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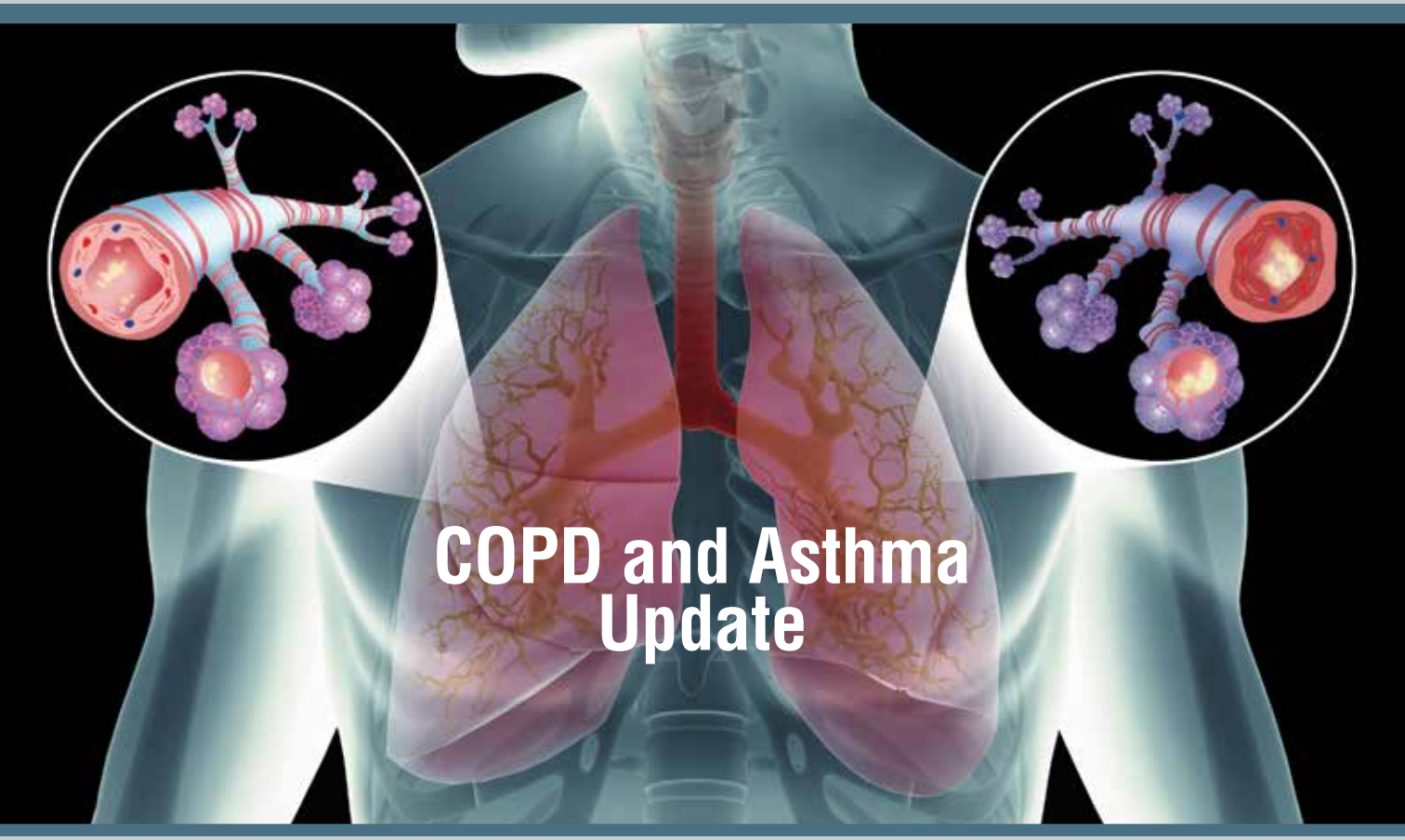

COPD and Asthma Update

Introduction

Jill Ohar, MD; James F. Donohue, MD

The heterogeneous and dynamic nature of chronic obstructive pulmonary disease (COPD) and asthma often make their diagnosis and treatment challenging. Recent advances in disease understanding and management have enabled clinicians to refine diagnoses and tailor treatment. COPD and asthma are commonly encountered in primary care; therefore, the authors aim to help primary care providers (PCPs) mitigate challenges by providing an overview of the recent changes and developments in the diagnosis and management of COPD, asthma-COPD overlap (ACO), and asthma, and by providing practical guidance for optimal patient outcomes.

Characteristic symptoms of COPD include dyspnea, cough, and sputum production. Using spirometry to confirm a COPD diagnosis is important, as is the subsequent classification of patients based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 ABCD assessment criteria, wherein patients are classified based on patient-reported symptoms and exacerbations.[1] Symptoms of COPD often go unrecognized until later stages because of the indolence of their appearance and progression. Therefore, objective testing in the form of spirometry is crucial. Comorbidities should also be considered. Once diagnosis is confirmed, a treatment plan comprising appropriate nonpharmacological or pharmacological management options can be developed.

Several therapeutic options for COPD have become available recently. Thus, awareness of different therapeutic options and their use in therapy is necessary for optimal results and to avoid undertreatment or overprescribing. Targeted treatments for patients unresponsive to standard care are emerging. However, further studies are needed to understand the role of individualized treatment in patients with COPD.

Like COPD, asthma is a heterogeneous disease, characterized by chronic airway inflammation. According to the Global Initiative for Asthma (GINA), "asthma is defined by the history of respiratory symptoms such as wheeze, chest tightness, shortness of breath, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."[2] Advances that have occurred in understanding of asthma pathogenesis and in treatment options should improve patient care with movement towards therapies directed at treatable traits. In the GINA report, practical recommendations are provided to assist clinicians with common problems encountered in their daily practice.[2] A stepwise approach to asthma management is recommended in most asthma treatment guidelines. Referral to a specialist or severe asthma clinic is necessary if diagnosis is difficult to confirm, asthma remains uncontrolled after long-term standard treatment, occupational asthma is suspected, or evidence or risk of significant treatment side-effects or comorbidities exists.

The presentation, etiology, and progression of asthma vary across age groups, so age-related factors should be considered when diagnosing and managing asthma.[2] Further, considering phenotypes and endotypes[3] (**DEFINED ON PAGES S5 AND S6**) and understanding the advantages and disadvantages of available therapies are essential to proper diagnosis and optimal treatment of severe asthma. Studies to better understand severe asthma and new therapies based on biomarkers are underway, and collaboration between PCPs and specialists is useful to maximize patient outcomes.

Poor medication adherence is a major barrier preventing patients with COPD or asthma from achieving treat-

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ment goals. Improper inhaler technique is an important contributor to poor adherence, and PCPs can help improve adherence by demonstrating and reinforcing proper inhaler technique.[4] Additionally, going beyond conventional educational approaches and empowering patients with necessary self-management skills can help patients achieve treatment goals.[5]

Appropriate management of patients with overlapping asthma and COPD features, or ACO, is even more challenging than the management of individual conditions. A commonly acceptable definition and standardized treatment algorithm are lacking. Further research to study the underlying mechanisms of ACO and to monitor biomarkers that predict response to therapy is needed to guide treatment.

This supplement has been developed to serve as clinical aid for PCPs to further understand and manage patients with COPD or asthma. ●

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Visit www.mdedge.com/COPD_Asthma_Update to view an infographic associated with this article.

Ever-evolving Concepts in the Asthma Management Landscape in the United States

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INTRODUCTION

Asthma is characterized by chronic airway inflammation and reversible airway obstruction and causes recurring respiratory symptoms such as cough, wheeze, dyspnea, and chest tightness.[1,2] Asthma is now considered a heterogeneous syndrome of somewhat distinct clinical and molecular phenotypes, with differences in genetic backgrounds, natural histories, degrees of severity, and responses to treatment.[2] Further, asthma is no longer considered a stable disease; it is dynamic and constantly changes in response to the environment.[3] The heterogeneous nature of asthma and numerous patient variables (eg, genetics, age, comorbidities, and triggers) can make diagnosis, treatment, and the primary goal of achieving asthma control challenging.[4]

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INCREASES IN BURDEN OF ASTHMA

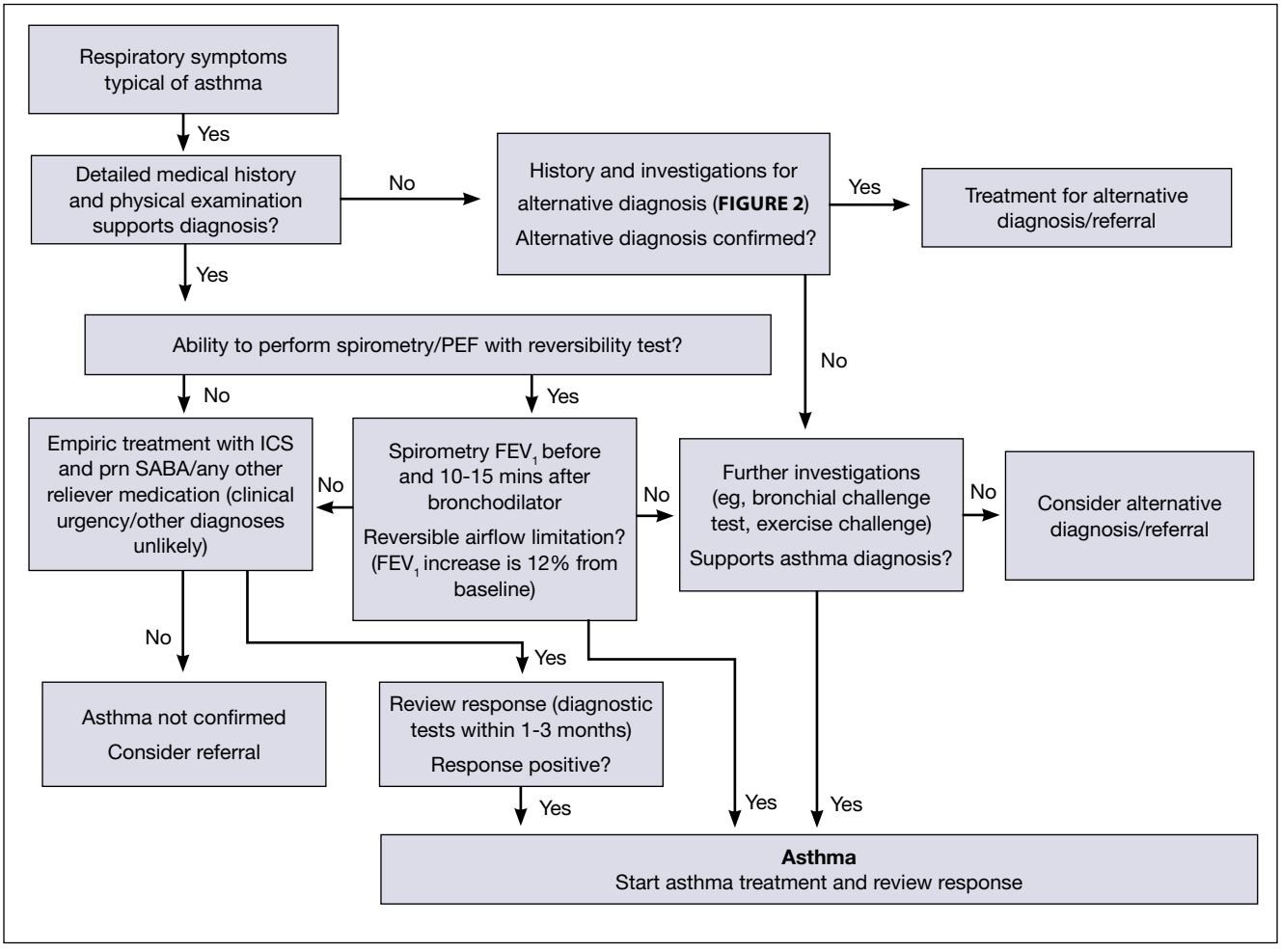
Asthma is a common condition that imposes substantial patient, health care system, and socioeconomic burdens. Globally, asthma prevalence increased by approximately 10% from 2005 to 2015 (~327 [7.6%] to ~358 [11.6%] million), and it is a top-11 cause for years lived with disability.[5] In the United States in 2016, 26.5 million (8.3%) people—6.1 million (8.3%) children and 20.4 million (8.3%) adults—had asthma; 3518 asthma-related deaths (10 deaths/million) occurred. Of note, despite regular introduction of treatment options, 12.4 million (46.9%) patients—3.3 million (53.7%) children and 9.1 million (44.9%) adults—continued to experience exacerbations.[6] Recently, the annual cost of asthma in the United States was estimated to surpass $80 billion.[7]

ADVANCED UNDERSTANDING OF ASTHMA ETIOLOGY

Our understanding of asthma etiology has evolved over time, revealing its multifactorial nature in relation to patient and environmental contributors.[8] The involvement of genetic and environmental factors, as well as cellular and molecular pathways, in asthma pathophysiology are now clearer.[9] Susceptibility genes include those associated with both type 2 cytokine producing helper T cell (Th2) and non-Th2 cell differentiation and function (eg, type 2 cytokines: interleukin [IL]-4, IL-5, and IL-13); influencing allergic inflammation and allergen-specific immunoglobulin E (IgE) production; epithelial biology; lung function; airway remodeling; and disease severity.[10] Environmental factors or triggers include indoor and outdoor allergens, smoking, air pollution, cold temperatures, exercise, occupational exposures, and viruses.[11]

Viral respiratory tract infections, primarily rhinovirus and respiratory syncytial virus infections,[12,13] and exposure to tobacco smoke (passive or second-hand)[14] were strongly associated with childhood asthma exacerbations; smoke-exposed children were twice as likely than unexposed children to be hospitalized with an exacerbation.[14] Moreover, active smoking

FIGURE 1 **Diagnostic flowchart for asthma in clinical practice**



Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; PEF, peak expiratory flow; prn, pro re nata; SABA, short-acting β_2-agonist.

was associated with gene polymorphisms and reduced lung function in adult-onset asthma.[15,16] Because avoiding triggers is difficult, and patients rarely adhere to avoidance strategies,[11] trigger avoidance should be encouraged as much as possible.

A clearer understanding of asthma etiopathogenesis has made identification of specific patient subgroups (eg, phenotypes and endotypes [see below]) possible.[17] Patients often develop allergic asthma at a young age; are usually atopic (ie, they develop IgE responses to specific allergens); have a personal or family history of other allergic diseases; and may have enhanced immune responses to specific allergic triggers.[18] Patients can also develop nonallergic asthma later in life and may not have obvious sensitization to allergens.[18]

Asthma phenotypes derived from cluster analysis capture clinically observable characteristics (eg, clinical, physiological, treatment response, and some inflammatory markers) without defining the direct underlying pathophysiologic mechanisms.[19,20] Phenotypes are classified into broad categories (eg, early or late onset asthma, allergic or nonallergic asthma) based on a single variable (eg, pattern of airflow obstruction, symptomatic triggers, and disease severity),[21] but also can be sub-classified into distinct phenotype subgroups, or subphenotypes such as, eosinophilic, neutrophilic, and paucicellular (ie, absence of an observable inflammatory process) asthma, exercise-induced, obesity-related, and smoking-related asthma.[18] Phenotypes exhibit variable sensitivities to steroid therapy.[22] For example, nonallergic asthma appears less responsive to steroids than allergic asthma.[22] The "steroid-refractory" phenotype refers to patients who do not respond to long-term corticosteroid therapies, leading to poor asthma control.[23] Asthma endotypes are defined based

on distinct pathophysiological or functional mechanisms.[17] Subtyping helps inform the choice of diagnostic tests, indicates long-term prognosis, and may predict responsiveness to targeted pharmacotherapies.[17] (Please refer to accompanying supplement article *Confronting the Challenges of Severe Asthma* for further details).

Identifying biomarkers suggestive of different pathogenic mechanisms can help classify specific asthma phenotypes or endotypes, ultimately allowing for individualized treatment.[24] Asthma biomarkers include elevated sputum and blood eosinophil counts and fractional exhaled nitric oxide (FeNO) levels, which identify eosinophilic asthma, and elevated allergen-specific IgE levels, which identify allergic asthma.[24] Importantly, biomarker-driven identification of asthma that is not solely by Th2-driven immunity has advanced our knowledge about asthma heterogeneity.

PROGRESS IN ASTHMA DIAGNOSIS

Asthma is one of the most common chronic disorders seen in primary care settings,[25,26] and patients may present with different asthma severities. Hence, comfort in diagnosis, awareness of available treatment options, and knowledge of when to refer to a specialist are important elements.[1,26,27] In the Global Initiative for Asthma (GINA) report, asthma is defined by a history of respiratory symptoms that vary over time and in intensity and variable expiratory airflow limitation (ie, variability over time assessed by spirometry [see below], greater than that seen in healthy individuals). Therefore, patient evaluation should begin with a thorough medical history, symptom assessment, and physical examination (**FIGURE 1**).[1]

Symptoms as reported by patients may be underestimated when broad, nonspecific questions are asked about well-being; therefore, simple-to-understand, directive, closed-ended questions such as those in the Asthma Control Questionnaire, Asthma Therapy Assessment Questionnaire, or asthma control test (ACT) should be asked.[1] These tests include 3 to 10 questions, with variable scoring values that provide somewhat quantitative data; are repeatable; and have acceptable clinical validity.[28] Of note, however, the validity and reliability of each test differ between children and adults.[28-30] The GINA report contains practical recommendations, including tools to confirm and document asthma diagnosis, algorithms to lessen over- or under-treatment (eg, criteria for variable expiratory airflow limitation), and descriptions of important screening tools to identify patients requiring additional assessment.[1,31]

Although asthma can be suspected based on clinical evaluation, diagnostic tests (eg, chest radiography, pulmonary function tests, specific blood tests, and spirometry)—some of which can be done in primary care settings—may be necessary to exclude comorbidities or masqueraders of asthma and to accurately diagnose asthma.[1,31] Further, an asthma diagnosis should ideally be confirmed objectively by demonstrating variable airflow obstruction using spirometry, airway hyper-responsiveness using peak expiratory flow (PEF) or bronchial provocation testing (also referred to as bronchial challenge testing), and reversibility after a bronchodilatory is administered.[25]

Spirometry is valuable but often underused in primary care settings.[32] Spirometry is difficult to perform in children less than 5-6 years of age. Its value is in helping to establish a diagnosis of asthma before initiation of chronic therapy.[1] Further, pre- and postbronchodilator spirometry monitoring is an important adjunct to distinguish asthma from other types of airway obstruction.[33]

Spirometric measurements of clinical importance include forced vital capacity (FVC; the volume of air that can be exhaled from fully inflated lungs) and forced expiratory volume in 1 second (FEV_1).[25] An FEV_1/FVC ratio of >0.75 to 0.80 in adults and >0.90 in children is considered normal.[1] Use of portable, hand-held, easy-to-use spirometers in the office setting can help avoid long waits for testing at hospital-based pulmonary function test centers, is relatively more convenient for patients, and provides more timely data to physicians,[32] presuming the test is conducted and interpreted properly.[34] Potential barriers to using spirometry in primary care relate to training and equipment costs.[34] However, some barriers may be overcome by implementing respiratory training programs such as respiratory and asthma toolkit programs, which provide multidisciplinary primary care training in health centers to augment guideline-based asthma care.[35,36] These programs substantially improve spirometry use, asthma severity assessment, execution of asthma action plans, and guide corticosteroid and other asthma medication use.[35,36]

The PEF test, which measures how fast a person can exhale, is another simple and convenient test that can be conducted in primary care settings. PEF tests like spirometry are effort-dependent, which may affect interpretation of results. PEF variability is associated with airway hyperreactivity and is a well-accepted diagnostic aid for implementation in primary care.[25] Establishing a patient's PEF "personal best" is an important guideline for assessing asthma control or deterioration; an average daily diurnal PEF variability of >10% in adults and >13% in children is diagnostic of asthma.[1]

The bronchial provocation test is recommended when patients have clinical features of asthma but normal spirometric findings on initial testing. The test, which involves

inhalation of nebulized methacholine, provocholine, histamine, or mannitol to induce bronchoconstriction in susceptible airways,[5,25] is essentially a dose-response test, in which the dose causing bronchoconstriction defines the level of airway reactivity. This test is carried out by specialists because of the equipment needed and risk of provoking severe airway obstruction.[37]

Additional investigations may refine asthma diagnosis and inform treatment.[1] For example, elevated sputum or blood eosinophil counts support an eosinophilic asthma diagnosis[1,38] and presence of atopy can be detected via a skin prick test or allergen-specific serum IgE levels. However, serum IgE testing is somewhat expensive, and expensive blood tests often ordered in a primary care setting have not proven to be more reliable than skin tests.[1,31] Patients with eosinophilic or allergic asthma may be candidates for novel, anti-IL-5 or anti-IgE biologics (Please refer to accompanying supplement article *Confronting the Challenges of Severe Asthma* for further details).

Nitric oxide (NO), a biological mediator produced by human lung epithelial cells that is present in exhaled breath, is purported to cause bronchial smooth muscle relaxation and acts as an inflammatory mediator.[39] Guideline updates highlight the diagnostic importance of FeNO testing.[1,31,39] FeNO levels are highest among patients with atopy and asthma.[40,41] These patients have high FeNO levels because of NO synthase upregulation resulting from airway eosinophilic inflammation.[39] In contrast, airway neutrophilic inflammation is associated with low FeNO levels because neutrophils decrease NO synthase levels. FeNO levels also can be used to determine response to inhaled corticosteroid (ICS) treatment and are effective in assessing compliance; FeNO levels should decrease with treatment if medications are taken appropriately.[42,43] Machines to measure FeNO, however, require regular calibration and may not be practical in a primary care setting.

Asthma comorbidities and differential diagnosis

Comorbidities and alternative diagnoses, such as vocal cord dysfunction, should be considered in patients with suspected asthma (**FIGURE 2**).[31,44] Comorbidities are important to document because they may share common clinical patterns and/or pathophysiological mechanisms with asthma and impact clinical presentation, management, and control.[45] Most importantly, they may influence the response to asthma medications. Allergic rhinitis, food allergies, atopic eczema, and gastroesophageal reflux disease may be present in children and persist into adulthood, while obesity, metabolic disorders, type 2 diabetes mellitus, heart disease, and psychiatric disorders are usually present only in adulthood.[44,45] Obesity, a major risk factor for asthma development, is associated with longstanding, low-grade systemic inflammation and increases systemic complexities.[46] For example, obesity is associated with increased eosinophil activity and asthma severity, and decreased macrophage activity, leading to steroid-refractory asthma.[46] Obese individuals with persistent asthma are more likely to have uncontrolled asthma and, for reasons yet to be determined, their response to corticosteroids is often suboptimal leading to poorer quality of life (QoL) than non-obese counterparts.[47,48]

MANAGING ASTHMA IN PRIMARY CARE

Asthma management can be challenging. In a primary care setting, the focus is often on acute treatment, resolving acute patient issues. Often, little time is available for in-depth discussions on prevention of illness and promotion of asthma guidelines and management.[26] Of note, in contrast to the annually updated GINA report,[1] the last National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP) guidelines update was in 2007.[31] Moreover, although guidelines are available, they are often cumbersome and underused in primary care;[36] general practice, pediatric and internal medicine physicians may be unaware or have access to standardized tools to monitor or manage asthma.[49]

Regardless, control of symptoms, maintenance of normal activity, and reduction of flare-ups, airflow limitation, and adverse events remain long-term objectives in asthma management.[1,31] Once an asthma diagnosis is made, emphasis is on determining the degree of asthma severity, initiating therapy, monitoring control over time, and making necessary adjustments (increases or decreases) to treatment (**FIGURE 3**).[1,26,31] Nonpharmacologic approaches such as smoking cessation, engaging in physical activity, avoiding occupational exposures, and minimizing indoor allergen exposure and medications that worsen asthma should be considered to help improve symptom control and/or reduce exacerbation risk.[1]

Although asthma is not curable, advancements have enabled an evolution in pharmacologic interventions, which form the mainstay of asthma management because they reduce airway inflammation and airway hyperreactivity.[1] These medications can be categorized as controller medications, which reduce inflammation and exacerbation risk, and reliever medications, which alleviate bronchospasm and acute symptoms.[1,31,50,51]

Among controller medications, ICSs were first used to treat asthma in the 1970s.[52] Long-acting β_2-agonists (LABAs) and leukotriene receptor antagonists (LTRAs) were approved by the US Food and Drug Administration (FDA) in the early and late 1990s, respectively.[53] The long-acting muscarinic

FIGURE 2 **Comorbidities and differential diagnosis of asthma**

Hyperventilation Glottic dysfunction	Psychopathologies	Smoking/ nicotine dependence	COPD	Respiratory infections
Rhinitis	**Asthma comorbidities**			Hormonal imbalance
Chronic sinusitis				Other*
	Gastroesophageal reflux disease	Obesity	Obstructive sleep apnea	

Chronic upper airway cough syndrome	Inhaled foreign body	Bronchiectasis	Primary ciliary dyskinesia	Congenital heart disease
Medication-related cough	**Asthma masqueraders**			Bronchopulmonary dysplasia
Central airway obstruction				Cystic fibrosis
Pulmonary embolism				Vocal cord dysfunction
Parenchymal lung disease	Cardiac failure	COPD	$Alpha_1$-antitrypsin deficiency	Hyperventilation, dysfunctional breathing

*Atopic dermatitis, allergic bronchopulmonary aspergillosis, bronchiectasis.

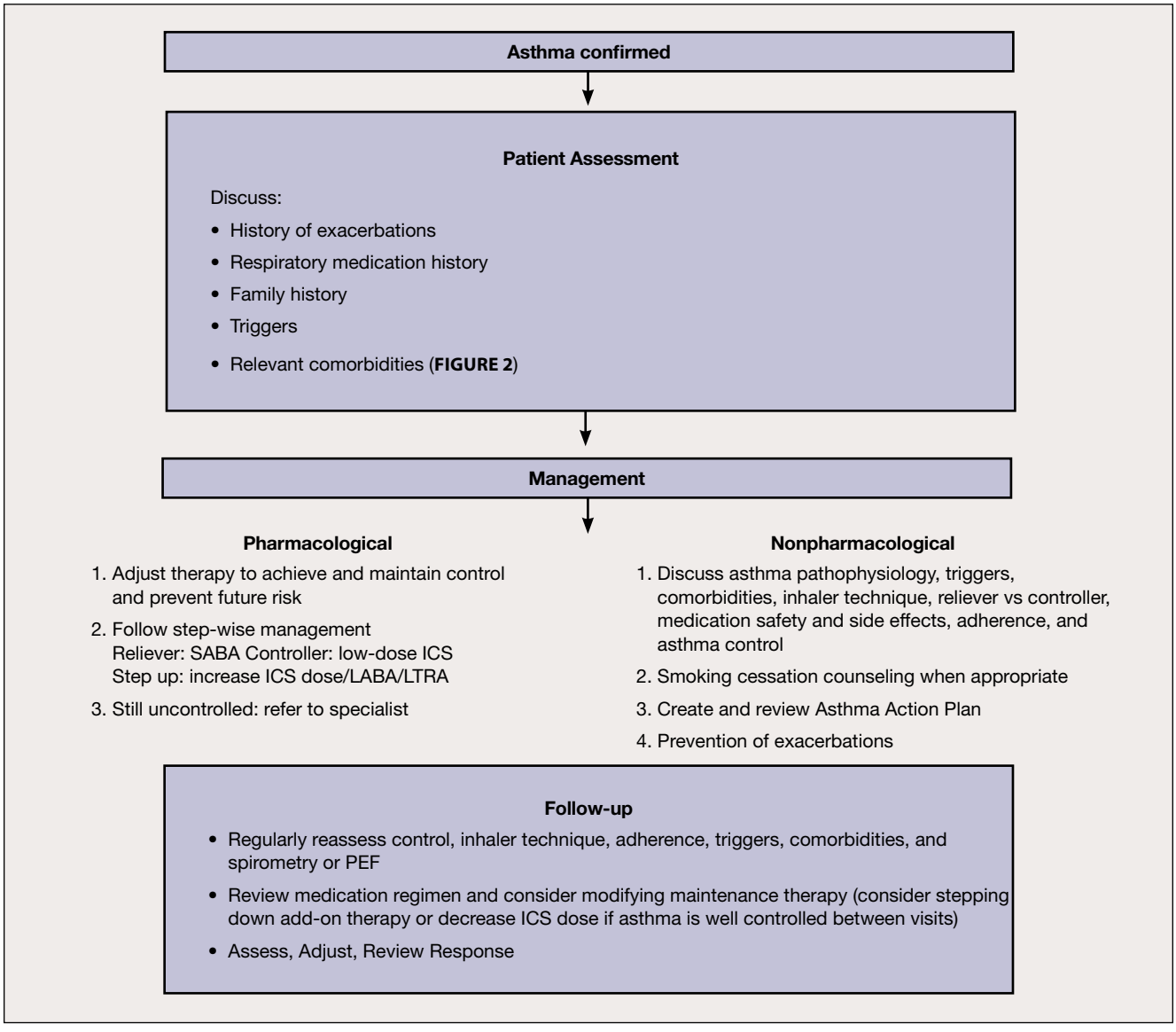
Abbreviation: COPD, chronic obstructive pulmonary disease.

antagonist (LAMA) tiotropium was approved for asthma in 2015.[54] More recently, targeted biologics for specific asthma phenotypes (eg, allergic and eosinophilic asthma) have become available.[55-57] ICSs are the standard-of-care controller medications for patients with asthma, regardless of severity.[1,31,51] Low-dose ICS is the first-line therapy for noncomplicated (mild-to-moderate) asthma in children and adults.[1] However, primary care providers (PCPs) may be uncomfortable in prescribing ICSs, especially to children, because of side effects and outdated guidelines.[58] Initial concerns raised several years ago were valid, but current recommendations have minimized adverse events.[1,31,59] Alternatives to ICSs, LTRAs, and theophylline are generally less effective than ICSs.[1,60] Increasing the ICS dose (to medium-dose and high-dose), along with add-on medications (LTRAs, LABAs, LAMAs, and biologics), is recommended in a step-wise manner as disease severity increases.[1,31,50] LABAs are recommended as controller medications in combination with ICS in multiple guidelines.[1,31,50,51] Their use in the United States was scrutinized because of a "black-box" warning issued by the FDA in March 2006, after results from the Salmeterol Multicenter Asthma Research Trial (SMART) raised concerns about the safety of salmeterol, a commonly used LABA.[61,62] Consequently, LABA monotherapy use substantially decreased and ICS monotherapy prescriptions increased.[63] However, results of supplementary studies, which addressed safety concerns, prompted removal of the warning for ICS/LABA medications in late 2017; nevertheless, the warning remains for single-ingredient LABA medications.[64] This change is likely to impact prescribing patterns.

Because asthma is variable and heterogeneous, adjustments (eg, stepping up or stepping down treatment) may be needed at regular intervals.[1] For severe uncontrolled or refractory asthma, patients should be referred to a specialist, who may escalate treatment to a LAMA (tiotropium), biologic (eg, anti-IgE and anti-IL-5), or oral corticosteroids (OCS); perform additional testing; or both.[1,31] If asthma is uncontrolled (≥1 OCS bursts in a year, regular reliever medication use, or impaired exercise tolerance or QoL), a specialist can help determine triggers and appropriate medication use.[1] Given the high cost of biologics, referral to a specialist may be an important first step before instituting these treatments.[27]

For patients with uncontrolled/refractory asthma, the concept of "treatable traits," where treatment targets an individual's needs based on genetic makeup, biomarkers, phenotype, and behavioral characteristics, has gained traction.[65] Goals of such individualized therapy are to improve clinical outcomes and efficacy and reduce side effects for those unlikely to respond to a particular controller/reliever.[66] Examples of "treatable traits" include elevated blood eosinophil counts and high FeNO levels, which are often predictors of ICS responsiveness.[42,43,67] Identification of such characteristics enables tailored treatment according to phenotype, which goes beyond the diagnostic labels of asthma.[65] However, the feasibility of this approach is yet

FIGURE 3 **Asthma management algorithm for primary care**



Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; SABA, short-acting β_2-agonist.

to be explored in primary care settings, given that patients with asthma may have comorbidities.

In addition to pharmacologic improvements, asthma medication delivery systems (ie, nebulizers, metered dose inhalers, dry powder inhalers, and the slow-mist inhaler Respimat) have evolved.[31,67] Regular patient education regarding how to properly take their medications is invaluable[36,68] but can be challenging because of variable activation and inhalation steps, and coordination of activation and inhalation.[69] The latter impediment is averted with nebulizers and the Respimat inhaler.[69]

Assessment of asthma control and potential reasons for lack of control

Despite available treatments, a significant subset of patients with asthma remain uncontrolled. Reasons for poor asthma control include physician-related barriers such as failure to adopt guidelines, communication barriers, time constraints, and poor adoption of asthma action plans.[70] Patient-related barriers include poor adherence to prescription instructions, inconsistent asthma perceptions, the cost of treatment, lack of access to medications,[1,71] and psychological factors that negatively impact adherence (eg, adoption or rejection of the

sick role, faulty symptom attribution, depression, and low self-esteem).[72]

Improper inhaler technique and not using a spacer are also common causes of treatment failure.[73] Poor symptom perception may result in significant overuse of reliever medications, irrespective of lung function, whereas underperception potentially delays treatment.[74] Adherence, inhaler techniques, and trigger avoidance should be monitored at every patient visit.[1] Here, as well, is where the asthma questionnaires provide important information to guide management decisions.[1]

Role of PCPs in teaching patients self-management

Given the chronic and heterogeneous nature of asthma, patients (and caregivers, when appropriate) should be educated about and possess the skills and tools needed for effective self-management.[1] As part of a coordinated care plan, asthma education is most successful when patients/caregivers and their PCPs, together, discuss who can educate them on important topics such as medication and device use, medication adherence, medication costs, disease, and trigger recognition.[1,31,75] A collaborative patient-centric approach, in which patients are encouraged to participate in shared decision making about treatment, is important to the education process.[1] Since patients with comorbid conditions are often distressed in terms of understanding their conditions, attending different appointments, and managing complex drug regimens, understanding what is most important to them is necessary for shared decision making.[76]

CONCLUSIONS

Asthma is a heterogeneous, dynamic disease, and its incident factors, pathogenesis, prognosis, treatment strategies, and corresponding responses remain inadequately understood. Patient-specific characteristics such as demographic, physiologic, and biologic markers help identify asthma phenotypes, which can be leveraged toward endotypic categorization, with the ultimate goals of identifying culprit pathways and preventative strategies, and improving specific therapies targeted toward an individual patient's disease. Optimal care involves a multidisciplinary approach, including PCPs, respiratory therapists, patient advocates, and pharmacists, who can play fundamental roles in reducing asthma exacerbations and persistent uncontrolled asthma at a time when advancements in disease knowledge and selection of effective medications have provided an opportunity for significant improvements. Partnering with asthma specialists provides an additional resource to ensure optimum asthma management and achieving the highest QoL. ●

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An Update on Treatment Options for Children and Adults With Asthma

Alan G. Kaplan, MD, CCFP(EM), FCFP; Mark L. Vandewalker, MD, FACAAI

INTRODUCTION

Asthma is a chronic heterogeneous disease with varied etiology, presentation, and progression.[1,2] It may be intermittent or persistent in nature, develop during childhood or adulthood, range in symptom severity from mild (intermittent) to severe refractory, and be triggered by numerous environmental factors.[1,3] The course of asthma varies depending on age or time of onset. While some children may outgrow the disease, others continue to have intermittent or persistent asthma throughout adulthood.[4] Furthermore, asthma may be associated with various comorbidities, which may vary by age and confound presentation, diagnosis, and management.[5] These factors should be considered and revisited when diagnosing asthma and formulating management plans.

DIAGNOSIS OF ASTHMA ACROSS AGE GROUPS

In general, a presumptive diagnosis of asthma can be made based on patient history, risk factors, and clinical examination. Features suggestive of asthma include presence of ≥1 prototypical symptom (wheeze, shortness of breath, cough, or chest tightness) and symptoms that worsen at night or early morning, vary over time and in intensity, and are triggered by viral infections (colds), exercise, allergen exposure, weather changes, laughter, or irritants (eg, car exhaust fumes, smoke, or strong smells).[1] In clinical practice, patients often receive "as-needed" treatment based on a presumptive diagnosis, without undergoing a thorough investigation or receiving a formal asthma diagnosis. Asthma diagnosis should, however, be confirmed using objective assessments such as spirometry, which reveals variable airway obstruction that is at least partially reversible.[1,6] Positive bronchodilator reversibility test is defined as increase in forced expiratory volume in 1 second (FEV_1) of >12% and >200 mL from baseline in adults, and increase in FEV_1 of >12% predicted in children.[1]

Further, identification of asthma phenotype (patients with similar clinically observable and physiological characteristics are grouped [eg, allergic vs nonallergic asthma, atopic vs non-atopic asthma]) and endotype (links specific pathophysiological mechanisms or pathways to a disease subtype [eg, interleukin (IL)-5- or IL-17-mediated asthma]) helps inform treatment choices (please refer to accompanying supplement article *Confronting the Challenges of Severe Asthma* for further details). Blood eosinophil count, serum total or specific immunoglobulin E (IgE) level, and fractional exhaled nitric oxide (FeNO) level are phenotypic biomarkers that reflect airway inflammation and/or atopy and may be useful predictors of asthma, particularly in young children who cannot perform spirometry.[7] For FeNO testing, patients blow into a hand-held device. FeNO levels correlate with bronchial hyper-responsiveness, blood eosinophil count, and serum IgE levels.[8] Further, because of diagnostic challenges in children, impulse oscillometry, where sound waves are used to detect airway changes[9]; electromagnetic inductance plethysmography, where patients wear a volume-sensing vest to measure chest and abdominal volume changes[10]; computed tomography scan[11]; and magnetic resonance imaging[11] are being evaluated for phenotyping.

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Unfortunately, diagnostic challenges are as varied as the disease. Physician barriers may include reluctance to confirm asthma diagnosis and lack of access to assessments (eg, spirometry and bronchial challenge, allergy, FeNO, and sputum eosinophil tests). Patient challenges may be specific to an age group or span multiple age groups (**FIGURE 1A**). Preschoolers with viral infections often wheeze[12]—the most common presentation of asthma early in life. However, acute wheezing may occur for various reasons, and not all preschoolers with acute wheezing have or develop asthma.[13,14] Approximately 30% of preschoolers with recurrent wheezing have asthma at age 6.[14,15] Three wheezing phenotypes in preschoolers are transient infant wheezers (few wheezing episodes during the first 2-3 years of life, and no wheezing after age 3), nonatopic wheezers (continued wheezing after age 3 during lower respiratory infection episodes), and atopic wheezers (wheezing starts by age 6, and most develop atopic asthma).[14] Atopy genetically predisposes children to develop an IgE-mediated response to common allergens.[16] Sensitization against common aeroallergens occurs by age 6, and wheezing prevalence steadily increases from infancy to adolescence.[9] Notably, children aged <5 years are often unable to perform reproducible spirometry[1]; therefore, diagnosis in very young children is often based on symptoms, clinical examination, and presence of risk factors such as atopy and family history.[13]

Primary care providers (PCPs) are often asked how the disease will progress, or which children will "develop true asthma" versus "outgrow asthma." The asthma predictive index (API; https://www.mdcalc.com/asthma-predictive-index-api) is a tool that uses simple, clinically based parameters to predict the likelihood that young children with recurrent wheezing will develop persistent asthma later in school age.[17] The interplay between genetic and environmental factors may affect persistence or relapse of childhood asthma in adulthood.[18]

Adults may develop asthma late in life as occupational or obesity-related asthma or as part of asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO). Diagnosis is challenging because new-onset asthma is often not considered in the differential diagnosis of adults with respiratory symptoms (**FIGURE 1A**). Further, diagnosis may be delayed because the presentation may mimic other diseases (eg, chronic obstructive bronchitis, bronchiectasis, congestive heart failure, upper airway obstruction, lung cancer with endobronchial lesion, and vocal cord dysfunction).[3]

Occupational asthma, which generally is classified as sensitizer-induced asthma or non-sensitizing, irritant-induced asthma, is under-recognized in clinical practice.[19] Sensitizer-induced asthma is caused by specific workplace exposures (**FIGURE 1B**), usually to a high-molecular–weight agent that induces asthma even at a low exposure level in individuals previously sensitized through an immunologic mechanism. In contrast, irritant-induced occupational asthma results from exposure to airway irritants and lacks sensitization. Although the prevalence is relatively low (≤10%), even with exposure to most known sensitizers, the socioeconomic impact on those affected during their productive years is substantial. Common barriers to diagnosis of occupational asthma include inadequate disease knowledge among workers and fear of losing their jobs, the latent period between first exposure and development of symptomatic asthma, and limited occupational history-taking and low index of suspicion by PCPs.[19,20] Referral to specialists is warranted when occupational asthma is suspected based on true adult-onset asthma with an occupational history, history of more severe symptoms during workdays versus holidays, serial spirometry and self-monitoring using at-home peak expiratory flow assessment at different times relative to work, allergen testing, and specific challenge tests. Lists of compensable occupational asthma or occupation-aggravated asthma, responsible institutions, procedures for administration and examination of cases, and allocation of disability vary across the United States.[21]

Late-onset asthma may present in older adults with multiple comorbidities, including psychological issues, and consequent polypharmacy, which may hinder diagnosis. Like very young children, older adults may have difficulties performing spirometry.[22] Inability to understand instructions, refusal to perform the test, and physical impairment are the most common reasons for nonperformance of spirometry.[22] If patients can perform spirometry, bronchodilator reversibility and improvement in lung function after a trial of asthma medications such as oral corticosteroid (OCS) or inhaled corticosteroid (ICS) should be conducted.[23,24] Otherwise, diagnosis may be aided with blood eosinophil, serum IgE, FeNO, and bronchial challenge tests.

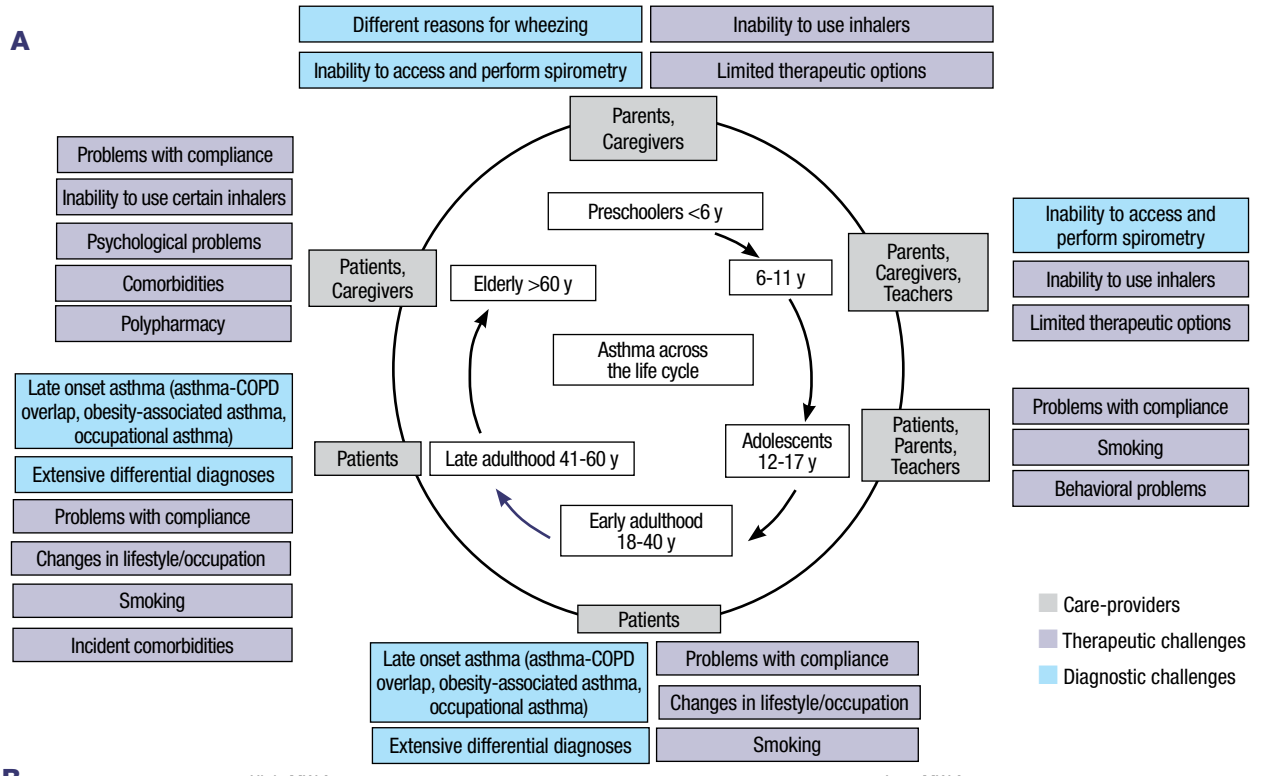
ACO should be considered in adults ≥40 years old who have symptoms and spirometric values suggestive of both COPD and asthma.[25] ACO diagnosis is challenging because differentiating typical asthma or COPD is problematic in the absence of specific biomarkers; therefore, a stepwise approach to the diagnosis of ACO is warranted, with referral for specialized investigations, if needed.[1]

MANAGEMENT OF ASTHMA ACROSS AGE GROUPS

As with diagnosis, PCPs, patients, and caregivers face management challenges, some of which are specific to a particular age group, while others span multiple age groups (**FIGURE 1**). For example, because proper timing, hand-breath coordination, and deep inhalation are required for optimal use

FIGURE 1 **Asthma diagnostic and therapeutic challenges, including (A) across the patient's life cycle, (B) with occupational asthma sensitizers, and (C) with definitions of asthma control**

A



B

High-MW Agents		
Foods (eg, dairy products): food-production workers, cooks	Wheat flower, α amylase: bakers	Vegetable gums: printers, carpet makers
Enzymes: workers in laboratories, pharmaceutical companies, bakeries	Fungi: office or laboratory workers	Animal allergens: farmers, animal workers (laboratory/veterinary)
Biological enzymes: detergent powder manufacturers	Insects: farmers, greenhouse workers	Fish proteins: fish and seafood processors
Plants, plant products, cereals, and grains: greenhouse, rain, and bakery workers; farmers; makers/users of latex products		

Low-MW Agents		
Phenol-formaldehyde resin: makers of wood products, foundry workers	Persulphates and henna: hairdressers	Aliphatic amines: lacquer handlers, soldering workers, spray painters, professional cleaners
Metal salts: refinery, jewelry, and metal-plating workers; stainless steel welders	Colophony fume: electronic solderers	Acrylic monomers: chemical-industry and dental workers, aestheticians applying artificial nails
Wood dusts: carpenters; sawmill and forestry workers	Hardwood dusts: woodworkers	Acid anhydrides: makers of epoxy resins for plastics
Diisocyanates: urethane paint sprayers, polyurethane foam manufacturers and installers, foundry workers handling urethane adhesives or urethane molds	Biocides: healthcare workers	Drugs: pharmaceutical workers, pharmacists

C

GINA	• Based on daytime asthma symptoms, night awakenings, activity limitation because of asthma, and reliever use[1]
NIH/NAEPP EPR-3	• Based on most severe impairment and risk category[6] • Impairment evaluated based on symptoms, night awakenings, interference with normal activity, SABA use for symptom control, FEV_1 or peak flow, and validated questionnaire scores such as the ATAQ, ACQ, and ACT • Risk based on exacerbations requiring OCS, progressive loss of lung function, and treatment-related AEs
CTS	• Based on daytime and nighttime symptoms, physical activity, frequency and severity of exacerbations, asthma-related school or work absenteeism, need for fast-acting β_2-agonists, and spirometry indices[36] • Sputum eosinophils also should be assessed, if feasible, as an additional measure of asthma control in patients with moderate-to-severe asthma
ATS AND ERS	• Severe asthma is defined as asthma which requires treatment with high-dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy[48]

Abbreviations: ACT, Asthma Control Test™; ACQ, Asthma Control Questionnaire; AE, adverse effect; ATAQ, Asthma Therapy Assessment Questionnaire; ATS, American Thoracic Society; CTS, Canadian Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; MW, molecular weight; NIH/NAEPP EPR-3, National Institutes of Health/National Asthma Education and Prevention Program Expert Panel Report 3; OCS, oral corticosteroid; SABA, short-acting β_2-agonist.

of most inhalers, preschoolers and older adults may be unable to execute proper inhaler technique. Additionally, factors such as comorbidities,[26] polypharmacy, complex drug intake schedule, drug and food interactions, long-standing uncontrolled asthma with worsening lung function and physiology, and ACO may complicate management in older adults.[27] Pressurized metered-dose inhalers with spacers and masks or nebulizers may be more appropriate for preschoolers, breath-actuated or dry powder inhalers may be used by older children,[1,28] and inhalers that are easier to use and require less training should be considered in older adults.[27] Slow-mist inhalers (SMIs) are newer options that can be used across all age groups. SMIs can be used with a valved holding chamber in preschoolers.[29,30] Because young children are completely dependent on parents and caregivers for treatment,[31] and older adults may require caregiver assistance, caregivers should be appropriately trained to optimize treatment and compliance. Although young adults and adolescents are able to use all types of drug delivery systems, suboptimal adherence with nonpharmacologic and pharmacologic treatment is a common problem.[32] Additionally, comorbidities such as atopy, rhinitis, obesity, and dysfunctional breathing (chronic or recurrent changes in breathing pattern, causing respiratory and nonrespiratory complaints) may be present in children,[33] while gastroesophageal reflux disease, obesity, and dysfunctional breathing may develop in young adults and persist into older age. Finally, costs and health coverage, lack of a PCP, and perception of asthma as a nonserious disease are some common additional barriers to ideal asthma management.

Treatment of asthma

Once asthma is confirmed, detailed discussions with patients or caregivers about exacerbations, respiratory medications, family history (eg, atopy or asthma), exacerbation triggers, relevant comorbidities, and family and social dynamics (supervisory role and school support in management) are needed to formulate an effective asthma management plan.[34] Long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and treatment side effects.[1] Nonpharmacologic and pharmacologic treatments form the cornerstones of long-term treatment and should be a part of each patient's action plan, which should be created, explained, and reviewed at each visit.

Nonpharmacologic options

Patients and caregivers benefit from disease education and discussions about prevention of exacerbations, including triggers and trigger avoidance; proper inhaler technique; the difference between reliever and controller medications, and corresponding safety and side effects; the importance of adherence and consequences of nonadherence; recommended lifestyle changes (eg, smoking cessation); and asthma control.[34] Patients should be referred to a certified asthma/respiratory educator, if available.

Pharmacologic options

Current Global Initiative for Asthma (GINA) guidelines describe asthma pharmacotherapies as reliever (rescue) or controller (maintenance) medications.[1] Reliever medications, which provide immediate relief of bronchospasm, open airways, and are used on an "as-needed" basis, include short-acting β_2-agonists (SABAs; inhaled [eg, albuterol] and oral), ICS/SABA and ICS/long-acting β_2-agonist (LABA) combinations, short-acting muscarinic antagonists (eg, ipratropium), and short-acting theophylline. A SABA/SAMA combination may also be potentially used as a reliever. Controller medications, which reduce airway inflammation, control symptoms, reduce future risks of exacerbations and lung function decline,[1] and are used for regular maintenance treatment, include ICSs (eg, beclometasone, fluticasone, ciclesonide, mometasone [**FIGURE 2**]), LABAs (eg, formoterol, salmeterol; often as ICS/LABA combination), leukotriene receptor antagonists (LTRAs; eg, montelukast), theophylline, long-acting muscarinic antagonists (LAMAs; eg, tiotropium), and immunomodulators (ie, biologics; anti-IgE [eg, subcutaneous omalizumab for severe allergic asthma] and anti–IL-5 [eg, subcutaneous mepolizumab and benralizumab, intravenous reslizumab for severe eosinophilic asthma] agents).

As mentioned, ICS/LABA (eg, ICS/formoterol) may be recommended as both a controller or reliever therapy.[1] In a recent systematic review and meta-analysis of data from 22,748 patients (16 randomized control trials; limited evidence for 4-11 years), single-dose maintenance and reliever therapy was associated with reduced exacerbation risk compared with fixed-dose ICS with or without LABA for maintenance and SABA as reliever therapy.[35]

Stepwise approach to asthma management

A stepwise approach to asthma management is recommended in most asthma treatment guidelines.[1,6,36] Although most guidance documents are updated regularly, the National Institutes of Health/National Asthma Education and Prevention Program Expert Panel Report 3 (NIH/NAEPP EPR-3) guidelines were last published in 2007 and, hence, do not provide guidance on medications approved in the United States since that time. Updated guidelines are expected in 2019. GINA 2018, the most up-to-date guidance, contains a treatment algorithm based on symptom severity, level of control, and patient age (**FIGURE 3**). However, because the GINA

FIGURE 2 **Low, medium, and high daily doses (μg) of inhaled corticosteroids[1]**

	Adults and adolescents (aged ≥12 years)			Children (6-11 years)		
	Low	Medium	High	Low	Medium	High
Beclometasone dipropionate (HFA)	100-200	>200-400	>400	50-100	>100-200	>200
Budesonide (DPI)	200-400	>400-800	>800	100-200	>200-400	>400
Budesonide (nebulized)	NA	NA	NA	250-500	>500-1000	>1000
Ciclesonide*	80-160	>160-320	>320	80	>80-160	>160
Fluticasone furoate (DPI)	100	NA	200	NA	NA	NA
Fluticasone propionate (DPI)	100-250	>250-500	>500	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-250	>250-500	>500	100-200	>200-500	>500
Mometasone furoate	110-220	>220-440	>440	110	≥220-<440	≥440
Triamcinolone acetonide	400-1000	>1000-2000	>2000	400-800	>800-1200	>1200

From GINA 2018 report[1]

*Ciclesonide HFA in adults and adolescents.

Abbreviations: DPI, dry powder inhaler; GINA, Global Initiative for Asthma; HFA, hydrofluoroalkane propellant; NA, not applicable.

report provides global guidance, it contains a few but significant differences from US guidance. Specifically, tiotropium (2.5 μg once daily) is approved for patients ≥6 years old[37] in the United States; however, it is recommended for patients ≥12 years old (mostly as 5 μg once daily) in the GINA treatment algorithm.[1]

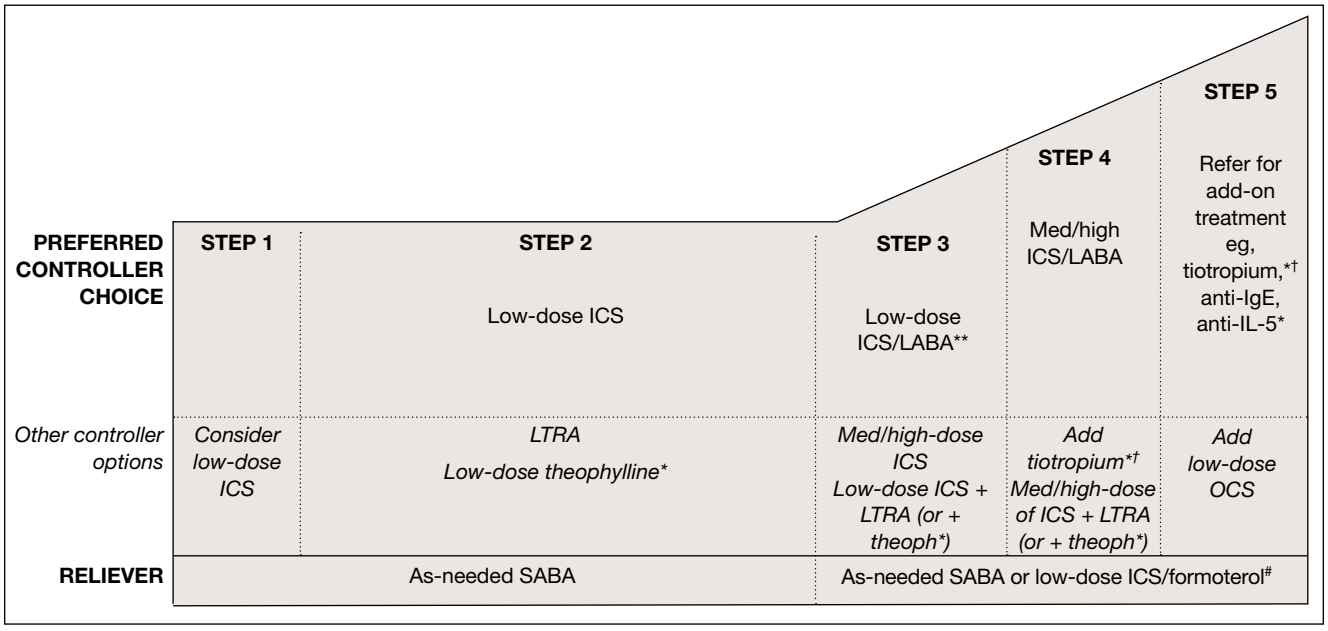
Sustained step-up (uncontrolled asthma), short-term step-up (during viral infections or seasonal allergen exposure), and day-to-day adjustments (as-needed doses of ICS±LABA±SABA, according to symptoms) may be needed for optimal asthma control.[1,38] For sustained step-up, medications should be added in a stepwise manner in patients with uncontrolled asthma despite 2 to 3 months of controller treatment.[39] Before stepping up, a detailed review of possible reasons for lack of control should be conducted to ensure correctness of diagnosis, correct use of inhalers, avoidance of triggers, compliance with pharmacologic and nonpharmacologic treatments, and treatment of comorbidities. Stepping therapy down in patients with well-controlled stable asthma should be considered to achieve optimal treatment with minimal side effects.

In the absence of up-to-date, clinically relevant US guidelines, we will consider the recommendations included in GINA 2018. Patients with intermittent asthma are included in **STEP 1**, where as-needed SABAs are recommended as reliever medication; low-dose ICS can be considered, especially when SABA monotherapy is insufficient. However, asthma is a chronic disease, and SABAs have limited application in managing chronic airway inflammation. This detail is relevant because, even in later treatment steps, patients often tend to increase SABA use rather than adding a controller medication as disease progresses, probably because of a misguided precedent set by the step 1 treatment.[40] Other reasons such as lack of education and awareness about treatment goals, higher cost of controller medications, poor compliance, problems with access to health care, distrust of healthcare providers, or misguided advice from relatives who confuse treatment of COPD with that of asthma may account for this behavior. For children with intermittent, viral-induced wheeze and no interval symptoms in whom SABAs are insufficient, as-needed ICS may be considered when the physician is confident of adherence.[1] Use of ICS/LABA intermittently as an alternative treatment option is being evaluated in the SYmbicort Given as needed in Mild Asthma (SYGMA) trials, wherein the efficacy and safety of as-needed budesonide/formoterol in patients with mild asthma are being assessed.[41]

Low-dose ICS is the preferred controller for patients with persistent, mild symptoms (**STEP 2**) because ICSs not only alleviate asthma symptoms but also reduce the risk of exacerbations, hospitalizations, and death. The dose can be stepped up to medium or high levels, as needed, at subsequent treatment steps.

The preferred step-up treatment for patients with uncontrolled asthma despite step 2 treatments is low-dose ICS/LABA (**STEP 3**). In children aged 6 to 11 years, increasing the ICS dose to medium levels is preferred over ICS/LABA. Alternative options in steps 2 and 3 are LTRAs or theophylline with low-dose ICS; however, theophylline is contraindicated in children <12 years old. Safety concerns associated with ICS/LABA use are alleviated and ICS/LABA use at step 3 is supported by results of 4 large, clinical safety trials (three conducted in adolescents/adults[42-44] and one in 4-11–year–olds[45]).

FIGURE 3 **Stepwise approach to control symptoms and minimize future risk[1]**



From GINA 2018 report[1]

Abbreviations: GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; med, medium; OCS, oral corticosteroid; SABA, short-acting β_2-agonist; theoph, theophylline.

*Not for children <12 years.

**For children 6-11 years, the preferred step 3 treatment is medium-dose ICS.

#Low-dose ICS/formoterol is the reliever medication for patients prescribed low-dose budesonide/formoterol or low-dose beclometasone/formoterol maintenance and reliever therapy.

†Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. Note: tiotropium is indicated for patients ≥6 years old in the United States.

These trials included >40,000 patients and results showed that, compared with ICS monotherapy, ICS/LABA did not significantly increase risk of serious asthma-related events[42-45] and significantly reduced exacerbation risk.[42-44]

Medium-dose ICS/LABA combination is the preferred step-up treatment at **STEP 4.** Alternative options are tiotropium (LAMA), LTRAs, or theophylline and high-dose ICS on a trial basis. If asthma remains uncontrolled, patients should be referred to a specialist, who may consider add-on tiotropium or biologics (**STEP 5**).

Per the GINA 2018 report, sublingual immunotherapy can be considered for house dust mite–sensitive adults with allergic rhinitis who have exacerbations despite ICS and have spirometry findings of FEV_1 >70% predicted. Allergen immunotherapy is the only disease-modifying therapy for asthma.[46] However, it is absolutely contraindicated in poorly controlled or uncontrolled asthma, but not contraindicated in well-controlled asthma, regardless of severity.[47]

Referral to a specialist or severe asthma center (if available) should be made if confirming diagnosis is difficult, occupational asthma is suspected, asthma remains uncontrolled or difficult to manage after long-term ICS/LABA treatment, any risk factors for asthma-related deaths are present (eg, prior near-fatal asthma attack, anaphylaxis, or confirmed food allergy), or evidence or risk of significant treatment side effects exists.[1] Before referral, PCP evaluations can include review of medication adherence, inhaler technique, and comorbidities; serial spirometry; chest X-ray; IgE levels; and eosinophil counts.

Assessment of asthma control

Because asthma is a variable disease, regular assessment of asthma control after treatment initiation is required, and adjustments to the maintenance treatment and asthma action plans should be made, as needed. However, the "definition" of asthma control, although similar in some respects, varies across guidelines (**FIGURE 1C**),[1,6,36,48] introducing another challenging aspect to asthma management.

CONCLUSIONS

The etiology, presentation, and progression of asthma vary across age groups; therefore, age-related factors should be

considered in the diagnosis and management of asthma. Nonpharmacologic and pharmacologic approaches form cornerstones of long-term asthma management. For pharmacologic management, controller medications should be added in a stepwise manner. Further, stepping down treatment should be attempted in patients with well-controlled, stable asthma to achieve optimal treatment with minimal side effects. Referral to a specialist or severe asthma center is warranted for patients with difficult-to-confirm diagnosis, uncontrolled asthma despite long-term treatment, risk factors for asthma-related deaths, and occupational asthma. ●

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Confronting the Challenges of Severe Asthma

Erwin W. Gelfand, MD; Michael E. Wechsler, MD

INTRODUCTION

Assessment and management of severe asthma can be challenging and should be tailored to individual patient characteristics. The estimated global prevalence of severe asthma, also referred to as difficult, therapy-resistant, or refractory asthma,[1] is 5% to 10%.[2] Even after ruling out alternative diagnoses and ensuring treatment of comorbidities, limiting trigger factors, and verifying compliance, patients with severe asthma can still experience poor asthma control, exacerbations requiring hospitalization, or treatment escalation despite high-intensity therapy.[1] Alternatively, many of these patients can maintain adequate control only when taking systemic corticosteroids. In 2014, an International Task Force supported by the European Respiratory Society and American Thoracic Society defined severe asthma in patients aged 6 years or older as asthma that required treatment with medications recommended for Global Initiative for Asthma (GINA) steps 4 and 5 (high-dose inhaled corticosteroids [ICSs] and long-acting β_2-agonists [LABAs] or leukotriene receptor antagonists [LTRAs]/theophylline) during the previous year, or treatment with systemic corticosteroids for at least 50% of the previous year to prevent asthma from becoming uncontrolled, or asthma that remains uncontrolled despite this therapy.[3] In a recent review, a panel of experts defined severe asthma as asthma requiring high-dose ICS plus a LABA and/or additional controller medication or requiring oral corticosteroids to attain asthma control, or asthma that remains uncontrolled despite such therapy and despite adequate adherence.[4]

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DISCLOSURES

Dr. Gelfand discloses that he has no real or apparent conflicts of interest to report.

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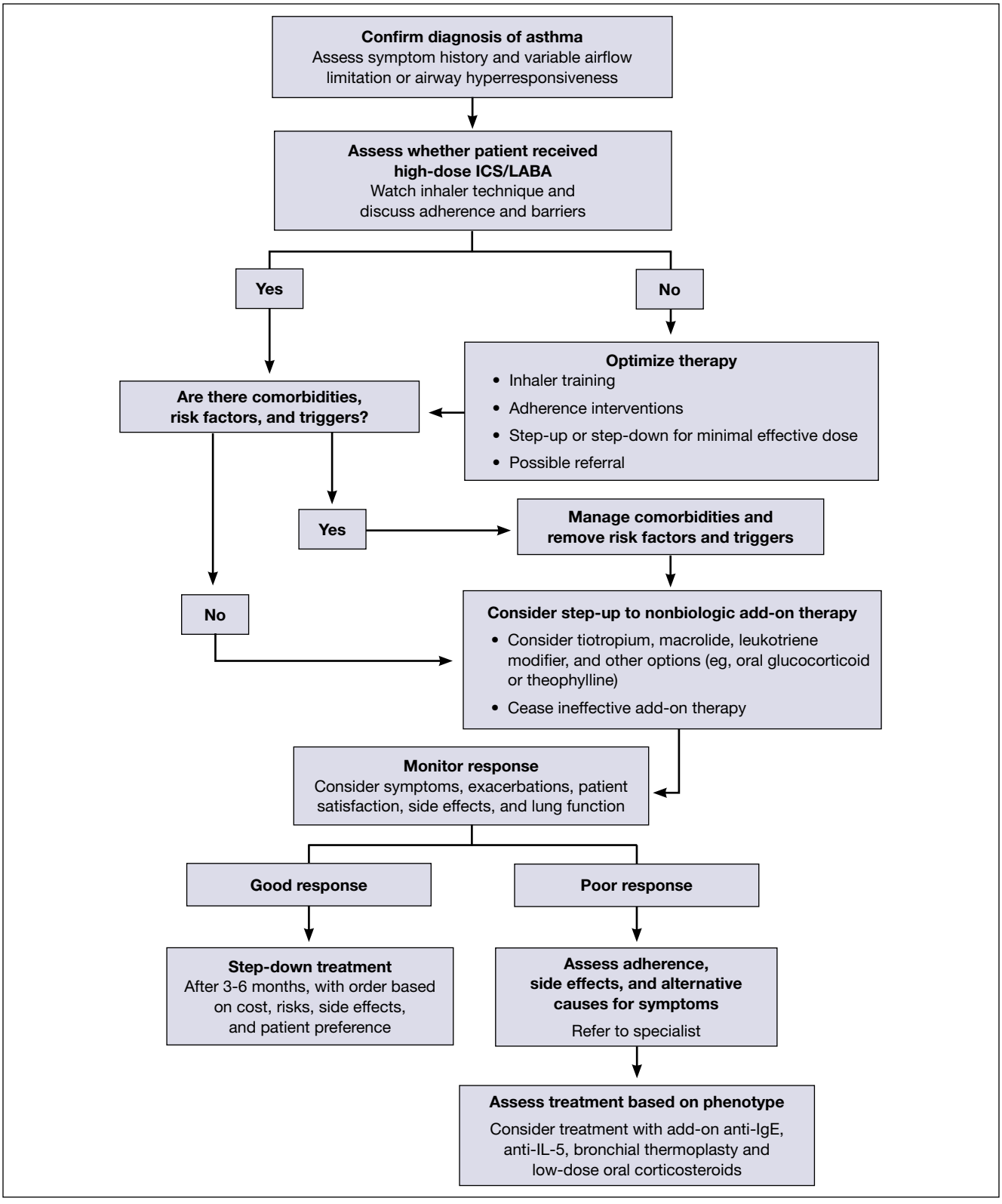
DIAGNOSIS AND MANAGEMENT OF SEVERE ASTHMA

For patients with persistent asthma symptoms and exacerbations, distinguishing severe asthma from asthma that is uncontrolled because of inconsistent patient behavior or other factors is important (**FIGURE 1**).[5,6] Persistent uncontrolled asthma is generally synonymous with severe asthma after common issues such as alternative diagnoses, incorrect inhaler use, poor medication adherence, presence of risk factors and/or comorbidities, and exposure to trigger factors (eg, sensitizing agents or irritants) have been identified and addressed. A controversial concern is the possible association of uncontrolled asthma with vitamin D deficiency. Evidence for the benefit of vitamin D supplementation in individuals with severe asthma was not seen in a large National Institutes of Health (NIH)-supported trial in adults.[7] Early intervention in young children or pregnant mothers may have some protective effects.[8,9] Referral to a specialist or severe asthma clinic should occur when asthma remains uncontrolled even after treatment with ICS/LABA for 3 to 6 months and sooner than 6 months when asthma is severe and difficult to manage.[5]

Asthma heterogeneity contributes to the complexity of its management. Asthma comprises diverse clinical phenotypes classified by cluster analyses, an approach that groups individuals with similar clinically observable and physiological characteristics.[10-12] Some commonly identified phenotypes include allergic, nonallergic, and late-onset asthma; asthma with fixed airflow limitation; and asthma associated with obesity.[5] Some proposed subtypes include aspirin-sensitive asthma, allergic bronchopulmonary mycosis, and severe late-onset asthma.[13] In contrast to the cluster approach, asthma endotypes link specific pathophysiological

FIGURE 1 **Algorithm to diagnose severe asthma**



Abbreviations: ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; LABA, long-acting β_2 -agonist.

Adapted from: Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med*. 2017;377(10):965-976.

mechanisms or pathways to a disease subtype.[12] For instance, interleukin (IL)-5- or IL-17-mediated asthma may be considered to be specific asthma endotypes. Asthma phenotypes may be present in more than one endotype, and endotypes may comprise more than one phenotype.[12,13] Furthermore, different endotypes may be present in the same patient at different times in response to different exposures, underscoring the complexity of a disease that is not stable in its origins. Despite advances in understanding asthma phenotypes and endotypes, these classifications are still evolving.[14]

Adding to the complexity, response to specific therapy may also be determined by underlying pathophysiologic or molecular pathways, asthma triggers, and genetics. Given that triggers vary over time, mechanistically, asthma is not a stable disease. For example, type 2-low and type 2-high endotypes are based on the presence of low or high levels of specific cytokines (IL-4, IL-5, and IL-13) that may be derived from Th2 cells, ILC2 (innate lymphoid) cells, or other type 2 cells. Patients with the type 2-high endotype are more responsive to ICSs, with greater improvement in lung function, than patients with the type 2-low endotype.[15] Similarly, whereas asthma triggered by allergens is generally responsive to steroids, asthma caused by other triggers (eg, viruses or cigarette smoke) is often less responsive.[16] Likewise, obese patients are generally less responsive to steroids.[17] A better understanding of phenotypes, endotypes, and underlying pathophysiology will enable better individualized treatment of severe asthma.

According to GINA recommendations, therapeutic options for severe or uncontrolled asthma include optimization of ICS/LABA dosage, maintenance low-dose oral corticosteroid treatment, and add-on bronchodilator treatment with the long-acting muscarinic antagonist (LAMA) tiotropium. Furthermore, patients with specific asthma phenotypes and endotypes may be treated with an LTRA or biologics (anti-immunoglobulin E [anti-IgE] or anti-IL-5 agents).[5] When asthma remains uncontrolled despite optimized therapeutic regimens, bronchial thermoplasty (BT) may be considered.[5] The US Food and Drug Administration (FDA) approved BT for asthma in 2010,[18] tiotropium in 2015,[19] and several biologics over the last few years (ie, mepolizumab in 2015,[20] reslizumab in 2016,[21] and benralizumab in 2017[22]), all of which may be included in the next iteration of the National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP) guidelines, which were last published in 2007.[23]

Before considering biologics, tests based on physiology or biomarkers—including in vitro reactivity to a perennial aeroallergen or skin tests, peripheral blood eosinophil counts, exhaled nitric oxide, or reversibility in pulmonary function testing (indicating reversible obstruction)—may aid in treatment decisions.[24] Primary care providers working in concert with pulmonary and allergy specialists can provide guidance for treatment choices. Given their costs, biologics should not be started without specialist input or without optimizing other adjunct therapies.

CLINICAL TRIAL EVIDENCE FOR ADD-ON ASTHMA TREATMENT OPTIONS

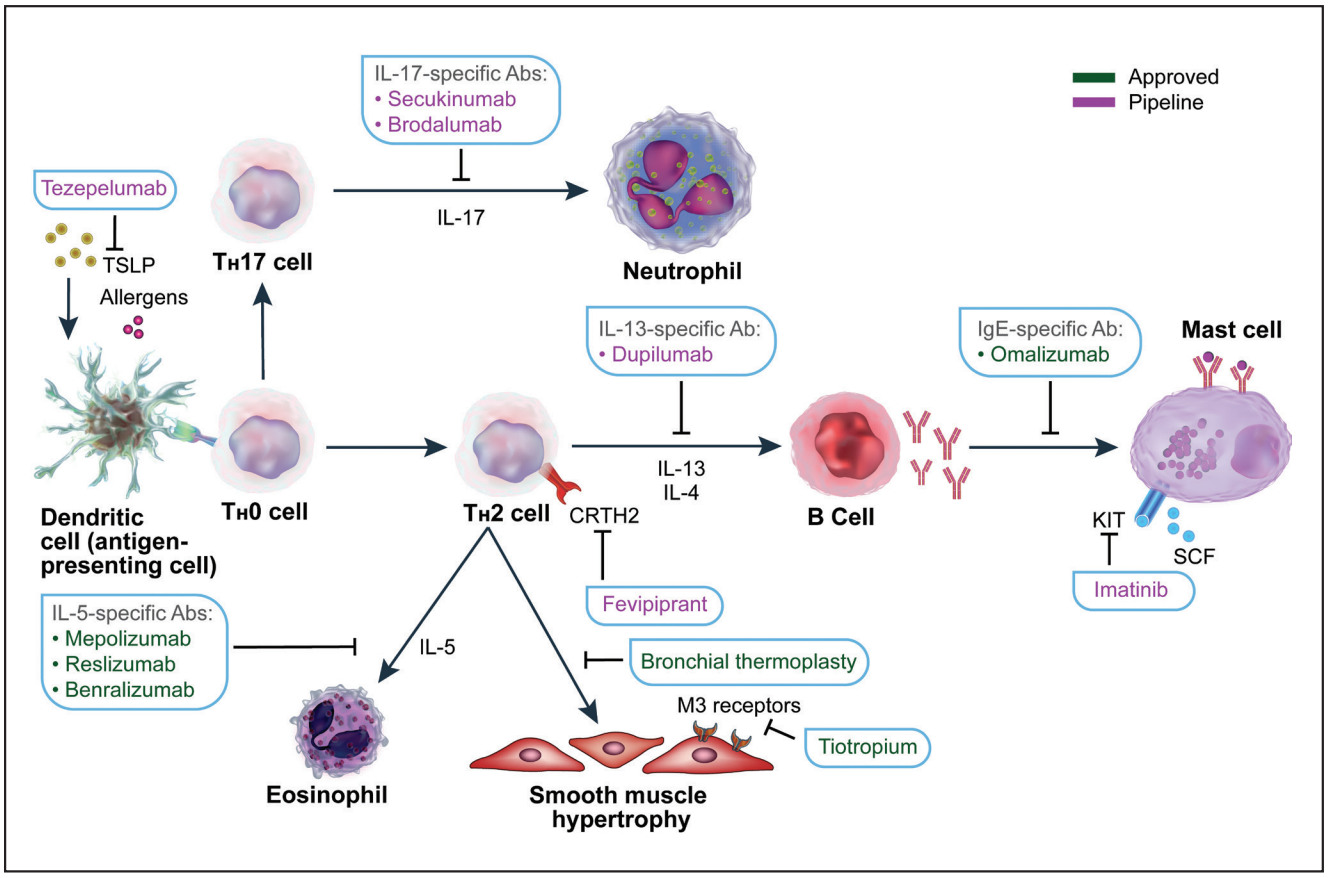
Pharmacologic therapies

For patients who are poorly controlled despite using ICS/LABA, add-on therapy should be considered. Newer FDA-approved pharmacologic (add-on tiotropium and biologics) and nonpharmacologic (BT) treatment options for severe, uncontrolled asthma have yielded variable benefits in patients. The add-on value and safety of tiotropium and biologics were demonstrated in various phase 3, randomized controlled trials (RCTs).[19] While biologics are approved for use in patients with severe persistent allergic (omalizumab)[25] or eosinophilic (mepolizumab,[20] reslizumab,[21] and benralizumab[22]) asthma, tiotropium is a bronchodilator that can be used regardless of asthma severity or phenotype/endotype.[19] The essence of individualized or personalized medicine is to understand underlying triggers and pathways to better assign treatment options to specific patients. Below we review currently approved add-on therapies, which are illustrated in **FIGURE 2**.

Tiotropium

Tiotropium bromide acts by blocking muscarinic receptor activity on lung smooth muscle cells. Once-daily, 2.5-µg dosing (2 puffs of 1.25 µg) is indicated for the long-term, once-daily maintenance treatment of asthma in patients aged 6 years and older in the United States[19] and is recommended as an add-on treatment option at GINA 2018 steps 4 and 5 for patients aged at least 12 years with exacerbation history.[5] Evidence from 2 replicate, phase 3 RCTs showed that once-daily tiotropium 5 µg for 48 weeks increased time to first severe exacerbation, reduced risk of exacerbation, and provided modest sustained bronchodilation versus placebo in adults (≥18 years) with poorly controlled asthma despite ICS/LABA treatment.[26] Similarly, in phase 3 RCTs of adolescents (12-17 years) and children (6-11 years) with severe symptomatic asthma, add-on tiotropium improved peak forced expiratory volume in 1 second within 3 hours after dosing ($FEV_{1[0\text{-}3h]}$) and trough forced expiratory volume in 1 second (FEV_1) compared with placebo.[27,28] Overall, adverse event (AE) incidence was comparable across treatment groups, and the most commonly reported AEs included nasopharyngitis, headache, bronchitis, and upper respiratory tract infection.[26]

FIGURE 2 **Mechanism of action of approved pharmacologic and nonpharmacologic therapies and biologics in development**



Abbreviations: Ab, antibody; CRTH2, receptor homologous molecule expressed on T helper 2 cells; IgE, immunoglobulin E; IL, interleukin; KIT, tyrosine kinase receptor KIT; M3, muscarinic receptor 3; SCF, stem cell factor; TSLP, thymic stromal lymphopoietin.

Omalizumab

Omalizumab, an anti-IgE monoclonal antibody, is recommended for patients at least 6 years of age with allergic asthma, as determined by in vitro reactivity to a perennial aeroallergen or positive skin test responses, and symptoms uncontrolled on GINA step 4 treatment.[5,25] IgE levels are often elevated in these patients. Evidence from several 24- to 52-week, phase 3 RCTs support the efficacy and safety of subcutaneous omalizumab in patients at least 6 years of age. In patients aged 12 years and older, omalizumab (add-on to ICS or ICS/LABA or ICS/LABA plus other controller medications) reduced asthma exacerbation rates, the proportion of patients experiencing an exacerbation, ICS dose, requirements for rescue medication, and emergency visits, and improved asthma symptoms and Asthma Quality of Life Questionnaire (AQLQ) scores compared with placebo.[29-32] Compared with standard care alone, add-on omalizumab reduced asthma exacerbation rates and rescue medication use and improved FEV_1 in patients with poorly controlled, moderate-to-severe allergic asthma.[33] Similarly, in children aged 6 to 12 years, add-on omalizumab reduced clinically significant asthma exacerbation rates and ICS dose, and improved Investigator's Global Evaluation of Treatment Effectiveness (IGETE) scores compared with placebo.[34,35] Furthermore, results of the ICATA study of inner-city children, adolescents, and young adults (age range 6-20 years) with persistent allergic asthma showed that omalizumab reduced the number of days with asthma symptoms and the proportion of patients with one or more exacerbations versus placebo.[36] In a Cochrane review involving 6382 adults and children, omalizumab was effective to some extent in reducing asthma exacerbations and hospitalizations, and eliminated ICS use completely in some patients recieving ICS compared with placebo.[37] In the PROSE study of children with allergic asthma, omalizumab

decreased rhinovirus infection duration by 1.2 days and the frequency of rhinovirus illnesses by 36%.[38] However, these clinical benefits need to be balanced with the need for subcutaneous administration every 2 to 4 weeks and high drug costs.[39] Additionally, improved asthma control with omalizumab, as indicated by change from baseline in Asthma Control Test total and IGETE scores, was not significantly different from placebo in a phase 4 RCT.[40] Further, in a systematic review of 6 long-term (≥52 weeks) studies, although omalizumab improved quality of life (QoL) and enabled some patients to completely withdraw ICS, no significant differences were detected in asthma exacerbation incidence versus placebo.[41] Overall, AE incidence was similar with omalizumab and placebo in adults, adolescents, and children across studies.[32,40,41] Most commonly reported AEs were asthma, upper or lower respiratory tract infection, nasopharyngitis, sinusitis, bronchitis, and headache.[31,40]

Anti-IL-5 therapies

Mepolizumab

Mepolizumab is an anti-IL-5 monoclonal antibody indicated for add-on maintenance treatment of patients at least 12 years of age with severe eosinophilic asthma uncontrolled on GINA step 4 treatment.[5] Evidence from 2 large, 32- to 52-week, phase 3 RCTs supported the efficacy and safety of subcutaneous or intravenous mepolizumab in some patients aged 12 years or older. In the MENSA study, mepolizumab reduced asthma exacerbation risk versus placebo.[42] In the DREAM study, different mepolizumab doses reduced asthma exacerbation rates compared with placebo.[43] Moreover, asthma control markers such as FEV_1 and St. George's Respiratory Questionnaire (SGRQ)[44] and Asthma Control Questionnaire (ACQ)-5[45] scores improved versus placebo.[42] Post hoc analysis of data from these studies showed that with mepolizumab, exacerbation rates decreased in patients with increased baseline blood eosinophil counts.[46] Subcutaneous mepolizumab also improved health-related QoL (HR-QoL), with improvements in SGRQ total score versus placebo in another phase 3b RCT (MUSCA).[47] Across studies, overall AE frequency was similar with mepolizumab and placebo.[42,43] Headache and nasopharyngitis were the most commonly reported AEs.[42,43,47]

Although the authors of a Cochrane review of 8 studies involving 1707 adults and children suggested that mepolizumab treatment could reduce asthma exacerbations, but only in some patients, and lead to improved HR-QoL,[48] they suggested additional data are needed to optimize treatment. Of note, the percentage reduction in exacerbation rates, although seemingly significant, may be biologically less important when exacerbation rates still hover around 1 per year.

Reslizumab

Reslizumab is another anti-IL-5 monoclonal antibody indicated for add-on maintenance treatment of adults (≥18 years) with severe eosinophilic asthma uncontrolled on GINA step 4 treatment.[21] Results of four 16- to 52-week, phase 3 RCTs support the efficacy and safety of intravenous reslizumab in adults.[49-52] In patients with baseline eosinophils of at least 400 cells/μL, reslizumab improved FEV_1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$), and AQLQ and ACQ scores, and reduced both rescue short-acting beta agonist use and asthma exacerbation frequency compared with placebo.[49-51] In a post hoc analysis, reductions in asthma exacerbations and improvements in lung function were greater with reslizumab than placebo in patients with late- vs early-onset eosinophilic asthma.[52] In a systematic review and meta-analysis of 5 studies, reslizumab reduced but did not eliminate asthma exacerbations and improved FEV_1, ACQ scores, and blood eosinophil counts versus placebo.[53] Overall, reslizumab was well tolerated, with similar or fewer AEs than placebo.[49,51,52] Most commonly reported AEs were worsening of asthma, headache, nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, and headache.[50]

Benralizumab

Benralizumab, the most recently FDA-approved monoclonal antibody, targets the IL-5 receptor and is indicated for add-on maintenance treatment of patients 12 years of age or older with severe, uncontrolled eosinophilic asthma (GINA step 5).[5,22] After the first 3 monthly subcutaneous doses, benralizumab may be administered every 8 weeks. Results of four 12- to 56-week phase 3 RCTs showed that subcutaneous benralizumab reduced annual asthma exacerbation rates, sputum and blood eosinophil counts, ACQ-6 scores, and corticosteroid dose, and improved prebronchodilator FEV_1.[54-57] AE incidence was similar in benralizumab and placebo groups; the most commonly reported AEs were worsening asthma, nasopharyngitis, and upper respiratory tract infection.

Although anti-IL-5 therapies are effective in many patients with eosinophilic asthma, multiple eosinophil-independent asthma mechanisms may contribute to a patient's condition. Further, tissue eosinophilia may be persistent in the absence of blood eosinophilia.[58] While this persistence may be due to inadequate dosing in some cases, a key factor determining whether a patient may benefit from any of the IL-5-targeted pathways is how best to assess persistent eosinophilia despite corticosteroid use and its importance. Frequently, persistent eosinophilia represents lung and airway eosinophilia, which requires specialized techniques (bronchoscopy or induced sputum) unavailable in some settings.

Authors of a Cochrane review of 13 studies on mepolizumab, reslizumab, and benralizumab versus placebo in 6000 adults and children with severe eosinophilic asthma and poor control concluded that these drugs can benefit some patients by reducing asthma exacerbation rates, but to varying degrees.[59] Further research is needed to help identify the "right" patient for these agents and how to choose among these agents.

Biologics in development

Several biologics targeting different biomarkers such as anti-IL-4/IL-13 (dupilumab),[60,61] IL-17 (brodalumab and secukinumab [AIN457]),[62] tyrosine kinase KIT (imatinib),[63] thymic stromal lymphopoietin (TSLP; tezepelumab),[64] and CRTH2 (fevipiprant)[65] are in development. Efficacy for some of these agents was demonstrated in phase 2 and 3 trials.[60,61,63] Of note, these therapies may target broader groups of patients than anti-IL-5 agents. For example, anti-IL-4/IL-13 therapy targets eosinophilic asthma and broader type 2 inflammation. Alternatively, blocking TSLP reduces exacerbation rates, seemingly independent of type 2 inflammatory status.[64] A significant unmet need is manifest by patients with non-type 2 severe asthma, for whom viable treatment options are lacking.

Nonpharmacologic therapy

Bronchial thermoplasty

BT may be considered at GINA step 5 for adults whose severe asthma remains uncontrolled despite optimized pharmacotherapy.[5] BT involves delivery of controlled thermal energy to airway walls with the help of the Alair Bronchial Thermoplasty System. Airway smooth muscle thickness, which could lead to chronic airway obstruction, is reduced and airway wall nerves, which could affect airway hyperresponsiveness, are ablated. Results of three 12- to 52-week RCTs, including the AIR2 trial, support BT use in select patients with severe asthma.[66-68] Patients who underwent BT had improved peak expiratory flow, increased symptom-free days, improved AQLQ and ACQ scores, and reduced exacerbations, rescue medication use, and days lost from work compared with controls. However, during treatment, more patients in the BT group than the control group had respiratory symptoms or worsening of asthma and respiratory tract infection, leading to recommendations for prophylactic corticosteroid use during the periprocedural period. In a follow-up of the AIR2 trial, reductions in exacerbation rates and emergency room visits after BT were maintained through 5 years.[69] Authors of a Cochrane review of the 3 RCTs concluded that BT improves QoL and reduces asthma exacerbation, but may not significantly improve asthma control scores, and recommended further studies to better understand the role of BT in different asthma phenotypes.[70]

REAL-WORLD EVIDENCE

Real-world studies are being conducted to better understand severe asthma, including its phenotypes, endotypes, and associated biomarkers.[71,72] A goal of the NIH/NHLBI-sponsored Severe Asthma Research Program was to better classify asthma types so that treatments specific to each subtype could be developed.[71] Several clinical severe asthma phenotypes in adults and children have been identified[72]; however, many questions remain unanswered, and underlying mechanisms accounting for different phenotypes remain undefined. In the ongoing, noninterventional, multicenter real-world study in severe asthma (ARIETTA), the utility of markers as clinically validated biomarkers over time are being assessed.[73]

Although new options are available for treatment of patients with severe asthma, evidence of their effectiveness in real-world clinical practice is limited, except for omalizumab.[74,75] Authors of a meta-analysis of 25 real-world studies involving 9213 adult and adolescent patients with allergic asthma concluded that add-on omalizumab resulted in good-to-excellent responses in a proportion of patients, with improvements in FEV_1 and AQLQ and Asthma Control Test scores, and reduced ICS use, exacerbations, and hospitalizations.[76] Although omalizumab is generally considered safe, higher incidences of cardiovascular and cerebrovascular events were observed in omalizumab- than non–omalizumab-treated patients aged 12 years and older with moderate-to-severe allergic asthma in a postmarketing observational cohort study.[77] Finally, in a prospective, open-label, observational postmarketing study of bronchial thermoplasty, the proportion of patients with severe exacerbations, emergency department visits, and hospitalizations significantly decreased, corroborating results from the AIR2 trial.[78]

Given the complexity of asthma diagnosis and treatment, more real-world studies are needed to understand the effect of approved therapies and how responses to an ever-changing environment can be best managed.

CONCLUSIONS AND RECOMMENDATIONS

Ensuring proper diagnosis of severe asthma, considering phenotypes and endotypes, and understanding advantages and disadvantages of available therapies are essential before an asthma treatment plan can be developed. While some newer asthma therapies are included in the GINA 2018 report, recommendations are not phenotype or endotype specific. A goal of future guideline development will be to individualize treatment recommendations based on patient phenotype or

endotype. Studies to better understand severe asthma and new therapies based on biomarkers are underway. For many patients with severe asthma, current guidelines are simply introductory and do not address the need for expertise, consultation, or diagnostic interventions. Careful scrutiny of published trials is required to assess true cost–benefit outcomes. Furthermore, the pace of new tools and therapeutics precludes guidelines from being up to date. Therefore, diagnosis and management of severe asthma remains a challenge, and collaboration between primary care providers and specialists is required to maximize improved patient outcomes. ●

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COPD Management in the Primary Care Setting

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States[1] and is predicted to rise from the fifth to the third leading cause of death worldwide by 2030.[2] In the United States, COPD is more common among women than men.[3] COPD is multifactorial in development and presentation. Etiologic causes include genetic and environmental factors (eg, occupational and environmental exposures), aging, and infections. Although cigarette smoking is a major risk factor for COPD, more than 20% of COPD patients are non-smokers.[3-5] Clinically, COPD is associated with substantial systemic morbidities[6] that impact disease severity and treatment outcomes. Primary care providers (PCPs) usually are the first medical contact for patients with symptoms of COPD and, therefore, play a vital role in diagnosis and care. Despite readily identifiable risk factors and national and international diagnosis and treatment guidelines,[6-8] COPD remains underdiagnosed and suboptimally managed,[9-15] contributing to its socioeconomic burden. In fact, COPD was undiagnosed in 81.4% of cases in a large-scale, international study[16] and in more than 70% of cases in a US-based study.[13] In this review, we discuss the role of PCPs in the diagnosis, assessment, monitoring, and management of patients with COPD.

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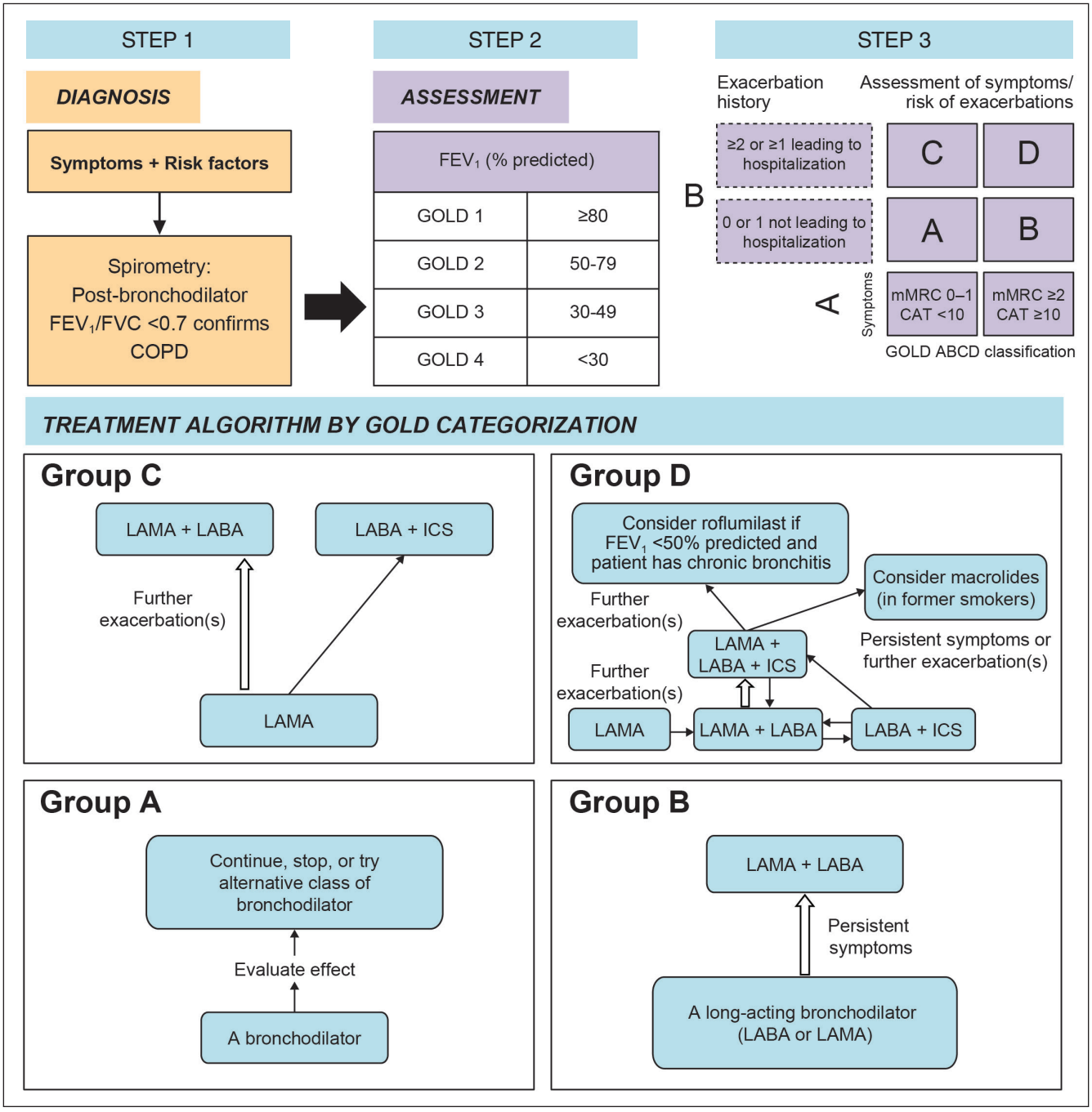
STEP 1: DIAGNOSIS OF COPD

Classic symptoms of COPD include dyspnea, cough, and sputum production as a result of airflow limitation secondary to airway narrowing and/or alveolar destruction. Smoking and exposure to occupational or environmental pollutants in individuals aged ≥40 years with respiratory symptoms should alert physicians to consider a COPD evaluation.[6,17] In some patients with underlying COPD, symptoms could be subtle (eg, activity limitation or generalized fatigue triggered by exertion). Therefore, clinical assessment should include detailed questioning about onset and pattern of respiratory symptoms, activity, smoking status, family history of COPD, and history of exacerbations.[4]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 report and other guidelines,[6-8] COPD diagnosis must be confirmed with spirometry assessment. Indeed, spirometry should be performed in all patients with suspected COPD (**FIGURE: STEP 1**). Spirometry, a simple, noninvasive test that can be ordered as an outpatient procedure when unavailable in primary care offices, can confirm COPD and indicate the severity of airflow limitation.[6] Use of spirometry in primary care settings facilitates early and accurate diagnosis of COPD[18,19] by measuring forced expiratory volume in 1 second (FEV_1)—the amount of air (in liters) forcibly exhaled in the first second after full inspiration—and forced vital capacity (FVC)—the total amount of air (in liters) exhaled during

FIGURE **Composite plan for diagnosis, assessment, and treatment of patients with COPD**



Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council.

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a forced expiratory maneuver. A post-bronchodilator FEV_1/FVC ratio <0.7 or the lower limit of normal indicates airflow obstruction.[6]

Several patient and PCP factors lead to delayed COPD diagnosis; underuse of spirometry is one of the largest contributors to underdiagnosis.[20-22] Reasons for underuse

include skepticism about the utility of spirometry in diagnosing COPD or its impact on outcomes,[23] difficulty in interpreting spirometry findings,[20] and lack of time, resources, or training.[24] Other potential causes of underdiagnosis include COPD in nonsmokers, general lack of COPD awareness, or lack of COPD guideline use. In a US-based survey, only 54% of participating PCPs were aware of any professional COPD guideline.[25]

COPD diagnosis can be challenging because clinical presentation can vary, including a range of airway obstruction severity and large spectrum of extra-pulmonary symptoms. "Frequent exacerbators"—patients who have ≥2 exacerbations per year separated by ≥4 weeks after the end of treatment for the previous exacerbation—are at high risk of morbidity and mortality, and exhibit accelerated decline in lung function, physical activity, and quality of life (QoL).[26] Therefore, distinguishing frequent exacerbators from infrequent or non-exacerbators is necessary to initiate appropriate therapeutic interventions.[6]

STEP 2: ASSESSMENT OF AIRFLOW LIMITATION

After COPD diagnosis is confirmed, assess severity of airflow limitation with spirometry to determine FEV_1 percentage of predicted normal, which can be used to categorize patients as GOLD spirometric stage 1, 2, 3, or 4[6] (**FIGURE: STEP 2**). Spirometry assessment is crucial for diagnosing COPD and can be helpful for determining the need for invasive interventions. However, spirometry values are not part of the classification scheme that defines treatment decisions because of the limited correlation between spirometry classification and functional ability, QoL, and future exacerbation risk. Treatment decisions are based on symptoms and exacerbation history.[6]

STEP 3: ASSESSMENT OF COPD BURDEN: SYMPTOMS AND EXACERBATIONS

Recording a thorough history of patient's symptoms, functional abilities and limitations, and past exacerbation episodes is important. Patient-administered, disease-specific, validated health status questionnaires can be used to assess symptoms. The most commonly used questionnaires are the COPD Assessment Test[6] (CAT; an 8-item questionnaire assessing the impact of cough, sputum, dyspnea, and chest tightness on health status) and the COPD Control Questionnaire[6] (CCQ; a 10-item, 3-domain questionnaire assessing symptoms, functional state, and mental state). In GOLD 2018, the CAT and the modified Medical Research Council (mMRC) questionnaire are recommended for assessing COPD symptoms, with CAT scores of ≥10 and mMRC scores of ≥2 representing high symptom burden (**FIGURE: STEP 3A**).[6]

Exacerbations are episodes of worsening COPD symptoms that last for 7 to 10 days beyond normal day-to-day variability and require changes in treatment (eg, antibiotics or systemic steroids), emergency room (ER) visits, or hospital admissions.[27] Exacerbations impede QoL, impair health status, and negatively influence COPD prognosis, and could be triggered by viral and bacterial infections, environmental factors such as pollutants, or changes in temperature.[6]

Determining patients' history of COPD exacerbations (**FIGURE: STEP 3B**) and addressing corresponding risk factors are critical steps in predicting the likely impact of COPD and risk of future exacerbations. Before GOLD 2017, spirometry was included in the ABCD classification tool. In the refined assessment, which began with GOLD 2017, spirometry is no longer used for classification. Currently the classification grid uses only symptoms and history of exacerbations to determine GOLD grade, which in turn determines treatment recommendations. Symptom severity (on the X-axis) and history of exacerbations (on the Y-axis) are used to classify COPD into 1 of 4 groups (GOLD A-D) (**FIGURE**).[6]

COPD shares many risk factors with other chronic diseases, and often patients with COPD have comorbid conditions,[28] most commonly metabolic syndromes[29-31]; mood and anxiety disorders[32,33]; cardiovascular disease[34]; lung cancer[35]; eye disorders such as glaucoma and cataracts[36]; excessive bone loss/risk of fractures[37,38]; and muscle wasting.[39,40] Identifying and addressing comorbidities are critical because they impact pulmonary rehabilitation outcomes[41] and mortality[42] and could confound prompt recognition of COPD exacerbations.

STEP 4: MANAGEMENT OF COPD

Goals of COPD management are to relieve symptoms, improve exercise tolerance and QoL, and reduce exacerbation risk and severity.[6] Pharmacologic and nonpharmacologic options for COPD are important. Smoking cessation reduces exacerbations, slows lung function decline, and improves survival among patients with COPD.[43–45] At every visit, all smokers regardless of COPD status should be encouraged and assisted to quit smoking. Employ the 5 As (ask, advise, assess, assist, and arrange) as a counseling strategy,[46] and consider pharmacotherapy such as nicotine replacement therapies, bupropion, nortriptyline, and varenicline[47] to help patients quit.

Pharmacotherapy

COPD medications can be broadly categorized into 2 types: bronchodilators and anti-inflammatory agents. Bronchodilators, which improve lung function, decrease hyperinflation, and improve exercise performance by decreasing airway smooth muscle tone, are the cornerstone of COPD treatment and include short- and long-acting β_2-agonists (SABAs [eg,

TABLE Medications commonly used for treating COPD

Class	Drug (brand name)
Short-acting β_2-agonists (SABAs)	Albuterol/salbutamol (Ventolin)
	Levalbuterol (Xopenex)
Long-acting β_2-agonists (LABAs)	Formoterol (Foradil)
	Indacaterol (Arcapta)
	Olodaterol (Striverdi)
	Salmeterol (Serevent)
Short-acting muscarinic antagonists (SAMAs)	Ipratropium bromide (Atrovent)
	Oxitropium bromide (Oxivent)
Long-acting muscarinic antagonists (LAMAs)	Aclidinium bromide (Tudorza)
	Tiotropium (Spiriva)
	Umeclidinium (Incruse Ellipta)
Combination: SABA + anticholinergic agents	Fenoterol/ipratropium (Berodual)
	Albuterol/ipratropium (Combivent)
Combination: LABA + LAMAs	Formoterol/aclidinium (Duaklir, Brimica)
	Indacaterol/glycopyrronium (Ultibro Breezhaler)
	Vilanterol/umeclidinium (Anoro Ellipta)
	Glycopyrrolate/formoterol (Bevespi)
	Olodaterol/tiotropium (Stiolto Respimat)
Combination: LABA + inhaled corticosteroids (ICS)	Formoterol/budesonide (Symbicort)
	Formoterol/mometasone (Dulera)
	Salmeterol/fluticasone (Advair)
Methylxanthines	Theophylline (Theo-Dur, Theo-24)
Phosphodiesterase-4 inhibitor	Roflumilast (Daliresp)

Abbreviations: COPD, chronic obstructive pulmonary disease.

albuterol/salbutamol and levalbuterol] and LABAs [eg, formoterol, indacaterol, olodaterol, and salmeterol]), and short- and long-acting muscarinic antagonists (SAMAs [eg, ipratropium bromide] and LAMAs [eg, aclidinium, glycopyrronium bromide, umeclidinium, and tiotropium]). Additional medications include the anti-inflammatory class of drugs methylxanthines (eg, theophylline) and phosphodiesterase-4 inhibitors (eg, roflumilast).[6]

GOLD 2018 recommends a specific progression of pharmacologic therapy, with details on initiation and subsequent escalation and/or de-escalation based on COPD grade (ABCD) (**FIGURE**).[6] Grade A patients (few symptoms and no exacerbations or 1 exacerbation not leading to hospitalization) should be treated with short- or long-acting bronchodilators. If patients experience symptomatic benefits, treatment should continue or an alternative or additional bronchodilator class could be used (**TABLE**). Grade B patients (high symptom burden and no exacerbations or 1 exacerbation not leading to hospitalization) should be treated initially with a long-acting bronchodilator, which provides more sustained bronchodilation and symptom control than short-acting bronchodilators.[48,49] Although LAMAs provide a greater reduction of exacerbations than LABAs,[50,51] choice of LAMA should depend on the individual patient's response. Among patients with persistent breathlessness, a combination of bronchodilators is recommended, and in cases of severe breathlessness, a combination of bronchodilators could be employed, even as initial therapy. If adding a second bronchodilator alleviates symptoms, de-escalation to a single bronchodilator is recommended.[6] In Grade C patients (few symptoms but ≥2 exacerbations or ≥1 exacerbation leading to hospitalization), LAMA monotherapy is recommended initially. LAMAs are recommended over LABAs for Grade C patients because the former are more effective for decreasing exacerbations than the latter.[50,51] In patients with persistent exacerbations, escalation to a LABA/LAMA or LABA/inhaled corticosteroid (ICS) could be considered. LABA/LAMA combinations are recommended over LABA/ICS because, in some clinical studies, they led to greater bronchodilation and reduction of exacerbations. In addition, LABA/LAMA is considered safer because chronic ICS use is associated with an increased risk of community-acquired pneumonia.[52,53] For Grade D patients (high symptom burden and ≥2 exacerbations or ≥1 exacerbation leading to hospital admission), initial LABA/LAMA therapy is recommended. If patients on LABA/LAMA continue to experience exacerbations or remain symptomatic, escalation to triple therapy with LABA/LAMA/ICS is recommended after ensuring that the patient is using the inhalers correctly and is adhering to therapy. Alternatively, consider switching to a LABA/ICS.[49] If exacerbations persist despite triple therapy, roflumilast can be added in patients with an FEV_1 <50% predicted and chronic bronchitis, and a macrolide could be added in former smokers at risk of exacerbation.[6] Roflumilast/LABA/±ICS was effective in reducing exacerbations and improving lung function in patients with frequent exacerbations, severe disease, and chronic bronchitis.[54-56] LABA/ICS might be the first choice in some patients with a history and/or findings suggestive of asthma-COPD overlap. ICSs also could be considered in

patients with high blood eosinophil counts (>300 cells/μL), although there is no consensus on this approach.[6]

Potential interactions among different disease-specific treatments must be considered in patients with multiple comorbidities, and efforts should be made to minimize polypharmacy. According to GOLD 2018, comorbidities in patients with COPD should be treated per usual treatment standards.[6]

Treatment strategies for COPD exacerbations should minimize the negative impacts of exacerbations and prevent future events.[6] Recommended therapeutic options for patients with mild exacerbations are short-acting bronchodilators alone, while patients with moderate COPD exacerbations also should receive oral corticosteroids and/or antibiotics. Patients with severe exacerbations (eg, sudden worsening of resting dyspnea, high respiratory rate, or decreased oxygen saturation) should be referred for ER evaluation or hospitalization.

Nonpharmacologic Management

Nonpharmacologic approaches that complement pharmacotherapy (eg, exercise training, self-management education, nutritional support, influenza and pneumococcal vaccination, and oxygen therapy[57]) can promote self-efficacy, relieve symptoms, and improve QoL.[58] Additionally, serum vitamin D levels are thought to be negatively associated with risk and severity of COPD,[59] and limited evidence suggests that vitamin D supplementation could help decreasing the risk of moderate-to-severe exacerbations in patients with low baseline vitamin D levels.[60] Therefore, assessment of serum baseline vitamin D levels and correction of deficiency might be useful in reducing risk of COPD exacerbation. Moreover, given the prevalence of reduced bone mineral density in patients with COPD,[37,38] vitamin D supplementation might be beneficial for maintaining bone strength in these patients. Furthermore, pulmonary rehabilitation programs can help COPD patients manage dyspnea and fatigue.[61] Consider referral to a pulmonary specialist at key time points, especially if patients are symptomatic at diagnosis, at discharge after hospitalization for an exacerbation, and when symptoms are progressively deteriorating.[6] For patients with severe disease, surgical options include bullectomy (for patients with very severe illness and large upper lobe bullae), lung volume reduction surgery, or lung transplantation.

STEP 5: MONITORING

Monitor for several factors during each patient visit, including but not limited to symptoms, exacerbations, airflow limitations, and smoking status[6]; adherence to and effectiveness of the treatment plan; inhaler technique to ensure correct use and to determine if a change in delivery system is needed to fit the patient's needs; adverse effects[6]; and the therapeutic regimen, with specific attention to dosages of medications, response, and adjustment as needed when worsening or improvement in symptoms occur. Adjustment of the treatment regimen is important for appropriate and individualized treatment. In the past, recommendations provided in the GOLD report were only for treatment initiation. However, patients with COPD might experience persistent symptoms after initial therapy or resolution of some symptoms. Therefore, in addition to being aware of the appropriate therapeutic option for initiation of treatment, PCPs also must be cognizant of recommendations for treatment escalation when symptoms worsen and de-escalation when symptoms improve (**FIGURE: TREATMENT ALGORITHMS BY GOLD CATEGORIZATION**).

PARTNERSHIP BETWEEN PCPS AND PULMONOLOGISTS

PCPs might refer patients with severe disease to a pulmonologist, who could optimize medical treatment and make recommendations about the appropriateness of surgery or lung transplantation.[6] A close working relationship between PCPs and pulmonologists can enhance patient care and improve disease outcomes. Consider referral for patients at high risk for exacerbation, frequent exacerbators, and those who need further testing that is not available in the PCP setting or assessment for surgical interventions.

CONCLUSIONS

Effective treatment of COPD in primary care settings, which is crucial for successful outcomes, is highly dependent on accurate diagnosis, assessment, monitoring, and management of symptoms and associated comorbidities. Spirometry confirmation of COPD is the first step. Patients should be staged using spirometry and classified using the refined GOLD ABCD assessment tool, which is based on assessment of symptom burden and exacerbation risk, determines the burden of COPD, and helps guide treatment recommendations. Nonpharmacologic interventions, including smoking cessation and pulmonary rehabilitation, are important features of COPD management. Finally, regular follow-up of symptoms, functional status, and exacerbations are key components of long-term management of patients with COPD. ●

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Interpreting Recent Developments in COPD Treatments

Sanjay Sethi, MD; Mark T. Dransfield, MD

PHARMACOLOGIC CHOICES FOR COPD

Primary care providers (PCPs) play a critical role in diagnosing, managing, and treating patients with chronic obstructive pulmonary disease (COPD), which is encountered routinely in everyday clinical practice.[1] Pharmacologic therapy alleviates COPD symptoms, reduces exacerbation severity and frequency, and improves patients' health status and exercise endurance.[2] Various medications, including bronchodilators (β_2-agonists and muscarinic antagonists), inhaled corticosteroids (ICSs), methylxanthines, and phosphodiesterase-4 (PDE-4) inhibitors, are available for treating COPD in the United States. The choice of medication should be made based on symptom severity and exacerbation risk, ease of use, availability, cost, and clinical benefit versus risk of adverse events (AEs).[2]

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Bronchodilators—which can be short- or long-acting—help reduce airflow obstruction by causing bronchodilation, reducing hyperinflation (and consequently decreasing air-trapping), and improving exercise performance.[1,2] Short-acting β_2-agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) are used for maintenance treatment in patients with mild disease, minimal symptoms, and infrequent exacerbations.[3] Long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are used for maintenance treatment when the disease severity is any greater (**TABLE**). Long-acting bronchodilators (LABDs) provide better symptom control, improved health status, and greater reduction of exacerbations than short-acting agents.[1] LABAs and LAMAs, which cause bronchodilation in different ways (**FIGURE**),[1] are used as either monotherapy or in combination (**TABLE**) to leverage complementary mechanisms of action. LABAs stimulate β_2-adrenergic receptors in airway smooth muscle, triggering cellular pathways that eventually cause relaxation of bronchial smooth muscle and bronchodilation, whereas LAMAs inhibit muscarinic receptors, thus reducing contraction of airway smooth muscle.[2,4]

ICSs have anti-inflammatory effects mediated by activation of glucocorticoid receptors.[5] In COPD, ICS monotherapy is not recommended; however, ICS/LABA combination improves lung function and health status, and reduces exacerbations.[2] Methylxanthines such as theophylline have modest antiinflammatory and bronchodilator properties[6]; several potential mechanisms for these effects have been postulated.[2] However, limited benefits and a narrow therapeutic window preclude common use.[2] PDE-4 inhibitors, which reduce inflammation by increasing intracellular adenosine 3',5'-cyclic monophosphate levels, modestly improve lung function and reduce exacerbations.[7]

Most pharmacologic agents for COPD are administered using inhalation devices[8] such as nebulizers, single- and multidose dry powder inhalers (DPI), metered-dose inhalers (MDIs), or slow-mist inhalers (SMIs) (**TABLE**).[2] Each type of inhalation device has a different mechanism for drug dispersal. Nebulizers, used for many years, aerosolize drug solutions.[9] DPIs rely on patients' inspiratory air flow to diffuse the inhalation powder and create an aerosol of drug particles.[8] MDIs deliver drugs

TABLE Examples of commonly used maintenance medications in COPD

Drug(s)	Brand examples (mcg)	Inhaler	Duration of action (hours)
LABA			
Arformoterol	Brovana (15 mcg/2 mL)	Nebulizer	12
Formoterol	Perforomist (20 mcg/2 mL)	Nebulizer	12
Formoterol	Foradil	Aerolizer (DPI)	12
Indacaterol	Arcapta (75)	Neohaler (DPI)	24
Olodaterol	Striverdi (2.5)	Respimat (SMI)	24
Salmeterol	Serevent (50)	Diskus (MDI)	12
LAMA			
Aclidinium	Tudorza (400)	Pressair (DPI, MDI)	12
Glycopyrronium	Seebri (15.6)	Neohaler (DPI)	12-24
Glycopyrronium	Lonhala (25 mcg/1 mL)	Magnair nebulizer	24
Tiotropium	Spiriva (18/2.5)	HandiHaler (DPI); Respimat (SMI)	24
Umeclidinium	Incruse (62.5)	Ellipta (DPI)	24
Combination of LABA and LAMA			
Glycopyrronium/formoterol	Bevespi (9/4.8)	Aerosphere (pMDI)	12
Indacaterol/glycopyrronium	Utibron (27.5/15.6)	Neohaler (DPI)	12-24
Tiotropium/olodaterol	Stiolto (2.5/2.5)	Respimat (SMI)	24
Umeclidinium/vilanterol	Anoro (62.5/25)	Ellipta (DPI)	24
Combination of LABA and ICS			
Budesonide/formoterol	Symbicort (160/4.5)	pMDI	-
Fluticasone/salmeterol	Advair (250/50)	Diskus (DPI)	-
Fluticasone/vilanterol	Breo (100/25)	Ellipta (DPI)	-
Combination of LABA, LAMA, and ICS			
Fluticasone/umeclidinium/vilanterol	Trelegy 100/62.5/25	Ellipta (DPI)	-

Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; pMDI, pressurized metered-dose inhaler; SMI, slow-mist inhaler.

Source: GOLD 2018[2] and prescribing information of the respective drugs.

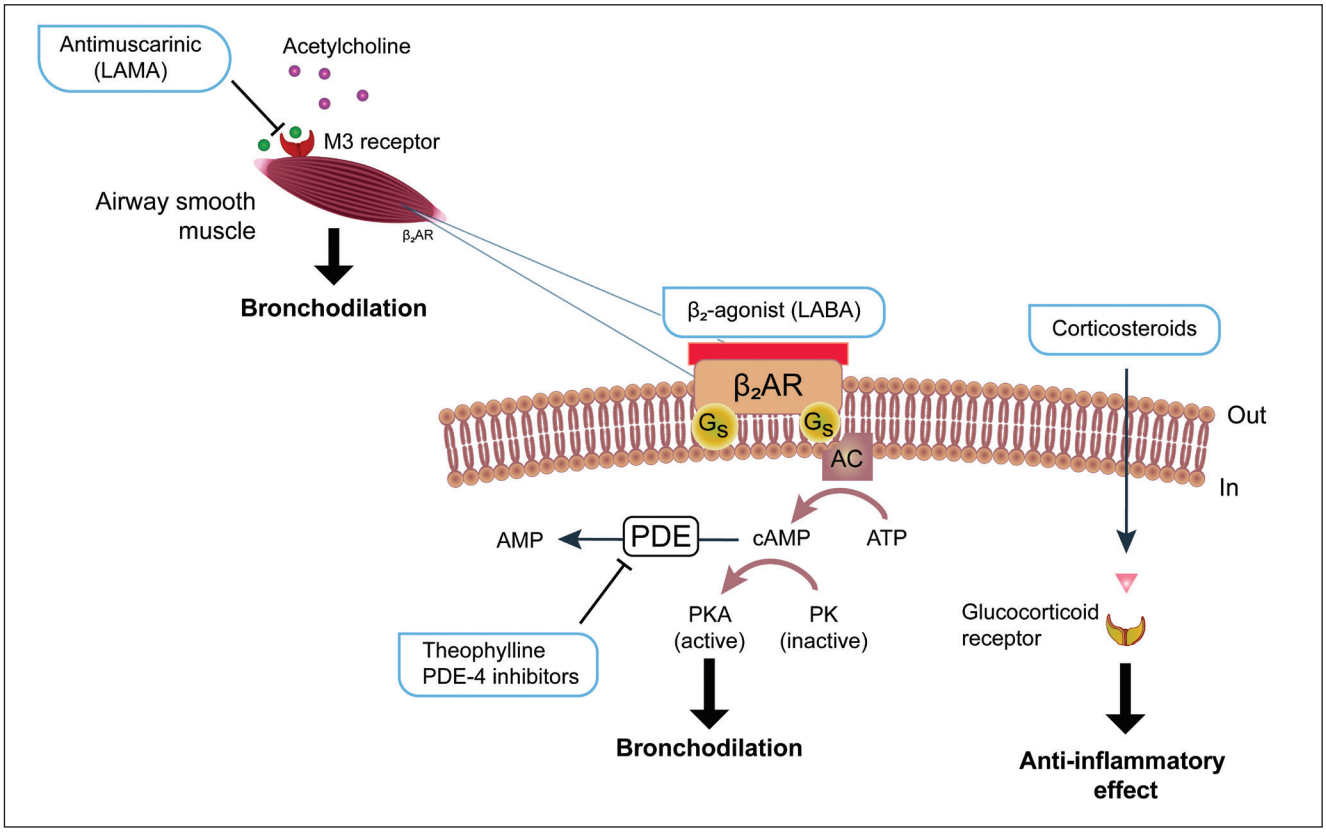
via a propellant spray, whereas nebulizers and SMIs produce an aerosol cloud of fine particles and, therefore, may be less dependent on inspiratory air flow rate for drug delivery.[10]

Because pharmacotherapeutic options for maintenance COPD treatment are rapidly evolving, PCPs should familiarize themselves with current treatment options and determine individual patient requirements. For individualized treatment regimens, symptom severity and exacerbation risk are major determinants. Additionally, factors such as dosing frequency, patient preference, inspiratory flow limitation, and physical and cognitive limitations that may affect correct delivery device use should be considered.[1]

CHANGES IN COPD GUIDELINES

In recent years, better understanding of COPD and its natural history has led to improvements in its diagnosis and management. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, updated numerous times since its original release in 2001, provides a well-accepted strategy for diagnosing and managing COPD.[2] In the GOLD 2011 report,[11] a multidimensional approach for assessment and management of COPD was introduced, where factors beyond spirometric measures of lung function (ie, forced expiratory volume in 1 second [FEV_1]) were included. Assessment of symptoms (using the COPD Assessment Test or modified Medical Research Council dyspnea scale) and history of exacerbations were included in this approach, enabling assessment of current symptoms, future exacerbation risk, and overall COPD burden. Patients are categorized as belonging to 1 of 4 groups (A, B, C, or D) based on severity of these parameters, where patients in Group D have significant symptoms and a history of frequent or severe exacerbation

FIGURE **Mechanism of action of the common pharmacologic agents for COPD**



Abbreviations: AC, adenylate cyclase; AR, adrenergic receptor; ATP, adenosine triphosphate; cAMP, adenosine 3', 5'-cyclic monophosphate; Gs, stimulatory G-protein; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; M3, muscarinic; PDE, phospodiesterase; PKA, protein kinase A

(see accompanying supplement article, *COPD Management in the Primary Care Setting*).[2] ABCD grouping informs the preferred and alternative treatment recommendations.[2]

While FEV_1 is correlated with clinical outcomes such as hospitalization and mortality at a population level, it has poor precision to predict outcomes at an individual patient level.[2] Moreover, since FEV_1 is poorly correlated with symptoms and exacerbation frequency,[12,13] it cannot be used as the sole determinant of treatment. These drawbacks were addressed in the GOLD 2017 report in which spirometry was separated from the ABCD assessment tool so that symptoms and exacerbations guide individualized treatment.[14] This revision reduced the complexity of patient classification, making it easier to use in primary care settings.

CURRENT STATUS OF COPD TREATMENT

Early diagnosis of COPD and timely treatment with maintenance medication can reduce symptoms and exacerbations, thereby potentially preserving exercise tolerance, reducing hospitalizations, and consequently reducing associated costs.[15] However, only 45% of patients were receiving maintenance medication for COPD in a retrospective analysis of US health care claims data.[16] Moreover, fewer patients under the care of PCPs (40%) than pulmonologists (64%) were treated with maintenance medications. Results of another retrospective claims data analysis indicated that, despite GOLD recommendations emphasizing use of inhaled bronchodilators, ICS, usually as ICS/LABA combination, was one of the most commonly prescribed maintenance medications in the United States.[17] Overall, these results suggest suboptimal use of appropriate maintenance medications.[16,17] Unfortunately, many PCPs are unaware of guideline recommendations[18] or have chosen not to incorporate them in their practices because of perceptions that they are too lengthy or irrelevant or are not consistent with their clinical experience.[19]

APPLYING GOLD RECOMMENDATIONS IN PRIMARY CARE

In GOLD 2018, an escalation (step-up)/de-escalation (step-down) strategy according to assessment of patients' symptoms and exacerbation risk, as well as response to treatment, is recommended.[2] For details on the GOLD treatment

algorithm and the use of spirometry in diagnosis, please refer to the accompanying supplement article, *COPD Management in the Primary Care Setting*. For group A patients, short- or long-acting bronchodilators are recommended, which can be continued if symptoms improve. An LABD is recommended for group B patients as initial therapy. However, in patients with severe or persistent breathlessness despite LABD monotherapy, dual LABD therapy is recommended. Step-down to a single LABD is recommended if symptoms do not improve despite adding a second LABD, and in such cases, comorbidities (eg, congestive heart failure) that could account for persistent symptoms should be thoroughly investigated. For group C patients, an LABD is recommended as initial therapy, with LAMAs preferable to LABAs because of better exacerbation benefit.[20,21] For patients with persistent exacerbations, LABA/LAMA or ICS/LABA combination is recommended, with a preference for the former.[2] For group D patients, initial therapy with LABA/LAMA and escalation to LABA/LAMA/ICS or switching to ICS/LABA is recommended, with subsequent addition of roflumilast or a macrolide if frequent exacerbations persist.[2] While GOLD 2018 suggests that LABA/LAMA is preferred over LABA/LAMA/ICS for this patient population,[2,22-25] results of the IMPACT trial showed that triple therapy significantly reduced the annual rate of on-treatment moderate/severe exacerbations compared with either LABA/LAMA (25% reduction) or ICS/LABA (15% reduction).[26] Significant improvements in trough FEV_1, St. George's Respiratory Questionnaire (SGRQ) score, and time to first on-treatment moderate/severe COPD exacerbation were also observed. These findings and additional studies in progress comparing triple therapy to dual therapies will likely impact future recommendations.

Four LAMA/LABA fixed-dose combination (FDC) inhalers are available in the United States (**TABLE**). Tiotropium/olodaterol is delivered using an SMI, umeclidinium/vilanterol and indacaterol/glycopyrronium are administered via DPIs, and formoterol/glycopyrronium is delivered using an MDI.[2,23] Use of 2 LABDs (ie, LABA/LAMA) is recommended because complementary mechanisms of action and interactions between pathways maximize bronchodilator response.[27] In numerous studies in patients with moderate-to-severe COPD with or without a history of recent (ie, in the previous year) exacerbation, LABA/LAMA combinations provided significantly better clinical outcomes than the ICS/LABA FDC of fluticasone/salmeterol. For example, various LABAs (olodaterol, salmeterol, and indacaterol) in combination with once-daily tiotropium (a LAMA) resulted in significantly improved lung function (ENERGITO study),[28] decreased lung hyperinflation and improved expiratory flow (OCTANE study),[29] and improved inspiratory capacity[30] vs ICS/LABA. In at least 3 studies, the once-daily LABA/LAMA FDC of vilanterol/umeclidinium caused significant and sustained improvements in lung function versus fluticasone/salmeterol.[31,32] Bronchodilation was significantly improved with the twice-daily LABA/LAMA combination of aclidinium/formoterol vs fluticasone/salmeterol in the AFFIRM study.[33] Further, in the ILLUMINATE (vs fluticasone/salmeterol),[34] SPARK (vs glycopyrronium),[35] LANTERN (vs fluticasone/salmeterol),[36] and FLAME (vs fluticasone/salmeterol)[24,25] studies, the once-daily LABA/LAMA combination of indacaterol/glycopyrronium resulted in significant improvements in lung function, fewer exacerbations, and a longer time to first exacerbation. Overall, AE incidence was similar between treatment groups across studies.[25,31,32,34,36] Authors of a Cochrane review of 11 studies, including some of the aforementioned studies, involving 9839 patients with mostly moderate-to-severe COPD without recent exacerbations concluded that LABA/LAMA treatment resulted in greater improvements in lung function (FEV_1) and quality of life (QoL), fewer exacerbations, and a lower risk of pneumonia than ICS/LABA.[22]

WITHDRAWAL OF ICS

Use of ICSs in combination with LABDs is recommended in patients with frequent exacerbations (ie, in group D patients after failure of LAMA/LABA treatment[37]); however, inappropriate use of ICSs in patients with COPD (ie, in groups A-C patients) has been reported.[37,38] Though generally safe, ICSs—alone or in combination with a LABA—in patients with COPD are associated with increased risk of pneumonia.[2,39,40] Most episodes of ICS-associated pneumonia in randomized clinical trials were moderate in severity, though some serious events leading to hospitalizations were also reported.[39,40] Pneumonia risk was confirmed in observational studies, where the association between ICSs and pneumonia-related hospitalization and mortality was reported.[39,40] Results of a health insurance database study showed that discontinuation of ICSs was associated with a 37% decrease in the rate of serious pneumonia.[41] Therefore, the concept of ICS withdrawal in patients with COPD where ICSs were not indicated or after extended periods of clinical stability has been tested and is now recommended.[2] Recent findings indicate ICSs can be withdrawn in low- or high-risk patients with COPD, provided maintenance treatment with LABDs is continued. In the INSTEAD[42] and OPTIMO[43] studies, no difference in lung function, breathlessness, health status, rescue medication use, or COPD exacerbations was observed among low-risk patients who switched to a LABA (indacaterol) from an ICS/LABA (fluticasone/salmeterol) combination or those who withdrew ICS from their ICS/LABA maintenance treatment. In the WISDOM study, high-risk patients were randomly

assigned to continued triple therapy (tiotropium/salmeterol/fluticasone) or withdrawal of fluticasone.[44] ICS withdrawal met the prespecified noninferiority criterion with respect to the first moderate or severe COPD exacerbation.[44] However, in 2 post hoc analyses of WISDOM, ICS withdrawal resulted in higher exacerbation in patients with a raised eosinophil count (≥300 cells/μL) and a history of frequent exacerbations (≥2/year).[45,46] Therefore, the decision to withdraw ICS needs to be individualized and carefully monitored, because withdrawing ICS to reduce unneeded therapy and pneumonia risk might ultimately increase exacerbation risk in some patients, namely in those with persistent symptoms, frequent exacerbations, and high eosinophil counts.

APPROPRIATE USE OF ICS/LABA

Initial treatment with ICS/LABA is recommended in some patients who have clinical features suggestive of asthma-COPD overlap (ACO).[2] For further details on ACO, please refer to the accompanying supplement article, *Asthma-Chronic Obstructive Pulmonary Disease Overlap: Diagnostic and Management Challenges*. Patients with ACO have clinical features of both asthma and COPD, and patients with more asthma than COPD features may therefore benefit from ICS therapy.[47] Patients with blood eosinophil counts in the higher range of normal or that are abnormally elevated have increased exacerbation risk.[48] In a post hoc analysis of 3 studies, fluticasone/salmeterol was associated with a significant reduction in exacerbation rates versus tiotropium or placebo in patients with blood eosinophils ≥2%, suggesting baseline blood eosinophil counts may serve as a marker for the efficacy of ICSs in reducing exacerbations in patients with COPD and a history of moderate or severe exacerbations.[49] The accuracy of blood eosinophil counts in predicting ICS benefits improves in a somewhat linear fashion. Therefore, defining a threshold of eosinophil count that best indicates potential benefit with ICS use in COPD is going to be difficult and will always need to be considered in the context of other clinical information. Based on thresholds used in clinical trials, the absolute counts of 150-300 cells/mL or a relative percentage of 2%-4% are plausible; however, more data are needed.[2,49,50]

APPROPRIATE USE OF TRIPLE THERAPY (LABA/LAMA/ICS)

Escalation to triple therapy (LABA/LAMA/ICS), which requires using 1 or 2 separate inhalers, is recommended when patients have exacerbations despite maximized treatment with LABA/LAMA or ICS/LABA.[2] Clinical trial evidence in patients with COPD and moderate-to-severe exacerbations is accumulating. Single-inhaler triple therapies are generally preferable to 2 different inhalers because the latter is associated with increased risk of inhalation errors and decreased adherence.[51] In GLISTEN, glycopyrronium plus fluticasone/salmeterol (separate inhalers) improved lung function and QoL, and reduced rescue medication use compared with placebo plus fluticasone/salmeterol.[52] In TRILOGY and TRINITY, beclomethasone/formoterol/glycopyrronium (single inhaler), improved lung function and reduced exacerbations compared with beclomethasone/formoterol.[53,54] Furthermore, triple therapy was noninferior to beclomethasone/formoterol plus tiotropium in TRINITY.[54] Results of randomized trials showed that once-daily fluticasone/umeclidinium/vilanterol (1 or 2 inhalers) significantly improved lung function and QoL compared with placebo plus fluticasone/vilanterol.[55,56] In addition, once-daily fluticasone/umeclidinium/vilanterol (single inhaler) significantly improved lung function and patient-reported outcomes, and reduced the moderate or severe exacerbation rates compared with twice-daily budesonide/formoterol in FULFIL.[57] AE incidence was similar across treatment groups. Recently, results of IMPACT further showed that single-inhaler triple therapy comprising fluticasone/umeclidinium/vilanterol significantly reduced the annual rate of moderate or severe exacerbations compared with fluticasone/vilanterol or umeclidinium/vilanterol.[26] As mentioned, these findings will likely influence future treatment recommendations. Despite triple therapy, many patients continue to have exacerbations.[54,58] These patients may benefit from other options such as PDE-4 inhibitors, macrolides,[2] or targeted biologics.

PDE-4 INHIBITORS

Roflumilast is indicated in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[2,59,60] In clinical trials, roflumilast reduced exacerbations and modestly improved lung function in patients with moderate-to-severe COPD treated with LABDs[61] and reduced exacerbation risk and hospital admissions in patients with severe COPD who were not controlled with an ICS/LABA (REACT study).[59] Furthermore, results from post hoc analyses of RE^{2}SPOND[62] and REACT[63] showed that roflumilast was more beneficial in patients with a prior history of hospitalization for a COPD exacerbation. Roflumilast initiation is often associated with troublesome gastrointestinal AEs and requires monitoring for other AEs[2]; therefore, escalation to roflumilast is best managed by specialists.

MACROLIDES

Chronic use of oral macrolides, such as azithromycin, reduces exacerbation risk and improves QoL in patients with

persistent COPD exacerbations who are refractory to standard care.[64-66] However, azithromycin was less beneficial in active smokers than nonsmokers and was associated with an increased risk of bacterial resistance.[64,65] Because oral macrolides increase the risk of antimicrobial resistance and need to be closely monitored, they are best managed by specialists.

EMERGING TREATMENTS

Biologics

Different COPD phenotypes may respond differently to treatment.[4,67] Approximately 20% to 40% of patients with COPD have an eosinophilic phenotype; in these patients, biologics such as mepolizumab or benralizumab—monoclonal antibodies against interleukin-5 (IL-5)—may be useful.[56,67] Results of 2 studies using different doses of mepolizumab (100 mg in METREX, 100/300 mg in METREO) in patients with COPD and an eosinophilic phenotype showed that 100 mg mepolizumab significantly reduced the annual rate of moderate-to-severe exacerbation compared with placebo.[58] Two phase III studies of the efficacy and safety of benralizumab in patients with moderate-to-very severe COPD (GALATHEA and TERRANOVA) are ongoing.[68,69] Further studies are needed to understand the role of different biologics in patients with COPD.

Mucolytics

Mucolytics, such as carbocysteine and N-acetylcysteine, reduce exacerbations and improve QoL in COPD patients not treated with ICSs.[2,70,71] However, the target population and correct dose and duration to achieve this benefit are not clear.[2] Clinical experience suggests patients who have concomitant chronic bronchitis and have difficulty clearing secretions are the potential target population. In such patients, an alternative approach is devices that enhance mucus clearance, such as a lung flute or Flutter valve.[72]

CONCLUSIONS

Several new therapeutic options for COPD have become available in recent years. Moreover, the GOLD report has been updated, emphasizing patient-reported symptoms and exacerbations to allow clinicians to develop treatment plans using the new ABCD tool. Awareness among PCPs of the full spectrum of therapeutic options and respective places in therapy is important for appropriate treatment of patients with COPD and avoiding undertreatment or overprescribing. Most emerging treatments target patients who do not respond to standard care. However, further studies are warranted to understand the role of individualized treatment of patients with COPD. ●

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Optimizing Adherence to Improve Clinical Outcomes in Patients with Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a common condition characterized by persistent and progressive airflow limitation, is a major cause of morbidity and mortality worldwide.[1,2] However, COPD can be treated effectively if diagnosed early. A multicomponent approach, including oral and inhaled medications (eg, corticosteroids, bronchodilators, or combination therapy) and nonpharmacologic interventions (eg, pulmonary rehabilitation, lifestyle advice, and self-management techniques), alleviates symptoms, slows disease progression, reduces the frequency and length of exacerbations and hospital admissions, and improves the quality of life.[3,4] Main treatment goals for stable COPD are reduction of symptoms and future risk of exacerbations, and treatment goals for exacerbations are to minimize the negative effects of the current exacerbation and to prevent future exacerbations.[1] Poor medication adherence among COPD patients is one of the key factors preventing patients from reaching treatment goals.[5,6] Major consequences of poor medication adherence in COPD patients include poor disease control and increased number of hospitalizations and deaths due to acute exacerbations.[7] Herein, we review ways in which primary care providers (PCPs) can help patients meet treatment goals, including making use of technological advancements in inhaler design and monitoring, which can improve patient adherence.

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DISCLOSURES

Dr. Garvey discloses that she is on the speakers' bureau for Boehringer Ingelheim.

Dr. Kaplan discloses that he is on the advisory board and speakers' bureau for Boehringer Ingelheim, AstraZeneca, Purdue Pharma, and Novartis. He is on the advisory board for GlaxoSmithKline and Mylan, is a speaker for Grifols, and advisor on Johnson & Johnson's smoking cessation website design outside of this submitted work.

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MEDICATION ADHERENCE IN COPD

Despite the availability of effective pharmacologic treatments and comprehensive treatment recommendations such as those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1] the prevalence of inadequately controlled COPD (assessed by control of symptoms, decline of pulmonary function, levels of physical activity, exacerbations, and quality of life)[8] is high, largely because of inadequate medication adherence.[9] Medication adherence among COPD patients is suboptimal and lower than that among patients with other chronic diseases such as diabetes, heart failure, and hyperlipidemia.[10] In a study involving more than 14,000 COPD patients, only 21% were adherent to maintenance COPD medications.[11] Further, a positive association was observed between nonadherence to maintenance COPD medications and nonadherence to medications for other chronic diseases, implying that the need to take medications for comorbid conditions does not negatively affect adherence to COPD medications.

Patient-related factors contributing to medication nonadherence can be grouped into 2 distinct patterns of behaviors: intentional and unintentional. Intentional nonadherence, which is a voluntary discontinuation or deviation from the prescribed medication plan, often stems from patients' health beliefs and incorrect understanding of the disease course and treatment goals.[3] Unintentional nonadherence results from factors outside patients' control, most commonly complex medication regimens and polypharmacy.[12] Patients with COPD are generally older adults who require medications for various comorbidities.[13] Additionally, factors such as cognitive impairment,[14] low health

literacy,[15] poor eyesight, physical disability, and musculoskeletal issues/lack of dexterity[3] can lead to inhaler incompetence and, thus, poor adherence. Moreover, difficulty in engaging with PCPs, daily fluctuations in symptoms, overuse of rescue medications, use of multiple inhalers, poor inhaler technique, and poor understanding of COPD also contribute to suboptimal adherence.[3,16] Finally, age-related pulmonary changes and decreased lung function[17] may impact adherence, particularly with inhalers that require deep inhalation for optimal medication deposition in the lungs (eg, dry powder inhalers [DPIs]). Importantly, some of these factors, such as overuse or underuse and poor inhaler technique, are modifiable.

Medication- and inhaler-related factors contributing to medication nonadherence include adverse effects, dosing regimens that require multiple drugs or doses, and routes of administration.[18-20] In general, the longer and more complicated the regimen, the greater the likelihood of nonadherence; moreover, patients prefer once-daily therapies to those requiring multiple doses a day.[18] Among COPD patients, adherence is higher for oral than for inhaled medications of the same class (eg, corticosteroids or β-agonists). Other factors contributing to poor COPD medication adherence include health system factors such as medication reimbursements and patient-PCP relationship and socioeconomic factors such as family/caregiver support, income, transportation,[21] and inhaler training.[22] According to hierarchical clustering, COPD patients usually fall into 1 of 3 distinct clusters of adherence: low inhaler use and high error rates, high inhaler use and high error rates, or good adherence, with only a little more than one-third of patients belonging to the good adherence cluster.[17]

COPD INHALER OVERUSE AND UNDERUSE

As mentioned before, COPD patients overuse and underuse medications for various reasons.[23] Approximately half of COPD patients report overuse of prescribed medications during exacerbations.[23] Underuse of COPD medications can be sporadic (eg, occasionally forgetting a dose) or systemic (eg, taking the medication once instead of twice a day over a long period of time).[24] The need to use multiple inhalers and switching treatments/inhalers often leads to confusion and consequent overuse, underuse, or both.[9,25,26] Development of dual, fixed-dose combination bronchodilators and potential triple dose combination inhalers (long-acting β_2-agonist/long-acting muscarinic antagonist/inhaled corticosteroid [LABA/LAMA/ICS]) might improve adherence among patients who require multiple medications.[27,28] Inhaler design potentially contributes to overuse and underuse, as well. Overuse is most prominent for inhalers without a dose counter, inhalers for which a dose can be loaded without actual inhalation, and inhalers lacking feedback on correct inhalation.[29]

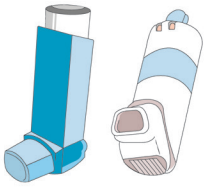
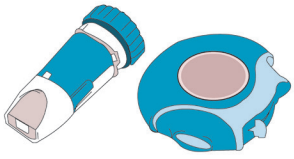
INHALER TECHNIQUE AND CHARACTERISTICS

Development of safe and efficacious inhalation therapy with targeted delivery of medication directly to the site of action depends not only on a pharmacologically active molecule but also a well-designed formulation and inhalation device. Common types of traditional inhalers for COPD medications include pressurized metered dose inhalers (MDIs), including chlorofluorocarbon- (nearly obsolete) and hydrofluoroalkane (HFA)-driven MDIs that are breath activated and may require spacer devices, and DPIs, which are also breath activated[30] (**TABLE**). Patient characteristics that should be considered by PCPs before prescribing an inhaled COPD medication include coordination abilities, comfort level with the inhaler, and prior experience with inhalers.[31]

Poor inhaler technique is a common issue with traditional COPD inhalers,[32,33] and improper use of an inhaler is associated with an increased risk of emergency room (ER) visits, hospitalizations, and the need for corticosteroid treatment.[32] Common patient errors related to inhaler technique include failing to exhale before actuation, prematurely stopping inhalation, incorrect positioning of the inhaler, incorrect rotation sequence, and lack of deep inhalation or breath holding after inhalation.[33] While many of these factors can be corrected with proper training, some cannot. Inhaler technique can be improved with adequate training and reinforcement. However, it can be challenging for PCPs in the current healthcare environment to commit to a continual and time-consuming process of training patients for correct inhaler technique.[34] Nurses, pharmacists, and respiratory therapists can potentially contribute to the improvement of inhaler technique in patients with COPD.

Performance of traditional inhalers is limited by the need for good coordination between patient inspiration and inhaler activation (MDIs) or sufficient inspiratory flow (DPIs).[33,35] Inability to maintain slow inspiratory flow rate and breath holding during MDI use may result in reduced lung deposition of the medication. Similarly, failure to forcefully and deeply inhale during DPI use results in higher medication deposition in the mouth and throat and poor bioavailability. Further, patients with severe airflow limitation may be unable to meet the peak inhalation flow rate required for correct inhaler use.[36] About 31% (28%-35%) of patients with chronic respiratory diseases, including COPD and asthma, cannot use their inhalers (either MDI or DPI) well enough to benefit from the prescribed medication.[37] With traditional inhalers, poor technique reduces the lung deposition of the medication[38] and consequently its efficacy.[33]

TABLE Important characteristics, advantages, and limitations of inhalers used in the treatment of COPD[38,55,74]

	Type of inhaler		
			
Characteristics	**MDI**	**DPI**	**SMI (Respimat)**
Formulation	Drug suspended or dissolved in propellant (with surfactant and cosolvent)	Drug blended in lactose, drug alone, or drug/excipient particles	Aqueous solution or suspension
Metering system	Metering valve and reservoir	Capsules, blisters, multidose blister packs or reservoirs	Unit dose blisters or reservoirs
Mean velocity of aerosol cloud	2-8.4 m/s	—	0.8 m/s
The spray duration	0.15-0.36 s	—	~1.2 s
Advantages	Reproducible dosing No contamination risk Independent of inspiratory flow	Breath-actuated (coordination not required)	Slow velocity aerosol Longer duration Does not require coordination High lung deposition Propellant-free
Limitations	Requires coordination between actuation and inspiration High oropharyngeal deposition Cold Freon effect Ozone-depleting properties Need for spacers in certain populations	Inspiratory flow-dependent Poor dose reproducibility Moisture-sensitive	Dose loading into the inhaler

Abbreviations: COPD, chronic obstructive pulmonary disease; DPI, dry-powder inhaler; MDI, pressurized metered-dose inhaler; m/s, meter per second; s, second; SMI, slow-mist inhaler.

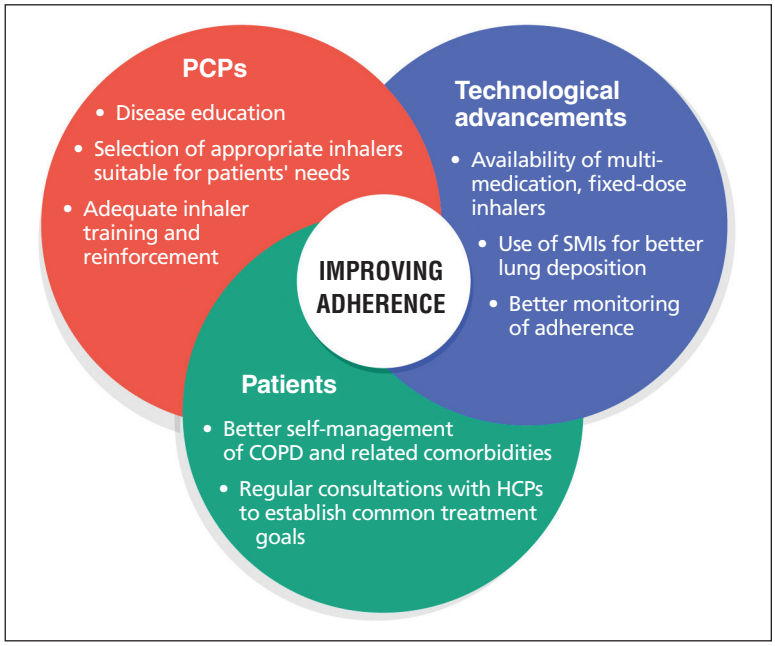
A relatively new inhaler, Respimat, which circumvents some of the patient-related limitations of traditional inhalers, is available. Respimat is a hand-held, propellent-free, slow-mist inhaler (SMI) that generates a single-breath, inhalable aerosol from a drug solution using a patient-independent, reproducible energy supply.[39] This inhaler provides a slower moving aerosol (0.8 m/s vs. 2-8.4 m/s) with longer duration (1.5 s vs. 0.15-0.36 s) than MDIs (**TABLE**).[39,40] In multiple studies, Respimat significantly improved lung deposition of drug aerosols compared to HFA-MDIs and DPIs, even in patients with poor inhaler technique.[39,41-43] As with other types of inhalers, PCPs should be familiar with proper Respimat technique to ensure appropriate patient training. Of note, inserting the cartridge into the inhaler until it clicks into place can be a challenge for certain patients, such as the elderly or patients with disabilities. To avoid this potential limitation, pharmacists can be instructed to preload the cartridge. Elderly patients with poor hand-lung coordination can be encouraged to use a spacer or a valved holding chamber to ensure correct use.[44] Importantly, patients consider spacers easy to use and maintain, and ease of use markedly influences patients' acceptance of the inhaler.[45] Moreover, previous experience with DPIs, MDIs, or both did not influence patient preference and acceptability.[46] Interestingly, patient satisfaction with their inhaler significantly correlated with treatment adherence in at least one study.[47]

CHANGING PATIENT BEHAVIOR

Different strategies involving patients, PCPs, and technology can be employed to help improve medication adherence and clinical outcomes (**FIGURE**). Acknowledging the disparity in treatment goals between physicians and patients is

important to overall patient care for therapeutic decision-making as well as improving physician-patient communication. Patients generally value more tangible and integrated concepts such as fast onset of action and decreased mortality over "text book" treatment goals, including prevention and treatment of exacerbations and improvement of health status, propagated by physicians.[48] Patients have personal beliefs about their illness and treatment, which can be grouped into 2 categories: patient perceptions of personal need for treatment (necessity beliefs) and patient concerns about potential adverse consequences of the disease state and the related treatment.[49] Addressing the "necessity-concern framework" of individual patients helps PCPs understand patients' treatment goals better, enhances engagement of PCPs with patients in shared decision-making related to the choice of treatments, encourages self-management, and supports optimal adherence to medications.[49,50] Authors of recent systematic reviews concluded that self-management programs reduce the probability of COPD-related hospital admissions and overall healthcare utilization, especially when used with other components of the chronic care model.[51,52] Key topics for discussion with patients are disease education, the gains in quality of life and lessening symptom burden that can be achieved with cooperation and following the action plan, and the benefits of referral to pulmonary rehabilitation.[53,54] Understanding and addressing barriers to adherence and proper inhaler techniques are important. Questions to consider include whether or not patients are using the correct inhaler technique, have adequate dexterity to use the inhaler, or have sufficient inspiratory flow rate to achieve adequate lung deposition of the medication (for DPIs), as well as whether or not the medication and inhaler are acceptable to the patient.[55]

FIGURE Strategies to improve medication adherence in patients with COPD



Abbreviations: COPD, chronic obstructive pulmonary disease; HCP, health care provider; PCP, primary care provider; SMI, slow-mist inhaler.

Inhaler technique training, which is often inadequate and not repeated at follow-up appointments,[33] can make patients uncomfortable using the inhaler and may result in nonadherence or discontinuation. In a survey of US patients with COPD, only 22% reported complete confidence in using inhalers.[56] When compared to patients with low confidence in using inhalers, those with greater confidence reported higher adherence rates and better COPD-related health status.[56] Choosing an inhaler suitable to patients' needs and abilities can enhance patients' confidence and improve long-term adherence.[56] Teaching proper technique with each new medication and assessing the technique at follow-up appointments, with retraining if necessary, is critical to maintaining optimal adherence. Several options for patient education are available, including physical demonstrations, audio-visual media, 'YouTube' videos, and graphical depictions of proper inhaler technique. Inhaler training via physical demonstration or audio-visual media has been shown to improve inhaler technique.[57-59] The "teach-back" strategy, where patients are taught how to use the inhaler and asked to explain or demonstrate proper technique back to the PCP, can be employed to ensure that patients understand and execute the correct technique.[60] In multiple studies with different types of inhalers, this strategy significantly improved the proportion of correct inhaler users.[60] While written literature is not as effective as teaching patients directly, a leaflet containing graphic figures depicting proper inhaler technique is a better option than purely written instructions.[61] However, educational interventions only improve inhaler technique effectively over the short term; periodical reinforcement and longer patient follow-up are recommended for long-term success.[57]

In addition to regular inhaler technique training, regular monitoring of medication adherence is important to achieve optimal outcomes. To this end, more efficient monitoring is possible with recent technological advancements, including spacer data loggers for MDIs,[62] the test of adherence to inhalers (TAI) tool,[63] dose counter-equipped inhalers to help patients track medication use,[64,65] pharmacy refill

information,[66] audio-based systems,[17,67] and electronic inhaler reminders.[68] TAI, a 12-item questionnaire, is a validated tool that is reliable and cost-effective in clinical practice, though it tends to underestimate adherence to inhalers compared to other sensitive methods.[69] Dose counter-equipped inhalers help patients avoid overuse of rescue medications.[64] By ensuring that patients do not use rescue medication beyond the recommended number of actuations, dose counters can reduce dose-related morbidity and mortality, and potentially improve the quality of life. Use of periodic reminders and adherence feedback improves patients' attitudes toward adherence and confidence in self-management of their disease.[68] In a recent study, nurse-guided training based on the repeated bio-feedback generated by an electronic device significantly improved inhaler adherence.[70] Moreover, pharmacies usually have patients' detailed medication and dispensing history and pharmacists can use that information to identify potential nonadherent patients in need of support.[71] Pharmacists can also play a key role by providing advice and education on dosage, inhaler technique, treatment expectations, and the importance of adherence, thereby supporting self-management, including recognition and treatment of COPD exacerbations.[72] In multiple studies, community pharmacists' interventions had a positive impact on improving patients' inhalation technique and adherence to inhaled medications through a comprehensive COPD support service.[61] The ideal role of community pharmacists in COPD management deserves further study, as the potential benefits to patients are quite positive.

While the need for inhaler technique assessment, education, and consolidation is acknowledged, more research is required to identify the optimal frequency of these interventions as preemptive measures against technique deterioration in patients.[61] Furthermore, ongoing evaluation of the impact of using specific, validated electronic monitoring devices on inhaled medication adherence in patients with chronic obstructive lung diseases such as asthma and COPD will improve our understanding of medication adherence in respiratory diseases overall. One such sophisticated method measures adherence using electronic data capture devices, which save the date and time of each inhaler actuation and transfer the data daily via a wireless connection to a web-based database.[73] COPD patients and PCPs can work together to effectively use these types of technological advances to attain optimal medication adherence.

CONCLUSIONS

Adherence to COPD medications is multifactorial, and poor adherence is a major barrier to COPD patients achieving their treatment goals. Patient education and empowerment to enable effective self-management of their COPD symptoms is essential. Moreover, because inhaler technique is an important contributor to poor adherence, physicians, nurses, physiotherapists, respiratory technicians, and pharmacists can make meaningful improvements in COPD outcomes by demonstrating and reinforcing proper inhaler technique. Furthermore, technological advances may soon allow adherence to be monitored more efficiently. The emergence of dual, fixed-dose therapies should help reduce administration complexity when multiple medications are required. In summary, PCPs can play key roles in improving COPD medication adherence and helping patients with COPD achieve treatment goals by going beyond conventional educational approaches and empowering patients with necessary self-management skills. ●

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Asthma-Chronic Obstructive Pulmonary Disease Overlap: Diagnostic and Management Challenges

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent chronic respiratory diseases that substantially impact patients' quality of life (QoL).[1] These diseases are distinguishable in their typical forms, but adults can present with chronic airflow limitation and features of both conditions[2]—a clinical entity referred to as asthma-COPD overlap (ACO).[3] Determining the basis of chronic respiratory symptoms in children and young adults is more straightforward than in older patients.[3,4] Asthma is the most prevalent chronic disease among children.[5] However, because COPD is common in adults older than age 40, distinguishing COPD from asthma with chronic airflow limitation might be challenging, particularly among smokers.[3,4] Further, some middle-aged adults with chronic respiratory symptoms have ACO.[3,6-9] Interim recommendations for identifying patients with chronic airflow limitation and differentiating asthma, COPD, and ACO are available as well as guidance on providing appropriate initial treatment.[3] However, definitive strategies for accurately diagnosing and treating ACO are needed.

Older patients and patients with a smoking history are often excluded from asthma clinical trials, and patients with asthma are often excluded from COPD clinical trials.[10] Therefore, information on the diagnosis, treatment, and prognosis of ACO is lacking. However, evidence indicates that spirometry, which is useful for the differential diagnosis of airway diseases, is underused in primary care settings.[11]

Patients with ACO have a poorer QoL, more rapid decline in lung function, higher mortality, more frequent exacerbations, and a disproportionately high use of health care resources compared with patients with asthma or COPD alone.[3]

DEFINITION AND EPIDEMIOLOGY OF ACO

In the Global Initiative for Asthma (GINA) 2018 report, the science committees of GINA and Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommended replacing the descriptive term asthma-COPD overlap syndrome with ACO to clarify that, rather than representing a single disease or phenotype, ACO includes patients with different forms of airway disease (phenotypes) caused by a variety of underlying mechanisms.[3] Because broad populations of patients with ACO usually are not included in clinical trials, the underlying mechanisms of ACO are not well known, and a formal definition of ACO is not available.[3] However, GINA 2018 includes a descriptor for use in clinical practice: "ACO is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD."[3] Accordingly, 9 features are used for diagnosing asthma, COPD, and ACO (**TABLE**).[3]

Other operational definitions of ACO have been described. In one, ACO is defined as the presence of 3 elements in a patient: significant smoking exposure, chronic airflow limitation, and asthma.[12,13] Another comprises 4 operational ACO

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TABLE **Clinical features used in the diagnosis of asthma, COPD, and ACO[3]**

Feature	Age of onset	Respiratory symptoms pattern	Lung function	Lung function between exacerbations	Past or family history	Time course	Chest X-ray	Exacerbations	Airway inflammation
Asthma	Usually during childhood but can start at any age	Varies over time. Usually triggered by exercise, emotions, dust, or allergens	Current and/or history of variable airflow limitation[a]	Normal	• Allergies • Personal history of asthma in childhood and/or family history of asthma	Often improves spontaneously or with treatment but may result in fixed airflow limitation	Usually normal	Exacerbations occur, but risk can be reduced considerably with treatment	Eosinophils and/or neutrophils
COPD	Usually age >40	Chronic, usually continuous symptoms, particularly during exercise	FEV_1 might improve with therapy but post-BD FEV_1/FVC <0.7 is persistent	Persistent airflow limitation	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Generally, slowly progressive over years despite treatment	Severe hyperinflation and other changes of COPD	• Exacerbations can be reduced with treatment • Comorbidities, if present, contribute to impairment	• Neutrophils ± eosinophils in sputum; lymphocytes in airways • May have systemic inflammation
ACO	Usually age ≥40 but symptoms may have started during childhood or early adulthood	Respiratory symptoms, including exertional dyspnea, are persistent, but variability may be prominent	Airflow limitation is not fully reversible, but often current or history of variability is present	Persistent airflow limitation	History of physician-diagnosed asthma, allergies, family history of asthma and/or history of noxious exposures	• Symptoms are partly but significantly reduced with treatment • Progression is usual and treatment needs are high	Similar to COPD	• Exacerbations might be more common than in COPD but are reduced with treatment • Comorbidities can contribute to impairment	Eosinophils and/or neutrophils in sputum
Likely asthma	Age <20	• Symptom variation over minutes, hours, or days • Worse during the night or early morning • Triggered by exercise, emotions, dust, or allergens	Record of variable airflow limitation (spirometry and peak flow)	Lung function normal between exacerbations	• Previously physician-diagnosed asthma • Family history of asthma and other allergic conditions (allergic rhinitis or eczema)	• No worsening of symptoms over time. Symptoms vary seasonally or from year to year • May improve spontaneously or respond immediately to BD or ICS over weeks	Normal		

CONTINUED

TABLE Clinical features used in the diagnosis of asthma, COPD, and ACO[3] (*continued*)

Feature	Age of onset	Respiratory symptoms pattern	Lung function	Lung function between exacerbations	Personal or family history	Time course	Chest X-ray	Exacerbations	Airway inflammation
Likely COPD	Age >40	• Persistent symptoms despite treatment • Daily symptoms and exertional dyspnea • Chronic cough and sputum precede onset of dyspnea, unrelated to triggers	Record of persistent airflow limitation (post-BD FEV_1/FVC <0.7)	Abnormal lung function between exacerbations	• Previous physician-diagnosed COPD, chronic bronchitis, or emphysema • Heavy exposure to a risk factor (tobacco smoke, biomass fuels)	• Symptoms worsening over time (progressive) • Rapid acting BD treatment provides only limited relief	Severe hyperinflation		

Abbreviations: ACO, asthma-COPD overlap; AHR, airway hyperresponsiveness; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

[a]eg, BD reversibility and AHR.

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classifications corresponding to different clinical presentations: (1) smokers with airflow limitation and an eosinophilic inflammatory pattern, (2) patients with asthma resistant to steroid treatment and a more neutrophilic pattern of inflammation, (3) elderly patients with asthma, remodeling of airways, and irreversible airflow obstruction, and (4) patients who had asthma as children and smoke as adults and develop irreversible airflow obstruction.[14] Patients with ACO generally are identified based on 1 of 2 clinical phenotypes: never-, ex-, or current smokers with a history of asthma and incomplete airflow obstruction reversibility, or smokers or ex-smokers with COPD (per GOLD criteria) with increased bronchodilator reversibility or bronchial hyperresponsiveness.[15]

Different ACO criteria have been used in studies[15]; therefore, global prevalence estimates vary (12.1% to 55.2% in patients diagnosed with COPD alone and 13.3% to 61% in patients diagnosed with asthma alone, based on a search of English-language literature published from 2000 to 2014).[16] Variation also could be because of differences in study populations (eg, asthma, COPD, and general populations). The wide variation in definition highlights the challenges associated with characterizing, diagnosing, and treating ACO, and the difference in prevalence reflects inconsistencies in diagnostic criteria for COPD and asthma used by investigators, disease ascertainment methods (spirometry-based vs symptom-based diagnoses), and population characteristics (eg, age and sex).

Inflammation mainly is present in the large airways in asthma vs small airways and lung parenchyma in COPD.[17] Typically, inflammation is driven by T helper type 2 (Th2) cells in asthma and T helper type 1 (Th1) cells in COPD.[17] The mechanisms underlying ACO are unclear. The construct of ACO is recent, although it is a new variation of an old question: do asthma and COPD have common origins and clinical expressions ("Dutch hypothesis"),[18] or are asthma and COPD distinct entities with different origins ("British hypothesis")?[19] Findings support both hypotheses,[20] but there is conflicting data regarding genetic factors underlying ACO.[21-23]

DIAGNOSING ACO

Diagnosing ACO can be challenging without a precise definition. However, several strategies are available.

According to GINA 2018, diagnosis should follow a stepwise approach.[3] Presence of chronic airway

disease should be confirmed through clinical history, physical examination, radiology, and screening questionnaires. If a patient exhibits ≥3 features of asthma or COPD in the absence of features of the other, then a diagnosis of asthma or COPD can be made (**TABLE**).[3] If a patient has a similar number of features of asthma and COPD, then a diagnosis of ACO should be considered. Spirometry should be used to confirm chronic airflow limitation, although it has limited value in distinguishing asthma with fixed airflow limitation, COPD, and ACO. Spirometry results at a single encounter might not be confirmatory, and timing of spirometry testing with clinical presentation and treatment initiation should be considered. Start initial therapy based on diagnosis, and consider referral to a specialist in cases of diagnostic uncertainty, unresponsiveness to treatment, presence of atypical signs/symptoms, or comorbidities.[3]

Other diagnostic guidelines are available. According to a simplified, 4-step algorithmic approach,[24] patients with airway disease are identified; eosinophilic airway inflammation (eg, measurement of blood eosinophil or fractional exhaled nitric oxide [FeNO] levels) or other asthma characteristics (eg, positive bronchodilator reversibility measured by forced expiratory volume in 1 second [FEV_1] ≥15% and ≥400 mL) are evaluated, and the need for inhaled corticosteroids (ICSs) is assessed. Then, presence of persistent airflow limitation is evaluated, and the need for optimization of bronchodilation (eg, long-acting β_2-agonist [LABA]/long-acting muscarinic antagonist [LAMA] combination therapy) is assessed. Finally, history of exacerbation is evaluated, and the most appropriate treatment for reducing episodes is identified based on the predominant disease characteristics.

According to Spanish Society of Pulmonology and Thoracic Surgery guidelines, diagnosis of ACO is confirmed when the following are present in any patient aged ≥35: significant smoking exposure (ie, smoker or ex-smoker >10 pack-years), chronic airflow limitation (postbronchodilator FEV_1/forced vital capacity <0.7) that persists after treatment with bronchodilators and ICSs, and a current diagnosis of asthma. When an asthma diagnosis cannot be established, positive results on a bronchodilator test (FEV_1 ≥15% and ≥400 mL) or elevated blood eosinophil count (≥300/μL) are diagnostic of ACO.[12]

Unfortunately, primary care providers (PCPs) tend to under-use spirometry when diagnosing asthma or COPD, primarily because of limited access to spirometry equipment and lack of training and time.[25,26] Absence of spirometry use can result in misdiagnosis, underestimation of disease severity, and inappropriate treatment. Evidence from studies conducted in primary care settings highlights the importance of diagnosing pulmonary disorders using spirometry rather than solely on clinical presentation.[27-29]

Based on recommendations: (1) persistent airflow limitation should be a major criterion for diagnosing ACO,[30] and (2) a history of atopy (genetic tendency to develop immunoglobulin E [IgE] antibodies against commonly encountered environmental allergens) and rhinitis can be considered additional minor criteria.[31] Identification of biomarkers specific for ACO would be an effective strategy for classifying patients and personalizing treatment.[32] Inflammatory biomarkers such as FeNO, blood eosinophil counts (≥300/μL), sputum eosinophil counts (≥3%), and allergen-specific IgE can be used to support an ACO diagnosis. In studies, these biomarkers,[33,34] as well as sputum neutrophil gelatinase-associated lipocalin,[35] were significantly higher among ACO patients than in those with COPD. However, the pragmatic problems associated with use of these biomarkers need to be considered: (1) the cut-off values are in dispute, and (2) the measurement of sputum eosinophils is complicated and not practical in the clinical setting.

TREATING PATIENTS WITH ACO

Goals of ACO treatment are to improve QoL; alleviate symptoms; improve pulmonary function; improve and maintain exercise tolerance and physical activity; prevent disease progression, airway remodeling, and exacerbation; prevent and treat complications and comorbidities; reduce mortality; prevent adverse effects of therapeutic agents; and improve patient outcomes.[10] Achieving these goals results in better disease control with minimal to no impact on patients' activities. Because patients with ACO generally are excluded from randomized controlled trials, evidence-based guidelines for pharmacotherapy for ACO are lacking; recommendations for treatment are guided by results from studies of asthma or COPD.

The most recent guidance regarding initial treatment of ACO is included in GINA 2018.[3] However, other recommendations also are available.[10,36-38] If patients show equal features of asthma and COPD, initial treatment should mimic that for asthma (low- or medium-dose ICSs based on symptom severity, and rescue medication [short-acting $beta_2$-agonists]) until further testing is performed.[3] This strategy highlights the important role of ICSs in preventing morbidity and mortality in patients with uncontrolled asthma, where even mild symptoms could lead to a life-threatening attack. However, initial therapy with ICS in ACO has not been studied. Further, the safety and tolerability of ICSs in ACO have not been examined, and long-term use of ICSs has been associated with an increased risk of pneumonia among COPD patients.[39] In patients with persistent symptoms, LABAs and/or LAMAs can be added.[3,40] A study comparing ICS/LABA vs ICS/LAMA for ACO is needed to determine which therapy is more beneficial.

In patients with ACO who previously were diagnosed with COPD, LABA and/or LAMA therapy should be started.[41,42] ICSs should be added to LABA in cases of uncontrolled moderate-to-very severe COPD and exacerbations.[42] In most cases, ICS/LABA is recommended for patients with ACO; consider "triple therapy" with ICS/LABA/LAMA in those with more severe symptoms and frequent exacerbations.[24]

Results of a real-world survey of treatment trends in patients with asthma, COPD, or ACO across the United States and Europe (Adelphi Respiratory Disease Specific Programmes 2012-2013) showed that most ACO patients were prescribed drug regimens similar to COPD treatment (ie, ICS/LABA/LAMA triple therapy).[43] However, ACO patients had more exacerbations than those with asthma or COPD alone, highlighting the need for a well-defined therapeutic strategy for ACO.[43]

Advice on reducing modifiable risk factors (smoking cessation), treating comorbidities, nonpharmacologic approaches (physical activity, vaccinations, and pulmonary rehabilitation), self-management strategies, allergen avoidance, and regular follow-up should also be provided to all patients with chronic airflow limitation.[3,36] PCPs can perform initial management of most patients with ACO.[3] However, referral for specialized treatment should be considered in patients with persistent symptoms, diagnostic uncertainty, and comorbidities that interfere with management of airway disease.[3] Patient instructions should be individualized and reinforced via written action/self-management plans.

Based on results of studies of patients with asthma and COPD, ACO treatment could be personalized based on disease phenotype; however, studies of patients with ACO are needed. Evidence indicates that patients with COPD and eosinophilic inflammation might respond better to ICS than those without eosinophilic inflammation,[44,45] and mepolizumab (an anti–interleukin [IL]-5 antibody) reduces exacerbation rates in patients with COPD and an eosinophilic phenotype (eosinophils ≥150/μL at screening or ≥300/μL in the previous year).[46] Mepolizumab and reslizumab, another anti–IL-5 antibody, reduce exacerbations in patients with severe eosinophilic asthma inadequately controlled with ICS.[47,48] Omalizumab—also an anti–IL-5 antibody—decreases asthma exacerbations and allergic pulmonary symptoms (dyspnea, wheezing, and bronchial hyperresponsiveness) and improves asthma control and health-related QoL in patients with ACO.[49-51] Benralizumab—an anti–IL-5 receptor α monoclonal antibody—reduces exacerbations in severe eosinophilic asthma uncontrolled with ICS/LABA.[52,53] Smokers with asthma respond better than nonsmokers with asthma to montelukast—a leukotriene receptor antagonist[54]—but worse to ICS,[55] likely because of reduced histone deacetylase 2 expression, which can be treated with low-dose theophylline.[56] Macrolides (eg, azithromycin) reduce frequency of exacerbations in COPD[57] and could be considered as a treatment option to reduce exacerbations in ACO, although increase in macrolide resistance and risk of cardiac arrhythmias need to be considered. In patients with non-eosinophilic severe asthma and those with COPD, azithromycin reduces exacerbation frequency,[58] albeit with hearing decrement side effect in the latter.[57] Roflumilast given with ICS/LABA reduces exacerbations and hospital admissions in patients with severe COPD,[59] however, its role in ACO is unclear.[60] Finally, predictors of response such as FeNO levels might be useful to gauge efficacy of ICS therapy in ACO patients[61] and could be helpful in adjusting treatment.

Lastly, some ACO research topics were proposed at a workshop conducted by the American Thoracic Society and the National Heart, Lung, and Blood Institute on ACO.[62] Participants recommended conducting longitudinal studies in broad populations to clearly define the prevalence and course of ACO, using imaging studies to assess airway diseases, investigating the role of comorbidities in ACO, identifying specific gene signatures linked with fixed airflow limitation, determining the effect of host genetics and environment on phenotype development, and developing novel and precise therapies for ACO treatment.[62]

CONCLUSIONS

ACO is a relatively new construct for the old concept of overlapping asthma and COPD features. Lack of a common, widely acceptable definition and standardized algorithms for ACO diagnosis and management leads to challenges in characterizing, diagnosing, and treating patients. Spirometry is under-used worldwide, indicating a need for PCP training and encouragement to incorporate spirometry as a diagnostic tool for airway diseases in routine practice. Clinical trials involving patients with ACO are necessary to generate evidence regarding optimal treatment. As with asthma and COPD, ACO treatment should be personalized and based on clinical and histologic phenotype. Identifying patients most likely to benefit from ICSs would help avoid unnecessary use of ICSs and reduce risk of pneumonia in patients with COPD features. In conclusion, developing precise therapies for ACO is needed, and monitoring biomarkers that predict response to therapy would help guide treatment decisions. ●

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