Severe Asthma Reference Guide
Phenotypes, Endotypes, Biomarkers, and Treatment

A CME/CE-certified supplement to CHEST® Physician

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About 5% to 15% of patients with asthma have severe or uncontrolled asthma and experience ongoing symptoms despite daily treatment with inhaled or systemic corticosteroids and supplemental medications such as long-acting β agonists. Patients with severe asthma account for much of the morbidity and mortality associated with asthma. Severe asthma is a heterogeneous disease. In the last decade, researchers have defined many of the biological mechanisms underlying severe asthma. More recently, new treatments, as well as biomarkers that can predict response to the new treatments, are contributing to the development of personalized therapy for patients with severe asthma.

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Learning Objectives

• Recognize and differentiate the phenotypes and endotypes of severe asthma
• Describe the mechanisms underlying the primary asthma endotypes
• Explain the role of biomarkers in identifying endotypes and determining appropriate therapy
• Identify the mechanisms of action of current and emerging therapies for severe asthma

Background

In the United States, a majority of patients with asthma respond to standard inhaled maintenance therapy. About 5% to 15% of patients have severe or uncontrolled asthma and experience ongoing symptoms despite daily treatment with inhaled or systemic corticosteroids and supplemental medications such as long-acting β2 agonists. Patients with severe asthma are more likely to experience repeated serious exacerbations that interfere with daily activities. These individuals account for much of the morbidity and mortality associated with asthma, and, because of their high rates of healthcare utilization and missed days of school and work, at least 50% of asthma-related costs. Asthma costs in the United States were an estimated $81.9 billion in 2013, including medical expenses, missed school and work days, and deaths.

Severe asthma in patients at least 6 years old is defined as asthma that would be uncontrolled if not for one of the following:

• High-dose inhaled corticosteroids (ICS) plus either a long-acting β2 agonist (LABA) or leukotriene modifier/theophylline for the previous year
• Systemic corticosteroids for at least 50% of the prior year
• Asthma that is uncontrolled despite these therapies

Uncontrolled asthma is defined as one of the following:

• Poor symptom control (ie, Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20, or not well controlled by National Asthma Education and Prevention Program/Global Initiative for Asthma guidelines)
• Two or more bursts of systemic corticosteroids for more than 3 days each in the prior year
• At least one hospitalization, intensive care unit stay, or mechanical ventilation in the prior year
• Forced expiratory volume in 1 second (FEV1) <80% predicted after bronchodilator withhold

Asthma is a heterogeneous disease; patients present with a variety of clinical characteristics (phenotypes), which are presumably the result of underlying biological mechanisms or endotypes. Biomarkers can contribute to the identification of patients with certain endotypes and help predict which patients are most likely to respond to certain therapies. Treatments targeting specific disease mechanisms have emerged in recent years, allowing for a more personalized approach to patients with asthma.

This monograph summarizes the current state of the science behind severe asthma phenotypes, endotypes, biomarkers, and therapies.
**Phenotypes**

Asthma phenotypes may be organized according to their association with specific triggers, patient characteristics, or features of clinical presentation (Table 1). These phenotypes present as clusters in patients with asthma.

**Phenotypic Clusters**

The National Heart, Lung, and Blood Institute’s Severe Asthma Research Program (SARP) conducted a cluster analysis in adults with mild, moderate, and severe asthma to identify which phenotypes most commonly present together. The cluster analysis was performed on 726 subjects using 34 variables.

Five phenotypic clusters were identified, which could be distinguished mainly by age of disease onset and lung function. Patients with frequent use of oral corticosteroids for asthma exacerbations, hospitalizations for severe near-fatal asthma, and increased medication requirements were assigned to clusters 3, 4, and 5. A similar cluster analysis in a pediatric cohort found 4 clusters based mainly on asthma duration, the number of asthma controller medications, and lung function. Children assigned to clusters 3 and 4 had the highest prevalence of comorbidity and high symptom burden. Table 2 integrates characteristics of adult and pediatric severe asthma clusters.

Researchers analyzing other adult asthma cohorts, including “real-life” clinic populations, have found clusters with similar characteristics. This finding suggests that these clusters are a stable feature of asthma that can be observed in multiple settings and across different regions of the world.

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**Table 1. Asthma Phenotypes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggers</td>
<td>• Atopic/nonatopic</td>
</tr>
<tr>
<td></td>
<td>• Aspirin (aspirin-exacerbated respiratory disease)</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td>• Exercise</td>
</tr>
<tr>
<td></td>
<td>• Occupational exposure to irritants</td>
</tr>
<tr>
<td></td>
<td>• Smoking</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>• Age of onset (childhood/adult/older adult)</td>
</tr>
<tr>
<td></td>
<td>• Gender</td>
</tr>
<tr>
<td></td>
<td>• Perimenopausal onset</td>
</tr>
<tr>
<td></td>
<td>• Race</td>
</tr>
<tr>
<td></td>
<td>• Obesity</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>• Exacerbation prone</td>
</tr>
<tr>
<td></td>
<td>• Steroid responsive/resistant</td>
</tr>
<tr>
<td></td>
<td>• Low lung function</td>
</tr>
<tr>
<td></td>
<td>• Less reversible airway obstruction</td>
</tr>
</tbody>
</table>

**Table 2. Severe Asthma Clusters, Severe Asthma Research Program (SARP)**

<table>
<thead>
<tr>
<th>Early-Onset Allergic Asthma*</th>
<th>Later-Onset Adult Asthma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric, Cluster 3</td>
<td>Pediatric, Cluster 4</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Adult, Cluster 4</td>
</tr>
<tr>
<td>Infancy</td>
<td>Preschool to early school age</td>
</tr>
<tr>
<td>Toddler to preschool</td>
<td>Teen or adult</td>
</tr>
<tr>
<td>Partly reversible</td>
<td>Adult</td>
</tr>
<tr>
<td>Reversible</td>
<td></td>
</tr>
<tr>
<td>Airflow obstruction</td>
<td></td>
</tr>
<tr>
<td>Daily OCS?</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hospitalization in past year?</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Common comorbidities</td>
<td>Sinus disease, GERD, obesity</td>
</tr>
<tr>
<td>Sinus disease, GERD, obesity</td>
<td>Less frequent comorbidity</td>
</tr>
<tr>
<td>Less frequent comorbidity</td>
<td>Less frequent comorbidity</td>
</tr>
<tr>
<td>Pneumonia, hypertension, obesity</td>
<td></td>
</tr>
<tr>
<td>Sinus disease, hypertension, obesity</td>
<td></td>
</tr>
</tbody>
</table>

*All clusters in this table are characterized by the use of multiple controller medications, high-dose ICS, multiple bursts of OCS, and acute visits for asthma care. GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; OCS, oral corticosteroids.
**Endotypes**

Endotypes are mechanisms of underlying disease, described in terms of the cells, cytokines, and mediators involved. One way of classifying endotypes is based on the profile of cytokines involved in the inflammatory response.

**Type 2 Inflammation**

Type 2 inflammation can be triggered by either allergens or nonallergens (e.g., irritants, pollutants, or infectious agents) and is characterized by one or any combination of the following processes:

- Eosinophilia (≥2% or ≥3% sputum eosinophils\(^ {18,19} \) or >300 blood eosinophils/µL)
- Atopy
- High levels of fractional exhaled nitric oxide (FeNO)\(^ {20} \)

The role of each of these processes in an individual patient can change over time.\(^ {6,15,21} \)

Type 2 inflammation is associated with production of one or more of the following type 2 cytokines: interleukin (IL)-4, IL-5, and IL-13.

**IL-4**

Drives immunoglobulin E (IgE) synthesis\(^ {6,15} \) and, in the presence of allergens, leads to mast cell activation.\(^ {6} \) IL-4 also plays a role in eosinophil trafficking.\(^ {22} \)

**IL-5**

Is necessary for eosinophil production, survival, and maturation.\(^ {6,15} \) It also stimulates eosinophil activation.\(^ {21} \)

**IL-13**

Plays a role in eosinophil trafficking and epithelial cell-mediated inflammation.\(^ {24} \) It induces bronchial hyperreactivity, stimulates mucus production,\(^ {15,21} \) and is associated with increased nitric oxide release.\(^ {25} \)

**Allergen-Triggered Type 2 Inflammation**

Allergen exposure leads to IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) production. These cytokines stimulate T-helper 2 (Th2) cells to release IL-4, IL-5, and IL-13.\(^ {15} \) Mast cells produce prostaglandin D2, which stimulates eosinophils, Th2 cells, and type 2 innate lymphoid (ILC2) cells by acting at the chemoattractant receptor-homologue molecule expressed on the Th2 cells (CRTh2) (Figure 1).\(^ {21} \)

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*Figure 1. Postulated Mechanism of Type 2 Eosinophilic Inflammation in Asthma*

In atopic asthma (left), eosinophilic airway inflammation and bronchial hyperreactivity are driven by adaptive T-helper 2 (Th2) cells that are stimulated by dendritic cells (DCs) to produce interleukin (IL) IL-5, IL-13, and IL-4, the 3 types driving immunoglobulin E (IgE) synthesis.

In nonatopic asthma (right), type 2 innate lymphoid (ILC2) cells produce IL-5 and IL-13 and thus cause eosinophilia and bronchial hyperreactivity. As there is no specific allergen involved and as ILC2 cells produce little IL-4, there is no associated IgE response from B cells.

CRTh2, chemoattractant receptor-homologue molecule expressed on Th2 cells; GATA-3, a transcription factor critical in immune response; MHCI, major histocompatibility complex class II; PGD2, prostaglandin D2; TCR, T-cell antigen receptor; NKT cells, natural killer T cells; TSLP, thymic stromal lymphopoietin; TSLPR, receptor for TSLP; Ym1, a marker of alternatively activated macrophages.

Source: Adapted from Lambrecht BN, Hammad H. The immunology of asthma. Nat Immunol. 2015;16(1):45-56.\(^ {15} \)
Nonallergen-Triggered Type 2 Inflammation
Irritants, pollutants, or infectious agents can produce the same inflammatory cascade as allergens by stimulating the production of IL-33, IL-25, and TSLP, which lead ILC2 cells to produce IL-5 and IL-13. Unlike Th2 cells, ILC2 cells produce little IL-4 (Figure 1).15

Type 2 Noneosinophilic Inflammation
Type 2 inflammation may also occur without eosinophilia. It may be associated with atopy and/or high FeNO and is driven by IL-4 and IL-13 (mechanism not shown).

Non–Type 2 Inflammation
Non–type 2 inflammation is characterized by the absence of type 2 biomarkers such as eosinophils, nitric oxide, and IgE. Less is known about non–type 2 inflammation than type 2 inflammation. Evidence suggests that irritants, pollutants, or infectious agents activate IL-33, IL-23, and IL-6 (Figure 2).21 IL-33 stimulates the Th17 cell to produce IL-6, IL-17, and IL-8; these cytokines, in turn, trigger neutrophil production.21 Th17 and Th1 activate neutrophilic inflammation through IL-6, IL-17, interferon gamma, and tumor necrosis factor alpha.15,21

Just as eosinophils are often associated with type 2 inflammation, neutrophils are a marker of non–type 2 processes. Definitions of sputum neutrophilia range more widely than those of sputum eosinophilia, with figures of >40% to >76% neutrophils used in studies.14,19,26

ICS therapy and smoking can confound assessment of inflammatory type. ICS therapy has been associated with increased airway neutrophils in some patients. Some patients (5/94) who were eosinophilic after ICS withdrawal have become neutrophilic after resuming ICS therapy.27 Smoking can induce neutrophilic inflammation as well as increase sputum eosinophils and IL-8.28

Mixed Endotypes
Paucigranulocytic Asthma
This designation includes patients with neither eosinophilia nor neutrophilia. It has been defined in some studies as patients with <3% eosinophils and <76% neutrophils in sputum.19,29 It is a common endotype in patients with stable asthma, accounting for as many as 40% of 508 patients with all levels of asthma severity.29 In one study, roughly 18% of 88 patients with severe asthma had paucigranulocytic disease.19 Paucigranulocytic disease often does not respond to anti-inflammatory therapies.30

Mixed Granulocytic Asthma
These patients have both eosinophilia and neutrophilia. Compared with other asthma endotypes, mixed granulocytic asthma is associated with the lowest lung function, worse asthma control, more symptoms, and greater health care requirements.31

How Common Is Each Endotype?
Across All Levels of Asthma Severity
In one cohort, roughly half of the patients with mild to moderate asthma displayed a gene signature for, or elevated markers of, type 2 inflammation (IL-5, IL-13, serum IgE, and/or eosinophilia).32 This is roughly consistent with a later study, in which almost half (44%) of the patients across all severity levels had either eosinophilic or mixed granulocytic asthma (Figure 3).29 Eosinophilic and paucigranulocytic asthma were the two most common endotypes in this cohort, accounting for 41% and 40%, respectively. This study used an unusually high threshold for neutrophilia of ≥76% sputum neutrophils, which may have reduced the proportion of neutrophilic and mixed endotypes.29
In one cohort, about 55% of patients with severe asthma displayed type 2 inflammation (sputum eosinophils ≥3%) (Figure 4). Another 6% had mixed granulocytic inflammation (≥3% sputum eosinophils as well as ≥76% sputum neutrophils).19

Putting It Together: Phenotypes and Endotypes

Researchers had hoped that each of the phenotypic clusters would be associated with a distinct endotype, and that this information could be used to select effective treatments for each patient. However, the results of the research on phenotypes and endotypes have not been so straightforward.

Studies by the SARP researchers have found that patterns of elevated levels of blood eosinophils and neutrophils do not differentiate among clusters 3, 4, and 5 (Figure 5).16 Additional cluster analyses incorporating blood eosinophils and sputum granulocytes as variables found heterogeneous patterns of inflammatory cells; again, the clusters could not be distinguished by particular underlying mechanisms of pathophysiology.14 A further evaluation incorporating bronchoalveolar lavage inflammatory data as variables in the cluster analysis also failed to distinguish between the clusters.33 Work by other research groups has found similar results.34 Therefore, the clinical phenotypes by themselves cannot be used to guide therapy. Biomarkers that indicate the underlying biological mechanisms of asthma are necessary to direct treatment.
Biomarkers

Biomarkers can be used to identify the mechanism of disease in a given individual so as to allow for precision treatment. Table 3 summarizes the benefits and disadvantages of specific biomarkers. Some biomarkers are used to identify patients most likely to respond to certain therapies, as indicated in Table 4. Currently available clinical and late-stage investigational biomarkers generally identify only type 2 inflammation (Figure 6).

**Table 3. Biomarkers: Pros and Cons**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE</td>
<td>• Easy to measure&lt;br&gt;• Identifies candidates for omalizumab therapy&lt;sup&gt;35,&lt;/sup&gt;</td>
<td>Does not predict omalizumab responsiveness&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sputum eosinophils</td>
<td>• ERS/ATS-recommended to guide treatment, along with clinical criteria&lt;sup&gt;11&lt;/sup&gt; &lt;br&gt;• Adjusting therapy based on sputum eosinophils was validated for reducing exacerbation frequency in adults&lt;sup&gt;37,38&lt;/sup&gt;</td>
<td>Technically challenging to perform; some patients cannot provide adequate samples&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>• Correlated with sputum eosinophilia&lt;sup&gt;39&lt;/sup&gt; &lt;br&gt;• Easy to measure&lt;sup&gt;8&lt;/sup&gt; &lt;br&gt;• ≥300 cells/μL, ↑ risk of asthma attacks, asthma-related ED visits&lt;sup&gt;40&lt;/sup&gt; &lt;br&gt;• &gt;400 cells/μL, ↑ rate of severe exacerbations&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Optimal cutoff not established&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>FeNO</td>
<td>• Correlated with sputum&lt;sup&gt;39&lt;/sup&gt; and blood eosinophils&lt;sup&gt;40&lt;/sup&gt; &lt;br&gt;• ≥50 ppb, ↑ Risk of asthma attacks, asthma-related ED visits&lt;sup&gt;40&lt;/sup&gt; &lt;br&gt;• Adjusting treatment based on FeNO reduced the risk of asthma exacerbations&lt;sup&gt;175&lt;/sup&gt;</td>
<td>Not recommended for guiding therapy in patients with severe asthma&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum periostin‡</td>
<td>• Marker of airway eosinophilia and IL-13 activity&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Not specific to asthma&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urinary bromotyrosine‡</td>
<td>• Has predicted asthma control and exacerbations in children&lt;sup&gt;44&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*Along with the presence of severe allergic asthma.</sup><br><sup>1</sup>In centers experienced with the specimen gathering and analysis technique.<br><sup>2</sup>Investigational.<br><sup>3</sup>No significant effect on asthma control or lung function.<br>ED, emergency department; ERS/ATS, European Respiratory Society/American Thoracic Society; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin.

**Table 4. Biomarkers: Predicting Response to Therapy**

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>Omalizumab</th>
<th>Mepolizumab</th>
<th>Reslizumab</th>
<th>Benralizumab</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IgE</td>
<td>NR</td>
<td>No&lt;sup&gt;36&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sputum eosinophils</td>
<td>Yes&lt;sup&gt;45&lt;/sup&gt;</td>
<td>NR</td>
<td>Yes&lt;sup&gt;46,47&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;48&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>NR</td>
<td>Yes&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;52,53&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;57&lt;/sup&gt;</td>
</tr>
<tr>
<td>FeNO</td>
<td>Yes&lt;sup&gt;54,1&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;49&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes&lt;sup&gt;58&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum periostin</td>
<td>Yes&lt;sup&gt;13&lt;/sup&gt; (ICS)</td>
<td>Yes&lt;sup&gt;49&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Urinary bromotyrosine</td>
<td>Yes&lt;sup&gt;55&lt;/sup&gt; (ICS)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>45</sup>In severe asthma.<br><sup>1</sup>American Thoracic Society-recommended to evaluate likelihood of steroid response.<br>CS, corticosteroids; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; NR, not reported.
The relationship between Type 2 inflammation and asthma biomarkers: Th2 cells engage allergen-specific B cells and mediate IgE class switching. Th2 cells and ILC2 produce effector cytokines, including IL-5 and IL-13, which, in turn, lead to eosinophil maturation and migration, upregulation of iNOS, and basilar secretion of periostin and DPP4 from the airway epithelium.

APC, antigen-presenting cell; DPP4, dipeptidyl peptidase-4; FeNO, fractional exhaled nitric oxide; ILC2, type-2 innate lymphoid cells; IgE, immunoglobulin E; IL, interleukin; iNOS, inducible nitric oxide synthase; Th2, T-helper type 2; TSLP, thymic stromal lymphopoietin.


Targeted Therapies, Type 2 Inflammation

All US Food and Drug Administration (FDA)-approved or investigational biologics for asthma are targeted to type 2 inflammation. Figure 7 depicts the targets of biologic therapies.57

Targets of biologic therapies: Omalizumab is an antibody against IgE. Mepolizumab and reslizumab are antibodies against IL-5. Benralizumab binds to the IL-5 receptor. Dupilumab is an antibody to the IL-4-α receptor subunit and inhibits both IL-4 and IL-13 signaling. Tezepelumab is an anti-TSLP monoclonal antibody. Fevipiprant is a CRTh2 antagonist.

APC, antigen-presenting cell; CRTh2, chemoattractant receptor-homologue molecule expressed on Th2 cells; DPP4, dipeptidyl peptidase-4; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type-2 innate lymphoid cells; iNOS, inducible nitric oxide synthase; Th2, T-helper type 2; TSLP, thymic stromal lymphopoietin.

Source: Adapted from Parulekar AD, Diamant Z, Hanania NA. Curr Opin Pulm Med. 2017;23:3-11.
Non-Type 2 Inflammation Treatment Approaches

Few treatments have demonstrated efficacy in patients with severe asthma who do not have markers of type 2 inflammation.

Macrolide Antibiotics
The oral macrolide azithromycin reduced asthma exacerbation by 40% compared with placebo after 48 weeks of therapy (P<0.001). Participants were adults with symptomatic asthma despite ICS/LABA therapy. Benefits occurred in patients with and without eosinophilic asthma (≥ or <3% sputum eosinophils or 300 cells/µL blood eosinophils). Azithromycin also significantly improved asthma-related quality of life and asthma control (Asthma Control Questionnaire 6).58

Bronchial Thermoplasty
This procedure is intended to decrease airway smooth muscle mass on the premise that smooth muscle hypertrophy can restrict airflow. A radiofrequency catheter threaded through a bronchoscope delivers thermal energy to a portion of the airways. The procedure is performed on an outpatient basis, with the patient sedated, in three sessions. Asthma symptoms may worsen for a few days after the procedure but generally return to baseline within a week.59 Bronchial thermoplasty received FDA approval in 2010 for the treatment of adults with severe persistent asthma not well controlled by ICS and LABA therapy.

A 5-year follow-up study of 162 patients who underwent this procedure reported:50
• Sustained decrease in exacerbations and emergency department visits (average, 44% and 78%, respectively)
• An 18% reduction in average daily ICS dose
• Stable pre-bronchodilator FEV\textsubscript{1} values in years 1 and 5

Macrolide antibiotics and bronchial thermoplasty are treatment options for asthma patients with type 2 inflammation and non-type 2 inflammation.

Novel Potential Therapies

IL-4 and IL-13 Inhibitors
IL-4 and IL-13 share a common receptor, IL-4R\textsubscript{α}. Dupilumab, a monoclonal antibody, binds to this receptor and inhibits the activity of IL-4 and IL-13. Dupilumab has been approved by the FDA for treatment of atopic dermatitis and is in FDA review for use in asthma, with a decision expected in October 2018 (Table 5).20,50-53,61-67 Two monoclonal antibodies targeting IL-13—lebrikizumab and tralokinumab—did not show sufficient benefit in late-stage trials and are no longer being studied for use in asthma.68,69

Thymic Stromal Lymphopoietin (TSLP) Inhibitors
TSLP is a cytokine that activates dendritic cells and mast cells. Tezepelumab is a humanized monoclonal antibody that binds to TSLP and has shown promise in a phase 2 clinical trial (Table 5).66

IL-33 Inhibitors
IL-33 plays a key role in innate and adaptive immunity, and high levels of IL-33 are associated with asthma.70 An IL-33 inhibitor, REGN3500, is in clinical trials (ClinicalTrials.gov Identifier: NCT03112577).

Non-Th2 Inflammation Targets

IL-17 Receptor Inhibitor
IL-17 is a cytokine produced by Th17 cells that binds to its receptors and activates several signaling cascades. These actions result in the induction of many cytokines, chemokines, and prostaglandins, ultimately leading to neutrophil recruitment. A phase 2 study of the anti-IL-17 receptor A monoclonal antibody brodalumab, which is FDA-approved for the treatment of moderate to severe plaque psoriasis, showed little benefit in asthma. Development has been discontinued.71,72

CXCR2 and CCR3 Antagonists
The CXCR2 antagonist navarixin has temporarily reduced neutrophil counts and reduced mild exacerbations in patients with severe neutrophilic asthma, with no significant change in FEV\textsubscript{1}.73 An oligonucleotide CCR3 antagonist has shown some efficacy in clinical trials.72

Tyrosine Kinase Inhibitor
The tyrosine kinase inhibitor imatinib, which can inhibit the major survival and growth factor for mast cells (KIT), was associated with an improvement in airway hyperresponsiveness and reductions in serum levels of the mast cell–derived protease tryptase. This research suggests that further studies on mast cell inhibition are warranted.74
Asthma is a heterogeneous disease with a variety of clinical presentations (phenotypes) and several underlying disease mechanisms (endotypes). The relationship between phenotypes and endotypes is neither simple nor direct; phenotypes cannot be used clinically as predictors of endotypes or therapeutic response. Therapies are now available that target cytokines identified as pathophysiologic actors in the disease process of some patients. Biomarkers can help identify patient endotypes and the patients most likely to respond to certain targeted therapies, enabling personalization of treatment in asthma.

Table 5. Biologics for Asthma: Outcomes in Clinical Trials

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Treatment Groups</th>
<th>Asthma Exacerbation Rate</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents FDA-Approved for Asthma Treatment</strong></td>
<td></td>
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<tr>
<td>Anti-IgE monoclonal antibody</td>
<td>Omalizumab; n=268</td>
<td>↓ 48%&lt;sup&gt;61&lt;/sup&gt;</td>
<td>↓ ICS doses, improved symptoms&lt;sup&gt;62&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Placebo; n=257</td>
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<tr>
<td>Anti-IL-5 monoclonal antibody</td>
<td>Mepolizumab; 75 mg IV, n=191; 100 mg SC, n=194</td>
<td>↓ 47% for IV; ↓ 53% for SC&lt;sup&gt;63&lt;/sup&gt;</td>
<td>↓ ED visit/hospitalizations; ↑ FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;63&lt;/sup&gt; ↓ oral GC dose, ↓ exacerbation rates&lt;sup&gt;50&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Placebo; n=191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IL-5 monoclonal antibody</td>
<td>Reslizumab; n=477</td>
<td>↓ 50% and ↓ 59%&lt;sup&gt;51&lt;/sup&gt;</td>
<td>↑ FEV&lt;sub&gt;1&lt;/sub&gt;; ↑ symptom control; ↑ quality of life&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-IL-5 receptor-α antibody</td>
<td>Benralizumab; 30 mg q8w; n=267, 239</td>
<td>↓ 51%&lt;sup&gt;52&lt;/sup&gt;; ↓ 28%&lt;sup&gt;53&lt;/sup&gt;</td>
<td>↑ prebronchodilator FEV&lt;sub&gt;1&lt;/sub&gt; and total symptom score&lt;sup&gt;52,53&lt;/sup&gt; ↓ oral GC dose, ↓ exacerbation rates&lt;sup&gt;64&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Placebo; n=267, 248 (2 studies; all with ≥300 eosinophils/µL)</td>
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<tr>
<td><strong>Agents in Development for Asthma Treatment</strong></td>
<td></td>
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<tr>
<td>Anti-IL-4 and anti-IL-13 antibody</td>
<td>Dupilumab; q2w 200 mg, n=631</td>
<td>↓ 47.7% (200 mg); ↓ 46.0% (300 mg)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>↑ FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;20,65&lt;/sup&gt; ↓ oral GC dose&lt;sup&gt;65&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>300 mg, n=633</td>
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<tr>
<td></td>
<td>Placebo, n=634</td>
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<tr>
<td>Anti-TSLP antibody</td>
<td>Tezepelumab; 70 mg q4w, n=145 210 mg q4w, n=145 280 mg q2w, n=146</td>
<td>↓ 61% to 71%&lt;sup&gt;66&lt;/sup&gt;</td>
<td>↑ prebronchodilator FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Placebo; n=148</td>
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<tr>
<td>CRTh2 receptor antagonist</td>
<td>Fevipiprant; dose-ranging study</td>
<td>NR</td>
<td>Optimal dose 150 mg/d ↑ FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

All comparisons significant vs placebo. CRTh2, chemoattractant receptor-homologue molecule expressed on Th2 cells; ED, emergency department; FEV<sub>1</sub>, forced expiratory volume in 1 second; GC, glucocorticoid; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; NR, not reported; TSLP, thymic stromal lymphopoietin.

Summary

Asthma is a heterogeneous disease with a variety of clinical presentations (phenotypes) and several underlying disease mechanisms (endotypes). The relationship between phenotypes and endotypes is neither simple nor direct; phenotypes cannot be used clinically as predictors of endotypes or therapeutic response. Therapies are now available that target cytokines identified as pathophysiologic actors in the disease process of some patients. Biomarkers can help identify patient endotypes and the patients most likely to respond to certain targeted therapies, enabling personalization of treatment in asthma.
REFERENCES


Severe Asthma Reference Guide: Phenotypes, Endotypes, Biomarkers, and Treatment Posttest and Evaluation Form

Original Release Date: October 1, 2018 • Expiration Date: October 1, 2019

Estimated Time to Complete Activity: 2.0 hours

To get instant CME/CE credits online, go to https://tinyurl.com/AsthmaGuide18. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. If you have any questions or difficulties, please contact: Global Academy for Medical Education at info@globalacademycme.com or (973) 290-8225.

POSTTEST CME/CE QUESTIONS

1. Which of the following best characterizes phenotypes of severe asthma?
   A. Each phenotypic cluster is associated with a specific disease mechanism
   B. Phenotypes can be classified by patient demographics, triggers, or clinical presentation
   C. Phenotypes and endotypes are synonymous; both denote mechanisms of underlying disease
   D. Phenotypes are key to choosing therapy

2. Which of these is associated with non-type 2 inflammation?
   A. High levels of eosinophils
   B. High levels of neutrophils
   C. Increased synthesis of IL-4
   D. Increased synthesis of IL-5

3. Which of the following biomarkers have been shown to predict response to anti-IL-5 therapies approved for treatment of severe asthma?
   A. Eosinophils in sputum or blood
   B. FeNO
   C. Serum IgE
   D. Serum periostin

4. Which of the following cytokines is/are targeted by dupilumab?
   A. IL-4 and IL-13
   B. IL-5
   C. IL-25
   D. IL-33

EVALUATION FORM

Please indicate your profession/background: (check one)
- MD/DO
- MSN/BSN/RN
- PA
- Resident/Fellow Researcher
- Administrator
- Student
- APN/NP
- Other; specify ________________________________________

LEARNING OBJECTIVES: Having completed this activity, you are better able to:

- Recognize and differentiate the phenotypes and endotypes of severe asthma
- Describe the mechanisms underlying the primary asthma endotypes
- Explain the role of biomarkers in identifying endotypes and determining appropriate therapy
- Identify the mechanisms of action of current and emerging therapies for severe asthma

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)
- Implement a change in my practice/workplace.
- Seek additional information on this topic.
- Do nothing differently as the content was not convincing.
- Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

OVERALL EVALUATION

The information presented increased my awareness/understanding of the subject.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

The information presented will influence how I practice/do my job.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

The information presented will help me improve patient care/my job performance.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

The program was educationally sound and scientifically balanced.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

Overall, the program met my expectations.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

I would recommend this program to my colleagues.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

Michael E. Wechsler, MD, MMSc
Amit D. Parulekar, MD, MS, FCCP
Authors demonstrated current knowledge of the topic.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

Authors were organized in the written materials.
- Strongly Agree
- Agree
- Somewhat Agree
- Disagree
- Strongly Disagree

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.

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