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Chapter 44: Asthma

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UPDATE SUMMARY

Update Summary

September 2023

The following sections, tables, and figures were updated:

- Numerous revisions were made throughout the chapter based on the recommendations from the 2023 Updates to the Global Initiative for Asthma (GINA) guidelines, including revisions to:
  - Desired Outcomes
  - Recommendations for SMART/MART therapy in the General Approach to the Management of Chronic Asthma
  - Recommendations to the General Approach to the Management of Acute Severe Asthma
  - Addition of the term anti-inflammatory reliever (AIR) therapy
- Extensive revisions have been to the Coronavirus Disease (COVID-19) section based on Centers for Disease Control and Prevention (CDC) data from the past 2 years and the National Institutes of Health (NIH) treatment guidelines.
- Revisions are done regarding the safety of leukotriene modifiers.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 79, Asthma.

KEY CONCEPTS

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KEY CONCEPTS

1. Asthma is a highly prevalent disease resulting from genetic predisposition and environmental factors; it is one of the most common chronic diseases of childhood.
2. Asthma is primarily a chronic inflammatory disease of the airways of the lung for which there is no known cure or primary prevention; the immunohistopathologic features include cell infiltration by neutrophils, eosinophils, T-helper type 2 lymphocytes, mast cells, and epithelial cells.
3. Chronic asthma is characterized by either the intermittent or persistent presence of variable degrees of airflow obstruction from airway wall inflammation and bronchial smooth muscle constriction; in some patients, persistent changes in airway structure occur.
4. Variability in response to medications requires individualization of therapy within existing evidence-based guidelines for management. This is most evident in patients with severe asthma phenotypes.
5. Ongoing patient education and forming a partnership in asthma care is essential for optimal health outcomes and includes trigger avoidance and self-management techniques.
6. The inflammatory process in asthma is treated most effectively with corticosteroids, with the inhaled corticosteroids (ICS) having the greatest efficacy and safety with long-term use. ICS may be used in combination with bronchodilators (short-acting or rapid-onset long-acting β_2-adrenergic receptor agonists) or with long-acting muscarinic agonists (LAMA) as daily maintenance therapy.
7. Acute bronchial smooth muscle constriction is prevented or treated most effectively with inhaled short-acting β_2-adrenergic receptor agonists (SABA) alone or in combination with ICS; or with rapid-onset, long-acting β_2-adrenergic receptor agonists (LABA) in combination with ICS.
8. Intermittent as-needed SABA with an ICS can be used concomitantly in mild persistent asthma. The combination of formoterol (a LABA) with ICS can be used as daily maintenance and reliever therapy in moderate persistent asthma to reduce exacerbation frequency.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the five short videos in the series Asthma Management Academy https://www.youtube.com/watch?v=pC2BrtVTYrU. These videos provide a brief overview of the following topics:

- Module 1 Scope of Asthma
- Module 2 Triggers
- Module 3 Medications
- Module 4 Medication Devices
- Module 5 Monitoring and Assessment

The videos are useful to enhance students understanding of the consequences of asthma, triggers, medications, delivery devices, and monitoring. These videos are also useful for patient education.

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INTRODUCTION

Asthma has been known since antiquity, yet it is a disease that still defies precise definition. The word asthma is of Greek origin and means “panting.” More than 2,000 years ago, Hippocrates used the word asthma to describe episodic shortness of breath; however, the first detailed clinical description of a person with asthma was made by Aretaeus in the second century.[1]

The Global Initiative for Asthma (GINA) provides a practical definition of asthma[2]: “Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.” The National Institutes of Health, National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3), adds that the variable airflow obstruction is often reversible either spontaneously or with treatment although reversibility may not be complete in some patients with asthma.[3] To guide our current understanding and clinical management of asthma, healthcare providers in the United States often turn to the NAEPP and GINA guidelines.

EPIDEMIOLOGY

1 An estimated 25.1 million persons in the United States have asthma (about 7.7% of the population).[4] Asthma is the most common chronic disease among children in the United States affecting approximately 4 million children in 2021.[4] Self-reported asthma is more common in persons with incomes below 450% of the the poverty threshold (prevalence rate 7.1%-10.4%) and among certain race and ethnic groups such as those who self-identify as non-Hispanic American Indian/Alaskan Native (12.3%) and non-Hispanic Black (10.9%).[4] Adults are nearly six times more likely to die from asthma than children. The rate of death from asthma is highest in those aged 65 years and older, females, and non-Hispanic Black people (who have two to three times the death rate of non-Hispanic Whites, Asian, or non-Hispanic native Hawaiian or Other Pacific Islander).[4] Biological differences in asthma factors between racial and ethnic groups have been observed (albuterol response, airway eosinophilia, low birth weight).[5–7] However, because asthma is a genetic disease strongly influenced by environmental exposures, it is not fully understood if such differences are related to environmental factors that may be tied to sociodemographic characteristics.[5,7]

Influenza infection can result in serious complications in people with asthma, even those with mild disease and those who are well-controlled on medication. An annual influenza vaccination is an essential preventative measure in people with asthma. However, between 2018 and 2020, only 54% of adults and 69% of children with asthma received the influenza vaccination. A higher percentage (77%) of children under 5 years received the influenza vaccine perhaps because they are more likely to have regular visits to the pediatrician.[4]

Approximately 65% of adults and 60% of children describe themselves as having persistent (vs intermittent) asthma. However, only 40% of adults and children report using long-term controller medications that are fundamental for the prevention and control of symptoms. Nearly 20% of children and 24% of adults report using a quick-relief medication (such as an inhaled short-acting inhaled β_2-agonist [SABA]) more than twice weekly, which is a marker for poorly controlled asthma.[4]

The estimated economic costs of asthma in the United States from 2008 to 2013 in US dollars was $80 billion in direct medical expenses, missed work or school, and death.[8] The societal burden of asthma (indirect medical expenditures such as loss of productivity and death) in the United States was $33 billion. Prescription drugs were the largest single direct medical expenditure per person.[8]

The natural history of asthma is still not well defined. Although asthma can develop at any age, it is principally a pediatric disease, with most patients with asthma being diagnosed by 5 years of age and up to 50% having symptoms by 2 years of age. Asthma is more common in boys until adolescence and between 30% and 70% of children with asthma will have marked improvement or become symptom-free by early adulthood but is more common in adult women than men. Asthma persists and becomes chronic in about 30% to 40% of patients. Generally, 20% or less develop severe chronic disease.[9] Atopy, a form of hypersensitivity to allergens, is present in 50% to 60% of children and adults with asthma; it is more common in adults who had the onset of disease during childhood and children with more severe asthma.[9]

In adults, most longitudinal studies have suggested a more rapid rate of decline in lung function in people with asthma when measured using forced expiratory volume in 1 second (FEV_1) and is more pronounced in those with severe disease.[9] Individuals with less-frequent asthma exacerbations and

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normal lung function on initial assessment have higher remission rates. Conversely, smokers have the lowest remission and highest relapse rates.[9] In those with persistent airway obstruction, asthma may become irreversible and worsen over time due to airway remodeling (described below). However, most patients do not die from disease progression and their life span is not different from the general population.

The worldwide prevalence, morbidity, and mortality from acute exacerbations of asthma have been relatively stable over the past 10 years.[10] However, those in the lowest sociodemographic groups are at a fivefold greater risk of death when compared to those in the highest sociodemographic group.[9] Most asthma deaths are preventable with appropriate recognition and treatment.[9]

Most deaths from asthma occur outside the hospital; death is rare after hospitalization. The most common cause of death from asthma is inadequate assessment of the severity of airway obstruction by the patient or healthcare professional and inadequate therapy. Thus, the key to preventing death from asthma is education to both patients and providers.[11,12]

ETIOLOGY

1 Epidemiologic studies strongly support the concept of a genetic predisposition plus environmental interaction to the development of asthma, yet the picture remains complex and incomplete.[13] Asthma represents a complex genetic disorder, in that the asthma phenotype is likely a result of polygenic inheritance of different combinations of genes. The initial genetic research focused on establishing links between atopy (genetically determined state of hypersensitivity to environmental allergens) and asthma. Genome-wide analyses found links with genes on multiple chromosomes that differ by racial groups.[13] Although genetic predisposition to atopy is a significant risk factor for developing asthma, not all atopic individuals develop asthma, nor do all patients with asthma exhibit atopy. Current efforts to identify asthma susceptibility are focused on epigenetics which are heritable characteristics that are modified by environmental influences.[13]

1 Environmental risk factors for the development of asthma include socioeconomic status, family size, exposure to secondhand tobacco smoke in infancy, and in utero, allergen exposure, ambient air pollution, urbanization, viral respiratory infections including respiratory syncytial virus (RSV) and rhinovirus, and decreased exposure to common childhood infectious agents.[9] The timing of and exposure to certain environmental factors during early childhood in genetically susceptible individuals is thought to predispose them to develop allergies and asthma by triggering the allergic immunologic system (T-helper cell type 2 [Th_2] [Th_2 high asthma] lymphocytes) to develop instead of the system to fight infections (T-helper type 1 [Th_1] [Th_2 low asthma] lymphocytes).[9,14] The first 2 to 3 years of life are most important for the exposures to produce an alteration in the immune response system.[14]

Risk factors for early (less than 3 years of age) recurrent wheezing associated with viral infections include preterm birth, low birth weight, male gender, and parental smoking. However, this early pattern is due to smaller airways, and these risk factors are not believed to be risk factors for developing asthma in later life.[14] Atopy is the predominant risk factor for children to subsequently develop asthma.[14] Asthma can begin later in life in adults. Occupational asthma in previously healthy individuals emphasizes the effect of the environment on the development of asthma.[9] The heterogeneity of the asthma phenotype is most obvious when reviewing the diverse list of protective factors and risk factors (Fig. 44-1).[14] These factors have relative degrees of importance. Environmental exposures are the most important precipitants of severe asthma exacerbations. Epidemics of severe asthma in cities have followed exposures to high concentrations of aeroallergens. Viral respiratory tract infections remain the single most common precipitant of severe asthma in children and are an important trigger in adults as well.[15] Other factors precipitating asthma exacerbations include air pollution, emotions, exercise, occupational exposures, and drugs.

FIGURE 44-1

Factors that are associated with protecting against, or risk for, developing asthma. These various factors have relative degrees of importance from patient to patient. *(Reprinted from van Tilburg Bernardes E, Arrieta MC. Hygiene hypothesis in asthma development: Is hygiene to blame? Arch Med Res. 2017;48(8):717–726.)*

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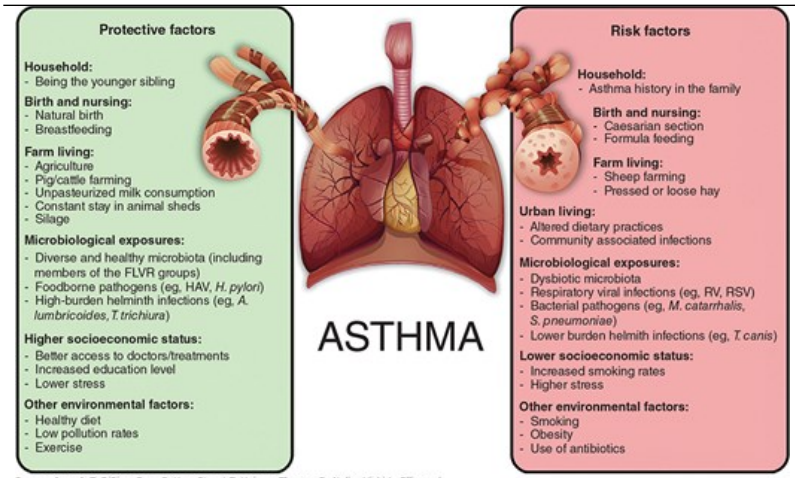

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PATHOPHYSIOLOGY

Asthma is a chronic airway inflammatory disease stemming from the effects of numerous inflammatory cells and mediators to manifest in clinical characteristics and pathophysiological changes leading to expiratory airflow limitation.[2] Airway narrowing is the ultimate endpoint of the inflammatory processes and is a function of airway smooth muscle contraction, with potential remodeling due to structural changes, and airway plugging by mucus hypersecretion which leads to the common symptoms of asthma, wheeze, shortness of breath, chest tightness, and/or cough. Symptoms may be intermittent (weeks or months between symptoms) or may occur frequently and may resolve spontaneously or following treatment. Over time, asthma can progress to persistent airflow limitations. In addition, bronchial hyperresponsiveness (BHR) is a characteristic functional abnormality of asthma and is the heightened response to a stimulus (eg, cat dander) not observed in healthy individuals that enhances the susceptibility to airway narrowing.[2]

To understand the pathogenetic mechanisms that underlie the many asthma phenotypes, it is critical to identify factors that initiate, intensify, and modulate the inflammatory response of the airways and to determine how these processes produce the characteristic airway abnormalities. Current and evolving treatments target these inflammatory processes (Fig. 44-2).

FIGURE 44-2

Diagrammatic presentation of the relationship between inflammatory cells, lipid and preformed mediators, inflammatory cytokines, and proposed pathogenesis and clinical presentation in asthma. (See text for details.) (IL, interleukin; PG, prostaglandin; TSLP, thymic stromal lymphopoietin; CXCL8, C-X-C motif chemokine ligand 8; ILC2, type 2 innate lymphoid cells; Th, T helper.) *(Reprinted from Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783–800.)*

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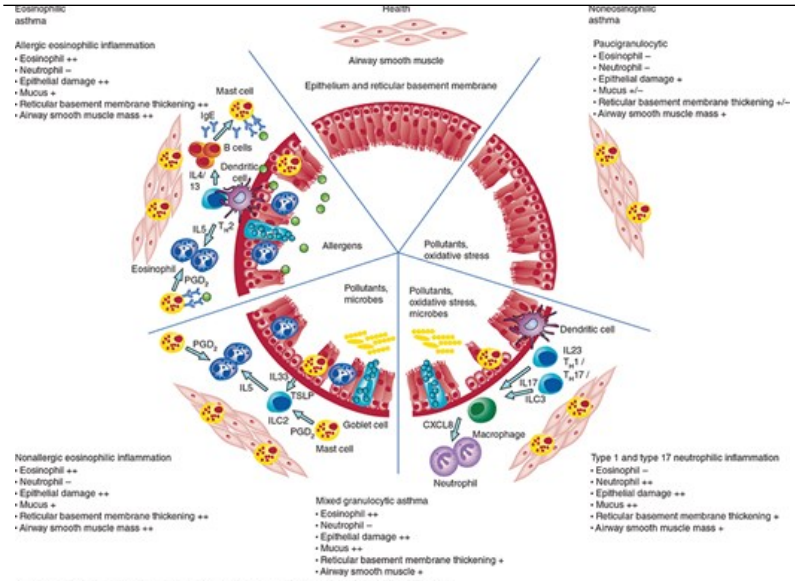

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Inflammatory Processes

Airway inflammation is multifaceted and the primary focus of asthma management and prevention. It has been demonstrated in all forms of asthma, and an association between the extent of inflammation and the clinical severity of asthma has been demonstrated in selected studies. Both central and peripheral airways are inflamed.

The use of inhaled allergen challenge models has contributed significantly to understanding the inflammatory cascade in the airways. Allergen inhalation in allergic patients causes an early-phase reaction (within minutes) that, in some cases, may be followed by a late-phase reaction (hours later). The early phase is initiated by the activation of cells bearing allergen-specific immunoglobulin E (IgE). It is characterized by the rapid activation of airway mast cells and macrophages leading to the rapid release of pro-inflammatory mediators such as histamine, eicosanoids, and reactive oxygen (O_2) species that induce contraction of airway smooth muscle, mucus secretion, and edema. The bronchial microcirculation has an essential role in this inflammatory process. Inflammatory mediators induce microvascular leakage with the exudation of plasma in the airways. Acute plasma protein leakage induces a thickened, engorged, and edematous airway wall and a consequent narrowing of the airway lumen. Plasma exudation may compromise epithelial integrity, and the presence of plasma in the lumen may reduce mucus clearance. Plasma proteins also may promote the formation of exudative plugs mixed with mucus and inflammatory and epithelial cells. Together these effects contribute to airflow obstruction (see Fig. 44-2).

The late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves the recruitment and activation of eosinophils, $CD4^+$ thymically derived lymphocytes (T-cells), basophils, neutrophils, and macrophages.[16] There is selective retention of airway T-cells, the expression of adhesion molecules, and the release of selected pro-inflammatory mediators and cytokines involved in the recruitment and activation of inflammatory cells.[16] The activation of T-cells after allergen challenge leads to the release of Th_2-related cytokines that may modulate the late-phase response.[16] The release of preformed cytokines by mast cells is the likely initial trigger for the early recruitment of inflammatory cells that then recruit and induce the more persistent involvement by T-cells.[9,16] The enhancement of nonspecific BHR usually can be demonstrated after the late-phase reaction but not after the early-phase reaction following allergen or occupational challenge.

In asthma, all cells of the airways are involved and become activated (Fig. 44-2). Included are eosinophils, neutrophils, T-cells, mast cells, alveolar macrophages, and dendritic cells, epithelial cells, fibroblasts, and bronchial smooth muscle cells. These cells also regulate airway inflammation and initiate the process of remodeling by the release of cytokines and growth factors.[17]

Inflammatory Cells

Epithelial Cells

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Bronchial epithelial cells participate in mucociliary clearance and removal of noxious agents. Stimuli such as allergens and air pollution stimulate epithelial cells to release various cytokines such as eicosanoids, peptidases, matrix proteins, periostin, cytokines, chemokines, and nitric oxide (NO).[16] Periostin is an extracellular matrix protein secreted by epithelial cells that induces the inflammatory cytokines, interleukin 4 (IL-4), and interleukin 13 (IL-13).[18] It has become important more recently as a biomarker of persistent eosinophilic airway inflammation and may have an integral role in airway remodeling, subepithelial fibrosis, and mucus regulation.[18,19] Epithelial cells can be activated by IgE-dependent mechanisms, viruses, pollutants, or histamine. In asthma, especially fatal asthma, extensive epithelial shedding occurs. The functional consequences of epithelial shedding may include heightened BHR, the release of the chemokine eotaxin that attracts eosinophils, altered permeability of the airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading pro-inflammatory neuropeptides. The integrity of airway epithelium may influence the sensitivity of the airways to various provocative stimuli. Epithelial cells may also be important in the regulation of airway remodeling and fibrosis.[9,16]

Eosinophils

Eosinophils play an effector role in asthma by releasing pro-inflammatory mediators, cytotoxic mediators, and cytokines.[9] Circulating eosinophils migrate to the airways by cell rolling, through interactions with selectins, and eventually adhere to the endothelium through the binding of integrins to adhesion proteins (vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]). As eosinophils enter the matrix of the membrane, their survival is prolonged by IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, eosinophils release inflammatory mediators such as leukotrienes (LTs) and granule proteins to injure airway tissue.[9]

Lymphocytes

Mucosal biopsy specimens from patients with asthma contain lymphocytes, many of which express surface markers of inflammation. There are two types of T-helper $CD4^+$ cells. Th_1 cells produce IL-2 and interferon-γ (IFN-γ), both essential for cellular defense mechanisms. Th_2 cells produce cytokines (IL-4, IL-5, and IL-13) that mediate allergic inflammation. It is known that Th_1 cytokines inhibit the production of Th_2 cytokines, and vice versa. It is hypothesized that allergic asthmatic inflammation results from a Th_2-mediated mechanism (an imbalance between Th_1 and Th_2 cells).[16] However, it has also been observed that there exists a low Th_2 cytokine phenotype of asthma in adults that appears more resistant to usual therapies for asthma.[16]

Th_1 and Th_2 Endotypes

Th_2 high asthma is characterized by activation of mediators such as IL-25 and IL-33 which subsequently activate IL-4, IL-5, and IL-13, as well as non-interleukin-dependent factors such as thymic stromal lymphopoietin (TSLP).[18,19] Inflammation occurs as a result of exposure of the airway epithelium to inhaled allergens, microbes, and inhaled pollutants (thus encompassing allergic and non-allergic inflammation) and occurs in approximately half of all patients with asthma.[19] The effects of these mediators result in inflammatory cell activation and secretion of IgE as well as the airway epithelium and smooth muscle.

Th_2 low asthma is described as neutrophilic asthma or mixed, pauci-granulocytic asthma, and is less well understood.[18,19] Patients are typically less responsive to corticosteroids, have fewer allergic symptoms, and are diagnosed later in life.

The T-cell population in the cord blood of newborn infants is skewed toward a Th_2 phenotype. The extent of the imbalance between Th_1 and Th_2 cells (as indicated by diminished IFN-γ production) during the neonatal phase may predict the subsequent development of allergic disease, asthma, or both. It has been suggested that infants at high risk of asthma and allergies should be exposed to stimuli that upregulate Th_1-mediated responses in order to restore the balance during a critical time in the development of the immune system and the lungs.

The basic premise of the Th_1 and Th_2 imbalance is that the newborn's immune system needs timely and appropriate environmental stimuli to create a balanced immune response. Factors that enhance Th_1-mediated responses include endotoxin exposure, such as increased exposure to infections

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through contact with older siblings and daycare attendance during the first 6 months of life.[20] Restoration of the balance between Th_1 and Th_2 cells may be impeded by frequent administration of oral antibiotics, with concomitant alterations in GI flora. Other factors favoring the Th_2 phenotype include residence in an industrialized country, urban environment exposure, diet, and sensitization to house dust mites and cockroaches.[18,19]

Mast cells

Mast cell degranulation is important in the initiation of immediate responses following exposure to allergens.[3] Mast cells reside throughout the walls of the respiratory tract, and increased numbers of these cells (threefold to fivefold) have been observed in the airways of patients with asthma and atopy.[21] Once binding of allergen to cell-bound IgE occurs, mediators such as histamine; eosinophil and neutrophil chemotactic factors; LTs C_4, D_4, and E_4; prostaglandins; platelet-activating factor (PAF); and others are released from mast cells (see Fig. 44-2). Histologic examination has revealed decreased numbers of granulated mast cells in the airways of patients who have died from acute asthma attacks, suggesting that mast cell degranulation is a contributing factor. Sensitized mast cells are also activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB).[22]

Alveolar Macrophages

The primary function of alveolar macrophages in the normal airway is to serve as “scavengers,” engulfing and digesting bacteria and other foreign materials. Macrophages are found in large and small airways, ideally located for affecting the asthmatic response. A number of mediators produced and released by macrophages have been identified, including pro-inflammatory and anti-inflammatory cytokines, reactive oxygen species, and eicosanoids.[23] In addition, alveolar macrophages are able to produce neutrophil chemotactic factor and eosinophil chemotactic factor, which in turn amplify the inflammatory process.

Neutrophils

The role of neutrophils in the pathogenesis of asthma remains somewhat unclear because they normally reside in low numbers in the airway. Though they usually do not infiltrate tissues showing chronic allergic inflammation, they are instrumental in the inflammation arising from occupational exposures such as particulate matter, ozone, and diesel exhaust. Neutrophils can be involved in late-phase inflammatory reactions. However, high numbers of neutrophils have been observed in the airways of patients who died from sudden-onset fatal asthma and in those with severe disease.[24] This suggests that neutrophils may play a pivotal role in the disease process, at least in some patients with long-standing or corticosteroid-resistant asthma.[24] The neutrophil can also be a source for a variety of mediators, including PAF, prostaglandins, thromboxanes, and LTs, that contribute to BHR and airway inflammation.[24]

Fibroblasts and Myofibroblasts

Fibroblasts are found frequently in connective tissue. Human lung fibroblasts may behave as inflammatory cells on activation by IL-4 and IL-13. The myofibroblast may contribute to the regulation of inflammation via the release of cytokines and to tissue remodeling. In asthma, myofibroblasts are increased in numbers beneath the reticular basement membrane, and there is an association between their numbers and the thickness of the reticular basement membrane.[9]

Inflammatory Mediators

Associated with asthma for many years, histamine is capable of inducing smooth muscle constriction and bronchospasm and is thought to play a role in mucosal edema and mucus secretion.[21] Lung mast cells are an important source of histamine. The release of histamine can be stimulated by exposure of the airways to a variety of factors, including physical stimuli (airway drying with exercise) and relevant allergens.[21] Histamine is involved in acute bronchospasm following allergen exposure; however, other mediators such as LTs are also involved.

Besides histamine release, mast cell degranulation releases ILs, proteases, and other enzymes that activate the production of other mediators of inflammation. Several classes of important mediators, including arachidonic acid and its metabolites (ie, prostaglandins, LTs, and PAF), are derived

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from cell membrane phospholipids.[21]

Once arachidonic acid is released, it can be metabolized by the enzyme cyclooxygenase to form prostaglandins. Prostaglandin D_2 is a potent bronchoconstricting agent; however, it is unlikely to produce sustained effects and its role in asthma remains to be determined. Similarly, prostaglandin $F_2\alpha$ is a potent bronchoconstrictor in patients with asthma and can enhance the effects of histamine.[21] However, its pathophysiologic role in asthma is unclear. Another cyclooxygenase product, prostacyclin (prostaglandin I_2), is known to be produced in the lung and may contribute to inflammation and edema owing to its effects as a vasodilator.

Thromboxane A_2 is produced by alveolar macrophages, fibroblasts, epithelial cells, neutrophils, and platelets within the lung.[25] It may have several effects, including bronchoconstriction, involvement in the late asthmatic response, and involvement in the development of airway inflammation and BHR.

The 5-lipoxygenase pathway of arachidonic acid metabolism is responsible for the production of the cysteinyl LTs.[25] LTC_4, LTD_4, and LTE_4 are released during inflammatory processes in the lung. LTs D_4 and E_4 share a common receptor (LTD_4 receptor) that, when stimulated, produces bronchospasm, mucus secretion, microvascular permeability, and airway edema, whereas LTB_4 is involved with granulocyte chemotaxis.

Thought to be produced by macrophages, eosinophils, and neutrophils within the lung, PAF is involved in the mediation of bronchospasm, sustained induction of BHR, edema formation, and chemotaxis of eosinophils.[26]

Adhesion Molecules

Adhesion molecules are glycoproteins that facilitate infiltration and migration of inflammatory cells to the site of inflammation by enhancing cell-cell communication.[27] Adhesion molecules are divided into families on the basis of their chemical structure. These families are the integrins, cadherins, immunoglobulin supergene family, selectins, vascular adressins, and carbohydrate ligands.[27] Those thought to be important in inflammation include the integrins, immunoglobulin supergene family, selectins, and carbohydrate ligands, including ICAM-1 and VCAM-1.[27] Adhesion molecules are found on a variety of cells, such as neutrophils, monocytes, lymphocytes, basophils, eosinophils, granulocytes, platelets, endothelial cells, and epithelial cells, and can be expressed or activated by the many inflammatory mediators present in asthma.[27]

Nitric Oxide

NO is produced by cells within the respiratory tract. It has been thought to be a neurotransmitter of the nonadrenergic, noncholinergic (NANC) nervous system.[28] Endogenous NO is generated from the amino acid L-arginine (L-Arg) by the enzyme NO synthase.[28] Three isoforms of NO synthase exist. One isoform is induced in response to pro-inflammatory cytokines, inducible NO synthase (iNOS), in airway epithelial cells and inflammatory cells of asthmatic airways.[28] NO produces smooth muscle relaxation in the vasculature and bronchials. However, it amplifies the inflammatory process and is unlikely to be of therapeutic benefit. Investigations measuring the fraction of exhaled NO (FeNO) concentrations have suggested that it may be a useful measure of ongoing allergic lower airway inflammation in patients with asthma and for guiding asthma therapy.[28]

Airway Smooth Muscle

The airway smooth muscle extends from the trachea through the respiratory bronchioles. Total smooth muscle mass decreases rapidly past the terminal bronchioles to the alveoli, so the contribution of smooth muscle tone to airway diameter in this region is relatively small. It is possible that the increased smooth muscle mass of the asthmatic airways is important in magnifying and maintaining BHR in persistent disease. However, the hypertrophy and hyperplasia are secondary processes caused by chronic inflammation and are not the primary cause of BHR.[29]

The airway smooth muscle is innervated by parasympathetic, sympathetic, and nonadrenergic inhibitory nerves.[30] Parasympathetic innervation of the smooth muscle consists of efferent motor fibers in the vagus nerves and sensory afferent fibers in the vagus and other nerves.[30] Normal resting tone of human airway smooth muscle is regulated by vagal nerve activity. Bronchoconstriction caused by vagal stimulation occurs in the small bronchi but is absent in the small bronchioles. The nonmyelinated C fibers are the predominate nerves of the afferent system are present throughout the airways

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with terminals in airway smooth muscle cells, epithelial cells, and airway ganglia.[30] These nerve endings probably represent the irritant receptors of the airways. Stimulation of these irritant receptors by mechanical stimulation, chemical, and particulate irritants, and pharmacologic agents such as histamine produces reflex bronchoconstriction.[30]

The NANC nervous system has been described in the trachea and bronchi. Substance P, neurokinin A, neurokinin B, and vasoactive intestinal peptide (VIP) are the best-characterized neurotransmitters in the NANC nervous system.[30] VIP is an inhibitory neurotransmitter. Inflammatory cells in asthma can release peptidases that can degrade VIP, producing exaggerated reflex cholinergic bronchoconstriction. NANC excitatory neuropeptides such as substance P and neurokinin A are released by stimulation of C-fiber sensory nerve endings.

Remodeling of the Airways

Acute inflammation is a beneficial response to tissue injury and generally leads to repair and restoration of the normal structure and function. In contrast, asthma is a chronic inflammatory process that leads to abnormal airway healing referred to as *remodeling*.[17] Repair involves replacing parenchymal cells with connective tissue that mature into scar tissue. In asthma, remodeling leads to extracellular matrix fibrosis, an increase in smooth muscle and mucous gland mass, and angiogenesis.[17]

The precise mechanisms of remodeling the airways are under intense study. Airway remodeling is of concern because it may represent an irreversible process that can have serious sequelae including the development of chronic obstructive pulmonary disease (COPD).[17] Observations in children with asthma indicate that some loss of lung function may occur during the first 5 years of life.[17] “Importantly, no current therapies have been shown to alter either lung growth or the progressive loss of lung function.”

Mucus Production

The mucociliary system is the lung’s primary defense mechanism against irritants and infectious agents. Mucus, composed of 95% water and 5% glycoproteins, is produced by bronchial epithelial glands and goblet-cells.[27] The lining of the airways consists of a continuous aqueous layer controlled by active ion transport across the epithelium in which water moves toward the lumen along the concentration gradient. Catecholamines and vagal stimulation enhance the ion transport and fluid movement. Mucus transport depends on its viscoelastic properties. Mucus that is either too watery or too viscous will not be transported optimally. The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. The bronchial glands are increased in size and the goblet cells are increased in size and number in asthma. Expectorated mucus from patients with asthma tends to have a high viscosity. The mucous plugs in the airways of patients who died in status asthmaticus are tenacious and tend to be connected by mucous strands to the goblet cells.[27] The airways of persons with asthma also may become plugged with casts consisting of epithelial and inflammatory cells. Although it is tempting to speculate that death from asthma attacks is a result of the mucous plugging resulting in irreversible obstruction, there is no direct evidence for this. Autopsies of asthmatics who died from other causes have shown similar pathology. In addition, some patients who have died of sudden severe asthma did not show the characteristic mucous plugging on necropsy.

Bronchial Hyperresponsiveness

Chronic inflammation is associated with nonspecific BHR and increases the risk of asthma exacerbations. Exacerbations are characterized by increased symptoms and worsening airway obstruction over a period of days or even weeks, and rarely, hours. Hyper-responsiveness of the airways to physical, chemical, and pharmacologic stimuli is a hallmark of asthma.[3] BHR also occurs in some patients with chronic bronchitis and allergic rhinitis.[3] Normal healthy subjects may also develop a transient BHR after viral respiratory infections or ozone exposure. However, the degree of BHR in patients with asthma is quantitatively greater than in other populations. Bronchial responsiveness of the general population fits a unimodal distribution that is skewed toward increased reactivity; individuals with clinical asthma represent the extreme end of this distribution. The degree of BHR within asthma correlates with its clinical course and medication requirement necessary to control symptoms.[3] Patients with mild symptoms or in remission demonstrate lower levels of BHR. The current understanding is that the BHR seen in asthma is at least in part due to and correlative with the extent of airway inflammation.[9]

Factors Contributing to Asthma Severity and Persistence

Viral Respiratory Infections

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Viral respiratory infections are primarily responsible for exacerbations of asthma, particularly in children younger than 10 years.[15] Children aged 5 years or younger may have wheezing (which may or may not be asthma) associated with upper respiratory tract infections.[2] Infants are particularly susceptible to airway obstruction and wheezing with viral infections because of their small airways. Approximately 30% to 40% of infants who have severe RSV bronchiolitis will have recurrent wheezing but the subsequent prevalence of asthma is 5% to 10% in children.[15] The most common cause of exacerbations in both children and adults is the rhinovirus, which is the most frequent virus associated with the common cold and distributed worldwide.[15] Other viruses isolated include RSV, parainfluenza virus, adenoviruses, coronavirus, and influenza viruses. Certain viruses (RSV and parainfluenza virus) are capable of inducing specific IgE antibodies, and rhinovirus can activate eosinophils directly in asthmatics.[15] The increase in asthma symptoms and BHR that occurs may last for days or weeks following the resolution of the symptoms of the viral infection. Evidence suggests a potential, but does not conclusively support, a beneficial effect of the influenza vaccine in preventing asthma exacerbations due to influenza infections.[3] However, patients with moderate-to-severe asthma should be vaccinated against influenza annually.[12]

Coronavirus Disease (COVID-19)

Patients with COVID-19 infection who have asthma are at increased risk of hospitalization and intensive care unit admission; having severe asthma increases that risk.[31] There is no conclusive evidence that treatment for COVID-19 improves or worsens the risk of mortality, intensive care unit admission, or need for ventilatory support in patients with asthma, presumably due to the interacting impact of asthma treatments on outcomes. Patients should be counseled to continue their asthma treatments if they are diagnosed with COVID-19. Chronic heart disease may increase the risk of mortality in patients with asthma, but it is unclear if other comorbidities, such as diabetes, hypertension, obesity, or chronic kidney disease, increase mortality risk. Females with COVID-19 and asthma may be at greater risk of hospitalization than males. Age and other demographic characteristics have not been conclusively or consistently shown to impact outcomes in patients with COVID-19 and asthma.[31]

Certain medications used to treat COVID-19 in non-hospitalized patients may interact with asthma medications. Specifically, ritonavir-boosted nirmatrelvir may increase blood concentrations of salmeterol and vilanterol due to potent inhibition of P450 CYP3A5, increasing the risk of cardiac adverse effects from these β_2-agonist.[32] Prescribers should consider an alternative antiviral treatment for COVID-19 or temporarily switch patients from a salmeterol or vilanterol-containing product to either ICS monotherapy or ICS-formoterol.[12]

For patients who become infected with COVID-19 and who use a nebulizer for delivery of asthma medications, every effort should be made to transition the patient to an inhaler with a valved spacer and tight-fitting face mask if appropriate. Nebulizers can transmit respiratory viral particles for at least 1 m from the patient which places others at risk of infection.[12] Importantly, inhalers and spacers should not be shared between patients, and spacers should be regularly cleaned and disinfected.

Patients with asthma should be encouraged to receive a COVID-19 vaccination. There are no data to indicate an increased risk of adverse effects in patients with asthma who are vaccinated.[12] However, vaccinations should be administered in a setting where treatment of anaphylaxis is available. Those who have a history of severe allergic reactions to one of thevaccine ingredients (e.g. polyethylene glycol in the Pfizer/BioNTech vaccine) should receive an alternative vaccine. Biologic drugs used for the treatment of asthma should not be administered on the same day as the COVID-19 vaccination simply to distinguish any emergent adverse effects between the two medications.[12] Patients with asthma can receive the annual influenza vaccination concurrently with the COVID-19 vaccination.

Environmental and Occupational Factors

The development and heterogeneity of persistent asthma are driven by complex gene-environment interactions. Agents and events that are known to trigger asthma are listed in Table 44-1. The mechanisms for inducing symptoms are as varied as the exposure factor and include both IgE- and cell-mediated reactions.[12] The World Allergy Organization (WAO) predicts an increase in the incidence and prevalence of asthma due to environmental exposures from climate change.[33] Greater temperature variability, industrial pollution, more frequent forest fires, a higher concentration of ground-level ozone, increased transboundary movement of respiratory infectious agents, and changes in aeroallergen distribution are all cited factors. Sulfur dioxide in the ambient atmosphere is highly irritating and presumably induces bronchoconstriction through mast cell or irritant-receptor involvement.[34] Asthma produced by repeated prolonged exposure to industrial inhalants is a significant health problem. It has been estimated that

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25% of adult-onset asthma worldwide is occupationally related.[34] Occupational asthma can be difficult to diagnose as the latency between exposure and symptom development can extend from months to years.[34] Persons with occupational asthma have the typical symptoms of asthma with cough, dyspnea, and wheezing. Typically, the symptoms are related to workplace exposure and improve on days off and during vacations.[34] Once occupational asthma has developed, the symptoms persist in most patients even after exposure is no longer present.[34]

TABLE 44-1

List of Agents and Events Triggering Asthma Exacerbations

Respiratory infection	Respiratory syncytial virus (RSV), rhinovirus, coronavirus, influenza, parainfluenza, *Mycoplasma pneumonia*, *Chlamydia*, chronic rhinosinusitis
Allergens	Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores
Environment	Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke (including second and third hand), wood smoke, energy-efficient buildings (increase indoor air pollution), meteorological conditions related to climate change, scented home products, cleaners, and perfumes
Emotions	Anxiety, stress, laughter
Exercise	Particularly in a cold, dry climate
Drugs/preservatives	Acetaminophen, Aspirin, NSAIDs (cyclooxygenase inhibitors), sulfites, benzalkonium chloride, nonselective β-blockers, higher airway reversibility to β_2-agonist
Occupational stimuli	Bakers (flour dust); farmers (hay mold); spice and enzyme workers; occupational cleaners, printers (Arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)
Host factors	Obesity, African American race, Hispanic ethnicity, low socioeconomic status

Stress, Depression, and Psychosocial Factors

Observational studies demonstrate an association between increased stress and worsening asthma, but the role is not clearly defined.[3] Bronchoconstriction from psychological factors is mediated primarily through excess parasympathetic input. Atropine has been shown to block experimental psychogenic bronchoconstriction. Persons with asthma are more likely to have depression than those without asthma. The episodic nature of both diseases may be related to abnormal expression of Th2 cytokines that have effects in the brain as well as the airway. It is most important to emphasize to both patients and parents of children with asthma that asthma is not an emotional disease. However, coping skills may benefit the patient who becomes emotionally distraught during an asthma exacerbation.

Chronic Rhinosinusitis

Disorders of the upper respiratory tract, particularly rhinitis and sinusitis, have been linked with asthma. The prevalence of allergic sensitization increases with asthma severity; nasal polyposis is often seen in those with allergic rhinitis. It has been postulated that the transport of mucus

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chemotactic factors and inflammatory mediators from nasal passages during allergic rhinitis into the lungs may accentuate BHR. However, chronic sinusitis may just represent a nonbacterial coexisting condition in patients with asthma and allergies because the histologic changes in the paranasal sinuses are similar to those seen in the lung and nose. Given that chronic rhinosinusitis is associated with severe asthma, especially in patients with nasal polyps, it would seem plausible that treatment of rhinosinusitis could improve asthma control. However, a large study of children and adults found that treatment of chronic sinonasal disease with intranasal corticosteroids for 6 months had no impact on asthma control or BHR, suggesting that the treatment of sinus disease and asthma should be separately managed.[12]

Gastroesophageal Reflux Disease

Symptoms of gastroesophageal reflux disease (GERD), as well as asymptomatic reflux, are common in both children and adults who have asthma.[12] Nocturnal asthma may be associated with nighttime reflux. Reflux of acidic gastric contents into the esophagus is thought to initiate a vagally mediated reflex bronchoconstriction. Also of concern is that most medications that decrease airway smooth muscle tone have a relaxant effect on gastroesophageal sphincter tone. There is no benefit from screening or treating asymptomatic reflux in patients with asthma (Evidence A).[12] However, for patients who have asthma and symptoms of reflux, a trial of anti-reflux medication may improve reflux symptoms; if there is no resolution, further evaluation is warranted.[12] Treatment with proton pump inhibitors does not improve asthma control even in those with documented reflux.[12]

Microbiome

As the role of microbes in human health and disease continues to unfold, there is an increased investigation into the airway and gastrointestinal microbiome's relationship to asthma.[35] Patients with asthma and other obstructive lung diseases have shown differences in the lower airway microbiome compared with healthy individuals.[35] Evidence suggests that treatment-resistant asthma and worse lung function of select patients may be correlated to microbiota differences in the sputum. The upper airway microbiome has different microbiota than the lower airway by which pressure and temperature changes favor certain bacterial populations.[35] In a population-based study following infants to children, those with an altered nasal microbiota (eg, persistent *Moraxella* sparsity) were found to be at higher risk for developing asthma.[36] The gut microbiota is better studied and correlates to the risk of allergic sensitization and infant response to viral respiratory tract infections. As these relationships of the microbiome are further studied, the potential for developing strategies for the prevention and development of asthma may be possible.

Female Hormones

Asthma symptoms may vary significantly during different stages of the menstrual cycle. Premenstrual worsening of asthma symptoms has been reported in 20% of women and worsening of pulmonary function has been observed in women who do not report worsening symptoms.[37] Women with premenstrual symptoms tend to be older, have a higher body mass index, more severe asthma, aspirin sensitivity, and a longer duration of asthma.[37] The pathophysiology is uncertain because estrogen replacement in postmenopausal women has been shown to worsen asthma, whereas estradiol and progesterone administration has been reported to both improve or have no effect on asthma in women with premenstrual asthma.[37] Some studies have reported an increase in ED visits by women who were premenstrual, whereas others have reported no association with the menstrual phase.[37] Pregnancy may cause worsening, improvement, or no change in asthma symptoms, and the changes seem to occur with equal frequency.[37]

Foods, Additives, Supplements, and Vitamins

Food chemicals, specifically sulfites used as preservatives, can trigger life-threatening asthma exacerbations. Beer, wine, dried fruit, and open salad bars, in particular, have high concentrations of metabisulfites.[3] Food avoidance is only recommended when there is clear documentation of allergy or food chemical sensitivity.[12]

Aspirin and other nonsteroidal anti-inflammatory drugs can cause severe asthma exacerbations (aspirin-exacerbated respiratory disease).[12] The mechanism is related to cyclooxygenase-1 (COX-1) inhibition. Inhaled corticosteroids (ICSs) are the primary preventive treatment although oral corticosteroids may be required; leukotriene receptor antagonists (LTRAs) may be useful.[12] Aspirin sensitivity occurs in 7% of adults with asthma and is associated with a more severe disease.[12] While nonselective β-blocking agents do not precipitate bronchospasm, they can prevent reversal.

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Vitamin D supplementation may be beneficial in reducing asthma exacerbations in patients who require oral corticosteroids and have low 25-hydroxyvitamin D plasma concentrations (<10 ng/mL [25 nmol/L]).[12] However, high-quality studies confirming improvements in asthma control or reductions in exacerbations are lacking.[12]

The impact of the maternal diet on allergy and asthma development has been a research focus of interest. In a systematic review, fish oil supplementation or dietary intake of fish during pregnancy had no consistent effects on the risk of wheezing, asthma, or atopy in the child.[12] Some evidence indicates that maternal intake of peanut and milk products are associated with a lower risk of allergy and asthma in offspring. Due to limited evidence, dietary changes during pregnancy are not yet recommended.

Obesity

Epidemiologic data suggest that obesity increases the prevalence of asthma and may reduce asthma control, although it is difficult to distinguish obesity-induced respiratory symptoms from true asthma symptoms because obesity often precedes the onset of asthma. Lung volume and tidal volume are reduced in obesity, promoting airway narrowing. Obesity also produces low-grade systemic inflammation that may act on the lung to worsen asthma. The mechanism may include the release of adipose-derived pro-inflammatory mediators such as IL-6, IL-10, eotaxin, tumor necrosis factor-α, transforming growth factors-β_1, C-reactive protein, leptin, and adiponectin or a result of common predisposing dietary factors. Being overweight or obese is a risk factor for childhood asthma, particularly in females; conversely, there is no evidence that having asthma increases the risk for obesity.[12]

Exposure to Tobacco Smoke and COPD Overlap

A thorough history that considers age, respiratory symptoms, past medical history, previous diagnoses, and treatments, as well as social and occupational risk factors, may identify relevant a smoking history or exposure to environmental tobacco smoke. The clinician is then faced with distinguishing asthma from COPD. First termed *asthma COPD overlap syndrome* (ACOS) and more recently *asthma COPD overlap* (ACO), some patients have clinical features of both asthma and COPD.[38] Physical examination findings, lung function measures, and radiology data are then combined with the history to confirm this syndromic diagnosis. GINA and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) provide recommendations for initial therapy of ACO if the diagnostic features are equally balanced between asthma and COPD.[38] However, GOLD no longer refers to ACOS due to a misperception that ACOS is a distinct disorder. Rather, GOLD emphasizes that asthma and COPD are different disorders with common traits and features and may coexist in the same patient. Given that patients with features of both asthma and COPD are most often excluded from clinical studies, the pathophysiology and treatment remain less defined for these patients. Compared to patients with either asthma or COPD alone, those with ACO have a greater symptom burden, physical impairment, and hospitalizations with worse quality of life.[39] The origins of ACO may begin in childhood regardless of smoking history, but smoke may have more severe effects on lung function in patients with asthma. Referral for expert advice and further diagnostic evaluation for ACO patients may be necessary. GOLD recommends clinicians prioritize asthma treatment for patients with ACO.[38]

CLINICAL PRESENTATION

Chronic Asthma

3 Classically, asthma is characterized by episodic and variable respiratory symptoms; however, the clinical presentation of asthma is as diverse as the number of triggering events (see “Clinical Presentation: Chronic Asthma”). Although wheezing is the characteristic symptom of asthma, the medical literature is replete with the warning that “not all that wheezes is asthma.” A wheeze is a high-pitched, whistling sound created by turbulent airflow through an obstructed airway, so any condition that produces significant obstruction can result in wheezing as a symptom. In addition, “all of asthma does not wheeze” is an equally justifiable warning. Patients may present with a chronic persistent cough (cough variant asthma) as their only symptom.[12]

There is no single diagnostic test for asthma. The diagnosis is based primarily on a thorough history gathered from the patient.[12] The patient may have a family history of allergy or asthma or have symptoms of allergic rhinitis, or atopic dermatitis. Reversibility of airway obstruction following administration of a SABA or excessive variability in twice-daily peak expiratory flow (PEF) over 1 to 2 weeks are diagnostic criteria. Patients with normal

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spirometry values can be challenged with exercise or substances that produce bronchoconstriction, such as methacholine or mannitol, to determine if they have BHR, but again, a positive challenge test is not diagnostic. Newer tests of inflammation in the airways such as induced sputum eosinophil and neutrophil counts or FeNO measurements are consistent with but not diagnostic of asthma. According to the 2020 Asthma Focused Updates, when the diagnosis is uncertain, a FeNO measurement is recommended as an adjunctive diagnostic test.[11] FeNO results should be interpreted in conjunction with other conditions or factors that influence FeNO levels in patients with asthma (eg, smoking, obesity, and corticosteroid use are associated with lower levels; whereas atopy, eosinophilic bronchitis are associated with higher levels).

GINA recommends confirmation of the diagnosis of asthma in patients already taking controller treatment using objective testing. The process depends on the patient's symptoms and lung function and may include a trial of either a lower or a higher dose of controller treatment.[12]

The frequency and severity of asthma symptoms vary widely. The intervals between symptoms can be days, weeks, months, or years. Asthma also can vary in its severity and is related to the intrinsic intensity of the disease process. Asthma severity is determined by lung function, symptoms, nighttime awakenings, rescue SABA use, interference with normal activity prior to therapy, and frequency of exacerbations requiring systemic corticosteroids.[40] Severity is most easily and directly measured in a patient who is not currently receiving asthma treatment. The NAEPP has provided a means of classifying asthma severity that is divided into two domains: impairment and risk.[3] This classification system is individualized for three age groups (0-4, 5-11, and greater than or equal to 12 years) and summarized in Table 44-2. Based on these domains, an individual's severity category is based on the greatest level of either impairment or risk. For example, a patient with several features consistent with mild persistent severity but who has one feature in the moderate persistent category is classified as having moderate persistent asthma. Although classifying severity is helpful for determining the initial treatment, subsequent management is determined by the level of symptom control. GINA has provided a slightly different framework for determining chronic therapy for children and adults based on symptom control and future risk of adverse outcomes.[12]

TABLE 44-2

Classifying Asthma Severity for Patients Who Are Not Currently Taking Long-Term Control Medications

	Children 0-4 and 5-11 Years of Age				
	Persistent				
	Components	**Intermittent**	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings (0-4 years)	0	1-2 × month	3-4 × month	>1 × week
	Nighttime awakenings (5-11 years)	≤2 × month	3-4 × month	>1 × week, but not n ightly	Often 7 × week
	SABA use for symptom control	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	FEV_1 > 80%	FEV_1 > 80%	FEV_1 60%-80%	FEV_1 < 60%
	5-11 years	FEV_1/FVC >	FEV_1/FVC > 80%	FEV_1/FVC 75%-80% (0.75-0.80)	FEV_1/FVC < 75% (0.75)

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		85% (0.85)	(0.80)		
	Exacerbations	**Intermittent**	**Persistent**		
Risk	0-4 years	0-1/year	≥2 in 6 months or ≥4 wheezing episodes/1 year lasting >1 day		
	5-11 years	0-2/year	>2 in 1 year		
	Recommended initial treatment	Step 1	Step 2	Step 3 and consider short-course of oral corticosteroids	
		Youths ≥12 Years of Age and Adults			
			Persistent		
	Components	**Intermittent**	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2 × month	3-4 × month	>1 × week, but not nightly	Often 7 × week
	SABA use for symptom control	≤2 days/week	>2 days/week, but not >1 × day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	FEV_1 > 80%	FEV_1 > 80%	FEV_1 60%-80%	FEV_1 < 60%
		[a]FEV_1/FVC normal	[a]FEV_1/FVC normal	[a]FEV_1/FVC reduced 5% (0.05)	[a]FEV_1/FVC reduced > 5% (0.05)
	Exacerbations	Intermittent	Persistent		
Risk		0-2/year	>2 in 1 year		
	Recommended initial treatment	Step 1	Step 2	Step 3 and consider a short course of oral corticosteroids	Step 4 or 5 and consider a course of oral corticosteroid

SABA, short-acting β-agonist.

[a]Normal FEV_1/FVC: 8 to 19 years 85% (0.85); 20 to 39 years 80% (0.80); 40 to 59 years 75% (0.75); 60 to 80 years 70% (0.70).

The frequency or chronicity of the symptoms is not necessarily associated with the severity of symptoms during exacerbations. Patients can present with a range from intermittent symptoms that require no medications or only occasional reliever use for severe persistent asthma symptoms despite treatment with multiple medications.

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CLINICAL PRESENTATION: Chronic Asthma

General

- Asthma is a disease of exacerbation and remission, so the patient may not have any signs or symptoms at the time of examination.

Symptoms

- The patient may complain of episodes of shortness of breath, chest tightness, coughing (particularly at night), wheezing, or a whistling sound from the chest when breathing. These often occur in association with exercise, but also occur spontaneously or in association with known allergens.

Signs

- Wheezing on auscultation (more typically on expiration), prolonged expiratory phase on auscultation dry hacking cough or signs of atopy (allergic rhinitis and/or atopic dermatitis) may occur.

Laboratory

- Spirometry demonstrates obstruction (reduced FEV_1/forced vital capacity [FVC]) with reversibility following inhaled β_2-agonist administration (FEV_1 increases by more than 12% and 200 mL). The FEV_1/FVC ratio is normally more than 75% to 80% (0.75-0.80) in adults and more than 85% (0.85) in children.

Other diagnostic tests

- Excessive variability in twice-daily peak expiratory flow (PEF) over 2 weeks (greater than 10% in adults and greater than 13% in children). A fall in FEV_1 of at least 10% following 6 minutes of near-maximal exercise. Elevated eosinophil count and IgE concentration in blood. FeNO less than 20 ppb in children younger than 12 years and less than 25 ppb in adults suggest a diagnosis other than asthma. Positive methacholine challenge (PC20 FEV_1 less than 12.5 mg/mL) or mannitol challenge (FEV_1 decrease of at least 15% from baseline after 635 mg or less).

Acute Severe Asthma

Uncontrolled asthma, with its inherent variability, can progress to an acute state where inflammation, airway edema, excessive mucus accumulation, and severe bronchospasm result in a profound airway narrowing that is poorly responsive to usual bronchodilator therapy (see “Clinical Presentation: Acute Severe Asthma”).[41] Although this progression is a common scenario, some patients experience rapid-onset or hyper-acute exacerbations.[41] Hyper-acute exacerbations are associated with neutrophilic as opposed to eosinophilic infiltration and resolve rapidly with bronchodilator therapy, suggesting that smooth muscle spasm is the major pathogenic mechanism.[41] In most cases, emergency department (ED) visits for acute severe asthma represent the failure of an adequate therapeutic regimen to control persistent asthma. Underutilization of anti-inflammatory drugs and excessive reliance on SABA are the major risk factors for severe exacerbations.[41] However, frequent exacerbations may represent a specific phenotype of asthma. A blunted perception of airway obstruction may predispose certain individuals to fatal asthma attacks.[41]

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CLINICAL PRESENTATION: Acute Severe Asthma

General

- Although an episode can progress over several days or hours (usual scenario), it can progress rapidly over 1 to 2 hours.

Symptoms

- The patient is anxious in acute distress and complains of severe dyspnea, shortness of breath, chest tightness, or burning. The patient is only able to say a few words with each breath. Symptoms are unresponsive to usual measures (inhaled β_2-agonist administration).

Signs

- Signs include expiratory and inspiratory wheezing on auscultation (breath sounds may be diminished with very severe obstruction), dry hacking cough, tachypnea, tachycardia, pale or cyanotic skin, hyper-inflated chest with intercostal and supraclavicular retractions, and hypoxic seizures if very severe.

Laboratory tests

- Peak expiratory flow and/or FEV_1 less than 40% of normal predicted values. Decreased arterial O_2 (PaO_2), and O_2 saturations by pulse oximetry (SaO_2 less than 90% [0.90] on room air is severe). Decreased arterial or capillary CO_2 if mild, but in the normal range or increased in moderate-to-severe obstruction.

Other diagnostic tests

- Blood gases to assess metabolic acidosis (lactic acidosis) in severe obstruction. Complete blood count if there are signs of infection (fever and purulent sputum). Serum electrolytes as therapy with β_2-agonist and corticosteroids can lower serum potassium, magnesium, and phosphate, and increase glucose. Chest radiograph if signs of consolidation on auscultation.

Exercise-Induced Bronchospasm

During vigorous exercise, pulmonary function measurements (FEV_1 and PEF) in patients with asthma increase during the first few minutes but then begin to decrease after 6 to 8 minutes.[2] Exercise-induced bronchospasm (EIB) is defined as a drop in FEV_1 of 10% or greater from baseline (pre-exercise value).[2] Most studies suggest that many patients with persistent asthma experience EIB.[3] The exact pathogenesis of EIB is unknown, but heat loss and/or water loss from the central airways play an important role.[42] EIB is provoked more easily in cold, dry air, ambient ozone, and airborne particulate matter; alternatively, warm, humid air can blunt or block it.[43] Studies have demonstrated increased plasma histamine, cysteinyl LTs, prostaglandins, and tryptase concentrations during EIB, suggesting a role for mast cell degranulation.[42] These findings led to the development of inhaled mannitol, an osmotic agent, as an indirect pharmacologic bronchoprovocation test to assist in the diagnosis of asthma.

A refractory period following EIB lasts up to 4 hours after exercise in some patients. The refractory period is thought to be caused by an acute depletion of mast cell mediators and the time required for their repletion.

EIB is believed to be a reflection of increased BHR associated with asthma. A correlation, though not perfect, exists between EIB and reactivity to histamine, methacholine, and mannitol. During periods of remission, a decreased sensitivity to the same degree of exercise is often observed. Many children and adults with EIB report no symptoms and have normal pulmonary function except in association with exercise.[2] Interestingly, elite athletes have a higher prevalence of EIB than the general population.[42]

Nocturnal Asthma

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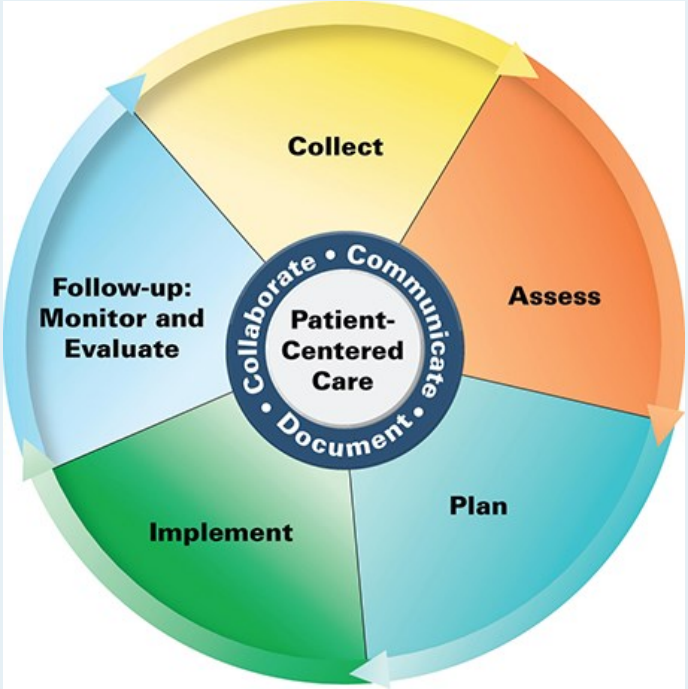
Worsening of asthma during sleep is referred to as *nocturnal asthma.* Patients with nocturnal asthma have significant declines in pulmonary function between bedtime and awakening.[2] Typically, their lung function reaches a nadir at 3 to 4 am. Although the pathogenesis of this phenomenon is unknown, it has been associated with diurnal patterns of endogenous cortisol secretion and circulating epinephrine and is associated with an increase in airway inflammation.[2]

Numerous other factors may affect nocturnal worsening of asthma, including allergies and improper environmental control, gastroesophageal reflux, obstructive sleep apnea, and sinusitis. Experts consider nocturnal symptoms to be a sign of inadequately treated persistent asthma. Awakening from nocturnal asthma is a sensitive indicator of both severity and inadequate control.

PATIENT CARE PROCESS

Patient Care Process for the Management of Persistent Asthma



Collect

- Patient characteristics (eg, age, race/ethnicity, sex, pregnancy status)
- Patient history (eg, past medical, known triggers, psychosocial history, gastroesophageal reflux disease)
- Family history (eg, asthma, allergy, atopic dermatitis)
- Home/work environment (eg, environmental, occupational, tobacco smoke, carpet/bedding, pets) (see Table 44-1)
- Current medications and prior response to controller therapies (eg, ICS+/−LABA; montelukast; LAMA; biologic therapies)
- Subjective and objective data (see Table 44-2)
    - Symptoms (description and frequency)
    - Nocturnal awakenings
    - Albuterol use frequency for symptom control

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- Activity limitation
- Exacerbation frequency
- Peak expiratory flow readings

Assess

- Comorbid conditions (eg, allergies, rhinosinusitis, obesity, obstructive sleep apnea, gastroesophageal reflux, smoking)
- Symptom frequency including exercise tolerance (see Table 44-2)
- Exacerbation history (eg, oral corticosteroid use, emergency department visits, hospitalization)
- Current medications that may contribute to or worsen asthma (eg, nonsteroidal anti-inflammatory drug [NSAID], aspirin) (see Table 44-1)
- Appropriateness and effectiveness of current medications in controlling symptoms and preventing exacerbations
- Inhaler technique (see Fig. 44-10) and adherence; potential barriers
- Socioeconomic barriers to obtaining medications
- Adherence to nonpharmacologic recommendations (eg, allergen avoidance, environmental control)

Plan*

- Tailored environmental modifications (eg, pet removal, carpet removal, pillow and mattress covers, exercise pretreatment, occupational exposures) (see Table 44-1)
- Medication therapy regimen: dose, route, frequency, duration, and MDI spacer; specify the continuation and discontinuation of existing therapies (see Tables 44-4, 44-7, 44-8, 44-10, and 44-13)
- Monitoring parameters include efficacy (eg, daily symptoms, nocturnal awakenings, albuterol use, exercise tolerance, peak expiratory flow [in selected patients]), and time frame (see Table 44-2)
- Patient/family education (eg, purpose of treatment, environmental modifications, drug therapies, inhaler technique)
- Self-monitoring of symptoms, albuterol use, peak expiratory flow (in selected patients)—where and how to record results (see Fig. 44-6)
- Referrals to other providers when appropriate (eg, specialist physician)

Implement*

- Provide patient/family education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up based on symptoms and medication changes

Follow-up: Monitor and Evaluate

- Determine symptom control and exacerbation outcomes
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

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Collaborate with patient, caregivers, and other healthcare professionals.

TREATMENT

Desired Outcomes

GINA's long-term goals for asthma management are: (1) to achieve good control of symptoms and maintain normal activity levels and (2) to minimize future risk of exacerbations, fixed airflow limitation, and medication-related side effects.[12] The importance of eliciting the patient's own goals is critical through an ongoing patient-healthcare provider partnership. Key components are strategies to facilitate effective communication and reduce the impact of impaired health literacy.[12] Self-management education reduces asthma morbidity in both adults and children (Evidence A).[12] GINA and NAEPP recommend control-based asthma management, adjusting pharmacological and nonpharmacological treatment in a continuous cycle of assessment, treatment adjustment, and review. Assessment includes symptom control, risk factors, inhaler technique and adherence, and patient preferences. Response review includes symptoms, exacerbations, medication side effects, patient satisfaction, and lung function.[11,12]

GINA differentiates between the preferred treatment options at a population level (based on efficacy, effectiveness, safety, availability, and cost) versus appropriate treatment options for individual patients. A shared decision-making approach is recommended and should include a discussion of preferred treatment options, patient characteristics or phenotype, patient/parent preferences, and practical issues (inhaler technique, adherence, and cost).[12] Evidence suggests that a shared decision-making approach may be associated with better outcomes.[12]

General Approach to Treatment

The NAEPP[3,11] and GINA[12] outline sound strategies for the management and treatment of asthma. The NAEPP EPR3 guideline was last published in 2007 and updated in 2020. The NAEPP 2020 Asthma Focused Updates specifically reviewed six topics for clinical management of asthma, but did not comprehensively revise the 2007 EPR3.[11] Therefore, healthcare professionals may need to use both the EPR3 and 2020 Focused Updates when managing a patient with asthma.

The GINA guidelines and the 2020 Asthma Focused Updates use different approaches in evaluating the literature and determining recommended treatment approaches. The NAEPP continues to utilize the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, an internationally accepted framework to determine the strength of a recommendation, however, is generally less nimble for incorporating new evidence. The GINA guidelines are updated every year, and thus, GINA is generally more current and can indicate emerging treatment strategies.[12] Thus, clinicians may consult both guidelines for these reasons. With the release of the 2020 Asthma Focused Updates, the GINA and the NAEPP overall guidance have become more similar and will be described in further detail for the management of chronic asthma.

General Approach to the Management of Chronic Asthma

As outlined in the 2020 Asthma Focused Updates, a stepped approach to managing persistent asthma is used for all ages (Fig. 44-3 to 44-5)[11]. Step of care depends upon whether the individual is newly diagnosed (treatment naïve) or if therapy is being adjusted to achieve control. If newly diagnosed, the initial step is based upon levels of impairment and risk which determine asthma severity (Table 44-2)[40]. All patients with persistent asthma (mild, moderate, or severe) should also be initiated on inhaled corticosteroid therapy.

5 An ICS is the preferred long-term controller therapy for persistent asthma in all patients due to potency and consistent effectiveness.[11,12] ICSs reduce BHR, improve lung function, and reduce severe exacerbations leading to ED visits and hospitalizations. ICS therapy is more effective than theophylline or the LTRAs. In addition, ICS therapy is the only treatment that has been documented to reduce the risk of dying from asthma.[11,12] Therapy is escalated as needed by increasing the dose of ICS or the addition of a second and then a third inhaled controller medication, typically a long-acting β_2-adrenergic receptor agonist (LABA) (preferred choice) or a long-acting muscarinic agonist (LAMA) (Fig. 44-3 to 44-5). All patients with asthma should have quick-relief medication (reliever therapy) available for acute symptoms. It is important to ensure that the patient can correctly use both the reliever and controller delivery devices. Once therapy has been initiated, patients are then evaluated 2 to 6 weeks later to rate their level of control (ie, well-controlled, not well-controlled, or very poorly controlled) using the same domains of impairment and risk in severity classification.[40]

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Based on their level of control, step therapy should be adjusted accordingly, and follow-up should continue every 2 to 3 months as indicated by clinical urgency.

FIGURE 44-3

Stepwise approach for management of asthma in ages 0 to 4 years. (ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; SABA, inhaled short-acting β_2-agonist; RTI, respiratory tract infection; PRN, as needed.) [a]Updated based on the 2020 guidelines. [b]Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The Food and Drug Administration (FDA) issued a Boxed Warning for montelukast in March 2020. *(Data from Reference 11.)*

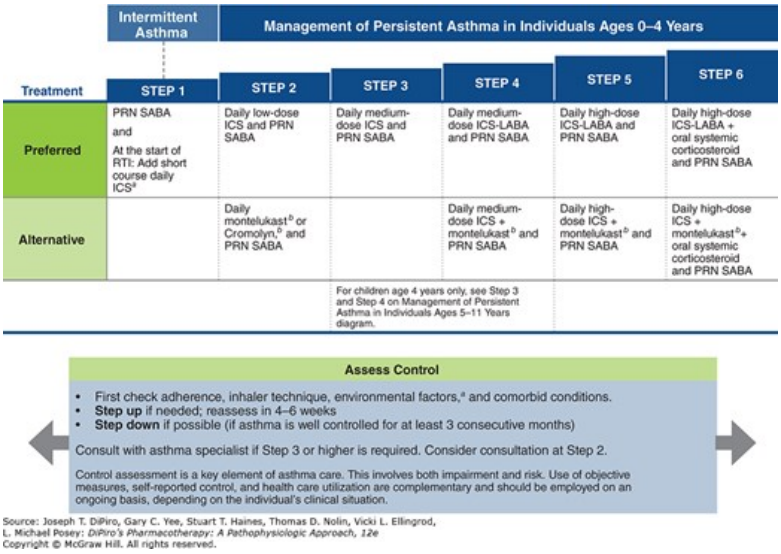

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FIGURE 44-4

Stepwise approach for management of asthma in ages 5 to 11 years. (ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist.) [a]Updated based on the 2020 guidelines. [b]Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020. [c]Omalizumab is the only asthma biologic currently FDA-approved for this age range. *(Data from Reference 11.)*

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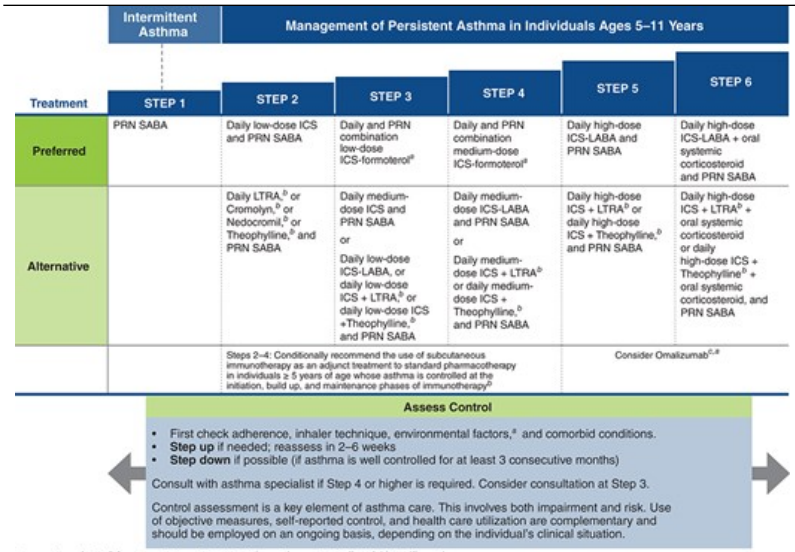

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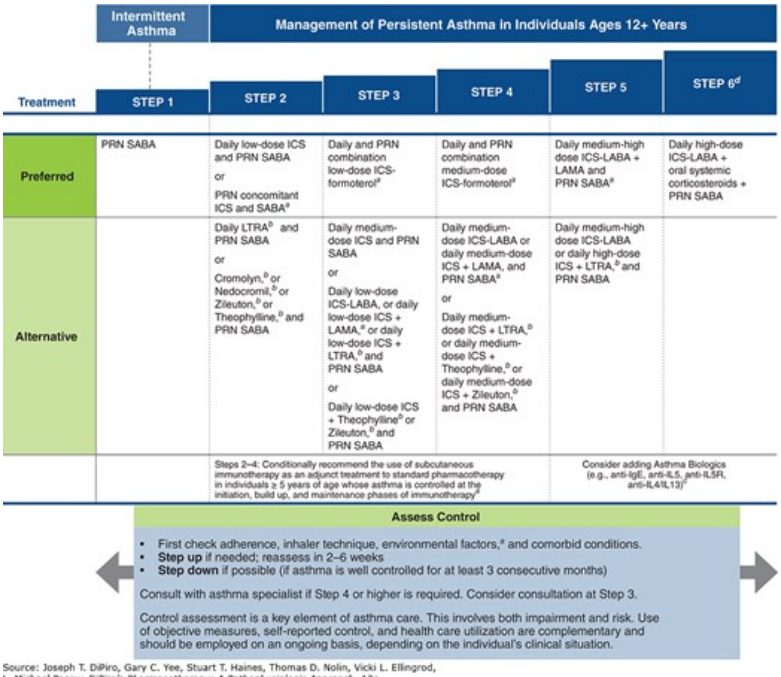
FIGURE 44-5

Stepwise approach for management of asthma in ages 12 years and older. (ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist.) [a]Updated based on the 2020 guidelines. [b]Cromolyn, nedocromil, LTRAs including zileuton and montelukast, and theophylline were not considered for this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that makes their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020. [c]The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (eg, anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6. [d]Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made. *(Data from Reference 11.)*



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The primary therapeutic differences between GINA and the 2020 Asthma Focused Updates are in Steps 1 and 2 therapy for adolescents and adults. For

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adolescents and adults, Step 1 therapy in the 2020 Asthma Focused Updates begins with as-needed rescue therapy (ie, SABA). Step 2 progresses to adding low-dose ICS or as-needed concomitant ICS plus SABA (anti-inflammatory reliever, AIR). GINA, on the other hand, prefers the use of ICS-formoterol taken as-needed in Steps 1 and 2. Both guidelines recommend the use of ICS-formoterol therapy for maintenance and as-needed use, known as Single Maintenance And Reliever Therapy (referred to as SMART in the 2020 Focused Asthma Updates and MART in GINA) as the preferred therapy for Steps 3 and 4 in patients aged 4 years[11] or 6 years[12] and older. Add-on LAMA with ICS-LABA (2020 Asthma Focused Updates and GINA) or MART (GINA) is recommended for Step 5 in patients 12 years and older.

When asthma remains poorly controlled with ICS-LABA with LAMA or SMART with LAMA, the addition of biologics can be considered.[11,12] There are currently no studies that support the selection of one biologic over another other than by criteria included in the labeling (eg, serum IgE or eosinophil levels).

SMART therapy reduces exacerbation rates and corticosteroid use but has inconsistent effects on asthma control and quality of life.[11] SMART therapy has only been used with formoterol as the LABA component due to its rapid onset of action and maximum allowable total daily dose. The maximum formoterol dose in children aged 4 to 11 years for SMART is eight inhalations of 4.5 µg/inhalation (total dose 36 µg formoterol). Budesonide was the inhaled corticosteroid studied in this age group. In patients aged 12 years and older, the SMART maintenance dose is one to two puffs once or twice daily plus a rescue dose of one to two puffs as needed up to a combined maximum of 12 puffs per day (total dose 54 µg formoterol). Importantly, ICS-formoterol (anti-inflammatory reliever - AIR therapy) should not be used concomitantly with ICS-salmeterol maintenance therapy.[11,12]

Although the alternative long-term control therapies (eg, LTRAs and theophylline), used as either monotherapy or concomitantly with ICS, improve symptoms, lung function, and reduce as-needed SABA use, they do not reduce BHR, suggesting minimal anti-inflammatory activity.[11,12] There are minimal to no differences in efficacy between these alternatives.

Other therapies reserved for the treatment of uncontrolled severe asthma after an optimal trial of high-dose ICSs in combination with LABA or LAMA or biologic therapy include bronchial thermoplasty and oral corticosteroids. The GINA guidelines also suggest considering treatment with azithromycin for its anti-inflammatory effects in adults whose asthma is uncontrolled despite higher doses of ICS-formoterol.[12] Due to significant adverse effects that occur with their long-term use, oral corticosteroids are prescribed at the lowest dose that maintains asthma control and administered daily or every other day. Bronchial thermoplasty reduces the airway smooth muscle mass by targeting the hypertrophied smooth muscle in the airways and delivers thermal energy in a controlled manner to the airway wall. This results in a reduced response to bronchoconstrictive stimuli. Bronchial thermoplasty is not recommended in the 2020 Asthma Focused Updates due to the relatively small improvements in asthma control and the moderate risk of harm observed in clinical trials. Moreover, there is an insufficient long-term follow-up in large numbers of patients to adequately assess its benefits and harms.[11] Both guidelines recommend a very careful selection of patients before using bronchial thermoplasty.

Patients with documented allergen sensitization with clinical symptoms can be considered for allergen immunotherapy, given either by subcutaneous injections or sublingually. The 2020 Asthma Focused Updates do not recommend sublingual therapy except in those who also have allergic rhinoconjunctivitis. Data regarding immunotherapy will continue to expand and be reviewed.[11,12] Patients suitable for subcutaneous therapy are those children aged 5 years and older who demonstrate allergic sensitization and adults with allergic asthma who have worsening asthma symptoms temporally related to allergen exposure and who have testing that confirms sensitization. Subcutaneous therapy is not recommended in patients with severe asthma due to the risk of systemic reactions. Subcutaneous treatment must be administered in a setting that is prepared to manage anaphylactic reactions. Sublingual treatment must initially be supervised by health professionals but may be continued at home if there are no systemic adverse effects observed.[11] Because treatment may involve weekly appointments for several years, patients need to carefully consider the burden of treatment before initiating allergy immunotherapy.

GINA provides general principles for stepping-down controller treatments.[12] Step-down therapy is warranted if symptoms have been well controlled and lung function has been stable for at least 3 months (Evidence D). Step-down therapy should only be initiated when the patient is expected to remain stable; for example, at a time when the patient has no evidence of a respiratory infection, will not be traveling, and is not pregnant. When engaging in a trial of treatment step-down, the patient should regularly monitor symptoms and PEF, and a follow-up visit with the provider should be scheduled (Evidence D). Stepping down ICS doses by 25% to 50% at 3-month intervals is considered feasible and safe for most patients (Evidence A).

GINA emphasizes three components of personalized asthma management: ASSESS, ADJUST, and REVIEW RESPONSE.[12] It is important to ASSESS and document symptom control and risk factors at every patient encounter. If symptoms are uncontrolled, check inhaler technique and adherence, and

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consider whether symptoms are due to a comorbid condition such as allergic rhinitis, GERD, or obesity rather than asthma. ADJUST therapy (intensify or de-escalate)—both drug therapy and nonpharmacological strategies; treat modifiable risk factors. REVIEW RESPONSE—assess and optimize asthma control about every 3 months.

Special Populations

Infants and Children Younger Than 5 Years

The management of asthma in children younger than 5 years follows the same stepwise approach as in older children and adults but many treatments have not been studied adequately (Fig. 44-3). Thus, many of the recommendations in this age group are extrapolated from older children and adults.[11,12] Because viral respiratory tract infections are a common cause of wheezing in young children, the 2020 Asthma Focused Updates now recommend starting a short (7-10 day) course of ICS with as-needed SABA at the start of a respiratory tract infection.[11] A suggested regimen is budesonide inhalation suspension, 1 mg, twice daily.[11] The primary differences in chronic management in this age group are that no controller treatment is necessarily indicated for Step 1 and the recommended treatment in Step 3 is doubling the dose of ICS rather than adding LABA as is recommended for older children and adults.[11,12] There is insufficient evidence to recommend ICS-LABA in young children at any step of therapy.[12] Most of the available ICS have been studied in young children but not all have marketing approval from the FDA in this age group. Lack of an approved indication in children younger than 5 years could affect insurance coverage for specific products. ICSs are available as MDI, DPI, and nebulized formulations but the preferred method of delivery is by MDI with a valved spacer and facemask in children younger than 3 years and valved spacer for older children, if needed.[12] Smaller spacers (less than 350 mL) are preferred because 5 to 10 breaths after actuation are required to inhale the complete dose. It is also recommended to not change the spacer type once a child is stable on a specific dose of ICS due to large differences in delivery between devices.[12] ICS use, even with low doses, causes reductions in growth velocity in children who are clinically important.[11,12] Thus, the lowest effective should be used and height should be regularly measured during treatment.[11,12]

The 2020 Asthma Focused Updates now recommends that a short course of daily ICS be initiated at the start of a respiratory tract infection in children who have had three or more episodes of wheezing triggered by presumed respiratory tract infections in their lifetime.[11] Treatment of moderate-to-severe asthma exacerbations may require the use of oral corticosteroids but nebulized budesonide at a dose of 1 mg twice daily for 7 days is effective at preventing exacerbations requiring treatment with oral corticosteroids. This dose did not affect linear growth but higher doses of other ICS (eg, fluticasone 750 µg twice daily for 10 days) may reduce the growth rate.[11] Therefore, the growth rate should be monitored regularly.

The FDA approval for montelukast (an LTRA) in children younger than 6 years was based on safety and pharmacokinetic studies establishing doses but not on efficacy, although improvement in symptoms and as-needed bronchodilators was noted. Montelukast is less effective than ICS in preschoolers with asthma or recurrent wheezing.[12] If montelukast is considered for therapy, parents should be counseled that the FDA has required a boxed warning of the risk of serious mental health side effects; a decision to use montelukast should be based on shared decision making between the provider and caregiver.

Older Adults

Older adults are at the highest risk of dying from asthma due to multiple contributing factors.[4] As in very young children, there have been few prospective studies evaluating drug therapies. In addition, older adults have a high comorbidity burden which may impact response to therapies differently than younger patients, and adherence to treatment can be more challenging when multiple medications for different diseases are prescribed. Control of comorbid conditions (obesity, smoking, depression, and rhinosinusitis) may be required to improve treatment outcomes.[12] Arthritis, vision impairment, and muscle weakness which may affect the inspiratory flow should be considered when selecting inhaler devices.[12] In addition, older adults may have difficulty distinguishing breathlessness due to aging or cardiovascular disease from symptoms of asthma.[12] Given their increased risk of osteoporosis and cataracts, older adults who require high doses of ICSs should have routine height measurements, bone mineral density determinations, and ophthalmic examinations.[12] Appropriate therapies for the prevention of osteoporosis should be instituted.[12] ICS use may contribute to skin bruising in older adults.

Pregnant Women

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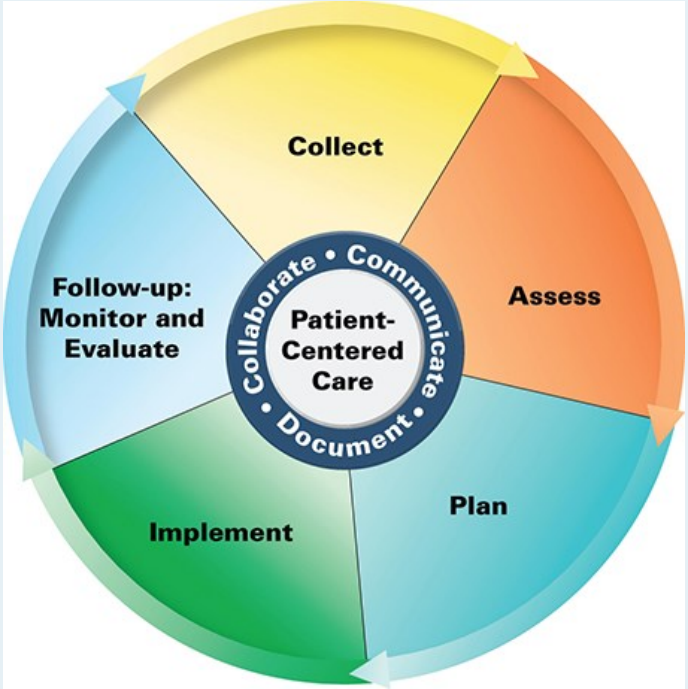
Asthma control may change during pregnancy; either improving or worsening and control may vary during each trimester.[12] Maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants.[12] More severe asthma is associated with increased risks, whereas better-controlled asthma is associated with decreased risks. The advantages of actively treating asthma during pregnancy far outweigh any risks of using ICS or albuterol and these medications are not associated with fetal abnormalities.[12] The safety of the newer biological treatments in pregnancy is unknown. Proper monitoring and control of asthma should enable a woman with asthma to maintain a normal pregnancy with little or no risk to the mother or her fetus. Patients should be monitored monthly to assess asthma control. ICS should not be discontinued in women planning a pregnancy or who are pregnant.[12]

Pregnant women are particularly susceptible to viral infections leading to exacerbations and worsening asthma symptoms. These asthma exacerbations should be aggressively treated to avoid fetal hypoxia.[12] Moderate-to-severe exacerbations should be treated with SABA, oxygen, and early administration of systemic corticosteroids.[12] Hyperventilation during labor may induce bronchoconstriction and should be treated with SABA.[12]

Patient Care Process for the Management of Acute Asthma



Collect

- Initial assessments
  - **A**irway, **B**reathing, **C**irculation
  - If signs of extreme distress, drowsiness, confusion, silent chest → start SABA, oxygen, consult ICU, consider intubation
- Patient characteristics (eg, age, race/ethnicity, sex, pregnancy status)
- Patient history (eg, past medical, known triggers, psychosocial history)
- Past exacerbation history (eg, past need for hospitalization, intensive care, or intubation). History of food allergy
- Current medications and prior response to controller therapies (eg, ICS+/−LABA; montelukast; LAMA; biologic therapies)

Assess

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- Degree of severity of exacerbation—MILD or MODERATE (see Fig. 44-8). Can talk in phrases or sentences
  - Can sit up
  - Not agitated
  - Respiratory rate elevation mild to moderate
  - No sign of accessory muscle use
  - Oxygen saturation 90% to 95% (0.90-0.95)
  - PEF rate>50% of predicted (or previous best)
- Degree of severity of exacerbation—SEVERE (see Fig. 44-8)
  - Can only talk in single words
  - Hunched forward. Agitated
  - Respiratory rate elevation severe (>30/min for adults)
  - Accessory muscle use evidence
  - Oxygen saturation <90% (0.90)
  - PEF rate ≤50% of predicted (or previous best)

Plan and Implement

- If MILD-MODERATE (see Fig. 44-8)
  - Start SABA
  - Consider ipratropium bromide
  - Titrate oxygen to keep 94% (0.94) or higher
  - Oral corticosteroids
- If SEVERE, use a team-based approach to immediately and simultaneously start SABA, oxygen, ICU involvement, and preparation for possible intubation (see Fig. 44-8)
  - Start SABA and ipratropium bromide
  - Titrate oxygen to keep 94% (0.94) or higher; use continuous oximetry and cardiac monitoring
  - IV corticosteroids (consider IV magnesium and high-dose ICS)

Follow-up: Monitor and Evaluate (see Fig. 44-8)

- Assess symptoms frequently
- If continuing deterioration, consider intubation and ICU transfer
- Measure lung function in all patients 1 hour after initial treatment if able
- Disposition

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- If continued signs/symptoms of distress and FEV_1 or PEF minimally improved, <60% predicted or personal best → continue treatment as above and reassess frequently
- If significantly improved clinical signs/symptoms and FEV_1 or PEF improved to 60% to 80% predicted or personal best → consider for discharge planning

General Approach to the Management of Acute Severe Asthma

The primary goal in the treatment of acute severe asthma is to prevent death by recognizing the signs of deterioration and providing rapid treatment. Initial assessment includes history, physical examination, and objective assessments. It is important that therapy not be delayed, so the history and physical examination should be obtained while therapy is being initiated. The brief history will assess for onset and causes of the exacerbation; severity of symptoms and if associated with anaphylaxis; medication use, adherence, and response to current therapy; and risk factors for asthma-related death. Guidance for the self-management of acute asthma exacerbation should be provided to patients and caregivers using a written asthma action plan (Fig. 44-6).[44] This tool provides an individualized plan of action for patients based on symptoms and peak flow measurements. The action to be taken is based on whether the patient is in the green ("doing well"), yellow ("getting worse"), or red ("medical alert") zone.[44] For patients in the yellow or red zones, instructions for rescue treatment, including the dose and frequency, are provided. Most importantly, the asthma action plan should clearly state when to seek emergency care. With the addition SMART in the asthma guidelines, an asthma action plan should account for repeated doses of formoterol when used as-needed in addition to regular maintenance therapy to ensure patient safety.[45] Patients should seek urgent care during an asthma exacerbation if the daily use of ICS-formoterol exceeds the maximum doses of formoterol recommended for chronic asthma management. An example SMART Asthma Action Plan has been published.[45] The asthma-related risk factors for death include a history of near-fatal asthma requiring intubation and mechanical ventilation; hospitalization or emergency care in the past year; current or recent use of oral corticosteroids; no current use of ICSs; poor medication adherence; overuse of SABA therapy (more than one canister per month); history of psychiatric disease or psychosocial problems; lack of a written asthma action plan; food allergy in a patient with asthma; and comorbidities such as pneumonia, diabetes, and arrhythmias.[12]

FIGURE 44-6

Asthma Action Plan. *(Reprinted from National Heart, Lung, and Blood Institute. Digital Toolkit: Asthma Action Plan [updated December 2000].)*

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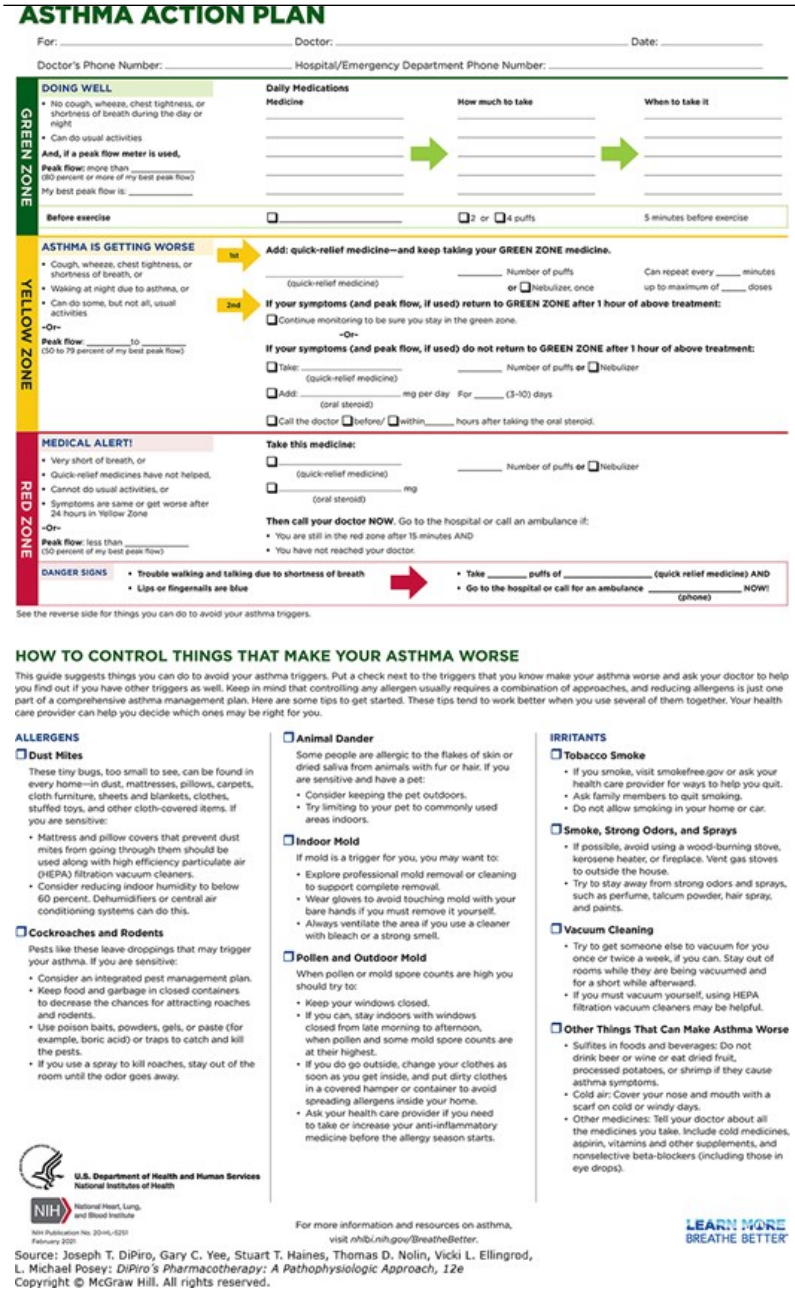

ASTHMA ACTION PLAN

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number: _____ Hospital/Emergency Department Phone Number: _____

GREEN ZONE

DOING WELL
- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____ (80 percent or more of my best peak flow)

My best peak flow is: _____

Daily Medications

Medicine	How much to take	When to take it
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
Before exercise: ☐ _____	☐ 2 or ☐ 4 puffs	5 minutes before exercise

YELLOW ZONE

ASTHMA IS GETTING WORSE
- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)

1st Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer, once — Can repeat every _____ minutes, up to maximum of _____ doses

2nd If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

☐ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

☐ Take: _____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer

☐ Add: _____ (oral steroid) _____ mg per day For _____ (3-10) days

☐ Call the doctor ☐ before/ ☐ within _____ hours after taking the oral steroid.

RED ZONE

MEDICAL ALERT!
- Very short of breath, or
- Quick-relief medicines have not helped,
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____ (50 percent of my best peak flow)

Take this medicine:

☐ _____ (quick-relief medicine) _____ Number of puffs or ☐ Nebulizer

☐ _____ (oral steroid) _____ mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:
- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS
- Trouble walking and talking due to shortness of breath
- Lips or fingernails are blue

- Take _____ puffs of _____ (quick relief medicine) AND
- Go to the hospital or call for an ambulance _____ (phone) NOW!

See the reverse side for things you can do to avoid your asthma triggers.

HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE

This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Keep in mind that controlling any allergen usually requires a combination of approaches, and reducing allergens is just one part of a comprehensive asthma management plan. Here are some tips to get started. These tips tend to work better when you use several of them together. Your health care provider can help you decide which ones may be right for you.

ALLERGENS

☐ Dust Mites

These tiny bugs, too small to see, can be found in every home—in dust, mattresses, pillows, carpets, cloth furniture, sheets and blankets, clothes, stuffed toys, and other cloth-covered items. If you are sensitive:
- Mattress and pillow covers that prevent dust mites from going through them should be used along with high efficiency particulate air (HEPA) filtration vacuum cleaners.
- Consider reducing indoor humidity to below 60 percent. Dehumidifiers or central air conditioning systems can do this.

☐ Cockroaches and Rodents

Pests like these leave droppings that may trigger your asthma. If you are sensitive:
- Consider an integrated pest management plan.
- Keep food and garbage in closed containers to decrease the chances for attracting roaches and rodents.
- Use poison baits, powders, gels, or paste (for example, boric acid) or traps to catch and kill the pests.
- If you use a spray to kill roaches, stay out of the room until the odor goes away.

☐ Animal Dander

Some people are allergic to the flakes of skin or dried saliva from animals with fur or hair. If you are sensitive and have a pet:
- Consider keeping the pet outdoors.
- Try limiting to your pet to commonly used areas indoors.

☐ Indoor Mold

If mold is a trigger for you, you may want to:
- Explore professional mold removal or cleaning to support complete removal.
- Wear gloves to avoid touching mold with your bare hands if you must remove it yourself.
- Always ventilate the area if you use a cleaner with bleach or a strong smell.

☐ Pollen and Outdoor Mold

When pollen or mold spore counts are high you should try to:
- Keep your windows closed.
- If you can, stay indoors with windows closed from late morning to afternoon, when pollen and some mold spore counts are at their highest.
- If you do go outside, change your clothes as soon as you get inside, and put dirty clothes in a covered hamper or container to avoid spreading allergens inside your home.
- Ask your health care provider if you need to take or increase your anti-inflammatory medicine before the allergy season starts.

IRRITANTS

☐ Tobacco Smoke
- If you smoke, visit smokefree.gov or ask your health care provider for ways to help you quit.
- Ask family members to quit smoking.
- Do not allow smoking in your home or car.

☐ Smoke, Strong Odors, and Sprays
- If possible, avoid using a wood-burning stove, kerosene heater, or fireplace. Vent gas stoves to outside the house.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints.

☐ Vacuum Cleaning
- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you must vacuum yourself, using HEPA filtration vacuum cleaners may be helpful.

☐ Other Things That Can Make Asthma Worse
- Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins and other supplements, and nonselective beta-blockers (including those in eye drops).

U.S. Department of Health and Human Services
National Institutes of Health

NIH National Heart, Lung, and Blood Institute

NIH Publication No. 20-HL-5251
February 2020

For more information and resources on asthma, visit nhlbi.nih.gov/BreatheBetter.

LEARN MORE BREATHE BETTER

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
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The physical examination should include the measurement of vital signs and the history to pay careful attention to complicating factors such as anaphylaxis and comorbid conditions that could be causing acute shortness of breath such as an inhaled foreign body, congestive heart failure, pulmonary infection, and pulmonary embolism.[12]

Objective assessments are keys to monitoring response to therapy and should be made before initiation of oxygen or drug treatment. Lung function testing by PEF or FEV_1 should be measured before treatment if possible and thereafter at 1 hour after starting treatment and then periodically until a response is achieved or no further improvement is evident.[12] Oxygen saturation is also monitored closely preferably by pulse oximetry and is a key parameter in young children who may not be able to perform lung function. Arterial blood gases are typically reserved for patients who are poorly responsive to initial treatment or deteriorating. A chest x-ray is rarely indicated unless there are physical signs of other or additional complicating features such as foreign body aspiration.

Oxygen therapy is initiated to achieve an arterial oxygen saturation of 93% to 95% in adolescents and adults and 94% to 98% in school-aged children and pregnant women or those with cardiac disease.[12] Oxygen therapy is continued until the patient has stabilized with continued use of pulse oximetry

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to monitor further oxygen need and response to medications.

The primary therapy of acute exacerbations is pharmacologic, which includes SABA and, depending on the severity, systemic corticosteroids, inhaled ipratropium, intravenous magnesium sulfate, and O_2. Treatments are typically administered concurrently to facilitate rapid improvement.

Serum electrolytes should be monitored in patients who take diuretics regularly and in patients with coexistent cardiovascular disease, as SABA can produce transient decreases in potassium, magnesium, and phosphate. The combination of high-dose β_2-agonists and systemic corticosteroids occasionally may result in excessive elevations of glucose and lactic acid.

The initial response is measured 1 hour after the first three inhaled bronchodilator treatments are administered and provide the best indicator for the need for hospitalization.[12] Indicators for hospitalization typically rely on the degree of respiratory distress, oxygen requirement, and frequency of need for inhaled β_2-agonists. Adjunctive indicators may include an initial FEV_1 less than 25% predicted or PEF that is less than 40% of their personal best, and post-treatment FEV_1 or PEF that is 40% to 60%.[12] Other indicators of severe asthma include monosyllabic speech, inaudible breath sounds, sitting hunched forward, and use of accessory muscles. Patients with lung function that is 40% to 60% predicted may be considered for discharge after assessment of risk factors for death from asthma and the likelihood for follow-up care. Those with higher lung function can be discharged after risk factor and follow-up care assessment.[12]

Discharge planning after an ED visit or hospitalization includes arranging follow-up care within 1 week as well as reviewing strategies to improve asthma management. Referral to a specialist is suggested for those who have been hospitalized or frequently seek care in the ED despite having regular primary care. Strategies for preventing future urgent care visits include ensuring the patient understands the cause of the exacerbation, how to modify risk factors, how to correctly use medications and for what purpose, and having a written asthma action plan that includes self-assessment of worsening symptoms and home PEF values.[12]

Figures 44-7 and 44-8 illustrate the recommended therapies for the treatment of acute asthma exacerbations in-home and ED/hospital settings.[12] Note that Fig. 44-7 is from the GINA guidelines and includes a recommendation to increase the frequency of ICS-formoterol which is not yet standard practice in the United States and is Evidence Grade A. The dosages of the drugs for acute severe exacerbations are provided in Table 44-3.[3,12]

FIGURE 44-7

Self-management of worsening asthma in adults and adolescents with a written asthma action plan. *(© 2022 Global Initiative for Asthma, used with express permission, www.ginasthma.org.)*

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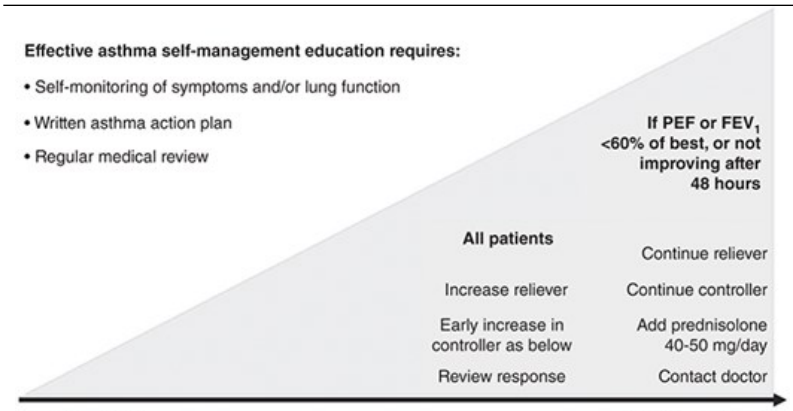

Medication	Short-term change (1-2 weeks) for worsening asthma	Evidence Level
Increase usual reliever:		
Low dose ICS/formoterol[a]	Increase frequency of reliever use (maximum formoterol total 72 mcg/day	A
Short-acting beta2-agonist (SABA)	Increase frequency of SABA use For pMDI, add spacer	A A
Increase usual controller:		
Maintenance and reliever ICS/formoterol[a]	Continue maintenance ICS/formoterol and increase reliever ICS/formoterol as needed[a] (maximum formoterol total 72 mcg/day)	A
Maintenance ICS with SABA as reliever	At least double ICS; consider increasing ICS to high dose (maximum 2000 mcg/day BDP equivalent)	B
Maintenance ICS/formoterol with SABA as reliever	Quadruple maintenance ICS/formoterol (maximum formoterol 72 mcg/day)	B
Maintenance ICS/other LABA with SABA as reliever	Step up to higher dose formulation of ICS/other LABA, or consider adding a separate ICS inhaler (to maximum total 2000 mcg/day BDP equivalent)	D
Add oral corticosteroids (OCS) and contact doctor		
OCS (prednisone or prednisolone)	Add OCS for severe exacerbations (eg, PEF or FEV_1 <60% personal best or predicted), or patient not responding to treatment over 48 hours. Once started, morning dosing is preferable.	A
	Adults: prednisolone 40-50 mg/day (maximum 50 mg) usually for 5-7 days. *Children 6-11 years:* 1-2 mg/kg/day (maximum 40 mg) usually for 3-5 days	D
	Tapering is not needed if OCS are prescribed for <2 weeks	B

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FIGURE 44-8

Management of asthma exacerbations in an acute care facility, for example, the emergency department. To obtain O_2 saturation in SI units (fraction) multiply the results expressed as a percentage by 0.01. *(© 2022 Global Initiative for Asthma, used with express permission, www.ginasthma.org.)*

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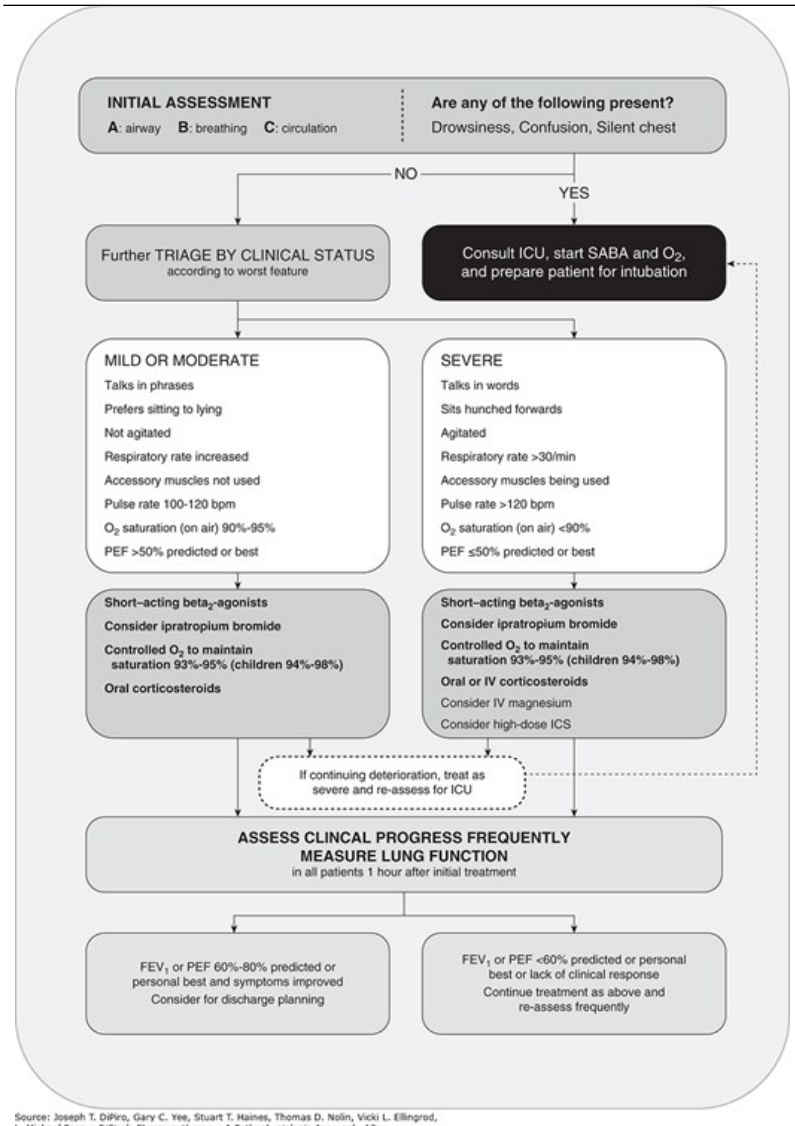

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TABLE 44-3

Dosages of Drugs for Treatment of Acute Severe Exacerbations of Asthma

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	Dosages		
Medications	**≥12 Years Old**	**<12 Years Old**	**Comments**
Inhaled β-Agonists			
Albuterol nebulizer solution (5 mg/mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL)	2.5-5 mg every 20 minutes for three doses, and then 2.5-10 mg every 1-4 hours as needed, or 10-15 mg/hr continuously if in the emergency department or hospitalized	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses, and then 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed, or 0.5 mg/kg/hr by continuous nebulization if in the emergency department or hospitalized	Only selective β_2-agonists are recommended. For optimal delivery, dilute aerosols to a minimum of 4 mL at gas flow of 6-8 L/min. Use face mask if <4 years
Albuterol MDI (90 µg/puff)	4-8 puffs every 30 minutes up to 4 hours, and then every 1-4 hours as needed	4-8 puffs every 20 minutes for three doses, and then every 1-4 hours as needed	In patients in severe distress, nebulization is preferred; use a VHC-type spacer with face mask if <4 years old
Levalbuterol nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 2.5 mg/1 mL, 1.25 mg/3 mL)	Give one-half the milligram dose of albuterol above	Give one-half the milligram dose of albuterol above	The single isomer of albuterol is twice as potent on a milligram basis Not recommended
Levalbuterol MDI (45 µg/puff)	See albuterol MDI dose above	See albuterol MDI dose above	See albuterol MDI dose one-half as potent as albuterol on a microgram basis Not recommended
Anticholinergics			
Ipratropium bromide nebulizer solution (0.25 mg/mL)	500 µg every 30 minutes for three doses, and then every 2-4 hours as needed	250 µg every 20 minutes for three doses, and then 250 µg every 2-4 hours	May mix in the same nebulizer with albuterol; only add to β_2-agonist therapy
Ipratropium bromide MDI (18 µg/puff)	8 puffs every 20 minutes as needed for up to 3 hours	4-8 puffs as needed every 2-4 hours	Not to be continued once hospitalized
Corticosteroids[a]			
Prednisone, methylprednisolone, prednisolone	50 mg in one or two divided doses (prednisone equivalent)	1 mg/kg (maximum 40 mg/day) in two divided doses (prednisone equivalent)	For outpatient "burst" use 1-2 mg/kg/day, maximum 60 mg, for 3-5 days in children and 40-60 mg/day in one or two divided doses for 5-7 days in adults

[a]No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for IV administration over oral therapy. The

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usual regimen is to continue the oral corticosteroid for the duration of hospitalization. The final duration of corticosteroid therapy for an acute exacerbation may be from 3 to 10 days. If patients are then started on ICSs, there is no need to taper the systemic corticosteroid dose. ICSs can be started at any time during the exacerbation.

Data from Reference 3.

Special Populations

Infants and Children Under 5 Years Old

Infants and children younger than 5 years of age may be at greater risk of respiratory failure than older children and adults. Although treated with the same drugs, these younger children require the use of a pressurized MDI with a spacer or face mask as opposed to a mouthpiece for delivery of aerosolized medication. The face mask should be sized appropriately and should fit snugly over the nose and mouth. The pressurized MDI with spacer is preferred over a nebulizer because of its greater effectiveness and nebulizers can spread infectious particles.[12]

Children with severe exacerbations present with oxygen saturation of 92% (0.92) or less, speak in monosyllabic words, and have increased heart rate (above 180 beats/min if 0-3 years or above 150 beats/min if 4-5 years), central cyanosis, and inaudible breath sounds which indicate minimal ventilation sufficient to cause wheezing.[12] Hypoxemia is treated with oxygen to achieve oxygen saturation of 94% to 98% (0.94-0.98). Avoidance of hypoxemia is critical and treatment should be initiated with nebulized β_2-agonists delivered by an oxygen-driven nebulizer. Treatment should begin immediately even if a full assessment has not been taken. Initial SABA treatment is two puffs of albuterol, or if the exacerbation is severe, six inhalations of albuterol with a spacer/facemask. Treatment with 2 to 6 puffs of albuterol (severity dependent) may be repeated every 20 minutes for three doses with reassessment at the end of this treatment. Subsequent doses by nebulizer or two to three inhalations by spacer/facemask can be given every hour, but if symptoms do not resolve after 10 inhalations administered over 3 to 4 hours then a hospital admission is advised.[12] For nebulizer therapy, a dose of 2.5 mg albuterol every 20 minutes for 1 hour is administered and appropriate infection control measures must be followed.[12] Ipratropium bromide 1 to 2 puffs by pressurized MDI and spacer or nebulizer (250 µg) can be administered concurrently with albuterol during the first hour only.[12] Oral corticosteroids are administered at the time of inhaled β_2-agonists or intravenously in children unable to swallow.

Nebulized magnesium sulfate may be administered as three doses in the first hour in children aged 2 years and older with severe exacerbations.[12] As in older children and adults, young children should be discharged with a prescription for oral corticosteroids for a 3- to 5-day treatment course and followed up within 7 days by a primary care provider.

Nonpharmacologic Therapy

Chronic Asthma

Although the mainstay of the management of asthma is pharmacologic therapy, it is likely to fail without concurrent attention to relevant environmental control and management of comorbidities that may contribute to respiratory symptoms and poor quality of life. Nonpharmacologic therapies are incorporated into GINA's recommendations for initiation of regular daily controller treatment, as well as the stepwise approach for adjusting treatment in adults, adolescents, and children.[11,12] The guidelines were designed to give healthcare providers a framework with which to develop the proper approach to the individualized therapy of patients. The heterogeneity of asthma demands an individualized approach to therapy with the basic goals of therapy as primary outcome measures.[11,12] The focus of controller therapy is the reduction of airway inflammation, control of symptoms, and reduction of future risks. Thus, current therapeutic options in asthma consist of acute reliever (rescue) medications for as-needed relief of breakthrough symptoms and exacerbations, and long-term control medications used for the prevention of symptoms and exacerbations and the suppression of inflammation and reduction of BHR.[11,12] Guidelines emphasize the importance of concurrently identifying and treating modifiable risk factors, such as active smoking and exposure to tobacco smoke, obesity, major psychological problems, major socioeconomic problems, confirmed food allergy, and allergen exposure if sensitized.[11,12] Occupational exposures, indoor allergens, and medications that may make asthma worse and should be evaluated when relevant.

In patients with known allergic triggers for their asthma, allergen avoidance has resulted in an improvement in symptoms, a reduction in medication use, and a decrease in BHR.[11] A multicomponent approach to environmental control is recommended in the 2020 Asthma Focused Updates because

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single-component interventions often are ineffective at improving asthma control.[11] Interventions should be tailored for individuals who have symptoms and/or positive allergy tests and who are exposed to specific allergens.[11] The 2020 Asthma Focused Updates provide a comprehensive evaluation of allergen mitigation strategies.[11] Some long-standing practices such as the use of acaricides to remove dust mites, carpet removal, use of air filtration systems, and purifiers are not effective even when included in a multi-component strategy.[11] However, if a home has pests (eg, cockroaches and mice) or a mold problem, a single component strategy to address the problem is warranted.[11] The use of HEPA vacuum cleaners, particularly for children, and impermeable pillow and mattress covers are recommended as part of a multicomponent strategy.[11]

Allergen-specific immunotherapy as either subcutaneous injections or sublingual administration is discussed in the section "General Approach to the Management of Chronic Asthma." Allergen treatment should be directed to specific allergens to which the patient has documented sensitivity. The 2020 Asthma Focused Updates only recommends subcutaneous therapy for asthma management which may improve symptom scores and reduce medication use in patients with documented allergen sensitivity.[11] In addition, it may have a disease-modifying effect and reduce clinical asthma severity over time.[11] The efficacy of multiple-allergen (vs single-allergen) subcutaneous immunotherapy is an area identified for future study.[11] The burden of frequent healthcare visits for immunotherapy administration must be considered before starting therapy as treatment will need to be continued for several years before there is sustained improvement in symptoms.

Acute Asthma

Infants and young children may be mildly dehydrated owing to increased insensible loss, vomiting, and decreased intake.[46] Unless dehydration has occurred, increased fluid therapy is not indicated in acute asthma management because the capillary leak from cytokines and increased negative intrathoracic pressures may promote edema in the airways.[46] Correction of significant dehydration is always indicated, and the physical examination and urine specific gravity may help to guide therapy in young children, in whom the state of hydration may be difficult to determine.

Oxygen therapy is the primary nonpharmacologic therapy for the management of acute asthma and is discussed in the section "General Approach to the Management of Acute Severe Asthma." Sedatives should not be given because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants.[46] Antibiotics are also not indicated routinely because viral respiratory tract infections are the primary cause of asthma exacerbations.[46] Antibiotics should be reserved for patients who have signs and symptoms of pneumonia (eg, fever, pulmonary consolidation, and purulent sputum from polymorphonuclear leukocytes).

Respiratory failure or impending respiratory failure as measured by rising $PaCO_2$ (greater than or equal to 45 mm Hg [6 kPa]) or failure to correct hypoxemia with supplemental O_2 therapy is treated first with noninvasive ventilation and eventually with intubation and mechanical ventilation if needed. Oral intubation facilitates secretion removal and bronchoscopy and decreases airway resistance.[47] Heavy sedation and neuromuscular blockade may be needed to reduce ventilatory dyssynchrony in order to improve lung volume and respiratory rate.[47] Oxygen consumption, CO_2 production, and lactate accumulation may be mitigated by using neuromuscular blockade in mechanically ventilated patients.[47]

Patient Education

7 The development of a patient–healthcare provider partnership in care through patient education and the teaching of patient self-management skills should be the cornerstone of any treatment program.[12] There are a number of published self-management programs for children and adults available through the American Lung Association, Asthma and Allergy Foundation of America, asthma treatment centers, and the guidelines from NAEPP and GINA. Asthma self-management programs have been shown to improve patient adherence to medication regimens, self-management skills, and use of healthcare services.[12]

Self-management programs instruct patients in the pathogenesis of asthma and the appropriate use of their medications (including the rationale for treatment and why controllers and relievers are needed), teach patients to recognize triggers for their asthma and early signs of deterioration, how to keep track of symptoms (with or without a diary), and take action.[12] Short-term home PEF monitoring can be used following an exacerbation to assess response to treatment, determine if symptoms seem excessive, assess a baseline for asthma action plans, or evaluate triggers (such as occupational triggers) and is typically recorded for a few weeks.[12] Longer-term PEF monitoring is generally only recommended for those patients with a history of

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sudden severe asthma exacerbations, difficult-to-control severe asthma, or poor symptom perception.[12]

The NAEPP has recommended a PEF monitoring system or symptom-based action plan using a traffic light scenario (based on a percentage of normal predicted values or personal best values): the green zone is equal to 80% to 100%, the yellow zone is equal to 50% to 79%, and the red zone is less than 50%. The yellow zone is cautionary and requires increasing as-needed bronchodilator use and possibly beginning prednisone if not improved, whereas the red zone warrants contacting the patient's healthcare provider.[44] Samples of clinically tested written action plans that are PEF or symptom-based are available from NAEPP and other sources.[44]

Patient education is essential before monitoring can be effective. It is successful regardless of the healthcare provider who provides it. The NAEPP and GINA advocate significant involvement of all points of patient care in the educational process. The provision of written action plans enhances the success of education and is considered an essential component of care.

Pharmacologic Therapy

β_2-Agonists

The β_2-agonists are highly effective bronchodilators. β_2-Agonists do not inhibit the late asthmatic response to allergen challenge or the subsequent BHR. Long-term administration of β_2-agonists does not reduce BHR, confirming a lack of significant anti-inflammatory activity. β_2-Adrenergic stimulation also activates Na^+-K^+-ATPase, produces gluconeogenesis, and enhances insulin secretion, resulting in a mild-to-moderate decrease in serum potassium concentration by driving potassium intracellularly. The chronotropic response to β_2-agonists is mediated in part by baroreceptor reflex mechanisms as a result of the drop in blood pressure from vascular smooth muscle relaxation, as well as by direct stimulation of cardiac β_2-receptors and some β_1 stimulation at high concentrations.

Table 44-4 compares the various short-, long-, and ultra-long-acting β-adrenergic agonists used in asthma in terms of onset and duration of action.[48] The β_2-agonists are functional or physiologic antagonists, in that they relax airway smooth muscle regardless of the mechanism for constriction. When administered in equipotent doses, all the short-acting drugs produce the same intensity of response; the only differences are in duration of action and cardiac toxicity.[48] Of note, using a potent CYP3A4 (eg, ritonavir) with a β_2-agonists (specifically salmeterol or vilanterol) may increase cardiac toxicity and may warrant a therapeutic change. All the β_2-agonists are more bronchoselective when administered by the aerosol route. Aerosol administration of a SABA provides more rapid response and greater protection against provocations that induce bronchospasm, such as exercise and allergen challenges, than does systemic administration.[48]

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TABLE 44-4

Onset and Duration of Action of β-Adrenergic Agonists

	Onset and Duration of Action[a]		
Agent	**Bronchodilation (hours)**	**Protection (hours)[a]**	**Onset of bronchodilation**
SABA			
Albuterol/levalbuterol	4-8	2-4	1-2 minutes
Terbutaline	4-6	2-4	1-2 minutes
LABA			
Formoterol	≥12	≥12	1-2 minutes
Salmeterol	≥12	≥12	10 minutes
Ultra-LABA			
Indacaterol	≥24	≥24	1-2 minutes
Olodaterol	≥24	≥24	1-2 minutes
Vilanterol	≥24	≥24	1-2 minutes

[a]Protection refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.

Both the intensity and duration of response to β_2-agonists are dose-dependent, and, more important, the dose-response relationship is dynamic. At increasing levels of baseline bronchoconstriction (irrespective of the stimulus), the dose-response curve is shifted to the right, and the duration of bronchodilation is decreased. This shift is reflected in the need for higher, more frequent doses in acute asthma exacerbations; the duration of protection against significant provocation is much less than the duration of bronchodilation in chronic stable asthma for short-acting inhaled β_2-agonists (see Table 44-4).[48]

Chronic administration of β_2-agonists leads to downregulation (decreased number of β_2-receptors) and a decreased binding affinity (desensitization) for these receptors.[48] Systemic corticosteroid therapy can both prevent and partially reverse this phenomenon. However, the use of ICSs has minimal ability to prevent tolerance to β_2-agonists.[48] Tolerance primarily reduces the duration of bronchodilation as opposed to diminishing the peak response, although the latter can occur as well. A significantly greater tolerance develops in other tissues (eg, lymphocytes and cardiac and skeletal muscle) compared with the lung, primarily as a result of the surplus β_2-receptors found in respiratory smooth muscle. Tolerance to the extra-pulmonary effects (cardiac stimulation and hypokalemia) may account for a lack of significant cardiac effects despite chronic inhaled β_2-agonist therapy. Thus, chronic β_2-agonist administration produces a tolerance that can be easily overcome by increasing the dose or by administering systemic corticosteroids. Most of the tolerance occurs within 1 to 2 weeks of regular administration and does not worsen with continued administration. As would be expected from a receptor phenomenon, cross-tolerance to all β_2-agonists develops.

Short-Acting β_2-Agonists

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4 The short-acting inhaled β_2-agonists are highly effective bronchodilators and the treatment of first choice for the management of acute severe asthma.[12] In adults, administration as either continuous nebulization in a large volume nebulizer or intermittent administration (every 20 minutes for three doses) over 1-hour results in equivalent improvement.[12] Systematic reviews of continuous versus intermittent SABA in severe acute asthma have conflicting findings.[12] There is no role for intravenous β_2-agonists in patients with severe asthma (Evidence A).[12] Effective doses of aerosolized β_2-agonists can be delivered successfully through mechanical ventilator circuits to infants, children, and adults in respiratory failure secondary to severe airway obstruction.

The doses of inhaled β_2-agonists for acute severe asthma exacerbations (see Table 44-3) have been derived empirically. The β_2-agonists follow a log-linear dose-response curve. In addition, the dose-response curve is shifted to the right by more severe bronchospasm or by increased concentrations of bronchospastic mediators, which is characteristic of functional antagonists. The ability to increase the dose of SABA by as much as 5- to 10-fold over doses producing adequate bronchodilation in chronic stable asthma is what contributes to their efficacy in reversing the bronchospasm of acute severe exacerbations. The nebulizer dose of inhaled β_2-agonists for children often is listed on a weight basis (milligrams per kilogram). The preferred method from both an efficiency and economic perspective with an MDI and spacer.[12]

The inhaled β_2-agonists produce similar efficacy whether delivered by MDI plus valved holding chamber (VHC) or nebulization in treating acute severe exacerbations in the ED and hospital. The preferred choice is an MDI with a valved spacer, particularly considering the risk of spreading infectious viral particles via nebulization.[12] Most DPIs are not used for acute severe asthma exacerbations due to the higher inspiratory flows required for adequate drug delivery.[12]

Unlike in children, nebulized albuterol is administered in adults in a fixed-dose (vs. a weight-based dose) in order to avoid excessive cardiac stimulation.[3] Conversely, children younger than 5 years are dosed based on weight and should have a fixed minimal dose (2.5 mg albuterol or equivalent) due to the resultant underdosing when weight-based dosing is used; higher doses (up to 10 mg based on weight) can be administered every 1 to 4 hours as needed (Table 44-3). Initial doses of inhaled β_2-agonists can produce vasodilation, worsening ventilation-perfusion mismatch, slightly lowering O_2 saturation or PaO_2.[12] High doses of inhaled β_2-agonists can produce a decrease in serum potassium concentration, an increase in heart rate, and an increase in serum glucose and lactic acid concentration. Electrolyte monitoring may be needed in patients with preexisting heart disease who receive frequent doses for an acute exacerbation.[9] Both children and adults receiving continuously nebulized β_2-agonists (not a recommended treatment)[12] have demonstrated decreased heart rate as their lung function improves which indicates elevated heart rate is not an indication to use lower doses or to avoid using inhaled β_2-agonists.

β_2-Agonists can exist as racemic mixtures (eg, albuterol, salmeterol, formoterol) or as single enantiomers (eg, levalbuterol, indacaterol, olodaterol, vilanterol). There is no evidence to support the use of levalbuterol over albuterol for the treatment of acute severe exacerbations in either children or adults with respect to efficacy or adverse effects.[49]

Primatene Mist® MDI is the only inhaled asthma medication available without a prescription and was reintroduced onto the market in late 2018 as an MDI with a hydrofluoroalkane propellant. Primatene Mist® should only be used for the temporary relief of mild symptoms of intermittent asthma in patients 12 years and older. If improvement is not seen within 20 minutes or symptoms become worse, or the patient requires more than eight inhalations in a 24-hour period or has a recurrence of symptoms within a week, the patient should see a physician for additional evaluation and treatment. Primatene Mist® is less effective than prescription SABAs.

A SABA is also indicated for the as-needed treatment of intermittent episodes of bronchospasm. They inhibit EIB in a dose-dependent fashion and provide complete protection for a 2-hour period following inhalation with varying levels of patient-dependent protection over 4 hours.[12] Although the regular administration of β2-agonists slightly decreases the protective effect, two inhalations prior to exercise still essentially block EIB completely (1% vs 5% drop in FEV_1).[12] The GINA guidelines also recommend low-dose ICS-formoterol taken before exercise but this treatment is not recommended by NAEPP.[11,12]

Long-Acting and Ultra Long-Acting Inhaled β_2-Agonists

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The two LABAs, formoterol and salmeterol, provide long-lasting bronchodilation (greater than or equal to 12 hours) and are dosed twice daily[50] (see Table 44-4). Formoterol, in combination with an ICS, may be dosed on a daily and as-needed basis (thus, more frequently than twice daily). Unlike the more water-soluble SABA, the long-acting agents are lipid-soluble, readily partitioning into the outer phospholipid layer of the cell membrane.[50] In addition, ultra-LABAs (indacaterol, vilanterol, and olodaterol) have a 24-hour bronchodilator duration of effect permitting once-daily dosing. Only vilanterol in combination with fluticasone furoate (with and without umeclidinium, an anticholinergic) is available for once-daily dosing for asthma in adults aged 18 years and older in the United States. Products containing indacaterol and olodaterol are only indicated for COPD but are being evaluated for asthma.

The LABAs and ultra-LABAs are more β_2-selective than albuterol and more bronchoselective by virtue of their property of remaining in the lung tissue cell membrane, which produces its longer duration.[50] The onset of action (time required to increase FEV_1 by 12% over baseline) is similar to that of albuterol for LABAs and ultra-LABAs with the exception of salmeterol which has an onset of approximately 10 minutes. LABAs are available as a single entity and as fixed-dose combinations with ICSs (see below) though single-entity LABA products are FDA-approved for use only with ICS. Patients need to be counseled to continue to use their SABA for acute exacerbations while receiving the ICS/LABA combination products, unless they are using SMART (ICS-formoterol).

As with SABA, tolerance can occur with chronic administration of LABAs and seems to plateau after about 1 week of regular therapy but response recovers rapidly after only 2 to 3 days of non-use.[50] Long-term trials have shown no diminution in bronchodilator response but a partial loss of the bronchoprotective effect against methacholine, histamine, and exercise challenge.[50] These effects do not seem to have a significant impact on the quality of asthma control with chronic daily use.

Concern for risks with LABA use began shortly after approval of the first available LABA, salmeterol, with reports of respiratory deaths in salmeterol users, and risks were evaluated in multiple meta-analyses which resulted in Boxed Warnings on the labeling of products containing an ICS-LABA.[12] In response to these findings, the FDA mandated several large clinical trials by the manufacturers to evaluate the risk of ICS-LABA therapy on serious asthma-related adverse effects. The results of these trials which included over 41,000 patients aged 12 years and older, and a single trial in children 4 to 11 years old, indicate that there is no significantly increased risk of asthma-related hospitalizations, intubations, or asthma-related deaths with ICS-LABA compared to ICS; the FDA has removed the Boxed Warning for ICS-LABA products but has retained it for single-ingredient LABA products.[51]

Corticosteroids

4 Corticosteroids are the most effective anti-inflammatories available to treat asthma.[11,12] Actions useful in treating asthma include: (a) increasing the number of β_2-adrenergic receptors and improving the receptor responsiveness to β_2-adrenergic stimulation, (b) reducing mucus production and hypersecretion, (c) reducing BHR, and (d) reducing airway edema and exudation. The glucocorticoid receptor is found in the cytoplasm of most body cells, explaining the multiple effects of systemic corticosteroids. There is no difference between glucocorticoid receptors found throughout the body; however, genetic differences in the glucocorticoid receptor among individuals may explain some of the variations in response.[52] The corticosteroids are lipophilic, readily cross the cell membrane, and combine with the glucocorticoid receptor. The activated glucocorticoid receptor complex then enters the nucleus, where it acts as a transcription factor leading to gene activation or suppression.[52] This leads to specific mRNA production, resulting in increased production of anti-inflammatory mediators and suppression of genes regulating the expression of several pro-inflammatory cytokines such as tumor necrosis factor-α, GM-CSF, interferon-γ, IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, and IL-13.[52] In addition, the activated glucocorticoid receptor complex can act directly with transcription factors, nuclear factor-κB, and activating protein 1 to prevent the action of pro-inflammatory cytokines on the cell.[52]

Given that glucocorticoids work by altering gene expression, the time required to see a particular effect depends on the time required for new protein synthesis, decreased formation of the particular mediator, and resolution of the inflammatory response. While the cellular and biochemical effects are immediate, variable amounts of time are required to produce a clinical response. β_2-Receptor density increases within hours of corticosteroid administration leading to improved responsiveness to β2-agonists. In acute severe asthma, 3 to 8 hours may be required before any clinical response is noted.[53] The chronic use of corticosteroids does not induce a state of corticosteroid dependence and there is no evidence of tolerance produced by chronic administration.

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The systemic and inhaled corticosteroids most commonly used in the treatment of asthma are compared in Table 44-5.[53,54] The pharmacokinetic and pharmacodynamic parameters (receptor binding affinity, bioavailability, clearance) influence the therapeutic index of inhaled corticosteroids. Higher receptor binding affinities and longer half-lives contribute to both improved efficacy but also increase the potential for systemic adverse effects. These factors affect the relative efficacy between products and thus may influence treatment decisions.

TABLE 44-5

Pharmacodynamic/Pharmacokinetic Comparison of the Corticosteroids

Systemic	Anti-inflammatory Potency	Mineralocorticoid Potency	Duration of Biologic Activity (hours)
Hydrocortisone	1	1	8-12
Prednisone	4	0.8	12-36
Methylprednisolone	5	0.5	12-36
Dexamethasone	25	0	36-72
	Receptor Binding Affinity[a]	**Oral Bioavailability (%)**	**Systemic Clearance (L/hr)**
Beclomethasone dipropionate/monoproprionate[b]	0.4/13.5	20/40	150/120
Budesonide	9.4	11	84
Ciclesonide/des-ciclesonide[b]	0.12/12	<1/<1	152/228
Flunisolide	1.8	20	58
Fluticasone proprionate	18	≤1	66
Mometasone furoate[c]	23	<1	53

[a]Receptor binding affinities are relative to dexamethasone equal to 1.

[b]Beclomethasone diproprionate and ciclesonide are prodrugs that are activated in the lung to their active metabolites beclomethasone monopropionate and des-ciclesonide, respectively.

[c]Mometasone furoate was studied in a different receptor system. Value estimated from relative values of beclomethasone dipropionate and fluticasone proprionate in that system.

Systemic Corticosteroids

Systemic corticosteroids are indicated in all patients with acute severe asthma exacerbations not responding completely to initial SABA administration (every 20 minutes for three doses) and should be administered within 1 hour of presentation to reduce the risk of hospitalization.[12] Clinical improvement is noted after approximately 4 hours.[12] IV therapy offers no therapeutic advantage over oral administration except in patients who are

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too dyspneic to swallow, vomiting, or intubated.[12] This therapy usually is continued until hospital discharge. There is no need to taper the systemic corticosteroid dose following discharge from the hospital in patients who are prescribed an ICS for outpatient therapy (Evidence B).[12] Adults are effectively treated with a 5- to 7-day course of therapy but children typically require only 3-5 days (Evidence A).[12] Very short courses (3-5 days) are effective in reducing hospitalization from acute exacerbations.[12] Use of the shorter-acting corticosteroids such as prednisone will produce less adrenal suppression than the longer-acting dexamethasone.[12] Dexamethasone for 1 or 2 days versus a 5-day course of prednisone/prednisolone may be an option for children and has the benefit of causing less vomiting.[12] If there is an inadequate response to dexamethasone, switching to prednisone should be considered.[12] Multiple daily dosing of systemic corticosteroids for the initial therapy of acute asthma exacerbations is warranted because receptor binding affinities of lung corticosteroid receptors are decreased in the face of airway inflammation. However, patients with less-severe exacerbations may be treated adequately with once-daily administration.[2]

The beneficial and adverse effects of corticosteroids in asthma are dose- and duration-dependent. Adverse effects can occur in adults and children even after a short duration (<14 days) of therapy. In adults, there is an increased risk of 1.8- to 5.3-fold in fracture, gastrointestinal bleeding, sepsis, venous thromboembolism, and heart failure (the only adverse events evaluated) in the 30 days following a short course of systemic corticosteroids.[55,56] A similar pattern is observed in children with a 1.8- to 2.2-fold increased risk in gastrointestinal bleeding, sepsis, and pneumonia.[57] Adverse effects of chronic daily use of oral corticosteroids are well known (Table 44-6). The clinician must continually balance the toxicity of chronic systemic corticosteroid therapy with the control of asthma symptoms. The ideal use is to administer the systemic corticosteroids in a short "burst" (<7 days) and then to maintain the patient on appropriate long-term control therapy with ICSs.[12]

TABLE 44-6

Adverse Effects of Chronic Systemic Glucocorticoid Administration

Hypothalamic-pituitary-adrenal suppression	Hypertension
Growth retardation	Skin striae
Skeletal muscle myopathy	Impaired wound healing
Osteoporosis/fractures	Inhibition of leukocyte and monocyte function
Aseptic necrosis of bone	Subcutaneous tissue atrophy
Pancreatitis	Glaucoma
Pseudotumor cerebri	Posterior subcapsular cataracts
Psychiatric disturbances	Moon facies
Sodium and water retention	Central redistribution of fat
Hypokalemia/hyperglycemia	

Inhaled Corticosteroids

The principal advantage of the ICSs is their high topical potency to reduce inflammation in the lung and low systemic activity.[53] The ICSs have high receptor binding affinity which is related to potency, and ICS products differ from each other in binding affinity by as much as 10- to 100-fold.[53] However, potency differences can be overcome simply by giving different microgram dosages of the drug (Table 44-5). Depending upon the microgram per inhalation, the potency differences between products will be reflected by the number of inhalations required to achieve the same therapeutic effect. Products that require more inhalations per dose or that must be administered twice daily may result in poorer adherence.

In the low-to-medium doses recommended (Tables 44-7 and 44-8), ICSs are safe for long-term administration. They do not reduce airway remodeling or prevent the loss of lung function seen in some patients with persistent asthma.[58] ICS therapy does not prevent the development of asthma in high-risk infants or induce asthma remission as BHR and other measures of inflammation return to pretreatment levels soon after the discontinuation of therapy.[12] The sensitivity and consequent clinical response to ICSs can vary among patients.[11,12]

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TABLE 44-7

Inhaled Corticosteroids and Comparative Daily Dosages in Adults and Adolescents (12 Years and Older)

	Comparative Daily Dosages (µg) of Inhaled Corticosteroids		
	Low Dose	**Medium Dose**	**High Dose**
Beclomethasone dipropionate DPI[a]	80-240	>240-480	>480
Budesonide DPI	180-540	>540-1,080	>1,080
Budesonide Nebules	unknown	unknown	unknown
Ciclesonide HFA[b] MDI[c]	160-320	320-640	>640
Flunisolide HFA MDI	320	320-640	>640
Fluticasone furoate DPI		100	200
Fluticasone propionate HFA MDI	888-264	264-440	>440
Fluticasone propionate DPI	100-300	300-500	>500
Mometasone furoate DPI	110-220	>220-440	>440

[a]Dry powder inhaler.

[b]Hydrofluoroalkane

[c]Metered-dose inhaler.

Data from Reference 59.

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TABLE 44-8

Inhaled Corticosteroids and Comparative Daily Dosages in Children (6 to 11 Years)

	Comparative Daily Dosages (µg) of Inhaled Corticosteroids		
	Low Dose	**Medium Dose**	**High Dose**
Beclomethasone DPI[a] dipropionate DPI[a]	80-160	>160-320	>320
Budesonide DPI	180-360	>360-720	>720
Budesonide Nebules	500	1,000	2,000
Ciclesonide HFA[b] MDI[c]	80-160	>160-320	>320
Flunisolide HFA MDI	160	320	>320
Fluticasone furoate DPI		100	200
Fluticasone propionate HFA MDI	88-176	176-352	>352
Fluticasone propionate DPI	100-200	200-400	>400
Mometasone furoate DPI	110	220-440	>440

[a]Dry powder inhaler.

[b]Hydrofluoroalkane.

[c]Metered-dose inhaler.

Data from Reference 59.

Aerosol delivery of the corticosteroid is variable and is influenced by the nominal dose from the specific device (eg, that dose that leaves the actuator) and any device attached to MDIs to improve inhalation technique. Different devices which contain the same chemical entity may result in twofold differences in delivery. Thus, the delivery method can make a significant difference in the relative dose or therapeutic index.[12]

All ICSs are approved for once- or twice-daily dosing. The ICSs have pharmacokinetic differences that result in different topical/systemic activity.[53] Most evidence is consistent with log-linear dose-response curves for both indirect (measures to assess efficacy such as lung function, BHR, symptom control) and direct responses (receptor activity). The log-linear nature of the dose-response curve for ICS clinical effects makes dose-response relationships for efficacy difficult to establish. Alternatively, comparative potency effects may be based upon the dose-response adverse effects on hypothalamic-pituitary-adrenal axis suppression.[53] Comparable ICS doses (see Tables 44-3 and 44-4) are based on extensive clinical trial data.[12] Clinically comparable doses take into consideration drug potency differences as well as device delivery differences but not the potential for systemic activity and potential adverse effects.

Because the glucocorticoid receptors within the various tissues are the same, differences in the pharmacokinetic profile are required to produce differences in the topical/systemic effect ratio (therapeutic index).[53] Pharmacokinetic properties that enhance topical selectivity include higher potency, rapid systemic clearance, poor oral bioavailability, and prolonged residence time in the lung.[53] Due to their high lipophilicity, systemic clearance of the available ICSs is very rapid, approaching the rate of liver blood flow with the exception of beclomethasone diproprionate and ciclesonide, which are prodrugs metabolized in the lung by esterases to the active compounds, beclomethasone monopropionate, and des-

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ciclesonide.[53] However, the ICSs differ markedly in their oral bioavailability, although they all undergo rather extensive first-pass metabolism to less active substances when absorbed.[53] The ICSs produce dose-dependent systemic effects, contributed by the orally absorbed fraction and the fraction absorbed from the lung. (Table 44-9). Essentially, all the drug that reaches the lung is absorbed systemically; thus, a slow absorption from the lung results in an apparent long elimination half-life and enhances topical selectivity by lowering the systemic concentration. The potential advantage of the drugs with low oral bioavailability is obviated by using an MDI plus spacer device for the drugs with higher oral bioavailability because appropriate spacers substantially reduce the oral amount delivered.[12] The use of VHCs also can increase systemic activity by increasing lung delivery of drugs that are not absorbed significantly orally.[53] Mouth rinsing and spitting will also reduce oral absorption and are particularly useful for DPI devices.[12]

TABLE 44-9

Effects of Inhaled Corticosteroids

Beneficial Effects	Potential Adverse Effects
• Decrease eosinophil numbers • Decrease mast cell numbers • Decrease T-lymphocyte cytokine production • Inhibit transcription of inflammatory genes in airway epithelium • Reduce endothelial cell leak • Upregulate β_2-receptor production • Reduce airway epithelial subbasement membrane thickening	• Hoarseness, dysphonia, thrush • Growth retardation, skeletal muscle myopathy • Osteoporosis, fractures, and aseptic necrosis of the hip • Posterior subcapsular cataract formation and glaucoma • Adrenal axis suppression, immunosuppression • Impaired wound healing, easy bruising, skin striae • Hyperglycemia/hypokalemia, hypertension • Psychiatric disturbances

The response to ICSs is somewhat delayed. Most patients' symptoms will improve in the first 1 to 2 weeks of therapy and will reach maximum improvement in 4 to 8 weeks.[3] Improvement in baseline FEV_1 and PEF may require 3 to 6 weeks for maximum improvement, whereas improvement in BHR requires 2 to 3 weeks and approaches maximum in 1 to 3 months but may continue to improve over 1 year.[2] Most of the improvement in these parameters occurs at low-to-medium doses, and there is a large variability in response, with 10% of patients not demonstrating an improvement in either parameter.

Local adverse effects from ICSs include oropharyngeal candidiasis and dysphonia that are dose-dependent. The dysphonia (reported in 5%-20% of patients) is due to a local corticosteroid-induced myopathy of the vocal cords. The use of a spacer device with MDIs can decrease oropharyngeal deposition and thus decrease the incidence and severity of local side effects.[12] In infants who require ICS delivery through a face mask, the parent should clean the nasal-perioral area with a damp cloth following each treatment to prevent oropharyngeal candidiasis.

Systemic adverse effects can occur with any of the ICSs given in a sufficiently high dose.[12] Long-term adverse effects of greatest concern include growth suppression in children, osteoporosis, cataracts, dermal thinning, easy bruising, and adrenal insufficiency and crisis.[2] Growth retardation may occur with low-to-medium ICS doses. However, the growth reduction is transient, in that growth velocity is reduced in the first 6 months to 2 years of therapy and then returns to normal.[12] The effect is small (1-2 cm total) and not cumulative, but does persist into adulthood (difference of 0.7% from adult height).[12] The suppression of the HPA axis and decreased bone mineralization are dose-dependent and are not significant clinically except at high doses. The risks, therefore, depend on the therapeutic index of each ICS and its delivery device.

Many of the ICSs, including fluticasone propionate, budesonide, ciclesonide, and mometasone furoate, are metabolized in the GI tract and liver by cytochrome (CYP) 3A4 isoenzymes. Potent inhibitors of CYP3A4 such as ritonavir, itraconazole, and ketoconazole have the potential for increased systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance.[12] Some cases of clinically significant Cushing's syndrome and secondary adrenal insufficiency have been reported.[12]

There is no specific pharmacologic or pharmacokinetic aspect of the current ICSs that allows for once-daily dosing because all the agents studied (both

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the older low-potency ICSs and newer high-potency ICSs) have been effective, provided that patients had relatively mild-to-moderate asthma. More severe patients may require multiple daily dosing. The inflammatory response of asthma has been shown to inhibit corticosteroid-receptor binding. Once asthma is controlled, many patients are able to reduce the ICS dose and maintain control.

Anticholinergics

Anticholinergic agents have a long history of use for asthma, with an evolving role in the chronic management of asthma.[60] Anticholinergics are competitive inhibitors of muscarinic receptors. Unlike β_2-agonists, they are not functional antagonists, rather they reverse cholinergic-mediated bronchoconstriction. This difference in mechanism supports the combined use of anticholinergics and β_2-agonists in the treatment of severe acute asthma exacerbations. The normal bronchial tone is maintained through parasympathetic innervation of the airways via the vagus nerve.[60] A number of the triggers and mediators of asthma (ie, histamine, prostaglandins, sulfur dioxide, exercise, and allergens) produce bronchoconstriction in part through vagal reflex mechanisms.[60] Studies consistently demonstrate that anticholinergics are effective bronchodilators in asthma. There is some evidence that anticholinergics may reduce allergen-induced and methacholine-induced airway responsiveness.[60]

Five muscarinic receptor subtypes (M_1 through M_5) have been identified; M_1, M_2, and M_3 are the principal receptors in the airway.[60] Available anticholinergics ipratropium, aclidinium (not indicated for asthma), glycopyrrolate (not indicated for asthma), and tiotropium are nonselective antagonists of M1, M2, and M3 receptors; umeclidinium bromide which is indicated for persistent asthma is selective for the M3 receptor. M1 receptors are found in epithelial cells and the ganglia and regulate electrolyte and water secretion; M2 receptors, on airway smooth muscle and parasympathetic neurons, have a limited role on smooth muscle constriction; M3 receptors are the primary subtype responsible for smooth muscle bronchoconstriction and mucus secretion.[60] Ipratropium bromide has a duration of action of 4 to 8 hours and is used for the relief of acute asthma symptoms in combination with SABA. The time to reach maximum bronchodilation for ipratropium is considerably slower than for aerosolized SABA (30-60 minutes vs 5-10 minutes). However, this difference is of little clinical consequence because some bronchodilation is seen within 30 seconds; 50% of maximum response occurs within 3 minutes. Ipratropium bromide is useful as adjunctive therapy in acute severe asthma not completely responsive to SABA alone.[12] Care should be taken when administering ipratropium bromide by nebulizer. If a tight mask or mouthpiece is not used, the ipratropium bromide that deposits in the eyes may produce pupillary dilation and difficulty in accommodation. There is no benefit to continuing combined anticholinergic therapy during hospitalization on the duration of stay or clinical outcomes.[12] In patients with persistent asthma who are intolerant to adverse effects from short-acting β_2-agonists may be prescribed ipratropium for rescue inhaler use.

Tiotropium bromide and umeclidinium bromide are long-acting inhaled anticholinergics with a duration of 24 hours. Tiotropium may be considered an add-on therapy in patients whose asthma is not well controlled with a medium-to-high dose of ICS and LABA combination therapy per the GINA guidelines in those 6 years and older and in those 12 years and older per the 2020 Asthma Focused Updates.[11,12] The addition of tiotropium modestly improves lung function and severe exacerbation requiring oral corticosteroid treatment.[11,12] Umeclidinium bromide is available as a combination inhaler with fluticasone and vilanterol and is indicated in patients aged 18 years and older.

Leukotriene Modifiers

Two cysteinyl LTRAs (zafirlukast and montelukast) and one 5-lipoxygenase inhibitor (zileuton) are available in the United States. These drugs have modest effects on bronchodilation, lung function, exacerbation frequency, and exercise-induced bronchoconstriction; patients with aspirin-induced asthma may benefit.[2] Clinical use of zileuton is limited due to the potential for elevated liver enzymes (especially in the first 3 months of therapy), and the potential inhibition of drugs metabolized by the CYP3A4 isoenzymes. They are not preferred alternatives in mild persistent asthma nor as alternative add-on therapy for moderate persistent asthma (see Tables 44-3 and 44-4).[11,12]

One major advantage of LT modifiers is that they are effective orally and can be administered once or twice a day. However, they are less effective in asthma than low doses of ICSs.[11,12] Although montelukast is approved for EIB in adults, it is significantly less effective than SABA. They are not as effective as LABAs when added to ICSs for moderate persistent asthma.[11,12] It is not yet possible to predict which patients respond best to LT modifiers, although there is some evidence that patients with aspirin-sensitive asthma do well. Other predictors may include preschool age, females, short duration of disease, minimal atopy, high cotinine levels, or high urinary LTE4 levels may respond favorably.[61] It is possible that genetic polymorphisms

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in the 5-lipoxygenase or LTC_4 synthase pathways or in cys-LT_1 receptors might predict better responders in the future.[61]

The use of montelukast and zafirlukast has fallen out of favor due to the increased observance of unusual adverse effects and modest therapeutic efficacy. Eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome) is a rare antineutrophil cytoplasmic antibody vasculitis characterized by eosinophil involvement and granulomatous necrotizing effects on small and medium vessels.[62] Other inflammatory skin reactions have been reported that resolve upon discontinuation of montelukast.[62]

Also worrisome are reports of adverse neuropsychiatric events which resulted in the FDA issuing mental health warnings with the use of montelukast beginning in 2008 and updated in 2009 and, most recently, in 2020. In one retrospective study where the investigators contacted parents and asked them to recall their child's symptoms, the relative risk of neuropsychiatric adverse reactions associated with montelukast was 12 times greater than with ICS.[63] The most frequently reported reactions are irritability, aggressiveness, and sleep disturbance; suicidality, though rare, was also reported. The risks were greatest within a few weeks of starting therapy, resulting in approximately 16% of children discontinuing therapy. Conversely, a meta-analysis of observational studies using population-based databases failed to find a clinically important association between montelukast and neuropsychiatric effects. However, the authors of the meta-analysis concluded that subject-specific studies are needed to confirm this finding.[64] While the data are not conclusive, it may be prudent for patients to closely monitor their child when initiating treatment with montelukast.[63]

Reports of fatal hepatic failure associated with zafirlukast have prompted an FDA warning for patients to be made aware of signs and symptoms of hepatic dysfunction.

Zileuton can be administered twice daily as controlled-release tablets. Efficacy data are more limited, liver function monitoring is recommended, and drug interactions are reported with warfarin and theophylline.

Biologic Agents

Table 44-10 outlines the available biologic agents as well as the biomarkers predicting therapeutic responses and the biomarkers modulated by therapy.[65] These agents are targeting the IgE pathway (relevant to allergic asthma) or IL-4, IL-13, and IL-5 pathways (relevant to the Th2 pathway and eosinophilic disorders) and are indicated for patients with moderate or severe asthma (depending upon the drug) along with other biomarker or other clinical indicator associated with treatment response. Tezepelumab blocks TSLP and is potentially a first in class drug.

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TABLE 44-10

Targeted Biologic Therapies for Asthma and Potential Biomarkers

Pathway	Biologic Agents Approved	Biomarkers Predicting Therapeutic Response	Route of Administration
IgE	Omalizumab	FeNO Blood eosinophils	Subcutaneous
IL-5	Mepolizumab Reslizumab	Blood eosinophils	Mepolizumab: subcutaneous Reslizumab: intravenous
IL-5Rα	Benralizumab	Blood eosinophils	Subcutaneous
IL-4Rα (IL-4/IL-13)	Dupilumab	Blood eosinophils	Subcutaneous
TSLP	Tezepelumab	–	Subcutaneous

CRTh2, chemoattractant receptor-homologous molecule expressed on Th2 cells; FeNO, the fraction of exhaled nitric oxide; Ig, immunoglobulin; IL, interleukin; R, receptor; TSLP, thymic stromal lymphopoietin.

Data from Reference 66.

These products are typically reserved for patients with moderate-to-severe persistent asthma who have poor symptom control despite treatment with optimal high-dose ICS-LABA and who haveallergic (or eosinophilic) biomarkers or need maintenance oral corticosteroids. Defining which patients have severe asthma and are candidates for biologic therapy is essential. The European Respiratory Society (ERS) and the American Thoracic Society (ATS) define severe asthma as “asthma which requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains uncontrolled despite this therapy.”[67] According to the GINA guidelines, somewhere between 3% to 10% of people with asthma have severe disease.[2]

The 2020 Asthma Focused Updates did not include an evaluation of biologic therapy because, at the time, the only biologic available was omalizumab. GINA provides step-wise guidance for treating difficult-to-treat asthma, including when to consider add-on biologic treatment.[12] Severe asthma incurs significant healthcare costs.[12] Affordability, availability, predictors of response, and patient preferences should be considered prior to selecting a biologic agent. Eligibility for biologic therapy should be determined by the patient’s age and the inclusion criteria used in clinical trials. In general, criteria for most biologic studies have included pre-bronchodilator FEV_1 between 40% and 80% of predicted and one or more exacerbations in the past year despite moderate-to-high dose ICS.[68] Although some biologics are approved for use in children younger than 12 years (omalizumab, mepolizumab, dupilumab), limited numbers of pediatric patients were included in the clinical trials. After the biologic agent is initiated, a trial of at least 4 months is recommended. If the trial results in an unclear response, the trial should be continued for 6 to 12 months, and for those with little to no response, a different biologic should be considered (if eligible). In those patients demonstrating a positive response, biologic therapy should continue and be reassessed every 3 to 6 months. With each assessment, considerations for decreasing or stopping oral corticosteroid therapy first and then other inhaled treatments are recommended, though patients should be on at least a moderate ICS dose. Testing for parasitic infections should be considered prior to starting biologic therapy as these infections can cause blood eosinophilia and untreated infections with a biologic on board can lead to disseminated disease.[12]

Anti-IgE

Omalizumab is a recombinant anti-IgE antibody approved for the treatment of allergic asthma not well controlled on oral corticosteroids or ICSs.[69] It is a humanized monoclonal antibody directed at IgE. Omalizumab binds to the Fc portion of the IgE antibody preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils.[68] The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of

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mediators in response to allergen exposure.

Omalizumab is administered subcutaneously every 2 to 4 weeks and the dosage is determined by the patient's baseline total serum IgE level (international units per milliliter [kIU/L]) and body weight (kilograms).[12] Treatment must be administered in a clinical setting for observation for anaphylaxis after each dose, so patient selection must be judicious to ensure commitment to therapy. Omalizumab is currently recommended for the treatment in patients greater than 6 years of age with moderate-to-severe asthma, which is not adequately controlled by ICS, ICS-LABA, and in some cases, oral corticosteroids. Elevated levels of FeNO (24 ppb or greater) and eosinophil levels greater than 260 eosinophils/μg/L while taking high dose ICS are predictive of exacerbation reduction response.[2]

Omalizumab is the biological agent with the greatest safety data in children and long-term safety data has been reassuring.[68] Patients taking omalizumab reported local injection site reactions (similar to all subcutaneous biologics) and rates of anaphylaxis at 0.1% which carries a Boxed Warning. Initial reports indicated increases in malignant neoplasms, however, observational studies have shown rates similar to placebo.

Anti-IL-5

Mepolizumab and reslizumab target IL-5 which regulates the terminal differentiation of eosinophils as well as eosinophil activation and recruitment to the airway.[68] These drugs are monoclonal antibodies directed against IL-5 to block activation of the IL-5 receptor on eosinophils. Benralizumab binds to the alpha subunit of the IL-5 receptor of eosinophils and prevents the binding of IL-5, thus mitigating downstream eosinophilic inflammation.[68]

Mepolizumab is approved for children 6 years and older and has demonstrated long-term safety data in children aged 6 to 11 years.[68] Benralizumab is approved for patients aged 12 years and older; reslizumab is approved for those with severe asthma, 18 years and older, and is the only biologic available that is administered intravenously. Mepolizumab and reslizumab are dosed every 4 weeks; benralizumab is dosed every 4 weeks for 3 months then every 8 weeks. Doses are to be administered in a healthcare setting by professionals who are prepared to manage anaphylaxis. Each of these drugs is indicated for patients with an "eosinophilic phenotype" which has not been formally defined by the FDA or any professional society. However, reductions in exacerbation rate of approximately 50% is observed when patients have a certain minimum peripheral blood eosinophil count which varies by drug.[68] Blood eosinophil counts may be a better predictor of response compared with sputum (airway) eosinophil numbers (airway eosinophils are the ideal biomarker but are difficult to measure clinically).[68] Responsiveness to exacerbation reduction appears to be more likely with blood eosinophil levels above 150 cells/μL (0.15×10^9/L) with mepolizumab, above 400 cells/μL (0.4×10^9/L) with reslizumab, and above 300 cells/μL (0.3×10^9/L) for benralizumab.[68] Benefits in reduced exacerbation rate have been observed in patients who require daily oral corticosteroid therapy while also having an oral corticosteroid-sparing effect.[68]

Patients aged 50 years or older who are to be treated with mepolizumab should receive a recombinant zoster vaccination (preferably not a live virus) 4 weeks prior to starting treatment.[68] Similar to omalizumab, the initial concerns for the development of malignancy with reslizumab were subsequently shown to be similar to placebo. As an intravenous therapy, the risk of anaphylaxis is higher with reslizumab. In addition to injection site reactions, common adverse effects for all anti-IL-5 monoclonal antibodies include respiratory tract infections, headache, and asthma worsening.[68]

Anti-IL-4/IL-13 (Dupilumab)

Dupilumab targets the IL-4α receptor, thus blocking IL4 and IL-13 signaling which are key cytokines that promote IgE synthesis and inflammatory cell recruitment. Dupilumab is approved for patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype and is administered subcutaneously every two weeks. Unlike mepolizumab, reslizumab, and benralizumab, FeNO levels above 25 ppb plus blood eosinophil levels of at least 150 cells/μL (0.15×10^9/L) predict response to dupilumab and asthma exacerbation rates are reduced by approximately 50%. In those on maintenance OCS, dupilumab reduces exacerbation rates and maintenance oral corticosteroid dose requirements.[68] Injection site reactions with dupilumab are relatively higher compared to other biologic agents. Patients have also developed eosinophilia (>3,000 cells/μg/L) and patients should be monitored for vasculitic-appearing rashes, worsening pulmonary or cardiac symptoms, or neuropathy with peripheral eosinophilia.[68]

Magnesium Sulfate

Intravenous and nebulized magnesium sulfate have been used in addition to standard therapies (β_2-agonists, systemic corticosteroids,

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anticholinergics, and oxygen) in children and adults with severe or life-threatening asthma. Magnesium sulfate is a moderately potent bronchodilator, producing relaxation of smooth muscle by blocking calcium ion influx into smooth muscles and it may have anti-inflammatory effects.[46] For patients with severe asthma exacerbations, current guidelines suggest that a single 2 g intravenous infusion can be helpful in reducing hospital admissions in adults who have an FEV_1 less than 25% to 30% predicted upon arrival in the ED, children and adults who have persistent hypoxemia after standard treatment, and children whose FEV_1 remains below 60% predicted after 1 hour of standard treatment (Evidence A).[12] There appears to be little benefit to adding intravenous or nebulized magnesium in patients with less severe asthma.[12] In children 2 years and older with acute severe asthma and symptoms for 6 hours or less, nebulized (or intravenous) magnesium may be considered during the first hour of standard treatment with nebulized albuterol plus ipratropium.[12] The adverse effects of magnesium sulfate include hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, cardiac, CNS, and respiratory depression.

Methylxanthines

Methylxanthines have been used for asthma therapy for more than 50 years, but are rarely used owing to the high risk of severe life-threatening toxicity and numerous drug interactions, as well as decreased efficacy compared with ICSs, LABAs, and biologics. Theophylline, the primary methylxanthine of interest, is a moderately potent bronchodilator with mild anti-inflammatory properties and is available for oral and intravenous administration but is not recommended in the GINA guidelines for acute exacerbations or persistent asthma.[12]

Theophylline has a log-linear dose-response curve and dosing requires monitoring of blood concentrations for both efficacy and toxicity (excessive blood concentrations can cause seizures and death). In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP 450 mixed-function oxidase microsomal enzymes (primarily the CYP1A2 and CYP3A4 isozymes), and drug interactions affecting metabolism will significantly affect blood concentrations (see Table 44-11).

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TABLE 44-11

Factors Affecting Theophylline Clearance

Decreased Clearance	% Decrease	Increased Clearance	% Increase
Cimetidine	−25 to −60	Rifampin	+53
Macrolides: erythromycin, TAO, clarithromycin	−25 to −50	Carbamazepine	+50
		Phenobarbital	+34
		Phenytoin	+70
Allopurinol	−20	Charcoal-broiled meat	+30
Propranolol	−30		
Quinolones ciprofloxacin, enoxacin, perfloxacin	−20 to −50	High-protein diet	+25
		Smoking	+40
Interferon	−50	Sulfinpyrazone	+22
Thiabendazole	−65	Moricizine	+50
Ticlopidine	−25	Aminoglutethimide	+50
Zileuton	−35		
Systemic viral illness	−10 to −50		

Alternative Therapies

Complementary therapies that patients might report using include acupuncture, homeopathy, herbal medicines, ayurvedic medicine, ionizers, osteopathy, and chiropractic manipulations. However, there are no studies of sufficient rigor to assess their efficacy.[2] Breathing and relaxation exercises have shown to provide small improvements in symptoms, quality of life, and psychological outcomes but not in exacerbation frequency.[2] Benefits may be due to relaxation effects, voluntary reduction in SABA use, and engagement in self-care, but the costs of certain intervention measures may be expensive.[2] In patients with low serum levels of Vitamin D, supplementation may be effective in reducing exacerbations requiring systemic corticosteroids (high-quality evidence).[2] Vitamin D is an inexpensive treatment alternative that may be useful only in those who are Vitamin D deficient.[2] There is little evidence to support using immunosuppressants such as methotrexate due to marginal steroid-sparing effects and the risk of significantly severe adverse effects.[2]

General Principles of Aerosol Therapy for Asthma

[4] [5] Aerosol delivery of drugs for asthma has the advantage of being site-specific and thus enhancing the therapeutic ratio. Inhalation of short-acting β_2-agonists provides more rapid bronchodilation than either parenteral or oral administration, as well as the greatest degree of protection against EIB and other challenges.[48] ICSs have been developed with rapid oral and systemic clearance to enhance lung activity and reduce systemic

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activity.[54] Specific agents (eg, formoterol, salmeterol, and ipratropium bromide) are only effective by inhalation. Therefore, an understanding of aerosol drug delivery is essential to optimal asthma therapy. Table 44-12 lists the factors determining lung deposition of therapeutic aerosols.

TABLE 44-12

Factors Determining Lung Deposition of Aerosols

Device	Device Factors	Patient Factors
Metered-dose inhaler (MDI)	Canister held inverted Formulation (solution or suspension) Actuator cleanliness Addition of a spacer device	Inspiratory flow (slow, deep) Breath-holding Tilting head back Coordinating actuation with inhalation Priming and shaking the device
Dry powder inhaler (DPI)	Device cleanliness Resistance to inhalation; Humidity	Inspiratory flow (deep, forceful); Tilting head back Maintaining parallel to ground once activated
Jet nebulizer (small volume)	Volume fill (3-6 mL) Gas flow (6-12 L/min); Dead space volume; Open vs closed system Thumb-activating valve; Mouthpiece vs face mask	Inspiratory flow (slow, deep) Breath-holding Tapping nebulizer
Ultrasonic nebulizer	Volume fill Not effective for suspensions Mouthpiece vs face mask	Inspiratory flow (slow, deep) Breath-holding Tapping nebulizer
Spacer device	Volume (≥650 mL) One-way valves Holding chamber vs open-ended Antistatic lining Mouthpiece vs face mask	Inspiratory flow (slow, deep) Time between actuation and inhalation (<5 seconds) Cleaning with detergent to reduce static Multiple actuations (all at once) decrease delivery Coordination of actuation and inhalation for the simple open-tube spacers

Using the appropriate inhalation technique is essential to achieving optimal drug delivery and therapeutic effect.[12] The components are illustrated in Fig. 44-9. Approximately 50% to 80% of a dose from MDIs and DPIs deposits on the oropharynx and is then swallowed; the rest is either left in the device or exhaled.[70] It is important that MDI actuation occurs during inhalation.[70] Many patients do not use their MDIs optimally, and patient instruction with demonstration is the most effective means of improving inhaler technique.[12] Even with instruction, up to 80% of patients, particularly young children and older adults, cannot master the use of an MDI.[12] For these patients, attachment of a VHC to the MDI can improve efficacy significantly. However, the addition of a VHC offers no advantage in patients who can use an MDI optimally alone.[70] Mouth rinsing following treatment with MDI- and DPI-ICSs is important to minimize local adverse effects and oral absorption.[12]

FIGURE 44-9

Instructions for inhaler use. *(Reprinted from NIH Publication No. 07-4051. Expert Panel Report 3: Guidelines for the Diagnosis and Management of AsthmaFull Report 2007.)*

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EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN: HOW TO USE YOUR METERED-DOSE INHALER

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor, nurse, other health care provider, or pharmacist to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below. A or B is the best, but C can be used if you have trouble with A and B. Your doctor may give you other types of inhalers.

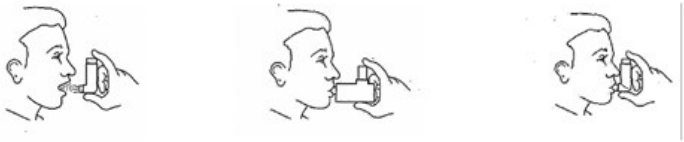
Steps for Using Your Inhaler

Getting ready	1. Take off the cap and shake the inhaler. 2. Breathe out all the way. 3. Hold your inhaler the way your doctor said (A, B, or C below).
Breathe in slowly	4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.) 5. Keep breathing in slowly, as deeply as you can.
Hold your breath	6. Hold your breath as you count to 10 slowly, if you can. 7. For inhaled quick-relief medicine (short-acting beta$_2$-agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other medicines.

L. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).

M. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.

N. Put the inhaler in your mouth. Do not use for steroids.



Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to your doctor, other healthcare provider, or pharmacist.

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*
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Medication Delivery: Device Determinants

Devices used to generate therapeutic aerosols include jet nebulizers, ultrasonic nebulizers, MDIs, and DPIs. The single most important device factor determining the site of aerosol deposition is particle size.[70] Devices for delivering therapeutic aerosols generate particles with mass median aerodynamic diameters (MMAD) from 0.5 to 35 µm.[70] Particles larger than 10 µm deposit in the oropharynx, particles between 5 and 10 µm deposit in the trachea and large bronchi, particles 1 to 5 µm in size reach the lower airways, and particles smaller than 0.5 µm act as a gas and are exhaled. The available MDIs, particularly for corticosteroid inhalers, are solution aerosols (vs suspensions) with extra-fine particle size distributions (MMAD of 1.1 µm) and high lung deposition.

In asthma, the target for drug delivery is the airways and not the alveoli. Respirable particles are deposited in the airways by three mechanisms: (a) inertial impaction, (b) gravitational sedimentation, and (c) Brownian diffusion.[70] The first two mechanisms are the most important for therapeutic aerosols and probably are the only factors that can be manipulated by patient technique.

Each delivery device within a classification generates specific aerosol characteristics, so the extrapolation of delivery data from one device cannot be applied to the other devices in the class. For instance, MDIs can deliver 15% to 50% of the actuated dose; DPIs, 10% to 30% of the labeled dose; and nebulizers 2% to 15% of the starting dose.[70] MDIs and DPIs are portable and convenient, unlike jet nebulizers. Small portable ultrasonic nebulizers have also been developed.

MDIs consist of a pressurized canister with a metering valve; the canister contains the active drug, low-vapor-pressure propellants such as HFA, co-solvents, and/or surfactants.[70] With any change in the components of an MDI, the FDA considers it to be a new drug that requires stability, safety, and efficacy studies prior to approval. The MDI drug is either in solution or a suspended micronized powder. To disperse the suspension for accurate delivery, the canister must be shaken. The metering chamber measures a liquid volume, and, therefore, the device must be held with the valve stem

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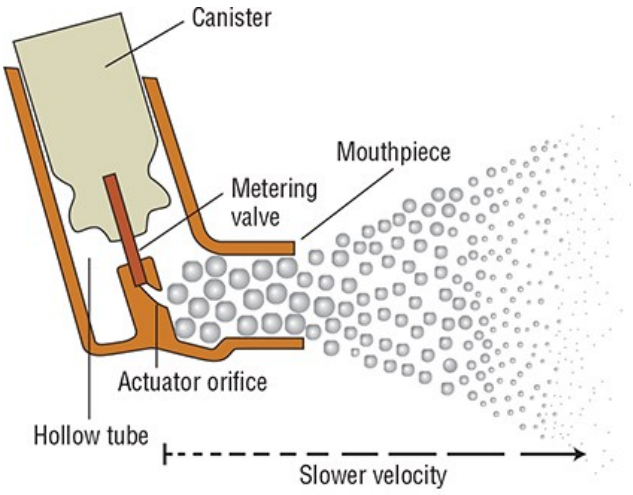
downward so that the chamber is covered with liquid[70] (Fig. 44-10). If not used for a period of time the drug in the chamber evaporates which could lead to an inadequate therapeutic dose. Some inhalers must be primed before first use to fill the chamber and after an interval of nonuse.[70] When the canister is actuated, the device releases the propellant and drug in a forceful spray whose particles are large (MMAD = 45 µm)[70] (see Fig. 44-10). As evaporation occurs, the particle size is reduced to a final MMAD of 0.5 to 5.5 µm depending on the MDI. The aerosol-cloud extends about 6 inches beyond the MDI at the lowest MMAD.[70] Each MDI has different conditions for storage, priming, and durations to expiration, so the clinician must become familiar with and counsel the patient on these factors.

FIGURE 44-10

Illustration of a metered-dose inhaler demonstrating the particle size difference as the aerosol-cloud extends outward.



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Spacer devices are used frequently with an MDI to decrease oropharyngeal deposition and enhance lung delivery.[12] However, not all spacer devices produce similar effects. The design of spacers varies from simple open-ended tubes that separate the MDI from the mouth to the VHC with one-way valves that open during inhalation (the preferred system); some VHCs have a face mask to accommodate drug delivery in children 5 years or younger. A VHC allows evaporation of the propellant prior to inhalation permitting a greater number of drug particles to achieve a respirable droplet size. VHC use also allows inhalation after actuation of the MDI, obviating the need for good hand-lung coordination.[70] Additionally, the large particles that normally would deposit in the oropharynx "rain out" in the spacer.[70] Spacer size may affect the amount of drug available for inhalation; a lower volume spacer (less than 350 mL) is advantageous in very young children.[12]

All the available spacers significantly reduce oropharyngeal deposition from MDIs, with the VHCs being superior to the open-ended tubes.[70] Reducing oropharyngeal deposits is an important factor in reducing local adverse effects (eg, hoarseness and oropharyngeal candidiasis) from ICSs.[70] The change in lung delivery depends on both the MDI and the drug, where one spacer device may enhance delivery with one MDI preparation and decrease delivery with others.[70] Therefore, once a patient is stabilized on a drug and chamber combination, the chamber should not be substituted in order to avoid changes in the dose delivered to the lungs. Finally, over time, holding chambers (eg, plastic) can build up static electricity that attracts small particles to the sides of the chamber, significantly reducing aerosol availability. Some spacers should be washed with household detergent with a single rinse and allowed to drip dry.[12] Other VHCs have been developed with antistatic materials.

Dry micronized powders can be inhaled directly into the lungs. A number of DPIs are now available for use in the United States.[70] Each DPI has unique characteristics with advantages and disadvantages (Table 44-13). The primary advantage of DPIs is that they are breath-actuated and require minimal hand-lung coordination, and it is thus easier to teach patients proper technique.[70] Some DPIs are more flow-dependent than others.[70] Thus, similar to MDIs and spacers, delivery data from one DPI cannot be extrapolated to another.

TABLE 44-13

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Characteristics of Commonly Used Inhalation Devices

Device	Drugs	Breath Activated	Dose Counter	Other Excipients	Disadvantages
MDI	All classes	No	No/yes	Propellants, surfactants, cosolvents	Requires coordination of actuation and inhalation. Large pharyngeal deposition. Difficult to teach. Priming, cleaning, and environmental considerations
Pressair (DPI)	Aclidinium	Yes	Yes	Lactose filler	Requires rapid inhalation to activate
Respiclick (DPI)	Albuterol	Yes	Yes	Lactose filler	Requires rapid inhalation to activate
MDI plus valved holding chamber	All classes	No	No		More expensive than MDI alone; less portable; some payers will not pay; inconsistent effect on delivery; nonstatic preferred
Jet nebulizers	All classes	No	—	Preservatives in some solutions	Significant Interbrand variability; expensive and time-consuming; less efficient than MDIs; contamination possible; preparations may be light and temperature-sensitive (short shelf life)
Ultrasonic nebulizer	Cromolyn solution, short-acting β_2-agonist solutions	No	—	Preservatives in some solutions	Same as for jet nebulizers and cannot be used for suspensions; battery-operated are portable
Flexhaler (DPI)	Budesonide	Yes	Yes	Lactose filler	Requires high inspiratory flow (60 L/min)
					Pharyngeal deposition
					Not approved for <6 years of age
Diskus (DPI)	Fluticasone; salmeterol; fluticasone/salmeterol	Yes	Yes	Lactose filler	Not approved for <4 years of age
					Requires inspiratory flow of 30-60 L/min
Ellipta (DPI)	Fluticasone furoate Fluticasone/vilanterol	Yes	Yes	Lactose filler	Not approved for <12 years of age (18 years for fluticasone/vilanterol)
					Requires inspiratory flow of 60 L/min
Aerolizer (DPI)	Formoterol	Yes	—	Lactose filler	Single-dose capsules. Not approved for <5 years of age
					Requires flow of 30-60 L/min

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Neohaler (DPI)	Indacaterol	Yes	—	Lactose filler	Single-dose capsules. Not approved for children. Requires flow of 60 L/min
Handihaler (DPI)	Tiotropium	Yes	—	Lactose filler	Single-dose capsule. Not approved for children. Requires flow of 20 L/min. Not FDA-approved in asthma
Twisthaler (DPI)	Mometasone	Yes	Yes	Lactose filler	Not approved for <4 years of age
Respimat (SMI)	Tiotropium Albuterol/Ipratropium Olodaterol	No	Yes	Preservative	Requires slow deep breath. Not approved for <12 years of age

Reported adherence to inhaled asthma medications has been less than 50% for adolescents and adults.[71] Adherence barriers are different in each patient population and should include a personalized approach. Device ease-of-use and ability to perform proper inhaler technique should be considered and assessed. Electronic sensors either attached to or integrated with MDIs and DPIs used in conjunction with smartphone applications have been developed to track and promote adherence. Although these technological advances will likely become commonplace in the future, the current cost (~$300 per device or for a 1-year subscription) for these devices and monitoring services are a significant barrier.

Nebulizer devices come in two basic types: the jet nebulizer and the ultrasonic nebulizer. Jet nebulizers produce an aerosol from a liquid solution or suspension placed in a cup. A tube connected to a stream of compressed air or O_2 flows up through the bottom and draws the liquid up an adjacent open-ended tube.[70] The air and liquid strike a baffle, creating a droplet cloud that is then inhaled.[70] Ultrasonic nebulizers produce an aerosol by vibrating liquid lying above a transducer at speeds of about 1 MHz.[70] Both produce similar degrees of lung deposition, with the exception that ultrasonic nebulizers are ineffective for nebulizing currently available micronized suspensions.[70] The aerosol output and lung delivery vary significantly among the commercially available jet nebulizers even when operated in the same manner.[70] Increasing fill volume will increase the total amount of drug delivered; however, it also will take longer for the patient to nebulize the dose.[70] The MMAD of the droplets is related directly to the gas flow, with flows of 5 to 12 L/min providing an aerosol cloud with an MMAD of 4 to 8 µm for most jet nebulizers.[70] Each jet nebulizer comes with optimal operating and cleaning instructions.

Medication Delivery: Patient Determinants

6 7 The most important patient factor determining aerosol deposition is inspiratory flow (see Table 44-12).[70] High inspiratory flows with MDIs increase the degree of deposition owing to impaction of particles of any size, thereby increasing deposition centrally (ie, throat and large airways) and decreasing peripheral deposition. The optimal inspiratory flow for most MDIs is slow and deep (approximately 30 L/min or 5 seconds for a full inhalation).[70] In general, DPIs require higher inspiratory flows (greater than or equal to 60 L/min) and a change in inhalation technique (ie, deep, forceful inspiration) for optimal dispersion of the powder, which, in turn, increases the amount of drug delivered to the larger central airways.[70] Patients should be cautioned not to exhale into DPIs because this causes loss of dose and moistens the dry powder, causing aggregation into larger particles. Patient factors that cannot be controlled include interpatient variability in airway geometry (particularly the differences between children and adults)[70] and the effects of bronchospasm, edema, and mucus hypersecretion. Mild obstruction increases aerosol deposition; however, severe obstruction probably leads to increased central deposition from impaction.[70] The absolute delivery to the lung is not as important as the consistency of delivery, assuming that a sufficient dose to produce the desired therapeutic effect is achieved. No single inhalation device is the best for all patients. Table 44-13 lists the differing characteristics of inhalation devices.

Delivery from high-resistance DPIs is more flow-dependent than from low-resistance DPIs. Thus, younger children and possibly older adults will have more variability in delivery from high-resistance devices.[70] Most children younger than 4 years of age cannot generate a sufficient inspiratory flow to use DPIs. Young children (younger than 4 years) and infants generally require the use of a face mask attached to either an MDI plus VHC or a nebulizer. The use of a face mask results in a reduction in lung delivery due to the portion of the aerosol inhaled nasally, so the doses of drugs used in these

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patients are often not decreased.

EVALUATION OF THERAPEUTIC OUTCOMES

The two domains of asthma control are “symptom control” and “future risk of adverse outcomes.”[12] Symptom control is assessed by asking about the frequency of daytime and night-time asthma symptoms, reliever medication use, and activity limitations. Poor symptom control is also an indicator of future risk for exacerbations.[12] However, even when perceived symptom control is good, an assessment of the future risk of exacerbations is critical. Determining the risk of future adverse patient outcomes includes assessment of the risk of future exacerbations, fixed airflow limitation (and thus diminished response to therapy), and medication adverse effects.[12] To assess the risk for future exacerbations (defined as a worsening of asthma requiring the use of systemic corticosteroids or an increase in the use of systemic corticosteroids), lung function should be measured before the start of treatment and then 2 months later when the maximum response to controller medications is likely attained.[12] This benchmark of “personal best” can then be used for ongoing risk assessment. Other factors that affect future risk of exacerbations include exacerbation history in the previous year (define as one or more exacerbations requiring systemic corticosteroids is a risk factor), history of intubation or intensive care unit stay for asthma, or asthma-related ED visits for urgent care.[12] Fixed airflow limitation can be affected by lack of ICS treatment, smoking exposure, and poor lung function. During ongoing care, spirometry should be measured yearly but long-term PEF monitoring is typically reserved for those with severe asthma.[12] The risk of adverse effects is influenced by oral drug administration, ICS dose, and potential drug interactions with cytochrome P450 inhibitors.[12] In addition, poor inhaler technique (such as not rinsing and spitting after ICS use) can lead to oral candidiasis or an increase in the swallowed fraction of the dose that could influence linear growth in children.

There are several simple screening questionnaires that can be used to assess asthma symptom control quickly in a clinic setting. The Asthma Control Test is a validated simple five-question survey for patients 12 years and older that yields a numerical score; a score of 19 or less indicates poor asthma control and several institutions have incorporated the survey into the electronic health record in order to evaluate changes over time.[12] There is a companion Childhood Asthma Control Test survey for children 4 to 11 years.[12] A number of other validated questionnaires exist such as the Asthma Control Questionnaire (ACQ) and the Test for Respiratory and Asthma Control in Kids (TRACK).[12]

Patients should also be asked about exercise tolerance but perceived good exercise tolerance may be biased by a sedentary lifestyle due to frequent bothersome symptoms. All patients on inhaled drugs should have their inhalation delivery technique evaluated periodically—monthly initially and then every 3 to 6 months. Before stepping up therapy, adherence, environmental factors, and comorbid conditions should be reviewed.[12]

Following initiation of anti-inflammatory therapy or an increase in dosage, most patients should begin experiencing a decrease in symptoms in 1 to 2 weeks and achieve maximum improvement within 4 to 8 weeks. The use of higher ICS doses or more potent agents may accelerate symptom improvement. Increases in FEV_1 and PEF should follow a similar time frame; however, a decrease in BHR, as measured by morning PEF, PEF variability, and exercise tolerance, may take 1 to 3 months.[12] Patients should be informed that following a viral respiratory infection, they may experience decreased exercise tolerance for up to 4 weeks.

Initial visits with the patient should focus on the patient’s concerns, expectations, and goals of treatment. Initial patient education should focus on asthma as a chronic lung disease, the types of medications, how they are to be used including inhaler technique, and when to seek medical advice. Written action plans should be provided. Both peak flow-based and symptom-based self-monitoring plans can be effective.[12] The first follow-up visit should include a repetition of the educational messages from the first visit, as well as a review of the patient’s current medications, adherence, barriers, and challenges.

CONCLUSION

Asthma is a complex disease. The precise defect in asthma has not been determined, and it may be that asthma is a clinical manifestation presentation of a heterogeneous group of diseases. Asthma is defined and characterized by excessive reactivity of the bronchial tree to a wide variety of noxious stimuli. The reaction is characterized by bronchospasm, excessive mucus production, and inflammation. The central role of inflammation in inducing and maintaining BHR is now widely appreciated. The goal of asthma therapy is to normalize, as much as possible, the patient’s life and prevent chronic irreversible lung changes. Drugs are the mainstay of asthma management and can control symptoms and reduce the number of exacerbations. In

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persistent asthma, therapy should be aimed at both bronchospasm and inflammation. Patients should be followed and monitored diligently for adverse drug effects. Although death from asthma is uncommon, underestimating the severity of obstruction and under-treating an acute exacerbation increases the risk of mortality. Most asthma deaths are avoidable.

ABBREVIATIONS

ACOS	Asthma COPD Overlap Syndrome
ACQ	Asthma Control Questionnaire
ACTH	adrenocorticotropic hormone
AIR	anti-inflammatory reliever
Arg	arginine
BHR	bronchial hyper-responsiveness
CFC	chlorofluorocarbon
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
DPI	dry powder inhaler
ED	emergency department
EIB	exercise-induced bronchospasm
EPR3	Expert Panel Report 3
FeNO	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GM-CSF	granulocyte-macrophage colony-stimulating factor
HFA	hydrofluoroalkane
HPA	hypothalamic-pituitary–adrenal
ICAM-1	intercellular adhesion molecule 1
ICS	inhaled corticosteroid

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IFN-γ	interferon-γ
IgE	immunoglobulin E
IL	interleukin
iNOS	inducible nitric oxide synthase
LABA	long-acting inhaled β_2-agonist
LAMA	long-acting muscarinic antagonist
LT	leukotriene
MART	maintenance-and-reliever therapy
MDI	metered-dose inhaler
MMAD	mass median aerodynamic diameter
NAEPP	National Asthma Education and Prevention Program
NANC	nonadrenergic, noncholinergic
NO	nitric oxide
O_2	oxygen
PAF	platelet-activating factor
PEF	peak expiratory flow
RCT	randomized controlled trial
RSV	respiratory syncytial virus
SABA	short-acting beta-agonist
SMART	single maintenance-and-reliever therapy
T-cells	thymically derived lymphocytes
Th_1	type 1 T-helper cell
Th_2	type 2 T-helper cell
TSLP	thymic stromal lymphopoietin
VCAM-1	vascular cell adhesion molecule 1
VHC	valved holding chamber

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VIP	vasoactive intestinal peptide

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SELF-ASSESSMENT QUESTIONS

1. The aerosol particle size most likely to deposit in the lower airways is:
   A. 10-20 µm
   B. 5-10 µm
   C. 1-5 µm
   D. 0.1-0.5 µm
2. Advantages of spacer devices include all of the following EXCEPT:
   A. Enhanced lung delivery
   B. Decreased oropharyngeal deposition of drug
   C. Increased percent of drug particles achieving respirable droplet size
   D. Standardization of spacers to make them substitutable
3. An objective assessment used to monitor response to therapy in an acute severe asthma exacerbation include which one of the following:
   A. Fraction of exhaled nitric oxide (FeNO)
   B. Impulse oscillometry
   C. Serum cortisol levels
   D. Pulse oximetry
4. Pharmacologic responses to β_2-agonists include all of the following EXCEPT:
   A. Increased neuromuscular transmission
   B. Smooth muscle relaxation
   C. Stimulate uterine contractions
   D. Vasodilation of the vasculature
5. A protective factor that may prevent the development of asthma includes:
   A. A mother who had a cesarean section
   B. Being obese
   C. Having older siblings

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D. Using antibiotics in childhood

6. Which one of the following statements is CORRECT about the major characteristics of marketed dry powder inhalers (DPIs) used to deliver drugs to the lungs?

   A. Drug delivery is breath-actuated, requiring minimal hand–lung coordination by the patient.

   B. DPI's have been standardized to require the same inspiratory flow rate.

   C. Only inhaled corticosteroids are available as a DPI.

   D. Slow inhalation from the device is needed for optimal lung deposition of the powder.

7. Which one of the following statements is CORRECT concerning the use of leukotriene modifiers in asthma management?

   A. The FDA issued a warning about serious mental health side effects of montelukast.

   B. LTRAs are more effective than LABAs as an add-on to ICS therapy for moderate persistent asthma.

   C. Montelukast has increased efficacy over short-acting inhaled β_2-agonists for the treatment of EIB.

   D. The use of leukotriene modifiers is limited due to the potential for renal toxicity.

8. Which one of the following statements is CORRECT concerning biologics in the treatment of asthma?

   A. Omalizumab blocks release of interleukin-5.

   B. Reslizumab is administered subcutaneously.

   C. Mepolizumab response is predicted by baseline blood eosinophil levels.

   D. Dupilumab blocks the IL-5 receptor.

Please refer to the following case vignette to answer Questions 9 and 10.

AB is a 37-year-old female who presents with the following: FEV_1 76% predicted, use of albuterol (for rescue) 5 to 6 days/wk, waking with asthma symptoms four to five times/mo, and increased asthma symptoms during her daily walk to work and workouts. She completed a 5-day course of prednisone 2 months ago. Her only medication is albuterol.

9. AB presents to the emergency room with shortness of breath, wheezing, and speaking in monosyllabic words. What is the best treatment option to initiate?

   A. Albuterol by metered-dose inhaler plus spacer

   B. Albuterol by metered-dose inhaler with spacer and ipratropium bromide with spacer

   C. Albuterol by metered-dose inhaler with spacer and ipratropium bromide with spacer and 40mg of prednisone

   D. Albuterol by metered-dose inhaler wand ipratropium bromide with spacer and 40mg of prednisone plus IV theophylline

10. After discharge from the ED, AB sees her provider a week later. Which of the following would be the most appropriate pharmacologic treatment options for AB?

    A. Continue SABA as needed to control symptoms

    B. Daily low-dose ICS with SABA as needed to control symptoms

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C. ICS-formoterol used daily and as needed for symptoms

D. Mepolizumab

11. Which one of the following is NOT a mediator associated with airway inflammation?

A. Histamine

B. Goblet-cells

C. Leukotrienes

D. Prostaglandins

12. Which of the following statements is CORRECT concerning ICS in the treatment of asthma?

A. Available ICS are equipotent based on a µg to µg comparison.

B. Advantages are high topical potency and low systemic activity.

C. Response to therapy is prompt, with resolution of symptoms within 3 to 4 days.

D. Therapeutic index is irrelevant to the delivery device

13. Regarding LABAs, all of the following are correct EXCEPT:

A. These are more β_2 selective and lipid-soluble than albuterol.

B. Combination ICS/LABA treatment provides greater asthma control than increasing the dose of ICS alone.

C. Tolerance may occur with chronic therapy.

D. Onset of action is slower than albuterol, approximately 30 minutes.

14. Which of the following medications does NOT trigger asthma symptoms?

A. Aspirin

B. Naproxen

C. Propranolol

D. Penicillin

15. Which one of the following is NOT a dry powder inhaler?

A. Diskus

B. Flexhaler

C. Respimat

D. Twisthaler

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Particles smaller than 1-5 µm will be exhaled before reaching the lower airways. Larger particles will be too heavy and deposit in the oropharynx or trachea and large bronchi. The drug needs to reach the lower airways for optimum effect.

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2. **D.** Spacers provide enhanced drug delivery by slowing the speed of the drug from the pMDI so that it can flow from the oropharynx into the airways. They also prevent the drug from depositing on the tongue and throat which can result in oral candidiasis with inhaled corticosteroid medications. Spacers also allow some of the propellant to evaporate so that more particles are in the respirable size range.

3. **D.** Pulse oximetry provides an objective assessment of improvements in oxygenation as a result of treatment with β_2-adrenergic receptor agonists and corticosteroids. FeNO is used to measure changes in airway inflammation with the use of controller therapy. Spirometry is a measurement of lung function but is not used in the assessment of acute asthma. Serum cortisol is used to measure the systemic effects of corticosteroids.

4. **C.** The primary effect of β_2-agonists is relaxation of smooth muscle in the airway which results in dilation of the bronchi and improves airflow.

5. **C.** Having older siblings is thought to expose a child to infectious agents that tip the balance in favor of immunologic T-helper type 1 development rather than T-helper cell type 2.

6. **A.** Unlike pMDI in which the actuation of the inhaler must be coordinated with inspiration, dry powder inhalers only typically require sufficient inhalation for adequate lung delivery.

7. **A.** Evidence continues to be published on the neuropsychiatric effects of montelukast. These effects often appear within a few weeks of starting therapy but in some patients may emerge more slowly over several months.

8. **C.** Response to mepolizumab, reslizumab, and benralizumab is dependent upon baseline blood eosinophil levels. Response to dupilumab is dependent upon both baseline blood eosinophil levels and FeNO levels.

9. **C.** AB is having a severe asthma exacerbation and should be treated to rapidly relieve airway obstruction. Patients with severe symptoms should receive both albuterol and ipratropium. Oral corticosteroids should be started within 1 hour. There is no role for IV theophylline for the management of acute exacerbations.

10. **B.** AB's symptoms indicate the need for controller therapy. ICS-formoterol used as a controller and reliever (SMART) has been shown to reduce the risk of exacerbations. Her symptoms suggest she needs more than just a low dose of ICS. Biologics are not indicated until maximal inhaled therapy has been tried and symptoms persist.

11. **B.** Goblet-cells produce mucus in the airway. Histamine, leukotrienes, and prostaglandins are produced by inflammatory cells such as eosinophils, basophils, macrophages, and mast cells.

12. **B.** Inhaled corticosteroids have a beneficial topical-to-systemic ratio compared with oral corticosteroids. Therapy with inhaled corticosteroids may show benefit within a week but requires several months for full benefit to be realized.

13. **D.** Most of the long-acting β_2-adrenergic receptor agonists have an effect within minutes; the exception is salmeterol which has an onset in about 10 minutes.

14. **D.** Aspirin and naproxen can precipitate asthma through cyclooxygenase-1 inhibition and β-blockers can block the β_2-adrenergic receptor and cause bronchoconstriction.

15. **C.** Respimat is a soft mist inhaler.

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