



Asthma Guideline Updates

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LEARNING OBJECTIVES

1. Analyze spirometry to determine the diagnosis and severity of asthma.
2. Classify patient symptoms to help guide the intensification of drug therapy.
3. Assess the differences in therapeutic recommendations between the GINA 2021 guidelines and the NHLBI 2020 Focused Update.
4. Design an initial therapeutic regimen consistent with the current treatment guidelines for asthma, and revise as appropriate according to therapeutic response.
5. Evaluate a patient's asthma therapy to maximize outcomes, and justify adjunctive therapy and modifications according to the needs, skill level, and preferences of the patient.

ABBREVIATIONS IN THIS CHAPTER

ACT	Asthma Control Test
COPD	Chronic obstructive pulmonary disease
FEV ₁	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
LABA	Long-acting β_2 -agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
NAEPP	National Asthma Education and Prevention Program
NHLBI EPR-3	National Heart, Lung, and Blood Institute Expert Panel Report 3
PFT	Pulmonary function test
SABA	Short-acting β_2 -agonist
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SMART (MART)	Single maintenance and reliever therapy .

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 airway inflammation. As one of the most common respiratory diseases in the world today, asthma affects about 300 million people worldwide, which is expected to increase to 400 million by 2025 (Dharmage 2019). 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 2021 Global Initiative for Asthma (GINA) guidelines estimate the global prevalence to be 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 costs 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 2021).

Etiology

Although asthma is one of the most common chronic conditions in both adults and children, much is unknown about its cause. Moreover, although there is a clear genetic predisposition to asthma, there is also an environmental component, which explains the international variation in prevalence. Asthma encompasses a range of heterogeneous phenotypes (clinical presentations) that differ in cause and pathophysiology. Several clinical phenotypes have been identified, the most common of which are allergic asthma, intrinsic asthma, neutrophilic asthma, aspirin-intolerant asthma, and extensive remodeling asthma (Sinyor 2021). Asthma is an umbrella diagnosis for several diseases with direct mechanistic pathways

(endotypes). The definition of these endotypes is central to asthma management because of therapeutic and prognostic implications (Kuruville 2019). Newer biologic agents are targeted toward recently defined endotypes. Although a family history of asthma is common, it is not necessary for the development and subsequent diagnosis of asthma. As the link between genetic factors and asthma phenotypes and endotypes is discovered, future treatment approaches may become directed to specific phenotypes and genotypes.

Asthma seems to occur during the development of the immune system in early childhood for most patients. One of the most commonly accepted theories is the hygiene hypothesis, or more recently reframed as “the old friends” theory, which involves the idea of innate immunity (van Tilburg Bernardes 2017). To understand innate immunity, the role of helper T cells within the immune system must first be recognized. Type 1 helper T (Th1) and type 2 helper T (Th2) cells are two forms of CD4⁺ helper T cells involved in cell-mediated immune responses. The hygiene hypothesis suggests that the development of certain infections in early life, exposure to other children, and minimal use of antibiotics are associated with a Th1-dominated immune response that seems to correlate with a lower incidence of asthma. In addition, the absence of these factors is theorized to alter the balance between Th1 and Th2 cytokine responses early in life and increase the likelihood that the immune response will down-regulate the Th1 immune response that fights infection.

BASELINE KNOWLEDGE STATEMENTS

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

- Concepts behind interpreting common pulmonary function tests such as FEV₁ and FEV₁/FVC ratio
- Underlying pathophysiology of asthma
- Pharmacology of β_2 -agonists, inhaled corticosteroids, long-acting antimuscarinic agents, biologics, and leukotriene modifiers 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. National Heart, Lung, and Blood Institute \(US\).](#) 2007.
- NHLBI. [2020 Focused Update to the Asthma Management Guidelines.](#) 2020.
- GINA. [Global Strategy for Asthma Management and Prevention.](#) 2021.

Therefore, the immune response will be dominated by Th2 cells. This process is thought to contribute to the expression of allergic disease and asthma (van Tilburg Bernardes 2017).

During infancy, several respiratory viruses, specifically respiratory syncytial virus and parainfluenza virus, have been associated with the inception or development of asthma (NHLBI 2007). Respiratory syncytial virus infection is associated with subsequent recurrent wheeze, and preventive treatment of premature infants with monthly injections of the monoclonal antibody palivizumab is associated with a reduction in recurrent wheezing in the first year of life. However, little evidence suggests this effect is sustained; thus, the long-term effect of palivizumab in the prevention of asthma remains unknown (Blanken 2013). Other evidence also indicates that certain respiratory infections early in life can in fact protect against the development of asthma by an interaction with atopy. The atopic state can influence the lower airway response to viral infections, which may then influence the development of allergic sensitization (GINA 2021; NHLBI 2007). This is an area of ongoing research that is not yet well defined.

Environmental factors are important to consider in the development, persistence, and severity of asthma. Many environmental factors can contribute to the development of asthma, including inhaled and ingested allergens, pollutants (particularly tobacco smoke), microbes, and psychosocial factors (GINA 2021). Evidence is inconclusive to recommend efforts to reduce or increase prenatal or early life exposure to common sensitizing allergens (e.g., pets) for the prevention of asthma and allergies. However, some evidence indicates that a reduction in inhaled allergen exposure in early childhood is associated with a lower risk of asthma diagnosis in children younger than 5 years (O'Connor 2018). Other environmental factors, including tobacco smoke exposure, air pollution, and diet, have been, and will continue to be, studied for their potential roles in the development and persistence of asthma. 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 were not designed for long-term follow-up to be able to provide recommendations (NHLBI 2007). However, exposure to outdoor pollutants, such as living near a main road, is associated with an increased risk of developing asthma. A recent study suggested that up to 4 million new pediatric asthma cases are attributable to exposure to traffic-related air pollution (Bowatte 2015). Environmental exposure and triggers may affect asthma differently at various times of a person's life, and risk factors for asthma in individual patients may change over time.

Certain prenatal risk factors are strongly associated 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 (Toppila-Salmi 2020; Hu 2017). In addition, data suggest that maternal obesity and weight gain during pregnancy pose an increased risk of asthma in children. A meta-analysis showed that maternal obesity in pregnancy was associated with a 2%–3% increase in the odds of the development of childhood asthma with each 1-kg/m² increase in maternal BMI (Forno 2014). However, although no recommendations can currently be made, unguided weight loss in pregnancy should be discouraged. Conversely, prenatal diet and nutrition may play a protective role in the infantile development of asthma. A recent study showed that maternal intake of foods commonly considered allergenic (e.g., peanuts and milk) was in fact associated with a decrease in allergy and asthma in the offspring (Fujimura 2019). These data were similar to those in a large Danish National Birth Cohort, which showed an association between the ingestion of peanuts, tree nuts, and/or fish during pregnancy and a decreased risk of asthma in the offspring. Epidemiologic studies and randomized controlled trials of maternal dietary intake of fish or long-chain polyunsaturated fatty acids during pregnancy have shown no consistent effects on a child's risk of wheeze, asthma, or atopy. Therefore, dietary changes during pregnancy are not recommended for prevention of allergies or asthma (GINA 2021).

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 (GINA 2021).

Airflow limitation is caused by four main changes in the airway, all of which are influenced by airway inflammation: bronchoconstriction, airway hyper-responsiveness, mucous hypersecretion, 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 immunoglobulin (Ig)E-dependent release of mediators from mast cells that include histamine, tryptase, leukotrienes, and prostaglandins, which directly contract airway smooth muscle (Yamauchi 2019). 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. Mechanisms influencing airway hyper-responsiveness include inflammation, dysfunctional neuroregulation,

and structural changes. Of these, inflammation appears to be the main factor determining the degree of airway hyper-responsiveness. Structural changes can occur, including hypertrophy and hyperplasia of the airway and smooth muscle. Throughout the disease, 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 (Sinyor 2021). Of note, different manifestations of asthma may have varying patterns of inflammation and intensity of exacerbation. However, inflammation triggers airway hyper-responsiveness and airway obstruction, leading to clinical asthmatic symptoms in all cases.

DIAGNOSIS

Physical Examination

When a diagnosis of asthma is suspected, a detailed medical history, physical examination, and spirometry testing should be obtained. The provider should assess whether recurrent episodes of airflow obstruction or symptoms of airway hyper-responsiveness are present and whether the airflow obstruction is at least partly reversible. Other diagnoses, such as vocal cord dysfunction, must be excluded. The presence of several clinical features increases the likelihood of an asthma diagnosis, but spirometry is needed to make a formal diagnosis.

Common phenotypes (e.g., observable clusters of characteristics) described in infancy and early childhood are wheezing: transient, nonatopic, late onset, and persistent. Most children with persistent wheezing (in whom asthma will subsequently be diagnosed) experience symptoms before 3 years of age. By age 3, the child will have abnormal lung function that persists to adulthood. By adolescence, most will have developed symptoms of atopic disease. Although about 50% of preschool children have experienced wheezing at some point, only about 10%–15% of children have a true diagnosis of asthma by the time they are school aged (Subbarao 2009). Distinguishing between the different phenotypes in early childhood is important to understand the role of risk factors and treatment selection.

There are several key symptom indicators for considering a diagnosis of asthma. Typically, patients with asthma present with wheezing. Wheezing can be defined as high-pitched whistling sounds heard in the expiratory phase. Patients may present with a history of cough (often worse at night) and recurrent wheezing, difficulty breathing, and periods of chest tightness. Symptoms of asthma often worsen on exertion, such as during exercise, strong emotional expression (e.g., laughing or crying), or periods of increased stress. Symptoms may also occur or worsen during viral infections, exposure to inhalant allergens or airborne irritants (e.g., tobacco smoke or chemicals), and/or changes in weather (Saglani 2019).

During the physical examination, the provider should focus on the upper respiratory tract, chest, and skin. The upper respiratory tract may show increased nasal secretions, mucosal swelling, and/or nasal polyps. Chest examination will reveal sounds of wheezing during normal breathing or a prolonged phase of forced exhalation. Examination may also reveal hyperexpansion of the thorax, use of accessory muscles, appearance of hunched shoulders, or 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 with each episode, the absence of any of these findings does not rule out asthma (Saglani 2019).

Spirometry

Pulmonary function tests (PFTs) such as spirometry are useful to diagnose the cause of respiratory symptoms and guide pharmacologic treatment. Spirometry should be performed by personnel who are trained in the equipment used and the appropriate patient coaching techniques to achieve acceptable and reproducible results. Pulmonary function test measurements take about 15 minutes to perform and up to 45 minutes if pre- and post-bronchodilator testing is warranted. Spirometry is performed to demonstrate the level of obstruction and assess 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 to be used as asthma monitoring tools only.

Three values from spirometry testing are useful for diagnosing asthma: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and 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 the Third National Health and Nutrition Examination Survey defines as less than 90% of predicted in children 5–18 years of age (or below the lowest 5% of the reference population) or less than 70% of predicted in adults (or below 5% of the reference population). However, caution is advised with use of FEV_1/FVC ratio as a cutpoint because it can result in a false-positive diagnosis of obstruction in older adults and a potentially false-negative diagnosis in younger adults, given a natural decrease in FEV_1 with age (Brigham 2015). The FEV_1 in patients with mild, or well-controlled, asthma may be normal (greater than 80% of the predicted value). After three acceptable FEV_1 and FVC measurements are obtained, the patient is administered a bronchodilator (e.g., albuterol), and the test is repeated. Airways in patients with asthma are typically responsive to bronchodilator treatment. Improvement in FEV_1 of 12% (or 200 mL) or greater after bronchodilator treatment indicates

bronchodilator reversibility and is consistent with a diagnosis of asthma (Brigham 2015). Conversely, chronic obstructive pulmonary disease (COPD) is not considered reversible, and there would be little, if any, improvement after bronchodilator treatment (NHLBI 2007).

DIFFERENTIATING BETWEEN ASTHMA AND COPD

Asthma vs. COPD

Asthma and COPD often have a similar 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 severe exacerbations. In contrast, neutrophil-mediated inflammation is the primary cause of airway obstruction in COPD. In COPD, eosinophils play a secondary role, initially only during exacerbations, but seem to play a larger part in inflammation and airway obstruction as lung function declines. Obstruction with COPD occurs from increased mucous production and decreased clearance. Direct bronchoconstriction plays only a minor role in airway obstruction in COPD.

Individuals with asthma tend to present at a younger age and have intermittent symptoms that are typically associated with a trigger exposure. In addition, PFTs show reversible airway obstruction. The most common complication of asthma 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. 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 usually 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 discussed in depth in the next chapter. Furthermore, a subset of patients can have both asthma and COPD, called asthma-COPD overlap, which is beyond the scope of this chapter.

CURRENT GUIDELINES AND UPDATES

Two organizations drive classification and treatment recommendations for asthma: GINA and the National Asthma Education and Prevention Program (NAEPP). The National

Heart, Lung, and Blood Institute (NHLBI) established the NAEPP. The GINA guidelines are updated annually, whereas the NAEPP published a focused update in 2020, but the previous full guideline update was in 2007. The recommendations from each organization vary slightly when classifying asthma, but both guidelines focus on raising awareness and ensuring appropriate diagnosis and management to reduce asthma-related morbidity and mortality.

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 two times per week, and any limitation(s) in daily activities because of asthma (Table 1). Asthma is considered “well controlled” if none of these factors are present. Asthma is considered “partly controlled” if one or two of these factors are present and “uncontrolled” if three or four factors are present.

The GINA guidelines classify asthma as mild, moderate, or severe. The GINA guidelines do not distinguish between “intermittent” and “mild persistent” asthma because this historically was an arbitrary distinction according to an assumption that patients with symptoms twice a week or less would not benefit from inhaled corticosteroids (ICSs). The GINA organization plans to review the definition of mild asthma in its 2022 guideline update. Severe asthma is asthma that remains “uncontrolled” despite optimized treatment with a high-dose ICS/long-acting β_2 -agonist (LABA), or that requires a high-dose ICS-LABA to prevent it from becoming “uncontrolled” (GINA 2021).

Initial treatment depends on presenting symptoms. The GINA guidelines no longer recommend SABA-only treatment for asthma in adults or adolescents. Although inhaled SABA therapies are highly effective for quick relief of asthma symptoms, patients whose asthma is treated with a SABA alone

(compared with an ICS) are at an increased risk of asthma-related death and urgent asthma-related health care, even if they have good symptom control. Patients with mild asthma are still at risk of serious adverse events, and exacerbation triggers are unpredictable (Dusser 2007). There is strong evidence that SABA-only treatment does not protect patients from severe exacerbations and that regular use of a SABA increases the risk of exacerbations. In addition, increased use of SABAs is associated with adverse clinical outcomes: dispensing more than 3 canisters per year (daily use) is associated with a higher risk of severe exacerbations, and dispensing more than 12 canisters per year is associated with a higher risk of death (Nwaru 2020; Stanford 2012). Reducing, and potentially eliminating, the need for a SABA reliever is both an important goal in asthma management and a measure of the success of asthma treatment (GINA 2021). Formoterol, a rapid-onset LABA, is as effective as a SABA as a reliever medication in adults and children, and formoterol reduces the risk of severe exacerbations by 15%–45% compared with as-needed SABA therapy alone (GINA 2021; Rabe 2006). Formoterol is only to be used in combination with an ICS (preferably in a single inhaler). Recent studies showed that severe exacerbations were reduced by about two-thirds in patients taking as-needed ICS/formoterol compared with an as-needed SABA (O’Byrne 2018). Exercise-induced bronchospasm was even more reduced when as-needed ICS/formoterol was used instead of an as-needed SABA (Lazarinis 2014). One long-term study showed that regular SABA use resulted in worse outcomes and lower lung function than early initiation of a daily low-dose ICS (Rodrigo 2012). Data also show that ICSs reduce the risk of asthma deaths, hospitalizations, and exacerbations requiring oral corticosteroids (Suissa 2000). As such, GINA now recommends that all adults and adolescents with asthma receive ICS-containing controller treatment to reduce the risk of serious exacerbations. The

Table 1. Assessment of Symptom Control

Assessment of Symptom Control			Level of Asthma Symptom Control		
In the past 4 weeks, has the patient had:			Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	None of these	1 or 2 of these	3 or 4 of these
Any night waking due to asthma?	Yes <input type="checkbox"/>	No <input type="checkbox"/>			
SABA reliever needed more than twice/week?	Yes <input type="checkbox"/>	No <input type="checkbox"/>			
Any activity limitation due to asthma?	Yes <input type="checkbox"/>	No <input type="checkbox"/>			

SABA = short-acting β_2 -agonist.

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ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low-dose ICS/formoterol (GINA 2021).

After optimizing ICS-LABA therapy, adding a long-acting muscarinic antagonist (LAMA) (tiotropium) may be considered. Using a LAMA as add-on therapy for adults and adolescents 12 years and older in step 5, and for children 6–11 years of age in step 4, has been expanded to include using triple therapy with ICS/LABA/LAMA if asthma is persistently uncontrolled despite treatment with an ICS/LABA. Therapy can be optimized by adding tiotropium in a separate inhaler (for patients 6 years and older) or using of triple combination inhalers (for patients 18 years and older). Data show modestly improved lung function when adding a LAMA to a medium- or high-dose ICS/LABA (GINA 2021; Sobieraj 2018). However, adding a LAMA does not improve symptoms, and it is important to ensure the patient receives a sufficient ICS (at least a medium-dose ICS/LABA) before considering adding a LAMA.

An update to the 2021 guideline involves adding azithromycin three times per week after specialist referral for adult patients with persistent symptomatic asthma despite use of a high-dose ICS/LABA. However, before considering or initiating azithromycin, the sputum should be checked for atypical mycobacteria, an ECG should be checked for long QTc, and the risk of increasing antimicrobial resistance should be considered (Taylor 2019). This recommendation stems from a meta-analysis of two clinical trials of adults with persistent asthma symptoms that found reduced asthma exacerbations among those taking a medium- or high-dose ICS/LABA with thrice-weekly azithromycin who had either an eosinophilic or non-eosinophilic profile (Hiles 2019). Treatment for at least 6 months is suggested because the clinical trials showed no clear benefit by 3 months.

The GINA report recommends assessing asthma severity retrospectively from the level of treatment required to control symptoms and exacerbations. The recommendations are to assess severity once the patient has been receiving controller treatment for several months. Most individuals with asthma can achieve symptom control and minimal exacerbations with controller treatment. However, some patients will not achieve symptom control, even with maximal therapy. In some patients, lack of symptom control may be 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 appreciate that uncontrolled asthma can occur at any level of asthma severity. 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.

NHLBI 2020 Focused Updates

The NHLBI Expert Panel Report 3 (EPR-3) 2007 guideline classifies asthma severity by level of impairment and risk of exacerbations instead of by the symptom-based classification used in the GINA guidelines. The level of impairment focuses specifically on the frequency of symptoms (both during the day and at night), intensity of symptoms, and functional limitations, as summarized in Appendix 1. The EPR-3 guidelines classify asthma as either intermittent or persistent. Intermittent asthma typically does not limit normal activity. On spirometry, the FEV₁ can be normal, especially if the individual is not experiencing an exacerbation. These individuals' symptoms are controlled by using a SABA (e.g., albuterol) as needed. Persistent asthma is described as mild persistent, moderate persistent, or 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 the severity of asthma, and the classification of asthma severity is based on the component that is the most severe. For example, if adults have minor limitations with normal activity and use an albuterol inhaler 3 days per week but are awakening more than once per week, they are considered to have moderate persistent asthma.

The NAEPP 2020 focused updates do not change the classification of asthma. Instead, these updates identify six priority topics for review: (1) fractional exhaled nitric oxide (FeNO) in diagnosis, medication selection, and monitoring of asthma; (2) remediation of indoor allergens in asthma management; (3) adjustable medication dosing in recurrent wheezing and asthma; (4) use of long-acting antimuscarinic agents in asthma management; (5) immunotherapy in the management of asthma; and (6) bronchial thermoplasty in adult severe asthma (NHLBI 2020).

Nitric oxide can be measured in exhaled breath and can serve as a measure of the level of airway inflammation. In individuals with asthma, FeNO may be a useful indicator of bronchial or eosinophilic inflammation in the airway. The 2020 focused updates conditionally recommend FeNO measurement as an adjunct to the normal asthma evaluation process in individuals 5 years and older for whom the diagnosis of asthma is uncertain when using history, clinical findings, clinical course, and/or spirometry (NHLBI 2020). In addition, in individuals with persistent allergic asthma for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies, the EPR-3 conditionally recommends FeNO measurement as part of ongoing asthma monitoring and management. However, in children 0–4 years of age with recurrent wheezing, the EPR-3 strongly recommends against the use of FeNO to predict the future development of asthma because of its unreliability in this respect (NHLBI 2020).

Environmental control has always been a cornerstone of asthma management. The 2020 focused updates provide several conditional recommendations on environmental control

strategies. The EPR-3 conditionally recommends against allergen mitigation interventions as part of routine management in individuals with asthma who do not have sensitization to specific indoor allergens (NHLBI 2020). However, in individuals with asthma who have symptoms related to exposure to specific indoor allergens as confirmed by history taking or allergy testing, the 2020 focused updates conditionally recommend a multicomponent allergen-specific mitigation intervention. In individuals with asthma who have sensitization or symptoms related to exposure to pests (e.g., cockroaches and rodents), the 2020 focused updates conditionally recommend use of integrated pest management alone or as part of a multicomponent allergen-specific mitigation intervention. In individuals with asthma who have sensitization or symptoms related to exposure to dust mites, the 2020 focused updates conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen mitigation intervention (NHLBI 2020).

Current standard of care for managing asthma is the use of scheduled, daily ICS treatment as the preferred controller therapy for individuals of all ages with persistent asthma (NHLBI 2007). The 2020 focused updates provide further recommendations as new evidence has emerged. The EPR-3 conditionally recommends a short course of ICSs at the onset of a respiratory tract infection in children 0–4 years of age with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections. In addition, the 2020 focused updates conditionally recommend either a daily low-dose ICS and an as-needed SABA for quick-relief therapy or an as-needed ICS and SABA used concomitantly in individuals 12 years and older with mild persistent asthma (NHLBI 2020). This recommendation does not apply to individuals 5–11 years of age because these therapies have not adequately been studied in this age group. The 2020 focused updates also provide a conditional recommendation against a short-term increase in ICS dose for increased symptoms in individuals 4 years and older with mild to moderate persistent asthma who are receiving daily ICS treatment and likely to be adherent to this therapy. The panel provides a strong recommendation for ICS/formoterol in a single inhaler as both daily single maintenance and reliever therapy (SMART) compared with either a higher-dose ICS as daily controller therapy and a SABA for quick-relief therapy or a same-dose ICS/LABA as daily controller therapy and a SABA for quick-relief therapy in individuals 4 years and older with moderate to severe persistent asthma. In addition, the panel made a conditional recommendation for ICS/formoterol in a single inhaler used as both daily controller and reliever therapy instead of a higher-dose ICS/LABA as daily controller therapy and a SABA for quick-relief therapy in individuals 12 years and older with moderate to severe persistent asthma (NHLBI 2020).

The role of LAMAs was not addressed in the EPR-3 2007 recommendations. Although LAMAs are key treatment agents in COPD management, their use in asthma management was

undefined. Since then, several trials have investigated LAMAs as controller therapy for individuals with asthma. The 2020 focused updates conditionally recommend against adding a LAMA to ICS therapy compared with adding a LABA to ICS therapy. However, if a LABA cannot be used (such as when the medication is contraindicated, the device that delivers the LABA is unsuitable for the individual, or when the LABA is unavailable for insurance or supply reasons), the Expert Panel does conditionally recommend adding LAMA to ICS controller therapy compared to continuing the same dose of ICS alone in individuals aged 12 years and older with uncontrolled persistent asthma (NHLBI 2020). For individuals 12 years and older with uncontrolled persistent asthma who are already receiving LABA/ICS therapy, it is acceptable to add a LAMA to the regimen compared with continuing the same dose of a LABA/ICS. Adding a LAMA may improve asthma control and quality of life but will not decrease the frequency of asthma exacerbations, need for oral corticosteroids, or use of rescue medications (NHLBI 2020).

The 2020 focused updates also address the role of immunotherapy for allergic asthma. Immunotherapy is the administration of an aeroallergen subcutaneously (subcutaneous immunotherapy [SCIT]) or sublingually (sublingual immunotherapy [SLIT]). As defined by the EPR-3, immunotherapy refers to treatments used to reduce the IgE-mediated allergic clinical response that is associated with asthma. Immunotherapy consists of the therapeutic administration of aeroallergens to which a person has demonstrated sensitization, with the goal of attenuating that individual's asthmatic response upon subsequent exposure to these aeroallergens (NHLBI 2020). The EPR-3 conditionally recommends SCIT as adjunctive treatment to standard pharmacotherapy in individuals 5 years and older with mild to moderate allergic asthma whose asthma is controlled at the initiation, buildup, and maintenance phases of immunotherapy. Subcutaneous immunotherapy should not be administered in individuals with severe asthma or while individuals are experiencing asthma symptoms. Subcutaneous immunotherapy should be administered in the office setting and under direct supervision because of the risk of systemic reactions. Unlike with SCIT, the EPR-3 recommends against SLIT in asthma treatment because the evidence reviewed did not support its use specifically for the treatment of allergic asthma (NHLBI 2020).

Finally, the EPR-3 examined studies that provided recommendations for the use of bronchial thermoplasty compared with multicomponent, standard-of-care, medical management. Multicomponent medical therapy consists of medium to high doses of ICS treatment, a LABA, omalizumab (in one study), and/or oral corticosteroids. Bronchial thermoplasty uses thermal energy to reduce the muscle associated with airway constriction in patients with asthma. Of note, available studies of bronchial thermoplasty did not include individuals treated with LAMAs, environmental interventions, and/

or newer biologic agents (NHLBI 2020). The EPR-3 conditionally recommends against the use of bronchial thermoplasty in adults 18 and older with persistent asthma. Bronchial thermoplasty has not been studied in individuals younger than 18 years. The evidence reviewed suggested small benefits, moderate risks, and uncertain long-term outcomes (NHLBI 2020).

Stepwise Approach to Treatment

Both guidelines recommend a stepwise approach in the treatment of asthma. The GINA 2021 updates propose two tracks for asthma treatment in adults and adolescents according to recent evidence about outcomes with the two reliever therapy choices for managing asthma (see Table 1). The first (preferred) track recommends using low-dose ICS/formoterol as the reliever, or rescue, therapy regardless of current symptom control. Using ICS/formoterol as the rescue inhaler better reduces the risk of exacerbations than a SABA reliever, with similar symptom control and lung function. However, ICS/formoterol should not be used as the reliever in patients prescribed a different ICS/LABA for their controller therapy. The second track recommends use of a SABA as an alternative reliever if the patient cannot use a low-dose ICS/formoterol inhaler or if ICS/formoterol is not preferred by patients who have no exacerbations on their current controller therapy. Before considering a regimen with a SABA reliever, it is important to consider whether patients will likely be adherent to daily controller therapy; if not, they will be exposed to the risks of SABA-only treatment. The recommendations vary only slightly for individuals younger than 12 years (Table 2). The 2020 focused updates state that SABAs can be used as needed for monotherapy in intermittent asthma and can also be used as a pretreatment for those with exercise-induced bronchospasm to prevent symptoms (NHLBI 2020), which is in contrast to the GINA updates.

The GINA updates recommend stepping up or down treatment within a track and using the same medication and delivery device at each step according to the patient's needs and preferences (GINA 2021). In some European countries, budesonide/formoterol (ICS/LABA) is approved as a quick-relief agent, but this indication has not yet been approved in the United States, despite the recommendation for use by GINA and the NHLBI 2020 focused updates. The guidelines define uncontrolled asthma as symptoms that occur at least 2 days per week or nighttime awakenings related to shortness of breath that occur more than twice per month in adolescents and adults 12 years and older (NHLBI 2020) or any number of night awakenings (GINA 2021). If asthma remains uncontrolled despite adherence to therapy, controller therapy should be "stepped up," meaning the dose of the existing ICS should be increased or an additional medication added to the current ICS dose. Both guidelines recommend an ICS/LABA (specifically formoterol) as the preferred controller therapy instead of an ICS as monotherapy (Table 3). 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 convenience and patient adherence. If further control is needed, the ICS dose can be increased. The 2020 focused updates now allow for substitution of a LAMA for a LABA when a LABA cannot be used because of tolerability, device challenges, or contraindication to therapy. A LAMA or LABA should always be used together with an ICS for optimal efficacy. Long-acting β_2 -agonists should never be used alone in asthma because of patient safety concerns demonstrated in the Salmeterol Multicenter Asthma Research Trial showing a statistically significant increased risk of asthma-related deaths on patients on salmeterol monotherapy (Nelson 2006). However, recommendations vary slightly depending on age (see Tables 3-6).

The EPR-3 guidelines and 2020 focused updates follow the same general order of therapy as the GINA guidelines. However, the main difference in the updated treatment recommendations in the 2020 focused updates is the recommendation for the use of ICS/formoterol as SMART (see Tables 1-4), which is discussed later in this chapter. Overall, the GINA guidelines and NHLBI 2020 focused updates vary only slightly. See Table 3 for a summary of these differences. The GINA guidelines define asthma severity by the therapy step required to achieve asthma control. Unlike the GINA guideline recommendations, the NHLBI 2020 focused updates, because of their narrowed scope, contain no specific recommendations for the use of biologics in asthma.

Both guidelines recommend assessing adherence and device technique 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. 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—can be used to assess treatment response. Five items on the ACT questionnaire pertain to symptoms and daily functions within the previous 4 weeks. The ACT questionnaire assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, effect on daily functions, and the individual's assessment of asthma control. Each question has a 5-point scale for individuals to rate. Total scores range from 5 (poor control of asthma) to 25 (complete control of asthma). An ACT score greater than 19 indicates well-controlled asthma for patients 12 years and older (Nathan 2004).

Once asthma remains well controlled for at least 3 months, the GINA guidelines recommend a step-down approach to find the lowest effective treatment that controls asthma; this will minimize the risk of potential adverse effects related to long-term use of high-dose corticosteroids. The approach to stepping down therapy should be individualized for each

Table 2. GINA – Initial Controller Treatment in Adults and Adolescents with Asthma

TRACK 1 <i>Preferred</i>	Step 1 – Step 2 Symptoms < 4–5 days per week	Step 3 Symptoms most days, or waking with asthma once a week or more	Step 4 Daily symptoms, or waking with asthma at least once per week, and low lung function	Step 5
Using ICS-formoterol as the reliever reduces the risk of exacerbations compared with using a SABA reliever	As-needed low dose ICS-formoterol	Low dose maintenance ICS/formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA; refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
			Short course OCS may also be needed for patients presenting with severely uncontrolled asthma	Consider high-dose ICS/formoterol
RELIEVER: As-needed low dose ICS-formoterol				

TRACK 2 <i>Alternative</i>	STEP 1 Symptoms < twice per month	STEP 2 Symptoms two or more times per month but less than 4–5 days per week	STEP 3 Symptoms most days, or waking with asthma at least once per week	STEP 4 Daily symptoms, or waking with asthma at least once per week, and low lung function	STEP 5
Before considering a regimen with SABA reliever, check if patient is likely to be adherent to daily controller therapy	Take ICS whenever SABA is taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA; refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R
					Consider high-dose ICS-LABA
RELIEVER: As-needed short acting β_2 -agonist					

ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LAMA = long-acting antimuscarinic antagonist; MART = maintenance and reliever therapy with ICS-formoterol; OCS = oral corticosteroid.

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patient on the basis of current treatment, risk factors, and patient preferences. It is recommended to taper oral corticosteroids to the lowest dose possible and to consider potential discontinuation. 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 2021). However, discontinuing the ICS, resulting in monotherapy with a LABA, is not recommended 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 increased risk of subsequent asthma exacerbation are greater when adult patients are treated with an ICS as monotherapy (Ahmad 2015). The GINA guidelines recommend use of an asthma action plan for all individuals, especially during step-down therapy, so that individuals are well educated on how to treat flares, should they occur (GINA 2021).

Table 3. GINA – Initial Controller Treatment in Children Aged 6–11 Years with Asthma

Preferred Controller	STEP 1 Symptoms < twice per month	STEP 2 Symptoms > 2 times per month, but less than daily	STEP 3 Symptoms most days, or waking with asthma at least once per week	STEP 4 Symptoms most days, or waking with asthma at least once per week, and low lung function	STEP 5
	Take low dose ICS whenever SABA is taken	Daily low dose maintenance ICS	Low dose maintenance ICS-LABA, or medium dose ICS, or very low dose ICS-formoterol maintenance and reliever	Medium dose maintenance ICS-LABA or low dose ICS-formoterol maintenance and reliever (MART). Refer for expert advice.	Refer for phenotypic assessment + higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
Other Controller Options	Consider daily low dose ICS	Daily LTRA or low dose ICS taken whenever SABA taken	Low dose ICS + LTRA	Add tiotropium or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side effects
Reliever	As-needed short acting β_2 -agonist or low dose ICS-formoterol reliever for maintenance and reliever therapy (as above)				

LTRA = leukotriene receptor antagonist.

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Single Maintenance and Reliever Therapy

Use of a combination inhaler containing budesonide and formoterol as both maintenance and quick-relief therapy has been recommended as an improved method of using ICS/LABA therapy. Published double-blind trials show that budesonide/formoterol delivered as SMART achieves better asthma outcomes than budesonide monotherapy or lower doses of budesonide/formoterol delivered in separate formulations (Chapman 2010). The 2020 focused updates place a strong recommendation on supporting SMART with ICS/formoterol in both step 3 and step 4 on the basis of several studies involving almost 21,000 subjects (NHLBI 2020). The GINA guideline, which refers to SMART as MART (maintenance and reliever therapy), began recommending ICS/formoterol as SMART in steps 3–5 with the 2021 guideline updates (GINA 2021).

TREATMENT

A variety of treatment strategies, both pharmacologic and nonpharmacologic, exist to reduce impairment and risk of exacerbation because of asthma. Pharmacologic treatment strategies include controller medications, reliever medications, and adjunctive add-on therapies. Treatment plans 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 every 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 specific trigger is identified for a patient, efforts must be made to avoid worsening of symptoms and asthma control because of these factors. Allergens and irritants are common triggers, especially those that are inhaled, such as cold air, tobacco smoke, pollen, or fumes from cleaning agents. Examples of avoidance of such triggers, respectively, include using a scarf to cover the mouth when outside in cold weather, limiting exposure to tobacco smoke, using air conditioning in the house rather than opening a window for ventilation, and having a patient with asthma limit time in the home during cleaning. Patients may consult an allergist for skin testing if no specific allergens can be identified, and allergen immunotherapy can be considered in those for whom exposure to the allergen is unavoidable or is treatment is insufficient to control asthma flares. Foods that contain sulfites (e.g., molasses, dried fruit, bottled grape and lemon juice, wine) may worsen symptom control. Although there is a possible association between

Table 4. Comparison of GINA 2021 vs. NHLBI 2020 Focused Update Stepwise Approach to Treatment in Individuals > 12 Yr of Age

Medication Class	Step 1 ^a	Step 2 ^b	Step 3 ^b	Step 4 ^b	Step 5 ^b	Step 6 ^b
Quick relief – NHLBI	SABA ^d PRN	SABA PRN	Low-dose ICS/formoterol ^c PRN			
Quick relief – GINA	Low-dose ICS/formoterol ^c PRN					
Controller – NHLBI	None	Daily low-dose ICS	Daily and PRN combination low-dose ICS/formoterol	Daily and PRN combination medium-dose ICS/formoterol	Daily medium-to high-dose ICS/LABA + LAMA and PRN SABA	Daily high-dose ICS/LABA + oral systemic corticosteroid and PRN SABA
		Alternative: LTRA, theophylline, or cromolyn	Alternative: LTRA, theophylline, or zileuton	Alternative: Medium-dose ICS + LTRA, theophylline, or zileuton	+	+
Controller – GINA (preferred track)	None	None	Low-dose maintenance ICS/formoterol	Medium-dose ICS/formoterol	Add on LAMA + Refer for phenotypic assessment + anti-IgE, anti-IL5/5R, and anti-IL4R + Consider high-dose ICS/formoterol	

^aIntermittent asthma.

^bPersistent asthma.

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

^dShort-acting beta agonist

PRN = as needed.

Information adapted from: 2021 GINA Main Report. Available at <https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf>; NHLBI Asthma Management Guidelines: Focused Updates 2020. Available at <https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates>.

other dietary allergens and asthma control, it is not well established (NHLBI 2007).

Pharmacologic Treatment

Short-acting β -Agonists

Available Agents

Box 1 lists available short-acting β_2 -agonists (SABAs). Short-acting β_2 -agonists are available in metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulized solutions.

Box 1. Short-acting β -Agonist Bronchodilators

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

Table 5. NHLBI 2020 Focused Update Stepwise Approach for Management of Asthma in Individuals ≥ 12 Yr

Treatment	Intermittent Asthma		Persistent Asthma			
	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA	Daily and PRN combination low-dose ICS/formoterol	Daily and PRN combination medium-dose ICS/formoterol	Daily medium-high dose ICS/LABA + LAMA and PRN SABA	Daily high-dose ICS/LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA ^a and PRN SABA or Cromolyn, ^a nedocromil, ^a zileuton, ^a or theophylline ^a and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS/LABA or daily low-dose ICS + LAMA or daily low-dose ICS + LTRA ^a and PRN SABA or Daily low-dose ICS + theophylline ^a or zileuton, ^a and PRN SABA	Daily medium-dose ICS/LABA or daily medium-dose ICS + LAMA, and PRN SABA or Daily medium-dose ICS + LTRA ^a or daily medium-dose ICS + theophylline ^a or daily medium-dose ICS + zileuton ^a and PRN SABA	Daily medium-high dose ICS/LABA or daily high-dose ICS + LTRA ^a and PRN SABA	
		Steps 2–4: Conditionally recommend subcutaneous immunotherapy as an adjunctive treatment to standard pharmacotherapy in individuals ≥ 5 yr of age whose asthma is controlled at the initiation, buildup, and maintenance phases of immunotherapy			Consider adding asthma biologics (e.g., anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4/IL-13) ^b	

^aCromolyn, nedocromil, LTRAs including montelukast, and theophylline were not considered in the 2020 focused updates and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a boxed warning for montelukast in March 2020.

^bThe Agency for Healthcare Research and Quality systematic reviews that informed the 2020 focused update report did not include studies that examined the role of asthma biologics (e.g., anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4/IL-13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in steps 5 and 6.

Information adapted from: National Heart, Lung, and Blood Institute (NHLBI). Asthma Management Guidelines: Focused Updates 2020. Available at <https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates>.

All MDIs currently available contain the propellant hydrofluoroalkane (HFA) to deliver the medication.

Mechanism of Action

Short-acting β-agonists have a quick onset and are used to rapidly relax bronchial smooth muscle from the trachea to the bronchioles through action on the β₂-receptors. Although SABAs are effective bronchodilators available to treat asthma symptoms, they do not affect the underlying mechanism of

inflammation and thus have limited ability to prevent exacerbations as monotherapy.

Efficacy and Place in Therapy

Short-acting bronchodilators are often called rescue inhalers because they are intended to treat acute bronchospasm in those with reversible obstructive airway disease. The GINA 2021 guidelines now distinctly recommend against SABA monotherapy because it yields a higher rate of

Table 6. NHLBI 2020 Focused Update Stepwise Approach for Management of Asthma in Individuals 5–11 Years of Age

Treatment	Intermittent Asthma		Persistent Asthma			
	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS/formoterol	Daily and PRN combination medium-dose ICS/formoterol	Daily high-dose ICS/LABA and PRN SABA	Daily high-dose ICS/LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA ^a or cromolyn ^a or nedocromil ^a or theophylline ^a and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS/LABA or daily low-dose ICS + LTRA ^a or daily low-dose ICS + theophylline ^a and PRN SABA	Daily medium-dose ICS/LABA and PRN SABA or Daily medium-dose ICS + LTRA ^a or daily medium-dose ICS + theophylline ^a and PRN SABA	Daily high-dose ICS + LTRA ^a or daily high-dose ICS + theophylline ^a and PRN SABA	Daily high-dose ICS + LTRA ^a + oral systemic corticosteroid or daily high-dose ICS + theophylline ^a + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunctive treatment to standard pharmacotherapy in individuals ≥ 5 yr of age whose asthma is controlled at the initiation, buildup, and maintenance phases of immunotherapy			Consider omalizumab ^b	

^aCromolyn, nedocromil, LTRAs including montelukast, and theophylline were not considered in the 2020 focused updates and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a boxed warning for montelukast in March 2020.

^bOmalizumab is the only asthma biologic currently FDA approved for this age range.

Information adapted from: NHLBI Asthma Management Guidelines: Focused Updates 2020. Available at <https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates>.

exacerbations than ICS-containing therapy (O’Byrne 2018). Short-acting β_2 -agonists should be used only as an adjunct to ICS-containing therapy and are an alternative to the preferred reliever therapy of ICS/formoterol. Ultimately, a sign of good asthma control will limit or eliminate the need for regular SABA use (GINA 2021). The 2020 focused updates state that SABAs can be used as needed as monotherapy in intermittent asthma as well as used as a pretreatment for those with exercise-induced bronchospasm to prevent symptoms (NHLBI 2020).

Adverse Effects Profile

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

Monitoring Values

Given the potential for cardiac-related adverse effects with SABAs, heart rate, blood pressure, and changes on ECG should be monitored and therapy modified as clinically indicated. In addition, it is recommended to assess proper inhaler technique and provide a spacer when needed to effectively deliver doses for MDIs because of potential difficulty in coordinating dose actuation with inhalation. Patients should be evaluated for airway symptoms and frequency of SABA use. Escalation of long-term anti-inflammatory maintenance treatment should be considered in patients who report increased use of SABAs or use on more than 2 days per week (NHLBI 2020).

Inhaled Corticosteroids

Available Agents

Box 2 lists available ICS agents.

Mechanism of Action

Inhaled corticosteroids are long acting, with a multifactorial mechanism of action. 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 induce vasoconstriction, leading to decreased mucosal blood flow, swelling, and discomfort. In addition to their anti-inflammatory properties, ICSs produce a local immunosuppressive state that limits the lung'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 initiation of therapy.

Efficacy and Place in Therapy

Inhaled corticosteroids continue to be recommended as the mainstay of asthma treatment by all guidelines, with or without combination formoterol. 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. Using an ICS with formoterol is now preferred for both reliever and controller therapy and may be stepped up or down, depending on asthma severity and control level (GINA 2021; NHLBI 2020).

Controversy regarding the use of ICSs in the pediatric population and their effect on adult height has existed for decades. The Childhood Management Asthma Program (CAMP) was a long-term study that enrolled children 5–12 years of age with mild to moderate persistent asthma. The CAMP aimed to determine whether long-term anti-inflammatory therapy could alter the natural history of mild to moderate asthma in children by improving lung growth as measured by post-bronchodilator FEV₁. From December 1993 to September 1995, 1041 participants were enrolled. Patients were randomized to treatment with budesonide 200 mcg and 400 mcg daily with nedocromil 8 mg twice daily or placebo for 4–6 years. Patients were then followed for around 13 years.

Box 2. Inhaled Corticosteroids

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

Adult height was determined at a mean age of 25 years for 943 of the original 1041 CAMP participants. The follow-up study found that those treated with budesonide had a mean adult height that was 0.5 inches less than in the placebo group (–0.5 to –1.9) at 24.9 years of age. This height deficit was observed 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 on both the dose of the drug and its therapeutic index (Covar 2012). Therefore, study investigators suggested using inhaled glucocorticoids with higher therapeutic indexes at the lowest effective dose in children with persistent asthma (Kelly 2012).

Adverse Effects Profile

Because these agents are corticosteroids, the most common risks are associated with the immunosuppressive nature of the drugs, though the risk associated with inhaled agents is much lower than with systemic agents. Use of ICSs is associated with oral candidiasis (commonly known as thrush), which occurs when the drug is deposited in the oropharynx rather than in the lungs. Patients should be instructed to rinse their mouths with water and spit after use of an ICS to reduce the risk of oral candidiasis. When receiving high doses, 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 an ICS 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, reduction in bone mineral density, and glaucoma/cataracts, which can occur with long-term use of high-dose ICSs.

Monitoring Values

The package insert indicates that ICSs can lead to reduced growth velocity in children who are being chronically treated. To reduce the effect, pediatric patients should be treated with the lowest effective dose of steroids, and the child's height should be monitored. As with all asthma treatments, the patient's FEV₁, peak flow, and other PFTs should be monitored to track progress and target the best treatment.

Combination ICSs and LABAs

Available Agents

Box 3 lists available ICS/LABA agents.

Mechanism of Action

Inhaled corticosteroids have both anti-inflammatory and immunosuppressive properties that help decrease the aggravating symptoms of asthma. Inhaled corticosteroids are most commonly used in combination with a LABA. Long-acting β -agonists provide additional benefit by relaxing bronchial

smooth muscle and inhibiting the release of hypersensitivity mediators from mast cells through action on the β_2 -receptors.

Efficacy and Place in Therapy

An escalated treatment for moderate to severe persistent asthma includes the combination inhalers that contain both a LABA and an ICS, specifically formoterol if it is also being used for reliever therapy. If a SABA is used as reliever therapy, the GINA 2021 guidelines do not specify which LABA should be used with an ICS as maintenance therapy. In contrast to the treatment of COPD, LABAs should not be used as monotherapy for asthma because of an associated increased risk of death (NHLBI 2020). Results of the Salmeterol Multicenter Asthma Research Trial (SMART trial) raised concerns about the safety of LABAs in asthma (Nelson 2006). At baseline, patients received standard asthma therapy, which included ICSs, 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 out of 13,176 patients) than in the placebo group (3 deaths out 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 was 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. The FDA analysis found that 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. Further studies and meta-analyses have shown that use of combination therapy (LABA plus ICS) is not associated with serious asthma-related events (Rodrigo 2012). The FDA revised the labeling on all available LABAs to recommend against the use of LABAs in asthma without another controller drug, such as an ICS (FDA 2016).

Adverse Effects Profile

Manufacturers' profiles indicate that common adverse effects of these agents include upper respiratory tract infections, pharyngitis, dysphonia, bronchitis, headaches, and nausea/vomiting. As with ICS monotherapy, there is a risk of oral candidiasis, which may be decreased by rinsing the mouth after taking doses.

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

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

Monitoring Values

As with other long-term control agents for asthma, continued monitoring of FEV₁, peak flow, and PFTs should be performed as clinically indicated. Monitoring height or length in preschool and school-aged children using intermittent ICS therapy should be considered (NHLBI 2020).

Long-acting Muscarinic Antagonists

Available Agents

Box 4 lists available LAMA agents. Although several LAMAs are on the market, only Spiriva Respimat and Trelegy Ellipta are FDA approved for the indication of asthma.

Mechanism of Action

Long-acting muscarinic antagonists antagonize the type 3 muscarinic receptors in bronchial smooth muscle, resulting in relaxation of muscles in the airway.

Efficacy and Place in Therapy

Long-acting muscarinic antagonists may be considered in uncontrolled persistent asthma as an alternative to LABAs when LABAs cannot be used (NHLBI 2020). Long-acting muscarinic antagonists should be used in addition to ICS therapy or in combination with ICS/LABA therapy if asthma symptoms remain uncontrolled. A systematic review primarily involving mild to moderate asthma found that adding a LAMA to ICS therapy better reduced exacerbations than placebo. In addition, this review found that patients taking an ICS/LABA had fewer exacerbations than those taking an ICS/LAMA. Therefore, an ICS/LABA is still the preferred combination, when feasible (Sobieraj 2018). The GINA 2021 updates recommend considering a LAMA in addition to a LABA/ICS when symptoms are persistent even on an optimized dose of a LABA/ICS (GINA 2021).

Adverse Effects Profile

Dry mouth was the most common adverse effect in trials. Those with glaucoma or at risk of urinary retention should avoid LAMA therapy or be very closely monitored for adverse effects (NHLBI 2020).

Monitoring Values

In older adult patients, renal clearance of tiotropium is decreased and plasma concentrations are increased because of decreased renal function. No dosage adjustments are recommended because of age or renal function; however, the manufacturers recommend monitoring patients with moderate to severe renal impairment for increased incidence of constipation, UTIs, and xerostomia because of the anticholinergic effect of LAMA therapy.

Leukotriene-Modifying Agents

Available Agents

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

Mechanism of Action

Package inserts indicate two distinct classes of leukotriene-modifying agents: LTRAs and 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, these medications 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. However, leukotriene-modifying agents can be considered as an alternative/adjunctive agent for those with persistent asthma in steps 2–5, especially for those with an allergic component to asthma (GINA 2021). A large systematic review showed that ICS treatment is superior to LTRAs in reducing exacerbations requiring systemic steroids; hence, an ICS is preferred to LTRA therapy for mild to moderate asthma (Chauhan 2012). Adding a LABA to the existing ICS therapy is preferred to using an LTRA in those 12 years and younger. Although LTRAs are less effective and have a slower onset than SABAs, LTRAs may 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 for leukotriene-modifying agents, the most common adverse effects include upper respiratory tract infections, fever, headache, pharyngitis, and cough. There is also an FDA boxed warning regarding a serious risk of development of neuropsychiatric effects in those taking montelukast. Patients should report any behavioral changes, including, but not limited to, agitation, aggression, anxiousness, dream abnormalities, hallucinations, depression, insomnia, and suicidal thinking (FDA 2020). There is some controversy in the literature regarding causation between these agents and psychiatric events. However, given no difference in studies between LTRAs and placebo for neuropsychiatric events, the consensus recommendation is to continue with caution and monitor for adverse effects. Additional consideration and monitoring should be given to patients with preexisting psychiatric disorders when prescribing medications in this class (Paggiaro 2011).

Monitoring Values

The package insert for zafirlukast (Accolate) indicates a serious risk of hepatotoxicity in up to 5% of patients taking zafirlukast (Reinus 2000). Regular monitoring of liver function tests (LFTs) is suggested because early detection is associated with a higher chance of recovery. Patients should be counseled to monitor for symptoms of hepatic dysfunction, including dark-colored urine, right upper quadrant abdominal pain, and nausea. If hepatotoxicity is suspected, the offending agent should be discontinued at once, and LFTs should be monitored serially until resolution is established. If hepatotoxicity occurs, therapy should not be restarted. Leukotriene-modifying agents should not be used in those with cirrhosis. Zafirlukast significantly increased the INR when used concomitantly with warfarin. In patients taking montelukast, close monitoring for the development of neuropsychiatric effects, especially in children, is recommended.

Chromones

Available Agents

The only available agent in this class is cromolyn sodium, which is available only as a nebulized solution.

Mechanism of Action

Cromolyn is a mast cell stabilizer that inhibits 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

Cromolyn is not recommended first line for asthma, though it can be considered as an alternative for mild persistent asthma. Cromolyn is indicated for use in pretreatment for exercise-induced bronchoconstriction and to reduce allergic response to a known allergen that is unavoidable. However, cromolyn is less effective at reducing exacerbations and rescue bronchodilator use than ICS therapy (Guevara 2006). Of note, cromolyn must be given three or four times per day and thus is not a good option for those with concerns regarding adherence (NHLBI 2007).

Box 4. Long-acting Muscarinic Antagonists

- Umeclidinium (Incruse Ellipta) – *not approved for asthma*
- Tiotropium bromide (Spiriva HandiHaler) – *not approved for asthma*
- Tiotropium bromide (Spiriva Respimat)
- Aclidinium bromide (Tudorza Pressair) – *not approved for asthma*
- Revefenacin (Yupelri) – *not approved for asthma*
- Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)

Adverse Effects Profile

According to the package insert, cromolyn is well tolerated, with headache and diarrhea as the most common adverse effects.

Monitoring Values

Long-term control of symptoms associated with asthma should be monitored, including FEV₁, peak flow, and PFTs.

Methylxanthines

Available Agents

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

Mechanism of Action

Theophylline has a multifactorial mechanism of action. Theophylline induces smooth muscle relaxation to result in bronchodilation, as well as inhibits the body's reaction to external allergic stimuli. Theophylline increases the force of contraction of diaphragmatic muscles by improving calcium uptake through adenosine-mediated channels (Jilani 2021).

Efficacy and Place in Therapy

This therapy, though not first line, can be used as an alternative to an ICS in those with mild persistent asthma. The usefulness of theophylline is limited by the required monitoring of blood concentrations and its adverse effect profile (NHLBI 2007).

Adverse Effects Profile

Theophylline may cause a variety of caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia when used at therapeutic concentrations. These adverse effects are increased with supratherapeutic concentrations. When concentrations are elevated, toxic symptoms include persistent vomiting, cardiac arrhythmias, and intractable seizures (Jilani 2021).

Monitoring Values

Theophylline has a low therapeutic index and requires regular monitoring of blood concentrations. Concentrations should be checked after initiating therapy, before dose adjustments, any time toxicity is suspected, and whenever a patient has a new or worsening illness that could affect drug clearance. Specific factors that affect drug clearance include, but are not limited to, age (specifically neonates, children, and older adults), concurrent diseases (e.g., acute pulmonary edema, congestive heart failure, cor pulmonale, fever, hypothyroidism, liver/renal disease, sepsis, and shock), and smoking status. Toxicity occurs when theophylline clearance is limited or reduced. A normal theophylline concentration is less than 20 mcg/mL. Patients will need to be counseled on signs and symptoms of severe toxicity related to theophylline, including nausea and/or persistent vomiting.

Biologics—Monoclonal Antibodies

Biologics (monoclonal antibodies) include anti-IgE, anti-IL-5, anti-IL-5 receptor blockers, and anti-IL-4 receptor blockers.

Available Agents

Box 5 lists available biologic agents.

Mechanism of Action

Omalizumab is an anti-IgE monoclonal antibody that inhibits the binding of IgE to mast cells and basophils. By decreasing bound IgE, activation and release of mediators in the allergic response are limited. Mepolizumab, reslizumab, and benralizumab are interleukin (IL)-5 antagonists. The IL-5 antagonists inhibit IL-5 signaling, reducing the production and survival of eosinophils. However, their mechanism of action in asthma has not definitively been established. Dupilumab is an IgG4 antibody that inhibits IL-4 and IL-13 signaling by binding to the IL-4R α subunit. Inhibition of the IL-4R α subunit inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, but the mechanism of action in asthma has not definitively been established (Edris 2019). Tezepelumab-ekko was approved in December 2021, and is an IgG λ antibody that binds to human thymic stromal lymphopoietin (TSLP) and prevents human TSLP from interacting with the TSLP receptor. Blocking TSLP reduces biomarkers and cytokines associated with inflammation, but the mechanism has not been definitively established.

Efficacy and Place in Therapy

Biologics are not to be used first line or as monotherapy but may be added on to a standard care regimen in Steps 4 and 5 for those deemed to have severe persistent asthma with Th2 cell inflammatory asthma phenotypes. Cost and coverage are the main factors limiting the usefulness of these products for asthma (GINA 2021). Medications in this class should be given a 3- to 6-month trial to assess for efficacy.

Adverse Effects Profile

The most serious adverse effect of omalizumab is the potential for anaphylaxis (Edris 2019). Therefore, omalizumab should only be administered by trained health care professionals who are equipped to treat anaphylaxis, if needed. Initial administration of omalizumab should be followed by a 2-hour observational period. If tolerated well, observation can be decreased to 30 minutes for subsequent injections.

Box 5. Biologic Monoclonal Antibodies

- Omalizumab (Xolair) – *subcutaneous injection*
- Mepolizumab (Nucala) – *subcutaneous injection*
- Reslizumab (Cinqair) – *intravenous infusion*
- Benralizumab (Fasenra) – *subcutaneous injection*
- Dupilumab (Dupixent) – *subcutaneous injection*
- Tezepelumab-ekko (Tezspire) – *subcutaneous injection*

Less severe, but common adverse effects with omalizumab include arthralgia, pain, fatigue, dizziness, fracture, pruritus, dermatitis, and earache. Mepolizumab, reslizumab, and benralizumab cause hypersensitivity reactions, headache, and injection site reactions. Dupilumab has a more favorable adverse effect profile than these other agents, and the most common adverse reactions are injection site reactions, oropharyngeal pain, and eosinophilia (Edris 2019).

Monitoring Values

There is an extended risk of parasitic infection after administration of these agents. Patients should be treated for helminth infections before starting biologic agents. In addition, mepolizumab increases the risk of developing herpes zoster infection (Edris 2019). Patients should be monitored for signs and symptoms of infection, and these should be reported to the prescribing provider. The omalizumab dose is calculated according to current weight and pre-dose IgE concentrations, so these should be monitored at least annually. Control of asthma symptoms, including FEV₁, peak flow, PFTs, and monitoring for malignancy (mepolizumab, reslizumab, and benralizumab), should be monitored as clinically indicated.

Allergen Immunotherapy I

Available Agents

Allergen immunotherapy may be given by SCIT or SLIT. Examples of available allergens include tree, grass, and weed pollens; animal dander; dust mites; mold; and cockroaches.

Mechanism of Action

Allergen immunotherapy given subcutaneously, known colloquially as an “allergy shot,” works by exposing a patient to gradually increasing doses of a specific allergen or allergens over months to years. Serial exposure to a specific allergen or allergens blunts the inflammatory IgE allergic response that can contribute to the pathology of asthma.

Efficacy and Place in Therapy

Allergen immunotherapy may be considered when the patient has an allergic component to asthma. Allergen immunotherapy may also be considered for patients who have a significant and obvious symptom-provoking allergy in order to reduce medication and symptomatic burden of allergic asthma (NHLBI 2020). However, patients should not receive allergen immunotherapy if they have unstable or severe asthma because control may be further compromised. The GINA 2021 guidelines allow for SLIT as add-on controller therapy for steps 2–4 in patients 12 years and older, though they have no recommendations regarding SCIT. However, GINA plans to review evidence about SCIT and SLIT in its next update. In contrast, the NHLBI 2020 focused updates specifically recommend against SLIT for allergic asthma but conditionally recommend SCIT as a suitable adjunct to traditional treatment of allergic

asthma. Sublingual immunotherapy is distinctly not recommended by the NHLBI guidelines because in studies, it did not improve asthma symptoms, control, or quality of life.

Subcutaneous immunotherapy should only be performed in the office while the patient is under the care of a medically trained professional in case of life-threatening systemic reactions. In contrast, SLIT is given as a tablet or aqueous solution that can be administered safely at home.

Adverse Effects Profile

The most common adverse effects with administration of SCIT involve local reactions such as itching, pain, paresthesia, heat, erythema, and induration. Sublingual immunotherapy adverse effects tend to be less severe and include oral irritation or itching. Systemic reactions for SLIT are less common and include pruritis, urticaria, and other upper respiratory reactions. In much more severe cases, anaphylaxis or death has been reported. Sublingual immunotherapy carries less of a serious reaction burden than SCIT (Virchow 2016).

Monitoring Values

Monitoring is done primarily in the first 30 minutes after administration of immunotherapy because this is when most adverse effects may occur. Subcutaneous immunotherapy is provided only in the office, and the first SLIT dose should be administered under medical supervision.

Emerging Therapies

Several novel drug classes have been developed for patients with asthma that is resistant to standard therapy. Imatinib, a tyrosine kinase inhibitor, was originally approved as an antineoplastic agent and is now being studied for severe, refractory asthma because of its evident immunosuppressive effects. By inhibiting the receptor tyrosine kinase *KIT*, imatinib reduces bone marrow mast cell numbers and serum tryptase concentrations. The reduced mast cell count and tryptase release lessen airway hyper-responsiveness and thus stunt the 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).

Management of Asthma Exacerbations

Exacerbations may be treated with a combination of strategies, which should be outlined in the patient’s asthma action plan. Depending on the level of exacerbation severity, some treatment strategies can be facilitated at home, whereas others may require patients to visit their medical office or urgent care. Treatments include repeated use of ICS/formoterol (maximum 12 puffs per day), albuterol as needed, supplemental oxygen (by home supply or at a medical office), and oral systemic corticosteroid therapy (e.g., prednisone 40–50 mg/day for 5–7 days) as warranted. Once exacerbation

symptoms are initially managed, patients should be reeducated on the use of rescue versus maintenance inhalers and their asthma action plan. The maintenance regimen should be adjusted to better control symptoms (NHLBI 2007).

Pharmacists can play a key role in managing uncontrolled asthma by providing an in-depth assessment of barriers to adherence, device technique, and education deficits before providing counseling and training.

Special Populations

Asthma in the Setting of COVID-19

Emerging data suggest that people with asthma are not at an increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe disease in people with well-controlled, mild to moderate asthma. It does not appear that people with asthma are at an increased risk of COVID-19–related death (GINA 2021). However, the risk of death from COVID-19 was increased in patients with asthma who had recently required oral corticosteroid therapy for asthma. Thus, it is important to ensure adequate symptom management and control and minimize the need for oral corticosteroid therapy in patients with asthma.

Many countries have in fact observed a reduction in asthma exacerbations and influenza-related illness. Although the reasons are unknown, this reduction may be related to increased handwashing as well as masking and social distancing. However, it is still important to advise patients to continue taking ICSs for the treatment of asthma. In one study of hospitalized adults 50 and older with COVID-19, there was a decreased risk of mortality in patients with

concomitant asthma taking an ICS compared with patients without an underlying respiratory condition (Bloom 2021).

Patients with asthma should be highly encouraged to be fully vaccinated against COVID-19. Given the risk-benefit, GINA recommends that all patients diagnosed with asthma receive the COVID-19 vaccine, if age-appropriate. If patients are using biologic treatment regimens to manage asthma, GINA recommends to avoid administering the COVID-19 vaccination on the same day as the biologic agent. The CDC recommends that patients with asthma, even those who are fully vaccinated, wear a mask in crowded settings, small indoor spaces, and areas with poor ventilation (GINA 2021).

Asthma in Pregnancy

Asthma symptoms in pregnant women can vary case to case 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. Although there is general concern about the use of any medication during pregnancy, the advantages of well-controlled asthma during pregnancy outweigh any potential risks of usual controller and reliever medications. Use of ICSs, β_2 -agonists, or montelukast is not associated with an increased risk of fetal abnormalities (Lim 2011). Inhaled corticosteroids reduce the risk of exacerbations during pregnancy (Schatz 2005). 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 not controlled

Patient Care Scenario

A 16-year-old female adolescent diagnosed with asthma presents to the clinic today for increased wheezing and shortness of breath. Her ACT score today is 15. She reports using her albuterol inhaler “a couple of times per day” and wakes up coughing at least once per 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 indicate that she has only been requesting refills of the albuterol inhaler. On questioning, the patient states that because she was feeling well about 9 months ago, she stopped taking her daily medications. What is an appropriate medication recommendation and plan for this patient?

ANSWER

This patient's asthma is uncontrolled. A score of 19 or less on the ACT indicates that asthma is not optimally controlled, and a score of 15 or less indicates that asthma is very poorly controlled. The patient reports increased albuterol use to compensate for increased shortness of breath. According to the patient, her asthma seems to have been well controlled on daily controller therapy and montelukast. Her asthma was previously controlled on budesonide/formoterol and montelukast; hence,

budesonide/formoterol 80/4.5 mcg (2 puffs twice daily) and montelukast 10 mg once daily can be reinitiated. However, she should be counseled to use budesonide/formoterol as both maintenance and reliever therapy and to discontinue albuterol. The patient should demonstrate inhaler technique. The importance of adhering to her prescribed regimen must be emphasized to the patient. The patient should be given an asthma action plan and return to the clinic in 1–3 months to assess asthma control.

1. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. 2021.

2. National Heart, Lung, and Blood Institute (NHLBI). *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. 2007.

(NHLBI 2007). During acute asthma exacerbations, it is imperative to aggressively treat patients with SABAs, oxygen, and early administration of systemic corticosteroids to avoid fetal hypoxia (GINA 2021). Of note, the 2020 focused updates do not address the treatment of asthma during pregnancy. The GINA guidelines make no recommendation regarding the use of MART during pregnancy; instead, they emphasize the need to use ICSs and ensure asthma control. Both guidelines recommend continuing current ICS therapy in pregnancy if asthma is well controlled (NHLBI 2020, GINA 2021).

Surgery in Individuals with Asthma

Although there are no specific recommendations regarding changes in therapy for those who undergo surgery, patients should have controlled asthma both before and after the procedure to reduce the risk of respiratory complications during surgery. Patients should be informed of these risks of surgery before consenting to the procedure. When lung function is not optimal, it may be prudent to administer oral systemic corticosteroids before surgery. Patients who have demonstrated poor lung function may be treated with intravenous hydrocortisone 100 mg every 8 hours during the procedure. Hydrocortisone should rapidly be reduced after surgery (GINA 2021). Patients should maintain regular controller therapy throughout the peri-operative period.

Treatment of Comorbid Conditions

Asthma control can be affected by several comorbid conditions, such as allergic bronchopulmonary aspergillosis, gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis/sinusitis, and stress/depression. These conditions should be closely monitored and managed appropriately to avoid any exacerbating symptoms and worsening of asthma control (GINA 2021).

Cough Variant Asthma

A subset of asthma is called cough variant asthma (CVA), sometimes described as “chronic cough.” Cough variant asthma may precede the development of classic asthma. Patients with CVA have cough as their predominant asthma symptom. A methacholine challenge test may be performed if symptoms and spirometry do not clearly indicate a diagnosis of asthma. Patients with CVA are less sensitive and less reactive to inhaled methacholine than patients with classic asthma. 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 ICSs considered first-line therapy (Niimi 2011).

ROLE OF THE PHARMACIST IN MANAGING ASTHMA

Asthma Action Plan

Adherence to therapy is incredibly important 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 least 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 improved efficacy (either by decreased symptoms or improved PFT results) with one delivery device over another in asthma (Dolovich 2005). Choice of device is often left to the provider or is based on the patient’s insurance formulary. Small-scale studies suggest that patients prefer inhalers with dose counters, ease of use, comfort of mouthpiece, and smaller size. It is important to provide patients with device options because satisfaction with therapy can lead to increased adherence (Darba 2016). For optimal adherence and appropriate inhaler technique, it is advisable to maintain consistent device choice for patients once their asthma is controlled, when possible. There are newer devices, such as the Digihaler, which has built in sensors that record how often the inhaler is used as well as measure inhalation airflow. Inhaler use is recorded as an event when the cap is opened or inhaled (Teva 2021). Additionally, other companies such as Propeller Health and Hailie have developed mobile health technology to improve asthma outcomes. Electronic inhaler sensors attach to inhalers and track medication use, reminders to promote adherence, and personalized guideline-based education. Improved inhaler use with the assistance of electronic sensors may lead to decreased risk of asthma exacerbation (Propeller 2022, Hailie 2022).

The pharmacist’s role in education should focus on providing an in-depth discussion of disease state management and the importance of adherence to prescribed treatment regimens. Adherence to therapy 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 low adherence lack understanding of their illness and options for management. Some nonadherence is unintentional, especially in the case of misunderstood directions. However, much of the nonadherence to asthma therapy is intentional (e.g., fear of adverse effects, cultural beliefs, practical lifestyle decisions, lack of perceived benefit). Many of the underlying causes of nonadherence (e.g., poverty, lack of social support, unhealthy home and/or work environment) are not easily correctible.

Therefore, it is important for pharmacists to 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 help facilitate applications for patient assistance programs for patients who are eligible. In general, patients are eligible for patient assistance programs when their income falls within the manufacturer-designated income cutoffs and are uninsured or have Medicare Part D.

Inhaler Education

To optimize medication delivery into the lungs, correct device technique is imperative. Poor technique is directly related to poor outcomes (Sanduzzi 2014). It has been suggested that 89% of patients use MDIs incorrectly (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 and demonstrating correct inhaler technique. Even though guidelines recommend instruction before a patient begins using 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 knowledge and understanding of use. Knowledge of correct technique among providers (e.g., 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 (e.g., placebo devices). The importance of device technique in drug delivery and effectiveness should be emphasized with the patient.

Patients' knowledge of inhaler techniques should be evaluated at each encounter and when there is suspected nonadherence, regardless of whether it is intentional or unintentional. Patients should be taught the purpose of each inhaler, either rescue or maintenance, and the steps used to ensure proper delivery of the doses. Educators should use simple language, intended for the age of the patient and caregiver they are teaching. Because there are several types of inhalers that have a set of distinct and separate instructions, each should be reviewed individually. Educators should first model appropriate use of the inhaler using a demonstration inhaler, if available. Educators should then use the teach-back method to allow patients to demonstrate back how they will use the inhaler at home. Patients and caregivers may be provided with educational handouts detailing the use of each inhaler for future reference. Table 7 outlines the different inhaler devices and how each is used.

Results of educational sessions should always be documented in the medical record, including the patient's ability to teach-back key information and demonstrate understanding and use of inhalers. Any unresolved issues, such as technique problems, should also be documented to assist with follow-ups.

Medication Access and Acquisition

A well-developed treatment plan is only effective as long as the patient can obtain the prescribed medications. It is imperative for prescribers to ensure that their patients have insurance or some plan for coverage of their medications. Inhalers are notoriously difficult for patients to obtain, given that formularies are constantly changing and that 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, such as manufacturer-funded savings cards and free trial offers. Uninsured patients may often qualify for manufacturer-based patient assistance programs, depending on program-specified income cutoffs. Patients with insufficient 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 for Medicare patients, patient assistance programs through the drug manufacturer, and other locally available assistance groups.

Practice Points

- Diagnosis of asthma should be confirmed with PFTs to establish the correct diagnosis and rule out other respiratory and non-respiratory conditions that may present with similar symptoms.
- Selection of initial therapy should be based on both objective and subjective (e.g., symptoms) data.
- Adherence to therapy is significantly influenced by patient preferences and perceptions. Pharmacists should routinely assess and incorporate these preferences and perceptions when making recommendations for the therapeutic regimen. Misperceptions and misinformation should be addressed.
- A low-dose ICS plus a SABA should be used as SMART for asthma. Formulations other than budesonide/formoterol have not been studied for as-needed only use, but beclomethasone/formoterol may also be suitable because both agents were well established for as-needed use within MART in the GINA 2021 update. Beclomethasone/formoterol as a single use inhaler is not available in the United States at present.
- Rinsing the mouth is not needed after as-needed low-dose ICS/formoterol because this was not required in any of the mild asthma studies, and there was no increase in risk of oral thrush.

Table 7. Inhaler Education

Inhaler Device	Available Products	Inhalation Technique
Metered Dose Inhaler		
HFA	Albuterol sulfate (Ventolin HFA)	1. Shake well before using
	Albuterol sulfate (ProAir HFA)	2. Inhaler should be primed with three or four test sprays into the air until a solid stream of medicine is seen before first use or if inhaler has not been used in several weeks
	Mometasone furoate (Asmanex HFA)	3. Patients should breathe all air out of lungs completely, then put mouthpiece to mouth and close the lips around the mouthpiece
	Levalbuterol tartrate (Xopenex HFA)	4. Then, actuate the dose by pressing down on the canister while breathing in a slow and deep breath. The breath should be held for as long as able 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
	Budesonide and formoterol fumarate dihydrate (Symbicort HFA)	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		
Diskus	Fluticasone propionate and salmeterol (Advair Diskus)	1. Patients should first remove inhaler from foil pouch and write the use-by date on the Diskus (30 days from opening)
	Fluticasone propionate (Flovent Diskus)	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 exhale completely away from the device, 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. These inhalers should not be used with a spacing device or holding chamber
		7. Because these inhalers contain a steroid, patients should rinse their mouth 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. Given the dose is a powder inside the inhaler, patients should ensure inhaler is stored in a cool, dry space and not cleaned with water at any time. Instead, a dry cloth or tissue may be used to clean the mouthpiece
Ellipta	Fluticasone furoate (Arnuity Ellipta)	1. Patients should first remove inhaler from original container and write the use-by date on the Ellipta (6 wk from opening)
	Fluticasone furoate and vilanterol (Breo Ellipta)	2. Patients should slide open the cover to the Ellipta until they hear a click. This loads the dose, so patients should ONLY slide the cover open when they are ready to use the device
		3. Device 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. Do not block the air vents of the device
		4. Patients should exhale completely away from the device and then place lips to cover the mouthpiece where the patients will steadily inhale through the mouth to deliver the dose into the lungs. This inhaler should not be used with a spacing device or holding chamber

(continued)

Table 7. Inhaler Education (*continued*)

Inhaler Device	Available Products	Inhalation Technique
		<ol style="list-style-type: none"> 5. Patients may hold the dose in the lungs for several seconds before exhaling 6. Because these inhalers contain a steroid, patients should rinse mouth 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. Given the dose is a powder inside the inhaler, patients should ensure inhaler is stored in a cool, dry space and not cleaned with water at any time. Instead, a dry cloth or tissue may be used to clean the mouthpiece
Flexhaler	Budesonide (Pulmicort Flexhaler)	<ol style="list-style-type: none"> 1. Inhaler should be held in an upright position with the cap facing upward. Inhaler must be primed before use. Hold the cap of the inhaler in one hand and twist the bottom portion with the other hand to remove the lid 2. Once cap is removed, twist the brown base fully in one direction and then in the other until it stops and clicks 3. Patients should exhale breath completely away from the inhaler, raise inhaler to mouth horizontally, and then place lips to mouthpiece. Then patients should inhale steadily through the mouth. This inhaler should not be used with a spacing device or holding chamber 4. Patients may hold dose in lungs for 10 s before exhaling 5. Place and twist the cap back onto the inhaler once dose actuation is complete 6. Because these inhalers contain a steroid, patients should rinse mouth with water after each use 7. Patients should use the dose indicator to show when to get a new inhaler 8. Given the dose is a powder inside the inhaler, patients should ensure inhaler is stored in a cool, dry space and not cleaned with water at any time
RespiClick and Digihaler	<p>Albuterol sulfate inhalation powder (ProAir RespiClick, Digihaler)</p> <p>Fluticasone propionate (ArmonAir Digihaler)</p> <p>Fluticasone propionate/salmeterol (AirDuo RespiClick, Digihaler)</p>	<ol style="list-style-type: none"> 1. Patients will not need to shake or prime the device before using. Open the cap until a click is heard, which means the dose is loaded 2. Patients should exhale completely, seal lips around the mouthpiece, 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 10 s before exhaling 4. Inhaler should be cleaned regularly by wiping down with dry cloth 5. Given the dose is a powder inside the inhaler, patients should ensure 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. Device should NOT be shaken or primed before use 2. Hold inhaler upright and twist white cap off colored base. This will remove cap and prepare dose for actuation 3. Breathe all air out of lungs, and place mouth to mouthpiece and seal the lips on the device. This inhaler should not be used with a spacing device or holding chamber. Hold the inhaler in a horizontal position and inhale quickly and deeply 4. Patients may hold the dose in the lungs for at least 10 s before exhaling. Do not exhale into the device 5. When finished with device, close the Twisthaler by twisting on the cap 6. Rinse mouth after use, given this inhaler contains a steroid 7. Given the dose is a powder inside the inhaler, patients should ensure inhaler is stored in a cool, dry space and not cleaned with water at any time

Appendix 1. NHLBI EPR-3 – Initial Classification of Asthma

Components of Severity	Intermittent			Persistent								
				Mild			Moderate			Severe		
	Age 0–4 yr	Age 5–11 yr	Age ≥ 12 yr	Age 0–4 yr	Age 5–11 yr	Age ≥ 12 yr	Age 0–4 yr	Age 5–11 yr	Age ≥ 12 yr	Age 0–4 yr	Age 5–11 yr	Age ≥ 12 yr
Symptoms	≤ 2 days/wk			> 2 days/wk but not daily			Daily			Throughout the day		
Nighttime awakenings	0	≤ 2 ×/mo		1 or 2 ×/mo	3 or 4 ×/mo		3 or 4 ×/mo	> 1 ×/wk but not nightly		> 1 ×/wk	7 ×/wk	
SABA use for symptom control	≤ 2 days/wk			> 2 days/wk, not daily	> 2 days/wk, not daily and no more than once/day		Daily			Several times per day		
Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Lung function FEV ₁ (% predicted)	N/A	> 80%	> 80%	N/A	> 80%	> 80%	N/A	60%–80%	60%–80%	N/A	< 60%	< 60%
Lung function FEV ₁ /FVC	N/A	85%	Normal ^a	N/A	80%	Normal ^a	N/A	75%–80%	Reduced > 5% ^a	N/A	< 75%	Reduced > 5% ^a
Asthma exacerbations requiring oral systemic corticosteroids	0–1/year			≥ 2 in 6 mo or wheezing ≥ 4 ×/yr lasting > 1 day AND risk factors for persistent asthma		≥ 2 per year		More frequent/intense events indicate greater severity				
Recommended step for initiating therapy	1			2			3			3 or 4		

^aNormal FEV₁/FVC by age: 8–19 yr, 85%; 20–39 yr, 80%; 40–59 yr, 75%, 60–80 yr, 70%.

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; N/A = not applicable.

Information adapted from: EPR-3 Guidelines for Diagnosis and Management of Asthma 2007. Available at https://www.ncbi.nlm.nih.gov/books/NBK7232/pdf/Bookshelf_NBK7232.pdf.

CONCLUSION

Asthma offers pharmacists many opportunities to assist in treatment selection and optimization. Pharmacists are well-versed in the pharmacotherapy and device options and can be instrumental in selecting the most therapeutically sound, least-expensive regimen that provides high patient satisfaction, adherence, and acceptance. Pharmacists should model best practices when documenting in medical records and in educating patients to take an active role in their health care.

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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 been using his friend's albuterol inhaler once daily and wakes at night coughing a few times a week.

- Which one of the following best classifies M.B.'s asthma severity using the National Heart, Lung, and Blood Institute (NHLBI) guidelines?
 - 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 – 1 tablet daily
 - Budesonide 80 mcg/formoterol 4.5 mcg – 2 puffs twice daily and as needed
 - Fluticasone 110 mcg – 1 puff twice daily
- A woman with asthma has received 6 months of a medium-dose inhaled corticosteroid (ICS) plus formoterol (single maintenance and reliever therapy [SMART]). Her ACT scores range from 16 to 18. Her weight at today's visit was recorded at 56 kg. Her most recent blood work from 3 days ago indicate that her serum IgE level was 278 units/mL. Which one of the following is best to recommend adding to this patient's regimen?
 - Omalizumab 300 mg subcutaneously every 4 weeks
 - Azithromycin 250 mg – 1 tablet orally three times weekly
 - Tiotropium 1.25 mcg – 2 puffs orally once daily
 - Prednisone 5 mg orally daily

Questions 4 and 5 pertain to the following case.

K.K. is a 14-year-old female adolescent with moderate persistent asthma with an allergic component. She spends much of her time playing sports outdoors in the summer. She is currently treated with mometasone HFA 220 mcg daily. Her technique has been assessed as adequate on many occasions. K.K.'s prescription profile shows that she has filled mometasone three times in the past 90 days and albuterol four times in the past 90 days. She reports two nocturnal awakenings per week and several missed school days because of asthma. K.K. falls asleep in class at least once a week, and her teacher is concerned about her school performance.

- K.K.'s provider is considering initiating montelukast as adjunctive therapy. Which one of the following is best to recommend regarding the use of montelukast for K.K.?

- Initiate a dose of montelukast 5 mg daily.
 - Montelukast is not indicated because she is unlikely to benefit.
 - The best time to administer the dose is first thing in the morning before outdoor exposure.
 - An extra dose of montelukast may be taken before soccer practice to prevent acute shortness of breath.
- K.K. starts monoclonal antibody therapy for asthma. Which one of the following would best indicate achievement of clinical asthma control in K.K., given the overall goals of asthma control outlined in the clinical guidelines?
 - Decrease in serum eosinophil counts
 - Infrequent use of a short-acting β_2 -agonist (SABA) rescue inhaler (two or three times per month)
 - Decrease in nocturnal awakenings to once per week
 - Increase in forced expiratory volume in 1 second (FEV1) readings by 20% of baseline

Questions 6 and 7 pertain to the following case.

L.T. is a 14-year-old male adolescent with moderate to severe asthma. He was recently initiated on fluticasone/salmeterol dry powder inhaler (DPI) 100/50 mcg per inhalation 1 puff twice daily and albuterol 1 or 2 puffs every 4–6 hours as needed. Today at L.T.'s 2-week follow-up in the clinic, his ACT score is 17, and he has nighttime awakening two or three times per week. You recognize that L.T. has been taking fluticasone/salmeterol regularly but has not been using the inhaler correctly.

- Which one of the following is a correct educational point to give L.T. regarding the fluticasone/salmeterol DPI (Advair Diskus)?
 - Prime the inhaler before each use.
 - Inhale with a forceful breath to activate the device.
 - Use a spacer with the inhaler to improve coordination of breath and dose.
 - Shake the inhaler before use.
- 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.?
 - Add montelukast 10 mg once daily.
 - Change to budesonide/formoterol 160/4.5 mcg – 2 puffs twice daily and as needed.
 - Change to fluticasone/salmeterol 500/50 mcg – 1 puff twice daily.
 - Change to fluticasone/salmeterol 250/50 mcg – 1 puff twice daily and add omalizumab 150 mg subcutaneously every 4 weeks.

8. A 10-year-old girl presents after recently obtaining pulmonary function tests (PFTs). Her FEV₁ was 84% of predicted with an FEV₁/forced vital capacity (FVC) ratio of 81%. The patient's current medications include albuterol HFA as needed and cetirizine 5 mg once daily. She has experienced nighttime awakenings because of shortness of breath two times per week for the past month and has required the 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?
- Fluticasone/salmeterol 250/50 mcg – 1 puff twice daily.
 - Budesonide/formoterol 80/4.5 mcg – 2 puffs twice daily and as needed (replacing albuterol)
 - Budesonide/formoterol 80/4.5 mcg – 1 puff twice daily and as needed (replacing albuterol)
 - Salmeterol 50 mcg – 1 puff twice daily.
9. A 26-year-old pregnant woman in her first trimester with well-controlled asthma presents to her family medicine clinic to establish care for her pregnancy. Her home medications include fluticasone propionate 220 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. Which one of the following is the best recommendation regarding the patient's asthma treatment in pregnancy?
- Continue fluticasone 220 mcg – 1 puff twice daily and albuterol as needed.
 - Change fluticasone to 110 mcg – 1 puff twice daily.
 - Change fluticasone to budesonide 180 mcg – 1 puff twice daily.
 - Change to budesonide/formoterol 160/4.5 mcg – 2 puffs twice daily and as needed.
10. A 10-year-old boy and his mother present to the clinic for medication education. The patient is currently prescribed an albuterol HFA as needed, montelukast 10 mg once daily, and fluticasone/salmeterol HFA 115/21 mcg – 2 puffs twice daily. His mother worries that her son is not getting all the medication from his inhalers because he still seems to cough 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 caretaker?
- Hold the inhalers horizontally and do not tilt or shake them.
 - Use a holding chamber (spacer) to help with timing of dose actuation and breath.
 - Exhale completely before forcefully breathing in the dose actuation.
 - Wait 30 minutes in between using each inhaler.
11. A patient asks whether he can be prescribed a budesonide/formoterol combination inhaler in place of his two budesonide and albuterol inhalers. His asthma is well controlled with budesonide 180 mcg – 2 puffs twice daily, and he has not had to use the 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 has 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?
- Change inhalers to budesonide/formoterol 160/4.5 mcg – 2 puffs twice daily and as needed because GINA guidelines recommend the combination regimen as an option for patients in Steps 3-5.
 - Continue current regimen because the budesonide/formoterol combination regimen is not approved for use as a rescue inhaler in the United States.
 - Change inhalers to fluticasone/salmeterol 250/50 mcg – 1 inhalation twice daily and as needed because data show this regimen is most effective at replacing the albuterol rescue inhaler.
 - Change inhalers to budesonide/formoterol 80/4.5 mcg – 2 puffs twice daily and as needed.
12. A 30-year-old woman is establishing care with your clinic today. She recently lost her job, and her insurance will become inactive at the end of the month. Her asthma is well controlled on budesonide/formoterol HFA, and she rarely uses extra doses as her rescue inhaler. She informs you that she will be unable to afford the medication once she is uninsured. The patient does not know when she will obtain health insurance again because she has no other job yet and cannot afford to purchase a plan on the health care exchange. She does not know what to do when she runs out of inhalers, so she has been only using the budesonide/formoterol HFA inhaler once daily instead of twice daily. Which one of the following is best to recommend for this patient?
- Discontinue the budesonide/formoterol HFA 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.
 - Recommend oral prednisone (\$4 at a local big-box store with a pharmacy) to decrease inflammation until she obtains insurance.
 - Encourage and help the patient apply for patient assistance from the drug manufacturers to receive the products for free while she is uninsured.
 - Encourage the patient to apply for the Low-Income Subsidy Program through Social Security.

Questions 13 and 14 pertain to the following case.

E.Z. is a 51-year-old man being seen in the clinic today. Although he has been given albuterol periodically through the years, he currently has no active prescription. E.Z. has been using his neighbor's albuterol inhaler when he has chest tightness and shortness of breath. Today in the clinic, spirometry with pre- and post-bronchodilator testing confirmed a diagnosis of asthma. E.Z.'s post-bronchodilator readings were as follows: FEV₁ 66% of predicted and FEV₁/FVC 77%.

13. Which one of the following best classifies E.Z.'s asthma?
- A. Intermittent
 - B. Mild persistent
 - C. Moderate persistent
 - D. Severe persistent
14. Using the NHLBI 2020 focused updates treatment algorithm, which one of the following is best to recommend as E.Z.'s initial treatment regimen?
- A. Albuterol HFA as needed to control symptoms of shortness of breath
 - B. Budesonide/formoterol 80/4.5 mcg – 2 puffs twice daily and as needed

- C. Fluticasone/salmeterol 250/50 mcg – 1 puff twice daily plus albuterol HFA as needed
 - D. Fluticasone HFA 220 mcg – 1 puff twice daily plus montelukast 10 mg once daily plus albuterol HFA as needed
15. A 37-year-old woman presents to the clinic for a follow-up on her asthma medications. She believes she is doing well on her current regimen of fluticasone 110 mcg – 1 puff twice daily plus albuterol HFA as needed; however, she still has to use the albuterol inhaler at least once daily. Which one of the following is best to recommend for this patient?
- A. Change the regimen to budesonide/formoterol 80/4.5 mcg – 2 puffs twice daily and as needed.
 - B. Continue the current regimen and initiate an oral prednisone taper for 7 days to decrease use of the albuterol inhaler.
 - C. Continue the current regimen and have the patient schedule albuterol use every 6 hours.
 - D. Change the regimen to fluticasone/salmeterol 250/50 mcg – 1 puff twice daily and continue albuterol as needed.

Learner Chapter Evaluation: Asthma Guideline Updates

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
 - Agree
 - Neutral
 - Disagree
 - Strongly disagree
1. The content of the chapter met my educational needs.
 2. The content of the chapter satisfied my expectations.
 3. The author presented the chapter content effectively.
 4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
 5. The content of the chapter was objective and balanced.
 6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.

7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: