

## EDITORIAL

# Clinical & Experimental Allergy

## Asthma control, airway responsiveness and airway inflammation

This editorial discusses the findings of the paper by Quaedvilieg et al. [5] pp. 1822–29.

I. D. Pavord

Department of Respiratory Medicine, Institute for Lung Health, Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK

Asthma control can be defined as the extent to which the various manifestations of asthma have been reduced or removed by treatment [1]. The manifestations of asthma have two important components: day-to-day symptoms and risk of future adverse events such as asthma exacerbations and the development of fixed airflow obstruction. Day-to-day symptoms can be assessed relatively simply by questionnaire. The Juniper Asthma Control Questionnaire (ACQ) is one of the most commonly used and best validated [1, 2]. The questionnaire is scored as the mean of the response to seven questions scored on a seven-point scale, with lower values representing better control. Five questions relate to day and nighttime symptoms over the previous 7 days, one to rescue  $\beta_2$ -agonist use over the last 7 days and one on the % predicted pre-bronchodilator forced expiratory volume in 1 s. There is an emerging consensus that scores  $< 0.75$  represent well-controlled asthma and  $> 1.5$  not well-controlled asthma [1, 3]. A shortened five-question symptom only questionnaire has been developed [4]. It performs almost as well as the longer questionnaire and may be a more suitable tool for clinical practice.

Airway inflammation and airway hyperresponsiveness are acknowledged to be key features of asthma but there is uncertainty as to how they contribute to asthma control and whether incorporating measures of these features might add to an overall assessment. The first of these questions has been addressed by Quaedvilieg et al. in this issue of the journal [5]. In a cross-sectional study of 134 patients attending a local asthma clinic, the authors assessed the relationship between the ACQ score, methacholine airway

responsiveness and eosinophilic airway inflammation assessed using induced sputum and exhaled nitric oxide concentration ( $FE_{NO}$ ). The ACQ score was modified from the original seven-item questionnaire by excluding the lung function question. Airway responsiveness and the sputum eosinophil count were significantly increased in patients with an ACQ score  $> 1.5$  compared with those with a score  $< 0.75$  whereas  $FE_{NO}$  was not. Although marginally better than simple spirometric indices, none of the measures reliably discriminated patients in different control categories. What are we to make of this data? What are the implications for use of these investigations in the clinic?

The clinical manifestations of airway diseases can be viewed as the consequence of different patterns of airway inflammation and a limited number of abnormal physiological responses which can be conveniently summarized using an A to E checklist. These include: Airway hyperresponsiveness, responsible for short-term variable bronchodilator responsive airflow obstruction; Bronchitis, which may be eosinophilic and corticosteroid responsive or neutrophilic and corticosteroid resistant; Cough reflex hypersensitivity; Damage to the airway and lung resulting in bronchodilator and corticosteroid resistant airflow obstruction, bronchiectasis and impaired gas transfer; and Extra-pulmonary conditions such as dysfunctional breathing, adherence to medication, deconditioning, rhinitis and obesity. These abnormalities can, and often do, occur independently and they are controlled by distinct pathogenic pathways. The weak relationship between symptoms, eosinophilic airway inflammation and airway responsiveness noted by Quaedvilieg et al. implies that C, D and E make a large contribution to symptoms, at least in a population of patients attending a hospital clinic.

Is there any evidence that measuring A (airway responsiveness) and B (bronchitis or airway inflammation) adds to an assessment of asthma control? Evidence suggests that both are particularly associated with risk. B can be clinically silent but it may also contribute to more gradual

### Correspondence:

Prof. I. D. Pavord, Department of Respiratory Medicine, Institute for Lung Health, Glenfield Hospital, University Hospitals of Leicester NHS Trust, Groby Road, Leicester, LE3 9QP, UK.

E-mail: ian.pavord@uhl-tr.nhs.uk

Cite this as: I. D. Pavord, *Clinical & Experimental Allergy*, 2009 (39) 1780–1782.

onset, bronchodilator resistant increases in airflow obstruction (exacerbations), particularly when coinciding with an acute inflammatory stimulus in patients with A and/or D [6]. Eosinophilic airway inflammation is closely related to aspects of airway remodelling, in particular thickening of the basement membrane [7] and neutrophilic airway inflammation is consistently associated with fixed airflow obstruction [8, 9]. Studies have shown that management algorithms that incorporate normalization of the induced sputum eosinophil count [10, 11] or airway responsiveness [12] as treatment goals result in fewer asthma exacerbations and less airway remodelling despite no overall improvement in symptom control. The beneficial effects of inflammation guided management are most obvious in patients with more severe disease, perhaps because exacerbations are more common and phenotypic diversity is greatest, and the clinical value of a more intensive assessment in this population is now widely accepted.

There is more uncertainty as to the value of an intensive management approach in patients with less severe asthma, in part because symptom-based management works well and assessment of airway responsiveness and induced sputum are not feasible in a patient population largely managed in primary care. Assessment of  $FE_{NO}$  as a surrogate marker of eosinophilic airway inflammation is feasible in primary care and we now have available reasonable inexpensive monitors to do this. Is the technique up to the job? Quaedvlieg and colleagues imply that it might not be as they found that  $FE_{NO}$  was less closely related to asthma control than airway responsiveness and the sputum eosinophil count. In addition, there have now been five clinical trials, which have failed to provide convincing evidence that addition of  $FE_{NO}$  to standard clinical management results in improved outcomes [13–17].

However, the absence of a relationship between  $FE_{NO}$  and symptoms does not necessarily mean that  $FE_{NO}$  tells us nothing about risk. In addition, there are a number of problems with the clinical trials evaluating  $FE_{NO}$  as a monitoring tool, which suggest that it might be premature to abandon  $FE_{NO}$  as a monitoring tool. First, many of the studies were underpowered to properly evaluate the effect of  $FE_{NO}$  monitoring on longer-term outcomes such as severe asthma exacerbations. Second, studies have not focused on patients who might particularly benefit from the additional information provided by  $FE_{NO}$ , such as newly identified patients who are being considered for corticosteroid therapy and those where C, D and E might be making an important contribution to asthma-like symptoms. Third,  $FE_{NO}$  cut points used for up and down-titration of corticosteroids have been inconsistent and, in many cases, are now known to be sub-optimal. Finally, the largest and most influential study [16] evaluated  $FE_{NO}$  as an adjunct to traditional symptom guided management, when all the evidence suggests it would work better as an

alternative. Despite these caveats, the studies have shown a consistent trend to a reduction in severe exacerbations of asthma of 20–40%; in one study this was achieved despite a 45% lower mean dose of inhaled corticosteroids [13].

There is a need for further studies exploring the use of  $FE_{NO}$  as an alternative to traditional management. These studies need to clearly define the population who would most benefit from inflammometry. I 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: 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. There is now more of a consensus that a  $FE_{NO}$  of  $< 25$  p.p.b. is strongly associated with successful reduction or discontinuation of inhaled corticosteroids [18–20] and a  $FE_{NO} > 50$  p.p.b. is a specific marker for a good response to corticosteroids [20, 21]. Values lying between 25 and 50 p.p.b. are indeterminate and clinical criteria should be used to guide corticosteroid treatment. In terms of end-points, the use of  $FE_{NO}$  to guide asthma management might lead to a reduction in corticosteroid dose, a reduction in asthma exacerbation, both or neither. Corticosteroid dose would be a rational primary outcome in a well-controlled population or in those newly presenting with airway disease whereas exacerbation frequency would be a better primary outcome in patients with poorly controlled asthma.

Existing and experimental new treatments largely target A and/or B and it is important that clinicians involved in managing patient with asthma and evaluating experimental treatments are capable of identifying patients displaying these characteristics. It is clear from the work of Quaedvlieg et al. work that the ACQ provides a very limited perspective. I agree with the authors that additional information is needed to provide the full picture needed for optimal management. This additional information is likely to be most valuable at the time of diagnosis and in patients with more complex disease. Induced sputum inflammatory cell counts and measures of airway responsiveness are ideal but in a primary care setting I still believe that  $FE_{NO}$  is the best current option.

## References

- 1 Reddel HK, Taylor DR, Bateman ED *et al.* An official American thoracic society/European respiratory society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180:59–99.
- 2 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14:902–7.

- 3 Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the asthma control questionnaire. *Respir Med* 2006; **100**:616–21.
- 4 Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; **99**:553–8.
- 5 Quaedvilieg V, Sele J, Henquet M, Louis R. Association between asthma control and bronchial hyperresponsiveness and airway inflammation: a cross-sectional study in daily practice. *Clin Exp Allergy* 2009; **39**:1822–29.
- 6 Pavord ID, Birring SS, Berry M, Green RH, Brightling CE, Wardlaw AJ. Multiple inflammatory hits and the pathogenesis of severe airway disease. *Eur Respir J* 2006; **27**:884–8.
- 7 Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002; **346**:1699–705.
- 8 Stanescu D, Sanna A, Veriter C *et al.* Airways obstruction, chronic expectoration, and rapid decline of FEV<sub>1</sub> in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; **51**:267–71.
- 9 Shaw DE, Berry MA, Hargadon B *et al.* Association between neutrophilic airway inflammation and airflow limitation in adults with asthma. *Chest* 2007; **132**:1871–5.
- 10 Green RH, Brightling CE, McKenna S *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; **360**:1715–21.
- 11 Jayaram L, Pizzichini MM, Cook RJ *et al.* Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006; **27**:483–94.
- 12 Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999; **159** (4, Part 1):1043–51.
- 13 Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005; **352**:2163–73.
- 14 Pijnenburg MW, Bakker EM, Hop WC, de Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005; **172**:831–6.
- 15 Shaw DE, Berry MA, Thomas M *et al.* The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; **176**:231–7.
- 16 Szeftler SJ, Mitchell H, Sorkness CA *et al.* Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008; **372**:1065–72.
- 17 de Jongste JC, Carraro S, Hop WC, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; **179**: 93–7.
- 18 Zacharasiewicz A, Wilson N, Lex C *et al.* Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005; **171**:1077–82.
- 19 Taylor DR, Pijnenburg MW, Smith AD, de Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006; **61**:817–27.
- 20 Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. *Lancet* 2008; **372**:1017–9.
- 21 Smith AD, Cowan JO, Brassett KP *et al.* Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005; **172**:453–9.