and colleagues described the potential significance of measuring **exhaled nitric oxide (eNO)** in disorders of the pulmonary system. Exhaled nitric oxide has been indicated to be a useful marker of airway inflammation in patients with asthma. Unfortunately, varied protocols make it difficult to compare and compile information from early studies on eNO and asthma.

An important issue is standardization of measurement techniques for eNO analysis. Measurement of eNO can be complicated by two factors: contamination by nasal nitric oxide and variable expiratory flow rates. The eNO concentration can be up to 1000 times higher in the nasal cavity and paranasal sinuses than concentrations found in the lower airways. Turbulent gas mixing during exhalation allows nitric oxide contamination from the nasal cavity. The eNO concentration is also highly flow dependent, allowing for measurement difficulty with variable flow rates. With high expiratory flow rates, nitric oxide levels will be lower than with a constant and slow expiratory maneuver. Techniques have been developed for measuring eNO that potentially overcomes these factors.[27]

Exhaled nitric oxide is an important measurement of the inflammatory component of both acute and chronic asthma in both children and adults. People with asthma who suffer from nocturnal asthma have higher eNO levels during the day and night than those who do not suffer from nocturnal symptoms.[28] Given recent efforts to standardize measurement techniques, information concerning the role and degree of inflammation in both acute and chronic asthma should be available. Information regarding the impact of corticosteroids on decreasing or suppressing inflammation should also be readily at hand for clinicians.

The adequacy of asthma control is often, but imperfectly, measured by assessing symptom control, improvement in physical findings, and improvements in pulmonary function, because these outcomes do not track each other consistently.[29] The available evidence supports that the measurement of FeNO is a marker of inflammation, is highly reproducible, is responsive to change in the underlying disease state, and is predictive of response to therapeutic intervention with anti-inflammatory medications. FeNO is elevated in patients with asthma and that the level of FeNO decreases after the administration of either inhaled or systemic corticosteroids. **Table 34–2** summarizes the usefulness of measuring FeNO.

BOX 34–4

Traditional Peak Flow Zones

Green Zone: Normal Zone
Predicted or personal best in the range of 80% to 100%

Yellow Zone: Caution Zone
Predicted or personal best in the range of 50% to 80%

Red Zone: Danger Zone
Predicted or personal best less than 50%

TABLE 34–2 Usefulness of Determining Fraction of Exhaled Nitric Oxide

Establish the correct diagnosis of asthma in corticosteroid-naive patients Chronic cough Exercise-induced bronchospasm Differentiate COPD from asthma Predictive of a favorable response to corticosteroids in subjects with asthma, COPD, or nonspecific respiratory symptoms
Titration of anti-inflammatory medication in patients with asthma
Attainment and maintenance of asthma control
Predictive of impending asthma exacerbation
Monitor asthma medication adherence

COPD, chronic obstructive pulmonary disease.

A FeNO of more than 35 parts per billion (ppb) in a steroid-naive patient presenting with respiratory symptoms is compatible with a diagnosis of asthma; however, the FeNO cannot be used to determine the classification of the asthma. Two devices are presently approved for FeNO measurement by the Food and Drug Administration (FDA). Reimbursement is presently very limited. The reluctance regarding third-party reimbursement was based on a review of several articles that concluded that methodology was heterogeneous and that there were different FeNO cutoffs, differences in definition of outcomes, and conflicting trial conclusions. Presently, FeNO measurement is an adjunct in the diagnosis and management of asthma. Reimbursement remains limited, but the practice is becoming more widespread and cost should become more competitive.

Pharmacologic Therapy

The purpose of pharmacologic therapy in the treatment of asthma is to prevent or control asthma symptoms, or at least to attempt to reduce the frequency or severity of acute exacerbations. Medications for asthma are classified as either long-term controllers or quick relievers in the new guidelines released by the expert panel.[1] The long-term **controller medications** are taken to decrease the degree of inflammatory mediator release in the airways. These medications include anti-inflammatory agents, long-acting bronchodilators, leukotriene modifiers, and immunomodulators.

Quick-relief medications are used to combat acute exacerbations of bronchoconstriction or provide quick, complete resolution of airflow obstruction and its accompanying symptoms of cough, wheezing, and chest tightness. This class of medications includes short-acting β_2-agonists and anticholinergics. Patients in all severity classes of asthma should receive a prescription for quick-relief medications for use during acute exacerbations.

Because the new asthma guidelines stress the importance of the inflammatory component in asthma, the following medication sections start with a description of the controller medications.

Controller Medications

Inhaled Corticosteroids

Corticosteroids are considered the most potent and consistent anti-inflammatory agents currently available by inhaled therapy in the long-term management of the inflammatory component of asthma. Anti-inflammatory medications are now stressed as the first line of treatment in the management of asthma. All asthma severity classes that have a persistent component are most effectively controlled with daily anti-inflammatory therapy.

Corticosteroids have been shown to suppress the release of certain inflammatory mediators. The use of corticosteroids in the management of asthma has been correlated with an overall reduction in asthma symptoms, an increase in lung function (as well as a decrease in the decline of FEV_1 over years of the disease), a decrease in airway hyperresponsiveness, a decrease in the frequency of acute exacerbations, and possibly a decrease in the amount of airway remodeling in both adults and children.[30]

The exact mechanism of action involved with corticosteroids and inflammation is not well understood. Several mechanisms appear to be actively and intimately involved. Corticosteroid therapy has provided evidence of an interference with the production of cytokines or suppression of cytokine release, a depression in the production of leukotrienes, and active recruitment of eosinophils. Clinical effects may take 2 to 3 weeks or more, but some newer agents, such as fluticasone, have demonstrated improvement in a day.

> **RESPIRATORY RECAP**
>
> **Asthma Controller Medications**
> - » Inhaled corticosteroids
> - » Nonsteroidal anti-inflammatory agents
> - » Long acting β_2-agonists
> - » Methylxanthines
> - » Leukotriene modifiers
> - » Immunomodulators
> - » Oral corticosteroids

Dosage and frequency of corticosteroids can vary, depending on the specific type of product or delivery device. However, dosing to effect is patient and time dependent. The ability to eventually wean patients off corticosteroids also depends on patient physiology. An attempt to decrease the dose of ICS should be made only after asthma has been well controlled for 3 to 6 months. Patients who have moderate to severe persistent asthma often have persistent symptoms and a decline in lung function with attempts to wean or decrease the dose or use of corticosteroids.

The dose and frequency of ICS vary with the corticosteroid to be administered. Adherence is enhanced as the frequency decreases. Most controller preparations are formulated to be given once or twice daily. In cases of uncontrolled asthma or increasing disease severity, the dosage and frequency can be increased. However, it is important to also review the patient's environmental control and medication technique before increasing the ICS dose.

The most common complications associated with the use of corticosteroids are persistent reflex cough, occasional dysphonia, sore throat, and oropharyngeal candidiasis. The majority of these short-term complications can be eliminated or greatly reduced with the use of spacer devices and rinsing the mouth after inhalation. Systemic toxic effects are a rare occurrence with inhaled corticosteroids. The effect of corticosteroids on the linear growth of preadolescents who are taking this class of medications long term is controversial.[31,32] The EPR-3 states the following:[1]

1. ICS are the preferred therapy for initiating long-term control therapy in children of all ages.
2. ICS, especially at low doses, and even for extended periods of time, are generally safe.

3. The potential for the adverse effect of low- to medium-dose ICS on linear growth is usually limited to a small reduction in growth velocity (approximately 1 centimeter in the first year of treatment) that is generally not progressive over time.
4. The potential risks of ICS are well balanced by their benefits.
5. High doses of ICS administered for prolonged periods of time (>1 year), particularly in combination with frequent courses of oral corticosteroid therapy, may be associated with adverse growth effects.

Nonsteroidal Anti-Inflammatory Medications

This class of long-term controller medications is predominantly used in adolescents and children. These medications are an alternative to low-dose ICS in patients who have mild persistent asthma. The two drugs in this category are cromolyn sodium and nedocromil (**Table 34–3**). Both medications have distinct properties but appear to have similar anti-inflammatory actions.[33] The mechanism of action with these medications appears to be chloride channel blockade, and they modulate mast cell mediator release and promote eosinophil release.[34]

These anti-inflammatories appear to reduce the need for quick-relief medications, reduce bronchial hyperresponsiveness, improve morning peak flows, and decrease the symptoms of nocturnal asthma.[35] Nedocromil may have a broader range of activity in protection of EIA,[36] cough-variant asthma,[37] and cold air–induced bronchospasm.

The side effects of these drugs are practically nonexistent. Both drugs have a strong safety profile with a low adverse event profile. Cromolyn is available as a solution for nebulization. The onset of action for both drugs may be 4 to 6 weeks to determine maximum benefit. Cromolyn and nedocromil in a pressurized metered dose inhaler (pMDI) were phased out in 2010 because they used chlorofluorocarbon propellants.

Long-Acting β_2-Agonists

This class of long-term controller medication is predominantly used to provide a longer duration of airway smooth muscle relaxation. This class of medication is

TABLE 34–3 Long-Term Controller Medications

Medication	Dose Strength	Adult Medium Daily Dose
Corticosteroids		
Metered dose inhalers (MDIs)		
Beclomethasone dipropionate (QVAR)	40 or 80 μg/puff	>240–480 μg
Budesonide (Pulmicort)	90, 180, or 200 μg/puff	>600–1200 μg
Fluticasone propionate (Flovent)	44, 110, or 220 μg/puff	>264–440 μg
Mometasone (Asmanex)	200 μg/puff	400 μg
Ciclesonide (Alvesco)	80 or 160 μg/puff	Starting dose in steroid-naive patients is 160 μg bid
Tablets		
Prednisone	1, 2.5, 5, 10, 20, 25, and 50 mg	40–60 mg/day for 3–10 days for control in exacerbation
Prednisolone	5 mg	40–60 mg/day for 3–10 days for control in exacerbation
Methylprednisolone	2, 4, 8, 16, 24, and 32 mg	7.5–60 mg/day or qod as needed for control
Nonsteroidal Anti-inflammatory Agents		
Nebulization		
Cromolyn sodium (Intal)	20 mg/2-mL ampule	1 unit dose qid
Long-Acting β_2-Agonists		
Dry powder inhalers (DPIs)		
Salmeterol (Serevent)	50 μg/puff	bid
Formoterol (Foradil)	12 μg/puff	bid
Methylxanthines (Oral)		
Theophylline (Slo-Bid, Theo-24, Theo-Dur, Uniphyl)	Various, depending on formulation	
Leukotriene Modifiers (Oral)		
Montelukast (Singulair)	10-mg tablets	qd
Combination Products		
Advair DPI or MDI (fluticasone/salmeterol)	100/50, 250/50, 500/50 (DPI) 45/21, 115/21, 230/21 HFA MDI	250/50 bid
Symbicort (budesonide/formoterol)	80/4.5, 160/4.5	160/4.5 bid

bid, twice a day; qid, four times a day; qod, every other day; qd, daily; HFA, hydrofluoroalkane.

not intended for relief of acute bronchospasm or for monotherapy (delivery without an ICS). LABAs have a bronchodilation duration of approximately 12 hours but a longer onset of action than SABAs. Two medications are in this class of controller: salmeterol and formoterol (refer to Table 34–3).

LABAs relax smooth muscle by stimulating the β_2 receptors, thereby increasing cyclic adenosine monophosphate (cAMP). LABAs have a 12-hour duration of effect; the molecule remains bound within the muscle cell wall because it is lipophilic. These medications work well as an adjunct therapy to anti-inflammatory medications in the long-term control of symptoms.[38,39] LABAs appear to work exceptionally well at controlling symptoms that occur at night[40] and at preventing exercise-induced exacerbations.

The complications of long-acting β_2-agonists are still somewhat controversial. There are reports of sudden severe asthma attacks that could have been worsened or initiated with the use of salmeterol.[41] Two studies that looked closely at this issue in a large cohort of patients found more deaths in patients who were taking salmeterol than in those who were not taking salmeterol.[42,43] Based on this data, clinicians need to pay close attention to properly educating patients who are using salmeterol. Salmeterol should be used only as a supplement to inhaled corticosteroids and never as a quick-relief medication.

The EPR-3 recommendations for the use of LABAs are as follows:[1]

1. LABAs are used as an adjunct to ICS therapy for providing long-term control of symptoms.
2. LABAs are not recommended as monotherapy for long-term control of persistent asthma.
3. The use of LABAs is not recommended to treat acute symptoms or exacerbation of asthma.
4. LABAs may be used before exercise to prevent exercise-induced bronchoconstriction, but frequent and chronic use of LABAs for exercise-induced bronchoconstriction may indicate poorly controlled asthma, which should be managed with daily anti-inflammatory therapy.

Methylxanthines

Theophylline is an alternative, but not preferred, therapy in mild to moderate persistent asthma. Slow-release theophylline is used primarily as adjuvant therapy for nocturnal asthma (refer to Table 34–3). The exact mechanism of action of methylxanthines in asthma is not well established.[44,45] Theophylline acts as a nonselective phosphodiesterase inhibitor. This results in an increase in cyclic guanosine monophosphate levels and cAMP levels that inhibit inflammation cells and produce bronchodilation. Recent studies indicate that low serum concentrations of theophylline may act as a mild anti-inflammatory medication.[46] This is possible most likely because of the decreased mediator release from mast cells and reactive oxygen species and the inhibition of neutrophil activity.

Theophylline is relatively safe. However, its use requires frequent monitoring of serum drug levels so that therapeutic, but not toxic, levels are achieved. Serum drug levels are affected by a patient's comorbidities and the presence of smoking and are therefore often difficult or impractical to manage. Potential toxic side effects include tachycardia, nausea and vomiting, central nervous system stimulation, arrhythmias, headache, seizures, hyperglycemia, and hypokalemia. The therapeutic serum range has recently been decreased from 10 to 20 mg/L to 5 to 15 mg/L to limit potential toxic effects. Pay close attention to other medications that patients using theophylline are receiving (e.g., antibiotics, β_2-blockers, quinolones).

Leukotriene Modifiers

Leukotriene modifiers also fall into the class of controller medications. This class of medications acts on the inflammatory cells known as leukotrienes. Leukotrienes are mediators that are released from mast cells, eosinophils, and basophils; they are responsible for airway bronchoconstriction, inflammatory cell recruitment, increased vascular permeability, and secretion production.

Montelukast is a leukotriene receptor antagonist (LTRA) that blocks the receptor sites on inflammatory cells for leukotrienes. Leukotriene receptor antagonists appear to work best in patients who have mild to moderate persistent asthma. Leukotriene receptor antagonists are an alternative, but not preferred, therapy to low- to medium-dose inhaled corticosteroids. Studies demonstrate a greater improvement in lung function and symptom scores with the use of ICS versus LTRA.[47] Regardless, LRTAs improve lung function, diminish asthma symptoms, and decrease the need for short-acting β_2-agonists, particularly in patients with allergies.[48,49]

Immunomodulators

There is currently one immunomodulator drug used for asthma: omalizumab, which has a trade name of Xolair. Omalizumab is a recombinant DNA-derived monoclonal antibody that inhibits the binding of IgE to the IgE receptor on the surface of mast cells and basophils. When the IgE receptors are bound by omalizumab, there is a reduction in surface-bound IgE, and therefore a decrease in the activation of mast cells and a decrease in the release of inflammatory mediators. Omalizumab is an alternate, but not preferred, drug in the treatment of moderate to severe persistent asthma in patients who have a positive skin test to aeroallergens and whose symptoms are inadequately controlled with ICS. It has been approved only for patients 12 years old and older.

Omalizumab is administered subcutaneously, and the dose is based on IgE level and patient weight. Omalizumab must be administered only in a closely observed clinic, because a rare adverse effect is anaphylaxis. The patient is directed to remain in the clinic for a period of observation following injection. Omalizumab has been shown to decrease the incidence of asthma exacerbations and emergency department visits, increase efficacy in patients with severe persistent allergic asthma who are already on high-dose ICS and LABA, and improve quality of life scores. Other than its adverse effects, the other drawback to omalizumab is its cost, which is approximately $1000 per month.[1]

Quick-Relief Medications

Short-Acting β_2-Agonists

This class of quick-relief medication is used predominantly to relieve airway bronchoconstriction and symptoms of cough, chest tightness, and wheezing. Short-acting β_2-agonists are the first-line medications used to treat an acute asthma exacerbation and for preventing exercise-induced bronchoconstriction. Before the 1990s, this was the first line of medications prescribed to result in overall control of asthma symptoms. Given the focus on the role of airway inflammation in the chronic management of asthma, SABAs have become rescue medications. This class of medications includes albuterol, metaproterenol, pirbuterol, and terbutaline (**Table 34–4**).

The mechanism of action is to relax smooth airway muscle and cause quick (15- to 30-minute) resolution to airway obstruction. Bronchodilation occurs primarily through β_2-adrenergic receptor stimulation in bronchial smooth muscle. These receptors are also present in airway epithelium, airway smooth muscle, mucus glands, and mast cells. The onset of action for a short-acting β_2-agonist is approximately 5 to 15 minutes under most circumstances of mild to moderate acute exacerbations.

Complications from SABAs are usually mild and self-limiting upon stopping the medication. Potential side effects include tachycardia, nausea, vomiting, tremors, headache, palpitation, paradoxical bronchospasm, and hypokalemia. Some potential complications from high use or prolonged use over time include subsensitivity (reduction in bronchodilation effect), increased airways hyperreactivity, and life-threatening episodes with overuse. The frequency of SABA use or prescription refills can be used as a marker of disease worsening or to indicate an increased risk of death or near death.

> **RESPIRATORY RECAP**
>
> **Asthma Quick-Relief Medications**
> - » Short-acting β_2-agonists
> - » Anticholinergics
> - » Systemic corticosteroids

Patients should be cautioned to use SABAs only as needed. If the patient uses a SABA more often than twice per week, this indicates decreased asthma control. A red flag for the practitioner is if the patient uses more than one canister of SABA per month,

TABLE 34–4 Quick-Relief Medications

Medication	Dose	Frequency
Short-Acting β_2-Agonists		
Metered dose inhalers		
Racemic albuterol (Ventolin HFA, Proventil HFA, Pro-Air HFA)	90 µg/puff	prn; q4h–q6h
Levalbuterol (Xopenex HFA)	45 µg/puff	prn, q6h
Pirbuterol (Maxair)	200 µg/puff	prn, q4h–q6h
Nebulization		
Racemic albuterol (Ventolin, Proventil, generic)	2.5 mg (0.5% solution	prn; q4h–q6h
Levalbuterol (Xopenex)	0.31 mg and 0.63 mg	
Metaproterenol (Alupent)	5% solution	
Oral tablets		
Albuterol (Repetabs, Volmax)	2 and 4 mg	prn; q4h–q6h
Metaproterenol	10 and 20 mg	
Terbutaline (Brethaire)	2.5 and 5 mg	
Syrup		
Albuterol	2 mg/5 mL	prn; q4h–q6h
Metaproterenol	10 mg/5 mL	
Subcutaneous injection		
Terbutaline	1 mg/mL injection	prn; q4h–q6h
Anticholinergics		
Metered dose inhalers		
Ipratropium bromide (Atrovent)	18 µg/puff	bid–qid
Nebulization		
Ipratropium bromide (Atrovent)	500-µg solution	bid–qid

HFA, hydrofluoroalkane; prn, as needed; bid, twice a day; qid, four times a day; q4h, every 4 hours; q6h, every 6 hours.

because this indicates that the patient has used his or her SABA approximately three times per day. The need for this much SABA is an indication that the underlying inflammation has worsened. The patient should seek medical attention in this event.

Anticholinergics

This class of quick-relief medication is used predominantly as an adjunct to short-acting β_2-agonists in acute severe exacerbations of airway bronchoconstriction in the emergency department. The mechanism of action of anticholinergics is airway smooth muscle tone relaxation through cholinergic innervation. Ipratropium is the primary asthma medication in the anticholinergic class. Ipratropium is a derivative of atropine without the common side effects of atropine (refer to Table 34–4).

The overall effectiveness of ipratropium bromide in the management of asthma remains controversial.[50–53] Its effectiveness for long-term asthma management has not been demonstrated. Adult patients who have asthma and a component of chronic obstructive pulmonary disease apparently experience some beneficial outcomes.

Studies in children have demonstrated that the use of ipratropium in combination with β_2-agonists in patients with acute exacerbations or severe airway obstruction may be beneficial. However, routine administration of this combination therapy does not appear to be beneficial.[54,55]

Systemic Corticosteroids

Systemic corticosteroids are usually combined with a short-acting β_2-agonist for a quick resolution of airway obstruction in an emergency department or hospital setting.[56] These drugs may be given either orally or intravenously. Normal dosage in this setting is 2 mg/kg (given every 6 hours, up to a maximum dose of 120 mg). The mechanism of action for systemic corticosteroids is the same as inhaled corticosteroids. The administration of a systemic corticosteroid in the ED is used to help prevent or ease the onset of the delayed (phase 2) asthmatic response. This phase 2 response is secondary to the event that led the patient to present to the ED. In the absence of a systemic corticosteroid, the patient may present to the ED again following discharge with more severe bronchospasm and inflammation than during the initial admission.

For outpatient use, systemic corticosteroids are prescribed for short-term burst therapy (once a day for 3 to 10 days). Normal dosing is prescribed at the lowest possible dose (0.5 to 2 mg/kg/day). Maximum dose is normally restricted to 60 mg for outpatient use. If chronic use of systemic corticosteroids is needed, a study has documented improved efficacy when the medication is given at 3 PM instead of in the morning.

Aerosol Therapy

The main routes of delivery for asthma medications are systemic or inhaled. The main routes of systemic delivery are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous).[1] Oral medications are mainly in either pill or liquid form. Parenteral medications are usually limited to patients who either are in the emergency department or are admitted to the hospital.

The inhaled route is more convenient and common because of fewer side effects and quicker onset of action. The disadvantages of the inhaled route are associated with the delivery device and the factors that affect drug penetration and deposition in the lungs. The main factors involved in penetration and deposition are physical (sedimentation, inertial impaction, and diffusion) and clinical (particle size, ventilatory pattern, and lung function).[57]

Nebulizers, pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs) are used for inhaled medications. Opinions have varied on the best and most efficient method, but available evidence suggests that all three devices are equally effective in treating an acute exacerbation.[58]

RESPIRATORY RECAP

Aerosol Delivery Devices for Patients with Asthma

- Metered dose inhaler
- Metered dose inhaler with accessory device
- Dry powder inhaler

Nebulizers

The small-volume nebulizer (SVN) is the most common device used to deliver medications to small children and patients requiring hospitalization. Although theoretically aerosol delivery and deposition in an asthmatic airway may be improved with a less dense gas (such as **heliox**),[59–62] there are potential problems with the use of nebulizers powered by heliox.[63] Heliox is best reserved for severe cases refractory to conventional therapy. A number of factors affect an SVN's performance.[58,64–66] The use of nebulizers relies on proper technique. Deposition of appropriate particle size in the lower respiratory tract depends on ventilatory pattern. To ensure optimal particle deposition, a slow breath (through the mouth) to total lung capacity with an end-inspiratory breath hold is ideal. With proper breathing technique, aerosol delivery with an SVN is equally effective with a mask or mouthpiece.

Continuous Aerosols

In a severe asthma attack, aggressive intermittent aerosol therapy may fail to relieve symptoms. Studies have demonstrated that continuous bronchodilator therapy is as effective or more effective than intermittent therapy. Continuous aerosol bronchodilator therapy has become a accepted alternative to intermittent therapy in emergency departments for patients who fail to respond to less aggressive therapy. Current evidence supports the use of continuous bronchodilator administration in patients with severe acute asthma who present to the ED to increase their pulmonary functions and reduce hospitalization.[67] Moreover, it appears to be safe and well tolerated.

Pressurized Metered Dose Inhalers

The pMDI is the most common device used to deliver medications in an ambulatory setting and is rapidly increasing in use in hospitalized and ED treatment. The canister is activated by compressing it into a mouthpiece, which causes a metered dose of the drug to be delivered for inhalation.

A number of factors can affect pMDI performance and drug delivery. A potential factor that can interfere with appropriate metered dose delivery is using medications from one manufacturer with an actuator or accessory device from another manufacturer. Most of the factors that affect optimal delivery involve patient delivery technique; this is especially the case in the very young or elderly. Factors critical in the effectiveness of pMDI performance include timing of actuation, lung volume, pMDI position to the mouth (without spacer), inspiratory flow rate, and the ability to perform a breath hold.[53] An alternative to using a spacer is the breath-actuated MDI. With such a device, the MDI actuates automatically as the patient begins to inhale, thus appropriately timing drug delivery with inspiration.

Compared with pMDIs with CFC as a propellant, pMDIs with hydrofluoroalkane (HFA) propellants have a softer, warmer spray. Each type of pMDI has its own instructions on priming, so it is important for the therapist to read the package insert and learn how many times any given pMDI needs to be primed and how and when to clean the pMDI actuator, so that this information may be taught to the patient.

Chlorofluorocarbon propellant pMDIs are being removed from the market and replaced with hydrofluoroalkane propellants. Some patients who were accustomed to a CFC pMDI may complain that their HFA pMDI does not provide relief because the sensation of the plume in the mouth is different. The asthma educator needs to be aware of this and be prepared to reinforce proper inhaler technique.

Spacers and Valved Holding Chambers

If patients find it difficult to properly use a pMDI or if an ICS pMDI is being used, patients should use a spacer or valved holding chamber to enhance optimal drug delivery. A spacer is a cylindrical or cone-shaped chamber that receives the pMDI actuator on one end and has a mouthpiece on the other. A valved holding chamber is a spacer with a one-way valve at the mouthpiece end that prevents the patient from exhaling into the chamber. Several of these devices also incorporate a flow signal that has an audible sound if the patient is inhaling too fast. With optimal MDI delivery technique, evidence exists (even with children) of no difference in deposition with or without a spacing device.[68]

With an accessory spacing device, a pMDI is actuated into the chamber, and the patient breathes the medication from a mouthpiece or mask attached to the chamber. For optimal medication availability, the valved holding chamber is preferred. This decreases the potential of medication being lost through the device on exhalation. Different spacing devices affect drug delivery,[57,69] and more studies are needed to evaluate new medications and spacing devices.

Another potential factor that may affect the amount of drug delivered with a spacing device is a static charge that occurs from washing the chamber. Antistatic chambers have also been developed. Generally, the device should be disassembled and washed in soapy water, rinsed, and allowed to air dry before use. Manufacturers' instructions should be followed regarding appropriate device cleaning.

Dry Powder Inhalers

Two types of DPI exist: single-dose devices (e.g., Spiriva Handihaler, Foradil Aerolizer), and multidose devices (e.g., Advair discus, Pulmicort Flexhaler).[57] DPIs are breath activated with a high inspiratory flow generated at the mouthpiece. Because of the requirement of a high inspiratory flow for actuation, DPIs are not indicated for use in children younger than 12 years. Several instructions are common to DPIs. The DPI must be kept level during inhalation, it must be kept in a dry location to prevent clumping of the powder, and the patient must not exhale into the DPI. Multidose DPIs have dose counters to alert the patient as to the remaining doses in the device.

Adjunctive Treatments

Oxygen, inhaled β_2-adrenergic agonists, and corticosteroids remain the cornerstones of therapy for asthma. This section discusses four alternative therapies to aerosolized medications in the treatment of a severe asthma exacerbation: helium–oxygen gas mixtures (heliox), magnesium sulfate, noninvasive ventilation, and invasive mechanical ventilation. Because of the risk of immediate respiratory decompensation, these therapies are normally administered in the confines of an intensive care unit or emergency department.

RESPIRATORY RECAP

Adjunctive Treatments for Asthma

- Heliox
- Magnesium sulfate
- Noninvasive ventilation
- Invasive ventilation

Heliox

Helium is a gas that is less dense than air, which may be beneficial in the treatment of asthma.[63] Heliox is not a stand-alone therapy to treat a severe asthma exacerbation, but rather is supportive therapy before intubation to allow time for bronchodilators and corticosteroids to take effect.[70] A difficulty in the provision of heliox in nonintubated patients is that the available gas mixtures in concentrations may not provide adequate supplemental oxygen to achieve acceptable oxyhemoglobin saturations (80% helium to 20% oxygen or 70% helium to 30% oxygen).

The therapeutic benefits of heliox are controversial. Reports of the therapeutic benefits of heliox are isolated primarily to the management of pediatric asthma[60,61,71] or the management of adult patients who present to the ED with a respiratory acidosis and/or a short duration of symptoms.[72] Some studies have shown that the use of heliox has no effect on FEV_1.[73,74] Given the safety profile of heliox and the short time to achieve a positive response, a brief trial of heliox may serve as a therapeutic bridge until corticosteroid therapy has taken effect. One study documented a rapid resolution (less than 60 minutes) to respiratory acidosis by using heliox, especially in patients who had brief duration of symptoms (less than 24 hours) and a severely acidotic pH (7.20 or less) at presentation.[75] Randomized trials in patients with asthma have reported benefit with the use of heliox.[61,76] The EPR-3 cites a meta-analysis of six studies that did not find a statistically significant improvement in pulmonary function or other measured outcomes in patients receiving heliox compared with oxygen or air.[1] The EPR-3 recommends consideration of heliox-driven albuterol nebulization for patients who have life-threatening exacerbations and for those patients whose exacerbations remain in the severe category after 1 hour of intensive conventional therapy.[1]

Magnesium Sulfate

Administration of magnesium sulfate is an alternative treatment for a severe asthma exacerbation.[77,78] The EPR-3 recommends intravenous magnesium sulfate in patients who have life-threatening exacerbations and in those whose exacerbations remain in the severe category after 1 hour of conventional therapy.[1] The mechanisms of action include calcium-channel blockade in the airway smooth muscle and inhibition of acetylcholine and histamine release. Magnesium may promote bronchodilation that would improve β_2-agonist delivery. A study comparing nebulized magnesium to salbutamol demonstrated a similar response,[79] but nebulized magnesium does not consistently have this bronchodilator effect. Other studies have documented no improvement in FEV_1 in patients who were treated with magnesium intravenously.[80–81]

The dose for intravenous magnesium is 2 g in adults and from 25 to 75 mg/kg up to 2 g in children administered over a half hour. The onset of action for magnesium can occur within minutes of administration. Potential side effects are usually minor (facial warmth and flushing). However, magnesium can be toxic with high serum levels. Signs of magnesium toxicity include hypotension, dysrhythmias, areflexia, and muscle weakness. The use of magnesium sulfate in the treatment of severe exacerbations is not recommended as a first-line therapy. The treatment has no apparent value in exacerbations of lesser severity.[1]

Noninvasive Ventilation

The use of noninvasive positive pressure ventilation (NIV) has taken a role in the management of patients who are at high risk for intubation and mechanical ventilation. NIV offers a viable means of overcoming increased work of breathing without an endotracheal tube. Uncontrolled studies have documented the use of noninvasive ventilation as a viable alternative to mechanical ventilation.[82,83] The key factor in the use of NIV is early initiation of the therapy in conjunction with bronchodilators and corticosteroids. Appropriate inspiratory flow is important to ensure patient comfort and to decrease the work of breathing. Avoiding delivery of excessive minute ventilation is important, because it could lead to hyperinflation and air trapping. The use of aerosolized medications with NIV is feasible.[84] NIV in patients with asthma is supportive and meant to be used in conjunction with established therapies. NIV may be useful in carefully selected patients with a severe exacerbation, even though there have been few trials of NIV in asthma.[85]

Invasive Ventilation

Invasive ventilation of patients with asthma is a treatment of last resort for patients experiencing respiratory failure because of severe airflow obstruction, increased mucus production, and/or severe airway inflammation.[85,86] Asthma resulting in intubation and mechanical ventilation is not a common event, occurring in less than 5% of patients treated. **Box 34–5** lists the general indications for mechanical ventilation in the patient with asthma. The obstructive nature of a severe exacerbation of asthma produces a ventilation-perfusion mismatch and increased work of breathing, but this rarely produces severe hypoxemia. The more difficult issue in the patient with acute asthma is optimizing the pH and Pa_{CO_2} because of bronchoconstriction, air trapping, and increased dead space.[87]

On intubation of a patient with acute asthma, full ventilatory support is usually provided (i.e., no spontaneous breathing by the patient). This allows optimization of the patient–ventilator interface under the best possible conditions. The principal goal of mechanical ventilation of the patient with asthma is to provide acceptable gas exchange while avoiding air trapping (auto-PEEP [positive end-expiratory pressure]). With auto-PEEP, alveolar overdistention may occur with concomitant hypotension and barotrauma.

BOX 34–5

Indications for Mechanical Ventilation of the Patient with Asthma

$Paco_2 > 40$ mm Hg (especially if increasing)
Refractory hypoxemia ($Pao_2 < 60$ mm Hg or $Fio_2 \geq 0.5$)
Mental status deterioration
Decrease or loss of breath sounds
Apnea

RESPIRATORY RECAP

Mechanical Ventilation of the Patient with Asthma

- » Avoid strategies that cause air trapping and auto-PEEP.
- » Consider PEEP to counterbalance auto-PEEP.
- » Avoid plateau pressure above 30 cm H_2O.
- » Permissive hypercapnia may be necessary.
- » Inhaled bronchodilators can be administered using nebulizers or pMDIs.

The choice of ventilator mode is often based on clinical preference or institutional bias. Either volume or pressure control modes can be used, and advantages and disadvantages exist for both. With volume control ventilation, auto-PEEP results in increased plateau pressures and alveolar overdistention. With pressure control ventilation, auto-PEEP results in decreased tidal volumes and respiratory acidosis. In patients with asthma with severe airflow obstruction, it may be difficult to deliver an adequate tidal volume with pressure control ventilation. Regardless of the mode chosen, auto-PEEP and plateau pressures must be monitored closely.

The ultimate goal of tidal volume selection in severe asthma exacerbation is to avoid overdistention of the alveoli. Generally, tidal volumes are set in the 5 to 8 mL/kg range and adjusted to minimize overdistention (i.e., to avoid a plateau pressure of more than 30 cm H_2O). This often results in a ventilator strategy of permissive hypercapnia. With permissive hypercapnia, $Paco_2$ is allowed to rise and an acidic pH is tolerated. The limits of safe $Paco_2$ and pH are debated, but general consensus suggests that $Paco_2$ levels of 80 to 100 mm Hg and pH levels of 7.15 to 7.20 are acceptable.[88,89]

The use of positive end-expiratory pressure when ventilating the patient with asthma is controversial. PEEP as a means to prevent atelectasis or collapse is not necessary. PEEP has been used to combat auto-PEEP. The intent is to counterbalance auto-PEEP by applying PEEP so that the patient will be better able to trigger the ventilator. However, care must be taken to avoid increased overdistention with the application of PEEP. PEEP has no role in counterbalancing auto-PEEP in the patient who is not attempting to trigger the ventilator.[90,91]

One study observed that there are three different responses to PEEP in the setting of auto-PEEP. In the biphasic response, expiratory flow and lung volume remained constant during progressive PEEP steps until a threshold was reached, beyond which overinflation ensued. In the classic overinflation response, any increment of PEEP caused a decrease in expiratory flow and overinflation. In the paradoxic response, a drop in functional residual capacity during PEEP application was commonly accompanied by decreased plateau pressures and total PEEP, with increased expiratory flow.[92] Generally, no more than 10 cm H_2O PEEP is used to counterbalance auto-PEEP. Some auto-PEEP that occurs during mechanical ventilation of the patient with asthma may not be measurable in the usual manner because of complete airway closure during the expiratory phase.[92]

The inspiratory-to-expiratory (I:E) ratio in a patient with airflow obstruction is important to avoid air trapping. The I:E ratio is determined by the inspiratory time (flow and tidal volume for volume control ventilation) and respiratory rate. The goal when setting the I:E ratio in patients with asthma is to allow adequate expiratory time to minimize auto-PEEP. Use of prolonged expiratory times requires a low respiratory rate and a shortened inspiratory time in the range of 0.8 to 1.2 seconds (high flow). Typically, a respiratory rate of 15 per minute or less is used.

When aggressive therapy fails to stabilize a patient's asthma and intubation occurs, the need to provide aerosol therapy remains important in the resolution of the acute exacerbation. Aerosol therapy of the intubated patient has been an area of debate.[93] Some support either nebulizers or MDIs as the most effective and efficient method from a clinical and financial standpoint. Aerosol delivery to intubated patients with either nebulizers or MDIs is less effective than when delivered to a spontaneously breathing patient. Many factors in intubated patients affect optimal aerosol delivery and deposition. Higher-than-standard doses may be necessary to elicit a desired response because of potential barriers involved with mechanically ventilated patients. Aerosol administration by both nebulizers and MDIs is an effective means of delivering medication to ventilated patients. Studies using both devices have demonstrated lung deposition efficiency of 5% to 15%.[94] Sufficient attention to detail, including the use of an efficient nebulizer and/

or adapter and proper placement and operating method, is required to provide optimal delivery.

The use of heliox with mechanical ventilation may be beneficial when a patient with asthma is difficult to manage with traditional ventilator manipulations.[95] Caution is warranted because the addition of heliox may result in ventilator malfunction. Many, but not all, of the current-generation ventilators are compatible with heliox. Inhalational anesthetics (e.g., isoflurane, halothane, enflurane) have a bronchodilatory effect and are used rarely in the most severe cases.

Mechanical ventilation of the patient with asthma may be a lifesaving measure, but it can also be associated with significant morbidity and mortality.[92,96–98] The major complications of mechanical ventilation of the patient with asthma include overdistention, pneumothorax, hypotension, air trapping, patient–ventilator asynchrony, and neuromuscular blocking agent–related myopathies.

Education

Asthma education begins at diagnosis and should be reinforced with each visit. The ability to modify morbidity and resource consumption through education has been well documented in asthma. Over the past 20 years, many programs and formats have been designed and implemented to demonstrate that asthma education is a main component of the overall successful management of the disease. The items in **Box 34–6** should be included in **asthma education programs**.[1]

Many studies of educational interventions are available in the literature, covering many different care settings. These include ambulatory clinics, allergy or pulmonary specialty clinics, emergency departments, hospitals, patient homes, and asthma camps. The impact of educational interventions has been evaluated regarding readmission rates, hospitalizations, compliance, ED visits, clinic follow-up rates, test scores, and behavior changes.

The rapid expansion of managed health care in the 1990s led to the study of the financial aspects of providing asthma education. Some of the earlier managed care education interventions assessed patients with asthma determined to be at high risk. Although these programs still exist, asthma educators are looking at ways to target a variety of patients with asthma because of a regression-toward-the-mean concept. The theory of regression toward the mean implies that patients with chronic conditions do not have steady-state healthcare resource consumption year after year. One year's high-resource consumers do not necessarily translate into the next year's high-resource consumers. Therefore, these earliest managed care programs and interventions resulted in a shifting of the costs from group to group or from year to year (**Table 34–5**).

The asthma education program needs to take a proactive approach. An asthma education program should provide education to the patient with asthma and include all potential caregivers (spouses, parents, older children, day-care providers, teachers, coaches, group leaders, and counselors). The National Cooperative Inner City Asthma Study (NCICAS) reported that often a child has several care providers in the home.[99] This pediatric study demonstrated the importance of involving as many caregivers as possible in the asthma education to ensure consistent management. This study also identified that pediatric asthma has additional educational barriers. Often education providers overlook the child to concentrate their educational efforts on the caregivers. However, children as young as 2 years can begin learning about their asthma and its management. As children age, the scope and the depth of the information will need

AGE-SPECIFIC ANGLE

Children as young as 2 years can begin learning about asthma and its management.

BOX 34–6

Educational Recommendations of the NAEPP

- Teach basic facts about asthma
- Teach the necessary medication skills (techniques, delivery devices, and dosing regimens)
- Teach self-monitoring skills: symptom-based, peak flow monitoring
- Teach relevant environmental control/avoidance strategies
- Provide a written asthma exacerbation treatment plan

From National Asthma Education Program, National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD: National Institutes of Health; 2007. NIH Publication 07-4051.

TABLE 34–5 Theoretic Look at Regression Toward the Mean

	Percentage of Resource Cost Consumption			
	Original Percentage of Patients	*Year 1*	*Year 2*	*Year 3*
High-resource consumers	10	80	10	4
Low-resource consumers	90	20	90	96

to continue to grow. As children grow into adolescents, they should receive all asthma information themselves.[100]

Asthma education information should be repeated several times for maximum effect, and educational objectives should be reinforced with written materials targeted for age appropriateness. Asthma self-management education should be modified to the needs of each individual patient. Cultural beliefs and unharmful practices should be approached and discussed with sensitivity and understanding. The education provider should be attentive and document the concerns of the patient and the family regarding medications and asthma management. Addressing concerns and explaining the rationale for treatment may be the overriding factor in patient compliance with chronic asthma management. The asthma educator also must be prepared to intervene and problem solve in the areas of medications, level of treatment, trigger avoidance, compliance, and self-management skills.

One of the indicators of a chronic condition is the ability to modify or reduce morbidity and mortality risks through patient education. Asthma is a chronic disease condition that has demonstrated this ability. An unlimited number of approaches or interventions are readily available to provide effective and efficient asthma education to healthcare providers. Perhaps one method is not truly better than another. The important features are to provide the resources and information at diagnosis and consistently thereafter to each patient with asthma individually.

CASE STUDIES

Case 1. Ambulatory Asthma Management

A 43-year-old woman with asthma presents to an inner-city emergency department with coughing, wheezing, and shortness of breath. She reports a respiratory viral infection within the last week that resolved with over-the-counter medicines in 3 or 4 days. Her initial physical examination reveals the following: respiratory rate of 36 breaths/min, labored; heart rate of 120 beats/min; blood pressure of 120/80 mm Hg; pulse oximetry of 93% in room air; inspiratory and expiratory wheezing upon auscultation; equal air exchange bilaterally; moderate intercostal retractions; and peak expiratory flow (PEF) of 290 L/min (60% of predicted). The initial treatment consists of six puffs of albuterol, administered via an MDI with a holding chamber. Each puff is given with the appropriate technique. Posttreatment PEF is 300 L/min (62% of predicted).

The woman reports that she stopped taking her beclomethasone about 2 months before this visit. The following additional information is acquired:

- *Reported medications*: Beclomethasone two puffs twice a day, and albuterol two puffs as needed and before exercise
- *Treatment before arrival*: None
- *Peak flow meter diary*: None
- *Unscheduled ED/MD visits in the past month*: 0
- *Unscheduled ED/MD visits in the past year*: 3
- *Hospital admissions in the past year*: 1
- *Prior intensive care unit (ICU) admissions*: 0
- *Cough or wheeze frequency*: Two times per week
- *Activity limitations*: Occasionally
- *Nocturnal cough or wheeze*: Two to three times per week
- *Work absenteeism*: 6 days per year

Approximately 20 minutes after the initial treatment, a second treatment is administered with six puffs of albuterol via pMDI and holding chamber as before. The patient is also given 60 mg of prednisolone. Posttreatment assessment reveals a respiratory rate of 24 breaths/min; heart rate of 100 beats/min; oxygen saturation of 95% breathing room air; inspiratory and expiratory wheezing upon auscultation; equal air exchange bilaterally; mild intercostal retractions; and PEF of 315 L/min (65% predicted).

Approximately 20 minutes after the second treatment, a third treatment of albuterol (six puffs) is administered, along with two puffs of Atrovent. Posttreatment assessment reveals a respiratory rate of 16 breaths/min; heart rate of 80 beats/min; oxygen saturation of 95% breathing room air; faint end-expiratory wheezes with auscultation and bilateral equal air exchange; no intercostal retractions; and PEF of 365 L/min (75% predicted).

The woman's next β_2-agonist treatment is withheld, and she is reassessed in 60 minutes. The prior assessment response is sustained upon physical examination, and the woman is readied for discharge. Based on the self-reported asthma history, the woman's chronic asthma is determined to be moderate persistent asthma. She is instructed to continue her albuterol treatments with two puffs every 4 to 6 hours for the next several days. She also is told to resume her beclomethasone therapy of two puffs twice a day for chronic inflammatory control. She is given a peak flow meter and instructed in its proper use. She is also instructed in the use of an asthma action plan with a peak flow diary that illustrates meter readings in three color-coded zones to assist her in self-management. She is also instructed to call her primary care physician and to schedule a follow-up visit in the next week to 10 days.

Case 2. Life-Threatening Asthma Management

A 10-year-old boy with asthma presents to an inner-city ED with dyspnea at rest, talking in phrases, agitated, and dusky in color. The boy's mother reports having administered three nebulizer treatments before arrival in the emergency department. The child's initial physical examination reveals the following: respiratory rate of 48 breaths/min, labored; heart rate of 170 beats/min; blood pressure of 160/100 mm Hg; oxygen saturation of 89% breathing room air; breath sounds muffled to inaudible;

severe intercostal and substernal retractions; and inability to perform a PEF.

The patient is then started on undiluted albuterol that was nebulized with 100% oxygen. An IV is placed and he is given 60 mg methylprednisone. During the aerosol treatment, an asthma history is taken from the boy's mother. She reports that her child had been outside playing basketball with his friends for most of the afternoon. Before this episode, he was in good health. The following information is acquired:

- *Reported medications*: Albuterol two puffs as needed before exercise
- *Treatment before arrival*: Three nebulized treatments with albuterol
- *Peak flow meter diary*: None
- *Unscheduled ED/MD visits in the past month*: 0
- *Unscheduled ED/MD visits in the past year*: 1
- *Hospital admissions in the past year*: 1
- *Prior ICU admissions*: 1 (3 years ago)
- *Cough or wheeze frequency*: With respiratory infections
- *Activity or play limitations*: Always
- *Nocturnal cough or wheeze*: One to two times per week
- *School absenteeism*: Three to four days per year

While receiving continuous albuterol treatments, the child is assessed every 20 minutes. Electrocardiography and pulse oximetry are monitored continuously. After the initial 20 minutes, 0.5 mg of ipratropium is added to the aerosol. Thirty-five minutes after treatment was started, the boy's status is a respiratory rate of 20 breaths/min, labored; heart rate of 80 beats/min; blood pressure of 200/100 mm Hg; oxygen saturation of 88% on continuous nebulizer; inaudible breath sounds; severe intercostal and substernal retractions; inability to perform PEF; and lethargy and drowsiness. Arterial blood gas results are pH 7.29, $Pa{CO_2}$ 52 mm Hg, $Pa{O_2}$ 60 mm Hg, HCO_3^- 26 mmol/L, and oxygen saturation of 87%.

The decision is made to intubate the child. After atropine, ketamine, and succinylcholine are administered, he is intubated with a 6.0 mm cuffed endotracheal tube. Upon arrival in the pediatric intensive care unit, the child is placed on the following settings: volume control continuous mandatory ventilation (VC-CMV), tidal volume 350 mL (7 mL/kg), PEEP 3 cm H_2O, mandatory breath rate 10 breaths/min, I:E ratio of 1:5, and $F{IO_2}$ 0.50. After 1 hour on the ventilator, the arterial blood gas results are pH 7.32, $Pa{CO_2}$ 46 mm Hg, $Pa{O_2}$ 120 mm Hg, HCO_3^- 22 mmol/L, and oxygen saturation 99%. The $F{IO_2}$ is weaned to 0.4. The patient is ventilated with permissive hypercapnia to prevent auto-PEEP and overdistention. Continuous ventilator waveform analysis is used to detect auto-PEEP, and the flow is increased to allow for a longer expiratory time. The patient is kept moderately sedated, and paralysis is not necessary at this time. The child is given albuterol via MDI through the ventilator circuit with 10 puffs every 30 minutes and 2 puffs of Atrovent every 6 hours. The patient remains on IV methlyprednisone.

After 6 hours of this therapy, the albuterol treatments are changed to a frequency of every hour. After 12 hours of mechanical ventilation and pharmacologic therapy, blood gas results are pH 7.42, $Pa{CO_2}$ 33 mm Hg, $Pa{O_2}$ 95 mm Hg on $F{IO_2}$ of 0.25, HCO_3^- 24 mmol/L, and oxygen saturation 99%. He is awake and triggering at a rate of 6 to 10 breaths/min above the mandatory rate. A spontaneous breathing trial is successful, he is extubated to a 2 L/min nasal cannula, 5.0 mg nebulized albuterol every hour, and IV methlyprednisone and ipratropium 0.5 mg every 6 hours.

KEY POINTS

- Asthma is a common chronic disease that is increasing in prevalence and severity.
- The pathophysiology of asthma is largely related to inflammation, hyperresponsiveness, and airway obstruction.
- The most identifiable predisposing factor for the development of asthma is atopy.
- Nocturnal symptoms of asthma are common.
- Exercise-induced asthma is characterized by transient airway obstruction after strenuous exercise.
- Occupational asthma is characterized by variable airway hyperresponsiveness in the workplace.
- The NAEPP has developed a four-tiered system to classify asthma disease severity.
- The most common ways to diagnose and monitor airflow obstruction in asthma are spirometry and peak flow meters.
- Asthma medications are classified as either long-term controllers or quick-relief medications.
- Inhaled medications are delivered by nebulizer, metered dose inhaler, or dry powder inhalers.
- Oxygen, inhaled β_2-agonists, and corticosteroids are the cornerstones of therapy for asthma.
- Mechanical ventilation is the treatment of last resort for patients with asthma and respiratory failure.
- Asthma education begins with diagnosis and should be reinforced with each visit.

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