ASTHMA PHENOTYPES AND ENDOTYPES

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PRECISION

ASTHMA PHENOTYPES AND ENDOTYPES

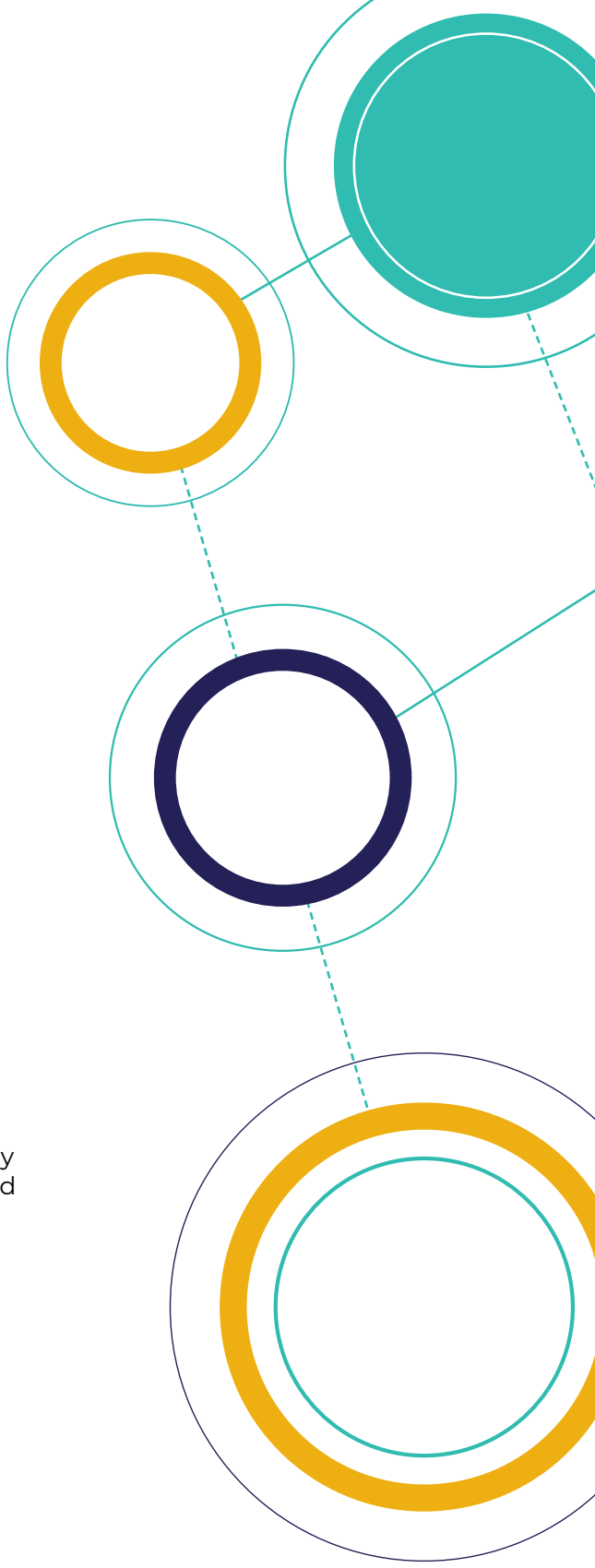
ASTHMA HETEROGENEITY

Asthma is a chronic, heterogeneous disease with multiple pathophysiologic, genetic, pharmacologic, and environmental origins.[1]

It is characterized by a combination of variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation; however, these may not be found in all patients, or may not be present to the same degree in all patients.[2] It is also recognized that even when patients with similar observable clinical characteristics are treated similarly, their response and level of symptom control can vary greatly.[3]

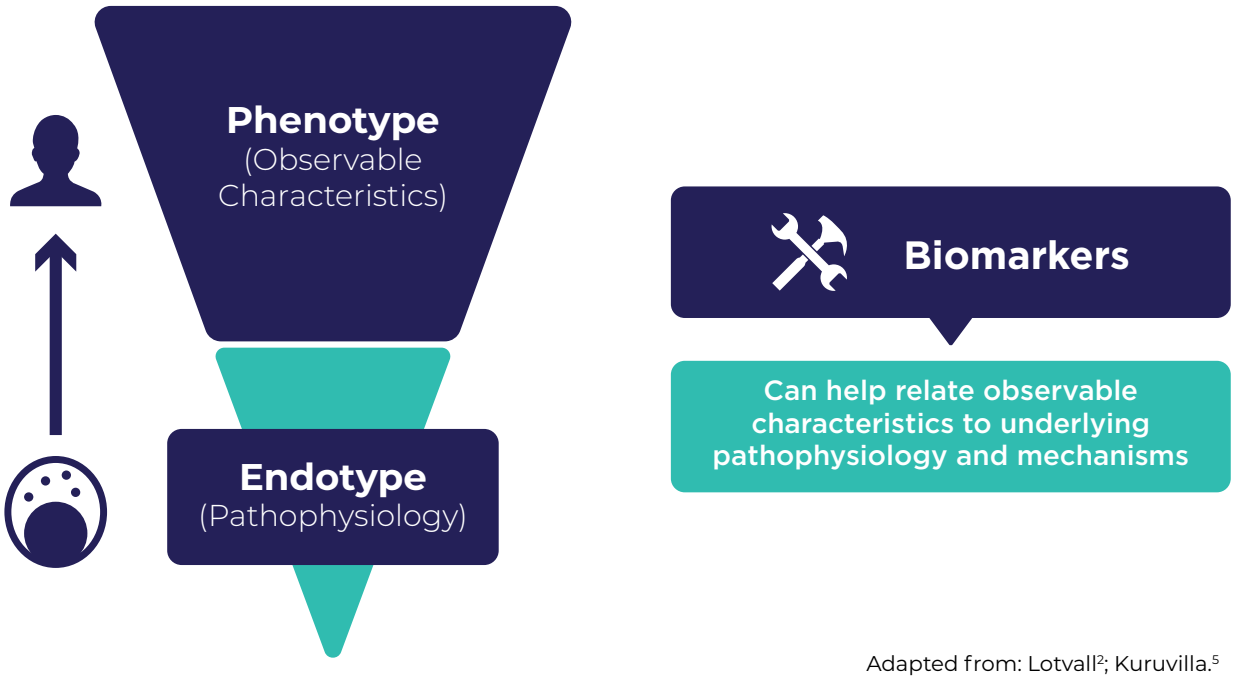
Clinical differences in treatment response are often the result of underlying variations in genetics and disease mechanisms.[4] This recognition of disease heterogeneity has shifted the focus of asthma management away from a one-size-fits-all approach. Treatment must be individualized, tailored not only to the severity of the disease, but also to the patient's specific characteristics and underlying pathophysiology.[3]

Asthma heterogeneity compels a precision approach to care.[3]



UNDERSTANDING
ASTHMA PHENOTYPES, ENDOTYPES, AND BIOMARKERS

Understanding asthma phenotypes and endotypes and the underlying biomarkers of disease pathophysiology can help practitioners tailor an individualized approach to treatment.



Adapted from: Lotvall[2]; Kuruvilla.[5]

Phenotypes represent groups of **observable characteristics** (eg, clinical, physiological, morphologic, and biochemical characteristics, as well as the treatment responsiveness)[2] that tend to track together and can identify clinically meaningful patient types.[2,6] Disease phenotype may significantly affect diagnostic test selection, long-term prognosis, and responsiveness to specific pharmacotherapies.[7] Phenotypes are clinically relevant from the perspective of presentation, triggers, and response to treatment, and they provide insight into the underlying mechanisms of disease.

Endotypes are a subtype of a condition with a distinct pathophysiology and underlying mechanisms.[2,6] Endotypes are therefore, a different form of classification from phenotypes and describe distinct disease entities with a defining etiology and/or a consistent pathophysiological mechanism.[2]

Biological markers (ie, **biomarkers**) are a broad subcategory of characteristics that can be measured objectively, accurately, and reproducibly, and evaluated as an indicator of normal and pathogenic processes, or pharmacologic responses to a therapeutic intervention.[8,9] **Biomarkers** can help relate observable characteristics (phenotypes) to underlying pathophysiology and mechanisms of disease (endotypes) in asthma patients.[2]

ASTHMA PHENOTYPES

Phenotyping for asthma is still evolving, and consensus on the defining features of each phenotype has not been reached.[6] However, phenotyping may allow for a greater understanding of disease heterogeneity and facilitate individualization of patient management by grouping patients with common clinical features.[10]

Categorization of phenotypes has been proposed according to[11,12]:

Clinical characteristics

Triggers

General inflammatory processes

Common Asthma Phenotypes

Many asthma phenotypes have been proposed. Some of the most common categorizations include: **early onset allergic, eosinophilic, neutrophilic, asthma with obesity, asthma with fixed airflow limitation, aspirin-exacerbated respiratory disease (AERD), and exercise-induced bronchoconstriction (EIB).**[6,11,13] Please **see Table 1** for a more detailed description of these phenotypes.

Additional information on cluster analyses conducted to identify asthma phenotypes can be found in the Appendix.

Establishing a phenotype in an individual with asthma is most important in a patient with moderate-to-severe disease who is not controlled with usual therapy.[7]

Table 1. Common Asthma Phenotypes[6,11,13]

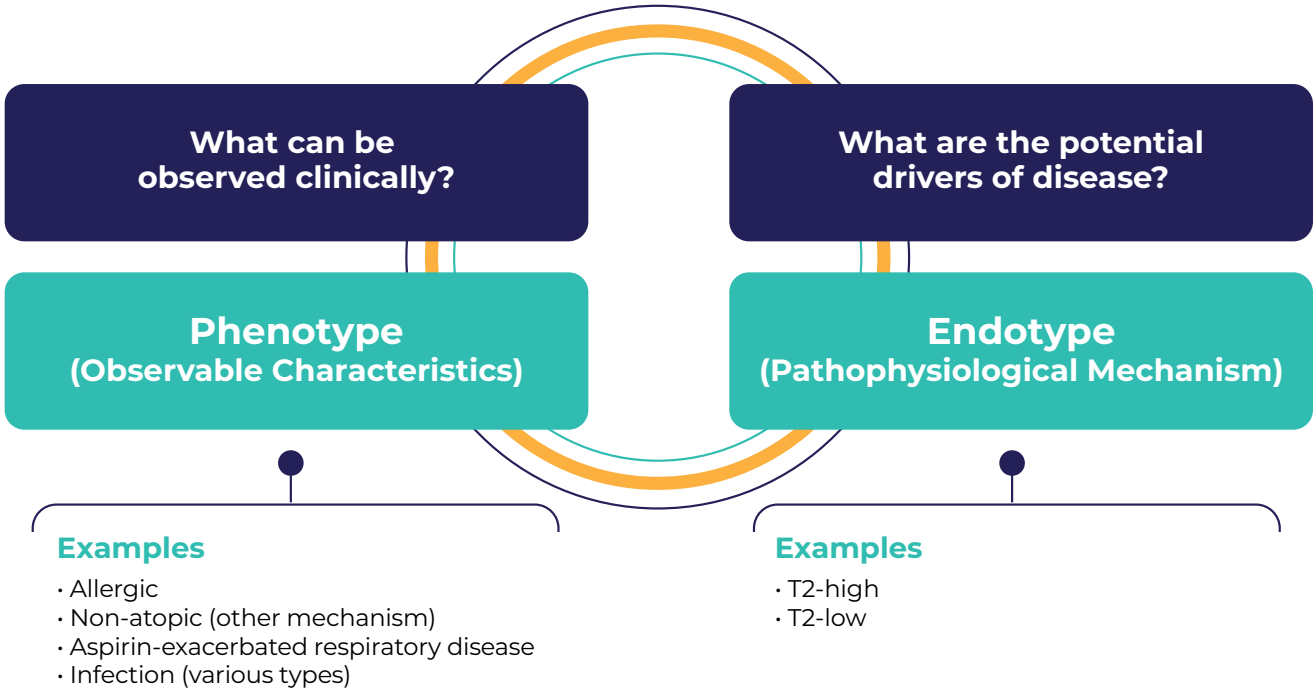
Early Onset Allergic	• Symptoms with allergen exposure • Associated with past or family history of allergic diseases • Often responds well to inhaled corticosteroids • Elevated serum IgE and demonstrated IgE-mediated hypersensitivity • Elevated Th2 cytokines
Eosinophilic	• Patients with adult-onset asthma (with high blood eosinophil counts) have been found to have a distinct phenotype of severe asthma with frequent exacerbations and poor prognosis[14] • Persistent airflow limitation and distal inflammation with air trapping are common, as is upper airway pathology such as chronic rhinosinusitis with nasal polyposis[14] • Patients with raised eosinophil counts may have a higher frequency of severe exacerbation, poorer disease control and show a greater response to anti-eosinophilic therapies[14] • Often requires higher doses of inhaled corticosteroid (ICS) or continuous or frequent systemic corticosteroid treatment
Neutrophilic	• Often difficult to treat, with less response to ICS • Decreased lung function • Sputum may be neutrophilic, neutrophilic and eosinophilic (mixed granulocytic), or contain only a few inflammatory cells (paucigranulocytic)[6,13,15]
Asthma with Obesity	• Adult onset, more common in women • Prominent respiratory symptoms • Little eosinophilic airway inflammation
Asthma with Fixed Airflow Limitation	• Accelerated decrease in lung function with irreversible or only partly reversible obstruction
Aspirin-exacerbated Respiratory Disease	• Tends to be more severe • Clinical tetrad of nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to any medication that inhibits cyclooxygenase-1 (COX-1) enzymes, namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)[16]
Exercise-induced Bronchoconstriction	• Reported in up to 90% patients with asthma, but may also occur in individuals without a known diagnosis[17,18] • EIB with asthma (EIB_A) is now the preferred term, instead of exercise-induced asthma (EIA), for the occurrence of bronchial obstruction after exercise in patients with asthma[18] • Intermittent symptoms with exercise • May be associated with atopy and elevated eosinophils; however, has also been reported with only low-level eosinophilic inflammation

ASTHMA ENDOTYPES

While phenotypes are clinically relevant with respect to presentation, triggers, and treatment response, they often provide little insight into the underlying mechanisms of disease. As a result, the focus is shifting from what can be observed clinically, to the potential drivers of the disease.[2]

Asthma endotypes are biologically distinct groups defined by a functional or pathophysiological mechanism that explains the observable characteristics of a phenotype.[2,6,7]

Focus Is Shifting Toward the Identification of Disease Mechanisms

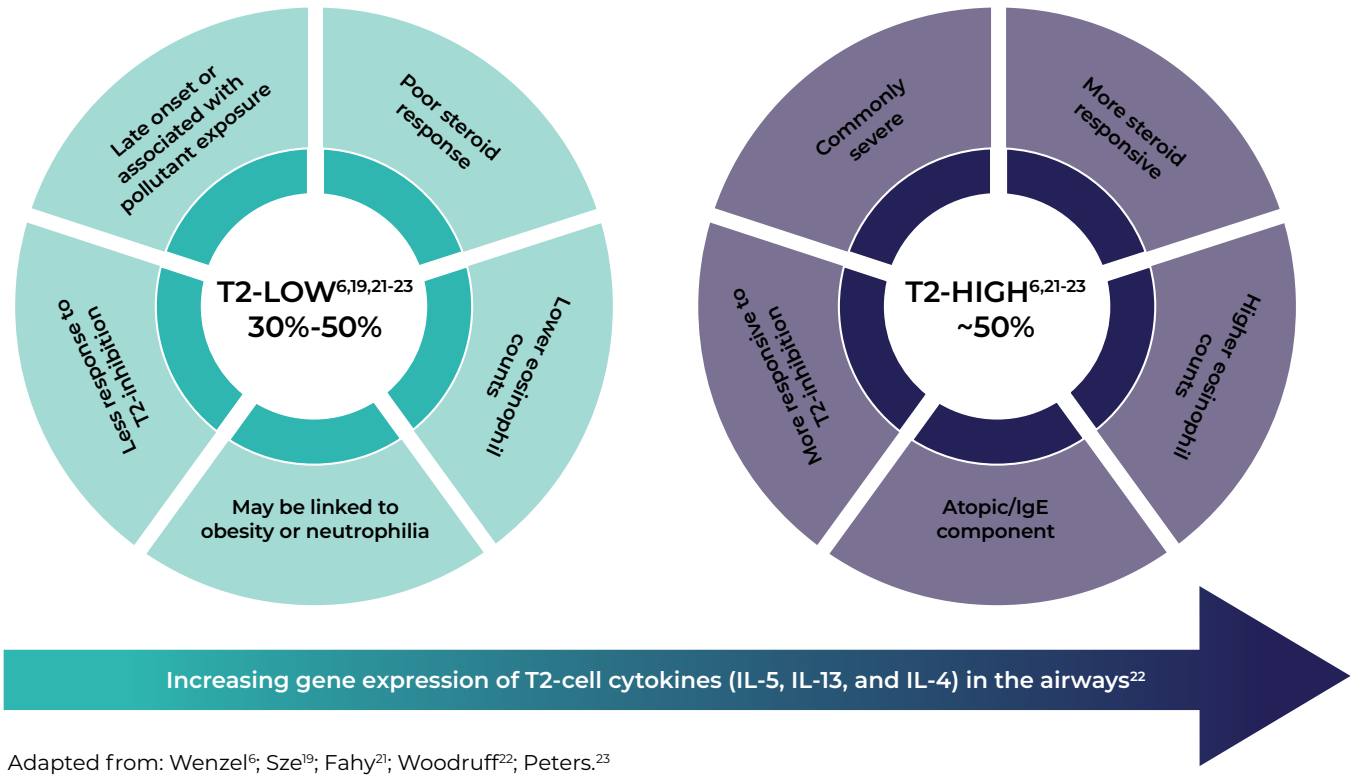


Adapted from: Lotvall.[2]

Asthma Endotype Classification

Like asthma phenotypes, endotype classification is still evolving; however, 2 distinct asthma endotypes have been identified[19,20]:

- **T2-high asthma** is characterized by eosinophilic inflammation and/or elevated IgE. T2-high asthma patients are generally responsive to steroids* and have greater disease severity[13]
- **T2-low asthma** is characterized by the absence of raised eosinophils and significant allergic disease, poor steroid response, and difficult to treat with current therapies that target T2-high mechanisms of disease.[13,19] T2-low asthma patients have either an increase in neutrophils or a paucigranulocytic (minimal inflammatory cells) profile in their sputum and airways[20]



Adapted from: Wenzel[6]; Sze[19]; Fahy[21]; Woodruff[22]; Peters.[23]

*Although T2-high asthma is generally corticosteroid-responsive, a notable subgroup of patients have persistent symptoms and uncontrolled asthma despite corticosteroid treatment.[21]

BIOMARKERS FOR T2-HIGH ASTHMA

Biomarkers can help relate observable characteristics to the underlying pathophysiology, predict disease severity, and have the potential to help predict treatment responsiveness.[24] The use of biomarkers is helping lay the foundation for "personalized" medicine, whereby medical treatments can be tailored to individual patient characteristics.[25]

An ideal biomarker would: (1) distinguish between disease and health with high predictive values, (2) provide information about disease prognosis and clinical outcomes, (3) change with disease progression and successful treatment, and (4) be reliable, reproducible, easy to collect, and cost effective to use in the clinical setting.[25]

Although there are no perfect biomarkers to date, several biomarkers have emerged that have proven useful in asthma and allergic airway disease, and more specifically, in patients with T2-high asthma. These include IgE levels, eosinophils, and fractional exhaled nitric oxide (FeNO).[24]

Detailed descriptions of the role of these biomarkers in asthma and their measurement and interpretation can be found below. A quick reference table of available asthma biomarkers and their associated cytokines and asthma phenotypes can be found in the Appendix.

IgE Levels

Role in Asthma

- IgE is the predominant biomarker for allergic asthma[26]
- Skin prick testing or serum specific IgE are biomarkers for allergic asthma[13,26]
- IgE production is stimulated early in the allergic asthma cascade by the release of IL-4 and IL-13 through activated Th2 cells.[26] IgE bound to mast cells initiates mast cell degranulation, and it also functions as an immunoregulator in the late phase of an allergic reaction[27,28]

Measurement and Interpretation

- When assessing for potential allergic triggers of asthma, patients should undergo aeroallergen skin prick testing and/or complete blood count (CBC) along with differential and serologic specific IgE measurement[26]
- Common aeroallergens associated with asthma include, dust mites, animal dander, cockroach debris, molds, and pollens from trees, grasses, weeds, and ragweed[13,29]
- Elevated levels of allergen-specific IgE suggest sensitization; however, clinical correlation is imperative as the presence of positive percutaneous or serum allergy testing (sensitivity) does not guarantee clinical relevance (allergy)[29]

Eosinophil Levels

Role in Asthma

- While the role of atopy in asthma is evaluated in the context of the clinical setting and total and specific serum IgE levels, it is also recognized that eosinophils play a role in the allergic pathway, and all biologics targeting allergic asthma show increased efficacy with increasing serum eosinophil levels[30,31]
- Blood eosinophil levels have been correlated with increased frequency and severity of asthma exacerbations, poor or inadequate control, and increased disease severity[30,31]
- Eosinophils are usually highly responsive to corticosteroids; however, in a subset of patients with severe asthma, lung and blood eosinophils persist despite continued high-dose systemic and inhaled steroids[6,32-35]
- Once inside the airway, eosinophils can damage lung tissue in multiple ways[30,36]:
  - Production of cytotoxic proteins that can directly damage bronchial epithelium
  - Production of proinflammatory cytokines and chemokines
  - Direct impact upon the nonimmune cells within the lung, which may contribute to airway remodeling and obstruction

Measurement and Interpretation

- Eosinophils can be measured in both blood and sputum[26]
- Whereas sputum eosinophil levels are not easy to measure on a routine basis, measuring peripheral blood eosinophil levels can be performed with a common and widely available blood test—**complete blood count (CBC) with differential**[26,30]
- A clear definition of an absolute blood eosinophil count that can be used to determine if uncontrolled asthma can be mitigated by therapies aimed at the eosinophil has not been established. Blood eosinophil levels may fluctuate with trigger exposures and inhaled and systemic corticosteroids, thus patients with eosinophil-driven disease may show low levels of serum eosinophils[37]

An elevated blood eosinophil count is only one of the clinical aspects that defines the eosinophilic phenotype of asthma.[38] For example, nasal polyposis, low forced expiratory volume in 1 second (FEV_1), frequent exacerbations, and responsiveness to systemic corticosteroids are also characteristic of the eosinophilic phenotype.[38,39]

Fractional Exhaled Nitric Oxide (FeNO)

Role in Asthma

- Nitric oxide is generated by airway epithelium and plays key roles in lung biology as a bronchodilator, and inflammatory mediator[13,40]
- FeNO is considered a marker of asthma with type 2 inflammation, is modestly associated with sputum and blood eosinophils, and can be used to measure inflammation and likelihood of response/adherence to ICS[13,40]

Measurement and Interpretation

- FeNO is easy to perform, can be used in children aged 4-17 years, and provides immediate results. The American Thoracic Society (ATS) recommends that FeNO >50 parts per billion (ppb; >35 ppb in children) be used to indicate that eosinophilic inflammation, and in symptomatic patients, corticosteroid responsiveness are likely. FeNO values between 25-50 ppb (20–35 ppb in children) are considered elevated, but should be interpreted cautiously with reference to the clinical context[40]
- In adult, steroid naïve, nonsmokers, a FeNO value >50 ppb is associated with a potentially good ICS response.[13] If FeNO values remain ≥50 ppb despite ICS, then corticosteroid resistance or noncompliance should be considered[20]
- The possibility of refractory Type 2 inflammation should be considered if a patient taking high-dose ICS or daily oral corticosteroids (OCS) has a FeNO ≥20 ppb[13]

While guidelines have been published on using FeNO clinically to identify eosinophilic airway inflammation and the likelihood of corticosteroid response, the use of FeNO as an asthma biomarker is still debated.[25,40] This debate is largely due to challenges with FeNO interpretation. For example, a recent analysis of more than 13,000 participants from the National Health and Nutrition Examination Survey found a large variation of normal FeNO values in the general population.[41] In addition, FeNO values can be impacted by age, sex, atopic status, tobacco smoking, ICS and OCS use, indoor and outdoor air quality, diet, and obesity.[24,26,40,42]

Patients with moderate-to-severe uncontrolled asthma or difficult-to-treat asthma can be considered for the following tests[13]:

- **Complete blood count (CBC) with differential, including blood eosinophil level**
- **Total IgE, skin prick testing, or specific IgE[26]**
- **Allergen testing (blood or percutaneous), if true allergic asthma is suspected**

BIOMARKERS FOR T2-LOW ASTHMA

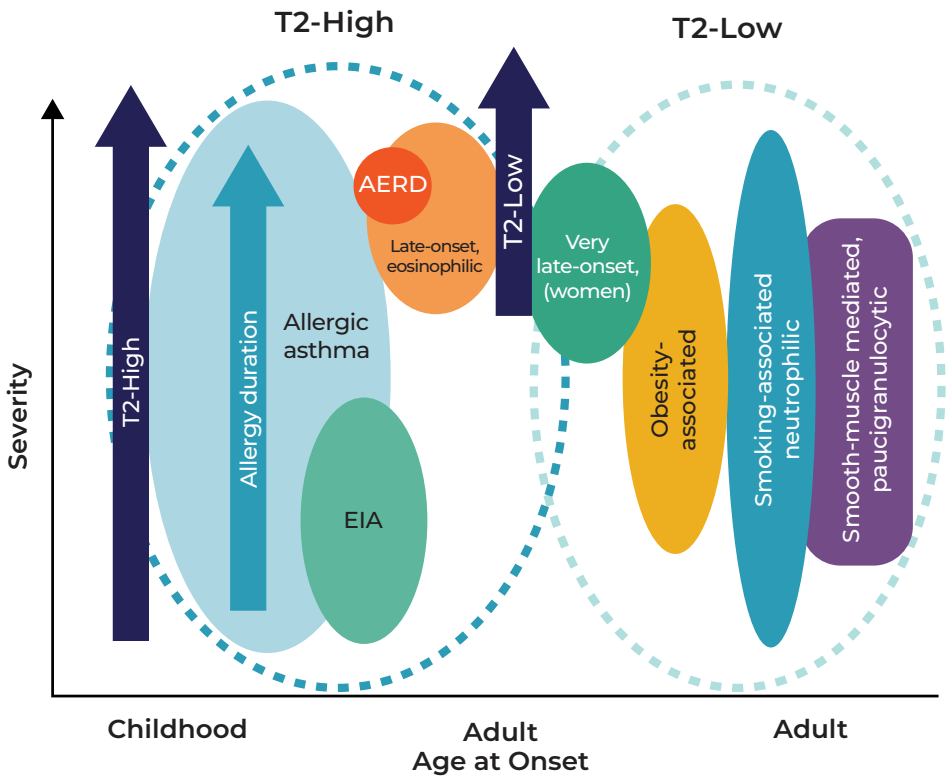
About 50% of patients with severe asthma may not have T2-high asthma, and may be classified as having a T2-low, Th1-high, and Th1/Th17-high profile.[43] These cellular markers of inflammation include neutrophilia or a paucigranulocytic pattern. Despite the importance of these patterns of inflammation, few biomarkers have emerged to define this subgroup.[24]

THEORETICAL GROUPING OF ASTHMA PHENOTYPES BASED ON ENDOTYPE

Considering patient phenotypes alongside underlying disease mechanisms offers a greater opportunity to inform asthma management decisions for a more tailored approach to care.[2,7,20,44]

The figure below presents a theoretical grouping of emerging asthma phenotypes based on the distinction between T2-high and T2-low asthma. T2-high asthma consists of both early- and later-onset disease of varying severities. T2-low asthma includes very late-onset, obesity-associated asthma, as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show little inflammation.[6]

Phenotypes Grouped by T2-High or T2-Low Endotype[6]



Adapted from: Wenzel.[6]

AERD, aspirin-exacerbated respiratory disease; **EIA**, exercise-induced asthma; **EIB**, exercise-induced bronchoconstriction.
Note: In those patients for whom exercise is the only trigger and do not have a formal asthma diagnosis, EIB rather than EIA is the preferred term.[18]

IMMUNOLOGIC PATHWAYS IN ASTHMA

Asthma is a chronic inflammatory disease of the airways in which many cells of the innate and adaptive immune systems act together with cells of the respiratory epithelium to cause airway hyperreactivity, mucus overproduction, airway wall remodeling, and airway narrowing.[45] This section will provide a high-level overview of the immunologic pathways involved in asthma.

Innate and Adaptive Immunity

The immune system refers to a collection of cells and proteins that provides protection against antigens, such as microbes (organisms such as bacteria, fungi, and parasites), viruses, cancer cells, and toxins. It can be simplistically viewed as having two "lines of defense": innate immunity and adaptive immunity. Innate and adaptive immunity are complementary, rather than mutually exclusive, mechanisms of host defense.[46]

Innate Immunity

Innate immunity represents the first line of defense to an intruding pathogen. It is **antigen-independent** (nonspecific), used by the host immediately or within hours of encountering an antigen, and has **no immunologic memory**. The primary function of innate immunity is the recruitment of immune cells to sites of infection and inflammation through the production of cytokines. Cells involved in the innate immune system include macrophages, neutrophils, eosinophils, mast cells, basophils, monocytes, innate lymphoid cells, and dendritic cells.[45,46]

Cells of the Innate Immune System[45,46]	
Macrophage 	Phagocytosis; Antigen presentation to T cells
Neutrophil 	Phagocytosis; Degranulation (discharge of cell contents)
Eosinophil 	Degranulation; Release of enzymes, growth factors, and cytokines
Mast Cell 	Degranulation; Release of histamine, enzymes, and cytokines
Basophil 	Degranulation; Release of histamine, enzymes, and cytokines
Monocyte 	Differentiate into macrophages and dendritic cells to elicit an immune response
Innate Lymphoid Cell 	Secrete cytokines to induce and regulate immune response
Dendritic Cell 	Antigen presenting cells; Intermediaries between the innate and adaptive immune responses

Adaptive Immunity

Adaptive immunity is **antigen-dependent** and **antigen-specific** and, therefore, involves a lag time between exposure to the antigen and maximal response. The primary functions of the adaptive immune response are antigen recognition; generation of pathogen-specific immunologic effector pathways that eliminate specific pathogens or pathogen-infected cells; and development of **immunologic memory**, which enables the host to mount a more rapid and efficient immune response upon subsequent exposure to the antigen. The cells of the adaptive immune system include T cells and B cells.[46]

T cells are activated through the action of antigen presenting cells (APC). This antigen presentation process stimulates T cells to differentiate into either cytotoxic T cells or T helper (Th) cells. Cytotoxic T cells (CD8+) are primarily involved in the destruction of cells infected by foreign agents. T helper (CD4+) cells play an important role in establishing and maximizing the immune response. While CD4+ cells have no cytotoxic or phagocytic activity, they mediate the immune response by directing other cells to perform these tasks. Once activated, CD4+ cells release cytokines that influence the activity of many cell types, including the APCs that activate them.[46]

Unlike T cells, B cells can recognize free antigen directly, without the need for APCs. The main function of B cells is to produce antibodies against foreign antigens. Five types of antibodies are produced by B cells: immunoglobulin A (IgA), IgD, IgE, IgG, and IgM. Each of these antibodies has differing biological functions and recognize and neutralize specific pathogens.[46]

Cells of the Adaptive Immune System[45,46]	
T cell 	T cells differentiate into: • T helper (Th) cells (CD4+): immune response mediators • Cytotoxic T cells (CD8+): cell destruction
B cell 	Produce immunoglobulins against antigen

Thymic Stromal Lymphopoietin (TSLP): A Key Mediator of Innate and Adaptive Immunity[47]

TSLP, an epithelial cytokine (alarmin), is a central regulator of the immune response to inhaled environmental insults such as allergens, viruses and pollutants, initiating a cascade of downstream inflammation. While TSLP drives a pronounced T2 inflammatory response, involving cytokines such as IL-4, IL-5 and IL-13, TSLP involvement has been demonstrated in non-T2 processes involving interactions with both immune and structural cell types. Evidence indicates that TSLP is a key mediator of asthma pathophysiology, driving eosinophilic (allergic and non-allergic) inflammation, non-eosinophilic inflammation and structural changes to the airway, through its actions on a wide variety of adaptive and innate immune cells and structural cells.

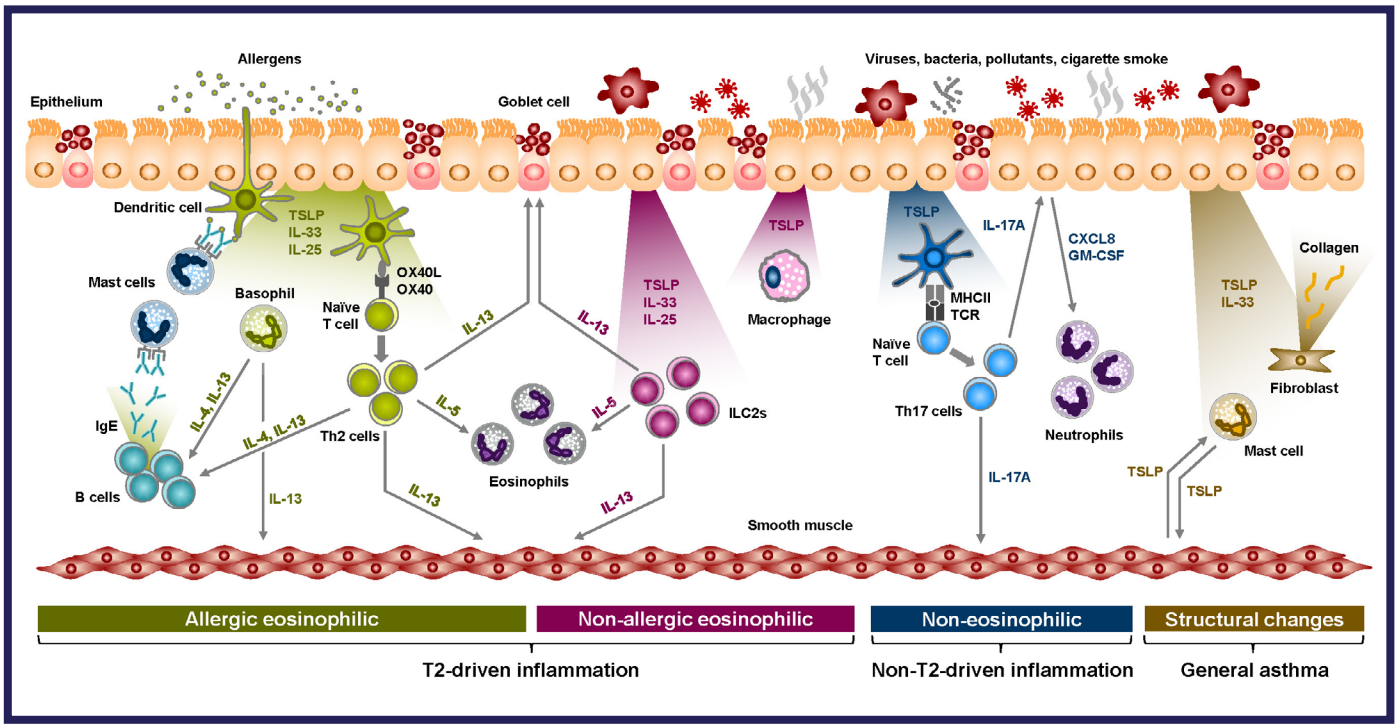
DIFFERENT PATHWAYS LEAD TO AIRWAY INFLAMMATION IN ASTHMA

Although asthma is classically associated with eosinophilia and Th2 cytokines (T2-high asthma), some patients show a neutrophil-predominant disease with an absence of Th2 cytokines (T2-low asthma).[45]

	T2-High Asthma[45,46,48]	T2-Low Asthma[45-48]
Also Called	T2, Type 2 High	Non-T2, Non-type-2
Characterized by	Eosinophilic inflammation and production of antigen-specific IgE	Neutrophilic or paucigranulocytic inflammation
Key Cells	Eosinophils, mast cells, Th2, Th9, Tfh, ILC2, B cells	Neutrophils, Th1, Th17, Th22, ILC3
Key Cytokines	IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, TSLP	IFN-γ, IL-1, IL-6, IL-8, IL-17, IL-22, TSLP

Adapted from: Lambrecht[45]; Warrington[46]; Samitas.[48]

The Spectrum of Asthma Inflammation



Adapted from: Gauvreau[47]; which was based on Brusselle[50]; Brusselle[53]; Lambrecht[45]; Allinne.[54]

GM-CSF, granulocyte-macrophage colony-stimulating factor; **CXCL,** chemokine (C-X-C motif) ligand; **IgE,** immunoglobulin E; **IL,** interleukin; **ILC,** innate lymphoid cell; **MHCII,** major histocompatibility complex class II; **OX40L,** OX40 ligand; **TCR,** T cell receptor; **Th,** helper T cell; **TSLP,** thymic stromal lymphopoietin.

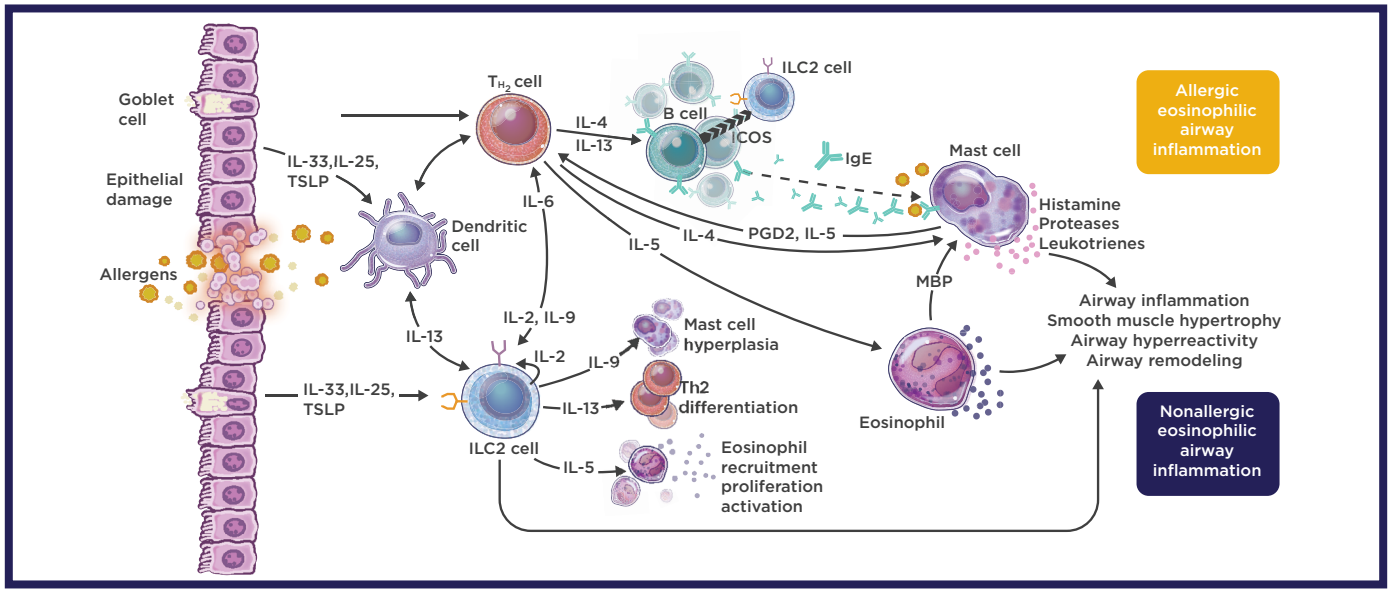
T2-HIGH ASTHMA

Allergic Eosinophilic Asthma[26,38,45,47-52]

- Dendritic cells present allergens to naïve T lymphocytes (CD4+ T cells), which promote production of **type 2 T helper (Th2)** cells
- Allergens and other airway exposures trigger the release of epithelial cytokines, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-25, which in turn stimulate dendritic cells and other airway immune cells
- Th2 cells produce proinflammatory cytokines—**IL-4, IL-5, IL-9,** and **IL-13,** leading to the production of immunoglobulin E (IgE) early in the cascade and later, eosinophils
- The production of the Type 2 (T2) cytokines such as IL-4 and IL-13 leads to increased **immunoglobulin E (IgE)** production by **B cells**
- IgE bound to **mast cells** initiates mast cell degranulation
- Activated **innate lymphoid cells (ILC2)** also secrete IL-5 and IL-13
- IL-5, along with eotaxins 1, 2, and 3, are growth factors and chemoattractants for eosinophils
- IL-5 is responsible for eosinophilic cell maturation in the bone marrow and airways, and promotes activation, recruitment to inflamed tissues, proliferation, and survival of eosinophils
- IL-5 exerts its biological actions by stimulating the IL-5 receptor expressed by eosinophils

Nonallergic Eosinophilic Asthma[26,38,45,47-52]

- Air pollutants, microbes, and glycolipids induce the release of epithelium-derived cytokines, including **IL-33, IL-25, and TSLP,** which activate **ILC2s** in an antigen-independent manner via their respective receptors (IL-17 receptor B; IL-17RB), ST2, and TSLP receptor (TSLPR)
- Activated ILC2s produce high amounts of **IL-5** and **IL-13,** leading to increased **eosinophils,** mucus hypersecretion, and airway hyperreactivity

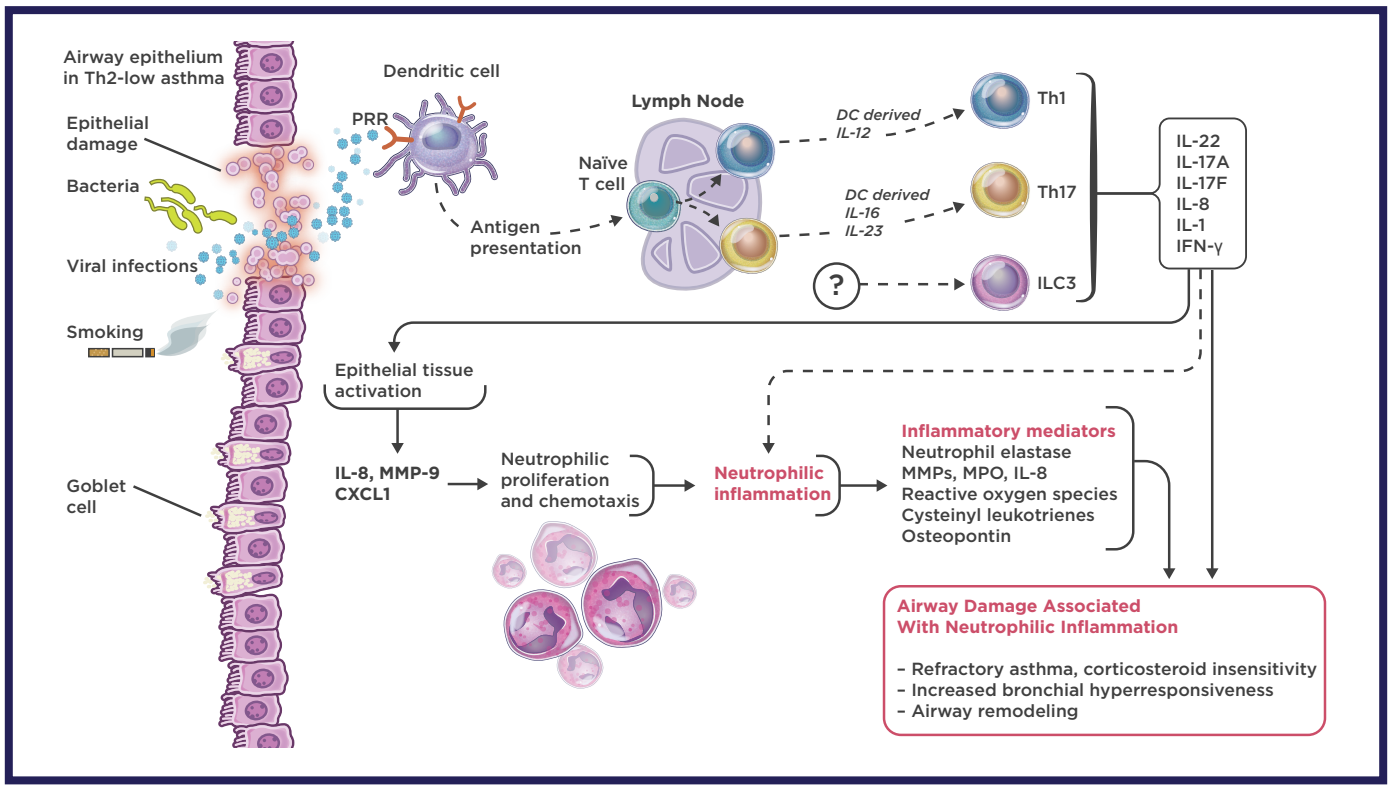


Adapted from: Lambrecht[45]; Samitas[48]; Brusselle.[50]

CCL, C-C motif chemokine; **ICOS,** inducible costimulator; **Ig,** immunoglobulin; **IL,** interleukin; **ILC,** innate lymphoid cell; **MBP,** major basic protein; **PGD2,** prostaglandin D2; **Th,** helper T cell; **TSLP,** thymic stromal lymphopoietin.

T2-LOW ASTHMA

Several inflammatory pathways have been proposed as possibly driving T2-low inflammation. Epithelial damage caused by nonallergic stimuli such as bacterial and viral infections, smoking, and exposure to environmental/occupational air pollutants may promote or activate Th17 that can lead to an immune imbalance and inappropriate immune responses.[45,47] Though not fully understood, TSLP is suggested to promote Th17 cell differentiation through TSLP-promoted dendritic cell activation.[47] The release of **IL-17** and **IL-22** from activated Th17 cells (and also potentially ILC3) may stimulate the synthesis and release of powerful **neutrophil chemoattractants**, such as **IL-8** and **CXCL1**. Inflammatory mediators released by neutrophils are implicated in the induction of airway damage, airway hyperreactivity, and the development of airway remodeling changes.[45,48] Damaged bronchial epithelium may also directly establish neutrophilic inflammation.



Adapted from: Lambrecht[45]; Samitas.[48]

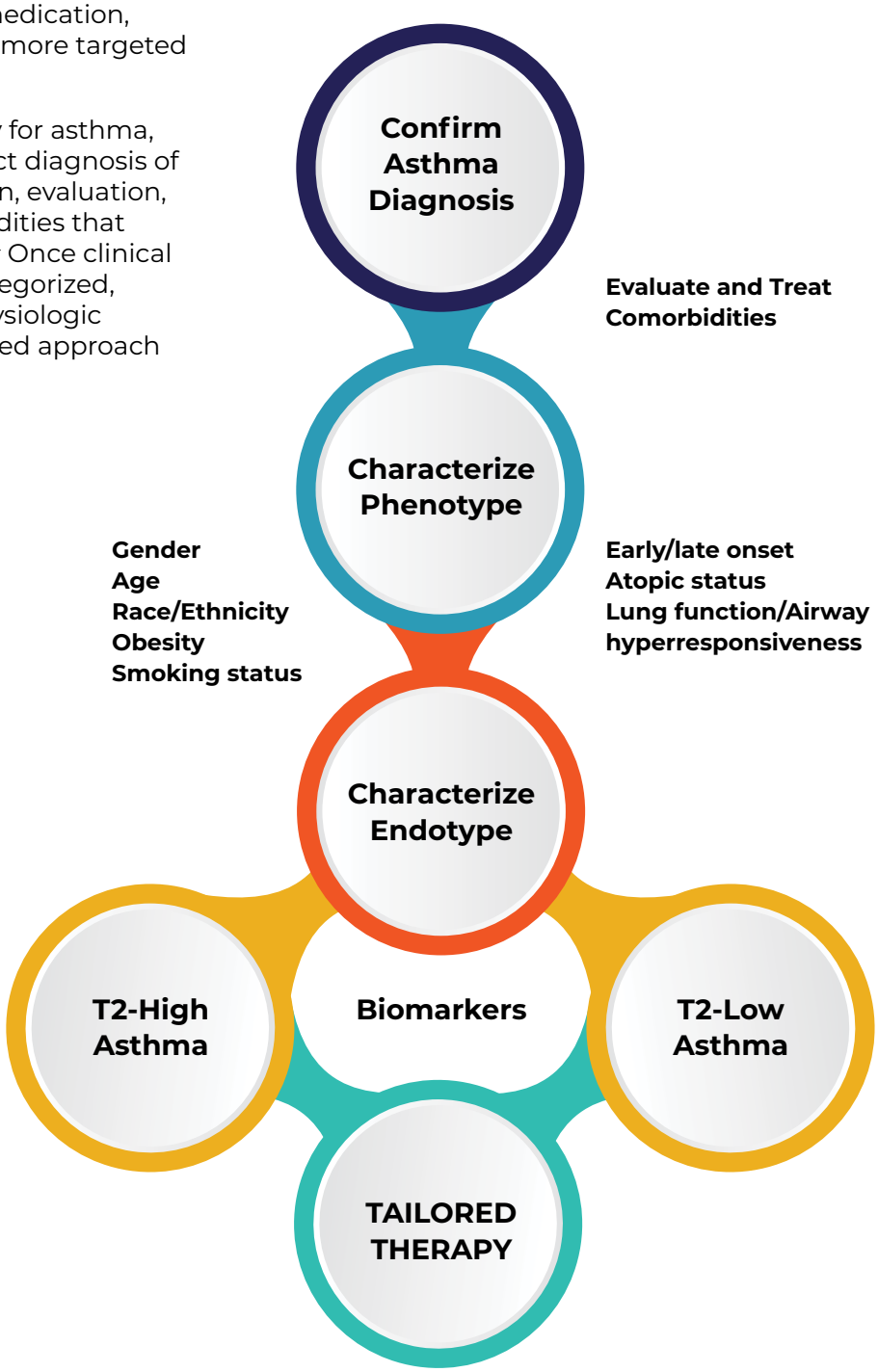
CXCL, chemokine (C-X-C motif) ligand; **DC,** dendritic cell; **IFN,** interferon; **IL,** interleukin; **ILC,** innate lymphoid cell; **MMP,** matrix metalloproteinase; **MPO,** myeloperoxidase; **PRR,** pattern recognition receptor; **Th,** helper T cell.

TAILORING THE APPROACH TO CARE

Asthma Disease Heterogeneity Requires a Precision Approach to Care

Patients with severe asthma are often not fully controlled with standard-of-care medication, often necessitating additional and more targeted therapeutic options.[44]

When considering tailored therapy for asthma, the first step is to ensure the correct diagnosis of asthma, including the identification, evaluation, and treatment of existing comorbidities that could be affecting disease control.[4] Once clinical characteristics (phenotype) are categorized, and potential underlying pathophysiologic mechanisms are identified, a tailored approach to care can be considered.



Refer to the Appendix for selected cluster analyses on asthma phenotypes.

Adapted from: Muraro.[4]

T2-HIGH ASTHMA: THERAPEUTIC TARGETS AND ASSOCIATED THERAPIES

Gaining an understanding of the various disease mechanisms underlying inflammation in asthma has led to the identification of potential therapeutic targets for disease management.

Several monoclonal antibodies directed at these therapeutic targets have been developed and are currently marketed, while others are still being studied or are in various stages of development. As the therapeutic landscape is continuously evolving, the information presented here should not be viewed as all inclusive, but rather, representative of information available at the time this resource was created.

T2-High Asthma: Therapeutic Target and Associated Therapies

Current monoclonal antibody therapies, and those in development, target either the cytokine or receptor.

	Function	Targeted Therapies*
IgE[27]	• Activation and degranulation of mast cells and basophils • Immunoregulator that mediates the development of eosinophilic inflammation	Anti-IgE Monoclonal Antibody 1. Busse W, et al. *J Allergy Clin Immunol.* 2001;108(2):184-190. 2. Soler M, et al. *Eur Respir J.* 2001;18(2):254-261. 3. Holgate ST, et al. *Clin Exp Allergy.* 2004;34(4):632-638. 4. Lanier B, et al. *J Allergy Clin Immunol.* 2009;124(6):1210-1216. 5. Milgrom H, et al. *Pediatrics.* 2001;108(2):E36.
IL-4[56,57]	• Mediates proinflammatory functions, including induction of the IgE isotype switch, expression of vascular cell adhesion molecule-1, promotion of eosinophil transmigration across endothelium, mucus secretion, and differentiation of Th2 lymphocytes leading to cytokine release • The IL-4 receptor alpha subunit is shared by both the IL-4 and IL-13 receptor complexes	Anti-IL-4 Receptor Alpha Monoclonal Antibody 1. Rabe KF, et al. *N Engl J Med.* 2018;378(26):2475-2485. 2. Castro M, et al. *N Engl J Med.* 2018;378(26):2486-2496.
IL-5[58]	• Maturation, growth, activation, and survival of eosinophils • Development, metabolism, and function of basophils	Anti-IL-5 Monoclonal Antibody 1. Bel EH, et al. *N Engl J Med.* 2014;371(13):1189-1197. 2. Ortega HG, et al. *N Engl J Med.* 2014;371(13):1198-1207. 3. Bjermer L, et al. *Chest.* 2016;150(4):789-798. 4. Castro M, et al. *Lancet Respir Med.* 2015;3(5):355-366. 5. Corren J, et al. *Chest.* 2016;150(4):799-810. Anti-IL-5 Receptor Alpha Monoclonal Antibody 1. Bleecker ER, et al. *Lancet.* 2016;388(10056):2115-2127. 2. FitzGerald JM, et al. *Lancet.* 2016;388(10056):2128-2141. 3. Nair P, et al. *N Engl J Med.* 2017;376(25):2448-2458. 4. Ferguson GT, et al. *Lancet Resp Med.* 2017;5(7):568-576.

T2-High Asthma: Therapeutic Target and Associated Therapies (cont'd)

	Function	Targeted Therapies*
IL-13[27]	• IgE synthesis, proliferation of bronchial fibroblasts, induction of airway hyperresponsiveness, enhanced mucus production, and recruitment of eosinophils and basophils • Stimulates bronchial epithelial cells to produce dipeptidyl peptidase-4 (DPP-4) and periostin	Anti-IL-13 Monoclonal Antibody 1. Hanania NA, et al. *Lancet Respir Med*. 2016;4(10):781-796. 2. Korenblat P, et al. *Respir Med*. 2018;134:143-149. 3. Panettieri RA, et al. *Lancet Respir Med*. 2018;6(7):511-525. 4. Busse WW, et al. *Eur Respir J*. 2019;53(2):1800948.
IL-33[49,51,59]	• Epithelial cell-derived cytokine produced in response to proinflammatory stimuli • One of the earliest-released signaling molecules following epithelial damage in asthma, and allergic disease • Recruitment and activation of many cell types, including T helper type 2 cells, mast cells, dendritic cells, eosinophils, and basophils	
TSLP[49,51,55]	• Epithelial cell-derived cytokine produced in response to proinflammatory stimuli • TSLP is also one of the first cytokines released following epithelial damage in asthma and allergic disease • Drives inflammation through effects on multiple cell types (dendritic cells, CD4+ T cells, eosinophils, basophils, mast cells, innate type II cells, as well as on CD8+ T cells, B cells, natural killer T cells, and smooth muscle cells)	Anti-TSLP Monoclonal Antibody 1. Menzies-Gow A, et al. *N Engl J Med*. 2021;384(19):1800-1809.

*Citations listed include only published, key Phase 3 clinical trials available at the time this resource was created. This is not an exhaustive systematic literature review of T2-high asthma targeted therapies.

IgE, immunoglobulin E; **IL**, interleukin; **TSLP**, thymic stromal lymphopoietin.

APPENDIX

Cluster Analyses of Asthma Phenotypes

Recent analyses (see table below) have sought to develop "clusters" (relatively homogenous patient groups) based upon age of asthma onset, gender, allergic status, asthma symptoms, and lung function, in addition to other factors.[7,60-62] Despite differing patient populations, study designs, and variables selected, the analyses identified several consistent phenotypes including mild asthma, early-onset allergic asthma, and a phenotype consisting of mostly females with late-onset, non-atopic disease and higher sputum neutrophil percentages. In addition, groupings emerged that showed early-onset asthma is highly associated with allergy, while patients with later-onset disease tend to have more severe airflow limitation and less allergy.[7] While differences exist among the analyses' findings, the cluster analyses underscore the importance of recognizing disease heterogeneity and the different pathophysiologic mechanisms that may affect therapeutic response and asthma control.[61]

Selected Cluster Analyses of Asthma Phenotypes*

	Haldar[60]	Moore[61]	Siroux[62]	Wu[63]	Fitzpatrick[64]
Methodology	k-means cluster analysis	Cluster analysis	Latent class analysis	Cluster analysis	Cluster analysis
Population	· Adults · Mild-moderate in primary care (n=184) · Refractory in secondary care (n=187)	· Adults (n=726) · Range of severity	· Adults in 2 large epidemiologic studies (n=641 in sample 1; 1895 in sample 2) · Range of severity	· Adults (n=378) · Range of severity	Children 6-17 years old (n=161)
Clusters Identified	**Early-onset Atopic Asthma** Evidence of airway dysfunction, symptoms, and eosinophilic airway inflammation. Associated with a significantly greater number of prior hospitalizations and asthma exacerbations requiring oral corticosteroids	**Early-onset Atopic Asthma, Infrequent HCU** Younger, predominantly female subjects with childhood onset/atopic asthma; normal lung function on <2 controlled medications **Early-onset Atopic Asthma, With HCU** Slightly older subjects, mostly female, with	**Actively Treated Allergic Childhood-onset Asthma** Atopic asthma and active disease; airway hyper-responsiveness (AHR) **Actively Treated Adult-onset Asthma** Adult-onset; mostly females with active disease; reported an asthma attack	**Mostly Healthy, Normal Lung Function** **Early-onset, Mostly Mild Disease With Fewer Asthma Symptoms, Near Normal FEV_1** **Predominantly Hispanic Women, Atopy, High Symptoms, Near Normal FEV_1**	**Late-onset Symptomatic Asthma With Normal Lung Function** **Early-onset Atopic Asthma With Normal Lung Function** **Early-onset Atopic Asthma With Mild Airflow Limitation** **Early-onset Atopic Asthma With Advanced Airflow Limitation**

Continued on next page.

*This is a representative sample of phenotype cluster analyses and should not be viewed as an all-inclusive list.
Adapted from: Desai.[11]

FEV_1, forced expiratory volume in 1 second; **HCU,** health care utilization.

APPENDIX (cont'd)

	Haldar[60]	Moore[61]	Siroux[62]	Wu[63]
Clusters Identified	**Obese, Noneosinophilic Asthma** Asthma symptoms with an absence of eosinophilic airway inflammation. Associated with obesity and with a preponderance in women **Benign Asthma** Asthma symptoms, airway inflammation, and measures of airway dysfunction frequently within normal limits and little evidence of significant airway hyperresponsiveness **Early-onset, Symptom-Predominant Asthma** Refractory asthma population. Minimal eosinophilic disease but significant asthma symptoms **Inflammation-predominant Asthma** Refractory asthma population. Significant eosinophilic inflammation but with few asthma symptoms; late-onset disease, and affecting a greater proportion of males	primarily childhood onset/ atopic asthma; normal lung function on >2 controller medications **Adult-onset, Obese** Primarily older, obese women; adult-onset; less likely to be atopic; decreased baseline pulmonary function. Report more symptoms, which appear to be disproportionate to their degree of airflow obstruction **Early-onset, Severe Obstruction, Some Reversibility** Atopic; often refractory. Severe reductions in pulmonary function at baseline, but many are able to reverse to the near normal range after bronchodilation **Later-onset, Severe Obstruction, Without Reversibility** Atopic, severe asthma. Less reversibility, suggesting fixed airway obstruction **Severe Obstruction, Without Reversibility** Atopic, severe asthma. Less reversibility, suggesting fixed airway obstruction	in the previous 12 months **Inactive/Mild Untreated Allergic Asthma** Early- or adult-onset; no/few asthma symptoms and no asthma treatment; atopic asthma **Inactive/Mild Untreated Non-allergic Asthma** Early- or adult-onset; no/few asthma symptoms and no asthma treatment; allergy-related variables (rhinitis, atopy and IgE <100 IU/mL) and AHR were lowest in this group	**Primarily Obese Females, Early-onset, Severe Asthma With Frequent Symptoms, Low Lung Function and Eosinophilic Inflammation** **Later-onset, Mostly Severe Asthma, Less Atopy, More Nasal Polyps, Sinusitis** **Early-onset, Severe Asthma, High Symptoms, Lowest Lung Function, High Sputum Eosinophils, High FeNO, High Corticosteroid Use**

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APPENDIX (cont'd)

Asthma Biomarkers[26,47,51,65]			
Biomarker	**Testing Method**	**Role in Asthma**	**Associated Cytokines**
IgE	Serum	Initiates mast cell degranulation; activates release of inflammatory mediators	IL-4, IL-13, TSLP
Eosinophils	Blood, Sputum	Produce cytotoxic proteins that damage bronchial epithelium; produce pro-inflammatory cytokines/ chemokines; promote airway remodeling and hyperresponsiveness	IL-4, IL-5, IL-13, TSLP
FeNO	Exhaled breath	Bronchodilator and inflammatory mediator. Modestly associated with eosinophils; used to measure inflammation and likelihood of response/ adherence to inhaled corticosteroids	IL-5, TSLP
DPP-4 (dipeptidyl peptidase-4)	Serum	Stimulates bronchial smooth muscle cell proliferation and human fetal lung fibroblasts; promoted fibronectin production	IL-13
Neutrophils	Sputum	Produce enzymes and other factors that contribute to eosinophil activity	IL-8, IL-17

Adapted from: Kim.[26]

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