



Asthma

By Rachael Hiday, Pharm.D., MBA, BCPS, BCACP; and Kristen D. Abbott, Pharm.D., BCACP

Reviewed by Ashley N. Crowl, Pharm.D., BCACP; and Marcella R. Brown, Pharm.D., MPH, MSBiomed, BCACP, BCGP

LEARNING OBJECTIVES

1. Analyze spirometry to determine the diagnosis and severity of asthma.
2. Assess the differences in the therapeutic recommendations between the GINA and the EPR-3 guidelines.
3. Classify patient symptoms to help guide the intensification of drug therapy.
4. Design an initial therapeutic regimen consistent with current treatment guidelines for asthma, and revise it as appropriate according to therapeutic response.
5. Evaluate a patient's asthma therapy to maximize outcomes, and justify adjunctive therapy and modifications on the basis of individuals' needs, skill level, and preferences.

ABBREVIATIONS IN THIS CHAPTER

ACT	Asthma Control Test
COPD	Chronic obstructive pulmonary disease
FEV ₁	Forced expiratory volume in 1 second
FEV ₁ /FVC ratio	Percentage of the FVC expired in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
LABA	Long-acting β_2 -agonist
NHLBI EPR-3	National Heart, Lung, and Blood Institute Expert Review Panel
PFT	Pulmonary function test
SABA	Short-acting β_2 -agonist

[*Table of other common abbreviations.*](#)

INTRODUCTION

Prevalence

Asthma is a complex disease that can be characterized by recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and inflammation. Asthma is one of the most common respiratory diseases in the world today, affecting about 300 million people worldwide, which is expected to increase to 400 million people by 2025. Asthma is a major cause of disability, health care use, and poor quality of life (To 2012). Asthma affects both adults and children, and the Global Initiative for Asthma (GINA) estimates that the global prevalence is 1%–21% in adults and up to 20% in children. Patient burden from exacerbations and daily asthmatic symptoms has increased by about 30% in the past 20 years and is expected to increase further as more countries urbanize (Reddel 2015). As a result, the economic impact of asthma is also expected to increase, including expenses that are both direct (e.g., medications and routine or urgent care) and indirect (e.g., missed work/school, decreased productivity, and decreased quality of life) (GINA 2018).

Etiology

Although asthma is one of the most common chronic conditions in both adults and children, much is unknown about its etiology. Moreover, although there is a clear genetic predisposition in asthma, there is also an environmental component that explains the international variation in prevalence. Asthma encompasses a range of heterogeneous phenotypes that differ in presentation, etiology, and pathophysiology. Identified risk factors for each asthma phenotype include genetic, environmental, and host factors (Burke 2003). Although a family history of asthma is common, it is not necessary for the development and subsequent diagnosis of asthma. As the linkage of genetic factors to different asthma phenotypes is discovered,

future treatment approaches may become directed to specific phenotypes and genotypes.

Asthma appears to develop during the development of the immune system. One of the most commonly accepted theories is the hygiene hypothesis, which revolves around the idea of innate immunity. To understand innate immunity, the role of helper T cells within the immune system must first be understood. Type 1 helper T cells (Th1s) and type 2 helper T cells (Th2s) are two forms of CD4⁺ helper T cell–mediated immune responses. Th1 cells produce interferon- γ , interleukin (IL)-2, and tumor necrosis factor β . Th1-dominated immune responses produce a phagocyte-dependent inflammation. Th2 cells produce a variety of interleukins that induce strong antibody responses. These immune responses include immunoglobulin E (IgE) and eosinophil differentiation and activation, as well as phagocyte-independent inflammation (Romagnani 2000). The hygiene hypothesis theory suggests that the development of certain infections in early life, exposure to other children, and minimal use of antibiotics are associated with a Th1 immune response and a lower incidence of asthma. In addition, the absence of these factors may alter the balance between Th1- and Th2-type cytokine responses early in life and increase the likelihood that the immune response will down-regulate the Th1 immune response that fights infection. Therefore, the immune response will be dominated by Th2 cells. This process is thought to contribute to the expression of allergic disease and asthma. Currently, there are no specific recommendations regarding immune-related

interventions or modifications, but several interventions (e.g., probiotic use) are under investigation (NHLBI 2007).

Environmental factors are the most important components to consider in the development, persistence, and severity of asthma. The two environmental factors that are significantly more likely to contribute to the development of asthma than other factors are airborne allergens (e.g., dust mites) and viral respiratory infections (e.g., respiratory syncytial virus and rhinovirus). Other environmental factors have been, and will continue to be, studied for their potential roles in the development and persistence of asthma: tobacco smoke exposure, air pollution, and diet. The association between these factors and the onset of asthma has not yet been defined because clinical trials investigating these factors have been inconclusive and not designed for long-term duration in order to provide specific recommendations (NHLBI 2007). Environmental exposure and triggers may affect asthma differently at different times of a person's life, and the risk factors for asthma in individual patients may change over time.

Certain prenatal risk factors are strongly correlated with the development of childhood asthma (Subbarao 2009). Prenatal maternal smoking has consistently been associated with early childhood wheezing. There is a dose-response relationship between prenatal exposure to tobacco smoke and decreased airway capacity in early life. The risk of developing asthma is further increased when combined with postnatal smoke exposure (Dezateux 1999). Conversely, prenatal diet and nutrition may play a protective role in infantile development of asthma. Several studies have shown that a higher intake of fish oil is associated with a lower risk of atopic disease (specifically eczema and atopic wheeze) up to 6 years of age. Higher prenatal vitamin E and zinc concentrations have also been associated with a lower risk of developing childhood wheeze up to 5 years of age (Martindale 2005). However, maternal diets that exclude different types of food during pregnancy do not protect against developing atopic disease or asthma (Kramer 2006).

Pathophysiology

Asthma is a chronic inflammatory disorder of the airways in which mast cells, eosinophils, neutrophils, T lymphocytes, macrophages, and epithelial cells play a role. This inflammation typically causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness. These episodes are usually associated with airflow obstruction that is reversible spontaneously or with treatment (NHLBI 2007).

Airflow limitation is caused by three main changes in the airway, all of which are influenced by airway inflammation: bronchoconstriction, airway hyper-responsiveness, and airway edema. During bronchoconstriction, the bronchial smooth muscle contracts to narrow the airways in response to exposure to allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from the mast cells that includes histamine,

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Concepts behind interpretation of common pulmonary function tests such as FEV₁ and FEV₁/FVC ratio
- Underlying pathophysiology of asthma
- Pharmacology of β_2 -agonists and corticosteroids in the chronic treatment of asthma

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- NHLBI. [Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma](#). Bethesda (MD): National Heart, Lung, and Blood Institute (US). 2007.
- GINA. [Global Strategy for Asthma Management and Prevention](#). 2018.

tryptase, leukotrienes, and prostaglandins, which directly contract airway smooth muscle (Busse 2001). External stimuli such as exercise, cold air, and irritants can also cause acute airflow obstruction. These mechanisms are not well defined, but the intensity of response appears related to underlying airway inflammation.

As asthma becomes more persistent, inflammation becomes more progressive. Once this progressive inflammation occurs, edema and mucous hypersecretion further limit airflow (NHLBI 2007). Mechanisms influencing airway hyper-responsiveness include inflammation, dysfunctional neuroregulation, and structural changes. Of these, inflammation appears to be the main factor in determining the degree of airway hyper-responsiveness. Selecting treatment directed toward reducing inflammation can reduce airway hyper-responsiveness and subsequently improve asthma control.

In addition, as asthma becomes more persistent, edema and mucous hypersecretion can further limit airflow. Structural changes, including hypertrophy and hyperplasia of the airway and smooth muscle, can occur. Throughout disease progression, the airways may experience remodeling. Incomplete reversibility of airflow limitation may occur. Over time, persistent changes in airway structure can occur, including fibrosis, mucous hypersecretion, epithelial cell injury, smooth muscle hypertrophy, and angiogenesis (Holgate 2006). Of note, different manifestations of asthma may have varying patterns of inflammation and intensity of exacerbation. However, in all cases, inflammation triggers airway hyper-responsiveness and airway obstruction, leading to clinical asthmatic symptoms.

DIAGNOSIS

Physical Examination

Common phenotypes (symptoms) described in infancy and early childhood are transient wheezing, nonatopic wheezing, late-onset wheezing, and persistent wheezing. Most children with persistent wheezing (in whom asthma will subsequently be diagnosed) will have symptoms before 3 years of age. By 3 years of age, the child will have abnormal lung function that persists into adulthood (Martinez 1995). By adolescence, most will have atopy. Although about 50% of preschool children have had wheezing at some point, only 10%–15% of children have a true diagnosis of asthma by the time they are school age (Sears 2003). Distinguishing among the different phenotypes in early childhood is important in understanding the role of risk factors and treatment selection.

When a diagnosis of asthma is suspected, the recommended method for establishing the diagnosis is to obtain a detailed medical history, a physical examination, and spirometry testing. The provider should determine that symptoms of recurrent episodes of airflow obstruction or airway hyper-responsiveness are present and that the airflow

obstruction is at least partly reversible. Other diagnoses such as vocal cord dysfunction must be excluded. The presence of several markers increases the likelihood of an asthma diagnosis, but spirometry is needed for a formal diagnosis.

There are several key symptom indicators for considering a diagnosis of asthma. Typically, most patients with asthma present with wheezing. Wheezing can be defined as high-pitched whistling sounds heard in the expiratory phase. The patient may present with a history of cough (often worse at night), recurrent wheezing, recurrent difficulty breathing, and recurrent periods of chest tightness. Symptoms of asthma often worsen on exertion such as exercising and strong emotional expression (laughing or crying hard) or during periods of increased stress. Symptoms may also occur or worsen during viral infections, exposure to inhalant allergens, airborne irritants (tobacco smoke or chemicals), and changes in weather.

During the physical examination, the provider should focus on the upper respiratory tract, chest, and skin. The upper respiratory tract may show increased nasal secretion, mucosal swelling, and/or nasal polyps. Examination of the chest will reveal sounds of wheezing during normal breathing or prolonged phase of forced exhalation. Examination may also reveal hyperexpansion of the thorax, use of accessory muscles, the appearance of hunched shoulders, or a chest deformity. Examination of the patient's skin may reveal areas of atopic dermatitis or eczema. However, because the disease is variable and different signs may be present or absent with each episode, the absence of any of these findings does not rule out asthma.

Spirometry

Pulmonary function tests (PFTs) such as spirometry can help diagnose the cause of respiratory symptoms and guide pharmacologic treatment. There is no difference between PFTs obtained in the office (spirometry) and those obtained in a pulmonary function laboratory as long as trained personnel calibrate, administer, and interpret the results. To reliably interpret PFT, three factors must be confirmed: (1) the volume-time curve reaches a plateau and expiration lasts at least 6 seconds; (2) results of the two best efforts on the PFT are within 200 mL of each other; and (3) flow-volume loops are free of artifacts and abnormalities (Anonymous 1995).

Pulmonary function tests take about 15 minutes and up to 45 minutes if pre- and post-bronchodilator testing is warranted. Spirometry reveals the level of obstruction and assesses reversibility in patients 5 years and older. Objective data are needed for a diagnosis of asthma because patient perception of airflow obstruction can be highly variable. Spirometry is recommended instead of measurements by a peak flow meter because of the wide variability in peak flow meters and reference values. Peak flow meters are designed for use as asthma monitoring tools only.

The three components of a spirometry reading useful for diagnosing asthma are the forced expiratory volume in

1 second (FEV_1), the forced vital capacity (FVC), and the percentage of the FVC expired in 1 second (FEV_1/FVC) ratio. The first step when interpreting PFT results is to determine whether an airway obstruction is present. An obstructive defect is indicated by a low FEV_1/FVC ratio, which is defined by the Third National Health and Nutrition Examination Survey as less than 85% of predicted in children 5–18 years of age or less than 70% of predicted in adults. After the first spirometry test, patients should be treated with a bronchodilator (e.g., albuterol) and the test repeated. The FEV_1 in patients with mild, or well-controlled, asthma may be normal (greater than 80% of the predicted value). Because asthma is typically reversible, an improvement is expected after bronchodilator treatment. The FVC typically “reverses” (i.e., greater than 12% or 200 mL improvement after bronchodilator use), indicating the obstruction is reversible (Pelligrino 2005). Conversely, chronic obstructive pulmonary disease (COPD) is not reversible, and little, if any, improvement occurs after bronchodilator treatment (NHLBI 2007).

CURRENT GUIDELINES AND UPDATES

The GINA organization and the National Heart, Lung, and Blood Institute Expert Panel Report (NHLBI EPR-3) drive the asthma classification and treatment recommendations. The GINA guidelines are updated annually, whereas the EPR-3 was last updated in 2007. The GINA and NHLBI EPR-3 recommendations vary slightly when classifying asthma. Uncontrolled asthma symptoms are an important risk factor for exacerbations. Potentially modifiable risk factors for exacerbations include high short-acting β_2 -agonist (SABA) use, inadequate use of inhaled corticosteroid (ICS) agents (e.g., not prescribed an ICS, poor adherence, incorrect inhaler technique), FEV_1 less than 60% of predicted, and exposure to tobacco smoke or allergens. In addition, comorbidities such as obesity, food allergy, and chronic rhinosinusitis increase the risk of exacerbation. Pregnancy can also increase the likelihood of an asthma exacerbation.

Global Initiative for Asthma

The GINA guidelines assess asthma symptom control on the basis of daytime asthma symptoms, nighttime awakenings because of asthma symptoms, quick-relief inhaler use more than twice per week, and any limitations in daily activities because of asthma. Asthma is considered “well controlled” if none of these factors is present. Asthma is considered “partly controlled” if one or two of these factors are present and “uncontrolled” if three or four factors are present.

Initial treatment is based on presenting symptoms. If the patient requires a SABA less than twice per month with no exacerbations in the past year, no controller medication is necessary. However, if the patient has one or more risk factors for exacerbation or has had an exacerbation requiring oral corticosteroids in the past year, a low-dose ICS should be

initiated as controller therapy. If the patient continues having asthma symptoms most days while using ICS treatment, the ICS dose should be increased to a medium or high, or using a combination of a low-dose ICS and a long-acting β_2 -agonist (LABA) should be considered.

The GINA report recommends assessing asthma severity retrospectively from the treatment level required to control symptoms and exacerbations. The GINA recommendations suggest assessing severity once the patient has received controller treatment for several months. The GINA guidelines classify asthma as mild, moderate, or severe. Mild asthma is well controlled with step 1 or step 2 treatment – with reliever medication used as needed as monotherapy, or with low-intensity controller treatment such as a low-dose ICS, leukotriene receptor antagonists, or cromolyn. Moderate asthma is well controlled with step 3 treatment with a low-dose ICS and LABA therapy. Severe asthma requires step 4 or step 5 treatment to achieve control. This control is defined as needing a high-dose ICS with a LABA to prevent the asthma from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment.

Most individuals with asthma can achieve symptom control and minimal exacerbations with controller treatment. However, some patients do not achieve this even with maximal therapy. In some patients, this is because of truly refractory asthma, but in many patients, it is likely because of other comorbidities, persistent environmental exposures, or psychosocial factors. It is important to distinguish between severe asthma and uncontrolled asthma. The most common problems that should be excluded before diagnosing severe asthma are poor inhaler technique, poor medication adherence, incorrect diagnosis of asthma, comorbidities and complicating conditions (e.g., gastroesophageal reflux disease, obesity, obstructive sleep apnea, rhinosinusitis), and ongoing exposure to irritants.

National Heart, Lung, and Blood Institute

The NHLBI EPR-3 guidelines classify asthma severity by both the level of impairment and the risk of exacerbations, instead of by symptom-based classification as in the GINA recommendations. The level of impairment focuses specifically on the frequency of symptoms (both during the day and at night), intensity of symptoms, and functional limitations. This is summarized in [Online Appendix 1](#). The NHLBI EPR-3 guidelines classify asthma as either intermittent or persistent.

Intermittent asthma typically does not limit normal activity. Patients may or may not have an exacerbation with intermittent asthma. On spirometry, the FEV_1 can be normal, especially if the individual is not having an exacerbation. Asthma for these individuals is controlled with a SABA (e.g., albuterol) as needed.

Persistent asthma is further subdivided into three groups: mild persistent, moderate persistent, and severe persistent. All components of severity (e.g., frequency of symptoms,

nighttime awakenings, use of a SABA for symptom control, interference with normal daily activity, and lung function) are considered when classifying asthma severity, and classification is based on the most severe component. For example, if an adult has minor limitations with normal activity and is using an albuterol inhaler 3 days per week but is awakening more than once per week, the individual is considered to have moderate persistent asthma.

Stepwise Approach to Treatment

Both guidelines recommend a stepwise approach to asthma treatment. Both guidelines also suggest using an inhaled SABA such as albuterol or levalbuterol as fast relief (e.g., rescue inhaler) for intermittent or exercise-induced symptoms of shortness of breath. In some European countries, a low-dose ICS plus a LABA is approved as a quick-relief agent. The theory is that increasing the ICS dose short term can lessen the severity of the acute exacerbation. In addition, the individual needs only one inhaler, instead of two separate inhalers. The GINA guidelines recommend this as an alternative to a SABA for quick relief. However, this combination of ICS and LABA medications has not been approved for use as a rescue inhaler in the United States.

Uncontrolled asthma is defined as having symptoms that occur at least 2 days per week or having nighttime awakenings related to shortness of breath more than twice per month. These individuals should be prescribed a daily controller medication, with both guidelines recommending therapy initiation with a low-dose ICS. If the individual's asthma remains uncontrolled despite adherence to therapy, controller therapy should be "stepped up," meaning the dose should be increased. When stepping up therapy, the two options are increasing the ICS dose (either with increased number of puffs per day or increased strength) or initiating a LABA to be used in combination with the ICS. The GINA guidelines recommend adding the LABA to the ICS before increasing the ICS dose, whereas the EPR-3 guidelines recommend increasing the ICS dose before considering adding a LABA. When adding a LABA to existing ICS therapy, it is beneficial to use a commercially available combination product. Combining the two medications into one inhaler increases patient convenience and adherence. If further control is needed, the ICS dose can be increased.

Overall, the GINA and EPR-3 guidelines vary only slightly. These differences are summarized in Table 1. The GINA guidelines define asthma severity by the therapy step required to achieve asthma control. Mild asthma is controlled with step 1 or 2 therapy. Moderate asthma is controlled with step 3 therapy. Severe asthma is controlled with step 4 or 5 therapy. The GINA guidelines and treatment algorithm have been updated more recently than the EPR-3 guidelines and treatment algorithm; thus, recommendations for tiotropium and mepolizumab are only discussed in the GINA recommendations. Tiotropium and mepolizumab

therapies are to be used as treatment alternatives in step 5. Although not ideal, oral corticosteroids can be given daily in severe asthma.

The EPR-3 guidelines follow the same general order of therapy as the GINA guidelines. The main difference is that in the EPR-3 guidelines, therapy is broken into a 6-step treatment algorithm as opposed to five steps with the GINA treatment algorithm. The EPR-3 recommends using omalizumab and oral corticosteroids as step 6 in therapy (NHLBI 2007).

Both guidelines recommend assessing adherence and device technique in each individual before stepping up therapy. Both guidelines also recommend assessing triggers and other comorbid conditions that may be increasing the frequency of shortness of breath symptoms. Assessment of treatment effectiveness is recommended at each visit. Treatment efficacy should be determined by symptomatic relief. Symptomatic relief can be achieved through patient questionnaires such as the Asthma Control Test (ACT), a self-administered tool endorsed by the American Lung Association and the American Thoracic Society for identifying those with poorly controlled asthma. Five items on the questionnaire pertain to symptoms and daily functioning within the previous 4 weeks. The ACT assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, effect on daily functioning, and overall self-assessment of asthma control. Each question has a 5-point scale for individuals to rate. The scores range from 5 (poor control of asthma) to 25 (complete control of asthma). An ACT score greater than 19 indicates well-controlled asthma (Nathan 2004).

Once asthma remains well controlled for at least 3 months, the GINA guidelines recommend a step-down approach to therapy to limit long-term medication exposure. Oral corticosteroids should be tapered to the lowest dose possible, and discontinuation should be considered. Discontinuing therapy alternatives such as tiotropium should be considered before decreasing the ICS dose. Stepping down ICS doses by 25%–50% at 3-month intervals is feasible and safe for most patients (GINA 2018). However, discontinuing the ICS, resulting in monotherapy with a LABA, is not indicated for asthma. Although the ICS dose can be decreased if step-down therapy is considered, the LABA dose should not be decreased if the patient is being treated with a combination inhaler (LABA plus ICS). In addition, the risk of decreased asthma control and the increased risk of subsequent asthma exacerbation are greater when adult patients are treated with an ICS as monotherapy. The GINA 2018 guidelines recommend that the LABA be discontinued in children before stepping-down the ICS dose. Developing an asthma action plan for all individuals, especially during step-down therapy, is important so that individuals are well educated on how to treat flares, should they occur (GINA 2018). The stepwise approach for managing asthma in children is summarized in Table 2 and Table 3.

Table 1. GINA vs. EPR-3 Stepwise Approach to Treatment in Individuals > 12 Yr

Medication Class	Step 1 ^a	Step 2 ^b	Step 3 ^b	Step 4 ^b	Step 5 ^b	Step 6 ^b
Quick relief – EPR-3	SABA as needed					
Quick relief – GINA	SABA as needed OR low-dose ICS/formoterol ^c					
Controller – EPR-3	None	Low-dose ICS	Low-dose ICS + LABA	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + oral corticosteroid
			OR		AND	
			Medium-dose ICS		Consider omalizumab in patients who have allergies	AND Consider omalizumab in patients who have allergies
		Alternative: LRTA, theophylline, or cromolyn	Alternative: LRTA, theophylline, or zileuton	Alternative: Medium-dose ICS + LRTA, theophylline, or zileuton		
Controller – GINA	None	Low-dose ICS	Low-dose ICS + LABA	Medium-dose ICS + LABA	Consider omalizumab	
				High-dose ICS + LABA	Consider mepolizumab	
				Add tiotropium	Add tiotropium	
					Add low-dose oral steroid	

^aIntermittent asthma.

^bPersistent asthma.

^cLow-dose ICS/formoterol for quick relief is not an approved indication in United States.

ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LRTA = leukotriene receptor antagonist; SABA = short-acting β_2 -agonist.

Information from: [National Heart, Lung, and Blood Institute \(NHLBI\). Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.](#) Bethesda, MD: NHLBI (US), 2007; and Global Initiative for Asthma (GINA). [Global Strategy for Asthma Management and Prevention.](#) 2018.

DIFFERENTIATING BETWEEN ASTHMA AND COPD

Asthma and COPD are often similar in presentation (e.g., shortness of breath, bronchoconstriction, wheezing), and both have underlying airway obstruction and inflammation. However, the mechanisms contributing to obstruction and inflammation and the complications of the diseases differ. In asthma, direct bronchoconstriction and eosinophil-related inflammation are primarily responsible for airway obstruction. Hypoxia is rare outside of serious exacerbations. In contrast, neutrophil-mediated inflammation is the primary cause of

airway obstruction in COPD. In COPD, eosinophils play a secondary role, initially occurring only during exacerbations, but seem to play a larger role in inflammation and airway obstruction as lung function declines. Obstruction with COPD occurs from increased mucous production and decreased clearance. Direct bronchoconstriction actually plays only a minor role in airway obstruction in COPD (GINA 2015).

Individuals with asthma tend to present at a younger age and have intermittent symptoms that are typically associated with a trigger exposure and PFTs indicating reversible airway obstruction. The most common complication of asthma

Table 2. Stepwise Approach for Managing Asthma in Children 0-4 Years of Age

Intermittent Asthma	Persistent Asthma: Daily Medication Consult with specialist if step 3 care or higher is required					
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	
<i>Preferred:</i> SABA as needed	<i>Preferred:</i> Low-dose ICS <i>Alternative:</i> Cromolyn or montelukast	<i>Preferred:</i> Medium-dose ICS	<i>Preferred:</i> Medium-dose ICS + either LABA or montelukast	<i>Preferred:</i> High-dose ICS + either LABA or montelukast	<i>Preferred:</i> High-dose ICS + either LABA or montelukast Oral systemic corticosteroids	Assess symptoms Step up, if needed; check adherence, inhaler technique, and environmental control Assess Control Step down, if possible, and asthma is well-controlled for at least 3 months
Patient education and environmental control at each step						
Quick-relief medication for all patients						
<ul style="list-style-type: none"> SABA as needed for symptoms (intensity is dependent on severity of symptoms) Viral respiratory infections: SABA every 4-6 hours up to 24 hours; consider short course of systemic corticosteroids if exacerbation is severe or patient has history or previous severe exacerbations Caution: Frequent use of SABA may indicate need to step up treatment 						

ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LRTA = leukotriene receptor antagonist; SABA = short-acting β_2 -agonist.

Information from: National Heart, Lung, and Blood Institute (NHLBI). [Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma](#). Bethesda, MD: NHLBI (US), 2007.

Table 3. Stepwise Approach for Managing Asthma in Children 5-11 Years of Age

Intermittent Asthma	Persistent Asthma: Daily Medication Consult with specialist if step 3 care or higher is required					
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	
<i>Preferred:</i> SABA as needed	<i>Preferred:</i> Low-dose ICS <i>Alternative:</i> Cromolyn or montelukast	<i>Preferred:</i> EITHER: Low-dose ICS + either LABA, LTRA OR Medium-dose ICS	<i>Preferred:</i> Medium-dose ICS + LABA <i>Alternative:</i> Medium-dose ICS + LTRA	<i>Preferred:</i> High-dose ICS + LABA <i>Alternative:</i> High-dose ICS + LTRA	<i>Preferred:</i> High-dose ICS + LABA + oral systemic corticosteroid <i>Alternative:</i> High-dose ICS + LTRA + oral systemic corticosteroid	Assess symptoms Step up, if needed; check adherence, inhaler technique, and environmental control Assess Control Step down, if possible, and asthma is well-controlled for at least 3 months
Patient education and environmental control at each step						
Quick-relief medication for all patients						
<ul style="list-style-type: none"> SABA as needed for symptoms (intensity is dependent on severity of symptoms). Short course of oral systemic corticosteroids may be needed Caution: Frequent use of SABA may indicate need to step up treatment 						

ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LRTA = leukotriene receptor antagonist; SABA = short-acting β_2 -agonist.

Information from: National Heart, Lung, and Blood Institute (NHLBI). [Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma](#). Bethesda, MD: NHLBI (US), 2007.

is exacerbations. When treated appropriately, most patients with asthma have a normal life span. Individuals with asthma often present with a dry cough, wheezing, or shortness of breath with intermittent episodes. Symptoms may be nocturnal and are usually related to trigger exposure. As discussed previously, triggers may be atopic (e.g., mold, pollen, animal dander, or food allergies), irritant related (e.g., perfumes, tobacco smoke, household chemicals), weather related, or exercise induced.

Conversely, COPD typically presents later in life and is most commonly associated with a history of tobacco use or occupational exposures. Unlike asthma, COPD is progressive, and symptoms worsen over months to years. Chronic obstructive pulmonary disease presents with at least some degree of irreversible airflow obstruction. Chronic obstructive pulmonary disease is categorized into chronic bronchitis and emphysema subtypes. Chronic bronchitis is demonstrated by a productive cough that is worse on awakening as well as earlier development of hypoxia and CO₂ retention. This can result in right-sided heart failure. Emphysema initially presents with exertional dyspnea that progresses over several years to dyspnea at rest (GINA 2015). Chronic obstructive pulmonary disease exacerbations increase in severity and frequency as COPD progresses. Chronic obstructive pulmonary disease will be discussed in depth in the next chapter.

TREATMENT

Many different treatment strategies, both medication based and nonpharmacologic, exist to reduce both impairment and risk of exacerbation owing to asthma. Any treatment plan should be developed as an agreement between the provider and the patient and/or caregiver and tailored to balance the risk-benefit of therapy as suited to that particular patient. Adequate patient education and planning for exacerbations should be considered a necessary part of each treatment plan.

Nonpharmacologic Treatment and Management of Triggers

Asthma may be triggered by a variety of environmental factors that can worsen the inflammatory response and lead to increased exacerbations. Once a patient-specific trigger is identified, all efforts must be made to avoid worsening of symptoms and asthma control caused by these factors. Allergens and irritants are common triggers for patients, especially allergens and irritants that are inhaled such as cold air, tobacco smoke, pollen, or cleaning agents. Examples of avoiding such triggers, respectively, include using a scarf to cover the mouth when outside in cold weather, limiting exposure to tobacco smoke, using the air conditioning in the house rather than open-window ventilation, and having the patient with asthma out of the house when it is being cleaned. Patients may consult an allergist for skin testing if specific allergens cannot be identified, and allergen immunotherapy can be considered in those for whom exposure to the

Box 1. Short-Acting β -Agonist Bronchodilators

- Albuterol sulfate (ProAir HFA)
- Albuterol sulfate inhalation powder (ProAir RespiClick)
- Albuterol sulfate (Proventil HFA)
- Albuterol sulfate (Ventolin HFA)
- Levalbuterol tartrate (Xopenex HFA)
- Albuterol sulfate, solution for nebulizer

allergen is unavoidable or insufficient to control flares. Foods that contain sulfites may worsen control of symptoms; examples include molasses, dried fruit, grape and lemon juice, and wine. Other dietary allergens are possibly associated with asthma control as well, though the relationship is not well established (NHLBI 2007).

Pharmacologic Treatment

Short-Acting β -Agonists

Available Agents

Available SABAs are listed in Box 1. These agents are available in metered dose inhalers and nebulized solutions. Previously, SABAs were available in a device that used chlorofluorocarbons (CFCs) to help deliver the medications from the inhaler. However, the Montreal Protocol prompted CFC discontinuation in respiratory devices because of the established harm to the environment. This led to the development of metered dose inhalers with newer propellants such as hydrofluoroalkane (HFA) and delivery devices. All metered dose inhalers available today contain the propellant HFA to deliver the medication.

Mechanism of Action

According to package inserts, SABAs have a quick onset and are used to rapidly relax bronchial smooth muscle from the trachea to the bronchioles through action on the β_2 -receptors.

Efficacy and Place in Therapy

Short-acting bronchodilators are often called “rescue inhalers” because they are intended to be used for acute bronchospasm in those with reversible obstructive airway disease. These bronchodilators can also be used as a pretreatment for individuals with exercise-induced bronchospasm to prevent symptoms (NHLBI 2007).

Adverse Effects Profile

According to package inserts, the most common adverse effects with SABAs include palpitations, chest pain, tachycardia, tremor, and nervousness.

Monitoring Values

Given the potential for cardiac-related adverse effects, elevations in heart rate and blood pressure, and ECG changes, patients should be monitored as clinically indicated. In addition,

Box 2. Inhaled Corticosteroids

- Ciclesonide (Alvesco HFA)
- Fluticasone furoate (Arnuity Ellipta)
- Mometasone furoate (Asmanex HFA)
- Mometasone furoate (Asmanex Twisthaler)
- Fluticasone propionate (Flovent Diskus)
- Fluticasone propionate (Flovent HFA)
- Budesonide (Pulmicort Flexhaler)
- Beclomethasone dipropionate (QVAR HFA)
- Budesonide inhalation, suspension for nebulizer

given the difficulty in coordinating dose actuation with breath, patients should be monitored for proper technique and provided with a spacer, when needed, to effectively deliver the dose. Patients should be evaluated for control of breathing symptoms, including frequency of SABA use. Those who tend to use SABAs more than 2 days per week should be considered for escalating long-term anti-inflammatory control treatment (NHLBI 2007).

Inhaled Corticosteroids

Available Agents

Available ICS agents are listed in Box 2.

Mechanism of Action

According to package inserts, ICS agents are long acting, and their mechanism of action is multifactorial. Inhaled corticosteroids reduce the initial inflammatory response by decreasing the formation and release of many inflammatory mediators such as histamine, eicosanoids, leukotrienes, and cytokines. Inhaled corticosteroids also reduce vasoconstriction and subsequent serum production, swelling, and discomfort. In addition to their anti-inflammatory properties, ICS agents produce an immunosuppressive state that limits the body's hypersensitivity reaction, which in turn may limit bronchospasm and other associated symptoms. The maximal benefit may not be realized for 1–2 weeks after initiating therapy.

Efficacy and Place in Therapy

Inhaled corticosteroids continue to be the mainstay of asthma treatment by all guideline recommendations. Inhaled corticosteroids are also preferred as the long-term control agent during pregnancy, especially budesonide because it has the most positive safety data. Inhaled corticosteroids are considered more effective than any other class of maintenance inhalers available to treat asthma. Although ICS agents improve function and reduce the risk of exacerbation, they do not appear to slow asthma progression in children (NHLBI 2007).

Controversy has existed for decades regarding ICS use in the pediatric population and the effect of ICS agents on adult height. A well-known study called the Childhood

Management Asthma Program (CAMP) trial compared budesonide 200 mcg and 400 mcg daily with nedocromil and placebo; after this study, children were enrolled in an optional observational cohort. Adult height was determined at a mean age of 25 years in 943 of the original 1041 CAMP participants. The follow-up study concluded that the adult mean height of those treated with budesonide was 1.2 cm less than in the placebo group (–0.5 to –1.9) at 24.9 years of age. This height deficit occurred 1–2 years after treatment initiation and persisted into adulthood, though the deficit was neither progressive nor cumulative. The study concluded that the systemic effects depended both on the dose and the therapeutic index of the drug. For this reason, study investigators recommend that inhaled glucocorticoids with a higher therapeutic index be used at the lowest effective dose in children with persistent asthma (Kelly 2012).

Adverse Effects Profile

Because ICS agents are corticosteroids, the most common risks are associated with their immunosuppressive nature, though the risk associated with inhaled agents is much lower than that with oral systemic agents. According to package inserts, ICS agents most notably can allow candida to flourish in the respiratory tract if the drug is deposited there rather than in the lungs. This is often called “thrush.” To prevent this, patients should rinse their mouths with water after using any agent containing a steroid. Patients should also be monitored for other signs of serious infection such as chickenpox or tuberculosis that may develop as a result of immunosuppression. More commonly, patients using ICS agents may have upper respiratory tract infections, throat irritation, sinusitis cough, and headache. Other potential more serious, but rare adverse effects include hypercorticism and adrenal suppression, reduced bone mineral density, and glaucoma/cataracts.

Monitoring Values

Package inserts state that ICS agents can lead to stunted growth velocity in children who are being chronically treated. To reduce the effect, pediatric patients should be treated with the lowest effective steroid dose. As with all treatment for asthma, the patient's FEV₁, peak flow, and other PFTs should be monitored to track the patient's progress and target the best treatment.

Combination ICS and LABA Therapy

Available Agents

Available ICS/LABA agents are listed in Box 3.

Mechanism of Action

According to package inserts, ICS agents have both anti-inflammatory and immunosuppressive properties that help with the aggravating symptoms of asthma. Long-acting β -agonists provide additional benefit by relaxing bronchial smooth muscle and inhibit the release of hypersensitivity

Box 3. Combination Inhaled Corticosteroids and Long-Acting β -Agonists

- Fluticasone propionate and salmeterol (Advair Diskus)
- Fluticasone propionate and salmeterol xinafoate (Advair HFA)
- Fluticasone furoate and vilanterol (Breo Ellipta)
- Mometasone furoate and formoterol fumarate dihydrate (Dulera)
- Budesonide and formoterol fumarate dihydrate (Symbicort HFA)
- Fluticasone propionate salmeterol (AirDuo RespiClick)

mediators from mast cells for up to 12 hours through action on the β_2 -receptors.

Efficacy and Place in Therapy

An equally preferred treatment for moderate to severe persistent asthma includes combination inhalers that contain both a LABA and an ICS. Unlike in COPD, LABAs are only to be used as combination therapy in those with asthma because the risk of death is increased with LABA monotherapy (NHLBI 2007). Results of the Salmeterol Multicenter Asthma Research Trial (i.e., SMART study) raised concerns about the safety of LABAs in asthma (Nelson 2006). At baseline, the patients received standard asthma therapy, including ICS agents, theophylline, leukotriene modifiers, or albuterol. Patients were randomized to either salmeterol twice daily or placebo. Trial results showed significantly more respiratory- and asthma-related deaths in the salmeterol group (13 deaths of 13,176 patients) than in the placebo group (3 deaths of 13,179 patients) with an RR of 4.37 (95% CI, 1.25–15.34; $p < 0.05$). A subgroup analysis suggested that this risk is greater in African American patients than in white patients.

Shortly after the study results were analyzed, the FDA conducted a meta-analysis to further investigate the findings. In the study, LABAs increased the risk of severe exacerbations that were driven by the number of asthma-related hospitalizations, especially in children 4–11 years of age. The FDA revised the labeling on all available LABAs to recommend against LABA use in asthma without another controller drug such as an ICS (FDA 2017). Further studies and meta-analyses have shown that combination therapy (LABA plus ICS) is not associated with serious asthma-related events (Rodrigo 2012).

Adverse Effects Profile

Package inserts state that the common adverse effects of ICS/LABA agents include upper respiratory tract infection, pharyngitis, dysphonia, bronchitis, headaches, and nausea/vomiting. As with ICS monotherapy, ICS/LABA agents carry a risk of oral candidiasis, which can be prevented by rinsing the mouth after using these agents.

Monitoring Values

As with other long-term control agents for asthma, FEV₁, peak flow, and PFTs should continue to be monitored as clinically indicated.

Leukotriene-Modifying Agents

Available Agents

Commercially available leukotriene receptor antagonists include montelukast (Singulair) and zafirlukast (Accolate). The only available 5-lipoxygenase inhibitor is zileuton extended release (Zyflo CR).

Mechanism of Action

Package inserts for the respective leukotriene-modifying agents state that the two distinct classes of leukotriene-modifying agents are the leukotriene receptor antagonists and the 5-lipoxygenase inhibitors. Both classes interfere with the pathway that allows mast cells, eosinophils, and basophils to release leukotriene mediators that participate in the slow phase reaction of anaphylaxis. As a result, leukotriene-modifying agents reduce symptoms associated with the inflammatory allergic component of asthma, including swelling of the airway and smooth muscle constriction.

Efficacy and Place in Therapy

Leukotriene-modifying agents are not suggested to be used first line, though they can be considered as an alternative for those with mild persistent asthma. Leukotriene-modifying agents can be added on to ICS therapy (as monotherapy or in combination with a LABA) for adults, but adding a LABA to the existing ICS therapy is preferred in those 12 years and younger. Leukotriene-modifying agents can also be used as a pretreatment for those with exercise-induced bronchospasms to prevent symptoms during physical exertion (NHLBI 2007).

Adverse Effects Profile

According to package inserts, the most common adverse effects with leukotriene-modifying agents are upper respiratory tract infection, fever, headache, pharyngitis, and cough. Those taking medications in this drug class also have a risk of developing neuropsychiatric effects. Patients should report any behavioral changes to their prescribing provider.

Monitoring Values

The package insert for zafirlukast states there is a serious risk of hepatotoxicity. Regular monitoring of liver function tests (LFTs) is suggested because early detection is associated with higher chances of recovery. Patients should be counseled to monitor for symptoms of hepatic dysfunction, including cola-colored urine, right upper quadrant abdominal pain, and nausea. If hepatotoxicity is suspected, the offending agent should be discontinued at once and the LFTs monitored serially until resolution is established. If

hepatotoxicity occurs, therapy should not be reinitiated. Leukotriene-modifying agents should not be used in those with cirrhosis.

Chromones

Available Agents

The two available agents in this class are cromolyn sodium and nedocromil, both of which are available only as a nebulized solution.

Mechanism of Action

Package inserts state that both cromolyn and nedocromil are considered mast cell stabilizers. Cromolyn and nedocromil inhibit the release of mediators such as histamine and leukotrienes from mast cells, thus reducing the allergic response that often triggers an asthmatic reaction.

Efficacy and Place in Therapy

Neither cromolyn nor nedocromil is recommended as a first-line treatment for asthma, though they can be considered as alternatives for mild persistent asthma. Cromolyn and nedocromil are indicated for pretreatment of exercise-induced bronchospasm and to reduce the allergic response to a known allergen that is unavoidable. Of note, cromolyn must be given three or four times per day and thus would not be a good option for those with concerns regarding adherence (NHLBI 2007).

Adverse Effects Profile

According to package inserts, both cromolyn and nedocromil are fairly well tolerated, with headache and diarrhea being the most commonly associated adverse effects.

Monitoring Values

Typical monitoring of long-term control of symptoms associated with asthma should be followed in those using cromolyn and nedocromil, including FEV₁, peak flow, and PFTs.

Methylxanthines

Available Agents

Currently, this class consists of only theophylline and theophylline extended release.

Mechanism of Action

The package insert states that theophylline's mechanism of action is multifactorial. Theophylline induces smooth muscle relaxation, resulting in bronchodilation as well as inhibiting the body's reaction to external allergic stimuli.

Efficacy and Place in Therapy

Theophylline therapy is not first line but can be used as an alternative to ICS therapy in those with mild persistent asthma. Theophylline's usefulness is limited by the required monitoring of blood concentrations and the agent's adverse effect profile (NHLBI 2007).

Adverse Effects Profile

The package insert states that, at therapeutic concentrations, theophylline may cause caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. These adverse effects are exaggerated with supratherapeutic concentrations. When concentrations are elevated, toxic symptoms include persistent vomiting, cardiac arrhythmias, and intractable seizures.

Monitoring Values

According to the package insert, theophylline is considered to have a low therapeutic index and therefore requires regular monitoring of blood concentrations. Concentrations should be checked after initiating therapy, before making dose adjustments, any time toxicity is suspected, or whenever a patient has a new or worsening illness that may affect drug clearance. Several specific factors that affect drug clearance include, but are not limited to, age (specifically neonates, children, and older adults), concurrent diseases (acute pulmonary edema, congestive heart failure, cor pulmonale, fever, hypothyroidism, liver/renal disease, sepsis, and shock), and smoking status. A normal theophylline concentration is less than 20 mcg/mL. Patients will need to be counseled on the signs and symptoms of severe toxicity because of theophylline use, including nausea and/or persistent vomiting. Toxicity typically occurs when the theophylline clearance is limited for reasons including pulmonary edema, heart failure, and acute hepatic disease and in those who have recently quit smoking.

Allergen Immunotherapy

Available Agents

Omalizumab (Xolair) is currently the only option available for allergen immunotherapy in the treatment of asthma.

Mechanism of Action

The package insert states that omalizumab is an anti-IgE monoclonal antibody that inhibits the binding of IgE to the mast cells and basophils. This prevents the mounting of an allergic reaction when the body releases allergic mediators.

Efficacy and Place in Therapy

Immunotherapy is not to be used as first line or monotherapy, but may be added on to a standard care regimen for patients deemed to have severe persistent asthma with a significant allergic component to their asthma. In particular, evidence is strongest for single allergens such as house dust mites, animal dander, and pollen. Immunotherapy is not to be used in children younger than 12 years (NHLBI 2007).

Adverse Effects Profile

The omalizumab package insert states that the most serious adverse effect is the potential for anaphylaxis. Thus, omalizumab should only be given by trained health care

professionals who are equipped to treat anaphylaxis, if needed. Less severe, but common adverse effects include arthralgia, pain, fatigue, dizziness, fracture, pruritus, dermatitis, and earache.

Monitoring Values

Omaliuzumab carries an extended risk of parasitic infection. Patients should be monitored for signs and symptoms, which should be reported to the prescribing provider. Patient doses are calculated on the basis of current weight and pre-dose IgE concentrations; thus, these should be monitored at least annually. Asthma symptoms including FEV₁, peak flow, and PFTs should be monitored as clinically indicated.

IL-5 Receptor Antagonists

Available Agents

The only agents available in this class are benralizumab (Fasenra), mepolizumab (Nucala), and reslizumab (Cinqair).

Mechanism of Action

Package inserts state that IL-5 inhibitors are monoclonal antibodies that bind to the IL-5 receptor on the surface of eosinophils and basophils, which lessen the inflammatory response to allergic triggers. The full mechanism is not yet clearly understood.

Efficacy and Place in Therapy

According to package inserts, IL-5 inhibitors are indicated in severe persistent asthma as adjunctive maintenance therapy for those 12 years and older who also have an eosinophilic phenotype. Although mepolizumab and benralizumab are both given subcutaneously, reslizumab is given as an intravenous infusion; all three agents are given monthly. Agents in this class are not to be used for acute asthma symptoms or in those with an acute exacerbation. Laboratory tests may show lower concentrations of sputum and serum eosinophils, though this would manifest clinically as improved asthma symptoms, as outlined in clinical treatment guidelines. Although patients should not have rapid reduction in an oral corticosteroid dose on initiation, those taking medications in this class may be able to reduce the oral corticosteroid dose significantly over time.

Adverse Effects Profile

According to package inserts for IL-5 inhibitors, the most common adverse effects include headache, injection-site reaction, back pain, fatigue, and pharyngitis. Patients who use these agents are at risk of acute hypersensitivity reactions such as anaphylaxis or angioedema. Agents should only be administered under the care of a trained health care professional equipped to treat anaphylaxis.

Monitoring Values

Given that IL-5 inhibitors are immunosuppressive agents, patients are also at risk of developing a helminth infection.

Patients should have ongoing monitoring for helminth infection and should be adequately treated for infection before restarting treatment with an IL-5 inhibitor.

Emerging Therapies

Several novel drug classes have been developed for patients whose disease has been resistant to standard asthma therapy. One such drug class is called the oral prostaglandin DP2 receptor (CRTh2) antagonists, with fevipiprant being the drug studied. One small phase II trial showed favorably improved eosinophilic production in those with allergic asthma (Gonem 2016). Investigators are recruiting for phase III trials, LUSTER 1 and 2 currently. Another drug that was originally approved as an antineoplastic agent is now being studied for severe refractory asthma. This drug is a KIT inhibitor called imatinib. By inhibiting KIT, imatinib reduces the number of bone marrow mast cells and serum tryptase concentrations. The reduced effect of mast cells and tryptase consequentially lessens airway hyper-responsiveness and thus stunts mast cell activation in those with allergic asthma. A proof-of-concept study showed reduced airway response to external stimuli after use of imatinib as well as reduced surrogate markers such as mean tryptase concentrations marking mast cell activity in the airways (Cahill 2017). Tiotropium, commonly used in COPD, is now also being investigated for asthma treatment in those whose diseases have not fully been controlled by ICS agents and bronchodilators. In a phase III randomized controlled study of patients taking ICS agents and LABAs, patients who used the add-on tiotropium soft mist inhaler had significantly improved FEV₁ peaks and troughs, suggesting that the add-on tiotropium soft mist inhaler is suitable adjunctive therapy for adolescents with uncontrolled asthma (Vogelberg 2018). Further studies are under way.

Management of Exacerbations and Treatment of Severe Asthma

Exacerbations may be treated with a combination of strategies, which should be outlined in the patient's asthma action plan. Treatment options include repeated or continuous use of SABAs, supplemental O₂, and oral systemic corticosteroid therapy. If symptoms fail to respond to these therapies, adding magnesium sulfate or heliox can be considered. Once exacerbation symptoms are initially managed, patients should be reeducated on using rescue versus maintenance inhalers and their asthma action plan, and patients' long-term inhaler choices should be adjusted to better control symptoms (NHLBI 2007).

Although many asthma cases can be controlled with an ICS with or without LABA therapy, severe asthma can be much more difficult to treat. Severe asthma is defined as asthma that requires a high-dose ICS plus a second controller, with or without systemic corticosteroids to maintain control, or asthma that remains uncontrolled despite this therapy (Chung 2016). Assessing eosinophil counts may help

Patient Care Scenario

A 16-year-old female adolescent with a diagnosis of asthma presents to the clinic today for increased wheezing and shortness of breath. Her score on the ACT today is 15. She reports using her albuterol inhaler “a couple times a day” and wakes up coughing at least once a night. Her medication list in the electronic medical record shows that she has been prescribed budesonide/formoterol 80/4.5 mcg (2 puffs twice daily), montelukast

10 mg (1 tablet once daily), and albuterol HFA (1 or 2 puffs every 6 hours as needed). However, pharmacy records show that she has only been filling the albuterol inhaler. On questioning the patient about this, she states that she was feeling great about 9 months ago, so she stopped taking all of her daily medications. What is an appropriate medication recommendation and plan for this patient?

ANSWER

This patient’s asthma is clearly uncontrolled. A score of 19 or less on the ACT shows that the patient’s asthma may not be optimally controlled, and a score of 15 or less shows that the patient’s asthma is very poorly controlled. The patient reports increased albuterol use to compensate for her increased shortness of breath. According to the patient’s account, she seems to have been well controlled on daily controller therapy and montelukast. The patient should be reeducated on the importance of using daily controller therapy (LABA plus ICS) to obtain control and continue controlling her asthma. Because the patient

is reporting nighttime awakenings every night and symptoms requiring the use of albuterol throughout the day, she should be initiated on step 5 therapy (high-dose ICS plus LABA). The patient’s asthma was previously controlled on budesonide/formoterol and montelukast, so she can be initiated on budesonide/formoterol 160/4.5 mcg (2 puffs twice daily) and can restart montelukast 10 mg once daily. She can use the albuterol inhaler as needed. The patient should be given an asthma action plan and should return to clinic in at least 3 months to assess asthma control.

1. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. 2018.
2. National Heart Lung, and Blood Institute (NHLBI). *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: NHLBI (US), 2007.

guide therapy in some adults, but this is not recommended in children. Assessing the IgE antibody may be useful in individuals with severe allergic asthma in order to consider a trial of omalizumab. Methotrexate therapy has a modest corticosteroid-sparing effect, though this effect is offset by the therapy’s potential for toxicity. Therefore, treatment with methotrexate is not recommended. Macrolide antibiotics are thought to modulate the immune system, improve tissue repair, and reduce inflammation. Macrolide antibiotics are commonly used in COPD exacerbations. However, the lack of documented clinical benefit as well as the concern for resistance prevents the recommendation for macrolides beyond treatment of acute bronchitis and sinusitis in patients with asthma. In severe asthma, antifungal therapy may be considered only if the patient has recurrent allergic bronchopulmonary aspergillosis. However, antifungal therapy should not be used in cases of positive fungal skin prick testing alone.

Pharmacists can play a key role in managing severe asthma by providing an in-depth assessment of these patients and assessing any patient barriers to adherence, device technique, and education deficits.

Special Populations

Asthma in Pregnancy

Asthma symptoms in pregnant women can vary and should be monitored at every prenatal visit. It is typically accepted that one-third of patients have improved symptoms, one-third

have worsened symptoms, and one-third notice no change in symptoms. Medications should be adjusted accordingly. Treatment agents in pregnancy include albuterol as the preferred SABA and budesonide as the preferred ICS. Budesonide is preferred because it has the most data on safety and efficacy during pregnancy. Although risks are associated with some asthma treatments, the risk to the fetus is higher if the mother’s asthma is uncontrolled (NHLBI 2007).

Surgery in Individuals with Asthma

Although no specific recommendations exist regarding changes in therapy for those undergoing surgery, patients should have controlled asthma both before and after the procedure. When lung function is not optimal, it may be prudent to give oral systemic corticosteroids before surgery. Patients who have had poor lung function, as evidenced by their systemic steroid course in the past 6 months or high-dose ICS use, may also be treated with intravenous hydrocortisone 100 mg every 8 hours during the procedure. Hydrocortisone should be rapidly reduced after the surgery (NHLBI 2007).

Treatment of Comorbid Conditions

Asthma control can be affected by several comorbid conditions, including allergic bronchopulmonary aspergillosis, gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis/sinusitis, and stress/depression. These conditions should be given special attention and managed appropriately to avoid any exacerbating symptoms and worsening of asthma control (NHLBI 2007).

Cough-Variant Asthma

A subset of asthma called cough-variant asthma (CVA), sometimes described as “chronic cough,” may precede the development of classic asthma. For patients with CVA, cough is the predominant asthma symptom. The biggest difference between asthma and CVA is the more prevalent cough response to methacholine-induced bronchoconstriction in CVA. Cough-variant asthma is also characterized by eosinophilic inflammation to the central airway, like in classic cases of asthma. Treatment for CVA is the same as for classic asthma, with ICS agents considered first-line therapy (Niimi 2011).

ROLE OF THE PHARMACIST IN MANAGING ASTHMA

Asthma Action Plan

Therapy adherence is vital to sustain good asthma control. Patients deemed to have moderate or severe persistent asthma, those with a significant history of exacerbations, and those with poorly controlled asthma should be equipped with an asthma action plan that outlines a stepwise approach for patients and caregivers to self-manage worsening symptoms. The plan should, at a minimum, include examples of worsening symptoms, which medications to take for various symptoms, and when the patient should seek immediate medical care.

Device Selection and Adherence

According to the guidelines, no evidence supports the improved efficacy (with either decreased symptoms or improved PFT results) with one delivery device over another in asthma (Dolovich 2005). The choice of device is often left to the provider or is based on the patient’s formulary. Small-scale studies suggest that patients prefer inhalers with dose counters, ease of use, comfort of the mouthpiece, and smaller inhaler size. It is important to provide patients with device options because satisfaction with therapy can lead to increased adherence (Darba 2016).

The pharmacist’s role in education must focus on an in-depth discussion of disease state management and the importance of adhering to prescribed treatment regimens. Therapy adherence can often decrease with long-term therapy. The median adherence rate for controller therapy has been reported to be only 46% of all doses, which can significantly contribute to increased hospitalizations (Boulet 2012). Lack of adherence results in poorly controlled symptoms, increased exacerbation rates, and increased health care–related costs and contributes to decreased quality of life (Sanduzzi 2014). Often, patients with poor adherence lack an understanding of their illness and the options for management. Some nonadherence is unintentional, especially if directions are misunderstood. However, much of the nonadherence with asthma therapy is intentional (e.g., fear of adverse effects, cultural beliefs, practical lifestyle decisions,

lack of perceived benefit). Moreover, many of the underlying causes of nonadherence (e.g., poverty, lack of social support, unhealthy home and/or work environment) are not easily correctable. Therefore, the pharmacist should uncover any potential barriers to care and educate patients on as many correctable adherence issues as possible. The lack of generic medications makes the cost of therapy a barrier to adherence and proper care, even if the patient is insured. Pharmacists can help identify the lowest-cost option for patients and facilitate applications for patient assistance programs in patients who are eligible.

Inhaler Education

To optimize medication delivery into the lungs, correct device technique is imperative. Poor technique is directly related to poor outcomes (Sanduzzi 2014). Studies have suggested incorrect use of metered dose inhaler technique in 89% of patients (Chapman 1993). In addition, patients have difficulty with technique when several different types of inhalers are incorporated into the treatment regimen. Risk factors for poor technique are inadequate education and instruction, poor vision, poor cognition, and low health literacy (Press 2011; Chapman 1993). Pharmacists can play a large role in assessing technique and demonstrating correct inhaler technique. Even though the guidelines recommend instruction before a patient begins the inhaler, only about 5% of children receive device demonstrations, and even fewer are evaluated on technique at initial and follow-up appointments (Sleath 2011). Initial and follow-up assessments are necessary for patients to demonstrate their knowledge and understanding of use. Knowledge of correct technique among providers (physicians, nurses, and respiratory therapists) has been documented to be inadequate (Dolovich 2005). Pharmacists should be competent in device technique and have appropriate materials available (placebo devices). Pharmacists should emphasize with the patient the importance of device technique in drug delivery and drug effectiveness.

Patients’ knowledge of inhaler technique should be evaluated at each encounter and when there is suspected nonadherence, whether intentional or unintentional. Patient’s should be taught the purpose of each inhaler, either rescue or maintenance, and the steps used to ensure proper delivery of the dosage. Educators should use simple language, intended for the age of the patients and caregivers they are teaching. Because several types of inhalers have a set of distinct and separate instructions, each inhaler should be reviewed individually. Educators should first demonstrate appropriate inhaler use with a demonstration inhaler, if available. Educators should then allow patients to demonstrate back how they will use the inhaler at home in what is called the “teach-back” method. Patients and caregivers may be provided with educational handouts detailing the use of each inhaler for future reference at home. Table 4 outlines the different inhaler devices and how each should be used.

Table 4. Inhaler Education

Inhaler Device	Available Products	Inhalation Technique
Metered dose inhaler (MDI)		
HFA	Albuterol sulfate (Ventolin HFA) Albuterol sulfate (ProAir HFA) Mometasone furoate (Asmanex HFA) Levalbuterol tartrate (Xopenex HFA) Budesonide and formoterol fumarate dihydrate (Symbicort HFA)	<ol style="list-style-type: none"> 1. Shake well before using. 2. Inhaler should be primed with 3 or 4 test sprays into the air before first use or if inhaler has not been used in several weeks. 3. Patients should breathe all air out of lungs completely and then put mouthpiece to mouth and close the lips around the mouthpiece. 4. Then, actuate the dose by pressing down on the canister while breathing in fully. The breath should be held for as long as possible or up to 10 s before exhaling gently. Patients may use a holding chamber, or spacer, to help with timing of dose actuation and breath. 5. Dose may be repeated for a second puff, if needed; wait 1 min in between puffs. 6. Inhaler mouthpiece should be cleaned with warm water weekly.
Dry powder inhaler (DPI)		
Diskus	Fluticasone propionate and salmeterol (Advair Diskus) Fluticasone propionate (Flovent Diskus)	<ol style="list-style-type: none"> 1. Patients should first remove the inhaler from the foil pouch and write the use-by date on the Diskus (30 days from opening). 2. Diskus should be held horizontally, like a hamburger, and should not be tilted or shaken or the powder in the inhaler may be prematurely released from the device. 3. Once the mouthpiece cover has been slid open, the lever should be pushed back to activate the Diskus. 4. Patients should then exhale completely away from the device and then place lips to cover the mouthpiece. 5. Patients will then forcefully inhale through the mouth to deliver the dose into the lungs. Patients may hold the dose in the lungs for several seconds before exhaling. 6. This inhaler should not be used with a spacing device or holding chamber. 7. Because these inhalers contain a steroid, patients should rinse their mouths out with water after each use. 8. The dose indicator will show how many doses remain, and the inhaler should be discarded once 30 days have passed since opening. 9. Because the dose is a powder inside the inhaler, patients should ensure the inhaler is stored in a cool, dry space and not cleaned with water at any time.
Ellipta	Fluticasone furoate (Arnuity Ellipta) Fluticasone furoate and vilanterol (Breo Ellipta)	<ol style="list-style-type: none"> 1. Patients should first remove inhaler from original container and write the use-by date on the Ellipta (6 wk from opening). 2. Patients should slide open the cover to the Ellipta until they hear a click. ONLY slide the cover open when patients are ready to use the device. 3. The Ellipta should be held horizontally, like a hamburger, and should not be tilted or shaken or the powder in the inhaler may be prematurely released from the device. 4. Patients should exhale completely away from the device and then place lips to cover the mouthpiece where patients will forcefully inhale through the mouth to deliver the dose into the lungs. This inhaler should not be used with a spacing device or holding chamber. 5. Patients may hold the dose in the lungs for several seconds before exhaling. 6. Because these inhalers contain a steroid, patients should rinse their mouths out with water after each use. 7. The dose indicator will show how many doses remain, and the inhaler should be discarded once 6 wk have passed since opening. 8. Because the dose is a powder inside the inhaler, patients should ensure the inhaler is stored in a cool, dry space and not cleaned with water at any time.

Table 4. Inhaler Education (*continued*)

Inhaler Device	Available Products	Inhalation Technique
Dry powder inhaler (DPI)		
Flexhaler	Budesonide (Pulmicort Flexhaler)	<ol style="list-style-type: none">1. Inhaler should be held in upright position with the mouthpiece facing up. The inhaler should NOT be shaken before use, but it should be primed before the first use.2. Patients should exhale breath completely and then place lips to mouthpiece and inhale forcefully through the mouth. This inhaler should not be used with a spacing device or holding chamber.3. Patients may hold dose in lungs for several seconds before exhaling.4. Because these inhalers contain a steroid, patients should rinse their mouths out with water after each use.5. Patients should use the dose indicator to show when to get a new inhaler.6. Because the dose is a powder inside the inhaler, patients should ensure the inhaler is stored in a cool, dry space and not cleaned with water at any time.
RespiClick	Albuterol sulfate inhalation powder (ProAir RespiClick) Fluticasone propionate and salmeterol (AirDuo RespiClick)	<ol style="list-style-type: none">1. Patients will not need to shake or prime the device before using.2. Patients should exhale completely and then breathe in forcefully through the mouth to deliver the dose. This inhaler should not be used with a spacing device or holding chamber.3. Patients may hold the dose in the lungs for several seconds before exhaling.4. Inhaler should be cleaned regularly by wiping it down with a dry cloth.5. Because the dose is a powder inside the inhaler, patients should ensure the inhaler is stored in a cool, dry space and not cleaned with water at any time.
Twisthaler	Mometasone furoate (Asmanex Twisthaler)	<ol style="list-style-type: none">1. This device should NOT be shaken or primed before use.2. Breathe all air out of lungs; place mouth to mouthpiece and seal the lips on the device. This inhaler should not be used with a spacing device or holding chamber.3. Hold the inhaler in a horizontal position and inhale quickly and deeply.4. Patients may hold the dose in the lungs for several seconds before exhaling.5. Rinse mouth after use because this inhaler contains a steroid.6. Because the dose is a powder inside the inhaler, patients should ensure the inhaler is stored in a cool, dry space and not cleaned with water at any time.

Results of educational sessions should always be documented in the medical record, including the patient's ability to teach-back key information and demonstrate their understanding of the use of inhalers. To help with follow-up visits, any unresolved issues (e.g., technique problems) should also be documented.

Medication Access and Acquisition

A well-developed treatment plan is only effective as long as patients can obtain the prescribed medications. Prescribers must ensure that their patients have insurance or some plan for medication coverage. Inhalers are difficult for patients to obtain because formularies are constantly changing, and the preferred agent in a class is sometimes convoluted for prescribers to identify. If possible, prescribers should consult the formulary of the patient's insurance before prescribing. Alternative resources are available for commercially insured patients (e.g., manufacturer-funded

savings cards and free trial offers). Patients without sufficient drug coverage through their Medicare Part D plan may be eligible for assistance through a variety of avenues, including the Low Income Subsidy program through the Social Security Agency, patient assistance programs through the drug manufacturer, and other locally available assistance groups.

CONCLUSION

Asthma offers the clinical pharmacist many opportunities to help select and optimize treatment options. Pharmacists are well-versed in the pharmacotherapy and device options and can be fundamental in selecting the most therapeutically sound, least expensive regimen that will provide high patient satisfaction, adherence, and acceptance. Pharmacists should model best practices when documenting in medical records and when educating patients to take an active role in their health care.

Practice Points

- Asthma diagnoses should be confirmed with PFTs to establish the correct diagnosis and rule out other respiratory and nonrespiratory conditions that may present with similar symptoms.
- Asthma classification is imperative for proper treatment selection.
- Selection of initial therapy should be based on both objective and subjective (e.g., symptoms) data.
- Therapy adherence is significantly influenced by patient preferences and perceptions. The pharmacist should routinely assess and incorporate these preferences and perceptions when recommending the therapeutic regimen. Misperceptions and misinformation should be addressed.
- Monitoring with symptom-based questionnaires (e.g., ACT) helps in assessing treatment response and escalating or de-escalating therapy.

REFERENCES

- [No authors listed]. [Standardization of spirometry, 1994 update](#). *Am J Respir Crit Care Med* 1995;152:1107-36.
- Boulet LP, Vervloet D, Magar Y. [Adherence: the goal to control asthma](#). *Clin Chest Med* 2012;33:405-17.
- Burke W. [Family history as a predictor of asthma risk](#). *Am J Prev Med* 2003;24:160-9.
- Busse WW. [Asthma](#). *N Engl J Med* 2001;344:350-62.
- Cahill KN, Katz HR, Cui J, et al. [KIT inhibition by imatinib in patients with refractory asthma](#). *N Engl J Med* 2017;376:1911-20.
- Chapman KR, Love L, Brubaker H. [A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects](#). *Chest* 1993;104:1332-7.
- Chung KF. [Dupilumab: a potential new treatment for severe asthma](#). *Lancet* 2016;388:3-4.
- Darba J, Ramirez G, Sicras A. [Identification of factors involved in medication compliance: incorrect inhaler technique of asthma treatment leads to poor compliance](#). *Patient Pref Adher* 2016;10:135-45.
- Dezateux C, Stocks J, Dundas I, et al. [Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma](#). *Am J Respir Crit Care Med* 1999;159:403-10.
- Dolovich MB, Ahrens TC, Hess DR, et al. [Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology](#). *Chest* 2005;127:335-71.
- Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA Review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). Updated December 2017.
- Global Initiative for Asthma (GINA). 2018. [Global Strategy for Asthma Management and Prevention](#).
- Global Initiative for Asthma (GINA). 2015. Asthma, COPD, and Asthma-COPD Overlap Syndrome (ACOS). Available for download at <https://ginasthma.org/asthma-copd-and-asthma-copd-overlap-syndrome-acos/>. Accessed December 11, 2018.
- Gonem S, Berair R, Singapuri A, et al. [Fevipirant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-center, randomized, double-blind, parallel-group, placebo-controlled trial](#). *Lancet Respir Med* 2016;4:699-707.
- Holgate ST, Polosa R. [The mechanisms, diagnosis, and management of severe asthma in adults](#). *Lancet* 2006;368:780-93.
- Kelly WH, Sternberg AL, Lescher R, et al. [Effect of inhaled glucocorticosteroids in children on adult height](#). *N Engl J Med* 2012;367:904-12.
- Kramer MS, Kakuma R. [Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child](#). *Cochrane Database Syst Rev* 2006;3:CD000133.
- Martindale S, McNeill G, Devereux G, et al. [Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life](#). *Am J Respir Crit Care Med* 2005;171:121-8.
- Martinez FD, Wright AL, Taussig LM, et al. [Asthma and wheezing in the first six years of life](#). *N Engl J Med* 1995;332:133-8.
- Nathan RA, Sorkness CA, Kosinski M, et al. [Development of the asthma control test: a survey for assessing asthma control](#). *J Allergy Clin Immunol* 2004;113:59-65.
- National Heart, Lung, and Blood Institute (NHLBI). [Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma](#). Bethesda, MD: NHLBI (US), 2007.
- Nelson HS, Weiss ST, Bleecker ER, et al. [The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol](#). *Chest* 2006;129:15-26.
- Niimi A. [Cough and asthma](#). *Curr Respir Med Rev* 2011;7:47-54.
- Pelligrino R, Viegi G, Brusasco V, et al. [Interpretative strategies for lung function tests](#). *Eur Respir J* 2005;26:948-68.
- Press VG, Arora VM, Shah LM. [Misuse of respiratory inhalers in hospitalized patients with asthma or COPD](#). *J Gen Intern Med* 2011;26:635-42.
- Reddel HK, Bateman ED, Becker A, et al. [A summary of the new GINA strategy: a roadmap to asthma control](#). *Eur Respir J* 2015;46:622-39.
- Rodrigo G, Castro-Rodriguez JA. [Safety of long-acting \$\beta\$ agonists for the treatment of asthma: clearing the air](#). *Thorax* 2012;67:342-9.

Romagnani S. [T-cell subsets \(Th1 versus Th2\)](#). Ann Allergy Asthma Immunol 2000;85:9-18.

Sanduzzi A, Balbo P, Candoli P, et al. [COPD: adherence to therapy](#). Multidiscip Respir Med 2014;9:60-9.

Sears MR, Greene JM, Willan AR, et al. [A longitudinal, population-based, cohort study of childhood asthma followed to adulthood](#). N Engl J Med 2003;349:1414-22.

Sleath B, Ayala GX, Gillette C, et al. [Provider demonstration and assessment of child device technique during pediatric asthma visits](#). Pediatrics 2011;127:643-8.

Subbarao P, Becker A, Brook JR, et al. [Epidemiology of asthma: risk factors for development](#). Expert Rev Clin Immunol 2009;5:77-95.

To T, Stanojevic S, Moores G, et al. [Global asthma prevalence in adults: findings from the cross-sectional world health survey](#). BMC Public Health 2012;12:204.

Vogelberg C, Engel M, Laki I, et al. [Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma](#). J Allergy Clin Immunol Pract 2018;6:2160-2162.e9.

Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

M.B. is a 22-year-old man who has had wheezing and coughing for the past year. In the past few months, M.B. has used his friend's albuterol inhaler three times per week and 1 night a week for coughing that awakens him during the night.

- Which one of the following best classifies M.B.'s asthma severity?
 - Intermittent
 - Mild persistent
 - Moderate persistent
 - Severe persistent
- Which one of the following is the best controller therapy to recommend for M.B.'s asthma?
 - Salmeterol 50 mcg – 1 puff daily
 - Montelukast 10 mg once daily
 - Mometasone 100 mcg/formoterol 5 mcg – 2 puffs twice daily
 - Fluticasone 110 mcg – 1 puff twice daily
- A 37-year-old African American man with asthma is concerned. "I have seen television commercials that my Advair medicine can cause bad asthma attacks. I want to breathe better, but I am nervous about taking my Advair now." His Asthma Control Test (ACT) score today is 15. His prescription profile shows that his fluticasone propionate 250 mcg plus salmeterol 50 mcg Diskus has been filled on time for the past 3 months. During that time, the patient has used 1 canister of albuterol and says he has only needed it a few times a week during this time. Which one of the following is the best response to give this patient?
 - It is recommended to avoid salmeterol in the African American population.
 - The fluticasone/salmeterol combination is appropriate for you because your asthma is not well controlled.
 - The salmeterol component should be discontinued because your asthma is well controlled.
 - The fluticasone component should be discontinued because your asthma is well controlled.
- A woman with asthma has received 6 months of high-dose inhaled corticosteroid (ICS) plus LABA therapy. She lives in a rural area, and transportation for medical visits is difficult. Her ACT scores are 16–18. Skin prick test results show sensitivity to feather mix, cat hair, Bermuda grass, hickory/pecan mix, and fungus. Presuming she has good device technique, which one of the following is best to recommend adding to this patient's regimen?

- Tiotropium 1.25 mg – 2 puffs twice daily
- Azithromycin 250 mg – 1 tablet three times weekly
- Ketoconazole 200mg – 1 tablet daily
- Methotrexate 2.5mg – 1 tablet daily

Questions 5 and 6 pertain to the following case.

A.B., a 6-year-old girl with asthma, has been receiving fluticasone propionate 44 mcg – 1 puff twice daily by metered dose inhaler with a holding chamber. Her mother reports that A.B. awakens 1 or 2 nights per month because of asthma. She has missed 3 days of school this semester and has trouble participating in activities during gym class. A review of her pharmacy profile for the past few months shows monthly refills for fluticasone and albuterol.

- Which one of the following is best to recommend for A.B.?
 - Increase fluticasone propionate to 110 mcg – 1 puff twice daily.
 - Discontinue fluticasone inhaler, and add fluticasone/salmeterol dry powder inhaler 250/50 mcg – 1 puff twice daily.
 - Add montelukast 10 mg once daily.
 - Change to budesonide 0.25mg/mL (nebulized) twice daily.
- Three years later, A.B. is now receiving fluticasone 250 mcg/salmeterol 50 mcg twice daily in a combination inhaler. She has had about one nighttime awakening episode per month for the past 6 months and has had to refill albuterol only twice in the past 6 months. She does use albuterol about 4–6 times per week before soccer practice. Which one of the following is best to recommend for A.B.?
 - Change regimen to fluticasone 100 mcg/salmeterol 50 mcg twice daily.
 - Change regimen to fluticasone 200 mcg/vilanterol 25 mcg once daily.
 - Change regimen to salmeterol 50 mcg twice daily.
 - Change regimen to fluticasone 110 mcg twice daily.

Questions 7 and 8 pertain to the following case.

L.T., a 14-year-old male adolescent, has a family history of asthma and a diagnosis of moderate to severe asthma. He was recently initiated on Flovent HFA metered dose inhaler 110 mcg/puff – 1 puff twice daily with albuterol 90 mcg/puff – 1 or 2 puffs every 4–6 hours as needed. Today is his 2-week follow-up at the clinic; L.T.'s ACT score is 17, and he is having nighttime awakening two or three times per week. He is using

his short-acting bronchodilator two or three times per week during the day, not including exercise. You recognize that L.T. has been taking his fluticasone regularly but has not been using the inhaler correctly.

7. Which one of the following is the best educational point to give L.T. regarding this metered dose inhaler (Flovent HFA)?
 - A. The inhaler should be primed before each use.
 - B. Inhale with a forceful breath to activate the canister.
 - C. A metered dose inhaler should only be used with a spacer.
 - D. Shake the inhaler before use.
8. After 1 month of treatment and improved technique, L.T. continues to have nighttime symptoms two or three times per week. Which one of the following is best to recommend for L.T.?
 - A. Add montelukast 10 mg once daily.
 - B. Change to fluticasone/salmeterol 250/50 mcg per puff, 1 puff twice daily.
 - C. Change to fluticasone/salmeterol 500/50 mcg per puff, 1 puff twice daily.
 - D. Change to fluticasone/vilanterol 200/25 mcg, 1 puff once daily.
9. A 10-year-old boy presents after recent pulmonary function testing. His FEV₁ was 84% of predicted with a percentage of the FVC expired in 1 second (FEV₁/FVC) ratio of 81%. The patient's current drug list includes albuterol HFA as needed and cetirizine 5 mg once daily. He has had nighttime awakenings because of shortness of breath twice weekly for the past month, but has only required his albuterol inhaler three times per week during the day. Which one of the following is the best initial controller medication to recommend for this patient?
 - A. Fluticasone/salmeterol 250/50 mcg – 1 puff twice daily
 - B. Fluticasone propionate 110 mcg – 1 puff twice daily
 - C. Fluticasone furoate 200mcg – 1 puff once daily
 - D. Salmeterol 50 mcg twice daily
10. A 26-year-old pregnant woman (first trimester) with well-controlled asthma presents to her family medicine clinic to establish care for her pregnancy. Her home drugs include fluticasone propionate 110 mcg twice daily and albuterol as needed. The patient has not had to use her rescue inhaler either at night or during the day in more than 30 days. Her last exacerbation was 3 years ago. She is requesting a refill on both inhalers. Which one of the following is best to recommend for this patient?
 - A. Refill both fluticasone 110 mg inhaler and albuterol inhaler.
 - B. Change fluticasone to budesonide 180 mcg – 2 puffs twice daily and refill albuterol.
 - C. Change fluticasone to budesonide 180 mcg – 1 puff twice daily and refill albuterol.
 - D. Change fluticasone to budesonide/formoterol 160/4.5 mcg – 2 puffs twice daily and refill albuterol.
11. A young boy and his mother present to the clinic for medication education. The patient is currently prescribed albuterol HFA as needed, montelukast 10 mg once daily, and fluticasone/salmeterol HFA 115/21 mcg – 2 puffs twice daily. The mother worries that her son is not getting all the medication from his inhalers because he seems to still be coughing a lot. She has both inhalers with her in the clinic today for you to assess technique. Which one of the following educational points on inhalation technique is best to give this patient and his caregiver?
 - A. Hold the inhalers horizontally and do not tilt or shake.
 - B. A holding chamber (spacer) will help with timing of dose actuation and breath.
 - C. Store in a cool, dry location to prevent moisture reaching the inhalation powder.
 - D. Wait 30 minutes in between using each inhaler.
12. A patient asks whether he can change his budesonide inhaler to a combination of budesonide/formoterol inhaler to be used in place of his albuterol inhaler. His asthma is well controlled with a budesonide 180 mcg twice daily, and he has not had to use his albuterol inhaler for the past 2 weeks. He travels throughout the United States and Europe for work and does not like to carry around two inhalers. He heard from some of his colleagues in Europe that the combination product of budesonide/formoterol is just as effective as albuterol and wants your opinion. Which one of the following is best to recommend for this patient?
 - A. The GINA guidelines recommend budesonide/formoterol for quick relief for patients in steps 3–5, so using budesonide/formoterol as a rescue inhaler is acceptable.
 - B. Recommend that the patient continue his current regimen because the combination regimen is not approved for use as a rescue inhaler in the United States.
 - C. Increase the budesonide dose to 160/4.5 mcg – 2 puffs twice daily to eliminate the need for an albuterol inhaler.
 - D. Add on montelukast 10 mg once daily for the patient to take with budesonide/formoterol, and discontinue the albuterol inhaler.

13. A 33-year-old patient is establishing care with your clinic today. She states that she recently lost her job and that her insurance will become inactive at the end of the month. Her disease is well controlled on fluticasone/salmeterol HFA, and she uses albuterol HFA as needed but will be unable to afford the medications once she is uninsured. The patient does not know when she will obtain health insurance again because she has no other job lined up and cannot afford to purchase a plan on the health care exchange. She has been using her fluticasone/salmeterol inhaler once daily instead of twice daily to avoid running out of her inhaler. Which one of the following is best to recommend for this patient?
- A. Stop using the fluticasone/salmeterol inhaler, and have the physician prescribe nebulized albuterol (available for \$10 at a local big-box store with a pharmacy) to use four to six times daily.
 - B. Recommend oral prednisone (\$4 at a local big-box store with a pharmacy) to decrease inflammation until she obtains insurance.
 - C. Encourage and help the patient apply for patient assistance from the drug manufacturers to receive the products for free while she is uninsured.
 - D. Encourage the patient to apply for Low Income Subsidy through Social Security.

Questions 14 and 15 pertain to the following case.

A.S., a 42-year-old man, is a nonsmoker. Although he has been given albuterol periodically throughout the years, he currently has no active prescription. A.S. has been using his neighbor's albuterol inhaler when he has chest tightness and shortness

of breath. Today in the clinic, he had spirometry with pre- and post-bronchodilator use, which confirmed a diagnosis of asthma. A.S.'s post-bronchodilator readings were FEV₁ 69% of predicted and FEV₁/FVC 77%.

14. Using the EPR-3 treatment algorithm, which one of the following is best to recommend as A.S.'s initial treatment regimen?
- A. Albuterol HFA as needed to control symptoms of shortness of breath
 - B. Fluticasone HFA 220 mcg – 1 puff twice daily plus albuterol HFA as needed
 - C. Fluticasone/salmeterol 250/50 mcg – 1 puff twice daily plus albuterol HFA as needed
 - D. Tiotropium 2.5mcg once daily plus albuterol HFA as needed
15. Three months later, A.S. returns to the clinic for a follow-up. He believes he is doing well on the regimen you recommended, but says he still has to use his albuterol inhaler at least once daily. Which one of the following is best to recommend for A.S.?
- A. Change regimen to fluticasone/salmeterol 250/50 mcg – 1 puff twice daily and continue albuterol as needed.
 - B. Initiate a prednisone taper for 7 days to help decrease use of the albuterol inhaler.
 - C. Continue current regimen and have the patient schedule albuterol use.
 - D. Change regimen to fluticasone/salmeterol 500/50 mcg – 1 puff twice daily and continue albuterol as needed.