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EDITORIAL

Monitoring of exhaled nitric oxide in primary care

See paper by Gruffydd-Jones *et al* on page 349

Arguably the most important recent advance in the field of assessment of airway disease has been the development of techniques to assess airway inflammation that are safe and feasible in most patients. Two techniques are in widespread use: analysis of induced sputum, where a differential and total cell count is used to determine the characteristics and intensity of the lower airway inflammatory response; and measurement of the fraction of exhaled nitric oxide (FeNO), where the concentration of nitric oxide in exhaled air is used to provide information about the presence of eosinophilic, corticosteroid-responsive airway inflammation. Measurement of FeNO is particularly relevant to primary care practice as the instruments needed to do this have become affordable and the technique provides an immediate result – making it ideal for monitoring purposes.

When considering whether to invest in new technology the clinician needs to be sure that the methodology is sound, that the measurement is feasible, that it is acceptable to patients, and that the measurement provides information about a clinically important aspect of the disease that can't be assessed by simpler means. Gruffydd-Jones ***et al*** address some of these questions in their paper in this issue of the *Primary Care Respiratory Journal*.[1] They used a standard technique and a commercially available chemiluminescence analyser to assess FeNO repeatedly in 22 adults and 15 children with asthma. Measurements were made at 2-weekly intervals for 12 weeks, and spirometry, asthma-related quality of life, and asthma control were also assessed. The ease of use of the FeNO monitor was assessed by patients and nurses using a 7-point rating scale fixed at both ends by 'very easy' and 'very hard'. All but two subjects were able to perform the exhaled manoeuvre required to assess FeNO. There was evidence of a learning effect over time, particularly in the children, and towards the end of the study acceptable readings were obtained from most attempts. Patient and nurse acceptability was high. The success rate and acceptability rating of FeNO measurements were probably not a lot different from those that would have been seen with spirometric manoeuvres or assessment of peak expiratory flow, although neither of these measures were assessed in the same way. The authors did not evaluate the latest portable and affordable FeNO monitor; however, this monitor employs a very similar expiratory manoeuvre and flow indicator system so it is unlikely that there is an important difference in ease of use and acceptability.

In their study, values of FeNO were noted to be variable between and within subjects.[1] Little of this variability was accounted for by changes in asthma symptoms, quality of life scores or lung function, suggesting that the measure might be providing information about asthma control that is not assessed by other means. The key question, which was not assessed by Gruffydd-Jones ***et al***, is whether this information is clinically important. However, there is mounting evidence from studies conducted in secondary care that FeNO measurement provides information about the presence of eosinophilic, corticosteroid-responsive airway inflammation and that its use results in more effective and economical use of inhaled corticosteroids.

The widespread application of non-invasive assessment of airway inflammation has led to a number of clinically important observations. Firstly, the presence of eosinophilic airway inflammation is not closely related to either the pattern or the severity of the airway dysfunction or symptoms. A raised sputum eosinophil count is seen in 70-80% of corticosteroid-naive patients with asthma, 50% of corticosteroid-treated patients with symptomatic asthma,[2] 30-40% of patients with cough,[3] and up to 40% of patients with chronic obstructive pulmonary disease (COPD).[4] Within diagnostic groups there is a weak correlation between the presence of eosinophilic airway inflammation and the severity of symptoms or disordered airway function.[5] Thus, little can be deduced about the presence and severity of eosinophilic airway inflammation from a standard clinical assessment.

Secondly, the presence of eosinophilic airway inflammation is more closely associated with a positive response to corticosteroids than any other clinical measure. Moreover, a positive response to corticosteroids is seen irrespective of the pattern of airway disease in which eosinophilic airway inflammation occurs.[4,6-9] Thus, if the clinical question is whether or not a patient with chronic respiratory symptoms should receive corticosteroid treatment (and I would argue that it often is), then the identification of

eosinophilic airway inflammation would be a better basis for making this decision than the findings of other tests.

Thirdly, the sputum eosinophil count is a better marker for titrating corticosteroid therapy than standard clinical measures. Studies in asthma[10,11] and COPD[12] have shown that management strategies where decisions about corticosteroid use and dose are guided by the sputum eosinophil count result in a lower frequency of exacerbations and more economical use of corticosteroids than management guided by traditional clinical measures.

Fourthly, studies have shown that, in non-smokers, FeNO levels correlate reasonably closely with the presence of eosinophilic airway inflammation when it is assessed more directly.[13-15] This is the most important feature of the test, and – apart from cigarette smoking – there appear to be no clinically important confounders of this relationship.[13] Thus, in assessing FeNO, one is identifying eosinophilic, corticosteroid-responsive airway disease, not asthma *per se*. As for sputum eosinophils, it has been shown that a raised FeNO level is a reliable indicator of a positive response to corticosteroids in a heterogeneous population of patients with symptoms suggesting airway disease.[16] This finding was independent of the clinical diagnosis at presentation – in particular, the label of asthma. The relationship between airway eosinophilia, FeNO levels and steroid responsiveness has been further employed to show that, when used as a guide to dose requirements, regular FeNO measurements result in more economical and effective use of inhaled corticosteroids.[17]

The link between eosinophilic airway inflammation and corticosteroid responsiveness, together with the development

Figure 1. Suggested algorithm for assessment of patients presenting with untreated airway disease. Eosinophilic airway inflammation can be assessed using induced sputum eosinophils or fraction of exhaled nitric oxide (FeNO). * Potentially treatable aggravating factors include rhinitis, anxiety-hyperventilation syndrome, vocal cord dysfunction, bronchiectasis and gastro-oesophageal reflux disease. **Symptomatic therapy includes short- and long-acting bronchodilator therapy, oral theophylline and mucolytics as well as specific treatments for the aggravating factors. ***There is limited evidence that some patients with symptoms suggesting airways disease have raised FeNO that is not reflective of eosinophilic airway inflammation and is not corticosteroid responsive. Therefore, a persistently raised FeNO after corticosteroid treatment should prompt a more thorough assessment of airway inflammation using induced sputum.

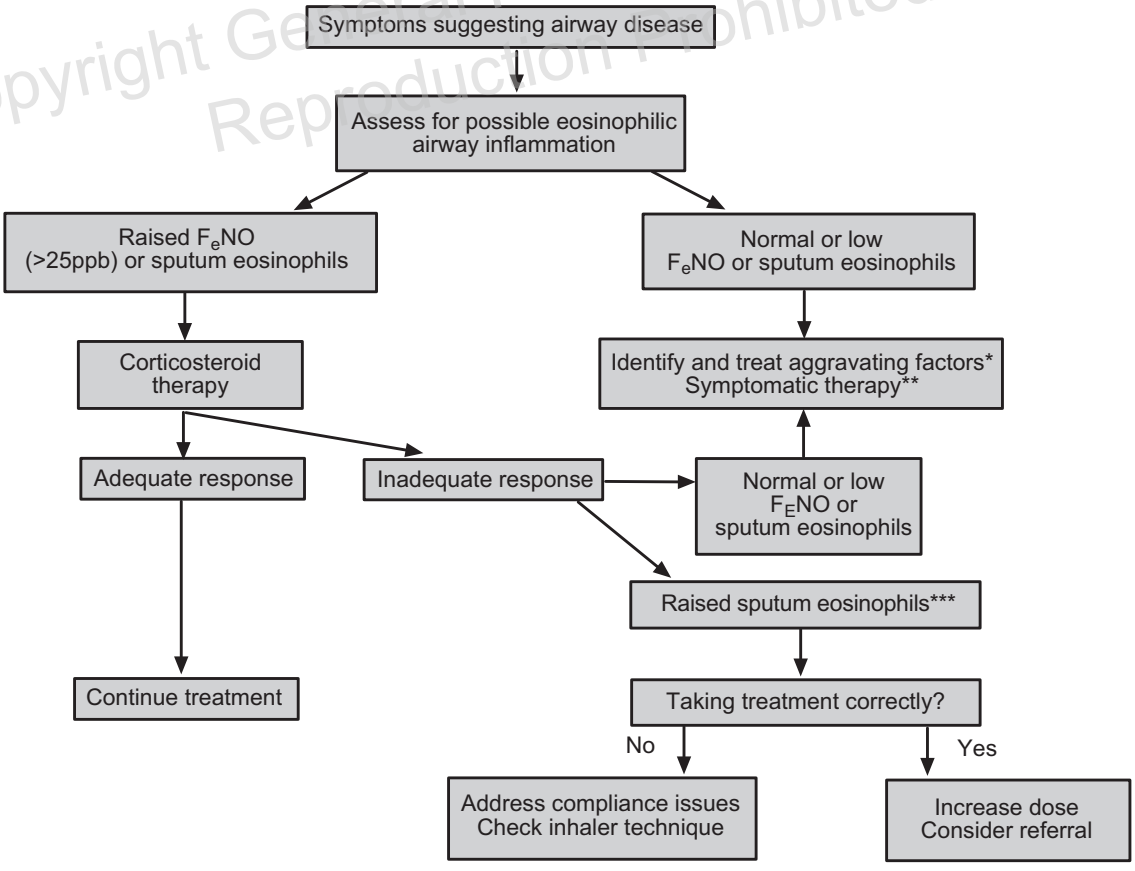

Table 1. An approach to monitoring inhaled corticosteroid (ICS) treatment in patients with airway disease using exhaled nitric oxide (FeNO).

FeNO	Low	Normal	Intermediate	High
Ppb	<5	5-25	25-50	>50
Symptoms controlled	Decrease/stop ICS	Decrease/stop ICS	No change	Increase ICS/refer
Symptoms uncontrolled	Decrease ICS, increase bronchodilators. Investigate for PCD and CF	Decrease ICS, increase bronchodilators	Assess compliance. Increase ICS	Assess compliance. Increase ICS/refer

ppb = parts per billion; PCD = primary ciliary dyskinesia; CF = cystic fibrosis

of inexpensive nitric oxide monitors, has opened the way for a new approach to the management of airways disease in clinical practice, with the emphasis being more on assessing airway inflammation rather than diagnostic labelling. The former rather than the latter will provide the clinician with the most relevant information for making therapeutic choices.

Figure 1 outlines an approach to the assessment of patients with newly-presented airway disease where decisions about use of corticosteroids are based on assessment of eosinophilic airway inflammation rather than recognition of patterns of symptoms and airway dysfunction. The use of FeNO measurements to titrate treatment in patients already taking inhaled corticosteroids has not been evaluated extensively and there are many remaining questions. Recent work suggests that low FeNO values might be of particular value as they reliably identify individuals where corticosteroid treatment can be safely reduced.[18,19] Table 1 outlines an approach to the interpretation of FeNO levels in patients who are already receiving treatment.

Whether this new approach to assessment of airway inflammation results in better outcomes and more economical use of treatment in a primary care setting remains to be determined. There will be those who conclude that use of this technology should be postponed until more definitive evidence is available. However, there will be others who are frustrated by empirical treatment trials and unsatisfactory classification systems and who feel that the time is already right for this new technology. Over 80% of patients with airway diseases are managed exclusively in primary care and one hopes that FeNO monitoring will continue to be evaluated in this setting. Gruffydd-Jones *et al* are to be congratulated in taking a lead on this.

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