

INVITED REVIEW

Severe asthma: from characteristics to phenotypes to endotypes

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Abstract

Asthma, and severe asthma, in particular, is increasingly recognized as a heterogeneous disease. While traditional views of asthma have centered around a childhood onset disease with an allergic component, several large scale network studies are now confirming that severe asthma can present in multiple different ways, only 30–50% of which meet traditional childhood onset allergic criteria. To understand the different groups better, initial studies have attempted to define phenotypes of severe asthma. A phenotype is defined as the integration of different characteristics that are the product of the interaction of the patient's genes with the environment. Both clinical and statistical approaches have identified at least 3–5 phenotypes of severe asthma. However, these phenotypes, in isolation, do not identify the immunopathology that makes these clinical phenotypes distinct or identifies a target population for a specific approach to therapy. As biological characteristics are identified, phenotypes should continue to evolve towards asthma endotypes. The identification of these endotypes, either by matching biology, genetics and therapeutic responses to therapy with clinically or statistically defined phenotypes or through unbiased genetic and genomic approaches, remains limited. Moving forward, this integration of genetics, biology and clinical characteristics should substantially enhance our ability to effectively treat complex heterogeneous diseases, such as severe asthma.

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Introduction

The syndrome that encompasses the term 'severe asthma' impacts the lives of millions of people around the world. While most asthma, as defined by reversible airflow limitation in the setting of appropriate symptoms, is well treated with current medications, approximately 10–20% of patients remain refractory to current gold standards for its treatment [1, 2]. This remaining percentage represents a heterogeneous group of individuals, some of whom appear to have a more severe form of traditional allergic asthma, whereas many others do not. This underlying heterogeneity becomes a challenge for patients, physicians and the researchers who hope to develop treatments for these severely and chronically ill patients.

Characteristics of severe asthma (Table 1)

Large scale studies of severe asthma in the last 10 years have greatly expanded our understanding of the range of characteristics associated with this syndrome of

severe asthma [3, 4, 5]. As part of these studies, some consistent characteristics have emerged, including the presence of frequent and/or severe exacerbations, low baseline lung function, reliance on high doses of inhaled and/or oral corticosteroids (CSs) and near daily symptoms. These core characteristics are not, however, universally seen, and while there are relationships between them, the relationships are modest. In addition to these classic clinical/physiological characteristics, additional clinical, physiological, radiological and immuno-inflammatory characteristics are being increasingly recognized, again, as related to some, but not all cases of asthma, and as discriminatory for more severe types of asthma. These characteristics include things like degree of bronchodilator responsiveness and persistent airflow limitation, presence/absence of atopy/allergy, obesity and inflammatory characteristics such as eosinophilia and neutrophilia. In addition, two recent large studies from the West Sweden Asthma Study suggest that rhinosinusitis and its symptoms, occupational exposures to gas, dust, fumes, smoking history and family histories of allergy/asthma, as well as female

Table 1. Characteristics variably associated with severe asthma

Symptoms
Wheeze, shortness of breath, cough, nocturnal awakenings, chest tightness
Airway obstruction
Complete or incomplete bronchodilator responsiveness
Severe exacerbations
Frequent exacerbations
Atopy/allergic responses
Non-steroidal anti-inflammatory reactions
Age at onset
Rhinosinusitis
Air trapping
Airway wall thickening
Inflammation
Eosinophilic, neutrophilic, paucigranulocytic

gender and old age are all characteristics, and in many cases, risk factors for multi-symptom asthma (as a surrogate for more 'severe' asthma [6, 7]. Clinical, cluster and genetic studies are also suggesting that the characteristic of age at onset, when dividing between childhood and adult onset disease is a discriminatory characteristic [8–10]. Thus, increasingly categorized patients from large datasets are helping to define both the overarching characteristics of most 'severe asthma' (symptoms/exacerbations/airflow limitation) and the wide range of characteristics that associate with and identify certain subgroups of patients.

Severe asthma phenotypes

While it has long been recognized that certain characteristics are seen in some asthmatics and not others, multiple characteristics are only rarely linked together to identify a subtype or as they are now termed, phenotype, of asthma. In fact, a phenotype is defined as the observable characteristics, with emphasis on multiple as opposed to singular characteristics, of an organism, which develop from the interaction of the organism with its environment. In relation to asthma, multiple different approaches have been used to identify phenotypes, including 'phenotypes' related to clinical characteristics (severity, fixed airflow limitation, age at onset), factors that associate with or trigger asthma (allergic, aspirin, obesity) and finally, pathobiological characteristics, including eosinophilic and neutrophilic inflammation [10]. As much is understood regarding relevant characteristics of asthma, phenotypes represent 'groupings' of several observable characteristics that tend to track together, and identify a clinically meaningful patient (Table 2). As can be appreciated, most of the characteristics that make up phenotypes of severe asthma are rather non-specific clinical (or even inflammatory) factors. They give little insight into the

Table 2. Replicated phenotypic groupings of characteristics

Hereditary, early onset allergic asthma
Poorly reversible, very severe, neutrophilic asthma
Late onset eosinophilic asthma
Late onset, symptom dominant, obese minimal inflammation

underlying pathobiology of the condition. Attempts to target and integrate more specific inflammatory biomarkers, including levels of specific and total IgE, sputum inflammatory cell analysis, exhaled breath condensate measures and nitric oxide (NO), have either not yet been studied and replicated in high enough numbers of patients/cohorts, been practical for clinical practice or been sufficiently studied using a phenotype directed approach. However, both clinically directed and less biased statistical approaches are now being reported, which consistently link and integrate the range of characteristics to better define phenotypes [8, 11–13]. Both biased/clinical and less biased/statistical analyses from both European and North American severe asthma cohorts strongly support the presence of several subgroups or phenotypes, probably with more similarities than differences in the phenotypes identified. For instance, all studies to date have identified an early onset, mostly atopic/allergic phenotype [8, 11–13]. In addition, a late onset, highly eosinophilic phenotype, as well as an additional late onset primarily female, less atopic and more obese phenotype have also been reported [8, 11, 12]. Unfortunately, none of these clinically characterized phenotypes, as reported, provide much insight into the underlying pathogenetic mechanisms that led to that phenotype, nor are there data to support their stability over time.

Moving from phenotype to endotype (Figure 1)

The challenge now is to link pathobiology to these clinical phenotypes, and perhaps to use pathobiology to identify clinical phenotypes not yet recognized. None of the phenotype approaches introduced above have globally identified a specific pathobiology, biomarker, genetic element, stability over time or critically, a robust response to therapy targeted to the biology associated with that phenotype. Probably, all of these factors would need to be incorporated into the phenotype to move that grouping of subjects from a phenotype to an 'endotype'. Endotype is a term applied to a 'subtype of a condition which is defined by a distinct functional or pathophysiological mechanism' [14]. While we are getting closer to defining asthma endotypes, confirmatory support for any specific endotype is still limited, perhaps related to the near absence of large scale and longitudinal studies that have incorporated pathobiology with clinical approaches. However, several partial

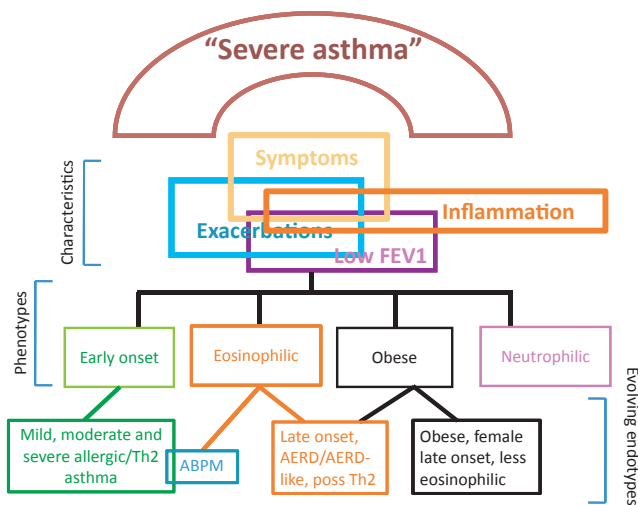


Fig. 1. Schematic diagram of relationship of the umbrella term 'asthma' to previously identified phenotypes and endotypes.

endotypes have been proposed, which appear to be clinically, statistically or molecularly definable. As has been noted by others, a fully defined endotype will require incorporation not only of pathobiology and its related biomarkers but also numerous clinical, physiological and genetic elements, as well as long-term stability (Table 3) [15].

Recently, six partial endotypes were proposed, of which, at least four are relevant to severe asthma [15].

These four include severe 'allergic' asthma, late onset persistent eosinophilic asthma, aspirin exacerbated airway disease (AERD) and allergic bronchopulmonary mycoses. Each of these four proposed endotypes fulfills the majority of the necessary characteristics. However, in all cases, the true underlying pathogenetic mechanism remains poorly identified, and in some cases, emerging data suggest that some of the factors proposed to define the specific pathobiology of an endotype may overlap across phenotypes. Whether a better understanding of pathobiology will eventually lead to endotypes initially defined molecularly, with the accompanying clinical characteristics secondary to the molecular process, remains to be determined. However, a study of molecular phenotyping in mild asthma suggests that this approach may be possible and even preferable [16].

Evolving endotypes of relevance to severe asthma (Table 3)

Severe early onset allergic asthma

Natural history and clinical characteristics. As noted, this group of severe asthmatic patients primarily developed their disease in childhood, although allergic asthma with onset in adulthood certainly occurs, usually with a history of allergic reactions of some sort

Table 3. Evolving endotypes in relation to severe asthma

	Natural history	Clinical	Genetics	Pathobiology	Biomarkers	Response to Rx
Early onset allergic	Childhood onset severe disease is persistent & probably progressive	Aeroallergen sensitivity other allergic diseases	17q12–21 Th2 pathway	Th2 cytokines, eos–less clear in severe disease	FeNO, increased specific IgE periotin	Mild responds to CSs/Th2 blockers. less clear in severe
Persistent eosinophilia	Adult onset, persistence and progression unknown	Often severe sinusitis, nasal polyps Subset with AERD	LT pathway HLA	Blood and lung eos despite CSs IL-5, cLT pathway	Sputum eos (not specific for this endo-type)	Anti-Th2/IL-5 LT modifiers
ABPM	Usually adult onset persistent, but progression unknown	Increased cough/mucus central bronchiectasis	CFTR?	Blood and lung eos, mixed adaptive immunity	Fungus specific IgE and IgG	CSs, anti-fungals, possibly anti-IgE
Obese-Female	Very late onset persistence and progression unknown	Very symptomatic, but less airway obstruction and few severe exacerbations hormonal ties	Unknown	Inconsistent reports	Unknown	No good studies of targeted Rx, but poorly CS responsive
Neutrophilic	Unknown	Fixed airway obstruction, few other defined clinical characteristics	Unknown	Neutrophils, possibly increased innate immune activation	Unknown	Possible response to macrolide antibiotics

since childhood [17]. It remains to be determined what percentage of these early onset patients had severe asthma since childhood, and how many progressively developed severe asthma over time [18]. However, this group appears to constitute around 40% of all severe asthmatics, and at least in the cluster analyses to date, appears to be an extension of mild to moderate to severe allergic asthma, with the most severe group identified by the highest number of positive allergy skin test reactions and the longest duration of disease [12]. They also commonly have a family history of asthma, supporting a genetic component. They appear to be generally reversible to bronchodilators, even back to a relatively normal forced expiratory volume in 1 s (FEV₁) [8, 12]. While the overall 'stability' of this early onset endotype has not specifically been studied, children who meet the 'Asthma Predictive Index' criteria are generally believed to have a persistent disease that would manifest in adulthood as early onset allergic asthma [19]. Small reports even suggest that although some children become asymptomatic as they reach puberty, bronchial hyperresponsiveness remains [20, 21].

Genetics. The family history of asthma suggests a genetic component. Indeed, multiple studies have reported associations of Th2 related genes to atopy/IgE levels [22, 23]. In addition, targeted genetic analysis of Th2 related genes in early onset clusters from the Severe Asthma Research Program show a general dose response, with greater numbers of Th2-related genetic polymorphisms with increasing severity of disease [24]. In contrast, a large scale meta-analysis of genome-wide association studies did not find genes associated with atopy or IgE associated with asthma or even early onset asthma [9, 25]. However, less well defined epithelial related genes, genes related to innate immunity and those with poorly defined function were stronger predictors of early onset, atopic asthma than genes related to atopy.

Pathobiology and biomarkers. The presence of increased specific and total IgE in this endotype has focused pathobiological studies on immediate hypersensitivity and Th2 adaptive immunity. Interestingly, however, very few studies have actually distinguished the pathobiology in early onset disease from later onset or 'atopic' asthma as identified by positive allergy skin tests from non-atopic. Despite these limited studies, studies of 'atopic asthma' have generally observed increases in IgE positive cells, IL-4 and IL-13 at the mRNA level, but with little difference between atopic and non-atopic asthma [26, 27]. This raises immediate questions about the specificity of these markers for atopic allergic asthma. In most cases, CS therapy decreases inflammatory cells; however, a study of severe early

onset asthma suggested that despite low eosinophils, lymphocytes in airway biopsies remain increased in the face of CS therapy [8]. Little is understood regarding the role of the mast cell, the epithelium or other cell types specifically in early onset allergic asthma, although a mast cell gene signature appears to track with a Th2-Hi signature in mild asthma [16]. Neither total or specific IgE are sensitive, nor are specific biomarkers for this phenotype, as atopy is identified in up to 50% of the general/healthy population, with even higher numbers in those with allergic rhinitis (AR) and no asthma [28].

Recent studies suggest that an epithelial Th2 gene signature exists in mild asthma, with increases in an IL-13 responsive gene known as periostin predicting an atopic, eosinophilic disease [16]. Similarly, elevations of NO, the primary product of inducible NO synthase (iNOS), are also reported to be a biomarker for an allergic asthma phenotype. iNOS is increased in human airway epithelial cells in response to Th2 cytokines, but its selectivity to Th2 inflammation is limited, as it can be induced by interferon gamma as well [29]. Furthermore, fractional exhaled NO (FeNO) can be elevated in AR patients in the absence of asthma [30]. More recently, periostin has been suggested as a possible biomarker for Th2 inflammation, although its specificity to early onset, allergic asthma is not known [31]. Thus, although there are suggestions of Th2 pathobiology in early onset allergic asthma, much has to be done to understand its selectivity in this phenotype, as well as its persistence (or lack thereof) in progressively more severe and CS treated patients.

Response to therapy. No clinical trials have specifically targeted early onset allergic asthma. Allergen desensitization is typically targeted to patients with both positive skin reactions and supporting clinical symptoms; however, the efficacy of allergy desensitization in asthma (when compared with AR) has undergone limited study with a meta-analysis suggesting modest efficacy [32]. Monoclonal antibodies to IgE (omalizumab) have also been targeted to 'allergic asthma'. However, the criteria for allergic asthma are not selective and include the presence of any specific IgE and a level of total IgE > 30 IU/mL. Despite this limited definition, omalizumab has shown efficacy in patients defined above, even when treated with inhaled CS and other controller medications [33–36]. Whether anti-IgE would be more effective in a better 'characterized' allergic and early onset endotype remains unclear.

Th2 modifying drugs are now beginning to be studied in asthma and its phenotypes. Both IL-4R α receptor antagonist (pitakinra) and antibody to IL-13 have been efficacious in an allergen challenge model in mild allergic asthmatics [10, 37]. However, neither approach has

been specifically studied in a chronic 'allergic asthma' endotype.

Adult onset, persistently eosinophilic severe asthma

Natural history/clinical presentation. As this proposed endotype has only been recognized in the last 10 years, much less is understood regarding the development and course of this endotype. However, it appears that the majority of this group develops disease in adult life, often in the late 20s to 40s. It is often associated with sinus disease and severe from the start. There is little evidence for additional allergic diseases (low level eczema compared with early onset disease) or allergic symptoms. Atopy, while less than that in early onset asthma, still is higher than in the general population, and IgE levels can also be elevated. Systemic CSs are often needed to prevent exacerbations, decrease symptoms and lower blood eosinophils, suggesting an element of CS resistance. Interestingly, this general endotype was identified by Haldar et al. when sputum eosinophilia was a key input into a cluster analysis [11]. In contrast, when lung eosinophilia was not included in the analysis, as in SARP, this endotype was not identified [12].

Aspirin exacerbated airway disease is probably a very similar endotype, or even a subendotype of this adult onset eosinophilic group in whom sensitivity to non-steroidal anti-inflammatory drugs has been identified. Like late onset persistent eosinophilic asthma, AERD starts late in life, and is associated with eosinophilia and sinus disease/nasal polyps [38]. This specific subset is perhaps the most distinct endotype yet identified, although much regarding the natural history of this endotype remains unclear.

Genetics. Despite the rather specific and clinically identifiable characteristics of this endotype, little is known regarding the genetics. Genetic variants in elements of the cysteinyl leukotriene (cysLT) pathway have been identified in AERD using targeted approaches, but the results have been variable, probably on the basis of the very small sample sizes [39, 40]. Pooled analyses across several severe asthma cohorts will be required to better understand the genetics of this group. Interestingly, few patients give a family history of asthma [8].

Pathobiology/Biomarkers. Lung eosinophilia is one of the hallmarks of this endotype. However, lung eosinophilia is not specific for this endotype, suggesting that other, but perhaps Th2 related, biomarkers may be more important. Pathologically, IL-13 and IL-5 are present in the lower airways and in association with nasal polyps, despite their generally observed suppression by CSs, with a gene expression study identifying the Th2

signature gene periostin in nasal polyps from AERD [41–44]. Other downstream 'Th2' signatures are increased in many of these patients, including 15 lipoxygenase 1, its product 15 hydroxyeicosatetraenoic acid, iNOS and eotaxins [41, 45–47]. The subset with AERD, and to some degree, the general phenotype, are associated with increases in the cysLT pathway, a pathway upregulated by Th2 cytokines. Elevations in FeNO and urinary cysLTs have also been reported [8, 11, 48, 49]. Whether distinct Th2 biomarkers will identify this phenotype remains to be assessed.

Response to therapy. Persistent eosinophilia in late onset disease implies a refractoriness of its eosinophilia and related immunobiology to CS, although high systemic doses are generally able to overcome this refractoriness [50]. Consistent with the high cysLTs levels, leukotriene modifiers can have a robust impact on the AERD subset, even in the face of systemic CS therapy [51, 52].

In addition to cysteinyl LTs, the presence of persistent eosinophilia suggests that Th2 cytokines could also contribute to the pathobiology, despite the lack of association with IgE/atopy. Recent drug trials blocking both the IL-4/-13 and IL-5 pathways support this concept [49, 53, 54, 55]. Results from separate studies of severe persistent eosinophilic asthma treated with a monoclonal antibody to IL-5 showed efficacy in diminishing blood and lung eosinophils and decreased exacerbations and systemic CS requirements. In addition, although the IL-4R α blocker, pitrakinra did not decrease exacerbations in a general population of moderate asthmatics on CS withdrawal; it was significantly better than placebo in reducing exacerbations in a pre-specified subanalysis of patients with baseline blood eosinophils > 350 mm³ [54]. While greater efficacy was not observed in early onset/high IgE subgroups, later onset, persistently eosinophilic disease despite CSs was associated with the more robust responses to Th2 targeted therapy.

This combination of pathobiology and response to therapy strongly supports a prominent element of Th2 immunity. However, the lack of clinical allergy and poor response to inhaled CS in this endotype suggests rather profound differences from the Th2 immunity associated with early onset allergic disease.

Allergic bronchopulmonary mycoses

Typically, allergic bronchopulmonary mycoses (ABPM) has referred to a complex form of a Type I hypersensitivity response to aspergillosis (i.e., ABPA). Other fungi have been described such that the term has been broadened to 'mycoses.' However, most studies have focused on aspergillus. It has alternately been considered as a phenotype of asthma or as a masquerader of asthma

(i.e., a different disease), in patients with severe disease. While clearly possible, it remains unknown whether mild asthma with fungal sensitization progresses to ABPM, and if it does, what are the predisposing factors for that progression.

Natural history/clinical features. In the absence of cystic fibrosis, ABPM is more commonly seen in adults. There is a relation to atopy, but typically, findings consistent with ABPM occur long after childhood, when most 'allergic asthma' develops. Little is understood regarding the predisposing factors to its development [56]. Cough and phlegm are generally present and often the initial manifestation of the disease. These symptoms are usually seen in association with bronchiectasis. Although obstruction is often present, bronchiectasis can exist without physiological evidence for airway obstruction. The disease is hallmarked by elevations in total IgE, blood eosinophils and IgE specific to the fungus of interest. The disease is generally believed to be progressive, but no large long-term follow-up studies have been reported.

Genetics. Little is understood regarding the genetics of this endotype. There is only modest evidence for family history of disease. Genetic polymorphisms in human leukocyte antigen (HLA)-related genes have been described, and the endotype has also been reported in relation to cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in the absence of cystic fibrosis (CF) [57].

Pathobiology/Biomarkers. Allergic bronchopulmonary mycoses typically involves the actual propagation of the fungi in the airway, separating it from asthma that is triggered by an airway sensitization response which occurs following inhalation of fungal elements and induces allergic reactions upon secondary exposure. The association with CF strongly suggests that abnormalities in epithelial function are likely to be critical to its pathogenesis, and almost certainly contribute to the central bronchiectasis and associated mucus generation observed in this endotype. The strong association with Type I hypersensitivity and specific IgE to fungi as well as the high numbers of blood and lung eosinophils, support a strong role for Th2 immunity in this endotype. In CF-related ABPA, OX40L was reported to be increased and *in vitro*, appeared to drive Th2 responses [58]. Further studies are needed in non-CF-related ABPA/M to determine whether similar pathways are engaged. However, supporting this concept, a recent study suggested that the Th2 chemokine CCL17 (Thymus and activation regulated chemokine/TARC) was a better biomarker of ABPA in patients with CF than total or specific IgE levels [59]. However, asthmatic

controls (as opposed to CF controls) have not yet been reported.

Response to therapy. Systemic CSs remain the mainstay of therapy, and indeed many patients will require life-long treatment with these drugs. The reasons behind the greater efficacy of systemic when compared with inhaled CSs is not clear, especially as the majority of the bronchiectasis appears to occur centrally, but suggests activation of systemic immunity, perhaps incorporating elements of several adaptive immune pathways [60, 61].

The only Th2 targeted approach that has been reported is the use of anti-IgE. No prospective studies have yet been completed, but a case series suggested efficacy in a group with probable ABPA (although rather low total IgE levels) [62]. Small placebo controlled studies have reported efficacy of itraconazole in ABPA, with case series suggesting next generation antifungals may be more efficacious [63]. Interestingly, a recent study also found efficacy of itraconazole in severe asthmatics with fungal sensitization but no bronchiectasis, suggesting overlap between fungal sensitized asthma and ABPA/M [64].

The future: possible emerging endotypes of severe asthma

As can be seen from the above, even 'proposed' endotypes of severe asthma continue to have many gaps in the understanding of their pathobiology, natural history, genetics and responses to targeted therapy. Additional phenotypes that could become endotypes include a group of symptomatic older women, generally with adult onset disease and a high body mass index. This phenotype was observed in both the Leicestershire, UK and SARP clusters, although the relation to inflammation varied between cohorts [11, 12]. Both cohorts identified these patients with very symptomatic disease despite moderately preserved lung function, with no history of atopy or allergic disease or high intensity health care utilization (including ICU stays or mechanical ventilation). In the SARP analysis, this cluster had age at onset in the mid 40s, and there was an association with natural or surgical menopause. This cluster also had persistent eosinophilic inflammation in SARP, but there was little evidence for inflammation in the European cohort. Although allergy does not appear to be associated with this phenotype, the importance of other factors, including aspirin sensitivity and hormonal changes remains unclear. Those who had the greatest improvement in objective measures such as bronchial hyperresponsiveness (BHR) were those with no/little evidence for more traditional allergic asthma. Nothing is known regarding lung specific pathobiology or

biomarkers. However, a recent follow-up study of obese patients who lost large amounts of weight following bariatric surgery suggested that while many patients improved markedly from asthma symptom perspective, only those with little/no evidence for IgE-mediated asthma had improvement in BHR [65]. This study supports the presence of a separate distinct obese endotype. Finally, a targeted, perhaps hormonally related, therapeutic approach has also not been attempted.

There has also been support for a 'neutrophilic endotype' in severe asthma. Several investigators have identified neutrophilia in association with high dose CS therapy and smoking [66]. However, in addition, there appears to be a clinical association with low FEV₁% predicted and air trapping on chest CT scan [67, 68]. A sputum gene expression analysis of this phenotype suggested that innate response genes were increased, including IL-1 family members [69]. Although, no biomarkers beyond neutrophils themselves have been explored, this group may respond to macrolide antibiotics [70].

Finally, 'smoker's asthma' has been suggested as another phenotype, although data to begin to support an 'endotype' are weak. This phenotype may be as complex as the heterogeneity of asthma itself. Clearly, asthma can arise after the initiation of smoking or before. In many asthmatics with high level of bronchial hyperresponsiveness, just exposure to passive smoke is enough to make them uncomfortable. Thus, the underlying airway immunobiology may vary considerably among smokers. While smoking asthma has been associated with more frequent exacerbations, lower lung function and poor response to CS therapy, little is

understood regarding the role of genetics, biomarkers or pathobiology[71–73].

Conclusions

Emerging data from large cohorts strongly support heterogeneity in severe asthma, with increasing acceptance of the presence of distinct phenotypes. Confirming that any of these phenotypes or subtypes within them are, in fact, endotypes requires additional study. Identifying the presence of distinct endotypes will require an integrated approach, which at one level describes and then links the natural history, clinical features, genetics, biology and perhaps, more importantly, molecular biology, but which then utilizes molecular therapeutic approaches targeting specific biological elements believed of importance. It is only with the evolution of these molecular descriptions and the ensuing interventions that complete endotypes of severe asthma will eventually be confirmed. No single proposed endotype meets all the criteria for this rigorous approach. However, ongoing molecular phenotyping studies from Europe and North America should take large steps to move us in that direction.

Author disclosures

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References

- Bateman ED, Boushey HA, Bousquet J *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004; **170**: 836–44.
- Bousquet J, Mantzouranis E, Cruz AA *et al.* Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; **126**:926–38.
- The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J* 2003; **22**:470–7.
- Dolan CM, Fraher KE, Bleecker ER *et al.* Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004; **92**:32–9.
- Moore WC, Bleecker ER, Curran-Everett D *et al.* Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; **119**:405–13.
- Lotvall J, Ekerljung L, Lundback B. Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. *Respir Res* 2010; **11**:163.
- Ekerljung L, Bossios A, Lotvall J *et al.* Multi-symptom asthma as an indication of disease severity in epidemiology. *Eur Respir J* 2011; **38**:825–32.
- Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004; **113**:101–8.
- Moffatt MF, Gut IG, Demenais F *et al.* A large-scale, consortium-based genome-wide association study of asthma. *N Engl J Med* 2010; **363**:1211–21.
- Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007; **370**:1422–31.
- Haldar P, Pavord ID, Shaw DE *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; **178**:218–24.
- Moore WC, Meyers DA, Wenzel SE *et al.* Identification of asthma phenotypes using cluster analysis in the

- Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181:315–23.
- 13 Siroux V, Basagana X, Boudier A *et al.* Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J* 2011; 38:310–7.
 - 14 Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008; 372:1107–19.
 - 15 Lotvall J, Akdis CA, Bacharier LB *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127:355–60.
 - 16 Woodruff PG, Modrek B, Choy DF *et al.* T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; 180:388–95.
 - 17 Brozek JL, Bousquet J, Baena-Cagnani CE *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126:466–76.
 - 18 Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol* 2002; 109:189–94.
 - 19 Guilbert TW, Morgan WJ, Zeiger RS *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985–97.
 - 20 Boulet LP, Turcotte H, Brochu A. Persistence of airway obstruction and hyperresponsiveness in subjects with asthma remission. *Chest* 1994; 105:1024–31.
 - 21 Vonk JM, Postma DS, Boezen HM *et al.* Childhood factors associated with asthma remission after 30 year follow up. *Thorax* 2004; 59:925–9.
 - 22 Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* 1997; 337:1720–5.
 - 23 Liu X, Beaty TH, Deindl P *et al.* Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 2003; 112:382–8.
 - 24 Slager RE MW, Hawkins G, Peters SP *et al.* Predictive model of severe atopic asthma phenotypes using interleukin4/13 pathway polymorphisms. *Am J Respir Crit Care Med* 2011; 183: A1332.
 - 25 Halapi E, Gudbjartsson DF, Jonsdottir GM *et al.* A sequence variant on 17q21 is associated with age at onset and severity of asthma. *Eur J Hum Genet* 2010; 18: 902–8.
 - 26 Humbert M, Durham SR, Ying S *et al.* IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against “intrinsic” asthma being a distinct immunopathologic entity. *Am J Respir Crit Care Med* 1996; 154: 1497–504.
 - 27 Humbert M, Grant JA, Taborda-Barata L *et al.* High-affinity IgE receptor (FcεpsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma. *Am J Respir Crit Care Med* 1996; 153:1931–7.
 - 28 von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001; 56:835–8.
 - 29 Guo FH, Uetani K, Haque SJ *et al.* Interferon gamma and interleukin 4 stimulate prolonged expression of inducible nitric oxide synthase in human airway epithelium through synthesis of soluble mediators. *J Clin Invest* 1997; 100:829–38.
 - 30 Scott M, Raza A, Karmaus W *et al.* Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax* 2010; 65:258–62.
 - 31 Arron J, Gui-Quan J, Erickson RW *et al.* Periostin is a systemic biomarker of eosinophilic airway inflammation in asthma. *Am J Respir Crit Care Med* 2011; 183:A4455.
 - 32 Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995; 151:969–74.
 - 33 Busse W, Corren J, Lanier BQ *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184–90.
 - 34 Soler M, Matz J, Townley R *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18:254–61.
 - 35 Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma. *Allergy* 2008; 63:592–6.
 - 36 Hanania NA, Alpan O, Hamilos DL *et al.* Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; 154:573–82.
 - 37 Gauvreau GM, Boulet LP, Cockcroft DW *et al.* Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. *Am J Respir Crit Care Med* 2011; 183: 1007–14.
 - 38 Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003; 111: 913–21; quiz 22.
 - 39 Sanak M, Simon HU, Szczeklik A. Leukotriene C4 synthase promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997; 350:1599–600.
 - 40 Van Sambeek R, Stevenson DD, Balasaro M *et al.* 5' flanking region polymorphism of the gene encoding leukotriene C4 synthase does not correlate with the aspirin-intolerant asthma phenotype in the United States. *J Allergy Clin Immunol* 2000; 106: 72–6.
 - 41 Saha SK, Berry MA, Parker D *et al.* Increased sputum and bronchial biopsy IL-13 expression in severe asthma. *J Allergy Clin Immunol* 2008; 121: 685–91.
 - 42 Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997; 99:837–42.
 - 43 Sanchez-Segura A, Brieva JA, Rodriguez C. T lymphocytes that infiltrate nasal polyps have a specialized phenotype and produce a mixed TH1/TH2 pattern of cytokines. *J Allergy Clin Immunol* 1998; 102:953–60.
 - 44 Stankovic KM, Goldsztein H, Reh DD, Platt MP, Metson R. Gene expression profiling of nasal polyps associated with chronic sinusitis and aspirin-sensitive asthma. *Laryngoscope* 2008; 118:881–9.
 - 45 Chu HW, Balzar S, Westcott JY *et al.* Expression and activation of 15-lipoxygenase pathway in severe asthma: relationship to eosinophilic phenotype

- and collagen deposition. *Clin Exp Allergy* 2002; 32:1558–65.
- 46 Zhao J, Maskrey B, Balzar S *et al.* Interleukin-13-induced MUC5AC is regulated by 15-lipoxygenase 1 pathway in human bronchial epithelial cells. *Am J Respir Crit Care Med* 2009; 179:782–90.
 - 47 Yamamoto M TY, Chibana K, Trudeau J, Holguin F, Wenzel S. Nitric oxide and related enzymes in asthma: relation to severity, enzyme function and inflammation. *Clin Exp Allergy* 2011. doi: 10.1111/j.1365-2222.2011.03860.x. [Epub ahead of print].
 - 48 Stirling RG, Kharitonov SA, Campbell D *et al.* Increase in exhaled nitric oxide levels in patients with difficult asthma and correlation with symptoms and disease severity despite treatment with oral and inhaled corticosteroids. Asthma and Allergy Group. *Thorax* 1998; 53:1030–4.
 - 49 Haldar PBC, Hargadon B, Gupat S *et al.* Mepolizumab (anti-IL 5) and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973–84.
 - 50 ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med* 2004; 170:601–5.
 - 51 Dahlen B, Nizankowska E, Szczeklik A *et al.* Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998; 157:1187–94.
 - 52 Dahlen SE, Malmstrom K, Nizankowska E *et al.* Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165:9–14.
 - 53 Nair P, Pizzichini M, Kjarsgaard M IM, Efthimiadis A, Pizzichini E HF, O'Byrne P. Mepolizumab in Prednisone-Dependent Asthma with Sputum Eosinophilia. *N Engl J Med* 2009; 360:985–93.
 - 54 Wenzel SIP, Otulana BA, Bleecker ER, Kuna P, Yen YP. Inhaled pitrakinra, an IL-4/IL-13 antagonist, reduced exacerbations in patients with eosinophilic asthma. *Eur Respir J* 2010; P3980.
 - 55 Wenzel S, Ind PW, Otulana BA *et al.* A Phase 2b Study Of Inhaled Pitrakinra, An IL-4/IL-13 Antagonist, Successfully Identified Responder Subpopulations Of Patients With Uncontrolled Asthma. *Am J Respir Crit Care Med* 2011; 183: A19045.
 - 56 Patterson K, Strek ME. Allergic bronchopulmonary aspergillosis. *Proc Am Thorac Soc* 2010; 7:237–44.
 - 57 Miller PW, Hamosh A, Macek M Jr *et al.* Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in allergic bronchopulmonary aspergillosis. *Am J Hum Genet* 1996; 59:45–51.
 - 58 Kreindler JL, Steele C, Nguyen N *et al.* Vitamin D3 attenuates Th2 responses to *Aspergillus fumigatus* mounted by CD4 + T cells from cystic fibrosis patients with allergic bronchopulmonary aspergillosis. *J Clin Invest* 2010; 120:3242–54.
 - 59 Latzin P, Hartl D, Regamey N, Frey U, Schoeni MH, Casaulta C. Comparison of serum markers for allergic bronchopulmonary aspergillosis in cystic fibrosis. *Eur Respir J* 2008; 31:36–42.
 - 60 Murdock BJ, Shreiner AB, McDonald RA *et al.* Coevolution of TH1, TH2, and TH17 responses during repeated pulmonary exposure to *Aspergillus fumigatus* conidia. *Infect Immun* 2011; 79:125–35.
 - 61 Fei M, Bhatia S, Oriss TB *et al.* TNF- α from inflammatory dendritic cells (DCs) regulates lung IL-17A/IL-5 levels and neutrophilia versus eosinophilia during persistent fungal infection. *Proc Natl Acad Sci USA* 2011; 108:5360–5.
 - 62 Tillie-Leblond I, Germaud P, Leroyer C *et al.* Allergic bronchopulmonary aspergillosis and omalizumab. *Allergy* 2011; 66:1254–6.
 - 63 Stevens DA, Schwartz HJ, Lee JY *et al.* A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000; 342: 756–62.
 - 64 Denning DW, O'Driscoll BR, Powell G *et al.* Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009; 179:11–8.
 - 65 Dixon AE, Pratley RE, Forgione PM *et al.* Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011; 128: 508–15 e1–2.
 - 66 Wenzel SE, Szefer SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. *Persistent inflammation associated with high dose glucocorticoids.* *Am J Respir Crit Care Med* 1997; 156:737–43.
 - 67 Busacker A, Newell JD Jr, Keefe T *et al.* A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. *Chest* 2009; 135:48–56.
 - 68 Gupta S, Siddiqui S, Haldar P *et al.* Qualitative analysis of high-resolution CT scans in severe asthma. *Chest* 2009; 136:1521–8.
 - 69 Baines KJ, Simpson JL, Wood LG, Scott RJ, Gibson PG. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. *J Allergy Clin Immunol* 2011; 127: 153–60, 60 e1–9.
 - 70 Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008; 177:148–55.
 - 71 Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004; 24:822–33.
 - 72 Chaudhuri R, Livingston E, McMahon AD *et al.* Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006; 174: 127–33.
 - 73 McSharry CP, McKay IC, Chaudhuri R, Livingston E, Fraser I, Thomson NC. Short and long-term effects of cigarette smoking independently influence exhaled nitric oxide concentration in asthma. *J Allergy Clin Immunol* 2005; 116:88–93.