Asthma

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LEARNING OBJECTIVES

1. Assess current evidence regarding therapies specific to the guidelines.
2. Design patient-centered therapy for patients with difficult-to-treat and severe asthma.
3. Design patient-centered therapy for patients with exercise-induced asthma.
4. Evaluate the role and place in therapy of pharmacotherapy on the basis of patient factors.

ABBREVIATIONS IN THIS CHAPTER

ACO	Asthma-COPD overlap
ACOS	Asthma, COPD, and asthma-COPD overlap syndrome
COPD	Chronic obstructive pulmonary disease
DPI	Dry powder inhaler
EIB	Exercise-induced bronchospasm
EPR-3	Expert Panel Report 3
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
HDM	House dust mites
ICS	Inhaled corticosteroid(s)
INCS	Intranasal corticosteroid
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibodies
MDI	Metered dose inhaler
OCS	Oral corticosteroid(s)
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PMA	Perimenstrual asthma
SABA	Short-acting β_2-agonist
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
Th2	T-helper cell type 2
T2	Type 2 inflammation

Table of other common abbreviations.

INTRODUCTION

Prevalence

Asthma is a common, yet complex chronic condition affecting people of all ages. According to the 2017 National Health Interview Survey data, over 25.1 million people in the United States are estimated to have asthma (CDC 2017), with over 42.6 million estimated to have asthma in their lifetime. With varying rates across different countries, it is estimated that 1%–18% of the world's population has asthma. Increased prevalence of asthma has been linked to lower socioeconomic status, such as patients in developing nations and poorer populations within developed nations (GINA 2019b).

According to CDC data, over 3500 people in the United States died of asthma in 2017 (CDC 2018). Adults were almost 5 times more likely to die of asthma than children, and non-Hispanic blacks were 2–3 times more likely to die of asthma than any other race group. Patients 65 and older were most likely to have asthma-related death. However, the overall trend of asthma as the underlying cause of death in the United States has decreased since 2001. Nevertheless, although countries like the United States have decreased the number of hospitalizations and deaths related to asthma, the social and economic burden on families, health care systems, and society across the globe is still significant (GINA 2019b).

Pathophysiology

Asthma is a condition of chronic airway inflammation, defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough (GINA 2019b). Our understanding of asthma continues to evolve, and the definition is not consistent across the globe. Symptoms of asthma and inflammation can vary over time, and in intensity, and result in variable expiratory airflow limitation. This variability can make asthma difficult for both patient and provider to track. Respiratory symptoms and/or airflow limitation can resolve spontaneously (or be absent for long periods) or

be triggered into exacerbation by factors such as exercise, changes in weather, allergen or irritant exposure, and viral infections. These features of airway hyperresponsiveness and chronic inflammation can persist even with normal lung function and no reported symptoms. With persistent inflammation, structural changes from hypertrophy and hyperplasia can result in airway wall remodeling. Patients with this remodeling may develop persistent or incompletely reversible airflow limitations.

Asthma is considered a heterogeneous disease (i.e., several etiologies) driven by gene-environment interactions (GINA 2019b). Perhaps the most important interaction occurs early in life (and in utero) when environmental factors may influence asthma development. Environmental factors include nutrition, ingested and inhaled allergens, pollutants, psychosocial factors, and microbes. The updated "biodiversity hypothesis" (i.e., extension of the "hygiene hypothesis") suggests that exposure to microbe-rich environments provides protection against allergic and autoimmune diseases but finds that declining biodiversity is generally more responsible for increasing human immune dysfunction (Rook 2010).

Information regarding the effect of diet, supplements and obesity in pregnancy and breastfeeding and delayed introduction of solids during early life has been reviewed, but not extensively or with conflicting results. At this time, the effects of maternal dietary changes (e.g., increased intake of allergenic foods), maternal weight loss in obesity, maternal exposure to allergens (e.g., pets), breastfeeding, and delaying solid food introduction (to infant) to prevent allergies or asthma are uncertain. Perhaps the most promising data analyses support sustaining prenatal 25(OH) vitamin D concentrations of at least 30 ng/mL to decrease the risk of asthma and wheezing in early life (age 0–3 years) (Wolsk 2017). According to the 2010 ARIA guidelines, parents should avoid exposing children to environmental tobacco smoke during pregnancy and after birth and should use vaginal delivery, when possible; breastfeed (for reasons other than asthma prevention); and avoid broad-spectrum antibiotics during the first year of life, when possible, to reduce the risk of early childhood development of asthma.

A series of other host factors are believed to contribute to the pathophysiology of asthma. These host factors are not always understood but include genetic makeup, sex, early growth characteristics, obesity, and depression. Before age 14, the biological male sex is almost twice as likely to have asthma as the female sex (GINA 2019b: Appendix). Of interest, this gap narrows and reverses in adulthood. This sex-based difference between childhood and adulthood asthma may be a result of the lung and airway size of the biological female sex, which is larger in infancy and smaller in adulthood than in the male sex.

BASELINE KNOWLEDGE STATEMENTS

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

- Concept of the "hygiene hypothesis"
- EPR-3 severity classification and stepwise approach to therapy
- EPR-3 assessment of control
- Pulmonary function testing parameters: FEV_1, FVC, FEV_1/FVC
- Symptom questionnaires, such as the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ)

Table of common laboratory reference values

ADDITIONAL READINGS

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

- NHLBI. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US). 2007.
- GINA. Global Strategy for Asthma Management and Prevention. 2019.
- GINA. Asthma, COPD, and Asthma-COPD Overlap Syndrome (ACOS). 2015.
- GINA. Difficult-to-Treat & Severe Asthma. 2019.
- ATS. An Official American Thoracic Society Clinical Practice Guideline: Exercise-Induced Bronchoconstriction. 2012.
- ATS. An Official American Thoracic Society Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels for Clinical Applications. 2011.

DIAGNOSIS

Diagnosis of asthma is most clear at first presentation, especially before respiratory treatment is initiated. The clinician must carefully evaluate the pattern of characteristic asthma symptoms, including wheezing, dyspnea, chest tightness, cough, and variable expiratory airflow limitation. Many symptoms that are worse in the early morning or night, that vary over time in frequency and intensity, and that have identifiable triggers are more indicative of asthma than of chronic obstructive pulmonary disease (COPD) in adult patients. These identifiable triggers include viral infections, exercise (see the Exercise-Induced Bronchospasm section that follows), allergen exposure, changes in weather, laughter, and irritants (e.g., car exhaust, smoke, or strong smells) (GINA 2019b).

Diagnosis should include pulmonary function tests (PFTs) to inform an accurate diagnosis (EPR-3 2007). Pulmonary function tests should demonstrate variability of forced expiratory volume in 1 second (FEV_1) over 12% and 200 mL (for patients older than 11 years) or a peak expiratory flow rate

(PEFR) change of 20% post-bronchodilator (GINA 2019b; NICE 2017). Testing can include post-bronchodilator PFT, PEFR, exercise challenge, or bronchial challenge (using methacholine or histamine, hypertonic saline or mannitol). Peak expiratory flow rate may be less reliable than PFTs for diagnosis because devices vary, especially when patients are very young or very old (EPR-3 2007). A commonly used PFT, spirometry, can be performed in the clinic for patients 5 years and older. Expiratory airflow obstruction that is reversible spontaneously or with β_2-agonist treatment is necessary for an asthma diagnosis. At any given time, PFT results can range from normal to obstructed lung function and should therefore be repeated on another occasion if normal and symptoms persist (GINA 2019b). In addition, patients with intermittent or mild asthma can have normal lung function (EPR-3 2007).

Diagnosing asthma in patients after they have started controller therapy can be challenging. Up to 25%–35% of patients have not had their asthma diagnosis confirmed with PFTs (GINA 2019b). Patients are asked to refrain from rescue short-acting β_2-agonist (SABA) use for at least 6 hours before testing (and for up to 2 days from their long-acting β_2-agonist [LABA]), when possible. Measuring lung function in patients already receiving controller therapy depends on current symptoms. One strategy is to step down monotherapy with the inhaled corticosteroid (ICS) dose by 25%–50% or consider reduction to a single ICS from combination therapy. Caution and close supervision should be used for patients at risk of exacerbation. After 2–4 weeks of therapy reduction, the patient should be reassessed for variable expiratory airflow limitation and symptoms (GINA 2019b).

A differential diagnosis in patients with asthma is usually straightforward. In pediatric patients, conditions such as an inhaled foreign body, cystic fibrosis, congenital heart disease, or bronchiectasis can be considered. In patients with a history of smoking, PFTs can rule out COPD or rule in asthma-COPD overlap (ACO). Other conditions that can lead to shortness of breath in an adult population and that should be considered include pulmonary embolism, medication-related cough, and congestive heart failure.

Phenotypes

The Global Initiative for Asthma (GINA) report provides guidance regarding the differing phenotypes within asthma. Phenotypes in asthma are recognizable clusters of demographic, clinical, and/or pathophysiologic characteristics, including allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity. These phenotypes can help group patients with asthma, specifically those outside the typical allergic asthma phenotype, and help clinicians recognize some of the key features and medication implications. For example, patients with the "non-allergic asthma" phenotype usually have less short-term response from an ICS. Patients with "adult-onset asthma" are often considered non-allergic and can require higher ICS doses or are sometimes refractory to corticosteroid treatment. However, information is limited, and more research is needed to fully use phenotype classifications in clinical decision-making (GINA 2019b).

A simpler framework incorporates the hygiene hypothesis and classifies asthma into two types of asthma phenotypes: the T-helper cell type 2/Type 2 inflammation (Th2/T2) and the non-Th2/T2 type (Arnold 2018). Recently, Th2 (which refers to the cytokine release from the Th2 cell) has been expanded to type 2 (T2) to recognize more diverse inflammation. These two phenotypes can also be called eosinophilic and non-eosinophilic asthma. Patients with T2 inflammation present at an early age, have asthma associated with atopy/allergy/elevated immunoglobulin E (IgE), have eosinophilia, have elevated fractional exhaled nitric oxide (FeNO), and respond to corticosteroids. Having the T2 inflammation type is considered a risk factor for severe asthma exacerbations, specifically in patients with severe refractory asthma (though not in mild to moderate asthma) (Semprini 2018). Patients with the non-T2 present later in life (greater than 20 years of age), may have neutrophilia, have a poor response to corticosteroids, are more likely to have a smoking history, and have asthma associated with respiratory infections (Arnold 2018; Okada 2010).

Newer Testing

Because patients with asthma with T2 inflammation have higher blood eosinophils and FeNO levels, these levels can be measured, and use of these results in clinical management is being clarified.

Blood or Sputum Eosinophil Testing

FeNO Testing

Sputum eosinophils have long been considered the gold standard test for airway inflammation, but because of technical difficulties, this test is not often performed in the outpatient setting (Arnold 2018). Blood eosinophil concentrations are easier to obtain and acceptable. Fractional exhaled nitric oxide testing measures the amount of nitric oxide exhaled in the patient's breath and corresponds with eosinophil concentrations in the blood. Fractional exhaled nitric oxide testing is quick, validated, noninvasive, and increasingly cost-effective (around $20 per test), making it optimal for outpatient care. However, FeNO can also be elevated from other conditions such as eosinophilic bronchitis, atopy, allergic rhinitis, or eczema. Fractional exhaled nitric oxide levels can also be lower in smokers, during early phases of the allergic process, during bronchoconstriction, during viral respiratory infections (increased or decreased), or in certain phenotypes (neutrophilic). No long-term studies are available with using FeNO to determine asthma exacerbation outcomes or outcomes that clearly indicate the appropriateness of withholding ICS in patients with low levels. Given these considerations, GINA does not recommend FeNO testing to determine when to add ICS treatment and uses FeNO levels for other guidance (Table 1).

Table 1. Summary of Fractional Exhaled Nitric Oxide Recommendations

Guideline	Recommended Use	Range
Global Initiative for Asthma (GINA)	As a factor in increasing ICS use or in considering biologic therapy in severe and difficult-to-treat asthma	> 20 ppb
American Thoracic Society (ATS)	(1) Detecting eosinophil airway inflammation, (2) determining the likelihood of corticosteroid response, (3) monitoring for potential need of corticosteroids, and (4) unmasking nonadherence	< 25 ppb (20 ppb for children) = eosinophilic inflammation less likely; ICS response less likely > 50 ppb (30 ppb for children) = eosinophilic inflammation; ICS response likely
National Institute for Health and Care Excellence (NICE)	If testing is available, use for diagnosis in addition to spirometry and peak flow variability	> 40 ppb (> age 17 yr) (> 35 ppb for patients age 5–16 yr) = asthma likely

ICS = inhaled corticosteroid(s); ppb = parts per billion.

Information from: Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available at www.ginasthma.org. Accessed November 30, 2019; National Institute for Health and Care Excellence (NICE). Asthma: Diagnosis Monitoring and Chronic Asthma Management, 2017; Dweik RA, Boggs PB, Erzurum SC, et al. Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. An Official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-15.

Conversely, the American Thoracic Society (ATS) produced clinical practice guidelines for interpreting FeNO in 2011 (Dweik 2011). The ATS strongly recommends that cutoff FeNO levels less than 25 ppb indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely. Levels greater than 50 ppb indicate that a response to corticosteroids is likely in symptomatic patients. The ATS also strongly recommends that FeNO testing be used in diagnosing eosinophilic asthma, an important distinction because some patients do not have eosinophilic asthma. The National Institute for Health and Care Excellence (NICE) guidance does not recommend blood eosinophil testing for diagnosis but provides a reference range if equipment is available (NICE 2017).

Asthma and COPD

Before our current understanding of ACO, a prospective observational study showed that patients with asthma were 12.5 times more likely to meet the criteria of COPD over 20 years, highlighting that asthma and COPD can have similar features over time (Silva 2004). In a randomized population-based group of patients older than 50, 55% of those with COPD also had asthma as the predominant phenotype (n=469 total patients; n=96 with COPD; n=53 with asthma) (Marsh 2015). This was followed by 19% with chronic bronchitis and/or emphysema phenotype without asthma (n=18). The "overlap" between patients with asthma and COPD led to questions about optimal treatment for patients with several obstructive lung diseases, and evidence for the clinical link between the two has increased over time (Guerra 2005). In 2009, this overlap in disease states was described as a syndrome caused by accelerated decline in lung function, incomplete lung growth, or both (Gibson 2009). Overlap appeared to be particularly relevant for understanding the mechanism for COPD progression because these patients had inflammatory markers of COPD (increased airway neutrophils) and features of airway remodeling (Hardin 2011). However, patients with clinical features of both asthma and COPD have been excluded from most clinical trials, making diagnosis and treatment difficult to fully understand in this population.

The GINA and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) collaborated in 2014 to create the guidance document on asthma, COPD, and asthma-COPD overlap syndrome (ACOS), which was last updated in 2015 (ACOS 2015). Through this collaboration, asthma and COPD were no longer presented as two separate conditions but as part of overlapping phenotypes (Reddel 2015). Despite the limited evidence, a stepwise process and tool was created to help determine whether the patient presented with mainly features of asthma, COPD, or both to aid in diagnosis and provide treatment recommendations (ACOS 2015). Steps include (1) diagnosing chronic airway disease, (2) providing a syndromic diagnosis in adults (Table 2; comparing the number of features favoring each diagnosis), (3) performing spirometry, (4) initiating treatment, and (5) referring to a specialist. This guidance document was specifically created for the primary care clinician and nonrespiratory specialist, as clarified in the 2015 update, after feedback that the approach was too simplistic (Reddel 2015).

Table 2. Syndromic Diagnosis in Adults for Asthma-COPD Overlap (Step 2)

Features (if present) Suggest:	Asthma	Chronic Obstructive Pulmonary Disease
Age at onset	• < 20 yr	• > 40 yr
Pattern of symptoms	• Variation over minutes, hours, or days • Worse during the night or early morning • Triggered by exercise, emotions including laughter, dust, or exposure to allergens	• Persistent despite treatment • Good and bad days but always daily symptoms and exertional dyspnea • Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	• Record of variable airflow limitation (spirometry or peak flow)	• Record of persistent airflow limitation (FEV_1/FVC < 0.7 post- bronchodilator)
Lung function between symptoms	• Normal	• Abnormal
Patient or family history	• Previous physician diagnosis of asthma • Family history of asthma and other allergic conditions	• Previous physician diagnosis of COPD, chronic bronchitis, or emphysema • Heavy exposure to risk factor: Tobacco smoke, biomass fuels
Time course	• No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year • May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	• Symptoms slowly worsening over time (over years) • Rapid-acting bronchodilator treatment provides only limited relief
Radiography	• Normal	• Severe hyperinflation
Diagnosis	Asthma / Some features of asthma; possible asthma	Features of both; could be ACOS / Some features of COPD; possible COPD / COPD

ACOS = asthma, COPD and asthma-COPD overlap syndrome; COPD = chronic obstructive pulmonary disease; FVC = forced vital capacity.

Information from: Global Initiative for Asthma (GINA). 2015 Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS).

Diagnosis of either asthma or COPD in primary care may be limited by less immediate access to spirometry or by results that are confusing to interpret (e.g., when patients fall out of the typical patterns of obstruction and reversibility). Using the 2015 ACOS five-step tool, if the provider systematically determines the patient has three or more features of both asthma and COPD, the patient with ACOS should be initiated on asthma treatment. This rationale is the result of the pivotal role of ICS in preventing morbidity and mortality in uncontrolled asthma. Adding a long-acting muscarinic antagonist (LAMA) and/or a LABA is typical. Patients with asthma within ACOS should not use LABA monotherapy (consistent with asthma management), and patients with COPD within ACOS are not recommended for ICS monotherapy (ICS/LABA combination instead). This combined approach follows the tenets of managing each condition separately in GINA and GOLD.

In recent GOLD guidelines, the authors report that the "S" for syndrome should be dropped from ACOS because "syndrome" is confusing and seems to connote a separate condition from both asthma and COPD, which was not the intention of the document. Asthma-COPD overlap and our understanding of diagnosis and treatment is important because patients with ACO have poorer health-related quality of life than patients with only asthma or only COPD (Kauppi 2011). In addition, patients with ACO have more frequent exacerbations, more rapid decline in lung function, and higher mortality and consume a disproportionate amount of health care resources (ACOS 2015). However, in the most recent 2020 GOLD guidelines, GOLD briefly reported no longer supporting the use of ACO terminology. The GOLD authors stated this change because asthma and COPD are different conditions that may coexist and that have common traits and clinical features. Treatment in patients with both should primarily follow the asthma guidelines (GOLD 2020).

CLINICAL GUIDELINES

The most recognized guidelines for asthma in the United States include the National Heart, Lung, and Blood Institute (NHLBI) Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3), GINA, NICE, and ATS. The EPR-3 asthma guidelines have widely been used in the United States but were last comprehensively updated in 2007. In 2018, the NHLBI instructed a 15-member committee, called the Expert Panel Report 4 (EPR-4) working group, to review the current evidence and provide an update to EPR-3 (Mensah 2018). The topics specifically reviewed included: (1) role of immunotherapy, (2) intermittent therapy, (3) effectiveness of indoor allergen reduction, (4) effectiveness and safety of bronchial thermoplasty, (5) clinical usefulness of FeNO and (6) role of LAMA as add-on to ICS. As of December 2019, a draft EPR-4 update was shared for an open public comment period ending in early 2020. However, at the time of this publication, the final version was not available to be included.

The GINA report is updated annually (since 2002), is geared toward primary care providers, and includes international socioeconomic considerations because the committee consists of experts from across the globe (Ballas 2018). The GINA guidance differs from the EPR-3 because it incorporates newer treatments and testing into its stepwise management; most clinicians would benefit from reviewing the more up-to-date guidance from the GINA report. Clinicians in the United States are most familiar with the EPR-3 as it continues to guide clinical management and standardized testing nationally. Since the EPR-3 has not changed in some time, this chapter will presume a baseline knowledge of EPR-3 asthma classification and management and focus on reviewing and comparing with updated guidance.

The NICE guidelines are published in the United Kingdom, and the intended audience is primary care providers taking care of patients with mild to moderate asthma. The NICE guidelines were last updated in 2017 (Ballas 2018; NICE 2017). The ATS is an international organization providing evidence-based clinical guidance for respiratory health. The ATS offers a variety of guidelines for specific areas within asthma, such as obesity and asthma, asthma management in older adults, and exercise-induced bronchoconstriction.

Classification and Management

The EPR-3 and GINA guidelines for classification and management are similar, with only a few differences. The EPR-3 guidelines classify asthma severity for a patient upon diagnosis and specifically when the patient is not receiving controller therapy. The EPR-3 classification of severity is based on impairment and risk of exacerbation and classifies patients as having either intermittent or varying levels of persistent asthma. The GINA guidelines instead classify asthma severity *retrospectively* based on the treatment level required to control symptoms and exacerbations. The GINA guidelines use this classification approach by recognizing that many patients are already receiving treatment and that it can take 3–4 months for the full benefit of treatment (Bateman 2007). Given this delay in treatment effect, the level of asthma severity in GINA varies over time compared with the EPR-3, which remains constant from diagnosis. The GINA severity levels include mild, moderate, and severe asthma and are not differentiated by intermittent or persistent categories (Table 3).

After severity classification and initial treatment selection by indicated step therapy, the EPR-3 guidelines assess a patient's level of asthma control to guide follow-up management (Table 4). These EPR-3 recommendations for control are based on age groupings and domains similar to classification. The GINA guidelines for control are similar but streamlined to focus on only four features within two domains: symptom control and future risk. Questionnaires, such as the Asthma Control Test (ACT) or the Asthma Control Questionnaire (ACQ), rate symptom control and are supported by both the EPR-3 and the GINA guidelines. The ACT reviews the past 4 weeks, and patients with scores over 19 are considered to have well-controlled asthma. The minimally clinical difference between sequential scores for a patient is 3 points (GINA 2019b). Future risk factors for adverse outcomes include a history of one or more exacerbations (in the previous year), low lung function, smoking, poor medication adherence and inhaler technique, and blood eosinophilia.

In summary, the overall stepwise therapy approach (diagnosis, the initiation of a selected step, stepping up and down based on control) between EPR-3 and GINA is similar. Most differences arise in the therapeutic choices and decision-making within each step (see Table 3).

Recommendations for Mild Asthma

Single-Inhaler Therapy

Since the last EPR-3 update, GINA has been integrating current literature to offer evidence-based options. Within each additional step, EPR-3 equally offers increasing the ICS dose or adding a LABA for controller therapy. Instead, GINA prefers combination ICS and formoterol with each step, except in step 2 (see Table 3). This GINA preference includes two key differences from EPR-3: the combination requires a lower dose of ICS (and is preferred to higher-dose ICS monotherapy), and formoterol is the preferred LABA. The GINA guidelines also provide guidance on adding SIT (single-inhaler therapy) or SMART (single maintenance and reliever therapy) as an off-label preference (approved in other countries), which incorporates efficacy and cost data. In addition, the GINA guidelines include adding tiotropium at step 4 or 5.

Concerns with SABA-Only Treatment

One of the key major changes in the 2019 GINA report includes no longer preferring SABA-only treatment for rescue, given

Table 3. Comparison of GINA and EPR-3 Stepwise Treatment in Age 12 Yr and Greater

Guideline	Group	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
EPR-3	**Severity (at diagnosis)**	Intermittent	Mild persistent	Moderate persistent		Severe persistent	
	Controller therapy	SABA as needed	Low-dose ICS Alternative: LTRA, theophylline, or cromolyn	Low-dose ICS + LABA OR Medium-dose ICS Alternative: LTRA, theophylline, or zileuton	Medium-dose ICS + LABA Alternative: Medium-dose ICS + LTRA, theophylline, or zileuton	High-dose ICS + LABA AND Consider omalizumab in patients with allergy	High-dose ICS + LABA + OCS AND Consider omalizumab in patients with allergy
	Rescue therapy	SABA as needed					
GINA	**Severity (according to treatment level)**	Mild asthma		Moderate asthma	Severe asthma		
	Controller therapy	Low-dose ICS/formoterol as needed (not approved in the United States) Alternative: Low-dose ICS when SABA is taken	Low-dose ICS OR Low-dose ICS/formoterol as needed (not approved in the United States) Alternative: LTRA, low-dose ICS when SABA is taken	Low-dose ICS/LABA Alternative: Medium-dose ICS, low-dose ICS + LTRA (and consider HDM SLIT for patients with allergic rhinitis and FEV_1 > 70% of predicted)	Medium-dose ICS/LABA Alternative: High-dose ICS, add-on tiotropium, or add-on LTRA (and consider HDM SLIT for patients with allergic rhinitis and FEV_1 > 70% of predicted)	High-dose ICS/LABA Refer for phenotypic assessment ± add-on tiotropium, anti-IgE, anti-IL-5/5R, anti-IL-4R Alternative: Add low-dose OCS	
	Rescue therapy	Low-dose ICS-formoterol as needed (not approved in the United States) Alternative: SABA as needed					

FEV_1 = forced expiratory volume in 1 second; HDM SLIT = house dust mite sublingual immunotherapy; IL = interleukin; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid(s); SABA = short-acting β_2-agonist.

Information from: Expert Panel Report 3 (EPR-3), Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program (NAEPP). 2007. NIH Publication 08-5846; Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019.

that it increases the risk of severe exacerbations and asthma-related death. Instead, GINA prefers low-dose ICS plus formoterol as needed for rescue, which is discussed in the following Selection Pearls of Pharmacotherapy section.

In both the GINA and the EPR-3 guidelines, patients are stepped up or down on therapy depending on the level of control (see Table 4). Both guidelines also recommend assessing adherence, device technique, triggers, and other comorbid conditions before stepping up therapy. The EPR-3 guidelines recommend stepping up one step for asthma that is not well controlled and one or two steps for very poorly controlled asthma (and to consider an oral steroid burst). Follow-up should be in 2 weeks for very poorly controlled asthma and 2–6 weeks for asthma not well controlled. The GINA guidelines recommend stepping up therapy after 2–3 months of controller therapy and reassessing it every 2–3 months. Patients may also benefit from a short-term increase of 1–2 weeks during a viral infection or seasonal allergen exposure.

Once asthma is well controlled for 3 months, therapy can be stepped down with preference for discontinuing add-on

Table 4. Summary of Control for EPR-3 and GINA for Age 12 Yr and Older

Guideline				
EPR-3	**Levels of control:**	Well controlled	Not well controlled	Very poorly controlled
	Symptoms:	< 2 days per week	> 2 days per week	Throughout the day
	Nighttime awakenings:	< 2 per month	1–3 times per week	> 4 per week
	Interference with normal activity:	None	Some limitations	Extremely limited
	SABA use for symptom control:	< 2 days per week	> 2 days a week	Several times a day
	FEV_1 or peak flow:	> 80% of predicted or personal best	60%–80% of predicted or personal best	< 60% of predicted or personal best
	Questionnaires: **ACQ:** **ACT:**	 0–0.75 > 19	 0.75–1.5 16–19	 > 1.5 < 16
	Exacerbations requiring oral steroids:	0 or 1 per year	≥ 2 per year	≥ 2 per year
	Recommended action:	• Maintain current step • Reassess in 1–6 mo • Consider step down if well controlled for 3 mo	• Step up 1 step • Reassess in 2–6 wk	• Consider short course of oral corticosteroids • Step up 1 or 2 steps • Reassess in 2 wk
GINA	**Levels of control:**	Well controlled	Partly controlled	Uncontrolled
	Daytime asthma symptoms > 2 per week: **Any nighttime waking because asthma:** **Reliever needed for symptoms > 2 per week:** **Any activity limitation because of asthma:**	None of these in the past 4 wk	1 or 2 of these in the past 4 wk	3 or 4 of these in the past 4 wk
	Recommended action:	• Reassess in 2–3 mo • Consider step down if well controlled for 3 mo	• Step up therapy as appropriate • Reassess in 2–3 mo	• Step up therapy as appropriate • Reassess in 2–3 mo • Reassess in 1 wk for those in exacerbation

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; EPR-3 = Expert Panel Report 3.

Information from: Expert Panel Report 3 (EPR-3), Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program (NAEPP). 2007. NIH Publication 08-5846; Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019.

therapies before decreasing the ICS dose. However, GINA recommends that the LABA not be discontinued or decreased in combination ICS therapy compared with reducing the ICS dose. In addition, LABAs are not indicated as monotherapy for asthma. Instead, GINA recommends stepping down the ICS dose by 25%–50% as appropriate. Patients at high risk of exacerbations should be monitored closely when therapy is stepped down. With any exacerbations, patient maintenance or controller therapy should be reassessed in 1 week.

PATIENT FACTORS

Difficult-to-Treat and Severe Asthma

In 2019, GINA included a section and summary pocket guide, "Diagnosis and Management of Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients." This guide provides a detailed approach for treating patients with these complex conditions. Some important additions to this section include specialist care recommendations such as additional testing,

interprofessional care, cost, and even enrollment in clinical trials, when available. Patients with difficult-to-treat or severe asthma, in particular, can have several comorbidities.

Difficult-to-treat asthma presents in around 17% of the adult asthma population and is defined as uncontrolled asthma despite appropriate GINA step 4 or 5 treatment or asthma that requires such treatment to maintain control. Severe asthma (or "severe refractory asthma") occurs in around 3.7% of adult patients with asthma, which is considered a subset of patients with difficult-to-treat asthma. Patients with severe asthma have uncontrolled asthma despite adherence to maximally optimized medications or have worsening symptoms when high doses are decreased. The GINA pocket guide provides a stepwise approach for treating these patients and an easy-to-use figure. The following paragraphs summarize the steps.

Step 1: Health care providers should confirm the diagnosis of difficult-to-treat asthma. Patients should be referred to a specialist at any time, but especially when there is (1) difficulty confirming the diagnosis, (2) frequent urgent health care use, (3) frequent oral corticosteroid (OCS) use, (4) suspicion for occupational asthma, (5) food allergy or anaphylaxis, (6) infection or cardiac-caused type of symptoms, (7) possible bronchiectasis, and (8) presence of several comorbidities. Providers should also recognize that persistent airflow limitation (nonreversible FEV_1) can occur with longstanding asthma.

Step 2: Health care providers should assess for contributing factors such as inhaler technique, adherence, comorbidities, modifiable risk factors and triggers, overuse of SABA rescue inhalers, medication adverse effects, and mood effects (anxiety, depression, and social difficulties). Incorrect use of inhalers can occur in up to 80% of patients, and up to 75% of patients are nonadherent. It is important to assess for medication use such as β-blockers or NSAIDs during this step. Oral and intraocular β-blockers should be cardioselective and are not contraindicated in asthma, but the risk-benefit should be considered and closely monitored during initiation. Aspirin and NSAIDs are also not contraindicated, but patients should be advised to discontinue use if asthma worsens. Regular use or overuse of SABAs causes β-receptor down-regulation (lack of response) and can result in increased use. Using three or more SABA inhalers per year (or 1.5 puffs or more per day) increases the risk of needing emergency services. Twelve or more inhalers a year (200 doses or more of SABA per month) increases the risk of death (GINA 2019b). Patients using a nebulized SABA are at a higher risk.

Step 3: Treatment optimization is addressed by providing self-management education, optimizing inhaled controller regimens, treating comorbidities and modifiable risk factors, considering nonpharmacologic add-on therapy (e.g., smoking cessation, lifestyle modifications, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance), trying nonbiologic medication (if not already using), and trying high-dose ICS (if not already using). These recommendations support the GINA treatment recommendations.

Step 4: Review the response to interventions in steps 1–3 after 3–4 months, depending on clinical urgency. At this visit, symptom control, exacerbation history, medication adverse effects, inhaler technique and adherence, lung function, and patient satisfaction should be assessed. If asthma is still uncontrolled, the diagnosis of severe asthma is confirmed, and the patient should be referred to a specialist (if not already). If asthma is controlled, consider stepping down treatment. However, if asthma becomes uncontrolled when treatment is stepped down, the diagnosis of severe asthma has been confirmed, and the patient should resume previous therapy and be referred to a specialist (if not already). If a patient's asthma remains well controlled after stepping down treatment, the patient does not have severe asthma.

Step 5: A specialist should assess patients for their inflammatory phenotype (T2 or non-T2), provide a more detailed assessment of comorbidities and differential diagnoses, assess the need for social and/or psychological support, and invite the patient to enroll in a registry (if available) or clinical trial. Patients with T2 inflammation are estimated to include 50% of people with severe asthma. These patients are relatively refractory to high-dose ICS and may have better results with OCS. Type 2 inflammation can be considered refractory when certain biomarkers are present (e.g., blood eosinophils 150 cells/mm^3 or more, FeNO 20 ppb or more, and/or sputum eosinophils 2% or more) while taking a high-dose ICS or a daily OCS. The specialist will consider additional testing.

Step 6: This step is divided into two parts. Step 6a: When there is no evidence of T2 inflammation, the specialist should review the asthma management basics, recommend avoiding relevant exposures, consider additional diagnostic investigations, try a nonbiologic add-on treatment (if not already using, such as tiotropium, a leukotriene receptor antagonist [LTRA], a low-dose macrolide [off-label]), and consider bronchial thermoplasty. Bronchial thermoplasty involves three separate bronchoscopies with a localized radiofrequency pulse (GINA 2019b). Long-term safety and efficacy have not consistently been shown, and bronchial thermoplasty is associated with a large placebo effect. When there is evidence of T2 inflammation, adherence and additional T2 phenotypes should be considered before considering a biologic.

Step 6b: This step gives guidance to add-on biologic T2-targeted treatments. Indication for treatment includes patients with poor control or exacerbations while taking a high-dose ICS/LABA who also have eosinophilic markers (or allergic biomarkers) or in those who need a maintenance OCS. Eligibility criteria for payers, predictors of response (e.g., childhood-onset asthma, clinical history suggesting allergen-driven symptoms, blood eosinophils of 260 cells/mm^3 or greater, or FeNO of 20 ppb or greater; baseline IgE concentration does not predict likelihood of response), cost, dosing frequency, route,

and patient preference are considered before selecting therapy. Guidance is provided for choosing between anti-IgE, anti-IL-5/anti-IL-5R, and anti-IL-4R. If the patient is not eligible for any therapy, move to step 6a. If the patient is eligible, therapy should be tried for at least 4 months. If the patient response is positive, move to step 7 or possibly extend the trial by 6–12 months. If response is not positive or minimal, the specialist can consider changing to a different therapy, if eligible, and move to step 7.

Step 7: This step is also divided into two parts. When reviewing patient response, patients with a positive response should be reevaluated every 3–6 months. Specialists can consider decreasing or discontinuing the OCS first and then other add-on medication. Inhaled therapy can also be decreased, but patients should continue at least a moderate ICS dose. Biologic treatment can be reduced, depending on observed benefit-risk. If patient response is minimal or not positive, the biologic should be discontinued and the patient reassessed; additional testing or treatment may be considered (e.g., high-resolution CT, add-on macrolide [off-label], bronchoscopy).

Step 8: Continue to optimize management, including two-way communication with the general practice provider, for ongoing care.

Comorbid Conditions

Comorbidities such as gastroesophageal reflux disease (GERD), obesity, chronic rhinosinusitis, confirmed food allergy, or hormonal influences are common in asthma and can increase the risk of exacerbation, even when few symptoms are present (GINA 2019b). These conditions can be challenging to control symptomatically using typical stepwise therapy.

Gastroesophageal Reflux Disease

Patients with asthma and GERD can present with a dry cough, the cause of which can be difficult to ascertain. Diagnosis and symptoms of GERD are more common in patients with asthma than in the population-at-large. Pharmacists recognize that medications such as β_2-agonists and theophylline can cause relaxation of the lower esophageal sphincter and possibly lead to more GERD symptoms. In a meta-analysis of randomized placebo-controlled trials evaluating adult patients with asthma using a proton pump inhibitor, PEFR was statistically significantly improved (mean difference 8.68 L/minute [95% CI, 2.35–15.02]) (Chan 2011). However, the confidence interval was wide, and the benefit was limited to morning PEFR. None of the changes in other secondary measures (FEV_1, asthma symptom scores, evening PEFR) were statistically significant.

Patients with asymptomatic GERD should not be prophylactically treated with a proton pump inhibitor (Mastronarde 2009). Treating these asymptomatic patients does not benefit asthma symptoms. Patients with symptoms suggestive of reflux and asthma may be reasonably empirically tried on a proton pump inhibitor or motility agent (e.g., metoclopramide), which is monitored for efficacy (GINA 2019b).

Obesity

Patients with obesity, especially those with a BMI of 30 kg/m^2 or greater and women with abdominal obesity, have an increased prevalence and incidence of asthma than do nonobese patients (GINA 2019b). Obesity can interfere with lung mechanics and increased rates of other comorbidities, and it is not known exactly why these patients with obesity develop asthma more commonly. In patients with obesity, it can be especially challenging to diagnose asthma, given that there may be other potential causes of wheezing and dyspnea (though not cough). In addition, patients with obesity and asthma may have more difficult-to-control asthma (GINA 2019b). This difficulty causes patients to be less responsive to ICS, possibly because of a different type of underlying airway inflammation (non-T2) or other contributing comorbid conditions. Weight loss of 5%–10% is recommended to improve asthma control and quality of life, especially after surgically induced weight loss. Patients with asthma should have their BMI reviewed (GINA 2019b).

In a 2012 systematic review, weight loss in addition to asthma medications led to a 48%–100% symptom remission (Juel 2012). Many trials for nonsurgical weight loss interventions included lasted 8 weeks and showed the rapid beneficial effect on markers of FEV_1, forced vital capacity (FVC), and PEFR. One study reviewed showed poorer control, worsening quality of life, and more steroid bursts with a 2.27-kg weight gain. Some of the studies in the review lasted longer, particularly the surgically induced weight-loss studies, and showed improvements in asthma severity, dyspnea, use of medications, exercise tolerance, acute exacerbation, and hospitalization. Despite the proven benefit in asthma symptoms, eosinophilic inflammation markers were not improved with weight loss.

Sinusitis/Rhinitis

Most patients with T2 asthma have concurrent persistent or intermittent rhinitis. These patients can have cough as a confounding symptom for the underlying cause. Chronic rhinosinusitis is associated with more severe asthma. According to the 2016 ARIA guidelines, patients with allergic rhinitis should be treated with an intranasal corticosteroid (INCS) (Brożek 2017). In a meta-analysis of patients with both allergic rhinitis and asthma, INCS compared with placebo significantly improved the following asthma measures: FEV_1 (standardized mean difference [SMD] 0.31; 95% CI, 0.04–0.58), bronchial challenge (SMD 0.46; 95% CI, 0.12–0.79), asthma symptom scores (SMD -0.42; 95% CI, -0.30 to -0.53), and rescue medication use (SMD -0.29; 95% CI, -0.01 to -0.58) (Lohia 2013). However, this improvement was not necessarily clinically significant and was most consistent when patients were not already taking an ICS or on both an INCS and an ICS by lung

delivery. One plausible reason for the improvement is that the intranasal delivery is also deposited into the lungs; however, this has not been confirmed in several drug delivery studies. These results support the unified airway theory indicating that the lower and upper airways are connected. Most studies in this meta-analysis excluded patients with severe asthma or with a recent exacerbation (past 1–3 months). In addition, most patients had mild asthma, and included both children and adults, which may indicate areas of further study.

Hormonal Influences

Concern of asthma management in the pregnant patient is often multifactorial, and hormonal fluctuations may contribute. Pregnant patients may be more susceptible to viral respiratory infections, such as influenza, and have mechanical respiratory changes such as decreases in functional residual capacity and expiratory reserve volume because of an enlarging uterus (LoMauro 2015). Because pregnant patients with asthma are at higher risk of worse outcomes (both mother [preeclampsia] and infant [preterm delivery, low birth weight, intrauterine growth restriction, increased perinatal mortality]), treating the pregnant patient with asthma can be challenging. Patients may also be more reluctant to take asthma medications during pregnancy because of concerns for safety (23%–36% of women stop the ICS in the first or second trimester) (Smy 2014). This provides an opportunity for pharmacists and other health care providers to educate on the safety and benefit of treatment during pregnancy (Lim 2012).

Women treated with ICS during pregnancy have a significantly lower risk of exacerbation than those not treated with ICS, and low to moderate doses of ICS are the preferred long-term treatment of asthma in pregnancy in any trimester (Smy 2014). Budesonide has been studied the most in pregnancy, and most studies show that ICS use in women during pregnancy is not associated with a significant risk of major malformations compared with women not using ICS. At the same time, high doses of ICS (e.g., over 1000 mcg of beclomethasone/day equivalent; 1470 mcg on average) during the first trimester compared with lower-dose equivalents may be associated with a small but significantly higher risk of congenital malformations (Blais 2009). With only these data, it is difficult to compare the effects of having moderate to severe asthma (with increased exacerbations) from ICS use (Smy 2014). At the same time, OCS are associated with an increased risk of congenital malformations (cleft lip with or without cleft palate) and decreased birth weight and should be used only when benefit outweighs risk to the fetus (according to the package insert). Currently, evidence is inconclusive in humans regarding the use of tiotropium in pregnancy.

In a systematic review, pregnant patients in the late second trimester had the highest rates of asthma exacerbation, mainly because of viral infections and nonadherence to ICS (Murphy 2006). Around 20% of pregnant patients required medical intervention for asthma, with 6% requiring hospitalization in any trimester. However, pregnant patients presenting with acute exacerbations may be less likely to be treated appropriately, placing the infant at risk of fetal hypoxia. These patients should aggressively be treated with a SABA, oxygen, and early systemic corticosteroids (GINA 2019b). If high SABA doses were used 48 hours before delivery, the infant's blood glucose concentrations should be monitored for the first 24 hours. Fortunately, exacerbations during labor and delivery are uncommon. Typical use of dinoprostone (prostaglandin E_2) during labor is considered safe in patients with asthma; however, caution is necessary when carboprost is used for severe postpartum hemorrhage because this can cause bronchospasm (Nelson-Piercy 2001).

Although the relationship between hormone concentrations and systemic inflammation are unclear, around 20% of women appear to have perimenstrual asthma (PMA), defined as asthma that is worse before menstruation (GINA 2019b). Other sources cite that up to 40% of women have PMA (Graziottin 2016). Those especially affected include women who have more severe asthma, have a higher BMI, have a longer duration of asthma, are sensitive to aspirin-exacerbated respiratory disease, or are older. Other risk factors for PMA include dysmenorrhea, premenstrual syndrome, shorter menstrual cycles, and longer menstrual bleeding (Sánchez-Ramos 2017).

Women with PMA are considered to have a difficult-to-treat asthma. In one case report, a patient with PMA followed for 4 years had an exacerbation 2 or 3 days before her menses (Lei 2018). The patient's dose was titrated on the basis of symptoms and FeNO testing, and she took prednisone 20–30 mg for 7 days 1 week before menstruation every month. This patient improved over 18 months on the 30-mg treatment, potentially from the regulation of sex hormone secretion with OCS. This particular patient was receiving a controller treatment of an ICS, a LABA, LTRAs, a xanthine derivative, and a cough suppressant.

A small study of 24 female patients with mild asthma (n=11 with PMA) alternating treatments of 1 month of ICS, 1 month of ICS plus placebo, and 1 month of ICS plus montelukast showed that only patients with PMA benefited from LTRA treatment versus placebo in PEFR and symptom scores but with minimal hormone concentration changes (Pasaoglu 2008). Intramuscular progesterone, oral contraceptives, and ICS have also been studied in PMA with limited evidence (Graziottin 2016). Currently, GINA recommends usual asthma treatment, LTRAs, and oral contraceptives with level D evidence for patients with PMA. More evidence to guide treatment in PMA is needed.

Although not discussed in this chapter, other comorbidities such as anxiety and depression, deconditioning, vocal cord dysfunction, obstructive sleep apnea, bronchiectasis, cardiac disease, and kyphosis (caused by osteoporosis) can all contribute to poor quality of life, respiratory symptoms, and exacerbations and should be investigated in patients with asthma (GINA 2019b).

Exercise-Induced Bronchospasm

Exercise can precipitate loss of heat, water, or both from the lungs because of hyperventilation of cooler and dryer air causing bronchoconstriction. Bronchoconstriction typically worsens minutes after stopping exercise (peak 5–10 minutes) or during vigorous exercise (EPR-3 2007). These symptoms typically resolve in 20–30 minutes. Physical activity can be a trigger for many patients with asthma; however, some patients with exercise-induced bronchospasm (EIB) may not have a known asthma diagnosis (Parsons 2013).

Diagnosis of EIB can be difficult to differentiate from symptoms of obesity/lack of fitness or inducible laryngeal obstruction. Exercise-induced dyspnea with noisy inspiration likely decreases the probability of symptoms from asthma (GINA 2019b). The NICE guidelines do not recommend testing with an exercise challenge, whereas the GINA report offers an exercise challenge test as an option to demonstrate variable expiratory flow limitation (GINA 2019; NICE 2017). The ATS recommends diagnosing EIB on the basis of serial lung function testing after an exercise or hyperpnea challenge, preferably FEV_1 over PEFR, rather than by symptoms alone (Parsons 2013).

Even though physical exercise is a trigger, patients with EIB should be encouraged to engage in regular physical activity for general health benefits. According to a 2013 Cochrane review, swimming is beneficial in lung function for patients younger than 19 years with asthma (Beggs 2013). At the same time, high exposure to chlorine in pools should be avoided (GINA 2019b). Understanding which exercise the patient engages in may support environmental influences and subsequent recommendations. For example, 30% of EIB on ice rinks is linked to cold, dry air and high-emission pollutants from the ice-resurfacing machines (Parsons 2013). Athletes, particularly high-level competing athletes, have a higher prevalence of respiratory conditions than non-athletes (GINA 2019b). These high-level competing athletes have higher rates of EIB and asthma. Elite athletes often have airway hyperresponsiveness (even without reported symptoms), higher lung volumes and expiratory flow, less eosinophilic airway inflammation, and more difficult-to-control symptoms (GINA 2019b).

Exercise-induced bronchospasm is typically treated by a preexercise SABA (or LABA), LTRAs, and long-term control therapy (if appropriate) (EPR-3 2007). Patients are instructed to use a SABA 15 minutes before exercise, which can be helpful for up to 2–3 hours, and LABAs can be protective for up to 12 hours; both will prevent EIB in 80% of patients. Use of LTRAs is approved in EIB and can prevent EIB in up to 50% of patients when used before exercise; however, up to 2 hours may be needed for effect.

Breakthrough EIB can indicate poorly controlled asthma and warrants a step-up in controller treatment, regardless of whether the patient has asthma as well. In addition, with more than once-daily use of SABA and LABAs, patients with EIB can develop tolerance to these medications preexercise because of desensitization of the β_2-receptors on mast cells and smooth airway muscles (Parsons 2013). Patients may also step up to a low-dose budesonide/formoterol as needed either before exercise or for relief of symptoms (noninferior to daily ICS with an as-needed SABA) or a daily ICS if daily SABA is needed (GINA 2019b; Parsons 2013). The ATS further clarifies EIB treatment by recommending the following: (1) not to support daily LABA use as monotherapy, (2) to support daily ICS use (awaiting 2–4 weeks for maximal effect), (3) not to use ICS preexercise, and (4) to support a daily LTRA. To a lesser extent, ATS suggests trying a daily preexercise mast cell stabilizer (i.e., cromolyn nebulized) or inhaled anticholinergic.

Patients with EIB should also be educated to warm up before exercise because this reduces the incidence and intensity of breakthrough bronchoconstriction (GINA 2019b). Specifically, 10–15 minutes of interval or combination warm-up exercise (vs. continuous high-intensity or low-intensity exercise) can create a "refractory period," or symptom reduction period, for up to 2 hours (Parsons 2013). Breathing through the nose and using a facemask to create warmth and humidity in the air may be helpful for cold weather exercise.

SELECTION PEARLS OF PHARMACOTHERAPY

Pharmacotherapy management of asthma falls into three categories: controller medications, rescue medications, and add-on medications. The goals of pharmacotherapy are to prevent exacerbations and asthma-related mortality, control symptoms, and reduce adverse effects from medications. When deciding on a treatment option for a patient, shared-decision making should be used and the following information discussed with the patient: (1) preferred medication based on efficacy, effectiveness, safety, and cost; (2) patient risk factors or phenotypes; (3) patient preference on the basis of goals and concerns; and (4) practical issues regarding inhaler technique and adherence to treatment regimen (GINA 2019b). Once a treatment regimen is decided on, it should follow control-based asthma management, which involves assessment of patient, treatment regimen, and patient response to therapy in a continuous cycle.

Bronchodilators

Short-Acting β-Agonists

β-Agonists are the most effective bronchodilators available for asthma treatment. Short-acting β-agonists are typically called *rescue* medication because they induce smooth muscle relaxation within minutes. Typically, patients with intermittent asthma were prescribed SABAs as needed for symptoms of shortness of breath or wheezing. However, SABAs do not target airway inflammation, which is the core issue with asthma, and are not known to protect against exacerbations. A significant change in the 2019 GINA report is a move away from the use of SABAs as needed in mild asthma, given that SABA agents do not reduce airway inflammation. The inhaled

steroid treatment as regular therapy in early asthma, also known as the START study (Busse 2008), evaluated patients age 5–66 years with a diagnosis of mild persistent asthma in the past 2 years to determine the safety and tolerability of long-term treatment with budesonide compared with placebo. Budesonide was dosed at 200 mcg once daily for patients younger than age 11 and at 400 mcg once daily for patients 11 and older. The primary outcome was time to first severe asthma-related event (SARE), and the study lasted 3 years. Fewer SAREs occurred with budesonide than with placebo, and the authors concluded that once-daily budesonide is safe and well tolerated in patients with newly diagnosed mild persistent asthma.

Another study evaluated patients 12 years and older with mild asthma and compared terbutaline 0.5 mg daily as needed with budesonide/formoterol 200 mcg/6 mcg as needed and budesonide 200 mcg dosed twice daily to determine whether budesonide/formoterol as needed was superior to terbutaline on the basis of electronically recorded weeks with well-controlled asthma (O'Byrne 2018). Budesonide/formoterol as needed was superior to terbutaline with respect to mean percentage of weeks with well-controlled asthma, according to patient report (34.4% vs. 31.1% of weeks, OR 1.14; 95% CI, 1.00–1.30; p=0.046). Budesonide/formoterol as-needed therapy was inferior to budesonide maintenance (34.4% vs. 44.4%; OR 0.64; 95% CI, 0.57–0.73). Although inhaled terbutaline is not a commonly used SABA in the United States, it is available in other countries. Inhaled terbutaline can require 30 minutes for initial response when evaluating these studies (according to the package insert). Furthermore, in another study that included 674 subjects, albuterol 100 mcg as needed was compared with budesonide/formoterol 200 mcg/6 mcg as needed; in this study, budesonide/formoterol had a lower rate of annualized exacerbation (RR 0.49; 95% CI, 0.33–0.72; p<0.001) (Beasley 2019).

Another concern with starting asthma management with a SABA is that this trains patients to rely on SABAs for acute symptom relief, and patients tend to think SABAs are more effective than ICS because of their mechanism and quick onset of action. Because of these studies and a desire to improve the management of asthma symptoms, the GINA report now recommends against the use of as-needed SABAs alone. A common mishap clinically is the use of short-acting muscarinic antagonists (SAMAs) to help manage asthma symptoms. Guidelines only recommend SAMAs (e.g. ipratropium) as an alternative to SABAs because their onset of action is not as quick as that of SABAs. In addition, SAMAs can be used with SABAs during an acute asthma exacerbation (GINA 2019b).

Efficacy of Metered Dose Inhalers vs. Nebulizers

Albuterol is supplied in several formulations, including an aerosol solution administered by metered dose inhalers (MDIs), a solution administered by nebulizers, or tablets and syrup for administration by mouth. Most patients with asthma are treated with an MDI or a nebulizer. Limited studies compare the efficacy of an MDI with that of a nebulizer solution, and most studies available contain small sample sizes and tend to be open label. One study evaluated the efficacy of albuterol by MDI compared with nebulizer in 2342 patients 18 years and older presenting to a large urban ED. The study had two phases: phase I occurred during the first 12 months of the study, and patients were treated with albuterol administered by nebulizer; phase II occurred during the remaining 18 months of the study, and patients were treated with albuterol administered by MDI. Primary outcomes included first and last PEFR and hospital admission rates. Albuterol administered by MDI had an 11% higher post-medication PEFR (p=0.001) and a 13.3% higher change in PEFR (p=0.002) than albuterol administered by nebulizer. However, hospital admission rates were similar among the two groups – 14.6% for nebulizer and 13.2% for MDI (Newman 2002). The consensus of the available literature suggests similar efficacy between albuterol administered by MDI and nebulizer; however, the dose of albuterol tends to be much higher when administered by nebulizer than by MDI, which can increase adverse effects without improving efficacy. Thus, for most patients, an MDI is recommended over a nebulizer (GINA 2019b).

Monitoring

Common adverse effects, according to SABA package inserts, include tremor, nervousness, tachycardia, and palpitations. Patients should be monitored as clinically indicated for an increase in heart rate, blood pressure, hypokalemia, and changes in ECG, if necessary. Most patients cannot coordinate the dose actuation with breath when using an MDI; thus, using a spacer or holding chamber is recommended with these devices (Vincken 2018). In addition, patients should be evaluated for inhaler technique and symptom control with SABAs, which includes assessing the frequency of SABA use at each follow-up.

Selecting an Inhaler Device

A variety of different inhaler devices are now available for managing asthma, including pressurized MDIs, dry powder inhalers (DPIs), breath-actuated MDIs, and soft mist inhalers. A literature review of errors associated with inhaler device characteristics and device handling highlights the importance of ensuring patients know how to appropriately use their inhaler (Lavorini 2019). All inhaler devices are associated with errors, which should be considered when selecting a device. Pressurized MDIs require a deep and steady inhalation at a rate of less than 60 L/minute and require the patient to coordinate the timing of dose actuation and breath. Most MDIs are available as suspensions, meaning they must be shaken before use, a step that is commonly overlooked. Patients may not take a deep enough inhalation, may not inhale fast enough, or may forget to hold their breath after

receiving the dose – all errors that can lead to decreased delivery of the medication. Breath-actuated MDIs help reduce the dose actuation timing errors (i.e., hand-breath coordination) because the aerosol is activated by the patient's inhalation. However, these MDIs still require a steady inhalation at the rate of 30 L/minute. Therefore, patients may consider breath-actuated MDIs easier to use than other MDIs, but they are typically not recommended in patients younger than 6 years. Although DPIs are also breath-actuated, they require the patient to take a rapid and forceful inhalation to receive the medication. Thus, a common problem with DPIs is that patients may not generate an effective inspiratory force for effective drug delivery. In addition, DPIs are typically formulated with lactose, which some patients may not tolerate. Soft mist inhalers also reduce the coordination of actuation and inhalation and deliver the medication at a slower velocity. These inhalers require a slow, deep inhalation, which some patients may be unable to do correctly. Assembling the currently available soft mist inhalers can also be complex.

It can be difficult to extract consistent results from comparisons of different inhaler devices, and studies usually include confounding factors, making results less generalizable. Therefore, one device has not consistently been proven to be more effective than another device. Rather, the provider and patient should work together to determine the best device for each individual. Factors associated with an increased risk of device error, independent of the device, include older age (p=0.008), patients with a lower education level (p=0.001), and those lacking instruction from a health care professional (p<0.001). Providers should consider the following when selecting a device: patient age, patient acceptability of the device, patient ability to use the device, and affordability of the device.

Long-Acting β_2-Agonists

The mechanism of LABAs is similar to that of SABAs, but LABAs have a longer duration of action, about 10–12 hours per dose compared with 4–6 hours with SABAs. Examples of LABAs include formoterol and salmeterol. This class of medication should always be used in conjunction with ICS for maintenance of asthma symptoms, as evidenced by the SMART study. This study compared the safety of adding salmeterol 42 mcg twice daily or placebo with usual asthma care in patients 12 years and older. A total of 26,255 subjects were analyzed, with a statistically significant increase in respiratory-related deaths (24 vs. 11; RR 1.16; 95% CI, 1.06–4.41) and asthma-related deaths (13 vs. 3; RR 4.37; 95% CI, 1.25–15.34) in participants using salmeterol, though this risk was primarily in African Americans (Nelson 2006). When a LABA is added to an ICS, however, this risk is not observed, and in December 2017, the FDA removed the boxed warning regarding asthma-related deaths on all ICS/LABA combination inhalers. As mentioned earlier, a low-dose ICS plus formoterol can also be used as needed to help more acutely with symptoms. If using low-dose budesonide/formoterol as the reliever inhaler, the patient should use the same combination for maintenance of asthma control as well, given that the guidelines do not recommend that a patient take two different LABAs (GINA 2019b).

Efficacy Between Agents

Few studies are available directly comparing salmeterol and formoterol, and most only compare one or two doses of the medication with each other to determine onset of action. One double-blind, placebo-controlled, crossover study compared the onset of action, duration of effect, and potency between salmeterol Diskhaler and formoterol Turbuhaler. The study found that formoterol 12 mcg is equipotent to salmeterol 50 mcg and that they have a similar duration of action for maintaining the FEV_1 15% above the baseline FEV_1 at 12 hours post-dose. Formoterol 12 mcg and 24 mcg had a quicker onset of action than salmeterol 50 mcg (onset of action 12.4 minutes, 3.6 minutes, and 31 minutes, respectively; p=0.05) (Palmqvist 1997). A more recent meta-analysis compared the efficacy and safety of formoterol with salmeterol and included seven studies that looked at various outcomes. When looking at the mean difference of FEV_1 12 hours after inhalation, the two agents did not differ (MD -0.02; 95% CI, -0.22 to 0.18). Overall findings from the meta-analysis demonstrated there were no clinically significantly differences between the two agents (Velayati 2015). Formoterol is not available as a standalone inhaler in the United States (it only comes as a nebulizer solution); however, as stated previously, these agents should not be used alone to manage asthma.

Monitoring

According to package inserts for LABAs, common adverse effects are similar to SABAs but are less severe. Patients may also experience dry mouth. Monitoring is also similar to that for SABAs. A systematic review that included five randomized controlled studies compared discontinuing a LABA with continuing use of an ICS over 12–24 weeks in 2781 adults whose asthma was well controlled. Primary outcomes included exacerbations requiring oral steroids, asthma control, and serious adverse events. The review found a potential increase in exacerbations when discontinuing the LABA (OR 1.74; 95% CI, 0.83–3.65). Although the confidence interval did not exclude that discontinuing the LABA might be beneficial, over 17 weeks, 19 of 1000 people who continued the LABA had an exacerbation, compared with 32 of 1000 people who discontinued the LABA (Ahmad 2015). Thus, the GINA report recommends that if a patient is taking the ICS/LABA combination, the ICS component should first be decreased before discontinuing the LABA.

Long-Acting Muscarinic Antagonists

Long-acting muscarinic antagonists are considered an add-on maintenance treatment in step 4 if patients need

more symptom control than with an ICS plus a LABA (GINA 2019b). Although many LAMA inhalers are on the market, the tiotropium bromide mist (Respimat) inhaler is currently the only FDA-approved agent for use in patients 6 years and older with a diagnosis of asthma. The asthma dose of tiotropium Respimat is 1.25 mcg 2 inhalations once daily. The 2.5-mcg dose, administered as 2 puffs/day for a total of 5 mcg/day, is reserved for patients with COPD.

Mechanism of Action

According to the package insert, tiotropium bromide competitively and reversibly binds to M_1–M_5 receptors but has a strong affinity specifically for the M_3 receptors in the bronchial smooth muscles, which inhibits the action of acetylcholine leading to smooth muscle relaxation.

Efficacy

A systematic review assessed the beneficial effect of adding a LAMA to combination treatment of an ICS and a LABA in adults with uncontrolled asthma. Three studies were included in this review, which involved 1197 patients already prescribed an ICS plus a LABA and who had a mean FEV_1 of 55%, indicating severe asthma. All three studies compared tiotropium bromide with placebo, and the primary outcomes investigated included exacerbations leading to OCS, validated measures of asthma control, and serious adverse events. Results demonstrated that over 48 weeks 328 out of 1000 patients taking an ICS plus a LABA were prescribed an OCS for an exacerbation, compared to only 271 out of 1000 taking tiotropium in addition to an ICS plus a LABA (OR 0.76; 95% CI, 0.57–1.02). When assessing asthma control using the Asthma Quality of Life Questionnaire, scores were no better for tiotropium add-on therapy than for an ICS plus a LABA alone, when considering a 0.5 minimal clinically important difference (MD 0.09; 95% CI, 0.03–0.20). There was a 0.07-L increase in the FEV_1 of patients taking tiotropium bromide compared with placebo (MD 0.07; 95% CI, 0.03–0.11), and there was no difference between tiotropium bromide and placebo regarding serious adverse events (Kew 2016). Evidence shows that adding tiotropium to an ICS plus a LABA modestly improves lung function and reduces asthma exacerbations. These medications may be continued indefinitely if the patient is receiving benefit. There is no established guidance on how long LAMAs should be tried; however, similar to other add-on medications, if there is no benefit after a trial of 3–6 months with tiotropium, the provider can consider discontinuing it and resuming previous therapy. If the patient's asthma is well controlled with a LAMA and the provider is considering a step-down in therapy, the guidelines recommend collaborating with an asthma expert to create a plan (GINA 2019b).

Monitoring

According to the package insert, common adverse effects with tiotropium bromide include dry mouth, urinary retention, sore throat, and headache. Patients may also have a bitter or metallic taste. These adverse effects may be increased if tiotropium bromide is used in patients with severe renal impairment, and these patients require closer monitoring.

Anti-Inflammatories

Inhaled Corticosteroids

Efficacy

Inhaled corticosteroids remain the primary maintenance treatment recommended by guidelines (NICE, EPR-3, and GINA 2019b) to help reduce the inflammatory response. Inhaled corticosteroids should be initiated in patients who have asthma symptoms or who require rescue medication more than twice a month (GINA 2019b). Most patients start with low-dose ICS (equivalent to budesonide at 400 mcg or less), and most clinical benefits from ICS are obtained at this low dose. However, some patients may have additional inflammatory risk factors (as described earlier in the Phenotypes section) or may not respond fully to a low dose, requiring a step up to a medium-dose ICS. Table 5 provides details on the ICS dose. As previously discussed, a small subset of

Table 5. Daily Doses of ICS in Age 12 Yr and Older

	Low-Dose ICS (mcg)	Medium-Dose ICS (mcg)	High-Dose ICS (mcg)
Fluticasone propionate HFA, DPI	100–250	> 250–500	> 500
Budesonide DPI	200–400	> 400–800	> 800
Mometasone furoate	110–220	> 220–440	> 440
Beclomethasone dipropionate HFA	100–200	> 200–400	> 400
Fluticasone furoate	100	—	200
Ciclesonide	80–160	> 160–320	> 320

DPI = dry powder inhaler; HFA = hydrofluoroalkane.

patients with asthma have severe or difficult-to-control disease. Therefore, few patients should require high-dose ICS beyond short-term use. If a high dose is given, providers must continuously assess risk-benefit because patients are more likely to have adverse outcomes at the higher doses. Up to 2 weeks may be needed for the effects from ICS and up to 3–4 months for the full benefit of these medications.

Several studies have shown a benefit of ICS in reducing exacerbations, hospitalizations, and morbidity. A nested case-control study that included 30,569 patients explored the effect of ICS on deaths related to asthma by examining prescription history before a patient's death. The authors found that for each additional canister of ICS filled, death from asthma was reduced by 21% (RR 0.79; 95% CI, 0.65–0.97). In addition, patients were 4.6 times more likely to die of asthma within 3 months after discontinuing the ICS (RR 4.6; 95% CI, 1.1–19.1). This study established that ICS lowers the risk of death from asthma and highlights the risk of abruptly discontinuing these agents (Suissa 2000). Another systematic review evaluating six randomized controlled trials to determine the risk of asthma exacerbations when reducing the ICS dose found a relative risk of 1.25 (95% CI, 0.96–1.62) in patients whose ICS dose was reduced compared with patients who maintained the same ICS dose (Hagan 2014). Thus, the guidelines recommend a 25%–50% reduction in the ICS dose for patients whose asthma has been well controlled for 3 months or greater (GINA 2019b). Fortunately, a more affordable ICS inhaler is now available from Teva. Fluticasone propionate is now available generically under the trade name ArmonAir RespiClick and is also available with salmeterol under the trade name AirDuo RespiClick. In addition, Mylan has a generic version of fluticasone/salmeterol available under the trade name Wixela. These inhalers cost around $100 per device. There are no head-to-head comparisons with the brand inhaler devices.

Monitoring

Common adverse effects associated with ICS, according to the package inserts, include upper respiratory infections, oral candidiasis, dysphonia, sinusitis, and cough. More serious adverse effects include hypercorticism, adrenal suppression, reduced bone mineral density, and glaucoma. A major concern of the past, which has been controversial because of inconsistent findings, is the association of reduced height with long-term ICS use. A systematic review evaluated the long-term (for more than 12 months) effects of ICS use in children with a diagnosis of asthma, specifically focusing on growth velocity and final adult height. Authors reviewed 16 randomized controlled trials that showed a statistically significant, but likely not clinically significant, reduction in growth velocity of -0.48 cm/year (95% CI, -0.66 to -0.29; I^2 = 48%). When evaluating the effect of ICS on final adult height, only one high-quality randomized controlled trial was included, which showed a mean reduction of -1.20 cm (95% CI, -1.90 to -0.50), representing a 0.7% reduction in height compared with that in non-ICS users (Loke 2015). Conclusions from this review, which are supported by the asthma guidelines, are that the overall reduction in height is minimal and not clinically significant, especially considering the benefit of ICS in managing asthma symptoms. In addition, the guidelines show that uncontrolled asthma may stunt growth in pediatric patients (GINA 2019b).

Oral Corticosteroids

Efficacy

Oral corticosteroids are no longer preferred for patients with severe or uncontrolled asthma in step 5, primarily because of the high risk of associated adverse effects with this medication class. Most other add-on medications should be considered before deciding to use OCS. Oral corticosteroids can be considered in patients who are adherent to step 4 therapy but still having frequent exacerbations or uncontrolled symptoms. For step 5 add-on treatment, the recommended OCS dose is equivalent to 7.5 mg or less of prednisone and should be used for the shortest duration possible. Tapering of OCS is not necessary if prescribed for less than 2 weeks.

Oral corticosteroids remain key in managing asthma exacerbations and should be initiated when (1) the PEF or FEV_1 is less than 60% of personal best or predicted or (2) the patient has not responded to treatment after 48 hours. The recommended dose for asthma exacerbations is equivalent to prednisolone 40–50 mg/day for 5–7 days in adults and 1–2 mg/kg/day (maximum 40 mg) for 3–5 days in children 6–11 years (GINA 2019b).

Monitoring

As stated previously, OCS are associated with several intolerable adverse effects when used both short and long term. Common adverse effects with OCS include increased appetite, weight gain, sleep disturbances, dyspepsia, hypertension, and infections. More serious long-term complications include increased fractures, osteoporosis, metabolic syndrome, intestinal ulcers/bleeding, obesity, stroke, and symptomatic coronary artery disease. As there appears to be a dose-response relationship regarding severity of adverse effects, it is recommended to only use 7.5 mg or less of prednisone (Lefebvre 2015). High-dose ICS or continuous/frequent OCS use can also contribute to poor quality of life and increase the likelihood of poor adherence.

Several drug interactions can occur, including risk of adrenal suppression with the use of P450 inhibitors (e.g., itraconazole and fluticasone) according to the package insert. During a 2013 review, ICS use with protease inhibitors caused significant adrenal suppression and Cushing syndrome while decreasing $CD4^+$ counts (Saberi 2013). For patients who cannot use alternative classes of respiratory or HIV medications, beclomethasone was considered a relatively safe ICS option and likely flunisolide (fluticasone was of the greatest concern). Prednisone is a CYP3A4 inducer that can interact with several medications by decreasing nifedipine and fentanyl concentrations;

caution should also be used when discontinuing the OCS. Medications that inhibit the CYP3A4 metabolism of prednisone, such as fluconazole and clarithromycin, can increase prednisone plasma concentrations and adverse effects. Concomitant use with montelukast and OCS causes severe peripheral edema in some patients, likely because of corticosteroid-induced renal tubular sodium and fluid retention. Prednisone can increase tendon rupture with fluoroquinolone use.

Leukotriene Modifiers – Montelukast

Leukotriene receptor antagonists bind to cysteinyl leukotriene receptors to help mitigate the inflammatory cascade response and complement other anti-inflammatory agents, like ICS. Leukotriene receptor antagonists are considered an add-on treatment to an ICS plus a LABA in steps 3 and 4 of the GINA report and may be considered as second-line monotherapy in step 2 for patients who cannot tolerate ICS or have concomitant allergic rhinitis. These agents are also beneficial in exercise-induced asthma. In the United States, two LTRAs are available: montelukast and zafirlukast. However, montelukast has been the most studied and has the best efficacy and safety profile (Paggiaro 2011).

Efficacy

When comparing LTRAs with ICS in mild asthma, several studies have shown better outcomes with ICS; thus the reasoning behind GINA's recommending ICS over monotherapy with an LTRA alone. However, in a study of 534 patients with mild asthma whose asthma was uncontrolled or who were not satisfied with a low-dose ICS, changing to montelukast daily for 6 weeks significantly decreased uncontrolled symptoms from 85.2% to 26.8% ($p<0.001$). In addition, patient and physician satisfaction significantly increased from baseline, and patients had increased adherence from 41% baseline with ICS to 88% at week 6 with montelukast ($p<0.001$). Finally, 79 patients were considered to have well-controlled asthma at the start of the study, and when changing from a low-dose ICS to montelukast, 73.4% of the 79 patients maintained asthma control at 6 weeks (McIvor 2016). Therefore, another role for montelukast is during step-down therapy from step 2 in patients whose asthma is well controlled on a low-dose ICS, though stronger evidence supports changing to as-needed low-dose ICS/formoterol (GINA 2019b). A LTRA may be considered if a patient cannot afford a low-dose ICS/formoterol inhaler.

Monitoring

Many long-term studies evaluating the safety profile of montelukast have determined that the occurrence and severity of adverse effects with montelukast are similar to those with placebo. Common adverse effects provided by the package insert include fatigue and cough. In addition, post marketing reports of behavioral changes and increased suicide rates have been reported; however, when reviewing 116 clinical studies, the frequency of these events between placebo-controlled groups and montelukast-treated groups did not differ (Paggiaro 2011). Recently, the FDA Pediatric Advisory Committee reevaluated neuropsychiatric adverse events (NAEs) associated with montelukast and found no increased association with serious NAEs, such as self-harm and inpatient depression disorder. However, the committee felt that health professionals and patients prescribed montelukast were not aware of the risk of mental health side effects. Thus in March 2020, the FDA promoted this warning to a boxed warning in the current package labeling (FDA 2020).

Patient Care Scenario

J.T., a 28-year-old white woman, presents to your internal medicine clinic for a follow-up of well-controlled asthma. She takes fluticasone 88 mcg 1 puff by mouth twice daily and has been taking this dose for the past 6 months. Before this, she was taking 2 puffs twice daily with no exacerbations or concerns. She is also prescribed an albuterol inhaler with instructions to take 1 or 2 puffs by mouth as needed for shortness of breath. She reports no asthma exacerbations or hospitalizations in the past year. She reports rarely using the ProAir; the last time she used it was 3 weeks ago before running a 5K race. The patient's ACT score is 24, and she feels her asthma is very well controlled. What is an appropriate plan for this patient's asthma management?

ANSWER

J.T.'s asthma is very well controlled, as indicated by her infrequent use of the albuterol inhaler and her ACT score greater than 20. According to the guidelines, there are several options a clinician may consider regarding this patient's continued step-down therapy. The first option would be to reduce the dose of fluticasone to 44 mcg twice daily or 88 mcg once daily. In addition, because the patient's current ICS dose is considered low, the clinician could change to low-dose ICS/formoterol as needed for asthma symptoms. Evidence guiding and/or comparing step-down therapies is limited, so patient risk factors and preference should be considered. Whichever option is chosen, the patient should follow up with her primary care physician in 1 month or sooner if symptoms worsen or she requires use of albuterol several times throughout the week.

1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019b. Available at www.ginasthma.org. Accessed November 30, 2019.
2. Suissa S, Ernst P, Benayoun S. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332-6.

Biologic Agents

Allergen Immunotherapy

Allergen-specific immunotherapy may be considered in patients who have concomitant allergic rhinitis and asthma. According to the guidelines, this therapy should be considered when a patient's asthma is not controlled on recommended step 3 treatment and the patient has an FEV_1 greater than 70% predicted. However, these therapies are not recommended in patients with severe or unstable asthma because they may lead to severe allergic reactions, causing severe bronchospasm. There are two approaches to allergen immunotherapy: subcutaneous immunotherapy (SCIT), often called "allergy shots," and a newer form of sublingual immunotherapy (SLIT). When comparing SCIT with SLIT, it appears that SLIT is more tolerable, and there is more current evidence regarding its effect on pertinent patient outcomes, such as reduced asthma exacerbations and reductions in glucocorticoid dose; thus, the guidelines recommend SLIT over SCIT (GINA 2019b). To determine whether a patient is a good candidate for immunotherapy, the patient must have symptoms (or a known history of symptoms) when exposed to an allergen and a positive presence of IgE to that allergen, as evidenced by a positive allergen skin test or serum test. These therapies can be considered in patients 5 years and older, though some evidence shows a better response to immunotherapy in patients with new-onset allergic asthma symptoms than in patients with longstanding asthma (Bousquet 1988).

Mechanism of Action

Allergen immunotherapy exposes patients to repeated doses of a specific allergen (though in the United States, it is common to include multiple allergens in one dose) to help interfere with the underlying immune pathophysiology in T2 asthma phenotypes. Example allergens include tree pollens, grass pollens, weed pollens, animal dander, dust mites, mold, and cockroach. Administering either SCIT or SLIT results in a shift of Th2 cells to Th0 and Th1 cells and produces IL-10 and transforming growth factor β regulatory T cells. This suppresses IgE and reduces the inflammatory response by suppressing mast cells, basophils, and eosinophils (Tsabouri 2017).

Efficacy

Subcutaneous immunotherapy is administered in the provider's office initially once or twice a week at a lower dose and gradually increased to the most effective dose, which typically takes about 3–6 months. Once the effective dose (which is individualized to each patient) is reached, these injections can be extended to once or twice a month. Subcutaneous immunotherapy is recommended to be continued for at least 3–5 years, given that the prolonged benefit is better when injections are discontinued after this duration (Des Roches 1996). When considering this therapy for patients, it is important to have a detailed conversation regarding the specifics of SCIT to ensure the patient can commit to scheduled visits.

Sublingual immunotherapy is available in four FDA-approved sublingual allergy tablets for allergic rhinitis. The available allergy tablets treat dust mite, grass pollen, and ragweed pollen allergens. The first dose of SLIT is administered in the provider's office to allow for observation of any adverse effects; then, patients are allowed to administer the medication at home. Sublingual immunotherapy is dosed once a day. Most evidence supporting SLIT is from house dust mites (HDM) and grass pollen allergens. A recent double-blind, randomized, placebo-controlled trial compared HDM SLIT (two different unit doses, 6-SQ or 12-SQ) with placebo in 693 patients with HDM allergy-related asthma not controlled by an ICS or an ICS plus a LABA. The study occurred over 18 months, but the primary outcome specifically focused on the last 6 months of the trial, when the ICS dose was being reduced. The primary outcome evaluated the number of patients who had a moderate-severe asthma exacerbation, and exacerbations were reduced with both 6-SQ and 12-SQ compared with placebo (HR 0.69; 95% CI, 0.49–0.96, p=0.03; HR 0.66; 95% CI, 0.47–0.93, p=0.02, respectively). There was no difference between the two treatment groups (Virchow 2016).

Monitoring

Common adverse effects with SCIT include local site reactions (redness and swelling at the injection site) and systemic reactions (hives, anaphylaxis, sneezing). Most serious systemic reactions occur within 30 minutes after SCIT is administered, which is why many patients are encouraged to remain at the provider's office for at least 30 minutes.

Common adverse effects with SLIT include oral pruritus, throat irritation, and edema around the mouth. No anaphylactic reactions or severe allergic reactions were reported in studies, and SLIT carries a much lower risk of anaphylaxis than SCIT (Virchow 2016). However, according to package inserts for SLIT, patients must receive a prescription for an epinephrine pen and be trained to appropriately use it if an anaphylactic reaction occurs. If patients have adverse effects in the mouth, therapy should temporarily be discontinued and not restarted until the oral mucosa is completely healed. In addition, according to the package inserts, SLIT is contraindicated in patients with eosinophilic esophagitis and severe or uncontrolled asthma.

Monoclonal Antibodies

Mechanism of Action

Efficacy

Monoclonal antibodies (mAb) are considered an add-on therapy in step 4 or 5 in severe, uncontrolled asthma and in patients with T2 inflammatory asthma phenotypes. Several biologics are available that target different inflammatory mediators to help improve severe asthma. However, because of cost and inconsistent insurance coverage, mAb are typically considered a last-line option. When choosing between biologics, it is recommended to choose the one

Table 6. Biologic Agents Used in the Treatment of Severe Asthma

Medication	Mechanism of Action	Indication[a]	Efficacy	Dosing	Adverse Effects
Omalizumab (Xolair)	Inhibits IgE binding on mast cells and basophils	Age ≥ 6 yr Positive allergy skin test IgE 30–1300 IU/mL (age 6–11 yr) or 30–700 IU/mL (age ≥ 12 yr)	Reduced asthma exacerbations by 25%	150–375 mg SC every 2–4 wks, depending on weight and pretreatment IgE concentration	Risk of anaphylaxis ~0.1%–0.2%, injection site reaction
Mepolizumab (Nucala)	Inhibits IL-5 from binding to its receptor, reduces production of eosinophils	Age ≥ 6 yr AEC ≥ 150–300 cells/mm^3	Reduced asthma exacerbations by 50% 50% reduction in OCS dose	40 mg (6–11 yr); 100 mg (≥12 yr) SC every 4 wks (*can be administered at home*)	Headache, injection site reaction, activation of herpes zoster
Reslizumab (Cinqair)	Inhibits IL-5 from binding to its receptor, reduces production of eosinophils	Age ≥ 18 yr AEC ≥ 400 cells/mm^3	Reduced asthma exacerbations by 50%–60%	3 mg/kg IV every 4 wks	Risk of anaphylaxis ~0.3%, antibody development
Benralizumab (Fasenra)	Binds to IL-5 receptor α, causes apoptosis of eosinophils and basophils	Age ≥ 12 yr AEC ≥ 300 cells/mm^3	Reduced asthma exacerbations by 25%–60%	30 mg SC every 4 wks, after three doses frequency extended to every 8 wk (*can be administered at home*)	Antibody development, headache
Dupilumab (Dupixent)	Binds to IL-4 receptor α, blocks signaling of IL-4 and IL-13	Age ≥ 12 yr AEC ≥ 150 cells/mm^3 FeNO ≥ 25 ppb	Reduced asthma exacerbations by 50%–70% 52% of patients able to discontinue OCS	Loading dose of 400–600 mg, then 200–300 mg SC every 2 wk (*can be administered at home*)	Injection site reaction, antibody development, hypereosinophilia

[a]AEC and FeNO are used more as a guide to treatment than as absolute values that must be present in order to treat with a biologic.

AEC = absolute eosinophil count; FeNO = fractional exhaled nitric oxide; IV = intravenous(ly); SC = subcutaneous(ly).

Information from: manufacturer package inserts and McGregor MC, Krings JG, Nair P, et al. Role of biologics in asthma. Am J Respir Crit Care Med 2018;199:433-45.

covered by insurance because no current head-to-head comparison studies prefer one agent to another (McGregor 2018). Table 6 lists detailed information on the currently available biologics. Most of these medications should be given a 3- to 6-month trial and, if effective, continued indefinitely. The current targets of mAb include anti-IgE, anti-IL-5/anti-IL-5R, and anti-IL-4R. Consider using an anti-IgE mAb if the patient has childhood-onset asthma and allergen-driven symptoms. Anti-IL-5/anti-IL-5R and anti-IL-4R should be considered in patients who have higher blood eosinophil counts (i.e., eosinophilic phenotypes) and nasal polyposis. Anti-IL-5/anti-IL-5R is better in patients with more exacerbations in the past year and adult-onset asthma, whereas anti-IL-4R can also be used to treat atopic dermatitis and in patients with higher FeNO levels (GINA 2019b).

Monitoring

Most patients tolerate these medications with only local injection site pain; however, some of these agents are associated with a boxed warning of anaphylaxis (omalizumab and reslizumab) and require additional monitoring. Specifically, according to the package insert, omalizumab must be administered by a health care professional, and the patient must be observed for 2 hours after the first three injections; then, observation can be reduced to 30 minutes. Although benralizumab, mepolizumab, and dupilumab do not carry a boxed

Practice Points

- **Comorbidities such as GERD, obesity, chronic rhinosinusitis, confirmed food allergy, and pregnancy are common in asthma and can increase the risk of exacerbation.**
- **The 2019 GINA report recommends no longer using SABA-only treatment because it increases the risk of severe exacerbations and asthma-related death.**
- **FeNO testing measures the amount of nitric oxide exhaled in the patient's breath and captures eosinophilic airway inflammation.**
- **Monoclonal antibodies (mAb) are considered add-on therapy in steps 4 and 5 for patients with severe uncontrolled or difficult-to-treat asthma with type 2 airway inflammation.**

warning related to anaphylaxis, hypersensitivity and anaphylaxis are listed as a warning/precaution. These medications do not require specific monitoring parameters, but patients should be monitored for signs of infection. All mAb should be evaluated for helminth infections before initiating treatment, and patients should receive appropriate treatment if positive for the infection. According to all mAb package inserts, if patients are already initiated on mAb and become infected with helminth, the mAb need not be discontinued unless initial treatment fails. Malignant neoplasms of various cancer types can occur with omalizumab and reslizumab but appear to have incidence rates similar to placebo. Immunogenicity can occur with mAb; however, the clinical relevance of antibody development against mAb has not yet been determined.

CONCLUSION

Asthma continues to significantly affect the health of populations. Our understanding and management of this complex respiratory condition continue to evolve. Advances in testing, such as FeNO or blood eosinophil, biologic medications, and optimal use of medications in mild, severe, and difficult-to-treat asthma, guide new treatment recommendations.

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Self-Assessment Questions

1. A 19-year-old man with asthma currently takes fluticasone/salmeterol dry powder inhaler (DPI) 100/50 mcg twice daily and does not forget to take his medication. He reports worsening dyspnea for the past 2 months and needs to use albuterol 90 mcg 2 puffs three or four times a week to relieve his symptoms. His ACT score is 17. The patient reports being hospitalized once in the past year for an asthma exacerbation triggered by an upper respiratory infection. He uses cetirizine 10 mg daily and azelastine 2 sprays in each nostril twice daily for mold and pet dander allergies. Today, his forced expiratory volume in the first second (FEV_1) is 74% of predicted. Which one of the following is best to recommend for this patient?

   A. Increase to fluticasone/salmeterol 500/50 mcg 1 puff twice daily.
   B. Change to fluticasone 250 mcg 1 puff twice daily.
   C. Increase to fluticasone/salmeterol 250/50 mcg 1 puff twice daily.
   D. Add tiotropium 1.25 mcg 2 puffs once daily.

2. A 68-year-old man has a medical history of persistent asthma, gout, hypertension, chronic pain, seasonal allergies, and tobacco abuse. He reports that he has been smoking 1 pack/day for over 40 years. The patient currently takes albuterol 90 mcg 1 or 2 puffs as needed, allopurinol 150 mg daily, amlodipine 10 mg daily, aspirin 81 mg daily, atorvastatin 20 mg daily, budesonide/formoterol 160/4.5 mcg 2 puffs twice daily, cetirizine 10 mg daily, gabapentin 300 mg three times daily, lisinopril/hydrochlorothiazide 20/12.5 mg daily, and nicotine gum 4 mg every 1–2 hours as needed. Today, he presents with worsening shortness of breath and a productive morning cough for the past 6–12 months. His pulmonary function tests (PFTs) show FEV_1/FVC (forced vital capacity) of 0.64 with a 10% increase in FEV_1 post-bronchodilator. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ACOS guidelines, which one of the following is best to recommend for this patient?

   A. Change albuterol to albuterol/ipratropium.
   B. Change budesonide/formoterol to umeclidinium/vilanterol.
   C. Add tiotropium once daily.
   D. Decrease budesonide/formoterol to 1 puffs twice daily.

3. A 20-year-old man has symptoms of dyspnea two or three times per week and nighttime awakenings twice a month; his ACT score is 16, and his FEV_1 is 75% of predicted. He currently takes mometasone/formoterol 100/5 mcg 1 puff twice daily. The patient was recently hospitalized for his breathing and has been on two steroid bursts in the past year. The provider is considering adding tiotropium Respimat. Which one of the following would best justify adding tiotropium to this patient's regimen?

   A. Reduced asthma exacerbations
   B. Reduced daily symptoms
   C. Improved lung function
   D. Decreased inhaled corticosteroid (ICS)/formoterol dose

4. A 23-year-old man has a history of persistent asthma; his home drugs currently include fluticasone/salmeterol 500/50 mcg 1 puff twice daily, tiotropium 1.25 mcg 2 puffs daily, albuterol 90 mcg 1 puff as needed, and ibuprofen 200–400 mg as needed for headaches (takes almost daily). In the past month, the patient reports using albuterol three or four times a week during the day. He reports no symptoms of allergic rhinitis. His ACT score today is 15. The patient has not been hospitalized for his breathing. He has good adherence to his medications, given his pharmacy fill data, and can demonstrate appropriate inhaler technique. Which one of the following is best to recommend for this patient?

   A. Add montelukast 10 mg daily.
   B. Add low-dose macrolide.
   C. Advise patient to refrain from albuterol overuse.
   D. Advise patient to refrain from ibuprofen use.

5. A 45-year-old man has a medical history of difficult-to-treat asthma, gastroesophageal reflux disease (GERD), hypertension, and obstructive sleep apnea. He currently takes fluticasone/vilanterol 100/25 mcg 1 puff daily and tiotropium 1.25 mcg 2 puffs once daily and uses albuterol 90 mcg about 1 puff three or four times per week. Comorbid conditions are appropriately managed with continuous positive airway pressure, omeprazole 20 mg daily, and hydrochlorothiazide 25 mg daily. Today, his ACT score is 18. According to GINA, which one of the following is best to recommend for this patient?

   A. Increase fluticasone/vilanterol 200/25 mcg 1 puff daily; follow up in 2 weeks.
   B. Increase tiotropium 2.5 mcg 2 puffs once daily; follow up in 6 weeks.
   C. Continue current therapy; follow up in 2 months.
   D. Increase fluticasone/vilanterol 200/25 mcg 1 puff daily; follow up in 3 months.

6. A 45-year-old woman has a history of moderate persistent asthma, migraine with aura, and obesity. She currently uses sumatriptan 50 mg as needed, fluticasone/salmeterol 250/50 mcg 1 puff twice daily, and albuterol 90 mcg 1 puff as needed. On further examination of her

symptoms, the patient appears to need albuterol only once a month prior to menstruation because of increased dyspnea. Given this presentation and the GINA guidelines, which one of the following is best to recommend for this patient?

A. Add an oral contraceptive.
B. Add tiotropium 1.25 mcg 2 puffs once daily.
C. Add montelukast 10 mg daily.
D. Increase fluticasone/salmeterol to 500/50 mcg 1 puff twice daily.

7. A 15-year-old male adolescent is a competitive swimmer with normal spirometry. He has been using albuterol 90 mcg 2 puffs 15 minutes before exercise. During his annual physical examination, he reports using albuterol daily for preexercise swimming and about two or three times per week for exercise-induced bronchospasm (EIB). The provider asks for your therapeutic recommendation. Which one of the following is best to recommend adding for this patient?

A. Montelukast 10 mg as needed for breakthrough EIB
B. Montelukast 10 mg daily
C. Fluticasone 110 mcg 1 puff before exercise
D. Fluticasone 110 mcg 1 puff as needed for breakthrough EIB

8. A 25-year-old man has severe, uncontrolled asthma. His pulmonologist is considering initiating a monoclonal antibody (mAb) and asks for your recommendation. The patient relies on his aunt to take him to appointments because he has no transportation of his own. You see in his chart that, last year, he had a herpes zoster outbreak. Which one of the following is best to recommend for this patient?

A. Omalizumab
B. Reslizumab
C. Mepolizumab
D. Benralizumab

9. A 48-year-old woman who recently established care at your clinic has a history of asthma, diabetes, GERD, hypertension, and obesity. Spirometry completed last month shows FEV_1/FVC 0.67 and FEV_1 14% improvement post-bronchodilator. She has been using albuterol 2 puffs two or three times per week for shortness of breath and cough. She also takes mometasone/formoterol 200/5 mcg 1 puff twice daily, montelukast 10 mg daily, and amlodipine 10 mg. Her blood pressure is 126/74 mm Hg, and she reports symptoms of GERD once or twice a week. Which one of the following is best to recommend for this patient?

A. Add omeprazole 20 mg daily.
B. Increase to mometasone/formoterol 200/5 mcg 2 puffs twice daily.
C. Add liraglutide 0.6 mg daily.
D. Add loratadine 10 mg daily.

10. A 10-year-old girl (weight 41 kg) has severe, uncontrolled asthma and allergic rhinitis. She is prescribed albuterol 90 mcg 1 puff by mouth every 4 hours as needed, fluticasone/salmeterol 500/50 mcg 1 puff twice daily, tiotropium 1.25 mcg 2 puffs once daily, and montelukast 10 mg daily. Her ACT score is 14, and she has had three asthma exacerbations, one involving hospitalization, in the past year. A week ago, she saw an allergist and had a positive skin test. Pertinent laboratory values today include serum immunoglobulin E 1100 IU/mL and FeNO 10. Which one of the following is best to recommend for this patient's asthma control?

A. Change albuterol to budesonide/formoterol as needed.
B. Initiate omalizumab 300 mg.
C. Initiate dupilumab 400 mg.
D. Increase tiotropium to 2.5 mcg.

11. A 7-year-old boy is awaiting discharge after being admitted for an asthma exacerbation. The hospital team plans to discharge him on budesonide 180 mcg inhaler 1 puff twice daily. His mother searched the Internet for the adverse effects of budesonide and is concerned about her son's height. Which one of the following is the most important educational point to share with the patient and his family regarding height and the use of ICS?

A. Evidence shows a clinically significant decrease in adult height, which is more significant with long-term use.
B. Evidence does not show a clinically significant decrease in adult height, and even with long-term use, this decrease is minimal.
C. Evidence is controversial, but there is a clinically significant decrease in adult height, and long-term effects on adult height are unknown.
D. Evidence is controversial, but there is no statistically significant decrease in adult height with short- or long-term use.

12. A 31-year-old woman with well-controlled asthma takes budesonide/formoterol 160/4.5 1 puff twice daily, tiotropium 1.25 mcg 2 puffs once daily, and albuterol 2 puffs every 4–6 hours as needed. She has never been hospitalized for an asthma exacerbation. She comes to the clinic for pre-pregnancy planning. The physician orders prenatal vitamins and asks for your recommendations for asthma medications in pregnancy. Together with close monitoring and adjustment, which one of the following is best to recommend for educating this patient?

A. All of her medications are considered unsafe in pregnancy.
B. Budesonide/formoterol is safe in pregnancy.

C. Tiotropium is safe in pregnancy.
D. Only albuterol is safe in pregnancy.

13. A 33-year-old woman with a history of asthma uses mometasone 220 mcg once daily and albuterol as needed. One year ago, after she developed an upper respiratory infection, she was hospitalized for an asthma exacerbation and given albuterol 0.25 mg by nebulizer every 4–6 hours as needed. Since then, the patient prefers albuterol solution by nebulizer and no longer uses the albuterol metered dose inhaler (MDI). Which one of the following is the best educational point to share with this patient regarding nebulizers versus MDIs?

    A. Efficacy between an MDI and a nebulizer is similar.
    B. Nebulizers are more effective than MDIs.
    C. Nebulizers prevent more hospitalizations.
    D. MDIs have more adverse effects.

14. A 13-year-old male adolescent was recently in the hospital for what may have been a severe asthma exacerbation. On discharge, the patient was taking albuterol 90 mcg 1 or 2 puffs every 4–6 hours as needed and fluticasone 220 mcg 1 puff twice daily. One month after discharge, the patient's condition is stable, and he reports no albuterol use since discharge. The provider would like to perform spirometry to diagnose asthma at the next follow-up. Which one of the following is best to recommend to aid in this patient's diagnosis?

    A. Reduce fluticasone dose to 88 mcg 1 puff twice daily.
    B. Reduce fluticasone dose to 110 mcg 1 puff twice daily.
    C. Change to fluticasone/salmeterol 113-14 mcg 1 puff twice daily.
    D. Change to fluticasone/salmeterol 55-14 mcg 1 puff twice daily.

15. A 34-year-old woman takes fluticasone 220 mcg 1 puff twice daily, albuterol 90 mcg 1 or 2 puffs as needed, loratadine 10 mg daily, and hydrochlorothiazide 25 mg daily. She is a healthcare worker and needs to start occupational postexposure to HIV for 4 weeks. The provider plans to prescribe the combination pill elvitegravir/cobicistat/tenofovir DF/emtricitabine. The provider notices a drug interaction warning in the electronic medical record system and asks for your recommendation on how to proceed. Which one of the following is best to recommend for this patient?

    A. Decrease to fluticasone 110 mcg 1 puff twice daily.
    B. Change fluticasone to beclomethasone 80 mcg 2 puffs twice daily.
    C. Increase to fluticasone 220 mcg 2 puffs twice daily.
    D. Change fluticasone to beclomethasone 80 mcg 1 puff twice daily.