

volume appears to be more of a gadget than a great progressive tool.

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Stability of inflammatory phenotypes in asthma

Ruth H Green, Ian Pavord

While asthma has long been recognised as a heterogeneous disease, recent interest has concentrated on the identification of phenotypes based on the pattern of inflammation in the airways. The application of induced sputum as a non-invasive ‘inflammometer’ has facilitated this process, resulting in the recognition of apparently distinct ‘eosinophilic’ and ‘non-eosinophilic’ phenotypes. The characterisation of patients in this way appears attractive since the response to treatment, particularly with inhaled corticosteroids, has been shown to differ according to the pattern and extent of inflammation. This has contributed to the concept of a ‘holy grail’ of individualised therapy based on phenotypic expression and a flurry of studies aiming to further

explain and refine the phenotypic diversity seen in both adults and children with asthma. A number of questions remain, however, and one important one raised by Fleming *et al*¹ is whether there are differences in the nature and significance of airway inflammation between adults and children with asthma.

Adult studies using induced sputum have consistently identified distinct eosinophilic and non-eosinophilic asthma subgroups. While the use of inhaled corticosteroids, which effectively suppress sputum eosinophilia, is a significant confounder, normal sputum eosinophil counts have been reported in up to 25% of adult patients with untreated symptomatic asthma² and for over 50% of adult patients treated with high doses of inhaled corticosteroids.³ Simpson and colleagues have suggested that airway inflammation in adult asthma could be further categorised into four inflammatory subtypes, namely, neutrophilic asthma (neutrophils >61%), eosinophilic asthma (eosinophils

>3%), mixed granulocytic asthma (neutrophils and eosinophils both increased) and paucigranulocytic asthma where neutrophils and eosinophils are both within the normal range.⁴ In populations of patients with stable adult asthma, the majority treated with inhaled corticosteroids, paucigranulocytic asthma appeared to be the most common inflammatory phenotype followed by neutrophilic inflammation.^{5,6} Non-eosinophilic asthma has also been reported in children with asthma.^{7,8} Paucigranulocytic asthma was the predominant finding in children with stable asthma, but in contrast with adults eosinophilic inflammation was more likely and neutrophilic inflammation uncommon.⁸ In adults studied during the stable phase, clinical features are similar across the inflammatory phenotypes although sputum eosinophilia appears to predict a greater likelihood of asthma exacerbation⁹ and non-eosinophilic patients may be more likely to be female subjects and non-atopic than the remaining group.² Findings in children differ in that the presence of eosinophilic inflammation appears to predict more severe persistent asthma with impaired lung function and increased AHR.^{8,10} Differences in inflammatory phenotypes have also been reported between adults and children presenting with an acute severe

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exacerbation of asthma with adults being much more likely to have neutrophilic or paucigranulocytic sputum whereas in children the common finding is of eosinophilic or mixed granulocytic inflammation.⁵

Adults and children with asthma may also differ in the way their inflammatory profile predicts treatment response, particularly response to corticosteroids. In adults, there is a body of evidence to show that non-eosinophilic asthma is associated with an attenuated response to corticosteroids both in the short and long term.^{11–13} Whether the same is true in paediatric asthma is not clear and there is some evidence to suggest the contrary. Children with difficult asthma given systemic corticosteroids in the form of either oral prednisolone or intramuscular triamcinolone demonstrated similar improvements in FEV₁ irrespective of whether they had eosinophilic or non-eosinophilic sputum before treatment.¹⁴ Furthermore, in adults, the presence of sputum eosinophilia almost invariably predicts a response to intramuscular triamcinolone (where corticosteroid adherence can be assured)¹⁵ but much higher rates of corticosteroid resistance have been reported in children.¹⁶

One problem with most studies that aim to characterise inflammatory phenotypes in asthma is that they confine their analyses to cross-sectional data measured at a single interval thus assuming phenotypic stability, a potentially significant limitation given that asthma, by definition, is a variable disease. The study by Fleming *et al* challenges this assumption by examining the hypotheses that inflammation would be found more frequently in children with severe compared with mild or moderate asthma and that sputum inflammatory phenotypes would be stable in children with asthma. Their findings are notable in that raised levels of inflammatory cells were common across the range of asthma severity but that significant phenotypic variability was seen with 63% of children demonstrating a change in inflammatory phenotype on repeated assessment. This variability does not appear to be due to changes in inhaled corticosteroid treatment, since changes in phenotype were not associated with changes in doses of inhaled corticosteroids although variable adherence in treatment cannot be fully excluded. Fleming *et al* discusses other possible mechanisms for this phenotypic instability including variations in allergen or viral exposure over time.

So, do these findings provide evidence for yet more differences between adult and paediatric asthma or do they go further and challenge our understanding of the concept of an inflammatory phenotype in asthma altogether? Does the suggestion of phenotypic instability draw into question the utility of inflammation in individualised asthma management? The available evidence suggests that adult asthma is associated with greater phenotypic stability than that reported by Fleming and colleagues in children. Early studies demonstrated that induced sputum differential cell counts are highly repeatable in the short term in adults with stable asthma with 95% of repeated sputum eosinophil measures lying within a twofold range of the original measurement when samples were taken 6 days apart.¹⁷ Simpson *et al* showed that the absence of a sputum eosinophilia was a consistent finding 4 weeks and 5 months after it was first demonstrated¹⁸ and we identified a subgroup of patients with predominantly non-eosinophilic sputum on repeated observations made over a period of 12 months.⁹ Jayaram *et al* showed that the pattern of sputum inflammation was similar at baseline and during exacerbations in adults with asthma studied longitudinally for 2 years, indicating that patients with non-eosinophilic asthma were far less likely to have eosinophilic exacerbations.¹⁹ Finally, in a prospective double-blind placebo controlled trial of inhaled corticosteroids in non-eosinophilic asthma patients had a bronchoscopy at baseline and then underwent repeated induced sputum six times over 6 months. None of the 11 patients studied demonstrated an airway eosinophilia at any point and at bronchoscopy all had normal basement membrane thickness.¹⁵ This supports the suggestion that the non-eosinophilic phenotype is stable in adults since increased basement membrane thickness has been shown to be a long term marker of eosinophilic airway inflammation.²⁰ The fact that inflammation using induced sputum has been shown to be a successful strategy to prevent asthma exacerbations in adults⁹ but not in children²¹ may also support the theory that the stability or significance of inflammation in the two groups differ, although there are other potential explanations including a failure to optimally suppress eosinophilic inflammation in the paediatric study.²¹ Nevertheless it is possible that, given the

apparent variability in inflammation over time in children, a management strategy using inflammation to guide asthma treatment which included more frequent measurements of airway inflammation would yield improved results in a paediatric population.

To conclude, phenotypic analysis using induced sputum does still appear to have value, not least as an inflammation to guide corticosteroid treatment in adults with refractory disease but question marks remain, particularly in children. Clearly asthma is a complex disease, and attempts to classify it on the basis of a single dimension such as inflammation represent a gross oversimplification. Even those studies which have gone further analysing multiple aspects of the disease using mathematical modelling techniques^{22–23} have not as yet included the dimension of time. Doing so adds yet another layer of complexity but a failure to include longitudinal changes in inflammation and other variables is likely to lead to inaccurate results. As proposed recently by Anderson,²⁴ perhaps we should now target our energies on the search of 'endotypes'—stable subgroups defined by unique and specific genetic or molecular characteristics rather than 'phenotypes' which, defined by biomarkers of disease activity, lead to uncertainty with time and changes in therapy.

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Bronchodilator responsiveness: interpret with caution

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Bronchodilator responsiveness (BDR) is widely considered to be a key diagnostic criterion for asthma, and is used to differentiate asthma from chronic obstructive pulmonary disease (COPD). Currently, the threshold of a 12% increase in FEV₁ from baseline following inhaled salbutamol, with at least a 200 ml increase in absolute terms, is recommended as a response indicative of asthma,¹ although recent British guidelines recognise the poor discriminatory function of this criterion.² Thus, despite this criterion being commonly used in clinical practice, there is uncertainty regarding its clinical utility, in particular its ability to differentiate asthma from COPD, or indeed, normal subjects.

One approach to enable a better understanding of the clinical utility of BDR is to determine the worldwide distribution of

BDR in health and disease, which has been undertaken by Tan and colleagues, and reported in *Thorax*.³ The authors report BDR in terms of change in FEV₁ and FVC following 200 µg of salbutamol delivered by metered dose inhaler via a spacer, in around 10 000 adults aged 40 years and older from 14 countries in North America, Europe, Asia and Africa who participated in the Burden of Obstructive Lung Disease study. The Burden of Obstructive Lung Disease methodology is robust and has many strengths, not the least of which is its multi-national nature and the central review of all spirometry, which increases confidence in the reliability of the lung function values obtained. The results of this study are, therefore, likely to be unbiased, and precise estimates of the populations described. The authors report that the most reliable metric of BDR was the change in FEV₁ relative to predicted FEV₁ (Δ FEV_{1p}). In healthy non-smokers, the threshold or upper limit of normality for Δ FEV_{1p} was 10% without heterogeneity across populations. The authors also report the more commonly used measure of change in FEV₁ from baseline, and give a threshold of 12%.

The values reported are consistent with the current ATS/ERS Task Force cut-offs for defining a clinically significant bronchodilator response.⁴ The authors propose that this strengthens the applicability of this measure for global interpretation of bronchodilator testing on the basis that values above this cut-off are beyond 95% of the distribution of healthy individuals and, as such, can be considered 'abnormal,' thus reflecting the presence of disease.

Although it is also proposed that such a cut-off discriminates healthy subjects from obstructed individuals, this unfortunately is not the case. Further analysis of their data indicates that BDR discriminates poorly between healthy subjects and individuals with airflow obstruction regardless of comorbid asthma (FEV₁/FVC <0.7, FEV₁ % predicted <80%). The authors found that BDR was consistent with a Gaussian (normal) distribution. The mean (SD) values for BDR expressed as Δ FEV_{1p} in healthy individuals was 2.6% (4.8) and 4.2% (5.7) in obstructed individuals. The Gaussian distribution gives the proportion of those above the cut-off of 10% as 6.1% (healthy), and 15.4% (obstructed). For healthy versus obstructed, the sensitivity was 15.4%, specificity 93.9%, likelihood ratio test positive 2.5, and test negative 0.9. These values, particularly for likelihood ratio negative, are not consistent with a good discriminatory test. Values for likelihood ratio positive and negative that are considered to represent clinically relevant changes in post-test probabilities of disease are 5 and 0.2, respectively.

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