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Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma

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ABSTRACT

Background: Severe asthma poses significant disease-related and economic burdens in the United States. Challenges in practice include how to define “severe asthma” for a given patient, knowing which are the right tests to perform and when, and having a better understanding of a patient’s asthma phenotype. Furthermore, current guidelines do not address a clear, practical approach to treatment that is based on a patient’s asthma phenotype. **Objective:** To develop a consensus on the definition of severe asthma, the role of biomarkers and phenotyping severe asthma, and the use of newer biologic therapies and bronchial thermoplasty to help guide practicing clinicians.

Methods: A roundtable meeting was convened with a panel of severe asthma experts to discuss areas in practice that are not adequately addressed by current guidelines, specifically phenotype-guided treatment.

Results: We describe a consensus on the definition of severe asthma, asthma phenotyping with the use of available biomarkers, and guiding principles for newer biologic therapies and bronchial thermoplasty.

Conclusion: To optimize therapy and improve outcomes such as daily symptoms, quality of life, exacerbations, and hospitalizations, a clear picture of a patient’s asthma phenotype is needed to guide therapy. Determining asthma phenotypes is the foundation of precision medicine for this persistent, often difficult-to-treat disease.

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Introduction

Severe asthma is a highly heterogeneous and burdensome disease that requires individualized assessment and management. The exact prevalence of severe asthma is unknown, but it has been reported to affect 5% to 10% of the asthma population.^{1,2} Although most patients with asthma respond favorably to treatment with low to moderate doses of inhaled corticosteroid (ICS), some patients have asthma that remains poorly controlled despite high doses of ICS with or without additional controlled therapies including long-acting β_2 -agonists (LABAs), long-acting muscarinic antagonists, leukotriene modifiers, and/or theophylline.³ Uncontrolled severe asthma significantly affects activities of daily living, morbidity, mortality, quality of life (QOL), and health care use.^{4–6} Although there have been significant advances in the understanding of asthma pathophysiology, severe asthma continues to challenge clinicians, and guidance on the individualization of care based on a patient’s asthma phenotype is needed.^{7,8}

In the United States, annual direct costs for asthma are estimated to be approximately \$50 billion.⁹ Understandably, with

progressively poorer responses to standard inhaled therapies, uncontrolled or severe asthma increases health care use, costs, and morbidity.¹⁰ Indeed, severe asthma accounts for approximately 50% of all asthma-related health care costs, direct (physician visits, hospitalizations, and medications) and indirect (missed school days and work absenteeism).¹¹ In a retrospective analysis of electronic medical record claims and records in the United States from 2004 through 2010, the incidence of uncontrolled asthma and severe asthma was found to be 17% and 8% of all patients with asthma, respectively.¹² Together with the fact that the Centers for Disease Control and Prevention has estimated the number of US individuals with asthma to be close to 25 million, these observations suggest that nearly 4.25 million people could have uncontrolled asthma and up to 2 million could have severe asthma. Casciano et al¹² also found that uncontrolled or severe asthma with increased eosinophil levels contributes to the economic burden of the disease. In patients with uncontrolled asthma and increased eosinophil levels, mean annual health care costs were \$28,644 vs \$14,188 for those without increased levels. Similarly, in patients with severe asthma and increased eosinophil levels, mean annual health care costs were \$33,192 vs \$13,168 for those without increased levels.¹²

Categorically, uncontrolled and severe asthma remains a health and economic burden in this country. We provide a consensus on a definition of severe asthma for practicing clinicians and the assessment of severe asthma phenotypes. We also discuss guiding principles for phenotype-based care and the use of biologic therapies and bronchial thermoplasty. This document is meant to present consensus opinion based on the participating panel members' interpretation of the medical literature and their personal practice experiences. It is neither a government-supported practice guideline nor an organization-supported practice parameter.

Methods

A roundtable meeting was convened to discuss the role of biologic therapies and bronchial thermoplasty in patients with severe asthma. Seven participants attended the roundtable meeting, which had the following goals: (1) define severe asthma for the practicing clinician; (2) discuss biomarker testing and how to better understand a patient's asthma phenotype; and (3) derive a consensus and guiding principles to aid clinician decision making regarding biologic therapy or bronchial thermoplasty for patients

with severe asthma. Select literature was retrieved by keyword search in PubMed and summarized as evidence to support the guidance derived by the panel. Participants acknowledged that the body of evidence needed to develop strong guidelines for the use of newer biologic therapies or bronchial thermoplasty is limited. However, guiding principles for practicing clinicians could be derived from available clinical trial evidence, experience in practice, and clinical logic.

Results

Defining Severe Asthma

There are several definitions for severe asthma outlined in available clinical practice guidelines (Table 1).^{1,13,14} This panel attempted to create a simple, unified definition for practicing clinicians that would be easily relatable to current practice while recognizing that not all uncontrolled asthma is severe and not all severe asthma is uncontrolled. After deliberation, the panel ultimately agreed to the following definition of severe asthma: asthma that, despite patient adherence, requires high-dose ICS plus LABA and/or additional controller medication or requires oral corticosteroids (OCSs) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy (Table 1). Important to the definition is acknowledgment that alternative therapies should be considered for any patient requiring high-dose ICS or OCS to control symptoms as part of an effort to decrease steroid exposure. In addition, panel members emphasized that inhaler technique, medication adherence, prescription fills and refills, allergen avoidance, comorbidities (eg, allergic rhinitis and gastro-intestinal reflux), medication side effects, and access to treatment and cost of treatment should be identified and addressed before concluding therapeutic failure. Without these steps, it is not possible to delineate whether a patient's persistent asthma symptoms are from the failure of a medication, inconsistent patient behaviors, or the progression of the disease. Clinicians also should bear in mind that a significant proportion of suspected severe asthma cases can involve other diseases that can mimic or worsen asthma. Thus, patients presenting with symptoms of severe asthma should be evaluated not only to confirm a diagnosis of asthma but also to exclude (or guide the treatment of) these other conditions.

The panel's definition assumes that all these assessments have been completed and that despite adherence to high-dose ICS plus LABA plus additional controller medications, a patient's asthma

Table 1
Comparison of Available Severe Asthma Definitions and the Consensus on a Definition for Severe Asthma From This Panel

Guideline	Year	Severe asthma definition
NHLBI and NAEPP-3 asthma guidelines	2007	Severe asthma defined as FEV ₁ <60% predicted, FEV ₁ /FVC decreased >5% and requiring step 5 or 6 treatment; persistent symptoms throughout the day, nighttime awakenings many times per week, SABA rescue use several times daily, and significant impairment of normal activities
ERS and ATS severe asthma guidelines	2014	Asthma (patients ≥6 y old) that requires treatment with guidelines-suggested medications for GINA steps 4–5 asthma (high-dose ICS + LABA or LTRA or theophylline) for previous year, or OCS for ≥50% of previous year, to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy Uncontrolled asthma defined as ≥1 of the following: Poor symptom control: ACQ score consistently >1.5, ACT score <20 (or “not well controlled” by NAEPP and GINA guidelines) Frequent severe exacerbations: ≥2 bursts of OCS (>3 days each) in previous year Serious exacerbations: ≥1 hospitalization, ICU stay, or mechanical ventilation in previous year Airflow limitation: after appropriate bronchodilator withhold FEV ₁ <80% predicted (in the face of decreased FEV ₁ /FVC defined as less than the lower limits of normal) Controlled asthma that worsens on tapering of these high doses of ICS or OCS (or additional biologics)
GINA guidelines	2017	Severe asthma is asthma that requires step 4 or 5 treatment (eg, high-dose ICS + LABA) to prevent it from becoming uncontrolled or asthma that remains uncontrolled despite this treatment
Panel consensus	2017	Asthma that, despite patient adherence, requires high-dose ICS + LABA and/or additional controller medication or requires OCS to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATS, American Thoracic Society; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OCS, oral corticosteroid; SABA, short-acting β -agonist.

remains symptomatic and uncontrolled. The panel's definition also assumes that, in absence of further actions, the patient would need (or could already be taking) regular OCS. At this point, and before regular use of OCS, additional medical interventions should be considered based on a patient's asthma phenotype.

Complications of OCS Use

The use of OCS is common practice for patients whose asthma remains uncontrolled despite adherence to standard high-dose inhaled therapies. Investigators found that 63% of patients with uncontrolled asthma used OCS more than once per week within the past year compared with 23% of patients whose asthma was controlled.⁶ However, treatment of asthma symptoms with OCS comes with significant acute and long-term burden. One observational study used health insurance claims data (1997–2013, Medicaid) from Florida, Iowa, Kansas, Missouri, Mississippi, and New Jersey to investigate the burden of OCS use in patients with severe asthma.¹⁵ Patients with severe asthma ($N = 3628$, mean age 57.6 years; 68% female) with more than 6 months of continuous medium and high OCS exposure had significantly higher risks of OCS-related complications, including infections and cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications vs those with low exposure.¹⁵ Furthermore, complications of OCS use were dose dependent. In another retrospective study (claims data from a large commercial database from 2003 through 2014; $N = 12,697$), the odds of developing associated complications were dose dependent (odds ratios 2.50, 2.95, and 3.32; $P < .05$ vs no exposure) for low (<5 mg/d), medium (≥ 5 –10 mg/d), and high (>10 mg/d) OCS exposure. Furthermore, the frequency of inpatient visits followed a similar dose-dependent pattern.¹⁶ Overall, complications related to OCS amounted to an estimated annual health care cost differential of up to \$8,560 among OCS users vs nonusers.¹⁷ Effective OCS-sparing therapies are needed for patients with severe asthma.

Panel Consensus on the Use of Regular OCS

When high doses of OCS are given regularly, patients have a greater risk of experiencing adverse events. Clinicians should avoid using OCS if possible and when other treatment options are available based on a patient's phenotype.

A Phenotype-Driven Approach to Asthma Management

There are well-recognized groups of patients with asthma who are, in general, more difficult to treat.¹⁸ These include the elderly, specific underserved minority groups, smokers, patients who are obese, patients with low vitamin D levels, patients with severe asthma who have frequent exacerbations, and patients with a strong allergic component to their asthma. However, an overarching unmet need in asthma management, and a gap in available clinical practice guidelines, is a phenotype-based approach to treatment. The need for asthma phenotype-targeted management has emerged as our understanding of the disease has improved.

One phenotypic classification, in particular, that has emerged as an important consideration in the therapeutic decision-making process is the inflammatory phenotype. Airway eosinophilia has long been recognized as a common feature in asthma, and patients with eosinophilic asthma ($>2\%$ eosinophils in sputum) generally show greater responsiveness to steroids compared with non-eosinophilic counterparts.¹⁹ More recently, studies evaluating the percentages of eosinophils and neutrophils in induced sputum have clarified the existence of 4 inflammatory subtypes that include eosinophilic, neutrophilic, mixed granulocytic, and pauci-granulocytic asthma.²⁰ Although the role of neutrophils in asthma remains to be fully elucidated, increased neutrophils have been reported in severe asthma and sudden-onset fatal asthma.²¹

Consistent with a longstanding recognition of the clinical and therapeutic relevance of eosinophilic asthma, the 2014 American Thoracic Society (ATS) guidelines conditionally recommend that treatment be guided by clinical criteria and sputum eosinophil counts (obtained by experienced centers) for adults with severe asthma.¹ Under circumstances involving a lack of access to sputum assessment, blood eosinophil counts could be of value in phenotypic evaluation. Wagener et al²² found that blood eosinophils had the highest accuracy in identification of sputum eosinophilia in patients with mild to moderate or severe asthma and concluded that the use of blood eosinophils can facilitate individualized treatment and management. Furthermore, peripheral blood eosinophil count at screening coupled with clinical characteristics, such as frequent exacerbations, has been shown to successfully predict treatment response.^{23,24} Asthma phenotyping is the path to precision medicine and there remains a large gap between current and ideal practice on this issue. Patients with truly severe asthma represent fewer than 10% of all patients with asthma but account for a disproportionate amount of health care-related medical costs for asthma.

Panel Consensus on Phenotyping

Asthma phenotyping by biomarker testing should be carried out at diagnosis. Global Initiative for Asthma guidelines state that asthma should be phenotyped when it becomes difficult to treat. When possible, the panel recommends that phenotyping be done sooner in the disease course to potentially prevent poor outcomes and before patients worsen.

Recommended tests include serum immunoglobulin E (IgE; allergic asthma; specific IgE recommended to identify allergic triggers to avoid) and blood eosinophils (T-helper cell type 2 [T_H2] type inflammatory asthma). Although not currently feasible for widespread use, induced sputum is generally considered the gold standard noninvasive method for assessing airway inflammation in asthma to identify inflammatory phenotype and could be valuable in phenotyping patients with asthma.²⁵ Moreover, sputum analysis allows for assessment of not only eosinophil levels but also other inflammatory cells (particularly neutrophils, which are not available from blood).

In addition, fractional exhaled nitric oxide (FeNO) is conditionally recommended as an aid for asthma diagnosis and as a marker for eosinophilic airway inflammation, symptom frequency, and frequency of emergency care use.^{1,26} It also can be used as a biomarker for steroid responsiveness; a higher FeNO indicates a patient will more likely respond to ICS therapy,²⁷ which could be useful information in patients with worsening disease and waning FeNO. These patients might not respond as well to ICS. In patients who are or will become nonresponsive to ICS, determining an appropriate treatment strategy beyond ICS is critical to maintaining asthma control and improving outcomes. The ATS guidelines on the use of FeNO in asthma concluded that FeNO might allow clinicians to (1) detect eosinophilic airway inflammation, (2) determine the likelihood of ICS responsiveness, and (3) unmask nonadherence to ICS therapy.²⁶ However, the European Respiratory Society and ATS guidelines for severe asthma suggest that clinicians do not use FeNO to guide therapy in adults or children with severe asthma, because the available evidence on its use as a marker might not outweigh the expenditure for the test.¹ If access prevents testing at diagnosis, then the panel recommends that testing be done when a patient's asthma remains uncontrolled despite treatment with high-dose ICS plus LABA therapy, but before the use of regular OCS.

Therapeutic Decision Making for Severe Asthma

Because not all patients with asthma respond well to standard inhaled therapies and 5% to 10% of patients are classified as having

severe asthma,¹ new approaches are in development. However, available guidance on treatment decisions is built on a stepwise approach to managing increasingly difficult-to-treat symptoms, not by the asthma phenotype of the patient. Furthermore, not all products in development become viable therapies for clinical application. Even rationally designed targeted biologic therapies can fail in clinical trials. Interleukin (IL)-13 is a pleiotropic T_H2 cytokine associated with underlying disease mechanisms in asthma including airway hyperresponsiveness, mucus hypersecretion, and eosinophilia. However, the anti-IL-13 therapies lebrikizumab and tralokinumab have shown less than hopeful results in patients with asthma and, based on available data, are unlikely to receive approval from the Food and Drug Administration (FDA).^{28,29}

Tiotropium

In 2015, tiotropium was approved for long-term, once-daily, maintenance treatment of asthma in patients at least 12 years of age.³⁰ In 2017, it was approved for the same use in children at least 6 years of age. Tiotropium exerts its bronchodilator effects by antagonizing muscarinic (m3) acetylcholine receptors in the airway. Previously, tiotropium was found superior to doubling the dose of ICS but non-inferior vs the addition of LABA therapy in African American adults with uncontrolled asthma already receiving ICS therapy.^{31,32} In 2 replicate randomized trials, tiotropium also was shown to increase the time to severe exacerbations in adult patients with poorly controlled asthma already treated with ICS plus LABA therapy.³³ Studies of patients with severe asthma 6 to 17 years of age showed that tiotropium added to standard background controller therapy improved peak forced expiratory volume in 1 second (FEV₁; 0–3 hours) at 12 weeks and was safe at 1 year.^{34–36} The most common side effects in these studies were mild or moderate and included asthma, bronchitis, decreased peak expiratory flow rate, headache, nasopharyngitis, rhinitis, upper respiratory tract infection, viral infection, allergic rhinitis, tonsillitis, and viral respiratory tract infection. No unexpected safety signals were found in this population of patients with asthma treated with tiotropium.

Panel consensus on the use of tiotropium

Tiotropium should be added to high-dose ICS plus LABA therapy in patients with uncontrolled asthma before the use of daily OCS, newer biologics, or bronchial thermoplasty. This approach is meant to help regain control of a patient's symptoms, improve lung function, and prevent exacerbations in the short term by added bronchodilator effects. As symptoms and lung function improve, efforts to determine the patient's asthma phenotype (if not already known) can be made to enable the next step in care to be appropriately individualized.

Omalizumab

Omalizumab was approved for moderate-to-severe persistent asthma in patients at least 12 years old in 2003 and then for patients 6 to 11 years old in 2016, with a positive skin test reaction or in vitro reactivity to a relevant perennial aeroallergen and increased serum IgE (minimum ≥ 30 IU/mL; recommended dosing is done by IgE level and body weight) in addition to symptoms inadequately controlled with ICS. This was the first targeted biologic for allergic asthma (IgE⁺) and its data have been previously reported.^{37–39} In a 48-week study of 850 of patients with severe asthma (defined as inadequately controlled despite treatment with high-dose ICS plus LABA [17% receiving OCS]), omalizumab therapy for 48 weeks decreased exacerbations by 25% and improved asthma QOL, but did not have an effect on asthma symptoms or lung function.⁴⁰ After stratifying patients by their baseline levels of T_H2 inflammatory biomarkers (post hoc), patients with severe asthma and higher levels of T_H2 biomarkers (eg, eosinophils) had greater

decrease of exacerbations than those without increased T_H2 biomarkers.⁴¹ More recent reports have shown that the long-term effectiveness and safety of omalizumab is sustained beyond 1 year in children and adults with severe allergic asthma.^{42–44}

Panel consensus on the use of omalizumab

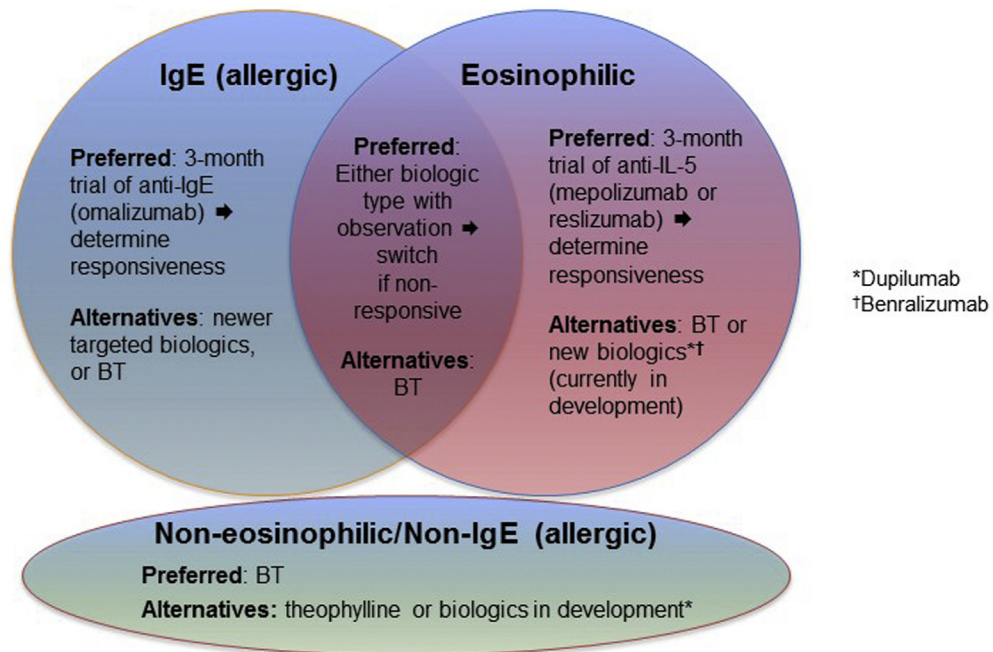
For IgE⁺ allergic severe asthma, omalizumab can be a first option for patients with persistent symptoms after failure of triple therapy (high-dose ICS + LABA and tiotropium) and before regular OCS use, newer targeted biologics, or bronchial thermoplasty (Fig 1). Treatment failure can be defined as the persistent lack of asthma symptom control or asthma disease worsening. This is evidenced by increased frequency of daily asthma symptoms (cough or dyspnea in the daytime or night or after exertion), increased short-acting β_2 -agonist use (>2 days/wk), decreased daily activity levels that were otherwise normal (eg, exercise or school attendance), or exacerbations despite adherence to prescribed treatment.¹¹

IL-5 targeted therapies

Because IL-5 is a pro-eosinophilic cytokine that is a potent mediator of eosinophil hematopoiesis and contributes to eosinophilic inflammation in the airways, IL-5 has been a primary target in asthma treatment. Currently, 2 anti-IL-5 antagonist monoclonal antibodies are available, mepolizumab and reslizumab, and 1 is in clinical development, benralizumab, which blocks the IL-5 receptor on eosinophils. Mepolizumab was approved by the FDA for add-on maintenance treatment of severe asthma in patients at least 12 years old who have an eosinophilic phenotype (≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L within 12 months before enrollment). Several trials have shown the efficacy of mepolizumab in severe asthma and eosinophilia (Table 2).^{23,24,45} Mepolizumab is administered subcutaneously every 4 weeks and has been associated with rare hypersensitivity reactions and rare *Herpes zoster* infections. The most common adverse events observed in trials of mepolizumab were headache, injection site reaction, back pain, and fatigue.

Reslizumab was approved by the FDA in 2016 and is an anti-IL-5 antagonist monoclonal antibody indicated for the add-on maintenance treatment of patients at least 18 years old with severe asthma and with an eosinophilic phenotype (≥ 400 cells/ μ L). Several trials have shown the efficacy of reslizumab in severe asthma with eosinophilia (Table 2).^{46–48} In duplicate randomized placebo-controlled trials, reslizumab significantly decreased airflow obstruction, significantly decreased exacerbations, and demonstrated a clinically meaningful improvement in Asthma Quality of Life Questionnaire score compared with placebo.⁴⁶ Reslizumab is given intravenously every 4 weeks and has a boxed FDA warning for anaphylaxis. The most common adverse event observed in trials of reslizumab was oropharyngeal pain.

Benralizumab is a monoclonal antibody that blocks IL-5 receptor- α and is currently in clinical development (Table 2). It induces direct, rapid, and nearly complete depletion of eosinophils by natural killer cell-mediated antibody-dependent cellular cytotoxic effects; previously, it has been associated with a decrease in airway eosinophils from baseline (≥ 300 cells/ μ L) and a depletion of other IL-5 receptor-bearing cells.⁴⁹ The increased efficacy of benralizumab is believed to be due to its targeting of the interleukin receptor, rather than the cytokine, which in turn enables luminal depletion of eosinophils. When administered intravenously as a single dose, it demonstrates an acute benefit in lowering asthma exacerbation rates in patients presenting with an exacerbation associated with eosinophilia.⁵⁰ Alternatively, it can be administered subcutaneously every 4 weeks for the first 3 doses followed by every 8 weeks thereafter. Using this dosing regimen, investigators in the recent ZONDA trial found that benralizumab treatment decreased the use of maintenance oral glucocorticoid therapy and preserved asthma



Note: Although chronic OCS is an accepted therapy in the NAEPP and GINA guidelines, the panel recommends that all other therapies be considered *prior* to employing maintenance OCS.

Figure 1. Therapeutics options for severe asthma. BT, bronchial thermoplasty; IgE, immunoglobulin E; IL-5, interleukin-5.

control in patients with severe eosinophilic asthma.⁴⁹ Although benralizumab remains under FDA review, a decision is expected at the end of 2017.

In severe asthma burdened by T_H2 -type inflammation, it is important to attenuate eosinophilia by affording patients an appropriately matched therapy. Anti-IL-5 therapy decreases eosinophil levels, and the decrease of eosinophils correlates with efficacy (eg, decreased exacerbation) in trials of patients with severe asthma.

Panel consensus on the use of anti-IL-5 therapies

For eosinophilic severe asthma, treatment with an anti-IL-5 therapy can be a first option for patients with persistent symptoms after failure of triple therapy with high-dose ICS plus LABA and tiotropium and before regular OCS use or bronchial thermoplasty (Fig 1). Anti-IL-5 therapy also can be considered for patients with IgE^+ who have eosinophilia and an inadequate response to omalizumab. Without direct-comparison studies, a recommendation for which agent should be used first cannot be determined.

Macrolide antibiotics

Evidence suggests that chronic or subacute infection with atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* could be responsible for poor symptom control in a subset of patients with asthma.^{51–54} In recent work, individuals with refractory asthma were evaluated using bronchoscopy, visual evaluation of the upper and lower airways, endobronchial biopsies, brushes and bronchoalveolar lavage for cell counts, histology, cultures, and polymerase chain reaction studies.⁵⁵ Patients identified as having positivity for *M pneumoniae* and *C pneumoniae* were treated with macrolide antibiotics, demonstrating significant improvements in percentage of predicted FEV_1 and Asthma Control Test scores after 6 months of therapy. Although the mechanisms by which macrolide antibiotics exert their therapeutic effects remain incompletely understood, they are associated with antimicrobial

and anti-inflammatory properties because of their capacity to alter protein synthesis.

Panel consensus on the use of macrolide antibiotics

Macrolide antibiotics are an effective therapeutic option frequently used in practice and can be considered under certain circumstances for patients with a non- T_H2 type inflammation asthma phenotype.

Bronchial thermoplasty

Bronchial thermoplasty is intended to decrease airway smooth muscle mass because smooth muscle hypertrophy can worsen bronchial hyperreactivity and bronchoconstriction.^{56,57} Several studies have shown that bronchial thermoplasty decreases airway smooth muscle mass by at least 60%.^{58–60} Furthermore, this procedure has been shown to alter the deposition of collagen and reduce α -smooth muscle actin and decrease inflammatory cytokines including transforming growth factor- β and RANTES (regulated upon activation, normal T-cell expressed and secreted).^{59,60}

In 2010, bronchial thermoplasty was approved for the treatment of adults with severe asthma and uncontrolled symptoms despite treatment with ICS and long-acting bronchodilators. Bronchial thermoplasty is performed using the Alair Bronchial Thermoplasty System (Boston Scientific, Marlborough, Massachusetts). A radio-frequency catheter is inserted through a bronchoscope to deliver a maximum of 120 J of thermal energy to airways that are 3 to 10 mm in diameter.⁶¹ In each session (3 separate sessions up to 45 minutes in duration that are done in 3-week intervals), different areas of the lung are targeted with 30 to 70 pulses of thermal energy. Special attention must be given to the bronchus, because incomplete treatment of this area can result in treatment failure. After each session, patients are monitored until their post-bronchodilator FEV_1 is at least 80% of what it was before the procedure. Although many patients experience increased symptoms within 72 hours after the procedure, these symptoms return to baseline within 1 week.

Table 2
Overview of Interleukin-5–targeted or Interleukin-5 Receptor-targeted Therapies for Severe Asthma

Study; agent	Patients	Characteristics	FEV ₁	Exacerbations	Steroid use ^a	Quality of life
Pavord et al, ²³ DREAM; IV mepolizumab 75, 250, 750 mg every 4 wk for 52 wk	621	Inadequate control on high-dose ICS + ≥1 other controller ± OCS; blood eos ≥300; ≥2 exacerbations in previous year	NS	39%–52% decrease ($P \leq .0005$ vs placebo)	NR	NS
Ortega et al, ²⁴ MENSA; mepolizumab 75 mg IV or 100 mg SC every 4 wk for 32 wk	576	Inadequate control on high-dose ICS + ≥1 other controller ± OCS; blood eos ≥150; ≥2 exacerbations in previous year	+98–100 mL ($P < .05$ vs placebo)	47%–53% decrease ($P < .001$ vs placebo)	NR	Clinically meaningful improvement in SGRQ score vs placebo
Bel et al, ⁴⁵ SIRIUS; mepolizumab 100 mg SC every 4 wk for 24 wk (steroid-sparing study)	135	Inadequate control on high-dose ICS + ≥1 other controller; 6-mo history of OCS (prednisone 5–35 mg/d or equivalent); blood eos ≥300 during 12-mo period before screening or ≥150 during optimization phase	NS	32% decrease ($P = .04$ vs placebo)	23% had 90%–100% decrease in OCS dose ($P = .008$ vs placebo); 54% with ≥50% decrease in daily OCS dose ($P = .03$ vs placebo)	Clinically meaningful improvements in ACQ-5 and SGRQ scores vs placebo
Castro et al, ⁴⁶ duplicate RCTs; reslizumab 3.0 mg/kg IV every 4 wk for 52 wk	953	Inadequate control on medium- to high-dose ICS + ≥1 exacerbation in past year; blood eos ≥400 cells/μL	+220 mL ($P < .0001$; pooled data vs placebo)	Study 1, 50% decrease; study 2, 59% decrease ($P < .0001$ for studies 1 and 2 vs placebo)	NR	Clinically meaningful improvement in AQLQ and ACQ-7 scores vs placebo
Bjerner et al ⁴⁷ ; reslizumab 0.3 and 3 mg/kg IV every 4 wk for 16 wk	315	Inadequate control on medium-dose ICS + ≥1 exacerbation in past year; blood eos ≥400 cells/μL	0.3 mg/kg + 115 mL ($P = .024$ vs placebo); 3.0 mg/kg + 160 mL ($P = .0018$ vs placebo)	NR	NR	Clinically meaningful improvement in AQLQ score (3.0 mg/kg vs placebo)
Corren et al ⁴⁸ ; reslizumab 3.0 mg/kg IV every 4 wk for 16 wk	496	Inadequate control on medium-dose ICS + ≥1 exacerbation in past year; unselected for eos; blood eos <400 cells/μL in 80%; blood eos ≥400 cells/μL in 20%	NS	NR	NR	71% had clinically meaningful improvement in ACQ-7 score vs placebo
Fitzgerald et al, ⁶² CALIMA; 30 mg SC benralizumab every 4 or 8 wk for 48 wk	1,306	Treatment with medium- or high-dose ICS + LABA for ≥1 y ± OCS increase; blood eos <300 and ≥300 cells/μL; ≥2 exacerbations in previous year	+116–125 mL ($P < .01$ vs placebo)	≥300 cells/μL, 36% decrease (every 4 wk; $P = .0018$ vs placebo); 28% decrease (every 8 wk; $P = .0188$ vs placebo); <300 cells/μL, 36% decrease (every 4 wk; $P = .015$ vs placebo); 40% decrease (every 8 wk; $P = .0048$ vs placebo)	NR	Clinically meaningful improvement in ACQ-6 score (every 4- and every 8-wk regimens vs placebo) and AQLQ score (every 8-wk regimen vs placebo) in patients with eos ≥300 cells/μL
Bleecker et al, ⁶³ SIROCCO; benralizumab 30 mg SC every 4 or 8 wk for 48 wk	621	Treatment with medium- or high-dose ICS + LABA for ≥1 year ± OCS increase; blood eos <300 and ≥300 cells/μL; ≥2 exacerbations in previous year	+106–159 mL ($P = .02$ vs placebo)	≥300 cells/μL, 45% decrease (every 4 wk; $P = .0001$ vs placebo); 51% decrease (every 8 wk; $P = .0001$ vs placebo)	NR	Clinically meaningful improvement in AQLQ score (every 8-wk regimen in patients with eos ≥300 cells/μL; $P = .0036$ vs placebo)

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; eos, eosinophils; FEV₁, forced expiration in 1 second; ICS, inhaled corticosteroids; IV, intravenously; LABA, long-acting β-agonist; NR, no response; NS, not significant; OCS, oral corticosteroid; RCTs, randomized controlled trials; SC, subcutaneously; SGRQ, St George's Respiratory Questionnaire.

^aAnalyses on corticosteroid-sparing effects in patients with severe asthma in many of these trials is ongoing.

Approval of bronchial thermoplasty was based on 3 randomized trials and long-term follow-up.^{56,64–67} In the Asthma Research Intervention (AIR) trial of patients with moderate-to-severe persistent asthma, fewer mild, but not severe, exacerbations were observed with improvement in symptom-free days, asthma control, and QOL compared with the control group at 3 and 12 months.⁵⁶ Similarly, the sham-controlled AIR-2 trial showed an improvement in QOL (sham control QOL also improved) and decreases in days lost from work, exacerbations (32% decrease in severe exacerbations), and health care resource usage (eg, 84% decrease in emergency department visits).⁶⁵ Other measures, such as lung function, symptom scores, and need for rescue medication, were not significantly different between bronchial thermoplasty and sham groups.

Five-year follow-up of patients in trials using bronchial thermoplasty showed a sustained decrease in exacerbations, decreased health care resource usage, and no further decline in lung function.^{66,68} The most common adverse event is temporary worsening of respiratory-related symptoms, which typically occurs within 24 hours of the procedure and resolves on average within 7 days. With each procedure, there is a 3.4% risk that these symptoms will require hospitalization. Overall, bronchial thermoplasty has proved an effective therapeutic option (in addition to macrolide antibiotics and OCS, which can be considered under certain circumstances) for patients with a non-T_H2 type inflammation asthma phenotype. Furthermore, bronchial thermoplasty has shown similar efficacy in patients with other asthma phenotypes and airway smooth muscle hypertrophy.

Panel consensus on the use of bronchial thermoplasty

For nonallergic, non-eosinophilic (non-T_H2) severe asthma, bronchial thermoplasty can be a first option for patients with persistent symptoms and who have variable airflow obstruction as demonstrated by bronchodilator reversibility after failure of triple therapy with high-dose ICS plus LABA and tiotropium but before regular OCS use or a targeted biologic (Fig 1). Bronchial thermoplasty also can be considered an alternative therapy for patients with allergic or eosinophilic asthma who have had an inadequate response to initial biologic therapy.

On the Near Horizon for Severe Asthma: Dupilumab

Interleukin-4 plays a critical role in the differentiation of CD4⁺ lymphocytes into T_H2 cells, induction of B-cell isotype switching to increase IgE production, upregulation of IgE receptors, expression of vascular cell-adhesion molecule 1, eosinophil transmigration into the lungs, inhibition of T-lymphocyte apoptosis, and mucus secretion. Dupilumab is a human monoclonal antibody that binds to the α -subunit of the IL-4 receptor and therefore is expected to inhibit downstream signaling of IL-4 and IL-13 cytokines of T_H2 cells that play a key role in allergy and asthma. Previously approved for the treatment of atopic dermatitis, dupilumab was shown to significantly decrease the odds of an asthma exacerbation in an early investigation.⁶⁹ In a more recent international phase 2b study of patients (N = 769) with severe asthma uncontrolled with medium- to high-dose ICS plus LABA therapy, dupilumab (200 or 300 mg subcutaneously every 2 or 4 weeks) increased lung function (+210–260 mL improvements in FEV₁ depending on the dose used; $P < .007$ vs placebo) and decreased exacerbations (54%–71% overall depending on the dose) regardless of baseline eosinophil count.⁷⁰ The most common adverse events with dupilumab in this study were upper respiratory tract infection and injection-site reaction.

Panel Consensus on the Use of Dupilumab

This agent currently remains under clinical investigation. However, FDA approval for an asthma indication is expected in the

near future. Once approved, anti-IL-4 therapy with dupilumab will likely be added to the biologic agents available for eosinophilic (high or low eosinophilia) and non-eosinophilic, elevated FeNO (T_H2) severe asthma after failure of triple therapy (high-dose ICS + LABA and tiotropium) but before regular OCS use (Fig 1).

Discussion

Although there have been significant advances in the understanding of asthma pathophysiology and the development of commensurate treatment modalities, severe asthma continues to pose significant challenges in real-world practice. These challenges are measured by daily asthma symptom burden, poor response to high doses of inhaled asthma medications, hospitalizations for asthma exacerbations, health care usage, lower QOL, and patient morbidity and mortality. Addressing important unmet medical needs in patients with severe asthma requires that clinicians use tests to assess asthma phenotype and treat based on the results of these tests. We describe a consensus on asthma phenotyping and guiding principles for newer biologic therapies and bronchial thermoplasty. Although several clinical practice guidelines exist, they do not provide guidance on a phenotype-specific approach to care, which has become increasingly important. Without practical guidance, clinicians could be unsure when to use a newer biologic or bronchial thermoplasty. Furthermore, efforts to sway practice away from the default position of using regular OCS when other therapeutic options exist should be at the forefront of discussion.

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