Subclinical phenotypes of asthma
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Purpose of review
Asthma is a heterogeneous disease. Identification of specific subphenotypes of asthma may further our understanding of pathophysiology and treatment response, leading to the better targeting of both existing and novel antiasthma therapies. An accurate and comprehensive clinicopathological classification system therefore remains an important priority for asthma research. The present review discusses the important recent literature in this field.

Recent findings
Cluster analysis in patients with severe asthma has suggested the presence of four distinct clinical phenotypes, two with eosinophilic airway inflammation, and two without. Patients with eosinophilic inflammation benefit most from a management strategy targeting the sputum eosinophil count. Molecular phenotyping utilizing gene arrays in steroid-naıve asthmatic individuals reveals two distinct subgroups (Th2-high and Th2-low) based on the expression of Th2 cytokine genes (IL-5, IL-13) and Th2-responsive genes. The Th2-high group exhibit clinical features typical of patients with eosinophilic disease. Targeting anti-IL-5 therapy to patients with evidence of eosinophilic airway inflammation and recurrent asthma exacerbations markedly reduces the asthma exacerbation rate, but day-to-day asthma symptoms remain unchanged.

Summary
The detailed phenotyping of asthma will allow the successful targeting of existing and novel therapies to those patients most likely to gain benefit.

Keywords
anti-interleukin-5, asthma, cluster analysis, gene arrays, phenotype

Introduction
Asthma has long been recognized as a heterogeneous disease. Identification of specific subphenotypes may further our understanding of pathophysiology, treatment response, prognosis, and the underlying genetic basis for the disease. An accurate and comprehensive system of classification therefore remains an important priority for asthma research despite the effort of many clinicians over several generations.

A review of the phenotypic characterization of asthma was published in this journal in 2007 [1]. In brief, we covered the eosinophilic versus neutrophilic pathological phenotypes, discussed refractory asthma as a distinct inflammatory phenotype, with particular focus on the role of tumour necrosis factor \(\alpha\) (TNF\(\alpha\)) in severe disease, and discussed phenotype-specific asthma management. The purpose of the present review is to discuss recent data of relevance to this field and the previous text will not be repeated.

Multidimensional phenotyping
There are numerous classifications of asthma based on proposed cause (allergic, nonallergic, occupational), pathology (eosinophilic, noneosinophilic), severity, and physiological parameters (type I brittle, type II brittle) [1]. In an attempt to provide a more integrated classification of asthma taking into account multidimensional parameters, we undertook k-means cluster analysis in three populations of asthmatic patients [\textsuperscript{2\#}]. The first group of patients were identified in primary care \(n=184\), and had predominantly mild to moderate asthma. The second group \(n=187\) were recruited from the Glenfield Hospital Difficult Asthma Clinic with predominantly refractory asthma, whereas the third group \(n=68\) had been studied previously with respect to targeting the sputum eosinophil count to reduce asthma exacerbations [3].

To determine the most appropriate variables for cluster modelling, we first performed principal components
analysis of 16 common clinical measurements and identified factors representative of symptoms, atopy/allergy, eosinophilic inflammation, psychological status, and variable airflow obstruction. So that the cluster analysis was not weighted, only one parameter that was representative of each factor was included in the model. These were atopic status (allergy domain), peak expiratory flow variability measured as amplitude percentage mean of the lowest and highest readings over 2 weeks (variable airflow obstruction domain), induced sputum eosinophil count (airway inflammation domain), and a modified Juniper Asthma Control Score to represent symptoms alone (symptoms domain). Psychological status was considered a consequence of the disease and therefore not included as an input parameter. However, performing the cluster analysis with the inclusion of the anxiety score (the parameter with the higher loading coefficient in the principal components analysis) did not alter the structure of the clusters. Sex, age, and BMI did not load significantly on the factor model but were considered significant determinants of the asthma phenotype and were also included. Methacholine PC$_{20}$, measured using the tidal breathing method was included for the primary care population only, as it had only been measured in 10% of the refractory patients in cases of diagnostic doubt.

The results of the study are summarized in Fig. 1. In the primary care population there were three distinct clusters. The first cluster described a subgroup with early onset atopic asthma, with evidence of airway dysfunction, symptoms, and eosinophilic airway inflammation. Clinically, this cohort was associated with a significantly greater number of previous hospital attendances and asthma exacerbations requiring oral corticosteroids when compared with the other primary care subgroups. Cluster 2 described an obese subgroup with a female preponderance, evidence of asthma symptoms, and an absence of eosinophilic airway inflammation. The third cluster had very little evidence of active asthma, a low rate of asthma exacerbations, and it is likely that a proportion of these patients did not have asthma at all. This cluster was labelled as 'benign asthma'.

In the difficult asthma population, four distinct clusters were identified (Fig. 1).

Two of these were similar to those in the primary care population, that is, the early onset atopic asthma cluster and the obese, noneosinophilic cluster. The main difference between patients in these clusters in primary versus secondary care was that patients in secondary care had more severe objective markers of disease. In addition, patients in the early onset atopic group in secondary care had a higher rate of failed clinic appointments compared with the other refractory clusters, suggesting that perhaps with improved concordance, they could be better controlled.

**Figure 1** Summary of asthma phenotypes observed using cluster analysis in a primary care population and a hospital-based severe asthma clinic

![Diagram showing the classification of asthma phenotypes](image-url)

Eos, eosinophilic. Reproduced with permission from [2**].
Two further clusters in the severe asthma cohort were specific for severe disease. One of these was a group of patients with refractory eosinophilic disease, with recurrent exacerbations, but relatively few symptoms. These patients were described as inflammation predominant although eosinophilic inflammation predominant would be more accurate to remove any confusion with neutrophilic inflammation. The other severe-specific cluster was a group of patients with early onset atopic disease with virtually no eosinophilic inflammation but very high symptom expression.

The importance of identifying these clusters in severe disease with respect to treatment approaches was highlighted by further analysis of a group of refractory asthmatic patients. These patients had been entered previously into a prospective randomized clinical trial comparing standard care versus treatment guided by the sputum eosinophil count on the rate of asthma exacerbations [3]. This study demonstrated that when corticosteroid treatment is guided by the sputum eosinophil count, there is a 60% reduction in severe asthma exacerbations and a significant reduction in hospital admissions. When cluster analysis was applied to the patients in the present study, three distinct clusters matching those described above were identified (eosinophilic inflammation predominant, obese female, and early onset symptom predominant). Cluster-specific analysis revealed that all of the benefit for preventing exacerbations occurred in the eosinophilic inflammation-predominant cohort [3.53 (SD, 1.18) versus 0.38 (SD, 0.13) exacerbation/patient/year, \( P = 0.002 \)]. In addition, sputum-guided therapy allowed successful down titration of corticosteroid therapy in early onset symptom-predominant asthma (mean difference, 1829 \( \mu \)g beclomethasone equivalent/day (95% confidence interval, 307–349 \( \mu \)g; \( P = 0.02 \), without compromising asthma control.

The identification of these clusters is the first major advance in the complex clinicopathological phenotyping of asthma. It will contribute to the tailored treatment of patients with appropriate therapies, and help to avoid the overuse of corticosteroids in patients who do not have corticosteroid responsive disease. The authors believe that this study is a landmark study in the phenotyping of clinical asthma. The challenge now is to identify the factors which lead to the development and sustained expression of these different phenotypes, and to develop novel phenotype-specific therapies.

**Molecular phenotyping**

Gene arrays are a powerful tool for the unbiased examination of gene expression programmes in tissues, and are now being used to examine the gene expression profiles in asthmatic airways. In an initial study, Woodruff *et al.* [4] identified periostin (POSTN), chloride channel regulator 1 (CLCA1), and serpin peptidase inhibitor, clade B, member 2 (SERPINB2) as epithelial genes that were specifically induced in asthma (as compared with both healthy controls and smokers with mild-moderate COPD), and directly regulated by IL-13 in *vitro*. In a further study, they therefore used this gene expression signature as a surrogate marker of the IL-13 inflammatory pathway [5**]. They hypothesized that this could be used to identify subsets of patients with asthma who differ in terms of the molecular mechanisms underlying their airway pathology, and that these subsets would constitute distinct inflammatory, pathological, and clinical phenotypes.

For the analysis, the researchers used microarray and PCR analyses of airway epithelial brushings from 42 mild to moderate corticosteroid-naive asthmatics and 28 healthy controls. Using unsupervised hierarchical clustering, they identified that approximately 50% (\( n = 22 \)) asthmatic individuals had consistently high expression of Th2 cytokine-induced genes, whereas the remaining 20 asthmatic individuals were not distinguishable from normal controls [5**]. These observations were validated on bronchial biopsies using quantitative PCR to detect Th2 cytokine mRNA. IL-5 and IL-13 mRNA expression was markedly increased in the Th2-high cluster compared with the Th2-low cluster or healthy controls. The Th2-low group of asthmatics did not differ from normal controls in their expression of IL-5 or IL-13 mRNA. IL-4 expression was low across all groups which may relate to the instability of IL-4 gene expression as IL-4 mRNA and protein expression is consistently increased in *in situ* in steroid-naive asthma [6,7]. IL-5 and IL-13 expression were highly correlated. In keeping with the reciprocal balance hypothesis regarding Th1 versus Th2 expression, Th1 cytokine expression was significantly lower in the Th2-high group. These findings were highly reproducible when re-analyzed in bronchial biopsy material obtained from a second bronchoscopy 1 week later. These findings support earlier work looking at IL-13 protein expression bronchial biopsies and induced sputum, with IL-13 detectable in about 50% steroid-naive patients [8].

With respect to clinical features, Th2-high and Th2-low asthma were indistinguishable in terms of demographic characteristics, lung function and bronchodilator reversibility. Both groups were atopic, but the Th2 group had more extensive sensitization. Interestingly, the Th2-high group had significantly worse bronchial hyperresponsiveness, higher serum IgE, greater eosinophilia [blood and bronchoalveolar lavage (BAL)]. The Th2-high group also had evidence of subepithelial fibrosis, a feature of eosinophilic asthma [9], whereas this was not present in Th2-low asthma. Epithelial mucin stores were also significantly increased in Th2-high asthma.
A very important finding was that only the Th2-high group responded clinically to a course of inhaled corticosteroids, with significant improvements in forced expiratory volume in one second (FEV₁). These findings are therefore entirely consistent with earlier study showing that patients with non eosinophilic asthma defined by sputum eosinophil count do not respond to inhaled steroids [9,10], and suggests that the Th2-low group identified, equates to the non eosinophilic phenotype, and the early onset symptom predominant non eosinophilic cluster in the study from Haldar et al. [2**]. This Th2-low, non eosinophilic group therefore defines a group of asthmatics with an unmet clinical need. It also suggests that patients with Th2-low asthma are unlikely to respond to Th2-specific therapy (vide infra).

Another study sought to discriminate asthma phenotypes on the basis of cytokine profiles in BAL in samples from patients with mild-moderate and severe asthma [11*]. Out of 25 cytokines measured in the BAL samples of 84 patients (41 severe, 43 mild-moderate) using bead-based multiplex immunoassays, 18 were detectable and included in the analysis. Initial unsupervised agglomerative hierarchical clustering delineated four subgroups of asthma that were independent of treatment. One group was said to be enriched for patients with severe asthma, although these only accounted for 60% of this group compared with approximately 50% of the total cohort. This cluster had high concentrations of BAL IL-2 and reduced FEV₁, forced vital capacity (FVC), and bronchodilator response compared with the other clusters. Classification methods for predicting methacholine sensitivity were also developed, and identified three distinct hyperresponder classes that varied in BAL eosinophil count and PC₂₀ methacholine. This study demonstrates that BAL cytokine profiles have potential to identify subgroups of asthma patients, but at this stage raises more questions that it answers.

**Phenotype-specific treatment: Anti-interleukin-5 therapy**

Because it is clear that not all asthma is the same, it is essential that new treatments for asthma are tested in those patients most likely to respond. In the past this has occurred fortuitously for β2-agonists, as nearly all clinical trials of asthma have required β-agonist reversibility as an entry criteria, and thus β-agonist trials are usually favourable. In practice however, FEV₁ reversibility of more than 12%, a common entry requirement, is only present in 30% of our difficult asthma patients, and so it is still unclear how much benefit long-acting β-agonists, for example, give to patients with poor bronchodilator responses.

For newer immunomodulators, it is unlikely that a therapy such as anti-IL-5 which targets eosinophilic inflammation, will be effective in non eosinophilic disease. The first published trials of anti-IL-5 treatment were disappointing [12–15], but took ‘all-comers’ with asthma, which will have included patients with both eosinophilic and non eosinophilic disease. Anti-IL-5 antibodies were very effective at reducing sputum and blood eosinophil counts, and reduced tissue eosinophils by approximately 60% [16], but asthma symptoms continued unabated, and bronchial hyperresponsiveness did not improve. Furthermore, there was no attenuation of the airway response to experimental allergen challenge, suggesting that eosinophils are also not important for this [13]. It has been argued that a 60% reduction in eosinophils within the tissue may not be adequate to reduce their pathological effects, but this seems unlikely because the reduction in eosinophils correlates strongly with a reduction in the deposition of tenascin, lumican, and procollagen III in the lamina reticularis [16].

These results with anti-IL-5 suggested that eosinophils do not play an important role in day-to-day asthma symptoms, variable airflow obstruction or hyper responsiveness. However, it is known that eosinophils represent an excellent biomarker for predicting whether patients will respond to corticosteroids [9,10], predicting which patients are at risk of exacerbations, and for guiding steroid therapy with a view to preventing these events [3]. This suggested that eosinophils might play a role in the pathophysiology of acute exacerbations but the early anti-IL-5 studies were not powered or designed to test this. There was a nonsignificant trend towards reduced asthma exacerbations in one anti-IL-5 trial [15].

In view of these data, we undertook a randomized, placebo-controlled, double-blind parallel group study of anti-IL-5 treatment (mepolizumab) in patients with severe asthma with evidence of eosinophilic inflammation and at least two severe exacerbations in the previous 12 months [17**]. The primary outcome was the number of severe exacerbations over the 12-month treatment phase.

Patients were eligible if they met the American Thoracic Society (ATS) definition of refractory asthma, had a sputum eosinophil count of more than 3% on at least one occasion in the previous 2 years in spite of high dose inhaled or oral corticosteroid therapy, and at least 2 severe asthma exacerbations in the preceding 12 months. Out of 449 patients in our refractory asthma clinic database, 149 (33%) were potentially eligible. Out of 110 patients approached, 63 were assessed for eligibility, and 61 underwent randomization.

With respect to the primary outcome, there was a marked reduction in the number of exacerbations in the patients receiving anti-IL-5 (2.0 per patient) compared with those
receiving placebo (3.4 per patient, \(P=0.02\); Fig. 2). Furthermore, we saw a significant improvement in quality of life score, suggesting that exacerbations have a significant impact of quality of life. Interestingly, there were no differences in lung function, airway hyperresponsiveness or symptoms between the active treatment group and controls. Also of great interest treatment with oral prednisolone at the end of the study led to improvements in lung function and symptoms in both the placebo and anti-IL-5 groups. This suggests that symptoms and lung function can be dissociated from eosinophilic inflammation, and are improved by corticosteroids through another mechanism. The present study therefore indicates that in patients with eosinophilic asthma, eosinophils contribute to the pathophysiology of exacerbations, but not day-to-day asthma.

A second smaller study of mepolizumab therapy in patients with persisting sputum eosinophilia in spite of oral steroid therapy was also published at the same time [18**]. Again, this study demonstrated a marked reduction in exacerbations in the anti-IL-5 group, at the same time as extensive steroid tapering. These studies were the subject of rather negative editorial in the same issue of the *N Engl J Med* [19]. The editorialist suggested that the patients studied represented a minority of asthma patients, and therefore that anti-IL-5 will be of limited use. We disagree strongly. Thirty-three percent of our difficult asthma clinic population were eligible, and the results were remarkable.

As anti-IL-5 targets exacerbations but not symptoms or lung function, it will be interesting to see if dual therapy with anti-IL-5 and IL-13 targets a broader aspect of clinical features in patients with Th2-driven eosinophilic asthma.

**Macrolide therapy**

As shown in Fig. 1, a proportion of patients with severe asthma have noneosinophilic disease, and it is known that a proportion of these have evidence of neutrophilic inflammation [20]. Using standard clinical measurements such as spirometry and airway challenges, it is not possible to separate eosinophilic from noneosinophilic asthma. Patients with noneosinophilic disease do not respond clinically to inhaled corticosteroids, and do not appear to respond well to oral corticosteroids [2**]*9*.

Macrolide antibiotics are of interest as they are known to have antineutrophilic properties [21]. Simpson *et al.* [22**] therefore performed a randomized double-blind placebo controlled trial of clarithromycin therapy for 8 weeks in 46 patients with severe asthma. In the treated group there were significant reductions in the number of sputum neutrophils and IL-8 concentrations, and a significant improvement in quality of life. When the data were analysed in subgroups with eosinophilic versus noneosinophilic disease, the benefit was confined to those with noneosinophilic disease. This supports the view that an antineutrophil approach may be beneficial in noneosinophilic asthma, and the results of a larger randomized controlled trial of macrolide therapy in severe noneosinophilic asthma are awaited.

**Conclusion**

These studies carry a very important message for the investigation of new therapies. It is clearly essential to choose an outcome that is likely to be responsive to the intervention, and to choose an intervention for an appropriate patient group. For example, in severe asthma, IL-13 is only present in the airways in about 50% of individuals [23*]. Treating patients with anti-IL-13 when it is already suppressed might be predicted to fail. There is an obsession with using bronchodilator reversibility of more than 12% as an entry criterion in clinical trials of asthma. In our mepolizumab study, mean bronchodilator reversibility was only 9%. Importantly, post hoc analysis of the mepolizumab group showed that the patients who received the greatest benefit from treatment, were those with a FEV1 bronchodilator response of less than 50 ml [24*]. So, although reversibility is a potentially useful diagnostic marker of asthma, using it as an essential entry criterion leads to recruitment of a highly specific subset of asthmatics, which will doom some treatments to failure. So for future trials of mepolizumab, we would urge that bronchodilator reversibility is not an essential entry requirement.
In summary, the clinical and molecular phenotyping approaches discussed in the present article are a significant advance in our understanding of the pathophysiology of asthma, revealing several distinct subclinical phenotypes, driven by different pathophysiological mechanisms. Clustering methodology to describe phenotypes is likely to become increasingly popular both clinically and at a molecular level, and we envisage that the two types of research will converge so that phenotypes defined rigorously by both clinical and molecular parameters will be achieved. This should help identify reliable biomarkers as well. The challenge now is to target these subphenotypes with appropriate existing and novel therapies. It is no longer helpful to think of asthma as a single disease entity for which one treatment will treat all patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 92).

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