



# Asthma Phenotypes as a Guide for Current and Future Biologic Therapies

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## Abstract

Asthma has been increasingly recognized as being a heterogeneous disease with multiple distinct mechanisms and pathophysiologies. Evidence continues to build regarding the existence of different cell types, environmental exposures, pathogens, and other factors that produce a similar set of symptoms known collectively as asthma. This has led to a movement from a “one size fits all” symptom-based methodology to a more patient-centered, individualized approach to asthma treatment targeting the underlying disease process. A significant contributor to this shift to more personalized asthma therapy has been the increasing availability of numerous biologic therapies in recent years, providing the opportunity for more targeted treatments. When targeted biologics began to be developed for treatment of asthma, the hope was that distinct biomarkers would become available, allowing the clinician to determine which biologic therapy was best suited for which patients. Presence of certain biomarkers, like eosinophilia or antigen-specific IgE, is important features of specific asthma phenotypes. Currently available biomarkers can help with decision making about biologics, but are generally too broad and non-specific to clearly identify an asthma phenotype or the single biologic best suited to an asthmatic. Identification of further biomarkers is the subject of intense research. Yet, identifying a patient’s asthma phenotype can help in predicting disease course, response to treatment, and biologic therapies to consider. In this review, major asthma phenotypes are reviewed, and the evidence for the utility of various biologics, both those currently on the market and those in the development process, in each of these phenotypes is explored.

**Keywords** Asthma · Endotypes · Eosinophils · IgE · IL-5 · IL-4 · IL-13 · Thymic stromal lymphopoietin (TSLP)

## Introduction

Asthma is a heterogeneous disease, with variable symptomatology, pathophysiology, and response to medications. The current paradigm underlying the approach to study of asthma therapeutics, especially biologics, is that asthma should not be considered a single uniform disease, but rather many different disease sub-entities with different etiologies and pathophysiologies. Asthma has been divided into multiple phenotypes, defined as “the visible characteristics of an organism resulting from the interaction between its genetic makeup and the environment” [1]. Subsequently, the term “endotype” was

coined to delineate distinct subtypes of asthma; an “endotype” specifically is as “a subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism” [2]. The division of asthma into phenotypes or endotypes is critical to the development of targeted immunomodulators and other specific treatment modalities to more effectively treat the diverse asthmatics encountered in clinical practice.

## Current Understanding of Asthma Pathophysiology

Asthma is an inflammatory disorder of the airways resulting in variable airflow obstruction and airway hyperresponsiveness. Increased airway wall thickness is a characteristic of asthma, with airway smooth muscle hyperplasia, thickened lamina reticularis layer of the basement membrane, increased extracellular matrix deposition, and increased submucosal glands.

There is a bias towards increased Th2 cells in the T cell compartment in asthma, although other T cell subsets are being described in some asthma phenotypes. Relatedly, while

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eosinophilic infiltration bronchial epithelium and submucosa is a characteristic feature of most asthma, absence of eosinophils and presence of neutrophils have notably been described in some fatal asthma cases.

## Th2-Mediated Inflammation

Th2-mediated inflammation is the most common driver of asthma, and the increased presence of Th2 cells is observed in the airways of the majority of patients with asthma [3]. Through epithelial-derived cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), Th0 cells are driven towards the Th2 cell pathway in response to allergens, infections, pollutants, and various other airway insults [4, 5]. Co-stimulation of naive T cells by IL-4 has also been shown to play a role in generating Th2 cells, although this differentiation can occur in its absence. Th2 cells, once derived, move to the airway epithelium and subepithelial mucosa and begin to excrete IL-5 and IL-13. It is believed that IL-4 co-stimulation during Th2 differentiation leads to increased IL-5 and IL-13 production, but this is not essential [6]. Another potential contributing mechanism, under certain circumstances, is direct production of IL-5 and IL-13 by type 2 innate lymphoid cells under the influence of IL-25, IL-33, TSLP, and leukotriene D4 [7]. Through various mechanisms, IL-5 and IL-13 drive many of the signature features of asthma including increased mucus secretion, IgE production, bronchial remodeling, and airway hyperresponsiveness [5].

The activities of several cytokines, most notably IL-4, IL-5, and IL-13, have been implicated in the pathophysiology of Th2-mediated asthma. IL-4 acts as a regulatory cytokine in the Th2 pathway, affecting processes both downstream and upstream of Th2 differentiation. It binds to the IL-4 receptor expressed on T helper cells, B cells, eosinophils, mast cells, bronchial epithelium, endothelium, and airway smooth muscle cells [5]. The IL-4R $\alpha$  receptor subunit then forms a complex with IL-2R $\gamma$  (type I signal) or IL-13R $\alpha$ 1 (type II signal). The type I signaling complex assists with Th0 differentiation into Th2 helper cells. The type II signaling complex results in downstream effects including IgE class switching in B cells, mast cell hyperplasia, goblet cell hyperplasia, and eosinophilia.

IL-13 has a multitude of effects in asthma pathology, playing a role in IgE class switching, goblet cell hyperplasia, eosinophilia, subepithelial fibrosis, and airway hyperresponsiveness [5, 6]. These are primarily accomplished through IL-13 binding to the IL-4R $\alpha$ /IL-13R $\alpha$ 1 heterodimer with similar overlapping effects to those of IL-4, which binds to the same heterodimer as explained above. IL-13 also binds to another receptor, IL13R $\alpha$ 2, believed to act primarily as a decoy receptor for excess IL-13 [8]. IL-4 and IL-13 share many functions, demonstrated by them sharing some signaling pathways, such as JAK1 and JAK3 [9]. One significant difference is that unlike IL-4, IL-13 has no effect on Th2 differentiation, as T cells do not possess IL-13 receptors [3].

IL-5 binds to the alpha chain of the IL-5 receptor and forms a complex with the  $\beta$  chain in association with IL-3 and granulocyte-macrophage colony-stimulating factor. IL-5 plays a prominent role in the recruitment, activation, and survival of eosinophils in airway tissue, which is augmented by eotaxin and RANTES [10]. IL-5 also has a lesser role on development of mast cells and basophils [5].

An additional type 2 cytokine, IL-9, contributes to T cell proliferation and differentiation, mast cell hyperplasia, and goblet cell hyperplasia [6]. It also increases B cell production of IgE and induces mast cells to be more responsive to allergens [11, 12].

Eosinophils are recruited into the airway through various cytokines and chemokines including IL-5, IL-13, eotaxin, P-selection, and vascular cell adhesion molecule (VCAM)-1 [10]. Eosinophils exert their effects on the airway through their release of major basic protein, eosinophilic cationic protein, eosinophilic-derived neurotoxin, and eosinophil peroxidase, along with the inflammatory lipid mediators cysteinyl leukotrienes C4 and D4, platelet-activating factor, and prostaglandin D2 [10, 13].

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is a G protein-coupled receptor that binds to prostaglandin D2 (PGD2). CRTH2 is expressed by Th2 cells, eosinophils, basophils, epithelial cells, and innate lymphoid type 2 cells (ILC2) and is involved in allergic and eosinophilic inflammation.

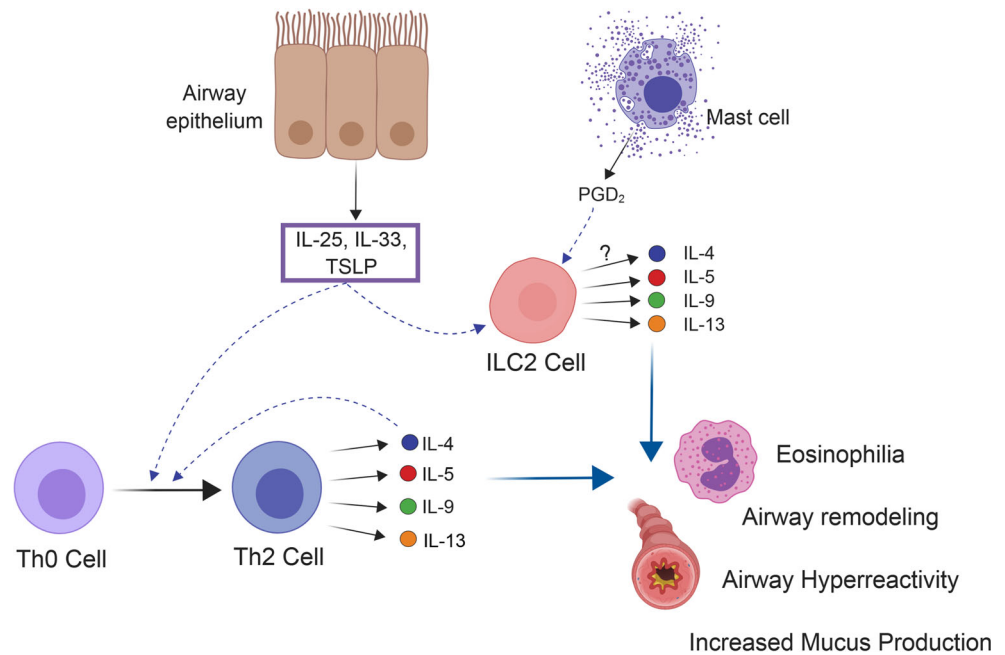
Together, type 2 cytokines drive a surge of downstream effects such as activation of airway epithelial cells, chemoattraction of mast cells, basophils, and eosinophils, and epithelial and sub-epithelial remodeling, which ultimately result in a hyperreactive airway prone to exaggerated responses to inhaled irritants [4]. Figure 1 depicts an overview of the components of Th2-mediated inflammation in asthma.

## Non-Th2-Mediated Asthma

Another clinically relevant pathway underlying asthma pathogenesis in some individuals is driven by Th17 cells, which secrete cytokines including IL-17A, IL-17F, IL-21, and IL-22 [14]. Differentiation of naive T cells into Th17 cells can be driven by TGF- $\beta$  and IL-6 and requires maintenance from IL-23. Airway epithelial cells contain receptors for IL-17A and IL-17F, which when activated, lead to the production of pro-inflammatory factors including IL-6, IL-1, TNF- $\alpha$ , and IL-8 [14]. Some studies have found increased IL-17-producing cells in asthmatics as compared to normal individuals.

Murine studies have also suggested a potential Th1-mediated inflammation pathway as an important factor in asthma pathology, a deviation from the common view that a greater ratio of Th2 to Th1 cytokines resulted in a higher likelihood of developing asthma [14]. Transfer of antigen-specific Th1 cells into ovalbumin-challenged mice resulted in airway hyperresponsiveness and

**Fig. 1** Airway epithelium-derived IL-25, IL-33, and TSLP drive naïve T cells towards the TH2 pathway with subsequent secretion of pro-inflammatory cytokines including IL-4, IL-5, IL-9, and IL-13. Under certain circumstances, ILC2 cells can also produce these cytokines through stimulation by epithelium-derived IL-25, IL-33, and TSLP as well as mast cell-derived PGD<sub>2</sub>. Downstream effects of pro-inflammatory cytokines include airway eosinophilia, increased mucus production, hyperreactivity, and airway remodeling. TSLP, thymic stromal lymphopoietin; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; ILC2, group 2 innate lymphoid cell



inflammation that was independent of IL-13 and IL-4 in one study [15]. Another study found Th1 inflammation dependent on IL-13 and IL-18 [16].

## Asthma Phenotypes and Endotypes

The study of asthma phenotypes and endotypes has gained momentum over time. The field has evolved from thinking of asthma as a simple dichotomy between intrinsic and extrinsic asthma, to now identifying multiple asthma subtypes with disparate clinical and laboratory features, outcomes, and response to therapy. The understanding of asthma phenotypes has become especially important as multiple biologic therapies begin to offer a targeted approach to treating asthmatic inflammation. Discussed below are common, well-described asthma phenotypes, and the utility of biologics, both current and in development, in these specific subsets of asthma.

### Allergic Asthma

Allergic (atopic) asthma is likely the most common overall phenotype of this disease [1, 17]. It typically presents in early childhood, although it can begin at any age [1]. It has several common associations including a positive family history of asthma and/or atopic, allergic rhinitis, atopic dermatitis, and early exposure to allergens [1]. Allergic asthma is felt to be largely mediated by the Th2 inflammatory pathway and is associated with high specific IgE levels [2]. Airway eosinophilia is a common feature of allergic asthma, and therefore, this phenotype has some overlap with the pathogenesis of eosinophilic asthma [2].

The typical allergic asthma sequence involves inhalation of a specific allergen, triggering cross-linking of allergen-specific bound IgE molecules on the surfaces of mast cells and basophils present in the subepithelial layer of the airways. These cells release of leukotrienes, cytokines, prostaglandins, and histamine [18, 19], which contract airway smooth muscle cells and cause increased mucus secretion, resulting in narrowed, constricted airways [18]. Through locally produced cytokines and chemokines, cells such as eosinophils, macrophages, neutrophils, and T lymphocytes are then recruited to the site of inflammation and release additional mediators, which in turn cause sustained bronchoconstriction and damage epithelial layers [18]. This damage, alongside profibrotic cytokines released by eosinophils and epithelial cells, may lay the foundation for the process of airway remodeling and other long-term inflammatory changes [18].

Numerous biomarkers have been utilized for both diagnosis and for therapeutic monitoring in patients with allergic asthma. Presence of specific allergen sensitization is utilized in the diagnosis of allergic asthma. IgE and specific IgE levels have been shown to correlate with asthma severity in children and adults with allergic asthma and are also predictive of decreased FEV1 and probability of wheezing [20]. FeNO levels have shown to be useful in monitoring adherence to inhaled corticosteroids, as values increase quickly once medication use is stopped [21]. Additionally, both peripheral blood eosinophil counts as well as FeNO levels predict risk for asthma exacerbation [22]. Periostin is an extracellular matrix protein upregulated by IL-13 which appears to assist in eosinophil recruitment to the lungs by facilitating eosinophil adhesion to fibronectin [10]. High periostin has shown to be predictive of an improvement in FEV1 levels following ICS, whereas

patients with low periostin levels, more indicative of non-Th2 asthma, typically do not have significant improvement in pulmonary function with ICS [23]. While FeNO, eosinophil levels, and periostin all are associated with general Th2-mediated asthma, they are not specific for which component of Th2-mediated inflammation is driving the asthma or which particular phenotype or endotype is present.

First-line controller therapy for allergic asthma is inhaled corticosteroids, with additions long-acting beta agonists and/or leukotriene receptor antagonists if needed. Treatment progresses stepwise based on symptom severity, number of exacerbations experienced, and failure of previous therapies [24, 25]. Most patients with mild-to-moderate asthma can obtain adequate control with this approach to management [24]. For patients with more severe asthma despite adherence to therapy, other treatment options should be explored, including biologic therapy [24]. There have been many biologics under investigation for this prominent phenotype of asthma.

Omalizumab, a monoclonal antibody that binds IgE, is a treatment option for patients with persistent allergic asthma inadequately controlled by ICS. Bousquet et al. pooled data from seven studies analyzing the effect of omalizumab as an add-on to current therapy and found that omalizumab significantly reduced the rate of asthma exacerbations by 38% ( $P < 0.0001$ ) and the rate of total emergency visits by 47% ( $P < 0.0001$ ) versus placebo [9]. Further analysis showed that the effectiveness of omalizumab on asthma exacerbations was unaffected by age, gender, baseline serum IgE, or using 2- or 4-weekly dosing schedule. Several studies have also shown that omalizumab can have corticosteroid-sparing effects in patients with previously uncontrolled asthma [26].

Dupilumab is an anti-IL-4R $\alpha$  monoclonal antibody that inhibits IL-4 and IL-13 signaling through their receptors, both of which contain an IL-4R $\alpha$  subunit. It has recently received FDA approval for severe asthma with elevated eosinophils and also for steroid-dependent asthma. In a post hoc analysis of a phase 2b, 24-week trial of dupilumab vs. placebo, Weinstein et al. demonstrated an improvement in FEV1 and decreased exacerbations with dupilumab 300 mg q2weeks in the subgroup of patients with concurrent allergic rhinitis, indicating efficacy in allergic asthma [27]. Further studies are needed to investigate the efficacy of dupilumab in this subgroup of patients.

Tezepelumab, an anti-TSLP monoclonal antibody, is currently being evaluated for use in severe asthma. In a double-blind, placebo-controlled trial of patients with allergic asthma, subjects treated with tezepelumab showed significantly improved FEV1 and decreased sputum and blood eosinophil count and FENO levels [28].

Several CRTH2 antagonists have been under investigation for asthma, though none are currently approved. Allergic asthma has been a phenotype of particular interest in the investigation of CRTH2 antagonists. A CRTH2 antagonist,

AZD1981, has been in clinical trials in allergic asthma. However, all doses in a phase 2b trial failed to achieve clinical efficacy endpoints [29]. Fevipirant is another CRTH2 inhibitor, which has been studied as an add-on therapy in patients with uncontrolled allergic asthma, based on positive aeroallergen skin prick test or specific IgE, in a phase 2b study. In this 12-week study, the primary endpoint of change in FEV1 compared to placebo was achieved [30].

## Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease caused by colonization of *Aspergillus fumigatus*, occurring most commonly in patients with chronic airway remodeling and inflammatory conditions, specifically asthma and cystic fibrosis [31]. In the context of asthma, it may be considered a complication rather than a phenotype. *Aspergillus fumigatus* is a saprophytic mold found worldwide in a multitude of settings including indoor and outdoor air, soil, compost piles, freshly cut grass, decaying vegetation, and sewage treatment facilities [31]. Effects of ABPA in relation to asthma include structural changes of the lower airways and dysfunction in innate and specific immune responses [32]. Once inhaled, *A. fumigatus* releases a variety of proteins that have direct effects on the pulmonary epithelia and macrophage inflammation, including epithelial cell detachment [33, 34]. Protease-containing culture filtrates of *Aspergillus* bronchial cells produce proinflammatory chemokines and cytokines including IL-8, IL-6, and monocyte chemoattractant protein (MCP-1), allowing for disruption of epithelial integrity and subsequent enhanced allergen exposure to the bronchoalveolar lymphoid tissue immune system. Additionally, MCP-1 has been shown to be a direct stimulant of Th2 cells, with potential of increasing inflammation and hyperresponsiveness through the Th2 inflammation pathway [35].

Elevated IgE levels much higher than those seen in allergic asthma are common in ABPA, often reaching as high as 30,000 IU/mL [31]. IgE levels are a useful marker of disease activity and can be used to follow patients for disease flares as well as follow-up after treatment [31]. Serum measurements for *Aspergillus*-specific IgE and IgG antibodies are other potential markers for disease management [31]. A recent report from Agarwal et al. showed that *Aspergillus*-specific IgG levels are useful in diagnosis of ABPA but not for treatment response [36].

Prednisone, at a typical starting dose of 0.5 mg/kg/day, is the treatment of choice in asthmatics with acute ABPA flares, as it is effective in clearing eosinophilic infiltrates and associated symptoms [31]. Following successful treatment of an acute phase of asthma symptoms, the prednisone dose should be tapered over 1–3 months [31]. If mucus impaction persists and results in atelectasis, bronchoscopy should be performed to confirm the diagnosis

and attempt to remove the mucus plugs [31]. Itraconazole can be used as a supplementary treatment to reduce exacerbations and lower the dose of steroid required [31].

There have been limited studies assessing the effectiveness of biologics in treatment of ABPA, though some authors report that omalizumab has resulted in decreased exacerbations and need for steroids in uncontrolled studies of ABPA patients [37]. Another group, Terashima et al., recently described successful treatment of a severe case of ABPA-associated asthma with mepolizumab [38]. There are currently no biologics with specific FDA approval for ABPA, and more studies are needed to determine their efficacy in treating this condition, especially as more biologics targeting Th2-mediated inflammation become available for clinical use.

### Eosinophilic Asthma

Eosinophils have been widely considered to play a prominent role in the pathogenesis of certain subtypes of asthma, including childhood-onset allergic asthma as well as adult-onset non-allergic asthma. While eosinophilia is often present in early-onset allergic asthma as one component of Th2-mediated inflammation, it may also be present independent of atopy. This adult-onset, non-allergic, eosinophil-rich disease is characteristic of the “eosinophilic asthma” endotype. The severe, adult-onset, highly eosinophilic asthma phenotype often is resistant to high-dose inhaled corticosteroids, requiring treatment with systemic corticosteroids or biologics that target eosinophilic inflammation [10, 13]. Severe eosinophilic asthma is often associated with sinusitis and nasal polyps, and sometimes overlaps with frank AERD.

IgE levels, blood eosinophil count, sputum eosinophil count, FeNO levels, and periostin levels, among others, have been investigated as potential biomarkers of eosinophilia and disease activity. Jia et al. compared age, sex, BMI, IgE levels, blood eosinophils, FeNO levels, and serum periostin levels in 59 patients with severe asthma and concluded that serum periostin was the best predictor of airway eosinophilia [10, 39]. However, while serum periostin testing is often not readily available, blood eosinophil count is easily accessible in clinical practice worldwide and has also shown to be a good predictive marker for response to biologic therapies targeting IL-5 [40].

Treatment for eosinophilic asthma begins with standard inhaled corticosteroid and bronchodilator therapy, but these are often not sufficient for control [10, 13]. Patients frequently show persistence of eosinophilic airway inflammation despite high-dose ICS and are often dependent on oral corticosteroids for adequate control. Several biologics targeting IL-5 or its receptor have recently been approved for treatment of eosinophilic asthma. In a 32-week study of 576 patients meeting criteria for eosinophilic asthma (eosinophil count of at least 150 cells per microliter in the peripheral blood at screening or

at least 300 cells per microliter at some time during the previous year), Ortega et al. reported significantly reduced asthma exacerbations with subcutaneous mepolizumab, a humanized monoclonal antibody against IL-5, as compared to placebo, as well as improvements in FEV1 and asthma severity scores [41]. Another recently approved biologic, benralizumab, targets the alpha chain of the IL-5 receptor [42]. It has been studied in two randomized, double-blind, placebo-controlled, phase 3 trials evaluating patients having asthma uncontrolled with high-dose ICS and a long-acting beta agonist (LABA) and eosinophil counts greater or equal to 300 cells/ $\mu$ L [42]. In both trials, SIROCCO and CALIMA, patients in the benralizumab treatment group showed significantly reduced annual asthma exacerbation rates and improved FEV1 compared to placebo [43, 44]. Reslizumab, another humanized monoclonal antibody against IL-5, had positive results for treatment of eosinophilic asthma in phase 3 trials. One trial showed improvements in FEV1 and decreased asthma symptom questionnaire scores in patients with inadequately controlled asthma and eosinophil counts greater than or equal to 400 cells/ $\mu$ L [45]. Another trial that had no minimum eosinophil count for inclusion did not see significant changes in FEV1 in the eosinophils <400 cells/ $\mu$ L subgroup, but did see significant improvement in FEV1 in the  $\geq 400$  cells/ $\mu$ L as well as larger improvements in asthma symptom scores and rescue inhaler usage [46].

Dupilumab, an anti-IL4R $\alpha$  monoclonal antibody, has recently received FDA approval for severe asthma with elevated eosinophils and also for steroid-dependent asthma. In a phase 3 trial, dupilumab demonstrated significantly decreased asthma exacerbations and improved FEV1, with greater results seen in those patients with blood eosinophils count greater than or equal to 300 cells/ $\mu$ L [47].

There are several biologic drugs under investigation for eosinophilic asthma. A monoclonal antibody targeting IL-33, etokimab, just completed a proof of concept study for use in adults with severe eosinophilic asthma, but results have not yet been released [48]. CRTH2 antagonists OC000459 and BI 671800 showed greater lung function improvement in patients with elevated peripheral blood eosinophils versus those with lower eosinophil counts [49, 50]. Fevipiprant is being evaluated in phase 3 trials of eosinophilic and other uncontrolled asthmatics at this time as well [51].

### Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to aspirin ingestion (Samter's triad) [52]. Patients with AERD tends to have more severe asthma with lower baseline FEV1 values than patients with aspirin-tolerant asthma, possibly due to more aggressive airway remodeling [53].

In patients with AERD, airway-protective PGE<sub>2</sub> is low, potentially due to decreased expression of prostaglandin E<sub>2</sub> receptors on mast cells, eosinophils, neutrophils, and T cells in respiratory mucosa [52]. When aspirin or NSAIDs cause COX-1 inhibition, this depletes the already deficient PGE<sub>2</sub> in AERD patients, triggering mast cell activation, synthesis of cysteinyl leukotrienes, and release other inflammatory mediators including histamine [54]. Downstream effects of these inflammatory mediators include bronchospasm, increased mucus production, flushing, edema, and nasal congestion [52]. Several studies have demonstrated that patients with AERD also have overexpression of IL-33 and thymic stromal lymphopoietin (TSLP), which can drive Th2 pathway inflammation [52, 55].

Several biomarkers have been shown to be valuable in distinguishing between aspirin-sensitive and aspirin-tolerant asthma. Park et al. have suggested that urine leukotriene E<sub>4</sub> (LTE<sub>4</sub>) is the most useful biomarker for distinguishing aspirin-sensitive asthma from aspirin-tolerant asthma and for monitoring treatment response in AERD [56]. Although not specific to AERD, blood and sputum eosinophil count are biomarkers of eosinophilic inflammation, which is a primary effector cell in AERD [56]. Serum periostin levels have also been shown to be high in this asthma phenotype and can aid in diagnosis of the AERD phenotype [57].

While initial treatment of AERD is based on standard asthma controller guidelines, [54] high-dose glucocorticoids are typically needed in this phenotype for adequate control of symptoms [52]. Leukotriene-modifying agents assist in symptom management and can serve as a safeguard from severe reactions in the event of accidental NSAID exposure [58]. In particular, the 5-lipoxygenase inhibitor zileuton has shown significant benefit [59]. Aspirin desensitization has proven therapeutic benefit in patients with AERD, but comes with the risk of precipitating a severe reaction and the potential side effects of gastric ulcers and bleeding [60].

Several retrospective and non-placebo controlled studies have explored the use of biologic therapy for the treatment of AERD. A retrospective analysis of mepolizumab in subjects with AERD by Tuttle et al. demonstrated evidence of improvement in nasal congestion, anosmia, and asthma symptoms, but no significant change in FEV<sub>1</sub> [61]. Weinstein et al. conducted a post hoc analysis of two double-blind placebo-controlled trials of reslizumab for asthma, which analyzed a subset of patients with nasal polyps both with and without aspirin sensitivity [62]. Aspirin-sensitive patients in this study demonstrated statistically significant decreases in asthma exacerbations and systemic corticosteroid bursts, improved asthma quality of life score, and significantly increased FEV<sub>1</sub> as compared to placebo [62]. A third group, Phillips-Angles et al., conducted a prospective, non-placebo-controlled study of the effects of omalizumab on patients with AERD [63]. Of the seven patients included in the study, six obtained tolerance

to NSAIDs after 6 months of treatment [63]. While a significant decrease in asthma exacerbations was reported, no significant improvement in FEV<sub>1</sub> was observed [63].

While these studies are promising, further prospective, randomized studies will still be needed to clarify the role of various biologics in asthmatics with AERD.

## Neutrophilic Asthma

The pathological and clinical characteristics of neutrophilic asthma are less defined than other asthma phenotypes. It is seen most commonly in patients with severe asthma and is frequently steroid-insensitive [1, 64]. The use of high-dose steroids could also contribute to the neutrophilic inflammation seen in severe asthma, as steroids have shown to decrease apoptosis of neutrophils in vitro [1].

The Th17 inflammatory pathway has been implicated as one of the main drivers of neutrophilic infiltration in asthma [65, 66]. Lung tissue sections from asthmatic patients have been shown to have overexpression of Th17-derived cytokines IL-17A and IL-17F, particularly in subjects with neutrophilic, steroid-resistant disease [67]. While the exact cause of neutrophilic inflammation in asthma is not entirely clear, external factors including allergens, tobacco exposure, diesel exhaust, occupational irritants, and viral infections have been hypothesized to play a role in triggering Th17-mediated airway inflammation [68, 69]. Sources of IL-17 cytokines other than Th17 cells include  $\gamma\delta$  T cells, cytotoxic T cells, invariant NK T cells, NK cells, and type 3 innate lymphoid cells (ILC3s) [70, 71]. Once derived, IL-17A and IL-17F stimulate airway cells, including bronchial epithelial cells and subepithelial fibroblasts, to secrete neutrophil chemoattractants, most prominently IL-8, which promotes migration of neutrophils to the site of inflammation [72–75]. Another cytokine involved in the Th17 pathway, IL-6, has been shown to facilitate the release of polymorphonuclear leukocyte (PMN) into peripheral blood, which increases the binding of PMN to vascular endothelial cells, inhibiting spontaneous apoptosis in neutrophils [76–78]. Given its strong association with the pathogenesis of neutrophilic asthma, IL-8 could become a clinical biomarker of this disease, aiding in diagnosis and monitoring response to treatment.

Patients with neutrophilic asthma typically have poor responsiveness to inhaled corticosteroids, and alternative treatment options are relatively limited. Several of the drugs that have been considered for use in neutrophilic asthma have also shown efficacy in chronic obstructive pulmonary disease.

Macrolides have been shown in multiple studies to have a potential benefit in these patients, as they reduce levels of IL-8, inhibit neutrophil elastase, and attenuate TNF- $\alpha$ - and IL-17 inflammatory responses [79, 80]. In one placebo-controlled trial of clarithromycin in severe refractory asthma, Simpson et al. demonstrated reduced airway IL-8 and neutrophil

numbers and improved quality of life [80]. Despite possible efficacy, caution should be exercised in long-term use of macrolides due to the adverse reactions and development of antibiotic resistance [64].

Another class of medication that has shown some potential in treatment of neutrophilic asthma is phosphodiesterase (PDE) inhibitors. Numerous early studies of candidate PDE inhibitors have demonstrated bronchodilatory and neutrophil inhibitory effects [64]. Currently, no PDE inhibitors are being trialed in neutrophilic asthma itself, though roflumilast, a PDE4 inhibitor approved for use in COPD, is currently in trials for obesity-related asthma [81]. Theophylline, long acting beta-agonists (LABA), and leukotriene receptor antagonists all have been shown to have some modest effects against neutrophil-driven inflammation, so could have potential benefit in neutrophilic asthma [64].

There are few studies addressing the use of biologics in neutrophilic asthma. One placebo-controlled clinical trial assessed the effect of brodalumab, an IL-17 antibody, in patients with moderate-to-severe asthma taking ICS [82]. It found no significant effect on asthma control scores, number of symptom-free days, or FEV1 [82]. However, the group did acknowledge a subgroup responding strongly to bronchodilators did show improvement of unclear significance, and may merit a future study [82]. Another IL-17 inhibitor, CJM112, is currently under investigation in uncontrolled, severe asthmatics without eosinophilia or high serum IgE, presumably targeting by default patients with more neutrophilic disease [83].

## Obesity-Related Asthma

Obesity is a risk factor for both childhood and adult asthma. With the substantial rise in the prevalence of obesity in recent decades, a clearer understanding of this phenotype is of increasing importance. While it has been repeatedly shown that obesity increases the prevalence of asthma, an exact causal relationship has yet to be elicited. Many mechanisms have been explored as contributing to obesity-related asthma, including mechanical, hormonal, and inflammatory factors [84].

Potential mechanical explanations for obesity-related asthma include the tendency for obese individuals to have proportionally lower lung volumes than those of normal body weight, often resulting in lower respiratory tidal volume and functional residual capacity [85]. Long-term implications of this include less stretching of airway smooth muscle, making the airway smooth muscle stiff and more conducive to narrowing [84]. Additionally, excessive adipose tissue can compress peripheral airways, leading to repeated opening and closing during tidal breathing, potentially causing rupture of alveolar-bronchiole attachments [86]. This process uncouples the airways from the retractive forces of the lung parenchyma, leading to further airway narrowing [86].

Obesity has long been recognized as a chronic low-grade inflammatory state. Cytokines, chemokines, and other inflammatory mediators released from adipose tissue are collectively referred to as *adipokines*. These inflammation drivers, such as IL-6, TNF- $\alpha$ , and VEGF, can potentially enter the bloodstream and contribute to causing asthma or exacerbating pre-existing asthma [84]. Oxidative stress from obesity has also been suggested to play a role in obesity-related asthma, but this link has not been fully established [87].

Some authors have discussed a hormonal basis of obesity-related asthma. Leptin, a satiety hormone released from adipose cells, is increased in obese individuals and has pro-inflammatory effects [84, 87]. Leptin is capable of regulating T cell proliferation and activation, recruiting macrophages, and facilitating angiogenesis [87]. Leptin is theorized to potentially play a role in immune modulation as well as a facilitator of airway inflammation, contributing to the complex phenotype [87]. However, other studies cast doubt on leptin playing a significant role [88].

Despite the apparent relationship of adipokines to obesity-related asthma, no specific biomarkers for the phenotype have been established [17]. This is possibly due to the fact that the exact mechanisms resulting in the disease are poorly understood and most likely multifactorial. Future studies that further define the relationship of obesity and asthma will hopefully yield valuable biomarkers for diagnosis and treatment of this complex association.

Obesity-related asthma is associated with a more diminished response to treatment with corticosteroids [17, 87, 89]. Despite this, guidelines for lean and obese patients are currently the same [89]. Studies characterizing the response of obese patients to controller medications and development of more targeted therapy for this population are needed [89].

Several studies have indicated that weight loss through lifestyle modifications or bariatric surgery can significantly improve symptoms and quality of life. A Scott et al. study of 46 patients with both obesity and asthma found that weight loss of 5–10% (through diet, exercise, or both) resulted in clinical improvement of asthma control in 58% of patients and improvements of quality of life in 83% [90]. Another study by Dixon et al. found that asthmatic patients undergoing bariatric surgery experienced significant improvement in asthma control and quality of life [91]. Proper treatment of comorbid sleep apnea can also have positive impact on asthma severity and progression.

There are few studies regarding the use of biologics specifically for obesity-related asthma. One group, Ortega et al., analyzed data from the DREAM trial and found that BMI had no specific impact on response to treatment with mepolizumab [92]. An oral PDE4 inhibitor, roflumilast, which is currently approved for use in COPD, is in trials for obesity-related asthma [81]. As the prevalence of obesity continues to rise, more novel approaches to obesity-related asthma must be explored.

## Exercise-Induced Bronchoconstriction

Exercise-induced bronchoconstriction (EIB) refers to acute airway narrowing resulting from exercise. It was initially believed that this phenomenon was only a trigger for patients with underlying asthma, but more recent research has concluded that EIB can occur in the absence clinical asthma [93]. To distinguish these two entities, several American professional medical societies have recommended the use of the terms exercise-induced bronchoconstriction with asthma (EIB<sub>A</sub>) and exercise-induced bronchoconstriction without asthma EIB<sub>WA</sub> [93]. While the EIB<sub>A</sub> involves triggering pre-existing airway hyperreactivity, EIB<sub>WA</sub> likely involves an alternative mechanism [93].

During the process of exercise, an increase in respiratory rate and tidal volume necessitates the airways to humidify larger quantities of air in shorter intervals of time. This eventually leads to excess water loss from the airways resulting in hyperosmolarity and relative dehydration [94]. An acute effect of this dehydration is the release of mediators including prostaglandins, leukotrienes, cytokines, and histamine, which are capable of stimulating airway smooth muscle causing contraction and increased vascular permeability [95]. Cold, dry air results in greater water losses, explaining the tendency for winter athletes to experience EIB [96]. Epithelial hyperosmolarity and dehydration specifically lead to increased production of IL-8, a potent attractor of neutrophils [97]. Other contributors to the pathogenesis of EIB include increased microvascular permeability, and autonomic dysregulation through reflex mechanisms induced by exercise and increased parasympathetic tone in athletes [98, 99].

Several biomarkers have been explored for potential utility to diagnose EIB and aid in management. Koh et al. found that blood eosinophilia has a high specificity and positive predictive value for the presence of EIB and that maximal fall in FEV<sub>1</sub> after exercise was increased in asthmatics with blood eosinophilia [100]. Buchvald et al. concluded that FeNO levels can be highly predictive of EIB in school-aged children [101]. Barreto et al. found increased concentrations of 8-isoprostane, a marker of oxidative stress, in adolescents and children with EIB, indicating a potential role for oxidative stress in the pathogenesis of EIB [102].

Controversy exists regarding therapy for EIB, particularly the use of  $\beta$ -agonists. While they have certain benefits in EIB including microvascular permeability and anti-exudative effects, they also decrease  $\beta_2$  receptor expression in airways over time, potentially reducing threshold for release of inflammatory mediators in response to osmotic and allergic stimuli [96]. One study concluded that regular  $\beta$ -agonist treatment leads to increased exercise-induced bronchoconstriction and a suboptimal bronchodilator response to  $\beta$ -agonist therapy [103]. The use of  $\beta$ -agonists in EIB should be conservative to slow the development of tolerance and tachyphylaxis, and the benefits of their use should be weighed against potential drawbacks [96].

Montelukast, a leukotriene D<sub>4</sub> inhibitor, has showed potential as therapy for EIB. In a 12-week double-blind trial, montelukast once-daily showed significantly improved area under the FEV<sub>1</sub> curve as compared to placebo, as well as a greater effect on maximal decrease in FEV<sub>1</sub> after exercise [104]. Additionally, tolerance to the medication and rebound worsening of lung function after discontinuation of treatment were not observed [104]. In another double-blind trial, montelukast (10 mg once in the evening) vs. salmeterol (50  $\mu$ g [2 puffs] twice per day) for 8 weeks, the montelukast group experienced more sustained inhibition of exercise-induced bronchospasm, while the salmeterol group saw initial efficacy but significant loss of bronchoprotection at weeks 4 and 8 [105].

The role of biologics in the treatment of EIB is unclear at this time. Little efficacy data exists for the use of biologics targeting Th2-mediated immunity in the treatment of EIB. There is an upcoming trial investigating the IL-5R antagonist, benralizumab, for the treatment of exercise-induced bronchospasm in patients with underlying moderate-to-severe eosinophilic asthma [106].

## Late-Onset Asthma

Late-onset asthma (LOA), or adult-onset asthma, can be defined as “asthma with onset of symptoms in adult life in a patient with no pre-existing, persistent respiratory symptoms” [107]. This is a broad definition, as LOA encompasses multiple phenotypes with different pathogenesis and severity. While both Th2 and non-Th2 inflammation pathways can contribute to late onset phenotypes [108], adult-onset asthma is often non-atopic, more severe, and features a faster decline in lung function than childhood-onset asthma [109]. Despite increased morbidity and mortality from asthma-related complications, asthma in older individuals is less characterized and understood than in younger adults and children [110].

A multitude of risk factors exist for the development of LOA. Obesity and aspirin-sensitivity can both contribute to the development of asthma in adulthood. Other potential contributors to adult-onset asthma include airway infections (viruses, *Staphylococcus aureus*, *Chlamydia pneumoniae*, etc.) smoking, occupational and environmental exposures, female sex, stressful life events, and depression [109–111]. Several LOA phenotypes have been proposed as being distinct. One group is composed predominantly of male, non-atopic patients featuring persistent sputum eosinophilia and frequent exacerbations and airflow limitation [112, 113]. This phenotype is often steroid-dependent for control of symptoms and has been associated with chronic rhinosinusitis, nasal polyps, and aspirin sensitivity [114, 115]. Another group identified exhibits a milder form of asthma and has no other significant defining features [116]. A third phenotype, smoking-related asthma, tends to include non-atopic male smokers with mild-to-moderate reduction in lung function [110, 111].

Useful biomarkers for LOA are dependent on the underlying pathophysiology. Eosinophils, FeNO, and periostin are frequently used for diagnosis and management of Th2 inflammatory asthma, including adult-onset persistent eosinophilic asthma [17, 108]. There is evidence that smoking-related asthma involves neutrophilic inflammation in a non-Th2-driven process, making neutrophils a potential biomarker in this subtype [17]. More studies are needed to better understand the pathophysiology of late-onset asthma and potential specific biomarkers.

A large percentage of patients with LOA respond poorly to corticosteroids [109]. Given the variety of causes, a targeted, phenotype-driven approach is likely to result in better treatment [109]. Mepolizumab has shown efficacy in treating severe eosinophilic asthma, as previously discussed in this review [41]. Lebrikizumab, a monoclonal antibody to IL-13, has also shown potential for treating adults with adult-onset eosinophilic asthma. In a study of adults with symptomatic moderate asthma despite treatment with inhaled glucocorticoids and in some cases a LABA, Corren et al. demonstrated that lebrikizumab improves overall lung function, to a greater degree in patients with high periostin levels at baseline [117]. Another alternative treatment option is bronchial thermoplasty, which has shown potential in improving lung function, airway hyperresponsiveness, quality of life and symptom scores, and decreased exacerbations in adult non-eosinophilic severe asthma [118–120].

Other potential treatment modalities for LOA can be obvious, such as smoking cessation in smoking-related asthma, and irritant avoidance and precautions in certain occupational exposure-related asthma.

## Asthma Phenotypes Identified by Cluster Analysis

Statistical analysis of large cohorts of asthmatics has been used as a tool to identify asthma phenotypes. Cluster analysis is a data mining technique used to group items into clusters using multiple variables, such that those items within a cluster have strong similarity, and the similarity between different clusters is weak. Predefined groups do not exist, so a method such as this can be used to potentially identify new asthma phenotypes in a cohort. While this method of defining phenotypes is meant to avoid clinical bias, cluster analysis is dependent on the variables chosen to group patients' asthma, so the process of investigators choosing important disease variables itself introduces some bias.

The first cluster analysis of severe asthma was undertaken in a single center in Leicester, UK [113]. Adults from two distinct patient populations were evaluated by cluster analysis. The first group included asthmatics recruited from a primary care setting with asthma of mild to moderate severity. The second group included patients with treatment-refractory asthma cared for by a specialist.

In the primary care group, three phenotypic clusters were identified. Cluster 1 had "early-onset atopic asthma", with active symptoms and eosinophilic airway inflammation. Cluster 2 was "obese asthmatics" who were predominantly female. They also had evidence of asthma symptoms, but lacked eosinophilic airway inflammation. Cluster 3 had "benign asthma" with little active disease.

In the group of treatment-refractory asthmatics in specialist care, there were four phenotypic clusters. Cluster 1 was analogous to cluster 1 of the primary care group, with "early-onset atopic asthma", but had more eosinophilic inflammation and airway dysfunction. Cluster 2, "obese asthmatics", was similarly analogous to cluster 2 in the primary care group. Interestingly, these two asthma phenotypes were found to be present across a spectrum of asthma severity. In contrast, cluster 3 and cluster 4 were specific to the treatment-refractory asthma population. Cluster 3 was a group of early-onset patients with significant symptoms, but without eosinophilia. Cluster 4 included patients with eosinophilic inflammation and few symptoms, who are male-predominant and have late-onset disease.

The "Severe Asthma Research Project" (SARP) cohort organized 726 adolescents and adults with severe asthma into phenotypic clusters [121]. Five distinct clusters were identified. Cluster 1 included younger, predominantly female patients, with childhood-onset, atopic asthma, and normal lung functions. These patients had fewer exacerbations than those in other clusters, yet had high rates of daily asthma symptoms. Cluster 2 was a large cluster of slightly older patients (mean age 33 years) who were also atopic and predominantly female. They had similar asthma symptoms and exacerbations to cluster 1, but received more controller asthma therapy. Cluster 3 was composed of mainly older women with adult-onset asthma, less atopic, and high rates of obesity. This cluster was characterized by decreased baseline pulmonary function, use of multiple asthma drugs, and asthma symptoms that were disproportional to the degree of airflow obstruction. Cluster 4 included patients with long-standing, childhood-onset atopic asthma, with no gender predilection, and severely-reduced, yet reversible, pulmonary function. Cluster 5 consisted of female-predominant, adult-onset asthmatics with long-standing disease, who had severely reduced lung function with only partial response to bronchodilators. Disease biomarkers were only assessed in a subset of patients in the SARP cohort, but in this subset, FeNO and blood eosinophils were similar across all five cohorts, sputum eosinophils were higher in clusters 3 and 4, and both sputum eosinophils and sputum neutrophils were elevated in cluster 5. Serum IgE was highest in clusters 1, 2, and 4, and lowest in clusters 3 and 5.

The "Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens" (TENOR) study examined the phenotypes of children, adolescents, and adults with "difficult-to-treat" asthma [122]. In children under age 12, five

clusters were identified. Cluster 1 included atopic white male patients with no secondhand smoke exposure. These patients had less airway obstruction and the lowest exacerbation rate. Cluster 2 was a group of females, also without secondhand smoke exposure, and with less airway obstruction than clusters 3, 4, and 5. The remaining pediatric patients fell into cluster 3 (non-atopic), cluster 4 (passive smoke exposure), or cluster 5 (non-white males).

In adolescents and adults, there were also five observed clusters in the TENOR study group. Cluster 1 was composed of white female patients, with mainly adult-onset asthma, without aspirin sensitivity, and with lower total serum IgE. All patients in cluster 2 had comorbid atopic dermatitis. Cluster 3 was composed of patients of male gender, and this group had better ATAQ scores and higher quality of life than other clusters, but lower mean FEV1/FVC ratios. The final two clusters were defined by non-white race (cluster 4) and aspirin sensitivity (cluster 5).

In the TENOR study, child clusters did not predict asthma outcomes, while in adolescents and adults, non-white and aspirin-sensitive clusters had a worse clinical prognosis regarding QoL and the aspirin-sensitive cluster also had worse prognosis for asthma exacerbations.

These and other cluster analyses have been useful in identifying subtypes of asthmatics and in lending support to asthma phenotypes already recognized by prior clinical studies. Published cluster analyses have used quite variable clinical and laboratory parameters of asthma to define their patients into clusters. Some clusters included asthma outcome measures like corticosteroid bursts and hospitalization rate as variables, while others did not. However, despite their differences, common themes emerge for the asthma phenotypes identified by many cluster analyses. Age of disease onset, atopic status, and presence of obesity are cluster-defining variables in many studies (Table 1).

**Table 1** Asthma sub-types determined by cluster analysis

|                                                                                           |                                                                                                       |
|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Leicester [113]                                                                           |                                                                                                       |
| Primary care group                                                                        |                                                                                                       |
| Cluster 1                                                                                 | Early-onset atopic asthmatics                                                                         |
| Cluster 2                                                                                 | Obese asthmatics                                                                                      |
| Cluster 3                                                                                 | Benign asthmatics                                                                                     |
| Treatment-refractory group                                                                |                                                                                                       |
| Cluster 1                                                                                 | Childhood-onset, atopic asthmatics                                                                    |
| Cluster 2                                                                                 | Noneosinophilic, obese asthmatics                                                                     |
| Cluster 3                                                                                 | Early-onset, non-eosinophilic asthmatics                                                              |
| Cluster 4                                                                                 | Late-onset, eosinophilic asthmatics                                                                   |
| Severe Asthma Research Program (SARP) [121]                                               |                                                                                                       |
| Cluster 1                                                                                 | Childhood-onset, atopic asthmatics with few exacerbations                                             |
| Cluster 2                                                                                 | Childhood-onset, atopic asthmatics with increased health-care utilization but preserved lung function |
| Cluster 3                                                                                 | Adult-onset, obese, non-atopic asthmatics                                                             |
| Cluster 4                                                                                 | Childhood-onset, atopic asthmatics with severe, reversible airflow obstruction                        |
| Cluster 5                                                                                 | Adult-onset asthmatics, with severe airflow obstruction, only partially reversible                    |
| Epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) [122] |                                                                                                       |
| Children                                                                                  |                                                                                                       |
| Cluster 1                                                                                 | Atopic white males                                                                                    |
| Cluster 2                                                                                 | Females without secondhand smoke exposure                                                             |
| Cluster 3                                                                                 | Non-atopic asthmatics                                                                                 |
| Cluster 4                                                                                 | Asthmatics with secondhand smoke exposure                                                             |
| Cluster 5                                                                                 | Non-white male asthmatics                                                                             |
| Adolescents and adults                                                                    |                                                                                                       |
| Cluster 1                                                                                 | White females with adult-onset asthma                                                                 |
| Cluster 2                                                                                 | Atopic asthma with comorbid atopic dermatitis                                                         |
| Cluster 3                                                                                 | Males with few symptoms but more airflow obstruction                                                  |
| Cluster 4                                                                                 | Non-white asthmatics                                                                                  |
| Cluster 5                                                                                 | Aspirin-sensitive asthmatics                                                                          |

## Conclusion

Asthma is now recognized to not simply be a single disease with a uniform underlying pathology, but instead should be regarded as clustered sub-entities with varied clinical presentation and underlying pathophysiologies. We are moving into an era where “one size fits all” treatment for asthma will no longer be the norm. Personalized treatment targeting the underlying cause and pathophysiology of the individual patient’s asthma will lead to improved treatment outcomes. Multiple biologics are already approved for severe asthma and many more are in the development pipeline. It will be critical as more biologics and targeted therapies become available to study them in specific asthma phenotypes and endotypes, thus facilitating the choice of best treatments for specific asthmatic patients encountered in the clinic setting.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** Not applicable.

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