

# Inflammometry: the current state of play

Ian D Pavord,<sup>1</sup> Peter G Gibson<sup>2</sup>

It is now 20 years since the late Freddy Hargreave and colleagues developed a valid, safe and feasible technique to assess airway inflammation using induced sputum.<sup>1–3</sup> At around the same time Kjell Alving and colleagues reported that the concentration of exhaled nitric oxide (FE<sub>NO</sub>) is raised in patients with asthma.<sup>4</sup> There has since been huge research interest in these techniques over the last 20 years and both are increasingly used in clinical practice. This has led to a number of key and often unexpected observations which have changed the way we think about inflammatory airway disease. First, the presence of eosinophilic airway inflammation, regarded as a *sine qua non* of asthma, is neither closely related to the pattern nor to the severity of airway dysfunction or symptoms.<sup>5–7</sup> Second, the presence of eosinophilic airway inflammation is more closely associated with a positive response to corticosteroids than other more traditional clinical measures, irrespective of the pattern of disease it occurs in.<sup>7–10</sup> Thus, if the clinical question is should a patient with symptoms suggesting airway disease receive corticosteroid treatment (and it often is), then the identification of eosinophilic airway inflammation would be a better basis for making this decision than categorising the patient or applying other tests. Third, a raised FE<sub>NO</sub> level appears to be just as good an indicator of a positive response to corticosteroids in a heterogeneous population of patients with symptoms suggesting airway disease.<sup>11–14</sup>

The close link between these markers and corticosteroid responsiveness together with the development of inexpensive nitric oxide monitors has led us to recommend a new approach to the management of airways disease with the emphasis more on assessing airway

inflammation and likely steroid responsiveness than on diagnostic labelling.<sup>15</sup> This approach, often known as inflammationometry, could be used to identify potentially corticosteroid disease and guide the initiation of treatment or to titrate treatment. The latter approach has been assessed in a meta-analysis<sup>16</sup> and a clinical trial<sup>17</sup> published in this edition of *Thorax*.

Petsky *et al*<sup>16</sup> combined two Cochrane reviews assessing the efficacy of sputum eosinophil guided asthma management in three adult studies including a total of 246 adults with mainly moderate to severe asthma and FE<sub>NO</sub> guided management in six studies including 786 children and 267 adults with milder asthma. Their analysis was compromised by differences in management algorithms, outcome measures and definitions of key outcomes but even so the sputum studies all showed a clear and consistent reduction in asthma attacks when management was guided by the sputum eosinophil count. What then are we to make of the study by Fleming *et al*<sup>17</sup> which found no evidence of improved outcome in children with severe asthma randomised to sputum guided management?

The discrepant finding is unlikely to be due to differences in the management algorithm, which was very similar to that successfully applied by Green *et al*.<sup>18</sup> A difference in the success rate of sputum induction is also unlikely to have been responsible but there was a suggestion that more frequent assessments of airway inflammation might have made a difference in favour of the sputum guided management. A retrospective analysis by Haldar *et al*<sup>19</sup> suggested that most of the benefit of sputum guided management occurred in patients who had discordant symptoms and eosinophilic airway inflammation, a pattern that is particularly common in patients with severe non-atopic, adult onset asthma. The key difference in the way treatment was applied in sputum guided management was that regular oral steroids were initiated early in patients recognised to have eosinophilic airway inflammation whether this was associated with symptoms or not. Could it be that these discordant phenotypes are less prevalent or are less consis-

tently defined in children with severe asthma? These possibilities cannot be discounted but an alternative, and in our view a more likely explanation, is that the sputum management algorithm failed because it was not applied correctly on a significant number of occasions. It is notable that eosinophilic airway inflammation was not controlled in many of the patients randomised to sputum guided management, in marked contrast to the findings of Green *et al*.<sup>18</sup> This may be because of a reluctance to step up to regular systemic corticosteroids, a treatment that might have had a large effect on inflammation and risk of asthma attacks. While the reluctance to make this big step in paediatric practice is readily understandable, our view is that this brave study of an important group of patients failed because the protocol was not followed, not because it was incorrect.

Petsky *et al*<sup>16</sup> conclude that the technical expertise required to perform sputum induction and analysis is a significant barrier to its use in routine clinical practice. In this respect FE<sub>NO</sub> has significant advantages as relatively inexpensive monitors are available, the technique is simple to perform and an immediate result is available. However, the outcomes of studies using FE<sub>NO</sub> to titrate asthma treatment have been variable and the meta-analysis showed no overall improvement in outcome in adults or children. Interpretation of the findings is not straightforward as many of the studies were underpowered to properly evaluate the primary outcome and FE<sub>NO</sub> cut points used for up and down-titration of steroids were inconsistent and often sub-optimal.<sup>20</sup> Furthermore, the largest study<sup>21</sup> evaluated FE<sub>NO</sub> as an adjunct to traditional symptom guided management and, illogically, used symptom control as the primary outcome, when all the evidence suggests it would work better as an alternative to symptom guided management against outcomes more closely linked to airway inflammation such as the number of asthma attacks. Most importantly, the studies have largely evaluated patients with mild to moderate asthma and influenced decisions about treatment across a range of treatment doses and against outcomes where the dose-response relationship is flat.<sup>20</sup>

We are concerned that the full potential of FE<sub>NO</sub> has not been explored and suggest that further studies evaluating the use of FE<sub>NO</sub> as an alternative to traditional management are required. One such study, published since the meta-analysis, has shown clear evidence of improved outcome in both mother and new born in

<sup>1</sup>Institute for Lung Health, Glenfield Hospital, Leicester, UK; <sup>2</sup>Department of Respiratory and Sleep Medicine, Centre for Asthma and Respiratory Diseases, Hunter Medical Research Institute at John Hunter Hospital, University of Newcastle, Newcastle, Australia

**Correspondence to** Professor Ian D Pavord, Consultant Physician and Honorary Professor of Medicine, Institute for Lung Health, Glenfield Hospital, Leicester LE3 9QP, UK; ian.pavord@uhl-tr.nhs.uk

pregnant women whose asthma was managed by reference to  $FE_{NO}$ .<sup>22</sup> Future studies need to clearly define the population who would most benefit from inflammometry. We suggest that there are two critical decision points with corticosteroid therapy in airways disease where the additional information provided by an objective marker of airway inflammation might be particularly valuable and where the potential benefits of appropriately applied treatment might be most marked: the decision to initiate what will often be life-long treatment; and the decision to step up therapy to high dose inhaled therapy or regular oral prednisolone in patients with more severe, complex airway disease. Perhaps future trials should focus on patients at these management points.

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