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Inflammometry to assess airway diseases

See **Comment** page 1015

The diagnostic labels used to characterise common airway diseases have always been a problem. The term asthma implies the presence of variable airflow obstruction; however, objective demonstration can be difficult. Commonly used tests, such as spirometry or serial peak-flow measurements, are neither sensitive nor specific,[1] especially in patients with mild disease and normal or near-normal lung function, or in those with fixed airflow obstruction. Conversely, the term chronic obstructive pulmonary disease (COPD) implies largely irreversible airflow obstruction, yet clinicians may attempt to confirm the presence of reversibility, and having done so, label the disease as having an "asthmatic" component. Furthermore, the use of specific diagnostic labels implies a probable natural history, and influences expectations about treatment outcomes.

Although causative factors in the various airway diseases are different, the natural history and treatment responsiveness are less distinct. For example, accelerated decline in lung function and fixed airflow obstruction are features of COPD, but not exclusively so; they also occur in some patients with asthma, and the mechanisms might be similar.[2] In view of this picture, diagnostic labelling on the basis of physiological data can be confusing and misleading.

Treatment with corticosteroids, usually by inhalation, is arguably the most important therapeutic intervention in patients with airway disease. Judicious use of these agents improves symptoms and reduces exacerbations. However, the response to inhaled corticosteroids is heterogeneous. The identification of clinical or physiological features that predict corticosteroid responsiveness in patients with symptoms that suggest airway disease is difficult, irrespective of the final diagnosis. A common approach is to base long-term use of corticosteroid on the response to a short-term trial of treatment. This approach is potentially flawed for several reasons.

First, symptoms that suggest asthma are non-specific, and are mimicked by acute conditions such as postviral bronchial hyper-responsiveness, anxiety hyperventilation syndrome, vocal cord dysfunction, and gastro-oesophageal reflux, and by chronic conditions such as COPD or bronchiectasis. Most of these conditions do not respond to corticosteroids, but spontaneous improvement over time leads to the mistaken belief that such treatment has been beneficial. The correct diagnosis is thus delayed, or inappropriate treatment might be increased when symptoms worsen. Second, it is not valid to draw inferences about the longer-term benefits of treatment (ie, reduction in exacerbation frequency) from the outcome of a short-term trial. Third, expectation, observer or ascertainment biases, and incomplete adherence to the prescribed treatment can also influence results. Most of these problems, together with the natural tendency of clinicians to be cautious in borderline cases, increase the likelihood that patients may be started on inappropriate corticosteroid therapy, with associated cost and potential toxicity.

An alternative approach is to identify the need for corticosteroids in relation to the underlying inflammation. It is logical that both the indications and the outcomes for anti-inflammatory treatment should be related to the presence of airway inflammation. There is now consistent evidence that eosinophilic airway inflammation is the most reliable predictor of a response to corticosteroids in patients with airway disease,[3–7] irrespective of which diagnostic label applies. The long-term benefits of corticosteroids on exacerbation frequency also occur predominantly in patients with evidence of eosinophilic airway inflammation.[8–10] Management strategies that seek to minimise eosinophilic airway inflammation substantially reduce the frequency of severe exacerbations, both in asthma[8,9] and COPD,[10] and hence result in more efficient use of corticosteroids.

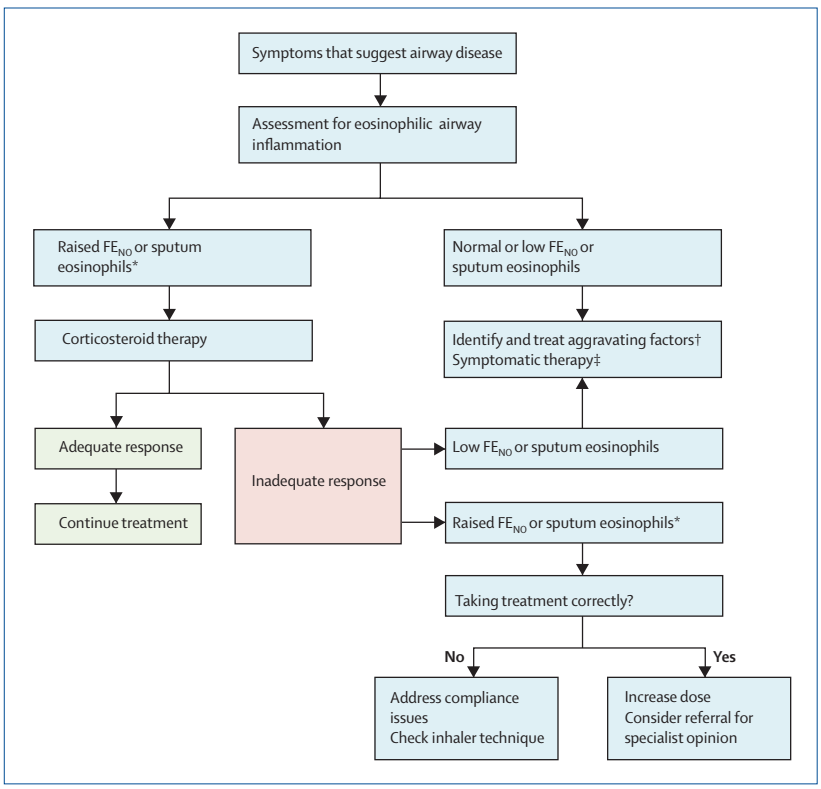

Figure: **Suggested algorithm for assessment of airways disease**
Eosinophilic airway inflammation can be assessed with use of induced sputum eosinophils or FE_{NO}. *Suggested normal adult range for sputum eosinophils is <2% and FE_{NO} <25 parts per billion. FE_{NO} >50 parts per billion is very predictive of response to corticosteroids and relapse when treatment is withdrawn. Interpretation of FE_{NO} at 25–50 parts per billion varies between individual patients. Induced sputum eosinophil count is likely to be more reliable indicator of corticosteroid response and relapse risk when FE_{NO} is in this range. †Potentially treatable aggravating factors include rhinitis, anxiety hyperventilation syndrome, vocal cord dysfunction, bronchiectasis, and gastro-oesophageal reflux disease. ‡Symptomatic therapy includes short-acting and long-acting bronchodilators, oral theophylline, mucolytics, and specific treatments for aggravating factors.

Assessment of eosinophilic airway inflammation with induced sputum is technically demanding, and results are not immediately available. These factors limit the clinical application of the method. By contrast, measurement of the fraction of nitric oxide in exhaled air (FE_{NO}) with new inexpensive monitors is simple and reliable. FE_{NO} concentrations correlate with the presence of eosinophilic airway inflammation, and, except for current cigarette smoking, there seem to be no clinically important confounders of this relation.[11] As with sputum eosinophils, a raised FE_{NO} is a reliable indicator of a positive response to corticosteroids in patients with symptoms of airway disease.[12] This finding was independent of the clinical diagnosis at presentation. More definitively, FE_{NO} levels above 50 parts per billion[12,13] and below 25 parts per billion[14] can, respectively, be used to identify which patients do and do not require long-term maintenance with inhaled steroids.

Thus regular monitoring of FE_{NO} is a promising way to identify whether a corticosteroid-responsive element is present (ie, eosinophilic airway inflammation). This distinction is particularly valuable in patients with multifactorial respiratory symptoms. The value of FE_{NO} as a guide to corticosteroid dose-requirements is less clear,[15–17] because none of the studies used optimum cutoffs for FE_{NO} or studied a population with uncontrolled asthma. Even so, there is a consistent trend of reduction in asthma exacerbation of around 25%, and in one study this was achieved with a 45% lower mean daily dose of inhaled corticosteroids.[15]

This approach does not preclude the need for pulmonary function tests, which are still needed to see whether there is frank airway obstruction, and to assess severity and trends. But functional measurements provide a limited perspective on which to predict potential response to treatment. Physiological testing complements rather than substitutes for identification of the nature of airway inflammation. The time is now technologically ripe for a change in emphasis. For the prescription of corticosteroids, diagnostic labelling should be superseded by a more targeted approach, on the basis of the measurement of airway eosinophilia, for which FE_{NO} is a good marker (figure). The identification of steroid-responsive airway inflammation can only improve the effectiveness with which we manage patients with persistent lower-respiratory-tract symptoms. We should move swiftly towards the assessment of inflammation (inflammometry) as an integral component in the management of patients with chronic airway symptoms.

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IDP has received lecture fees from Aerocrine AB Solna, a manufacturer of nitric oxide analysers. DES declares that he has no conflict of interest. PGG, or his institution, have received funding for travel costs and speakers fees for educational symposia funded by the Thoracic Society of Australia and New Zealand, the European Respiratory Society, AstraZeneca, Novartis, and GlaxoSmithKline, and research funding for studies from GlaxoSmithKline and Pharmaxis. DRT has received lecture fees and financial support for a research study from Aerocrine AB Solna.

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Severe childhood asthma: a common international approach?

Although most children with asthma are easy to treat with low doses of safe drugs, many remain symptomatic despite every effort.[1] The nomenclature for this group is confused, and studies are difficult to compare because of the proliferation of terms that describe poorly defined clinical entities. To clarify, we propose the term problematic asthma to describe children with chronic symptoms or acute severe exacerbations, or both, despite prescription of multiple drugs. Such therapies usually include high doses of inhaled or oral corticosteroids, combined with standard add-on therapy with long-acting β_2 agonists (leukotriene-receptor antagonists and theophylline).[2,3]

Children with problematic asthma have either difficult asthma or severe therapy-resistant asthma. Careful specialist assessment is needed to ascertain into which of these subcategories the child falls. In children with difficult asthma, the predominant problem will not be resolved by prescribing a more sophisticated asthma drug (eg, concordance with a prescribed drug is poor, the environment is adverse, or if there are major underlying contributory psychological features). Severe therapy-resistant asthma needs innovative therapeutic approaches, and can be subphenotyped as responders to novel therapies, such as cytokine or other immune-specific agents.

The approach to problematic asthma might vary with the age of the child but, generally, three steps need to be taken to separate difficult from severe therapy-resistant asthma. First, confirmation that the problem is due to asthma requires complete diagnostic re-evaluation. Second, the paediatrician needs to systematically exclude substantial comorbidities, such as underlying systemic diseases, gastro-oesophageal reflux, and rhinosinusitis, and a personal or family psychosocial disorder. Third, adherence to drug, inhaler technique, and the child's environment need re-evaluation. There is no uniform agreement on how best to take all the three steps.

In one protocol,[4] a nurse-led home and school visit was used. Non-adherence was addressed by: obtaining computerised prescription records to see which drug had been collected;[5] such drugs and spacers available within the home were inspected; and the child's ability to use the inhaler was tested. Pet ownership is common even if the child is sensitised to the pet. Moreover, pets can cause steroid resistance through mechanisms mediated by interleukins 2 and 4.[6,7] At least some evidence exists to show that pets can worsen asthma by non-IgE-mediated mechanisms.[8,9] Passive exposure to smoke was observed first hand, because such exposure probably contributes to steroid resistance as has been documented with active smoking.[10,11] A long-term trial of removing pets, reducing household smoking, and taking the prescribed drug is preferable to high-dose oral corticosteroid or other immune-suppressive