## REVIEW ARTICLE

# Severe and Difficult-to-Treat Asthma in Adults

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PATIENTS WITH SEVERE ASTHMA MAKE UP ONLY 3%[1] TO 10%[2] OF THE POPUlation of adults with asthma, but their care is estimated to account for more than 60% of the costs associated with asthma, which are primarily for medications.[3] Health care costs per patient for severe asthma are higher than those for type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD).[4] Severe asthma also imposes a substantial burden owing to symptoms, exacerbations, and medication side effects, which have profound consequences for mental and emotional health, relationships, and careers.[5]

Considerable progress in understanding and treating severe asthma has been made in the past 5 years. Advances include formulation of a standardized definition[2] and evidence-based treatment guidelines,[2] compilation of substantial evidence about phenotypic patterns and biomarkers, and the availability or near-approval of novel targeted treatments.

In this review, we focus on severe and difficult-to-treat asthma in adults. We first outline an integrated approach to assessment and management, to ensure that the patient has severe asthma and, if so, to determine whether the care takes full advantage of currently available treatments that are not based on monoclonal antibody techniques. We also outline the underlying pathobiologic features of the airway in severe asthma and describe new therapeutic agents that have been developed to target this condition.

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## DEFINITIONS

In 2014, a consensus definition of severe asthma was published that drew a distinction between difficult-to-treat asthma and severe asthma.[2] Difficult-to-treat asthma is asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids or other controllers, or that requires such treatment to remain well controlled. Severe asthma is a subset of difficult-to-control asthma; the term is used to describe patients with asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids combined with a long-acting $\beta_2$-agonist (LABA), a leukotriene modifier, or theophylline for the previous year or treatment with systemic glucocorticoids for at least half the previous year. The term is also used to describe asthma that requires such treatment in order to remain well controlled; it excludes patients in whom asthma is vastly improved with optimization of adherence, inhaler technique, and treatment of coexisting conditions.[2] The criteria for uncontrolled asthma[2] include exacerbations, poor symptom control, lung-function impairment, or a combination of these (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The lung-function criterion[2] (forced expiratory volume in 1 second [$FEV_1$] of <80% of the predicted value on a single occasion) is debatable.

## INTEGRATED MULTIDISCIPLINARY APPROACH TO ASSESSMENT AND MANAGEMENT

As outlined in Figure 1, and in Table S2 and Figure S1 in the Supplementary Appendix, the first step is to confirm the diagnosis of severe asthma. This includes confirming the diagnosis of asthma and checking that patients have adhered to conventional treatment and that coexisting conditions have been treated. Implementation of these critical steps results in the reclassification of the disease in approximately 50% of patients who were thought to have severe asthma.[6] The next step is to implement an adequate trial of therapy with high-dose inhaled glucocorticoids and LABAs. Assessing adherence and inhaler technique is critical, since problems with these account for 50 to 80% of cases of uncontrolled asthma.[1] Dispensing records or electronic monitoring of inhaler use may suggest poor adherence. It may also be suggested by a positive therapeutic response to intramuscular slow-release formulations of glucocorticoids, such as triamcinolone, or by suppression of the fraction of exhaled nitric oxide (Feno) after 5 days of directly observed therapy with inhaled glucocorticoids.[7]

Finally, it is imperative to perform an assessment for coexisting conditions and aggravating factors (Fig. 1) and to evaluate and treat patients accordingly (Table S3 in the Supplementary Appendix). Medication problems include overuse of short-acting $\beta_2$-agonists, which can increase airway hyperresponsiveness; overuse can be habitual.[8] Environmental exposures, such as occupational exposures and tobacco smoke (associated with progression to severe asthma and reduced glucocorticoid sensitivity), are of particular concern and must be addressed. Patients should be assessed for coexisting conditions (e.g., rhinosinusitis), and treatment should be escalated if appropriate.[9] Patients with severe asthma, especially those with a history of smoking, may have clinical features of both asthma and COPD (often called asthma–COPD overlap[10]); these patients have high morbidity and a high rate of health care use. Psychosocial problems, including anxiety and depression, are common in patients with severe asthma and are associated with rates of exacerbations and emergency department visits

**Figure 1 (facing page). An Integrated Multidisciplinary Approach to Assessment and Initial Management of Difficult-to-Treat and Severe Asthma in Adults.**

MART (maintenance and quick-relief therapy) involves a low-dose inhaled glucocorticoid and formoterol as the patient's regular therapy and as quick-relief therapy. This regimen reduces exacerbations and allows the use of lower doses of inhaled glucocorticoids; this treatment is approved by many regulators but not by the Food and Drug Administration. Details about differential diagnosis and coexisting conditions are available in Tables S2 and S3, respectively, in the Supplementary Appendix. LABA denotes long-acting $\beta_2$-agonist.
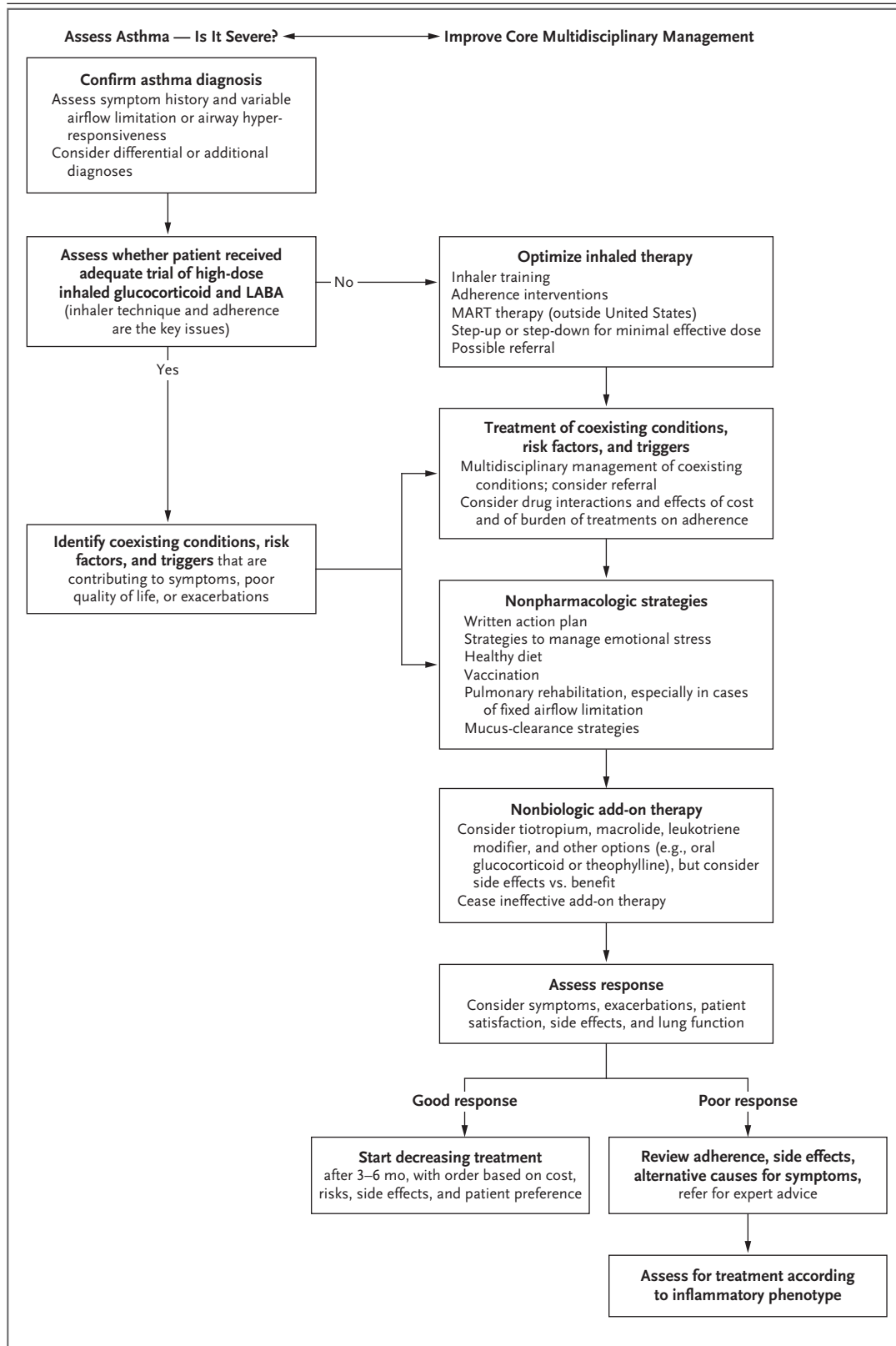
that are at least five times as high as those among patients with asthma but without psychosocial problems.[11]

Before deciding whether a patient needs biologic add-on therapies (which are expensive), a trial of tiotropium, a long-acting muscarinic antagonist, is warranted because of its much lower cost. It increases lung function and time to first exacerbation.[12] Daily administration of oral glucocorticoids should be avoided, if possible, because of the associated serious side effects.

A further advance has been the development of clinics that specialize in patients with severe asthma.[13-15] Systematic assessment and multidisciplinary treatment of patients in such clinics have increased identification of coexisting conditions[14] and have improved outcomes.[13,15]

## MECHANISMS AND PHENOTYPES

For patients with persistently uncontrolled asthma despite implementation of systematic assessment and multidisciplinary treatment, the next step is assessment for targeted treatment. Treatment is tailored according to the diverse pathobiologic processes that can underlie clinical presentations (Fig. 2 and Table 1). The common pathways of these processes are asthma phenotypes characterized by exacerbations, persistent symptoms, reduced lung function, or a combination of these.[16] Most, but not all, of these phenotypes are associated with evidence of cellular inflammation in the airway (Fig. 2). New asthma treatments not only have allowed clinicians to care for patients for whom prior treatment was ineffective but also have served as biologic probes that have helped in understanding the complex pathobiology of asthma. Outlined here
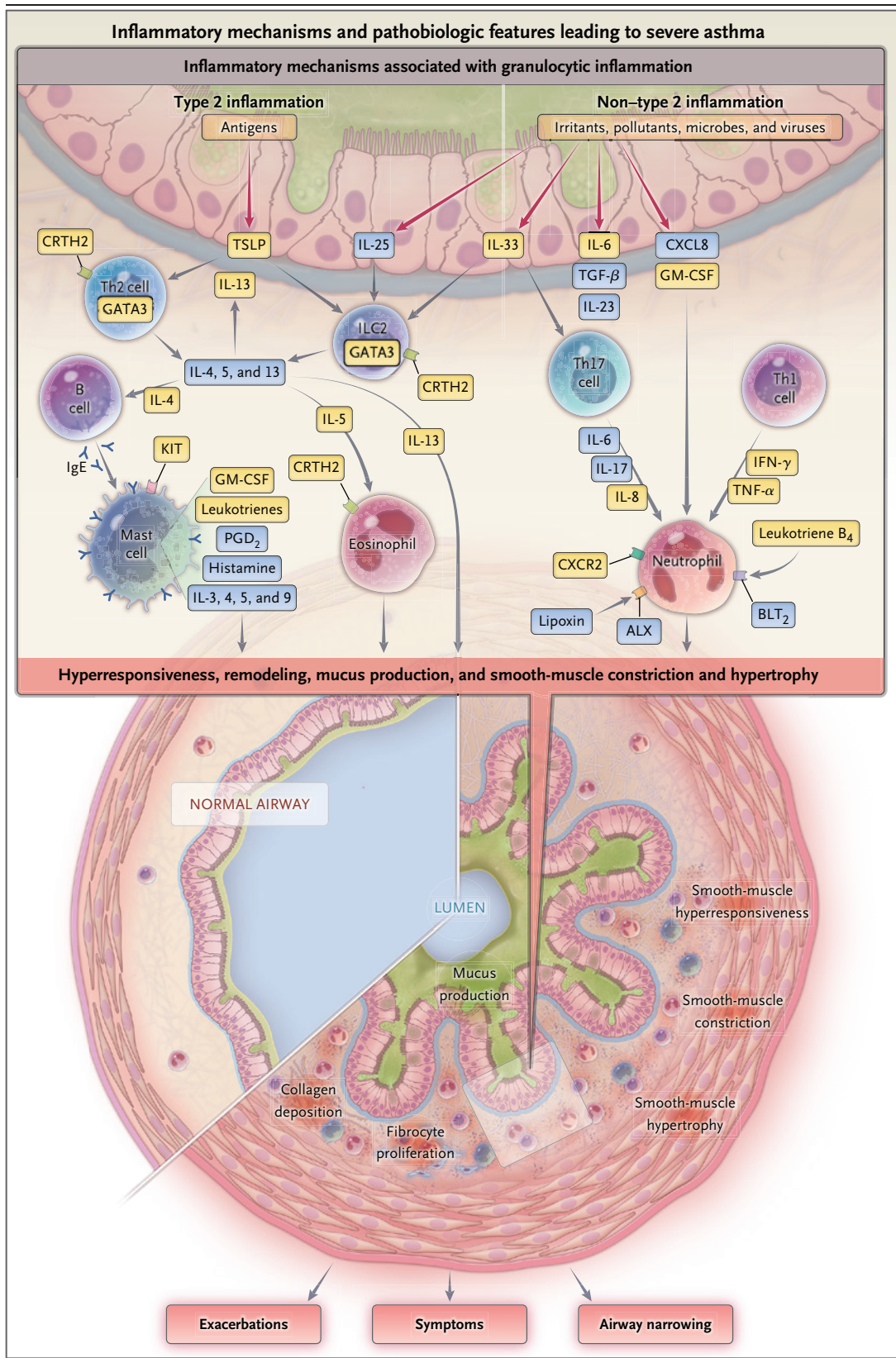
**Assess Asthma — Is It Severe?** ←————→ **Improve Core Multidisciplinary Management**

**Confirm asthma diagnosis**
Assess symptom history and variable airflow limitation or airway hyper-responsiveness
Consider differential or additional diagnoses

↓

**Assess whether patient received adequate trial of high-dose inhaled glucocorticoid and LABA** (inhaler technique and adherence are the key issues)

— No → **Optimize inhaled therapy**
Inhaler training
Adherence interventions
MART therapy (outside United States)
Step-up or step-down for minimal effective dose
Possible referral

↓

**Treatment of coexisting conditions, risk factors, and triggers**
Multidisciplinary management of coexisting conditions; consider referral
Consider drug interactions and effects of cost and of burden of treatments on adherence

Yes ↓

**Identify coexisting conditions, risk factors, and triggers** that are contributing to symptoms, poor quality of life, or exacerbations

↓

**Nonpharmacologic strategies**
Written action plan
Strategies to manage emotional stress
Healthy diet
Vaccination
Pulmonary rehabilitation, especially in cases of fixed airflow limitation
Mucus-clearance strategies

↓

**Nonbiologic add-on therapy**
Consider tiotropium, macrolide, leukotriene modifier, and other options (e.g., oral glucocorticoid or theophylline), but consider side effects vs. benefit
Cease ineffective add-on therapy

↓

**Assess response**
Consider symptoms, exacerbations, patient satisfaction, side effects, and lung function

Good response ↓                Poor response ↓

**Start decreasing treatment**
after 3–6 mo, with order based on cost, risks, side effects, and patient preference

**Review adherence, side effects, alternative causes for symptoms,** refer for expert advice

↓

**Assess for treatment according to inflammatory phenotype**

**Inflammatory mechanisms and pathobiologic features leading to severe asthma**

**Inflammatory mechanisms associated with granulocytic inflammation**

Type 2 inflammation — Antigens

Non–type 2 inflammation — Irritants, pollutants, microbes, and viruses

CRTH2 · Th2 cell GATA3 · TSLP · IL-13 · IL-25 · IL-33 · IL-6 · TGF-β · IL-23 · CXCL8 · GM-CSF

ILC2 GATA3 · CRTH2

B cell · IL-4, 5, and 13 · IL-4 · IL-5 · IL-13

Th17 cell · Th1 cell

IgE · KIT · GM-CSF · Leukotrienes · CRTH2 · PGD₂ · Histamine · IL-3, 4, 5, and 9

Mast cell · Eosinophil

IL-6 · IL-17 · IL-8 · IFN-γ · TNF-α · Leukotriene B₄

CXCR2 · Neutrophil · Lipoxin · ALX · BLT₂

**Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy**

NORMAL AIRWAY

LUMEN

Mucus production

Smooth-muscle hyperresponsiveness

Smooth-muscle constriction

Collagen deposition

Fibrocyte proliferation

Smooth-muscle hypertrophy

Exacerbations · Symptoms · Airway narrowing

**Figure 2 (facing page).** Inflammatory, Immunologic, and Pathobiologic Features Leading to Severe Asthma.

Type 2 inflammation is most commonly initiated by the adaptive immune system on recognition of allergens through the actions of thymic stromal lymphopoietin (TSLP), which stimulates type 2 helper T (Th2) cells and innate lymphoid cells of group 2 (ILC2) to differentiate and produce the type 2 cytokines interleukin (IL) 4, IL-5, and IL-13. This differentiation depends on activation of the GATA3 transcription factor. These cytokines result in the production of IgE (through the action of IL-4) and subsequent activation of mast cells (which depend on stem cell factor and its receptor, KIT, for normal development and survival) and activation and recruitment of eosinophils through IL-5. IL-13 acts on smooth muscle to induce hyperresponsiveness and remodeling; it also stimulates the epithelium to increase cytokine production and stimulates mucus production. Mast cells produce multiple mediators and cytokines that cause airway smooth-muscle contraction, eosinophil infiltration, remodeling, and amplification of the inflammatory cascade through additional cytokine production (IL-3, IL-4, IL-5, and IL-9). Mast cells also synthesize prostaglandin $D_2$ ($PGD_2$), which stimulates upstream cells and eosinophils through its actions at the receptor known as CRTH2. The type 2 pathway can also be activated by factors such as infectious agents and irritants that stimulate the innate immune system through production of such cytokines as IL-33 (through its receptor ST2) and IL-25 (through its receptor IL-17RB), which in turn stimulate ILC2 and Th2 cells. The cytokines released in response to these agents can also activate non–type 2 pathways. Type 17 helper T (Th17) cells and their products can play a major role in attracting and stimulating neutrophils. The epithelium also produces cytokines that stimulate Th17 cells; in addition, it produces cytokines that directly stimulate neutrophils. These innate immune stimuli also activate type 1 helper T (Th1) cells, which are more classically involved in host defenses against pathogens and can also stimulate neutrophils. In addition, some patients may have reduced ability to synthesize pro-resolving compounds such as lipoxins, which have a role in down-regulating neutrophilic inflammation and antagonizing effects of leukotrienes. Some patients with severe asthma may not have cellular evidence of activation of these pathways and are considered to have "paucigranulocytic" asthma. To produce clinical presentations of severe asthma, these phenotypic inflammatory patterns can induce or combine with any or several of the following: airway hyperresponsiveness, smooth-muscle hypertrophy, structural airway remodeling, or mucus secretion. Substances in yellow have been or are currently being targeted for treatment of severe asthma. ALX lipoxin $A_4$ receptor, $BLT_2$ leukotriene $B_4$ receptor 2, CXCL8 CXC motif chemokine ligand 8, CXCR3 CXC chemokine receptor 3, GM-CSF granulocyte–macrophage colony-stimulating factor, TFG-$\beta$ transforming growth factor $\beta$, and TNF-$\alpha$ tumor necrosis factor $\alpha$.

is our current understanding of the various inflammatory phenotypes that underlie severe asthma.

## INFLAMMATORY PHENOTYPES

### Persistent Type 2 Inflammation

Type 2 inflammation in the airway is characterized by the presence of cytokines (interleukin-4, interleukin-5, and interleukin-13) that were originally recognized as being produced by type 2 helper T (Th2) cells. These cytokines are also produced by innate lymphoid cells (which do not express B- or T-cell receptors) in response to infectious agents and pollutants and other "nonallergic" stimuli (Fig. 2).[17] Since interleukin-4 and interleukin-5 promote the production of IgE and eosinophils, respectively, this inflammation is frequently characterized by eosinophils and may be accompanied by atopy. In mild-to-moderate asthma, type 2 inflammation is common and generally promptly resolves after treatment with glucocorticoids. However, in the context of severe asthma, this phenotype is characterized by persistent evidence of active type 2 inflammation despite high-dose therapy with inhaled glucocorticoids. Sputum eosinophilia, defined as 2% or more of leukocytes in a sample, is seen in more than half of patients with severe asthma[16,18] and has been labeled glucocorticoid-resistant asthma.[2]

Multiple processes can contribute to persistent type 2 inflammation in severe asthma, including some that appear mechanistically homogeneous, such as allergic bronchopulmonary aspergillosis and aspirin-exacerbated respiratory disease. Another cause is allergen exposure at home or at work. Furthermore, nonallergic stimuli can activate pathways and cells other than helper T cells to produce type 2 cytokines (Fig. 2).[19] This may explain why cluster analyses[20-23] (in which computer algorithms identify groups of patients with similar features) identify high-eosinophil-count clusters not only in association with severe asthma and atopy but also in association with fewer allergies. Patients in the group with fewer allergies tend to have adult-onset asthma, with more severe airflow limitation and airway hyperresponsiveness. Another cluster, comprising women with a high body-mass index and late-onset asthma, is associated with high use of health care resources and has been variably associated with persistent type 2

**Table 1. Features Associated with Pathobiologic Characteristics of Severe Asthma, According to Phenotype.***

| Characteristic | Eosinophilic Airway Inflammation | Neutrophilic Airway Inflammation | Mixed Eosinophilic and Neutrophilic Inflammation | Paucigranulocytic (Noninflammatory) Asthma | Hyperresponsive and Variable Obstruction | Fixed Obstruction |
|---|---|---|---|---|---|---|
| Frequency | Very common | Common | Not common | Variable | | |
| Markers in patients receiving high-dose inhaled glucocorticoids | Blood eosinophil count ≥300/μl, $F_{ENO}$ ≥20 ppb, sputum eosinophils ≥2% | ≥40–60% polymorphonuclear neutrophils in sputum | Type 2 markers and neutrophilic markers | No type 2 markers and ≤40–60% sputum polymorphonuclear neutrophils | Increased bronchoprovocation | Minimal pulmonary-function test reversibility |
| Causes and contributing factors | Allergic exposures, idiopathic, occupational exposures, ABPA, AERD | Infections, sinusitis, smoke, irritants, pollutants, occupational exposure, glucocorticoid treatment | Combination of the factors contributing to eosinophilic and neutrophilic airway inflammation | Smooth-muscle hypertrophy, airway remodeling and hyperplasia, neurohumoral factors, glucocorticoid treatment | Type 2 inflammation in particular but may occur with any inflammatory pattern, postviral effects, occupational sensitizers, inhaled oxidant exposure, neurohumoral and hormonal factors | Speculative causes include smoking, severe asthma in childhood, mucus hypersecretion, bronchiectasis, possibly untreated type 2 asthma |
| Clinical features | Early onset, allergic, with high IgE; later onset with eosinophils; later onset, obesity, female sex, variable airway obstruction; exacerbations; sinusitis; nasal polyps | Low lung function, poor response to inhaled glucocorticoids, purulent mucus production, bronchiectasis | Combination of the features of eosinophilic and neutrophilic airway inflammation | Fixed or variable obstruction | Hyperresponsive and variable airway obstruction, exacerbations with low-level exposures, dyspnea and wheezing at rest | Fixed obstruction, dyspnea with low-level exertion, exacerbations |

* ABPA denotes allergic bronchopulmonary aspergillosis, AERD aspirin-exacerbated respiratory disease, and $F_{ENO}$ fraction of exhaled nitric oxide.

eosinophilic inflammation.[23-25] Most of the recently approved biologic interventions target type 2 inflammation.

*Neutrophilic Inflammation*
Less well characterized are patients with severe asthma who have neutrophilic inflammation (variably defined as exceeding 40 to 60% neutrophils) in induced sputum samples; some have no evidence of eosinophilic inflammation during treatment with glucocorticoids.[26,27] Although neutrophils in the sputum may sometimes relate to glucocorticoid use, the clinical characteristics of patients with neutrophilic predominance differ from those with type 2 inflammation,[26,27] suggesting different pathobiologic pathways. Some patients have coexisting infections in the sinuses or airways; others report exposure to occupational or environmental sensitizers, including tobacco smoke.[28] In patients with mild asthma, those with neutrophilic inflammation, especially those without coexisting eosinophilic inflammation, are less likely to have short-term responses to glucocorticoids than those with eosinophilic inflammation[29]; however, similar studies have not been undertaken in patients with severe asthma. Macrolide therapy has been proposed for moderate-to-severe asthma,[30] but evidence is inadequate to direct treatment in patients who meet the criteria for severe asthma.

*Mixed Inflammation*
Some patients with severe asthma have evidence of persistent neutrophilic and eosinophilic inflammation in sputum. This overlapping phenotypic cluster appears to have the greatest disease burden and airflow limitation and involves the greatest use of health care resources.[26,27] Interleukin-6 and interleukin-17[31] may promote dual Th2 and type 17 helper T (Th2–Th17) cell presence in the airway, which promotes both types of inflammation (Fig. 2); these cytokines are therefore of potential interest as treatment targets for patients with mixed inflammation,[16] although we know of no such trials currently under way.

*Paucigranulocytic Phenotype*
Some patients do not have notable cellular inflammation in their airways; their airflow limitation is presumably due to other mechanisms (described below). The prevalence of the pauci-

granulocytic phenotype depends on the threshold for excess neutrophils.[16] However, overall, this phenotype is not as common as the others, so its finding (e.g., in some obese patients) should prompt reconsideration of the diagnosis of asthma. This inflammatory pattern is also seen in patients with mild asthma and, less commonly, in some patients with severe asthma who are receiving treatment with high-dose inhaled glucocorticoids.[16] Proven treatment options are limited.

### ADDITIONAL PATHOPHYSIOLOGICAL MECHANISMS

In severe asthma, structural changes such as airway remodeling may be superimposed on the aforementioned phenotypes, contributing to airway obstruction (Fig. 2). These structural changes may be characterized by collagen deposition (making the airways less compliant),[32] proliferation of airway smooth muscle,[33] and excess mucus production.[34] Emerging noninvasive methods for quantifying these pathological features include high-resolution computed tomography.[35] In addition, all these changes can occur in the context of persistent airway hyperresponsiveness to external stimuli, which is a common feature of severe asthma. The mechanisms leading to hyperresponsiveness are poorly understood but may include abnormalities of smooth muscle, as well as neurohumoral influences. Targeting these factors is an active area of investigation.

## NEW THERAPIES

Since 2003, several new targeted therapies for severe asthma have been introduced. The challenge facing clinicians is to identify patients who are most likely to have a response to these interventions, which are often expensive. For patients with a poor response to core multidisciplinary management of their asthma (Fig. 1), an approach to identify those for whom a trial of the following therapies should be considered is outlined in Figure 3. The approach is based on an integrated assessment of clinical features and biomarkers. Since most current phenotype-based options are directed at persistent type 2 inflammation, assessment commences with relevant peripheral biomarkers (i.e., blood eosinophil count and F$_{ENO}$ and IgE levels), supplemented as necessary by sputum cellular indexes. Figure 3 shows additional options for patients with a poor response despite phenotype-based treatment.

### ANTI-IGE

Omalizumab (Table 2) is a monoclonal antibody that binds to free IgE, preventing activation of cells such as mast cells, basophils, and dendritic cells and down-regulating the high-affinity receptor for the Fc region of IgE (FcεRI). Omalizumab has been available for clinical use in the United States since 2003. It has been tested almost exclusively in patients with allergic asthma, as defined by an IgE level of 30 IU per milliliter or more and at least one positive aeroallergen skin test or an elevated specific aeroallergen IgE level. When added to inhaled glucocorticoids (in most studies, without concomitant LABAs), omalizumab reduced severe exacerbations by 45% and hospitalizations by approximately 85% and allowed lower doses of inhaled glucocorticoids and a small decrease in the use of quick-relief therapy, with inconsistent effects on lung function.[37] In patients with uncontrolled severe allergic asthma and a history of exacerbations treated with high-dose combination therapy, omalizumab reduced exacerbations by 25 to 35%[38]; a biomarker analysis in this population suggested that a F$_{ENO}$ level of at least 19.5 ppb identified patients with a reduction in exacerbations of approximately 50%.[38] Baseline IgE levels are not predictive of response but are needed along with body weight to calculate the drug dose according to current treatment guidelines.

### ANTI–INTERLEUKIN-5

Interleukin-5 plays a central role in promoting eosinophilic inflammation (Fig. 2). Anti–interleukin-5 monoclonal antibodies are now available for the treatment of patients with severe eosinophilic asthma and recurrent exacerbations (Table 2). Mepolizumab and reslizumab, both of which bind to interleukin-5, have been approved by several regulatory agencies in the United States and Europe. Benralizumab, which binds to the interleukin-5 receptor, producing eosinophil apoptosis, is nearing Food and Drug Administration (FDA) approval. The majority of studies performed involving patients with severe asthma have been conducted with mepolizumab. In patients with two or more exacerbations in the previous year and a blood eosinophil count of at least 300 per microliter, mepolizumab reduces exacerbations by 40 to 60%.[39] As compared with placebo, mepolizumab has also been shown to allow a mean 50% reduction of oral glucocorti-
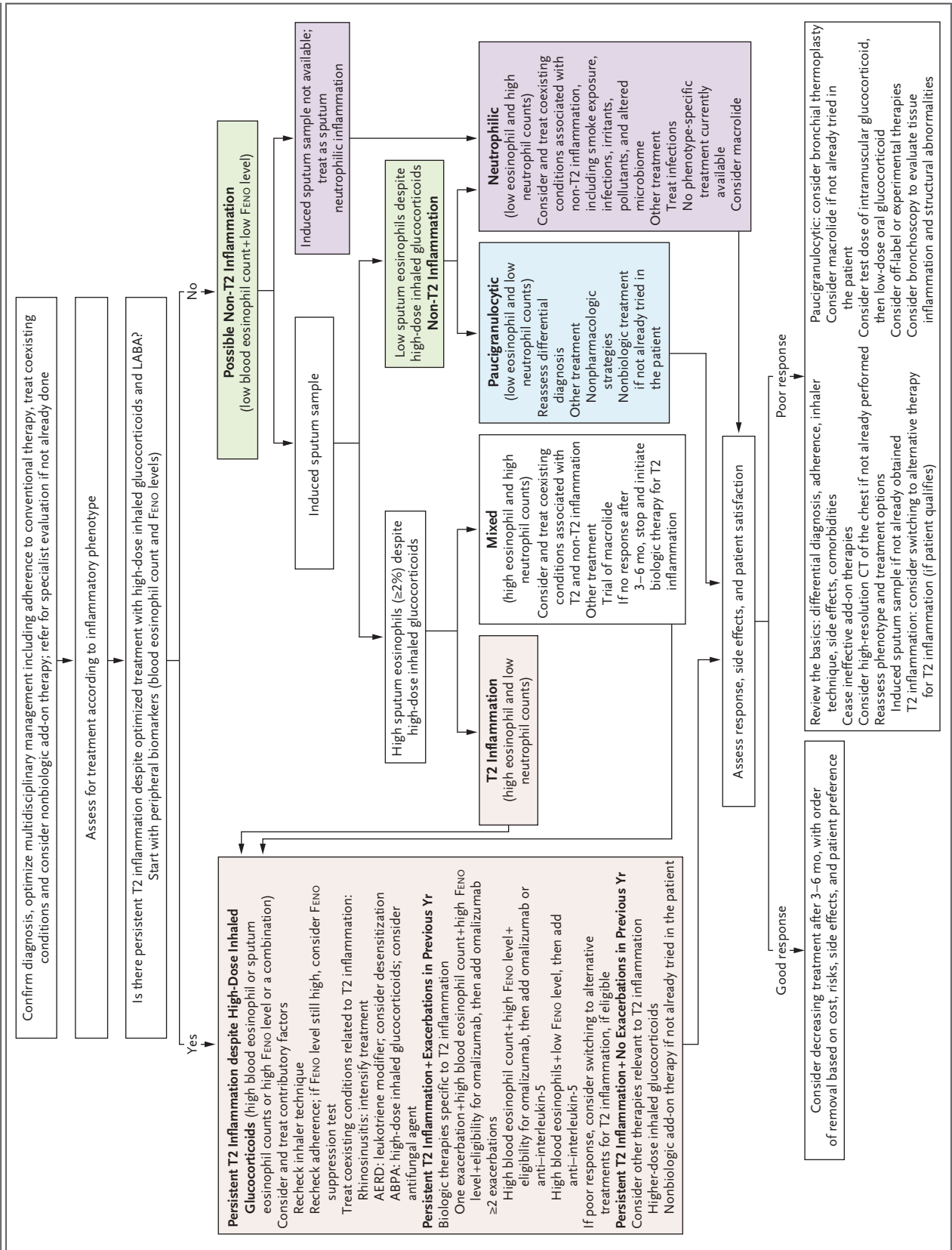
Confirm diagnosis, optimize multidisciplinary management including adherence to conventional therapy, treat coexisting conditions and consider nonbiologic add-on therapy; refer for specialist evaluation if not already done

Assess for treatment according to inflammatory phenotype

Is there persistent T2 inflammation despite optimized treatment with high-dose inhaled glucocorticoids and LABA? Start with peripheral biomarkers (blood eosinophil count and FeNO levels)

Yes

No

**Possible Non-T2 Inflammation** (low blood eosinophil count+low FeNO level)

Induced sputum sample not available; treat as sputum neutrophilic inflammation

Induced sputum sample

Low sputum eosinophils despite high-dose inhaled glucocorticoids **Non-T2 Inflammation**

High sputum eosinophils (≥2%) despite high-dose inhaled glucocorticoids

**Neutrophilic** (low eosinophil and high neutrophil counts)
Consider and treat coexisting conditions associated with non-T2 inflammation, including smoke exposure, infections, irritants, pollutants, and altered microbiome
Other treatment
Treat infections
No phenotype-specific treatment currently available
Consider macrolide

**Paucigranulocytic** (low eosinophil and low neutrophil counts)
Reassess differential diagnosis
Other treatment
Nonpharmacologic strategies
Nonbiologic treatment if not already tried in the patient

**Mixed** (high eosinophil and high neutrophil counts)
Consider and treat coexisting conditions associated with T2 and non-T2 inflammation
Other treatment
Trial of macrolide
If no response after 3–6 mo, stop and initiate biologic therapy for T2 inflammation

**T2 Inflammation** (high eosinophil and low neutrophil counts)

**Persistent T2 Inflammation despite High-Dose Inhaled Glucocorticoids** (high blood eosinophil or sputum eosinophil counts or high FeNO level or a combination)
Consider and treat contributory factors
Recheck inhaler technique
Recheck adherence; if FeNO level still high, consider FeNO suppression test
Treat coexisting conditions related to T2 inflammation:
Rhinosinusitis: intensify treatment
AERD: leukotriene modifier; consider desensitization
ABPA: high-dose inhaled glucocorticoids; consider antifungal agent
**Persistent T2 Inflammation+Exacerbations in Previous Yr**
Biologic therapies specific to T2 inflammation
One exacerbation+high blood eosinophil count+high FeNO level+eligibility for omalizumab, then add omalizumab or anti–interleukin-5
≥2 exacerbations
High blood eosinophil count+high FeNO level+eligibility for omalizumab, then add omalizumab or anti–interleukin-5
High blood eosinophils+low FeNO level, then add anti–interleukin-5
If poor response, consider switching to alternative treatments for T2 inflammation, if eligible
**Persistent T2 Inflammation+No Exacerbations in Previous Yr**
Consider other therapies relevant to T2 inflammation
Higher-dose inhaled glucocorticoids
Nonbiologic add-on therapy if not already tried in the patient

Assess response, side effects, and patient satisfaction

Good response

Poor response

Consider decreasing treatment after 3–6 mo, with order of removal based on cost, risks, side effects, and patient preference

Review the basics: differential diagnosis, adherence, inhaler technique, side effects, comorbidities
Cease ineffective add-on therapies
Consider high-resolution CT of the chest if not already performed
Reassess phenotype and treatment options
Induced sputum sample if not already obtained
T2 inflammation: consider switching to alternative therapy for T2 inflammation (if patient qualifies)

Paucigranulocytic: consider bronchial thermoplasty
Consider macrolide if not already tried in the patient
Consider test dose of intramuscular glucocorticoid, then low-dose oral glucocorticoid
Consider off-label or experimental therapies
Consider bronchoscopy to evaluate tissue inflammation and structural abnormalities

coids in patients with severe asthma.[40] The higher the number of prior exacerbations[39] and the higher the baseline blood eosinophil count,[41] the greater the reduction in exacerbations and (in the case of eosinophil numbers) the greater the $FEV_1$ improvement and reduction in symptoms. In a post hoc analysis of two studies of mepolizumab involving patients receiving high-dose therapy with inhaled glucocorticoids and LABAs, the effect on exacerbations was not significant in patients with baseline eosinophil levels less than 300 per microliter.[41] After treatment is started, blood eosinophil counts decline by an average of 75% within a month and failure to achieve this decrease raises questions about biologic efficacy; FENO is minimally reduced.[39] Reslizumab has been tested mostly in patients with a blood eosinophil count of at least 400 per microliter. There are no comparative studies between these anti–interleukin-5 treatments, and eosinophil cutoff levels have varied.

### BLOCKADE OF INTERLEUKIN-4 AND INTERLEUKIN-13 SIGNALING

Blockade of interleukin-13 has the potential to alter airway inflammation and smooth-muscle reactivity (Fig. 2), but one of two anti–interleukin-13 monoclonal antibodies, lebrikizumab, failed to provide consistent improvement in patients with type 2 inflammation.[42] The other, tralokinumab, continues in development (ClinicalTrials.gov numbers, NCT02194699 and NCT02281357). Of note, these drugs reduce FENO but increase circulating eosinophil counts.[42]

Dupilumab is another compound that has been tested for use in patients with severe asthma but has not yet been approved by the FDA for asthma (Table 2). Dupilumab is a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor that blocks both interleukin-4 and interleukin-13 signaling. A recent study showed a 60 to 80% reduction in exacerbations and a clinically important increase in $FEV_1$ with dupilumab in patients with asthma who were previously treated with medium-dose or high-dose inhaled glucocorticoids and LABAs[36]; notably, the blood eosinophil count (whether <300 per microliter or ≥300 per microliter) did not affect the response.[36] The patients in this study had higher levels of IgE than patients in studies of anti–interleukin-5,[39,41] raising the question of whether dupilumab may be particularly useful for patients with elevated IgE levels. Whether a minimum eosinophil count is necessary to produce efficacy has not been reported. Dupilumab reduces FENO and IgE levels but, like anti–interleukin-13, increases the blood eosinophil count, mostly temporarily.

### OTHER ANTIINFLAMMATORY THERAPIES

Other therapies that target additional moieties or pathways, outlined in Figure 2, are being tested in severe asthma or have shown efficacy in asthma challenges in humans but have not yet shown clinical efficacy in severe asthma.[43] These include therapies primarily targeting adaptive pathways of type 2 inflammation, including anti-CRTH2 (chemoattractant receptor homologue expressed by type 2 helper T cells), anti-TSLP (thymic stromal lymphopoietin), and a GATA3-specific DNA enzyme (DNAzyme),[43] and therapies targeting both adaptive and innate pathways of type 2 inflammation, such as anti–interleukin-23 and a soluble ST2 (interleukin-33 receptor) antibody.[44] Interventions primarily targeting neutrophilic pathways (e.g., anti–granulocyte–macrophage colony-stimulating factor,[45] CXCR2 antagonists targeting the receptor on neutrophils,[46,47] and an anti–interleukin-17 antibody[43]) have had only limited success, but only one of these studies[46] targeted the neutrophilic phenotype that would presumably be most responsive to such interventions. A recent study suggested that targeting mast cells might modify airway biology in a potentially beneficial manner in patients with severe asthma and little evidence of type 2 inflammation.[48] Immunosuppressive agents have been used in severe asthma with inconclusive evidence of efficacy and cannot be currently recommended.[2]

### BRONCHIAL THERMOPLASTY

Bronchial thermoplasty, approved by the FDA in 2010, involves radiofrequency ablation of airway

**Table 2. New Drugs for Severe Asthma in Adults.***

| Drug (Trade Name) and Dosage | Biologic Mechanism of Action | Suggested Clinical Population | Clinical Effects | Effects on Biomarkers | Adverse Effects and Cautions |
|---|---|---|---|---|---|
| **Approved** | | | | | |
| Omalizumab (Xolair), subcutaneous injection every 2 to 4 wk depending on dose (for dosing according to weight and IgE, see www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf) | Anti-IgE; binds to Fc receptor of free IgE (also reduces production of IgE) | Persons with IgE ≥30 IU/ml (upper limit of IgE varies according to weight and regulatory authority), positive skin test or elevated specific IgE level in response to perennial aeroallergen; best response in those with $F_{ENO}$ ≥20 ppb | Reduced exacerbations, small reduction in symptoms, minimal effect on $FEV_1$ | Small reduction in $F_{ENO}$, no reduction in circulating total IgE (measured by available assays) | Anaphylaxis (in an estimated 0.2% of patients); monitor for helminthic infection |
| Mepolizumab (Nucala), 100 mg given by monthly subcutaneous injection | Anti-interleukin-5; binds circulating interleukin-5 | Best response in those with two or more exacerbations in past year and ≥300 eosinophils/μl† | Reduced exacerbations, reduced symptoms, small or moderate effect on $FEV_1$ | Reduction in circulating eosinophils, no change in $F_{ENO}$ | Cases of zoster (rare); avoid in persons with active helminthic infection |
| Reslizumab (Cinqair), 3 mg/kg given by monthly intravenous infusion | Anti-interleukin-5; binds circulating interleukin-5 | Tested primarily in patients with more than one exacerbation in the past year and ≥400 eosinophils/μl | Reduced exacerbations, reduced symptoms, small or moderate effect on $FEV_1$ | Reduction in circulating eosinophils, no change in $F_{ENO}$ | Oropharyngeal pain slightly greater than with placebo, anaphylaxis (rare); avoid in persons with active helminthic infection |
| **Phase 3 testing** | | | | | |
| Benralizumab, given by subcutaneous injection | Anti-interleukin-5; binds interleukin-5 receptor with resultant lysis of eosinophils | Phase 3 efficacy primarily in those with two or more exacerbations in past year and ≥300 eosinophils/μl | Reduced exacerbations, reduced symptoms, moderate effect on $FEV_1$ | Reduction in circulating eosinophils, no change in $F_{ENO}$ | Not yet available |
| Dupilumab, given by subcutaneous injection | Anti-interleukin-4 and interleukin-13; binds common receptor subunit for interleukin-4 and interleukin-13 receptor | Tested primarily in patients with more than one exacerbation in the past 1 or 2 yr and ≥300 eosinophils/μl‡ | Reduced exacerbations, improved $FEV_1$ | Temporary increase in eosinophils, reduction in $F_{ENO}$ by approximately 30% | Reports of eosinophil counts >5000; may affect metabolism of CYP450 substrates; avoid live vaccines, most likely should avoid in persons with active helminthic infection |
| Fevipiprant, pill taken by mouth | Anti-CRTH2; blocks signaling at CRTH2 (the $PGD_2$ receptor) | To be defined; most likely type 2 | Most likely improved $FEV_1$ and reduced symptoms | Reduction in sputum eosinophils, no effect seen in peripheral blood or $F_{ENO}$ | Not yet available |

* The drugs listed have been approved by the Food and Drug Administration or are in phase 3 testing for asthma. CRTH2 denotes chemoattractant receptor homologue expressed by type 2 helper T cells, $FEV_1$ forced expiratory volume in 1 second, and $PGD_2$ prostaglandin $D_2$.
† In patients with at least three exacerbations, this drug may be effective if the eosinophil count is at least 150 per microliter.
‡ In one study,[36] patients with an eosinophil count of less than 300 also had a good response. However, the precise characteristics of this population with a lower eosinophil count still requires definition.

smooth muscle during three outpatient-administered bronchoscopic sessions. The only sham-controlled trial undertaken showed an increase in exacerbations during the treatment period and a large placebo effect but suggested a reduction in exacerbations and symptoms in the subsequent year when the initial exacerbations were excluded.[49] The clinical trials excluded patients with three or more exacerbations per year, $FEV_1$ below 60%, or chronic rhinosinusitis. Long-term follow-up studies have not compared bronchial thermoplasty with placebo, and no clear evidence exists to guide patient selection. Guidelines suggest that the procedure be restricted to trials or registries.[2]

## CONCLUSIONS

Patients who present with uncontrolled asthma despite the use of high-dose pharmacologic therapy have high asthma morbidity. In many patients, asthma can be well controlled after optimizing what is currently considered standard asthma treatment, including improving inhaler technique and adherence to treatment and systematically addressing coexisting conditions. With advances in identification of phenotypes with various pathophysiological mechanisms, the heterogeneous underpinnings of the disease are beginning to be exposed. New targeted treatment options are now available for a substantial proportion of patients with truly severe asthma who have the persistent type 2 inflammation phenotype despite the administration of high-dose inhaled glucocorticoids. However, considering the high cost of recent and forthcoming therapies,

substantial research is needed to identify the patients most (or least) likely to have a response to new treatments; research is also needed to develop surrogate markers for exacerbations, to reduce the length of early-phase studies. Particular areas of need relate to identifying the roots of the disease and relevant treatment targets in patients without type 2 inflammation or with progressive or permanent airway obstruction. The effort to target these processes will be an even greater challenge because of the likely diversity of causes and will require support to recruit and study large cohorts and follow them longitudinally.

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