

Severe Asthma in Primary Care: Identification and Management



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ABSTRACT

Most patients with asthma are managed by primary care providers. Severe asthma is associated with substantial morbidity and health care resource use, and long-term sequelae of severe asthma include airway remodeling and a greater risk of developing chronic obstructive pulmonary disease. These consequences highlight the importance of early identification and improved management of patients with severe asthma. Although treatment guidelines can be confusing and it can be difficult to keep abreast of updates, routine assessments of lung function, frequency and severity of exacerbations, symptom control, and medication adherence in the primary care setting provide the necessary information for identifying severe asthma and determining appropriate management strategies. An increased understanding of asthma pathophysiology and its relationship to disease activity has identified therapeutic targets and associated biomarkers. Biologic therapies directed at these targets offer individualized targeted treatment of severe asthma. We review evidence-based guidelines for identification and management of severe asthma, clarify the relationship of asthma control and asthma severity, and provide an overview of new biologic therapies offering additional treatment options for patients with severe asthma.

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According to the National Health Interview Survey–2012, approximately 40 million people in the United States have suffered from asthma during their lifetimes (13% of the population), and 26 million people (8% of the population) currently have asthma.¹ Rates are greater for young adults aged

18–24 years (10.3%) compared with adults aged 25 years and older (8.1%–9.4%).² Approximately 5% to 10% of the total adult asthma population have severe asthma.³ Asthma severity strongly influences the patient's health-related quality of life and health care resource utilization.⁴ Activities and lifestyle are typically more restricted for those with more severe asthma,⁴ and common comorbidities, particularly rhinosinusitis, nasal polyps, obesity, and obstructive sleep apnea, contribute to asthma severity.^{3,5} The long-term consequences of severe asthma are still being elucidated, but evidence suggests increased burden and a risk of negative outcomes. For example, longitudinal studies of children with asthma determined a 32-fold greater risk of developing chronic obstructive pulmonary disease in those with severe asthma compared with those with no wheezing, while controlling for smoking and childhood allergic disease, as well as abnormal patterns of lung-function growth and decline.^{6,7} Despite being less prevalent than milder asthma, severe asthma accounts for a large portion of asthma-related costs.^{3,8} A review of US studies estimated that costs for individuals with severe asthma are approximately

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1.7- to 5-fold greater than costs for individuals with mild asthma.⁹

A majority of patients with asthma are managed by primary care providers,¹⁰ putting these providers at the frontline of asthma management to identify at-risk patients and provide appropriate treatment and education.¹¹ In a 2012 survey, only 22% of patients with asthma were regularly treated by a specialist, and 48% of patients had never visited a specialist.¹² Therefore, it is important for health care providers to perform routine asthma control assessments and appropriately question patients to monitor asthma severity.¹³ Primary care providers who do not regularly perform pulmonary function tests should refer patients with asthma to specialists.¹³ Pulmonary function testing can identify severe asthma independent of other symptoms in patients who have chronic airflow obstruction with a forced expiratory flow in 1 second (FEV₁) <80% of predicted normal. Furthermore, the long-term consequences of undertreated severe asthma underscore the need for specialist referral.¹⁴ During the past decade, research has identified substantial heterogeneity in asthma phenotypes based on an individual's clinical presentation and physiologic characteristics.^{15,16} These developments have led to new targeted therapies. Patients with severe asthma that remains uncontrolled despite maximizing controller medications may benefit from further characterization and a tailored treatment approach to achieve ultimate asthma control. This type of treatment often requires consultation with a specialist.¹⁰

The purpose of this review is to help clarify the distinction between asthma severity and asthma control, to help primary care providers better recognize severe uncontrolled asthma and the consequences thereof, and to review recent advances in asthma pathophysiology and new targeted treatment options for patients with severe asthma.

DEFINING SEVERE ASTHMA

Asthma was historically considered a disease of airway smooth muscle hyperreactivity, that is, bronchoconstriction, in response to environmental triggers. Chronic airway inflammation is now considered a hallmark of the disease, even in patients with occasional symptoms or recent-onset asthma.¹⁶ Assessment of asthma severity was largely based on the frequency of daytime and nighttime symptoms, degree of functional impairment, and frequency of exacerbations.¹⁷ Increased understanding of the underlying pathophysiology of asthma is reflected in more recent practice guidelines, in which the frequency of symptoms and exacerbations are considered elements of asthma control, and disease severity is defined by the medication type and dosage a patient requires to

maintain adequate disease control.^{3,16} Thus, symptom control is assessed independently of, and incorporated into, the definition of asthma severity.

In 2014, the International European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force published guidelines updating the definition of severe asthma,³

incorporating the Global Initiative for Asthma stepwise approach to achieve good symptom control.¹⁶

The ERS/ATS guidelines define severe asthma in people aged 6 years and older as (1) asthma that requires Global Initiative for Asthma step 4-5 treatment with medium- to high-dose inhaled corticosteroids (ICS) and 1 or more additional controller medication(s) (eg, long-acting β_2 -agonist,¹⁸ long-acting muscarinic antagonist, leukotriene modifier, and theophylline) or systemic corticosteroids for at least half the previous year to prevent asthma from becoming “uncontrolled,” or (2) asthma that still remains “un-

controlled” despite this therapy.³ The definition of uncontrolled asthma per these guidelines requires the presence of at least 1 of the following: poor symptom control (according to easy-to-use questionnaires), frequent severe exacerbations, serious exacerbation (requiring hospitalization), or airflow limitation (**Figure 1**). The determination of asthma control highlights the importance of regular and thorough assessment of asthma control.

Severe asthma that remains uncontrolled is associated with substantial short- and long-term consequences, including limitations in physical and functional activities, impaired sleep, and obesity.¹⁴ Although the impact of asthma is greater on physical than mental functioning, poorly controlled asthma is negatively associated with school performance, attention, and concentration and may increase symptoms of depression and anxiety.^{14,17} In addition, airway remodeling can lead to functional damage of the airways and possible development of chronic obstructive pulmonary disease. Of course, oral corticosteroid use to treat severe uncontrolled asthma has its own consequences of osteoporosis, decreased growth velocity in children, risk of infection, and cataracts.^{14,16}

ASSESSING ASTHMA CONTROL

Primary care providers should assess asthma control at every opportunity, and direct questioning is critical because many patients do not fully understand the definition of or how to gauge asthma control. Some patients may forget past events or unconsciously self-impose activity limitations. In addition, responses to general questions, such as “are your asthma symptoms under control?” or “have you had any problems with your asthma since your last visit?” can vary widely depending on the severity and frequency of symptoms that a

CLINICAL SIGNIFICANCE

- Severe asthma accounts for the majority of morbidity and health care utilization by patients with asthma.
- There is a need to improve identification of patients with severe asthma who are inadequately treated/controlled.
- Novel biologic therapies are available and in development that target specific underlying mechanisms of disease, with the goal of improving severe asthma control and patient outcome.

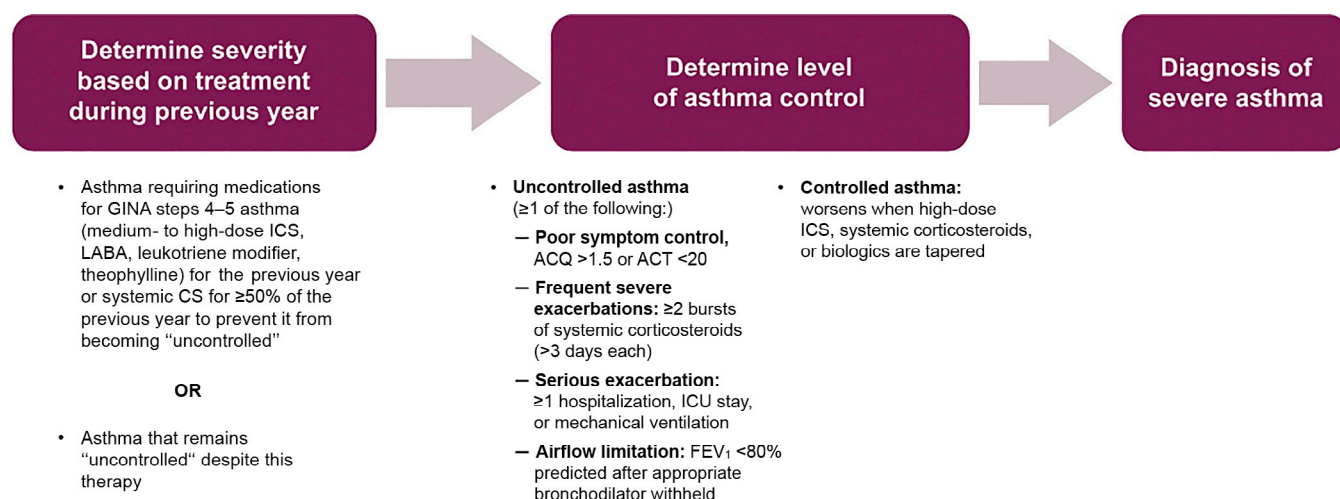


Figure 1 Definition of severe asthma based on the International European Respiratory Society and American Thoracic Society Task Force guidelines.³ ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; FEV₁ = forced expiratory volume in 1 second; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; ICU = intensive care unit; LABA = long-acting β_2 -agonist.

patient may consider unacceptable.¹⁶ Probing for specifics about exacerbation episodes, including oral corticosteroid use, emergency department/urgent care visits, and hospitalizations, as well as frequency, severity, and triggers of asthma exacerbations, will provide a more complete picture of the patient’s level of control.¹⁷

The 2 patient questionnaires referred to in the ERS/ATS guidelines are brief and straightforward for the patient to complete. The Asthma Control Questionnaire¹⁹ consists of 7 questions, 6 of which ask the patient to recall symptom frequency and experiences during the past week (nighttime waking, symptoms on waking, shortness of breath, wheeze, activity limitation, and rescue medication use) and an assessment of prebronchodilator FEV₁ percent of predicted normal value (<http://www.qoltech.co.uk/index.htm>).²⁰ Each question is scored from 0 to 6 and averaged to obtain the final score. Greater scores indicate worse control; poorly controlled asthma is defined as a score >1.5.²⁰ The Asthma Control Test²¹ is an easy-to-score measure of asthma control that does not require measurement of FEV₁.²² Each of 5 questions (shortness of breath, nighttime symptoms, rescue medication use, work or school impairment, and patient rating of asthma control over 4 weeks) is scored from 1 to 5, and scores are totaled (<https://campaign.optum.com/optum-outcomes/what-we-do/disease-specific-health-surveys/asthma-control-test-act.html>). Higher scores indicate better control; a score <20 is considered not well controlled and <15 is very poorly controlled. The minimum clinically important difference is 3 points.¹⁶

Periodic lung function assessment is particularly important for patients who may not recognize symptoms until airflow has become severely obstructed.^{17,23} For example, patients may have unconsciously accommodated to their condition, or they may attribute symptoms to a different cause and thus not report them.¹⁷ The primary method for quantification of airflow limitation is spirometry to assess FEV₁, forced vital capacity, and FEV₁/forced vital capacity ratio.²³ Normal values have been

well established, and reduced measurements are associated with symptom severity and outcomes.^{17,24} Spirometry is the most objective and accurate measurement of airflow limitation, but it is rarely used in primary care.¹³ Staffing and time constraints, equipment cost and quality, and concerns about proper interpretation and adequate training are common and valid barriers to routine use of spirometry by primary care providers.²⁵ An initial investment in equipment and training may be worthwhile in practices that manage a substantial population of patients with asthma, but if not, outside referral for spirometry testing should be considered.

The recommended criteria for assessment of asthma control have some drawbacks, as they are subjective measures that require patients to recall symptoms over time. In addition, although spirometry provides objective measurements, accurate results require properly functioning and calibrated equipment and trained staff. However, use of the above criteria to define asthma control provides the benefits of an objective framework to assess a patient’s symptoms and a complete picture of a patient’s condition, particularly if the patient has seen multiple providers.¹⁷

IDENTIFYING THE PATIENT WITH SEVERE ASTHMA

Assuming accurate asthma diagnosis and exclusion of other possible conditions with similar symptoms, severity can be determined by the treatment the patient is receiving and how well that treatment is managing his or her asthma. For instance, a patient receiving high-dose ICS and 2 other controller medications who continues to experience exacerbations and/or require oral corticosteroid bursts for 3 days or more has severe asthma. A patient is also considered to have severe asthma if his or her disease is controlled on high-dose ICS with other controllers but he or she cannot taper the dose of

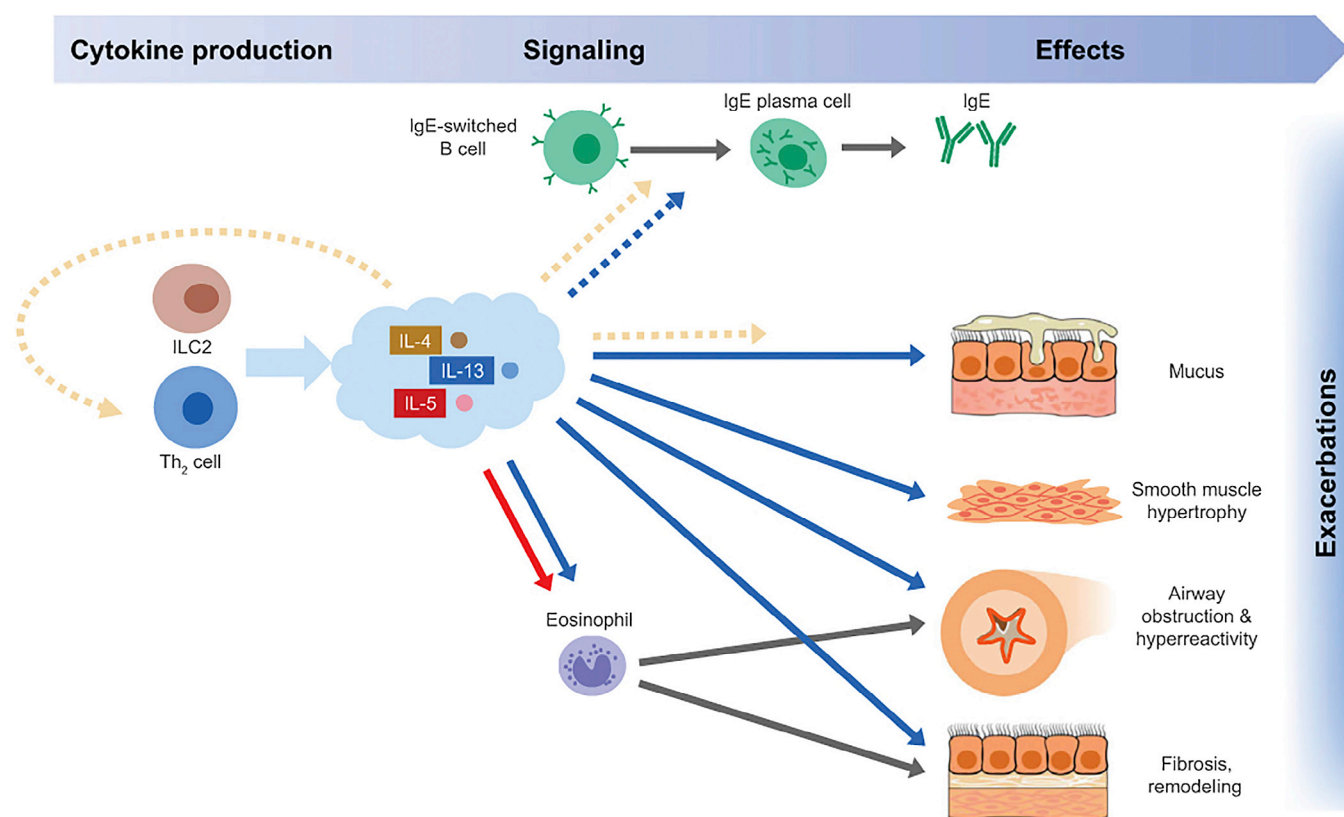


Figure 2 Overview of inflammatory cytokine pathways and signaling in type 2 asthma. Type 2 cytokines (interleukin [IL]-4, IL-5, and IL-13) recruit effector cells (eg, eosinophils) and mediate B-cell class switching to produce immunoglobulin E (IgE) upon exposure to antigens. Cytokines also play a central role in the hallmark effects of asthma.³⁰ Adapted with permission from John Wiley & Sons Ltd from Robinson D, Humbert M, Buhl R, et al. Revisiting type 2–high and type 2–low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy*. 2017;47:161-175. © 2017 The Authors. Th₂ cell = T helper type 2 cells.

ICS without experiencing a worsening in asthma. What options exist for these severe asthmatics? Until recently, their primary choice was repeated courses of oral corticosteroids. However, long-term use of oral corticosteroids has been associated with safety concerns, including type 2 diabetes, osteopenia/osteoporosis, dyspeptic disorders, obesity, hypertension, cataracts, and obstructive sleep apnea.²⁶ Frequent oral corticosteroid bursts may lead to large cumulative doses over time, which may increase the detrimental effects of their use.²⁷

Asthma has traditionally been characterized by phenotype, or clusters of clinically observable characteristics, such as age, sex, body mass index, atopy, and clinical features, including lung function and exacerbation history.^{15,16} Commonly identified phenotypes include allergic asthma, nonallergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity. However, phenotypic characterization does not usually provide insight that will help guide treatment choice. More recently, asthma is increasingly characterized by endotypes, which reflect distinct subtypes of asthma that have a specific underlying biological mechanism.^{15,28} Growing insight into the underlying pathophysiology of these endotypes is helping to identify biomarkers associated with specific endotypes that may predict response to therapies targeting the underlying mechanisms.

One of the best-studied asthma endotypes is type 2–high (T2–high) asthma.^{15,29,30} Patients with T2–high asthma have greater concentrations of mediators associated with a type 2 immune response (eg, eosinophils, basophils, mast cells, type 2 helper cells, group 2 innate lymphoid cells, and B cells) and type 2 cytokines, including interleukin (IL)-4, -5, and -13, in the airway epithelium (**Figure 2**).

INDIVIDUALIZING TREATMENT OF SEVERE ASTHMA

For a patient with severe asthma, a blood test to assess concentrations of serum immunoglobulin E (IgE) and eosinophils can be a first step to identifying whether the patient has a type 2 endotype and finding a treatment that targets a particular pathway.³⁰ Increased IgE concentrations are associated with allergic asthma and can exacerbate the inflammatory response to allergens by releasing mediators such as histamine, prostaglandin, and leukotrienes that result in bronchoconstriction. Allergic asthma is defined by a total serum IgE concentration of 30-700 IU/mL combined with positive skin prick test or positive specific IgE at a concentration >0.35 kU/L.^{31,32} Measurement of total IgE alone is not

necessarily diagnostic.¹⁷ Currently, the primary applications of total IgE measurements are to determine dosing of the anti-IgE antibody omalizumab and screening for allergic bronchopulmonary aspergillosis.³⁰

Eosinophil-mediated inflammation is associated with severe asthma, more frequent exacerbations, and decreased lung function via both the IL-5 and IgE pathways.^{17,31,33} Eosinophils release a variety of mediators that promote further inflammatory responses and also release other compounds that can cause tissue damage and promote airway remodeling.³³ Patients with more severe asthma may have greater concentrations of sputum eosinophils. However, testing for sputum eosinophilia is labor intensive and not readily available.¹⁶ Blood eosinophil counts are commonly used and accepted. Other biomarkers that may prove useful are fractional exhaled nitric oxide (FeNO), a marker of airway inflammation shown to correlate with eosinophilia, and periostin, a protein associated with chronic airway inflammation for which secretion in bronchial epithelial cells is stimulated by IL-4 and IL-13. Tests for FeNO are becoming more widely available,¹⁶ but FeNO can also be elevated in nonasthma conditions, such as atopy, allergic rhinitis, and eczema.¹⁶

Currently approved therapies that target type 2 pathways include omalizumab, mepolizumab, reslizumab, and benralizumab (**Table 1**).^{29,34} Omalizumab, an anti-IgE monoclonal antibody, has demonstrated efficacy in reducing exacerbation rates and ICS use in patients with allergic asthma and high IgE concentrations.³⁵ It was the first monoclonal antibody for the treatment of asthma and acts to inhibit

proinflammatory mediator release and production of new mediators from mast cells. Omalizumab is appropriate only for patients with evidence of allergic asthma by positive skin test or specific IgE.

Both mepolizumab and reslizumab are monoclonal antibodies directed against IL-5. Interleukin-5 plays critical roles in the development, differentiation, recruitment, activation, and survival of eosinophils via binding to the IL-5 receptor.³³ Mepolizumab and reslizumab block the binding of IL-5 to the IL-5 receptor. In studies of patients with severe asthma and elevated eosinophil concentrations, these anti-IL-5 drugs reduce severe asthma exacerbations, improve FEV₁ and asthma-related quality of life, and, in the case of mepolizumab, reduce the need for oral corticosteroids. Both agents are approved as add-on maintenance therapy for patients with severe eosinophilic asthma.^{36,37}

Benralizumab targets eosinophils using the IL-5 receptor to attract natural killer cells to remove eosinophils by apoptosis. Benralizumab is a humanized afucosylated monoclonal antibody that binds the alpha subunit of the IL-5 receptor (unlike mepolizumab and reslizumab, which target the IL-5 ligand) and induces direct, rapid, and nearly complete depletion of eosinophils and basophils via enhanced antibody-dependent cell-mediated cytotoxicity.^{39,40} In patients with severe uncontrolled asthma, benralizumab reduces exacerbations, improves FEV₁, and, in patients using daily oral corticosteroids, reduces oral corticosteroid use.⁴¹⁻⁴³ Benralizumab is approved by the US Food and Drug Administration as add-on maintenance therapy for patients aged 12 years and older with severe eosinophilic asthma.^{38,44}

Table 1 Summary of Currently Approved Biologic Therapies for Asthma

Compound (Brand Name)	Manufacturer (Approval Date*)	Target	Formulation/Dosage	Asthma Indication
Omalizumab [†] (XOLAIR) ³⁵	Genentech/Novartis (2003)	Humanized monoclonal antibody against IgE	Subcutaneous injection: 75-375 mg every 2 or 4 wk (divide doses of >150 mg to >1 injection site to limit maximum injection to ≤150 mg per site)	Moderate to severe persistent asthma in patients aged ≥6 y with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS
Mepolizumab (NUCALA) ³⁶	GlaxoSmithKline (2015)	Humanized monoclonal antibody against IL-5	Subcutaneous injection: 100 mg every 4 wk	Add-on maintenance treatment of patient with severe asthma aged ≥12 y with an eosinophilic phenotype
Reslizumab (CINQAIR) ³⁷	Teva Pharmaceuticals (2016)	Humanized monoclonal antibody against IL-5	Intravenous infusion: 3 mg/kg every 4 wk over 20-50 min	Add-on maintenance treatment of patients with severe asthma aged ≥18 y with an eosinophilic phenotype
Benralizumab (FASENRA) ³⁸	AstraZeneca (2017)	Humanized monoclonal antibody against IL-5Rα	Subcutaneous injection 30 mg every 8 wk (30 mg every 4 wk for the first 3 doses)	Add-on maintenance treatment of patients with severe asthma aged ≥12 y with an eosinophilic phenotype

Information from drug prescribing information; please refer to full prescribing information for complete clinical and safety information, including details on dosing and administration, and warnings and precautions.

ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin.

*Date of US Food and Drug Administration approval for asthma indication.

[†]Omalizumab is also indicated for chronic idiopathic urticaria in patients aged ≥12 years who remain symptomatic despite H₁ antihistamine treatment.

Table 2 Summary of Biologic Therapies in Phase 3 Clinical Development for Severe Asthma

Drug Name (Manufacturer)	Route of Administration	Target	Populations Studied	Phase/Approval Status
Dupilumab ^{45,46} (Sanofi-Genzyme, Regeneron)*	Subcutaneous	IL-4Rα (inhibits IL-4 and IL-13 signaling)	• Asthma diagnosis ≥12 mo • Medium- to high-dose ICS/LABA • FEV₁ 40%-80% predicted • ACQ ≥1.5 • ≥1 systemic CS burst	Phase 3

ACQ = Asthma Control Questionnaire; CS = corticosteroid; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IL = interleukin; LABA = long-acting β₂-agonist; OCS = oral corticosteroid; R = receptor.

*Dupilumab is approved as DUPIXENT for atopic dermatitis.

Dupilumab is a fully human anti-IL-4 monoclonal antibody in phase 3 development for severe asthma (Table 2). Currently approved to treat atopic dermatitis, dupilumab targets both IL-4 and IL-13 signaling and reduces ICS and long-acting β₂-agonist use in patients irrespective of baseline blood eosinophil counts.⁴⁵ Clinical studies of dupilumab indicate that targeting IL-4/IL-13 may be another therapeutic option for patients with severe T2-high asthma. These cytokines have a variety of functions, including eosinophil recruitment and immunoglobulin class switching for IgE production.

Aside from biologics, bronchial thermoplasty can be considered for patients with severe asthma.^{3,16} Thermal energy directed to the airway walls reduces smooth muscle mass, on the basis of the theory that smooth muscle hypertrophy/hyperplasia plays a key role in severe asthma.³⁴ The ERS/ATS guidelines recommend bronchial thermoplasty only in

clinical studies, which highlights the limited data available for this treatment approach.³ At present, long-term consequences are unknown. There is limited information about patient selection, but it is most often applied to patients who do not qualify for or respond to available biologic therapies⁴⁷ or as an adjunct for patients receiving biologic therapy who remain uncontrolled.

CLINICAL PRACTICE RECOMMENDATIONS FOR IMPROVING IDENTIFICATION AND MANAGEMENT OF SEVERE UNCONTROLLED ASTHMA

Asthma guidelines provide recommendations for step therapy based on disease severity and degree of asthma control. The

- **Patient:** 47-year-old female diagnosed with asthma 15 years ago; non-smoker
 - Comorbidities: hypertension, high cholesterol treated with ACE inhibitor and statin
 - History of allergic rhinitis
 - Asthma has been controlled on low-dose ICS and as needed SABA

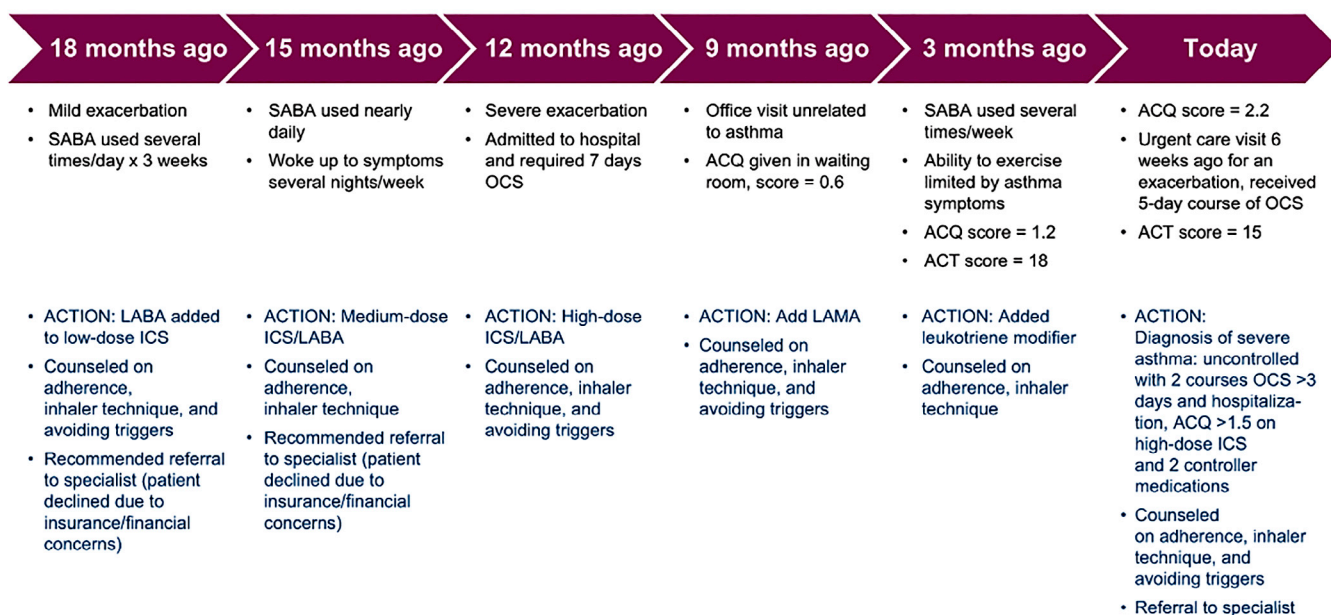


Figure 3 Example of a patient with severe asthma illustrating evidence-based treatment recommendations for step-up therapy. ACE = angiotensin-converting enzyme; ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ICS = inhaled corticosteroid; LABA = long-acting β₂-agonist; LAMA = long-acting muscarinic antagonist; OCS = oral corticosteroid; SABA = short-acting β₂-agonist.

decision to make a sustained step-up in therapy is less clear. The “Asthma Yardstick” is a practical resource to assist in managing step-up therapy strategies across severity classifications.³² Knowing the phenotype and/or specific characteristics of the patient’s condition may improve therapy. Specialist referral may be necessary to identify the phenotype/endotype and rule out potential confounding conditions. Before referral, primary care providers play a valuable role in addressing factors that may contribute to poor asthma control, such as poor adherence, poor inhaler technique, and comorbidities.¹⁰ Targeted therapies are available to provide focused treatment on specific mechanisms responsible for challenging symptoms.³² Importantly, targeted therapies may require several months of treatment to determine their efficacy for individual patients. **Figure 3** provides an illustration of a typical patient with severe asthma and evidence-based treatment recommendations.

CONCLUSIONS

Patients with severe asthma represent a small portion of asthmatics overall, but the impact of severe disease on health care costs and resource use, health-related quality of life, and productivity is significant. Identification of severe asthma considers both treatment and level of disease control. Patients should be routinely assessed using patient questionnaires and objective measurements, such as spirometry. Stepwise therapy recommendations offer individualized treatment strategies but may not be effective for all patients. An increased understanding of asthma phenotypes/endotypes and the development of biological therapies (particularly eosinophil-targeted), such as anti-IgE and anti-IL-5 monoclonal antibodies, offer patients new treatment options for better asthma control.

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