



# Asthma phenotypes and endotypes: a personalized approach to treatment

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## Purpose of review

Asthma is quite common and is better described as a syndrome with a heterogeneous presentation than as a single disease. Although most individuals can be effectively managed using a guideline-directed approach to care, those with the most severe illness may benefit from a more targeted therapy. The review describes our current understanding of how asthma phenotypes (observable characteristics) and endotypes (specific biologic mechanisms) can be employed to gain insight into asthma pathobiology and personalized therapy.

## Recent findings

Our understanding of the heterogeneity of asthma is increasing. The concept of asthma phenotype has become more complex, incorporating both clinical and biologic features. Several asthma endotypes (e.g., allergic bronchopulmonary mycosis, aspirin-exacerbated respiratory disease, severe late-onset hypereosinophilic asthma, etc.) have been proposed, but further research is needed to delineate specific mechanisms underlying asthma pathogenesis. Several biologic therapies targeting certain phenotypes are in development and are expected to broaden our armamentarium for treatment of severe asthma.

## Summary

Asthma is a heterogeneous condition with diverse characteristics and biologic mechanisms. Severe asthma is associated with significant morbidity and even mortality and represents a major unmet need. Stratification of asthma subtypes into phenotypes and endotypes should move the field forward in terms of more effective and personalized treatment.

## Keywords

asthma, biomarkers, endotypes, personalized medicine, phenotypes

## INTRODUCTION

Asthma is a disease of chronic inflammation and remodeling of the airways that is quite common and is associated with significant morbidity and mortality. Although most patients can be managed with standardized, conventional medications, some suffer from a disease that is more severe and more difficult to control [1]; this small group accounts for more than 50% of healthcare utilization related to asthma and is at increased risk of asthma-related death [2]. Ideally, such patients may benefit from a more personalized approach to therapy, and this type of approach to asthma treatment is rapidly evolving to the point in which specific therapeutic targets (i.e., cytokines) are serving as biomarkers of disease expression [3<sup>••</sup>]. The review outlines the current knowledge on asthma phenotypes and endotypes [3<sup>••</sup>, 4–11] that can be used to understand how personalized, targeted therapy may improve strategies for asthma management.

## SCOPE OF THE PROBLEM

Asthma currently affects approximately 300 million people worldwide [12] and causes 250 000 deaths annually [8], and it impacts people of all races, ages, and both sexes although there are ethnic and sex disparities with higher death rates in minority groups and in women [13]. Approximately 5–10% of those afflicted with asthma have severe disease that is poorly controlled [1,4]. Although this is a relatively small percentage of the overall asthmatic population, the healthcare burden associated with

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## KEY POINTS

- Asthma is a complex heterogeneous condition, best understood in terms of underlying phenotypes (observable characteristics) and endotypes (specific biologic mechanisms).
- Asthma can be divided into Th2-high and Th2-low disease.
- One treatment does not fit all when it comes to severe asthma and a personalized approach to management is recommended.
- Strategic use of biomarkers and molecular phenotyping and endotyping should enable better matching of patients with efficacious asthma treatment in the future.

care for these individuals is high. Consensus guidelines [14,15] were developed primarily for individuals with allergic asthma but not all patients, particularly those with severe disease, fall into this category; it is imperative to better understand the characteristics of patients with severe asthma to develop more effective therapies with which to treat them.

## REVISITING THE DEFINITION OF ASTHMA

Asthma was previously viewed as a single disease characterized by chronic airway inflammation and airway remodeling. In fact, even several decades ago, this was seen as an advance in understanding pathobiology since antiinflammatory therapy was moved to the forefront of management. More recently, investigators have recognized that such a view is simplistic and does not account for the heterogeneity of the disease. Asthma is seen as multidimensional, involving clinical, physiologic, and pathologic domains. These different domains may coexist, but are not necessarily related [2]. Wenzel [16] introduced the concept of the asthma 'syndrome,' indicating that patients with many different characteristics can be included in the 'umbrella' term of asthma. The umbrella incorporates the key clinical features of asthma severity (i.e., lung function, symptoms, and exacerbations) and includes patients with both allergic (i.e., Th2 high) and nonallergic (i.e., Th2 low) inflammation [17]. Understanding the heterogeneity of asthma sets the stage for debunking the theory that it is one inflammatory disease with one major approach to treatment.

## ASTHMA PATHOBIOLOGY: Th2 AND BEYOND

The simplistic view of asthma envisions the process as allergy driven in all cases, which has led to a linear

representation of the Th2-inflammation hypothesis in which allergen combined with genetic susceptibility leads to a heightened Th2-immune response [18]. In turn, Th2 immunity upregulates eosinophilic inflammation and tissue damage and results in mediator release, airway hyperresponsiveness (AHR) and ultimately, to symptoms. However, this simple Th2-driven hypothesis unfortunately fails to explain the heterogeneity of asthma [18]. For example, Th2-targeted treatments are not always clinically effective particularly when patients are not carefully selected based on underlying disease characteristics. Furthermore, this hypothesis cannot explain why AHR and tissue remodeling are not clearly linked to inflammation. A deeper understanding reveals that the core physiologic abnormality of AHR is not always a result of eosinophilic (or Th2-high) inflammation [8]. The asthma syndrome is quite complex both genetically and based on observed characteristics. There are more than 100 genes believed to contribute to asthma manifestations [11,19,20]. These include primary disease conferring genes, asthma severity modifying genes, and asthma treatment modifying genes. One well known example is the substitution of arginine for glycine at position 16 of the  $\beta$ -receptor [20], which has been associated with more severe asthma and with decreased response to beta agonist. Understanding the limitations of the Th2 hypothesis has led to attempts to group patients together based on common underlying pathophysiologic characteristics and mechanisms. Thus, the terms 'phenotype' and 'endotype' have been introduced to the asthma literature.

## ASTHMA PHENOTYPES AND ENDOTYPES

In 2000, the National Heart Lung and Blood Institute published guidelines on the definition of severe asthma [21]. Based on the need to better understand and treat severe asthma, the Severe Asthma Research Program (SARP) was developed. The investigators studied 726 patients who met the American Thoracic Society criteria for severe asthma [22]. Cluster analysis was used [23] to group patients with common observable characteristics, known as phenotypes. Phenotypes represent the outward manifestation of an individual's underlying genetics [24] and include clinical (e.g., triggers and body mass index), physiologic (e.g., lung function indices), and inflammatory measures. The SARP investigators were the first to use this terminology, now widely accepted as a way to characterize asthma patients [5,6,9,11,16]. They identified five clusters of patients that differed based on age, sex, age of asthma onset, presence of atopy, presence of obesity, degree of lung dysfunction, and reversibility of airflow obstruction.

Following the initial introduction of the concept of phenotype to characterize asthma, multiple studies have advanced the field [25–27]. In 2006, Simpson and colleagues [28] used sputum analysis to identify four asthma phenotypes based on the predominant inflammatory cell type (i.e., eosinophilic, neutrophilic, etc.) identified in the sample. The SARP investigators had collected induced sputum from a subset of patients. When these were combined with the other clinical characteristics [29], the number of phenotypes was reduced to four. The major distinctions apparent from these groupings was the separation of patients with mild–moderate, early-onset asthma with eosinophilic or paucigranulocytic predominant sputum patterns from those with more severe disease in spite of appropriate antiinflammatory therapy, greater healthcare utilization, and sputum neutrophilia.

As phenotypes do not provide insight into the underlying disease process, the term endotype was proposed to indicate a subtype of a condition defined by a specific biologic mechanism [24]. The relationship between asthma phenotypes and endotypes and how they are integrated into the asthma “syndrome” is shown in Fig. 1. Several

endotypes have been proposed as a result of expert consensus. These include clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response. The most common of these endotypes and their characteristics [24] are shown in Table 1. Allergic bronchopulmonary mycosis is associated with colonization of the airways by mold and sensitization likely because of genetic susceptibility, and this endotype is characterized by recurrent exacerbations and a poor prognosis. Perhaps a better understood endotype is aspirin-exacerbated respiratory disease. In this case, leukotriene-related genetic polymorphisms are thought to be a root cause of this form of severe asthma [11]. Severe late-onset hyper-eosinophilic asthma is not thought to be Th2-driven in spite of marked peripheral and tissue eosinophilia and response to IL-5 antibody. Allergic asthma is apt to be composed of multiple endotypes with different subtypes of Th2-dominant mechanisms [10].

The concept of asthma endotype has more recently evolved to a molecular level using gene expression profiling of patient airway samples [3<sup>22</sup>]. Results from such studies support the idea that there is more than one Th2-high asthma endotype. Woodruff *et al.* [30] demonstrated a Th2-high airway inflammatory endotype that shared expression of several epithelial genes including periostin. Bronchial biopsies from the Th2-high subgroup showed high levels of the cytokines IL-13 and IL-4. Another study [31<sup>2</sup>] used the Th2 biomarker, fractional exhaled nitric oxide (FeNO), and clustered patients into groups based on bronchial epithelium expression of FeNO-correlated genes. Two of the clusters with more severe disease had higher expression of Th2-high and TNF- $\alpha$  signaling genes. Interestingly, one of these clusters had high neutrophil levels. Other cytokines demonstrated to be important in Th2-high asthma [7] include IL-25 [32], IL-33 [33], and thymic stromal lymphopoietin (TSLP) [34]. Although there has been less attention given to Th2-low asthma endotypes [8], these are generally thought to have an airway neutrophilic pattern characterized by increased expression of gene pathways such as IL-1 $\beta$  and TNF- $\alpha$  [3<sup>22</sup>,35,36]. IL-17 has been recognized as a key cytokine in Th2-low severe asthma [4,37,38<sup>2</sup>].

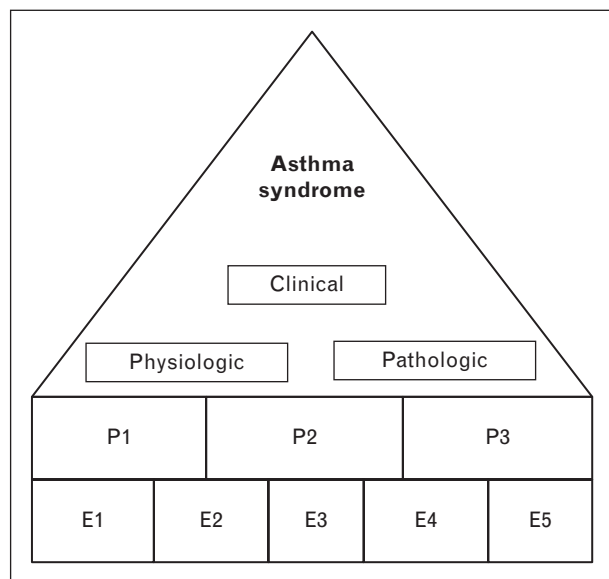


**FIGURE 1.** Schematic representation of the asthma syndrome and its phenotypes and endotypes. The asthma syndrome is multidimensional, involving clinical, physiologic, and pathologic domains that coexist but are not necessarily related. Groups of patients with asthma may share observable characteristics or phenotypes (P) as well as specific biological mechanisms or endotypes (E). Phenotypes and endotypes form the ‘foundation’ of understanding the asthma syndrome. Note that a phenotype may be explained by more than one endotype and that an endotype may be present in more than one phenotype.

## DIAGNOSTIC EVALUATION OF SEVERE ASTHMA

The approach to the patient with severe asthma should start with a meticulous history, physical examination, and basic testing with the goal to confirm the diagnosis. Misdiagnosis of nonasthmatic conditions as uncontrolled asthma has been

**Table 1.** Selected endotypes and their characteristics (modified from reference [24])

| Proposed endotype                          | Clinical findings                                          | Biomarkers                                | Histopathology                               | Epidemiology                                 | Proposed mechanism/genetics                                 |
|--------------------------------------------|------------------------------------------------------------|-------------------------------------------|----------------------------------------------|----------------------------------------------|-------------------------------------------------------------|
| Aspirin-sensitive asthma                   | Nasal polyposis, severe rhinosinusitis, more severe asthma | Eosinophils, urinary leukotrienes         | Often eosinophilic                           | Adult onset, poor prognosis, 2–5% prevalence | Eicosanoids-related; leukotriene-related gene polymorphisms |
| ABPM                                       | Severe, mucus production                                   | Blood eosinophils, high IgE, high FeNO    | Bronchiectasis, eosinophils, PMNs            | Adult onset, long duration, poor prognosis   | Colonization of airways; HLA and rare CF variants           |
| Allergic asthma                            | Allergic rhinitis, allergen-associated symptoms            | Positive skin prick tests, high IgE, FeNO | Eosinophils, subbasement membrane thickening | Childhood onset, history of eczema           | Th2 dominant; Th2 pathway single nucleotide polymorphisms   |
| Severe late-onset hypereosinophilic asthma | Severe exacerbations, late-onset disease                   | Blood and sputum eosinophils              | Tissue eosinophilia                          | 20% of severe asthmatics                     | Nonatopic, genetics unknown                                 |

ABPM, allergic bronchopulmonary mycosis; CF, cystic fibrosis; FeNO, fractional exhaled nitric oxide; HLA, human leukocyte antigens; PMNs, polymorphonuclear leukocytes.

reported to be as high as 12–30% [1]. Thus, the clinician should have some degree of skepticism when faced with the severe asthmatic refractory to therapy. Criteria for making the diagnosis of asthma [14] include the presence of generally more than one type of respiratory symptom that is variable in nature, often worse nocturnally and brought on by classic asthma triggers (e.g., exercise, laughter, cold air, etc.). All patients should have spirometry with bronchodilator to assess for reversibility of airflow obstruction. Although not performed routinely in all centers, FeNO, complete blood count with differential, and a radioallergen sorbent test profile can assist in identifying the phenotype and should be considered on a case-by-case basis. When the diagnosis is questionable, the clinician should consider the broad differential for severe asthma [1] and order appropriate testing to exclude other conditions. Complete pulmonary function testing including lung volumes by plethysmography and carbon monoxide diffusing capacity of the lung may be helpful. High-resolution computed tomography scans of the chest can exclude alternative diagnoses such as bronchiectasis or hypersensitivity pneumonitis. Provocative challenges with agents such as methacholine can be useful to rule out AHR, a diagnostic feature of asthma. Comorbidities (i.e., chronic obstructive pulmonary disease, gastroesophageal reflux disease, chronic sinusitis, allergic rhinitis, obesity, obstructive sleep apnea, etc.) should be evaluated since these entities can alter the phenotype, be part of the same pathophysiologic process, confound the diagnosis, and even alter response to therapy [39,40]. The asthma–chronic obstructive pulmonary disease overlap syndrome provides an excellent example of how a comorbidity can alter the phenotype and obfuscate diagnostic and management efforts. The SARP investigators used a combination of tests of lung structure and function to assess severe asthma and to distinguish it from milder disease [41]. They combined results of endobronchial biopsies with those from state-of-the-art imaging studies to demonstrate that histopathologic features of airway remodeling could be correlated with radiographic findings of airway wall thickening and air trapping. Although such testing is far from routine, it can be viewed as a novel way to phenotype asthma and even to distinguish it from other forms of obstructive lung disease.

**PERSONALIZED APPROACH TO ASTHMA MANAGEMENT**

Current consensus guidelines for asthma management [14,15] provide a reasonable framework for

treating most patients with allergic disease. The major goal of these guidelines is to achieve disease control and reduce the risk of future deterioration [14,15]. Although the guidelines do discuss the management of patients with severe asthma, they were not designed for a phenotype or endotype-driven approach to care. Inhaled corticosteroids are recommended for all patients with persistent asthma [14,15]. However, since asthma is not always Th2-high or eosinophilic in nature, one can reasonably question this recommendation. Some patients, including a number who are obese, may have discordance between symptoms and eosinophilic airway inflammation [23]. In other words, there is an obese phenotype that is highly symptomatic but has predominantly noneosinophilic inflammation [29,42–44]. In these individuals, monitoring eosinophilic inflammation with measures such as FeNO may allow for down titration of inhaled corticosteroids without loss of asthma control [45,46]; this is particularly important because inhaled corticosteroids at high doses are associated with side-effects [47] and should be used prudently. On the other hand, there is another group of individuals who have a paucity of symptoms but a great deal of eosinophilic inflammation [48]. These individuals are prone to frequent exacerbations that may be reduced by targeting corticosteroid therapy to levels of eosinophilic inflammation. Some of these individuals may have the severe, late-onset hypereosinophilic endotype and provide an excellent example of why asthma management must be personalized. In the initial clinical trials involving anti-IL-5 therapy, the drugs did not appear particularly effective [7,49,50]. However, with better characterization of patients, it was found that those with persistent sputum eosinophilia in spite of systemic corticosteroids were the ones who responded best to this specific biologic therapy [51–54].

A variety of different biologic therapies are in various stages of development. The only Food and Drug Administration-approved biologic therapy for asthma at the time of this writing is omalizumab, an anti-IgE molecule [7]. There is now more than a decade of experience with this drug, which seems to work best in patients with the most severe, inadequately controlled disease [55], demonstrated atopy, and significant bronchodilator reversibility on spirometry testing. In a posthoc analysis of a randomized clinical trial [55], comparing omalizumab to placebo as add-on therapy in severe asthmatics who were poorly controlled on standard therapy, investigators demonstrated the utility of biomarkers to identify the patients who would benefit the most from the drug [56]. The analysis

showed that those with greater peripheral eosinophilia, higher levels of FeNO, and higher levels of periostin had the greatest reduction in exacerbation rates with omalizumab compared with placebo. These biomarkers are all Th2 associated. Studies such as these reinforce the importance of an individualized approach to asthma management.

Biologic therapies under development include monoclonal antibodies directed against specific cytokines. Those that have received the most press include the Th2-related cytokines such as IL-5, IL-4, and IL-13. Anti-IL-5 treatment in carefully selected patients [57] has been associated with decrease in asthma exacerbations [54,58], a steroid-sparing effect, and with some agents, improved lung function [58,59]. Anti-IL-4/13 blockade appears to be most efficacious in patients with Th2-high asthma, specifically with increased peripheral eosinophils and periostin [60,61]. Regulators of Th2-type cytokines such as IL-25, IL-33, and TSLP are attracting attention and inhibitors of TSLP are in development [7]. Approximately half of asthmatic patients have Th2-low asthma [62], yet much less is known about this heterogeneous group. Appropriate biomarkers and individualized therapies remain more elusive. Molecules of interest include the cytokines IL-17, IL-1 $\beta$ /TNF- $\alpha$  [3<sup>22</sup>], and a chemokine receptor (CXCR2) [10], all of which are associated with neutrophilic inflammation.

There are other therapies for severe asthma that can be utilized in a personalized approach to care although the specific indications for such treatments have not been protocolized. There is an accepted superior treatment for the aspirin-exacerbated respiratory disease endotype [63]. As this endotype is associated with upregulation of leukotriene synthesis, treatment with a 5-lipoxygenase inhibitor blocks the leukotriene synthesis pathway upstream. Although not guideline endorsed [1], antifungal agents may be considered in conjunction with systemic steroids to treat patients with the allergic bronchopulmonary mycosis endotype; this treatment will need further investigation but may be a bridge to omalizumab in such patients. Macrolides have antiinflammatory properties that target neutrophils and their mediators [64,65]. A randomized double-blind, clinical trial of azithromycin compared with placebo as add-on therapy for 6 months for patients with exacerbation-prone severe asthma showed that the macrolide significantly reduced severe exacerbations in the subgroup with noneosinophilic asthma [66]. Bronchial thermoplasty is a Food and Drug Administration-approved treatment of severe persistent asthma that involves delivery of radiofrequency energy to the airways using flexible bronchoscopy in an effort to reduce airway smooth

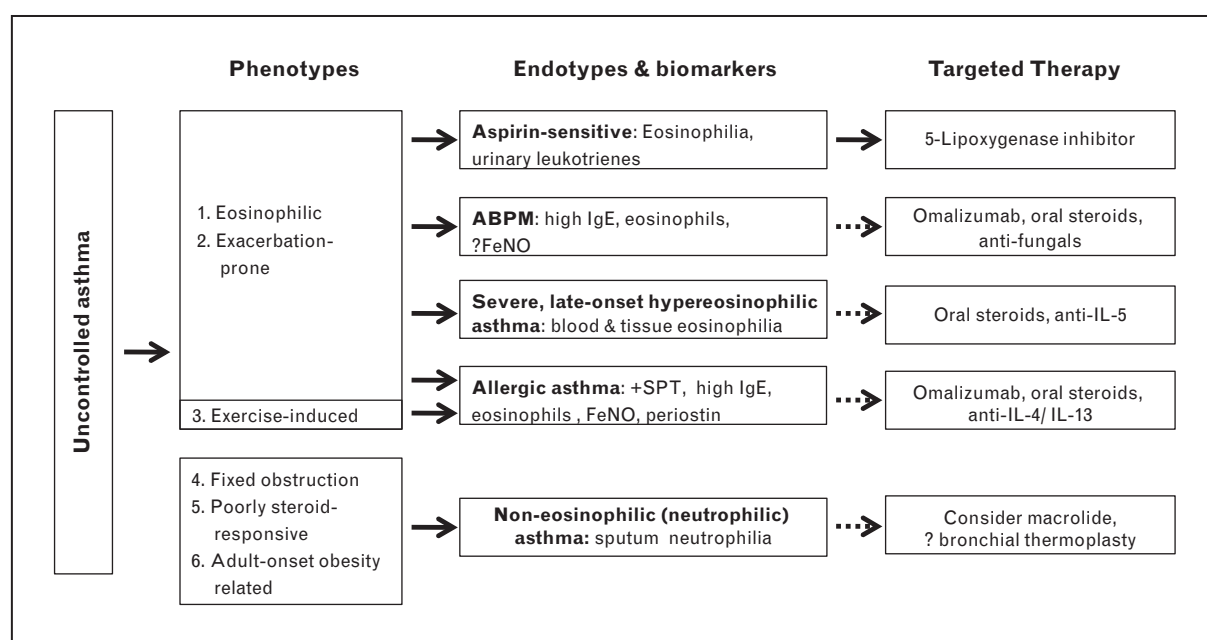


**FIGURE 2.** Personalized treatment algorithm for uncontrolled asthma: beyond the guidelines. Uncontrolled asthma can be visualized as comprised of different phenotypes with corresponding endotypes and biomarkers. Targeted therapy based on current knowledge is shown. Solid arrows indicate accepted therapy that is currently in use. Dashed arrows are used to indicate that some of the recommended therapies are not considered standard-of-care or not yet clinically available. ABPM, allergic bronchopulmonary mycosis; FeNO, fractional exhaled nitric oxide; IL, interleukin; SPT, skin prick tests.

muscle and responsiveness in asthma [67]. The exact subgroup that would benefit the most from this therapy has not yet been definitively identified. Figure 2 shows a proposed personalized treatment algorithm for uncontrolled asthma that goes beyond the guidelines and incorporates knowledge about both selected phenotypes and endotypes in recommendations for targeted therapy.

## CONCLUSION

Asthma is a heterogeneous disease with diverse characteristics and biologic mechanisms. Severe asthma represents a major unmet need. Recommendations of current guidelines, while providing a helpful framework for treatment, are insufficient for some of the sickest patients. Therapy for Th2-high asthma does not benefit all individuals since not all patients have Th2-high disease. Stratification of asthma subtypes (i.e., phenotypes and endotypes) with appropriate use of biomarkers should drive drug development and guide management. More specific biomarkers are needed including those that are easily measured and consistently reliable. Novel biomarkers that incorporate imaging might help to quantify asthma severity as well as to identify particular phenotypes (i.e., asthma–chronic obstructive pulmonary disease overlap syndrome). Although current biologic therapies in development provide

relief to only small percentages of patients, they represent a major advancement toward improving asthma care in this difficult to treat population.

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## Conflicts of interest

*There are no conflicts of interest.*

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- of special interest
- of outstanding interest

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