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Asthma phenotypes today

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Summary
PubMed databases were searched for articles regarding asthma phenotypes. Asthma has long been recognized as a heterogeneous disease, with hallmark features including age of onset, pattern of severity and other clinical characteristics, but recently it is no longer considered as single disease but rather as a series of complex, overlapping individual phenotypes, and a novel classification of the disease according to the nature of the underlying airway inflammation has been suggested . It has become increasingly clear that asthma is a complex syndrome. Recognition of specific subphenotypes may improve our understanding of underlying genetic basis and of pathophysiologic mechanisms as well as of response to treatment.

Definition

***"Phenotype: the visible characteristics of an organism resulting from the interaction between its genetic makeup and environment"* (1)**

Asthma is a common airway disorder that is characterized by the presence of chronic inflammation, resulting in airflow obstruction and bronchial hyperresponsiveness that causes wheezing, coughing, and dyspnea (2). Asthma impacts significantly on the rising burden of chronic disease in developed countries; approximately 5 to 10% of patients have a refractory disease, that remains poorly controlled despite maximal inhaled therapy (3). Asthma, like many chronic disorders, is a genetically complex disease; many genes (>100 have been identified) are likely to contribute to its different manifestations. Although asthma has long been recognized as a heterogeneous disease (4, 5), only in recent years it is seen not as single disease but rather as a series of complex, overlapping individual phenotypes, each defined by its unique interaction between genetic and environmental factors (6). A precise definition of asthma phenotypes is becoming increasingly important, because recognition of specific subphenotypes may further improve our understanding of underlying genetic basis, pathophysiologic mechanisms, treatment response and prognosis.

Classification

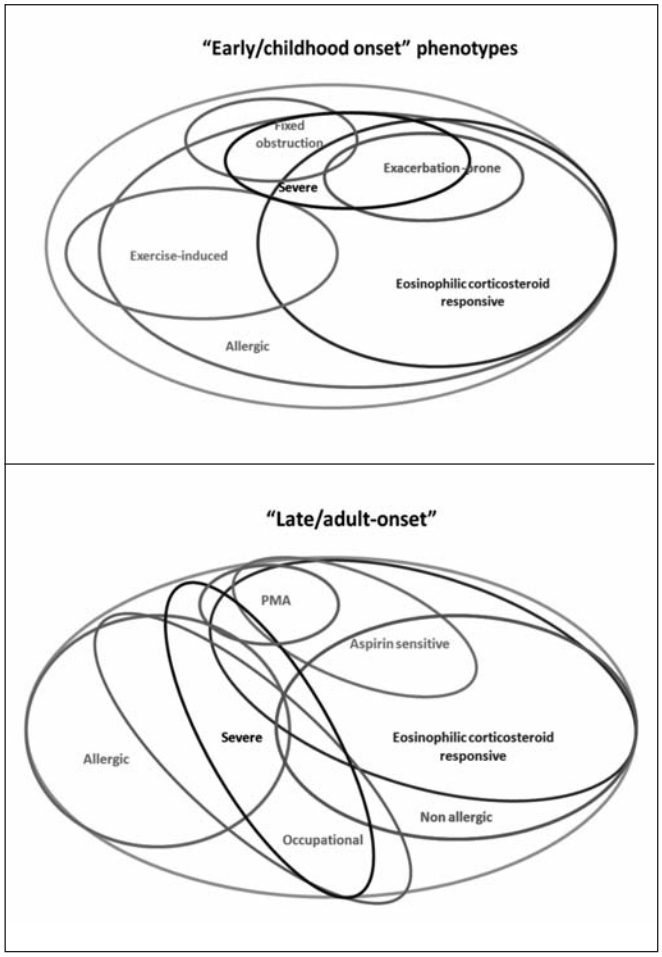
In 2006, Wenzel (7) proposed that the different asthma phenotypes were partly dependent on different disease processes in each individual; adult phenotypes of asthma were therefore subdivided into three basic categories (7):

Clinical or physiological phenotypes
- Severity-defined
- Exacerbation-prone
- Defined by chronic restriction

• Treatment-resistant
• Defined by age at onset
Phenotypes related to the following triggers
• Aspirin or on-steroidal anti-inflammatory drugs
• Environmental allergens
• Occupational allergens or irritants
• Menses
• Exercise
Inflammatory phenotypes
• Eosinophilic
• Neutrophilic
• Pauci-granulocytic
Adapted from Wenzel (7).

There may be overlap between phenotypes, and they may change over time (Fig. 1).

Figure 1 - Venn diagram of phenotypes of childhood and adult-onset asthma. Adapted from Wenzel (7)



Early onset asthma

The age of onset differentiates asthma phenotypes because patients with early-onset asthma (onset before 12 years of age) show a significantly greater likelihood of having allergic sensitization than patients with late-onset disease (8). Additionally, patients with early-onset asthma are much more likely to have a history of eczema and a family history of asthma (8). Recent studies seem to show an association between some genetic polymorphisms and early-onset asthma (9) and intrauterine exposures causing epigenetic regulation may also affect asthma risk (10). Despite a longer duration of disease and a increased susceptibility to frequent exacerbations (7), people with early-onset asthma were shown to have better lung function than those with late-onset disease (11). The allergic phenotype shows a good response to inhaled corticosteroids (12) and, when indicated (asthma mild to moderate, coexistence of allergic rhinitis), to allergen immunotherapy, one of the best examples of phenotype-oriented therapeutic approach and, still today, the only potentially disease-modifying therapy (13); the long-lasting and preventive effects of specific immunotherapy should be taken into account when the efficacy is evaluated (14). In allergic asthma, treatment guidelines now recommend omalizumab (a recombinant humanized monoclonal anti-IgE antibody that binds to the Fc-region of the IgE molecule) as add-on option for patients with moderate-to-severe disease uncontrolled on high-dose inhaled corticosteroids and long-acting β-agonists (15). Omalizumab is well-tolerated and, in patients (children and adults) with uncontrolled allergic asthma, significantly improves pulmonary function and quality of life, and decreases clinical symptoms (16-19).

Adult-onset asthma

Adult-onset asthma is a subtype of asthma characterized by a significantly lower likelihood of allergic sensitization, female predominance, higher degree of severity, more frequent association with nasal polyposis (20) and different genetic background (21). In adult-onset asthma, some patients present with marked airflow restriction, probably related to airway inflammation and remodeling, and with a faster decline in forced expiratory volume in 1 second (FEV_1), compared with nonasthmatic subjects (22-24). Lee et al. (22) examined demographic and clinical characteristics associated with persistent airflow limitation (Table 1).

Table 1 - Risk factors independently associated with persistent airflow limitation in asthma

•Adult onset
•Male sex
•African American ethnicity
•Nonallergic (intrinsic) asthma
•Genetic predisposition (eg, ADAM33)
•Smoking history
•Aspirin intolerance (AERD)
•Some phenotypes of occupational asthma
•Poor airway function shortly after birth

Adapted from Lee et al. (22)

Aspirin-exacerbated asthma

Asthma that is exacerbated by aspirin, also referred to as Aspirin-Exacerbated Respiratory Disease (AERD), is associated with adult-onset disease, and represents a distinct clinical syndrome characterized by chronic hyperplastic rhinosinusitis, nasal polyps, and asthma attacks after ingestion of aspirin and other nonsteroidal antiinflammatory drugs. Aspirin-sensitive asthma is associated with little evidence of atopy, raised airway leukotrienes, and high numbers of eosinophils in both tissue and blood (Table 2).

The prevalence of AERD in adult asthmatic populations is approximately 10% to 20%, but increases to 30% to 40% when asthma is associated with chronic hyperplastic sinusitis and nasal polyposis (25-27). This asthma phenotype is frequently poorly responsive to inhaled steroids, and is therefore present most often in patients with severe asthma. The association with raised leukotrienes predicts a good response to drugs that modify leukotriene pathways (28, 29), but not all patients respond. Although this phenotype is very distinct clinically and pathologically, the underlying pathogenesis remains poorly understood (30).

Table 2 - Clinical features of aspirin-exacerbated respiratory disease

• Adult onset
• Female predominance
• Asthma that is usually moderate to severe
• Chronic hyperplastic eosinophilic sinusitis (usually moderate to severe)
• Anosmia
• Nasal polyps
• Tissue and circulating eosinophilia
• Sensitivity to aspirin and nonselective (cyclooxygenase-1 inhibiting) nonsteroidal anti-inflammatory drugs
• Overproduction and overresponsiveness to cysteinyl leukotrienes
• Atopy typically not present

Adapted from Borish L et al. (6)

Asthma inflammation and its subphenothypes

Since the introduction of noninvasive procedures to estimate airway inflammation in asthma, the recognition of inflammatory subphenotypes based on the pattern of airway inflammation seems particularly useful in increasing our understanding of the disease; moreover, the identification of inflammatory subphenotypes can assist clinicians in management of individual patients.

Eosinophilic asthma

Eosinophilic asthma is the best studied pathological phenotype; eosinophils have been reported in sputum, lavage and endobronchial biopsies of many people with asthma (around 50% of patients have eosinophilic involvement) (31-34), but some studies suggest that eosinophilic inflammation might be present in a greater proportion of asthmatic patients than previously believed, since this inflammation could be predominant in a distal portion of the lung, not assessed by standard methods (35, 36). Eosinophilic inflammation, measured by sputum eosinophil count, increases with asthma severity (37). Patients with eosinophilic asthma have a significantly increased short term response to inhaled corticosteroids than those with non-eosinophilic asthma (38). Sputum eosinophil count and exhaled nitric oxide levels are predictors of clinical response to corticosteroids (39, 40); however sputum eosinophils and elevated levels of eosinophil cationic protein often persist in asthma patients despite ICS therapy, particularly in severe disease (32). Eosinophilic airway inflammation appears to be closely related to the risk of severe asthma exacerbations (41). Persistent eosinophilic inflammation in severe asthma is often associated with adult-onset disease, and with aspirin sensitivity (8). The eosinophil phenotype in severe asthma may persist over a 5-year period (42). In patients with uncontrolled asthma, two studies have shown that treatment with mepolizumab, an anti- interleukin-5 monoclonal antibody, can significantly reduce sputum eosino-

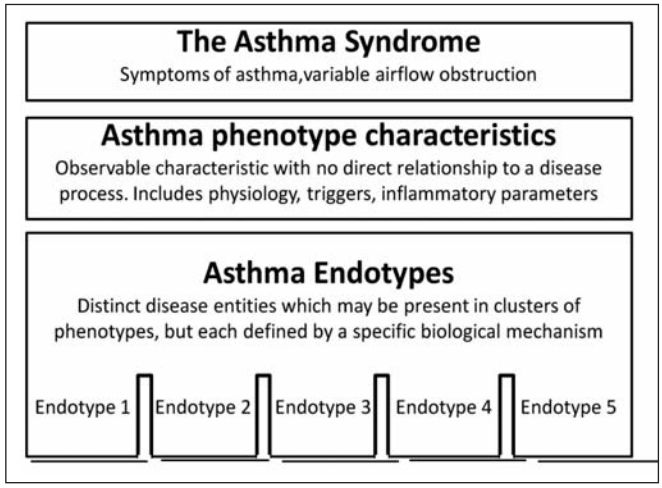
philia, the number of exacerbations and can improve the quality of life (43, 44); these data indicate the importance of a correct phenotyping of refractory eosinophilic asthma. An asthma subphenotype associated with a high type 2 helper T-cell (Th2) phenotype has been recently described (45). This high-Th2 phenotype has been defined as an IgE level greater than 100 ng per milliliter and more than 0.14×10^9 eosinophils per liter in the peripheral blood (45). In patients with asthma, the high-Th2 phenotype has been associated with an increase in circulating periostin, a matricellular protein induced by interleukin-13 and expressed by airway structural cells. Recently, Corren and colleagues reported the effects of an interleukin-13 inhibitor, lebrikizumab, in a cohort of patients with moderate asthma who were symptomatic despite taking inhaled glucocorticoids and, in most cases, an additional long-acting beta-agonist (46). Although there was an effect on airflow obstruction in all the patients who were treated with lebrikizumab, the effect was greater in patients who had circulating levels of periostin above the median and exhibited the high-Th2 phenotype than in those without this phenotype. These data provide a proof of concept that asthma therapy can be targeted to susceptible patients.

Noneosinophilic asthma

The use of induced sputum (47), along with bronchoscopy studies of patients with severe asthma (32), have clearly demonstrated that eosinophilic inflammation is not universally present, with noneosinophilic asthma further divided into neutrophilic and pauci-granulocytic phenotypes (32, 33). Neutrophilic asthma may be present either alone or in conjunction with eosinophilic inflammation (49). According to some studies, this inflammatory phenotype may account for as many as 50% of adult-onset asthma cases (49) and for the majority of non-allergic asthmatic children (50). In adults, neutrophilic asthma is seen most commonly in females (51), expecially in obese (52) and in women with menopausal asthma (53). Neutrophilic asthma phenotype is associated with more severe disease (54) and has been reported in autopsies of patients who died soon after the onset of a severe exacerbation (55, 56), but noneosinophilic inflammation has also been confirmed in patients with milder disease (51). Noneosinophilic patients are less likely to be atopic (51). The cause of neutrophilic inflammation is unknown but may involve multiple factors, such as environmental (sometimes occupational) exposure to bacterial endotoxin, bacterial biofilms, particulate air pollution, cigarette smoke, infections (viruses and intracellular pathogens, especially chlamydial respiratory infection) (31). In the pathogenesis innate immunity, oxidative stress and Th1/Th17 responses are involved (57). Corticosteroids are generally less effective in neutrophilic than in eosinophilic inflammation[7], and, paradoxically, may promote neutrophilic asthma by inhibiting neutrophil apoptosis (7, 58). Noneosinophilic asthma is associated with a reduced short-term and long-term response to corticosteroid therapy (36), and the absence of a steroid response is predicted by baseline exhaled nitric oxide (59). Anti-neutrophilic therapies have not been systematically studied yet; there is some evidence that long-acting β2-agonists, in contrast with corticosteroids, inhibit neutrophilic inflammation in the airways (60, 61). These results may explain why combination inhalers containing a long-acting β2-agonist and a corticosteroid can be more effective in treating asthma, as they target not only eosinophilic but also neutrophilic inflammation (62). Recent studies have shown that once-daily tiotropium provides useful additional bronchodilatation when added to a LABA in some patients with severe asthma (63, 64); moreover a noneosinophilic sputum profile is associated with a better response (65). Theophylline may be useful in treating neutrophilic asthma and reversing corticosteroid resistance in patients with severe disease and in smokers. The mechanism whereby theophylline reverses corticosteroid resistance is currently being explored, but it is known that this is not mediated via inhibition of phosphodiesterases (PDEs) (62). Roflumilast, a selective PDE4 inhibitor, is currently licensed for use in patients with severe COPD, and therefore there has been increased interest in its potential for the treatment of severe noneosinophilic asthma. Roflumilast increases lung function in patients with mild to moderate asthma, an effect that is comparable to a low dose of inhaled corticosteroids (66). It has long been recognized that macrolides have anti-inflammatory effects that might be independent of their antibiotic effects (67). In patients with severe neutrophilic asthma, a course of clarithromycin significantly reduced sputum neutrophil numbers and CXCL8 concentrations, with some improvement in symptoms (68). Recently, Montelukast, a cysteinyl leukotriene receptor antagonist, showed secondary anti-inflammatory properties, apparently unrelated to conventional antagonism of CysLT1Rs . These novel activities enable montelukast to target eosinophils, monocytes,

and, in particular, the corticosteroid-insensitive neutrophil (69). In a recent study, montelukast and formoterol showed interactive inhibitory effects on activated human neutrophils; these findings may explain the efficacy of montelukast and LABA when used in combination with inhaled corticosteroids in the treatment of severe asthma, possibly by controlling neutrophil-driven inflammation of the airways (70). Several uncontrolled or small studies suggested that anti-TNF therapies (TNF blocking antibodies infliximab or soluble receptor etanercept) might be useful in reducing symptoms, exacerbations, and airway hyperresponsiveness in patients with severe asthma (71, 72), but a recent large multicenter trial with the humanized antibody golimumab showed no beneficial effect on lung function, symptoms, or exacerbations, and there were increased reports of pneumonia and cancer (73).

Figure 2 - Asthma is made up of different endotypes. Adapted from Lotvall et al. (75)



Endotypes

Although phenotypes are usually clinically relevant, they do not necessarily relate to the underlying disease processes. Recently, a different classification of disease entities within the asthma syndrome was proposed, whereby asthma is divided into distinct disease entities with specific mechanisms, called "asthma endotypes." While phenotypes rely on observable characteristics, endotypes relate to the underlying functional or pathological mechanisms. As such, endotypes are distinct disease entities, not equivalent to phenotypes, but which may be present within clusters of phenotypes (74). Using these criteria, a PRACTALL (PRACTical ALLergy) consensus report produced by experts from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology, was able to identify several asthma endotypes (Fig. 2) (75).
The authors selected 7 parameters (clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response) to define an endotype and each endotype should fulfill at least 5 of the 7 parameters; asthma phenotypes can be present in more than 1 endotype, and endotypes can contain more than 1 phenotype.

Proposed endotypes
• Aspirin sensitive Asthma
• ABPM (Allergic bronchopulmonary mycosis)
• Allergic asthma (adults)
• API(asthma-predictive indices)-positive preschool wheezer
• Severe late-onset hypereosinophilic
• Asthma in cross-country skiers
Adapted from Lotvall et al. (75).

Even severe asthma can present in multiple different phenotypes, and initial studies have been identified at least four endotypes (75):

• Severe early-onset allergic asthma
• Adult-onset, persistently eosinophilic severe asthma
• ABPM (Allergic bronchopulmonary mycosis)
• Late-onset, obese, female, less eosinophilic
Adapted from Wenzel (76).

The last endotype includes a group of symptomatic older women, generally with adult-onset disease and a high BMI. This phenotype was observed in UK and USA clusters (77, 78). Obese patients show very symptomatic disease, despite preserved lung function. Allergy does not appear to be associated with this endotype and in the European cohort there was little evidence for inflammation (78). With regard to the response to therapy, there is a association between increased BMI and reduced therapeutic effect of ICS-containing regimens (79). Weight reduction in obese patients with asthma improves lung function, symptoms, morbidity, and health status (80). Patients who lost weight following bariatric surgery improved markedly asthma symptoms, lung function and quality of life (81).

Conclusion

In conclusion, it has become increasingly clear that asthma is a complex syndrome. To improve our understanding of asthma, it will be necessary to classify patients according to the underlying disease mechanism rather than clinical characteristics. The classification of patients with asthma by phenotype/endotype will facilitate future research to test novel therapeutic targets and endotype-specific treatments.

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