

NO More Dogma

A great deal of dogma has developed around the widely supported and appealing argument that the fraction of nitric oxide in exhaled breath (F_{ENO}) is a marker of airway inflammation that can be used to monitor asthma and guide management. The assumptions that F_{ENO} is a marker for asthma and also reflects eosinophilic airway inflammation and asthma control have been widely promoted in the medical literature (1, 2) and by industry. However, studies that have examined these assumptions have cast considerable doubt on their validity.

There are convincing community data that F_{ENO} better reflects processes that are occurring in the atopic rather than the asthmatic airway (3, 4). The associations of F_{ENO} with eosinophilic inflammation are inconsistent (5–8) and particularly difficult to interpret in patients with asthma treated with inhaled corticosteroids (9). Furthermore, changes in airway eosinophilia associated with nonsteroidal treatments are not consistently associated with changes in F_{ENO} (6). Studies that have investigated whether increased F_{ENO} predicts worsening asthma either spontaneously or during stepwise treatment withdrawal have provided inconsistent results. The available data indicate that daily F_{ENO} measurements appear only as good as peak flow, symptom reports, and bronchodilator use for predicting loss of control (10).

With such confusion regarding key elements of the argument that F_{ENO} measurements can be used as “inflammometry” in asthma management, the appropriate test is the randomized controlled trial. Two widely cited randomized controlled studies include one from New Zealand by Smith and colleagues (11) and the other from “Old Zealand” reported by Pijnenburg and colleagues (12) that compared algorithms including F_{ENO} measurements to standard protocols for managing asthma without the use of F_{ENO} . In the study by Smith and colleagues (11), the only clinically significant outcome was that the F_{ENO} group could maintain the same level of asthma control with a significantly lower dose of inhaled corticosteroid (ICS). However, the study design favored a reduction in ICS dose in the F_{ENO} group. If asthma was controlled and F_{ENO} was less than 15 ppb, the dose of ICS was reduced, but if F_{ENO} was greater than 15 ppb, the dose stayed the same. In the comparison arm, if symptoms were controlled at one visit, subjects had to wait for an additional 2 months before having the opportunity to reduce the dose. The second study, reported by Pijnenburg and colleagues (12) and performed in children, demonstrated as the only significant outcome a statistically greater improvement in airway responsiveness (AR) in the F_{ENO} group compared with the control group at the end of the study. However, this group had increased airway reactivity compared with the control arm at baseline, and it is likely that some of the observed improvement was due to a regression to the mean at follow-up.

The outcomes from three subsequent randomized controlled studies have cast further doubt on the validity of the argument that measurement of F_{ENO} can aid asthma management. Shaw and colleagues (13) reported a lower daily dose of ICS at the end of the study in a F_{ENO} managed group but the same cumulative

dose of steroids overall and no significant clinical benefits in the F_{ENO} arm. On the other hand, in the study reported by Fritsch and colleagues (14), ICS dosage at the end of the study was significantly higher in the F_{ENO} group than in the control group. In this clinical trial, there was a small but statistically significant improvement in forced mid-expiratory flows in the F_{ENO} arm but no significant improvements compared with the control arm for any other clinical outcome. Another study reported recently by Szefer and colleagues compared two management protocols: one based on the National Asthma Education and Prevention Program (NAEPP), and the other a standard treatment modified on the basis of F_{ENO} (15). The clinical trial randomized 546 patients with asthma between 12 and 20 years of age to either protocol who were then followed for 46 weeks. Asthma symptoms, pulmonary function, and asthma exacerbations did not differ between groups. However, the F_{ENO} group received higher doses of inhaled corticosteroids (difference 119 $\mu\text{g}/\text{d}$, 95% confidence interval of 49–189; $P = 0.001$) than controls.

In this issue of the *Journal*, de Jongste and colleagues report a well-conducted study of intensive telemonitoring of asthma from 15 centers in the Netherlands and Italy that included measurements of F_{ENO} (16). One-hundred-and-fifty-one atopic children with asthma were randomized to daily symptom monitoring or symptom plus daily F_{ENO} monitoring arms. Families were phoned every 3 weeks and the children’s ICS dose was adjusted according to average daily F_{ENO} in the preceding 3 weeks plus symptoms or according to symptoms alone. Children were seen at 3, 12, 21, and 30 weeks for examination and lung function testing. Both groups showed an increase in symptom-free days, improvement of FEV_1 , and quality of life, and a reduction in steroid dose. None of the changes from baseline differed between groups. This study clearly demonstrates that monitoring of F_{ENO} that is more intensive than is possible for the majority of asthmatics fails to deliver the benefits anticipated by proponents of “inflammometry” using F_{ENO} . Even if the nonsignificant tendency for a reduction in the rate of exacerbations in the F_{ENO} arm argued by the authors was real, an unrealistic number of asthmatics would have to participate in daily F_{ENO} measurements to prevent a single exacerbation.

There can be no doubt that adding regular assessments of F_{ENO} to management plans of most children and adults with asthma will add unjustifiable costs without providing clinical benefit. Whether there is a role for monitoring F_{ENO} to aid management of severe asthma is untested.

Anthony Burgess observed that, “every dogma has its day.” Although we still might learn about processes in the lung that involve nitric oxide by measuring F_{ENO} , it is now time to accept that promoting the routine use of F_{ENO} as an “inflammometer” to guide management of asthma is barking up the wrong tree.

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Exhaled Nitric Oxide Still Alive, Not Laid to Rest

The interrelationships between the fraction of nitric oxide in exhaled air (F_{ENO}), eosinophilic airway inflammation and steroid responsiveness, together with the ease with which F_{ENO} may be measured, have prompted a series of randomized trials designed to confirm that using F_{ENO} to optimize inhaled corticosteroid (ICS) therapy will improve asthma outcomes (1–3). The latest are reported in this issue of the *Journal* (pages 93–97) (4) and also recently in *The Lancet* (5). Overall, we must accept that, notwithstanding any weaknesses of the various F_{ENO} -based treatment algorithms, the routine use of F_{ENO} in this setting does not fulfill earlier expectations. This is disappointing given the enthusiasm generated by proof of concept studies in which induced sputum eosinophilia, for which F_{ENO} is used as a surrogate marker, was successfully used to guide asthma treatment (6).

It is important to highlight features in these studies that may have resulted in the “negative” outcome for F_{ENO} . First, there was little left to achieve. In the study by de Jongste and colleagues (4), 151 children with mild/moderate asthma were randomized to have their ICS dose adjusted on the basis of regular home monitoring of F_{ENO} or symptom scores. Over half of the improvement in symptoms was achieved during the first 6 weeks in both management groups and before significant ICS dose adjustments had occurred. The authors attributed this to frequent monitoring and telephone contacts. Similarly, in the study by Szeffler and colleagues (5), in 546 adolescents, almost all of the improvements in symptoms were dramatically accomplished during the run-in.

These outcomes are welcome; they indicate that using a biomarker, which may not always be available, cannot achieve more than intensive patient support but not that the biomarker has no role.

The studies confirm that using *high* F_{ENO} levels to prompt an increase in ICS dose and improve asthma outcomes was ineffective. This reflects the lack of specificity for high F_{ENO} levels: they do not always result from increased airway inflammation (7) even though, in steroid-naïve patients with uncontrolled symptoms, they are predictive of steroid responsiveness (8, 9). However, in both studies (4, 5), the combination of a high symptom score and *low* F_{ENO} resulted in “no change” in ICS dose: symptoms invariably trumped F_{ENO} levels. This design weakness means that no meaningful judgment regarding the utility of a low F_{ENO} can be made from these data. The cup is half empty. The predictive value of a low F_{ENO} for the absence of eosinophilic airway inflammation has been shown to be high (1), permitting steroid unresponsive symptoms to be differentiated from those which are steroid responsive. This is critically important in the management of individual patients. Further, repeatedly low F_{ENO} levels have been shown to predict the absence of long-term steroid requirement in children (10), and in adults consistently low values predict a low risk of deterioration in asthma control (9).

In these studies, the majority of participants were children, not adults, and all-comers were enrolled; for these reasons, con-