The multiple dimensions of airways disease: targeting treatment to clinical phenotypes

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Purpose of review

The recognition that asthma and chronic obstructive pulmonary disease (COPD) are not single diseases, but syndromes made up of multiple separate disorders that overlap, has led to attempts to develop a new taxonomy for the disorders of airflow obstruction. A better understanding of the distinct disorders of airways disease has the potential to inform on underlying mechanisms, risk factors, natural history, monitoring and treatment.

Recent findings

Recent attempts to describe the different phenotypes have largely been based on cluster analysis. Preliminary evidence suggests that there may be five distinct phenotypes of airways disease. To date, however, no simple allocation criteria have been validated that enable clinicians to allocate individual patients to specific phenotypic groups. The concept of differential treatment responses in different phenotypes of airways disease has been established with the demonstration that eosinophilic asthma preferentially responds to inhaled corticosteroid therapy or monoclonal antibody against interleukin-5, and severe refractory noneosinophilic asthma to macrolide antibiotics.

Summary

The priority is to further define the distinct phenotypes that make up the syndromes of asthma and COPD. This knowledge could lead to treatments specifically targeted for defined phenotypic groups, rather than for asthma and COPD in general, which represents the current management approach.

Keywords

airways disease, asthma, COPD, phenotypes

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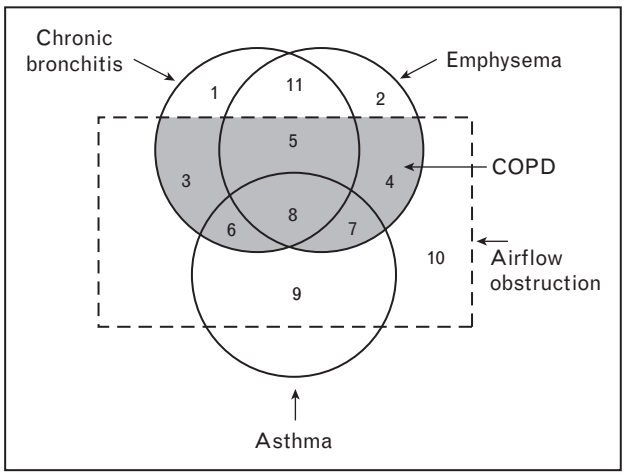
Introduction

An increasing understanding of the clinical heterogeneity of asthma and chronic obstructive pulmonary disease (COPD), and a consequent awareness of the inadequacy of current definitions, has led to attempts to develop a new taxonomy for airways disease [1–4]. Taxonomy remains the paradigm for biological models of classification and is based empirically on the principle that similarity measured across a number of different characteristics predicts relationships of biological significance with greater probability [5]. Defining the various phenotypes is not simply an academic exercise, but a research priority with great clinical relevance because of the potential to inform on their risk factors, underlying pathophysiological processes, natural history, monitoring and, most importantly, treatment.

Current international guidelines propose that the diagnosis of COPD requires the presence of incompletely reversible airflow obstruction to be confirmed by spirometry with a ratio of postbronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) less than 0.7 in the absence of a defined pathology such as bronchiectasis or tuberculosis to otherwise explain the airflow obstruction [6]. Asthma is also diagnosed using functional criteria, based on the presence of variable airways obstruction with the requirement for an increase in FEV1 of 12% or more following bronchodilator or peak flow variability of at least 15% [7].

Conceptually, since the time of the Ciba symposium in 1959, COPD has been thought of as an overlap between chronic bronchitis, emphysema and subtypes of asthma associated with chronic airflow limitation [8]. This was first expressed in a nonproportional Venn diagram by Snider [9]. Subsequently, the widely recognized representation of this diagram presented by the American Thoracic Society (ATS) cemented the presence of airflow obstruction into this definition of COPD (Fig. 1) [10]. However the Venn diagram method has limited clinical utility, as do other graphical formats incorporating proportional or alternative conceptual classification systems for both COPD and asthma [4,5,11–13]. For example,

Figure 1 Conceptual Venn diagram of chronic obstructive pulmonary disease proposed by American Thoracic Society



The subsets comprising chronic obstructive pulmonary disease (COPD) are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction, although in variant asthma special manoeuvres may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2 and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known aetiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis (subset 10), are not included in this definition. Reprinted with permission from [10].

reversible airflow obstruction is the defining characteristic of asthma, yet is present in a substantial proportion of COPD patients [14,15]. Conversely, irreversible airflow obstruction is a defining characteristic of COPD, but is commonly present in patients with long-standing severe asthma who have an accelerated loss in lung function [16,17]. Indeed, the classification of patients as having asthma or COPD may vary day-to-day when based on established diagnostic criteria, due to their overlap and inherent variability in bronchodilator responsiveness [14]. The situation is similar when symptom complexes are considered, with many patients with asthma having chronic sputum production, consistent with the definition of chronic bronchitis. Furthermore, in COPD, the severity of emphysema varies widely in patients with the same severity of airflow obstruction, and chronic bronchitis symptoms are equally distributed irrespective of emphysema severity [18].

Key points

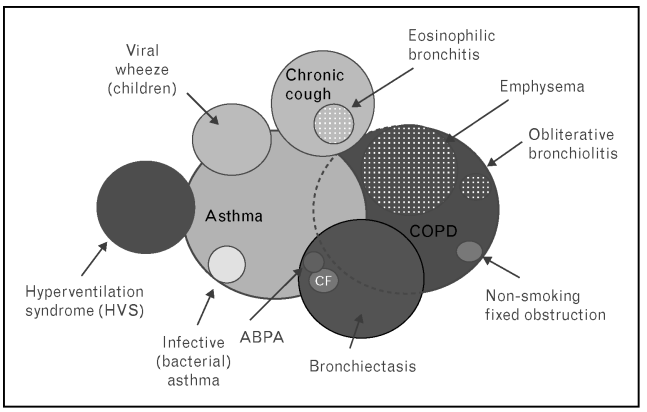
- Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous airway diseases that can be characterized across multiple dimensions.
- There has been increasing interest in cluster analysis and other methods that may identify clinically relevant phenotype groups in airways disease.
- The therapeutic value of this approach will be confirmed if therapies targeted to specific phenotypes are shown to lead to clinically important benefits.

Thus, the current classification of obstructive airways diseases does not adequately account for the various diseases which make up COPD and asthma (Fig. 2). Recently, different statistical techniques have been used to better understand and describe the multiple dimensions of airway disease with the ultimate goal being identification of distinct subgroups of patients with different prognosis or response to treatment.

Defining asthma phenotypes

A number of criteria have been used to define asthma phenotypes based on clinical or physiological characteristics (such as severity, tendency to exacerbation, resistance to treatment and age at onset), environmental triggers and pathobiology [4]. Since the 1990s the main focus has been on Th2-mediated eosinophilic inflammation as

Figure 2 Conceptual Venn diagram illustrating the overlapping relationship between syndromes characterized by disordered airway function



The asthma labels include some but not all children with viral-induced wheeze, patients with cough as their predominant symptom, patients with significant smoking history and degree of fixed airflow obstruction (COPD), who have features such as steroid responsiveness, eosinophilic airway inflammation and marked reversibility, more associated with an asthma phenotype, and patients with bronchiectasis. The degree of overlap represents approximately the degree to which a proportion of patients with any one syndrome has features of another. ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis. Reprinted with permission from [3].

central in the asthma paradigm [19]. In short, a helper T-cell population induced by interleukin (IL)-4 is able to produce a panel of cytokines (such as IL-4, IL-13, IL-5, IL-9) which induce traits associated with classic asthma [20]. However, whilst Th2 immunity is undoubtedly important in some types of asthma, it has been pointed out that the Th2-inflammation hypothesis does not explain why airway hyper-responsiveness and tissue remodelling are not clearly linked to inflammation; why existing T-cell immunosuppressives and new Th2-targeted treatments, which often worked well in Th2-disease models, have no or marginal effectiveness in the clinic; why many patients have recurrent exacerbations despite treatment; why substantial disease remains when anti-inflammatory therapy is optimised; why asthma shares some genetic risk factors with COPD; and why some patients have severe asthma [20]. More recently, a simple classification schema based on distinct inflammatory cell profiles has been identified, namely eosinophilic, neutrophilic, mixed and paucigranulocytic – depending on the presence or absence of eosinophils and/or neutrophils [4,21•]. This work suggests that a significant proportion of human asthma may be driven by different inflammatory processes.

Whether the molecular mechanisms underlying these clinical and cellular phenotypes of asthma differ is uncertain. However, using gene expression analyses of airways epithelia, Woodruff *et al.* [22••] classified patients with asthma based on high or low expression of IL-13-inducible genes. Two evenly sized and distinct subgroups, 'Th2-high' and 'Th2-low' asthma were identified, the latter indistinguishable from the control group. These subgroups differed significantly in expression of IL-5 and IL-13 in bronchial biopsies and in airway hyper-responsiveness, serum IgE, blood and airway eosinophilia, subepithelial fibrosis and airway mucin gene expression. The lung function improvements expected with inhaled corticosteroids were restricted to Th2-high asthma. This study suggests that asthma can be divided into at least two distinct molecular phenotypes defined by the degree of Th2 inflammation.

Defining phenotypes in chronic obstructive pulmonary disease

The degree of irreversible airflow limitation remains the defining characteristic of COPD and thus its most important phenotypic expression [23]. However, other phenotypic expressions to be considered in the characterization of patients with COPD include the degree, type and distribution of emphysema and its physiologic expressions as measured by diffusing capacity, the degree of hyperinflation, the presence of systemic involvement as measured by the BMI, the exercise capacity and the degree of functional dyspnoea [23]. These factors have all been shown to have prognostic value and determine response to therapies. For example, noninvasive ventilation in patients with hypercapnic respiratory failure, lung volume reduction surgery in patients with upper lobe disease and oxygen for hypoxemic patients have all been shown to reduce mortality. More recently identified phenotypic characteristics include markers of airway inflammation such as exhaled nitric oxide, sputum eosinophils and neutrophils [24,25].

Using cluster analysis to define phenotypic groups in airways disease

More recent attempts to describe the different phenotypes in both asthma and COPD have largely been based on a collection of methods known as cluster analysis [26]. Based on measured characteristics, individuals are grouped based on their differences (or similarities). The groupings are constructed such that the degree of association is strong between members of the same cluster and weak between members of different clusters. Although cluster analysis is dependent on the selection of individuals, nature and number of variables and methodology, it is more data-driven than other methods of defining phenotypes and as a result may be less susceptible to bias from historical or *a priori* assumptions about classifications.

Cluster analysis has been applied to random populations of patients with airways obstruction, and to different populations of asthma and/or COPD of differing severity. One such analysis identified five distinct phenotypic groups [27••]. Distinct clinical phenotypes of airways obstruction defined by cluster analysis are as follows:

(1) Severe and markedly variable airflow obstruction with features of atopic asthma, chronic bronchitis and emphysema in smokers.
(2) Features of emphysema alone in smokers.
(3) Atopic asthma with eosinophilic airways inflammation.
(4) Mild airflow obstruction without other dominant phenotypic features.
(5) Chronic bronchitis in nonsmokers.

These findings are similar to those from a previous cluster analysis of patients with diagnosed asthma or COPD [3]. Importantly they confirm the presence of an overlap phenotypic group made up of smokers with markedly reversible and variable airflow obstruction, with features of chronic bronchitis, emphysema and atopic asthma. This group is of particular interest, as it represents the group with the most severe disease, based on the degree of airways obstruction, quality of life and healthcare utilization. There is not a strong evidence base for the treatment of this overlap group, as the patients would have been excluded from the major randomized

controlled trials (RCTs) of asthma due to their smoking history [28], and from major randomized controlled trials of COPD due to their marked bronchodilator reversibility and atopy [29].

Cluster analysis in asthma

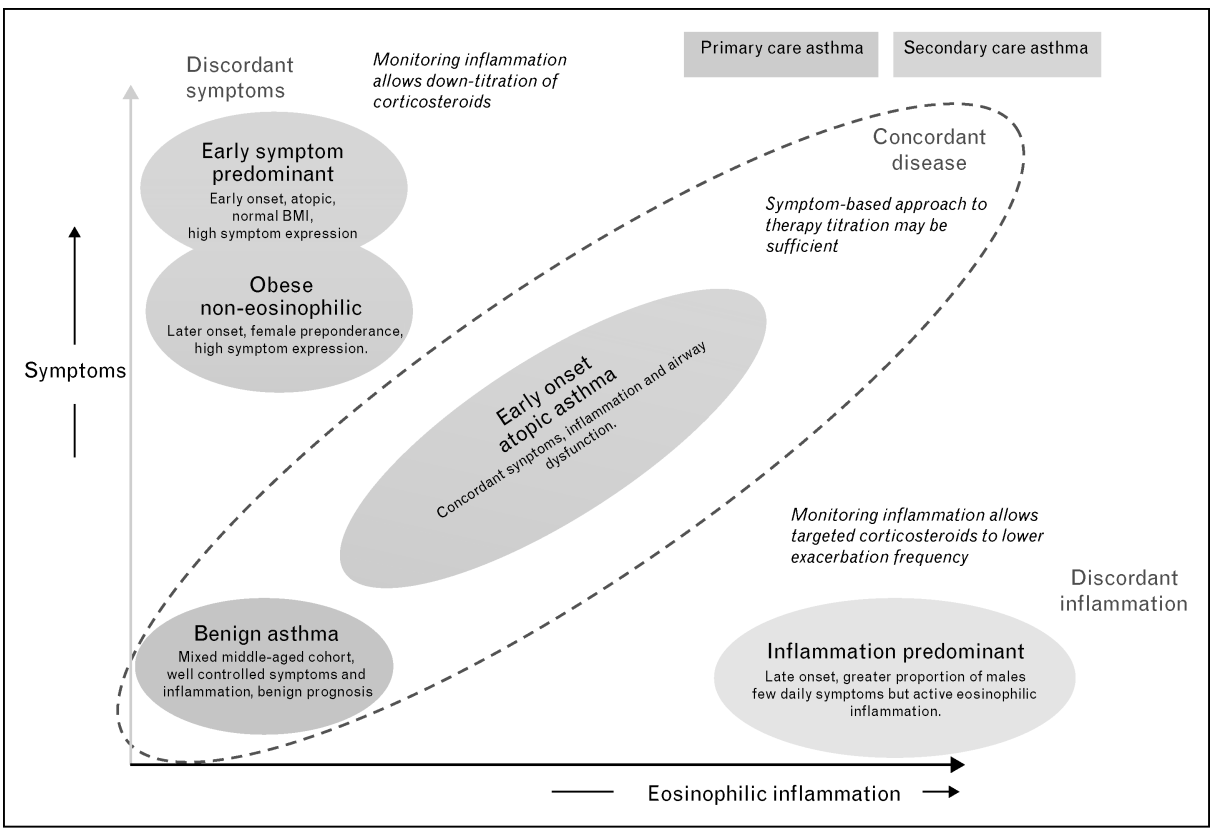
In asthma, a cluster analysis has been undertaken in two distinct populations, a group recruited from primary care with mild-to-moderate asthma, and one from secondary care with refractory asthma (Fig. 3) [5]. Two clusters characterized by early onset atopic and obese noneosinophilic asthma were common to both asthma populations. Two clusters characterized by marked discordance between symptom expression and eosinophilic airways inflammation (early onset symptom predominant and late-onset inflammation predominant) were specific to refractory asthma.

The other major cluster analysis in asthma studied a well characterized population with severe persistent disease [30••]. Three clusters were identified with early onset atopic asthma, with differences in severity, medication use and healthcare utilization. Another cluster comprised late-onset nonatopic obese women. The final cluster included late-onset older asthmatics with severe obstruction and marked morbidity. This study also addressed the important issue of how individuals with severe asthma could be allocated to the distinct clusters identified. Utilizing discriminant analysis they identified the strongest discriminatory variables based on pre and postbronchodilator lung function measures, age of onset and asthma duration, sex and frequency of beta agonist use and dose of corticosteroids. A tree-analysis was then performed using subsets of the variables to assess classification of patients. Using just pre and postbronchodilator FEV1% predicted and age of onset, 80% of patients in the sample were assigned to the appropriate cluster (Fig. 4). This observation suggests that a simple method for phenotyping of asthma subclasses can be based on these clinical variables, and confirmed the proof of concept of this approach.

Cluster analysis in chronic obstructive pulmonary disease

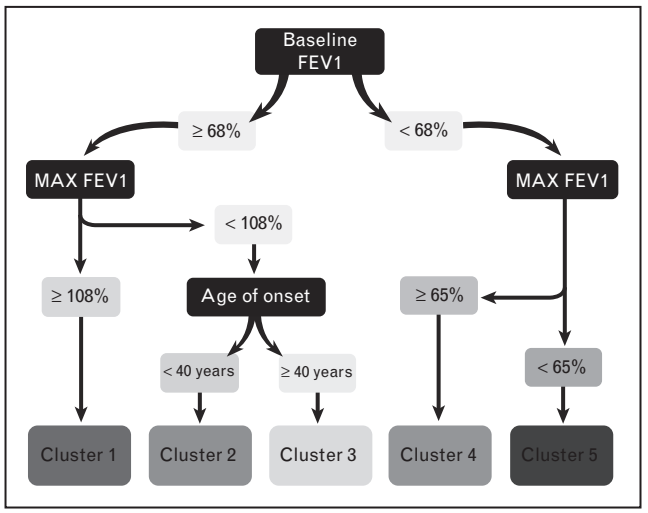
The technique of cluster analysis has also been applied to a population of patients with COPD in a respiratory clinic [31]. This identified that COPD patients with similar

Figure 3 A summary of clinical phenotypes of asthma identified using cluster analysis in primary and secondary-care asthma populations



The clusters are plotted according to their relative expression of symptoms and inflammation because these are the two clinically pertinent and modifiable dimensions of disease. The plot highlights greater discordance to be a feature of secondary asthma. Reprinted with permission from [5].

Figure 4 Allocation of patients to phenotypic groups identified by cluster analysis of severe asthma population



Using three variables (prebronchodilator FEV1, postbronchodilator FEV1 and age of onset of asthma), 80% of patients could be assigned to the correct cluster of asthma severity. Reprinted with permission from [30••].

degrees of airflow obstruction belong to different phenotypes in terms of age and comorbidities, different patterns of symptoms and outcomes such as frequency of exacerbations and predicted mortality. These findings indicate the real need for a multidimensional assessment of COPD. However, as with asthma, any COPD phenotypic groups that are identified will require an iterative validation process before their relevance to clinical outcomes is determined [32].

Other statistical methods to define phenotypic groups in asthma and chronic obstructive pulmonary disease

Other methods of trying to understand multivariate data that have been used to identify novel asthma and COPD phenotypes include principal component analysis [31], factor analysis [24,33] and discriminant analysis [30••]. Factor analysis allows reducing multiple disease characteristics to a few independent factors, with each factor grouping associated parameters. Using this technique in patients with chronic stable asthma, Rosi *et al.* [33] demonstrated that airway function, baseline airway hyper-responsiveness and eosinophilic inflammation in sputum are nonoverlapping dimensions. Also using factor analysis, Laperre *et al.* [24] identified that airflow limitation, features commonly associated with asthma (B2-response, total serum IgE, airway hyper-responsiveness), exhaled nitric oxide, and sputum inflammatory cell counts are separate, largely independent dimensions that characterize patients with COPD. Principal components analysis is the commonest form of factor analysis and reduces a large number of variables to a much smaller number of components, explaining the variability in the data set. Using this method, Roy *et al.* [34] explored the heterogeneity of COPD using biomarkers of airway and systemic inflammation and pulmonary function. Like Laperre *et al.* [24], they demonstrated dissociation between airway inflammation and lung function.

Individualized treatment targeted to specific phenotypes

Current treatment guidelines for COPD and asthma are based on randomized trials of highly selected subgroups of patients. Travers *et al.* [29] demonstrated that only about one in twenty people with COPD identified from a large general population survey would have met the inclusion criteria for the major RCTs informing consensus guidelines in COPD. Similarly most of the participants with current asthma on treatment in the community would not have been eligible for the major asthma RCTs either [28]. Not only does this make it difficult for clinicians to know to what extent the safety and effectiveness of various treatments apply to a given individual but also limits knowledge of COPD and asthma since studies restricted by these criteria cast no light on the complexity of the various clinical phenotypes.

The clinical utility of identifying the different phenotypes of asthma and COPD is demonstrated by subsequent RCTs which compare the differential response to various therapies depending on the disease phenotype. Patient selection is likely to be critical, as highly specific therapies will probably only have efficacy in patients for whom the target of interest is a dominant component of their disease.

With the concept of asthma as a Th2-mediated disease central to the asthma paradigm, a considerable amount of work on targeting treatment to phenotype relates to the application of treatments based on biomarkers that reflect this state such as sputum eosinophila and exhaled nitric oxide (FeNO). For example, in the second part of their cluster analysis in three independent asthma populations, Haldar *et al.* [5] compared differences in outcomes such as exacerbation frequency and change in inhaled corticosteroid (ICS) dose in a refractory asthma population. They showed that all the benefit for preventing exacerbations occurred in the inflammation-predominant group. In addition, sputum-guided therapy allowed successful down-titration of ICS therapy in early symptom-predominant asthma without compromising asthma control.

Their findings suggest that in most patients with mild to moderate asthma, in which there is concordance between inflammation and symptoms, a symptom-based approach may be appropriate. However, in refractory severe asthma and obese symptom predominant noneosinophilic

phenotype seen in primary care, there may be marked discordance which means this approach has major limitations. In the symptom-predominant phenotypes in which eosinophilic airways inflammation is not a major factor, persistent symptoms may lead to over-treatment of ICS with standard management regimes. Identifying that eosinophilic airways inflammation is not a feature of these patients by monitoring of FeNO may allow a reduction in ICS use without worsening of asthma control. In contrast, in the airways inflammation predominant phenotype, identifying uncontrolled eosinophilic airways inflammation by FeNO or other measures would allow titration of management with an increase in steroid treatment.

Other studies have also shown that asthma patients with eosinophil airways inflammation have a greater short-term response to treatment with ICS therapy than those with noneosinophilic asthma [22••,35]. In one study, the eosinophilic group had a five-fold reduction in bronchial hyper-responsiveness with ICS therapy which was associated with a reduction in sputum eosinophils and FeNO [35]. These findings have led to strategies whereby such monitoring forms the basis of long-term asthma management [36–38], although opinion is divided regarding its clinical utility [25,39].

The phenotype of eosinophilic asthma may also represent a group which may preferentially respond to monoclonal antibody against IL-5, illustrating the potential of targeted therapy in specific phenotypic groups [40,41]. Patients with refractory asthma, a sputum eosinophil percentage of more than 3% on at least one occasion in the previous 2 years despite high-dose corticosteroid showed significantly fewer severe exacerbations and improved quality of life.

The lack of clinical response to ICS in noneosinophilic asthma also indicates that this subgroup has a clinical need that is poorly met by current therapies. One novel approach which has been examined is whether patients with noneosinophilic asthma may respond to antibiotic therapy. This has been suggested in a 'proof of concept' study in which the macrolide antibiotic clarithromycin reduced neutrophilic inflammation and quality of life in patients with severe refractory noneosinophilic asthma [42]. Alternatively, it has recently been suggested that the neutrophilic phenotype is essentially the result of the effects of ICS therapy [21•].

A well established phenotypic characteristic of asthma is the relatively lesser efficacy of ICS or oral steroid therapy in tobacco smokers [43,44]. It has been proposed that this is due to smoking reducing the activity of histone deacetylase (HDAC), a nuclear enzyme involved in the switching off of activated inflammatory genes [45]. Although ICS therapy may lead to similar reductions in sputum eosinophils between smokers and nonsmokers with asthma, the FEV1 increases only in nonsmokers [46]. Contrasting findings were observed with leukotriene receptor antagonist therapy, in which efficacy was similar in smokers and nonsmokers. There is also evidence for the efficacy of low dose theophylline in smokers with asthma, possibly due to an increase in HDAC activity [47].

A lesser body of work has also been done targeting treatment to phenotypes of COPD. In contrast to asthma, FeNO is less useful in predicting the short-term ICS response in stable COPD, although it predicts treatment response in acute exacerbations of COPD. Dummer *et al.* [48] showed that whilst a raised FeNO is a weak predictor of short-term response to oral steroids in patients with stable, moderately severe COPD, a normal FeNO result has clinical utility in predicting the absence of a response. It was pointed out that in the context of treating COPD, in which at best only 20% of patients will demonstrate steroid responsiveness, this information would help the clinician avoid prescribing unnecessary ICS treatment [48]. Similarly Antus *et al.* [49], using FeNO levels at hospital admission in patients admitted for an acute exacerbation of COPD, showed that those with higher FeNO levels at the onset of the exacerbation were discharged home sooner. In a similar vein, it has been shown that sputum eosinophilia in patients with COPD is associated with a short-term response to steroid, demonstrated by increased airway calibre and improved health-related quality of life [50].

Conclusion

There is now sufficient evidence to suggest that both asthma and COPD are complex heterogeneous disorders with distinct risk factors, pathophysiological processes, natural history and treatment responses. Through both a better understanding of phenotypic groups and their characterization, it may be possible to develop simple allocation criteria to enable clinicians to allocate individual patients to specific groups. If it can be determined that phenotypes vary in their response to different pharmacological treatments, then the ultimate goal of treatment specifically targeted to defined phenotypic groups can be achieved. However, a greater understanding of the interrelationship between clinical disease and its cellular and molecular basis is required to achieve this goal.

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