



Perspectives

Exhaled nitric oxide in asthma care: the conundrum continues

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Current measures that assess asthma severity and control are imperfect; they include the use of medical history, symptom scores, and objective measures of lung function. Increasingly, fraction of exhaled nitric oxide (FeNO) is being used by some clinicians as an adjunct to standard guidelines-based asthma care.^{1–4} Measures of airway inflammation, such as bronchial biopsy and sputum eosinophil counts, are unrealistic for routine asthma care and underscore the need for a noninvasive biomarker of eosinophilic inflammation. The introduction of FeNO devices to the market was initially met with significant enthusiasm, and despite conflicting data regarding its clinical usefulness, some allergists have incorporated FeNO devices into routine asthma care. Questions remain, however, regarding its utility, interpretation, cost benefit, and target population.⁵ Two studies recently published in the *Annals*, by Chipps et al⁶ and LaForce et al,⁷ explore such issues and shed light on the gaps in our knowledge regarding the optimal use and application of FeNO in clinical practice.

Controlling airway inflammation leads to improved asthma outcomes.^{1–3} Predicting airway inflammation based on medical history, symptom scores, and lung function testing can be challenging because patients may not report symptoms accurately or always have spirometric abnormalities. FeNO has been proposed as a noninvasive biomarker of eosinophilic airway inflammation that would be more applicable to real-world asthma care than cumbersome measures, such as bronchial biopsy and sputum eosinophil counts.⁵ The American Thoracic Society Clinical Practice Guidelines strongly recommends the use of FeNO in the diagnosis and monitoring of eosinophilic airway inflammation and in determining the likelihood of corticosteroid responsiveness; both the AAAAI and ACAAI have endorsed these recommendations.^{4,8} Nitric oxide is a gaseous signaling molecule that is generated by 3

isoenzymes of nitric oxide synthase (NOS).⁹ Inducible NOS (iNOS) is induced by inflammatory stimuli and is found in airway epithelial cells of some patients with asthma. Eosinophilic airway inflammation may affect FeNO levels through iNOS or other pathways.⁴ It has been hypothesized that a high FeNO can be considered a marker for corticosteroid responsiveness, whereas a low FeNO can predict the absence of eosinophilic inflammation and therefore a poor response to inhaled corticosteroids (ICSs).^{4,9} Serial FeNO measurements may be helpful in measuring response to ICSs and adherence to therapy.^{4,9} A great deal of enthusiasm followed the introduction of FeNO devices to the market with the hopes that monitoring of this surrogate marker would translate to better asthma control.

Large randomized clinical trials examining the role of FeNO measurements in asthma care to date have produced conflicting data. An early study by Smith and colleagues¹⁰ found a significant reduction in maintenance doses of ICSs without compromise of asthma control with the addition of FeNO measurements to clinical guidelines management. The initial enthusiasm generated by this study has been moderated by subsequent studies, such as that by Szeffer et al published in *The Lancet* in 2008, which did not find any added benefit in asthma control with the added use of FeNO measurements compared with standard of care.^{11,12} Barnes and colleagues⁹ cautioned that significant design issues mar these studies. Therefore, it is problematic to draw any definitive conclusions regarding the utility of FeNO measurements from existing literature. Emerging literature on this topic is similarly mixed. A recent study by Syk and colleagues¹³ found that in a group of 187 asthmatic adults, those with FeNO-guided management in a primary care setting had half the number of asthma exacerbations compared with those with standard asthma care. Such studies rekindle hope for the clinical utility of FeNO measurements in asthma care but are tempered by publications such as the Best Adjustment Strategy for Asthma in the Long Term trial, published in *JAMA* in 2012, which found no benefit with FeNO-based management. This study of 342 adults with mild to moderate asthma taking ICSs found no improvement in the time to treatment failure

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in a group managed with exhaled nitric oxide measurements compared with groups with standard guidelines-based management by physicians or symptom-based adjustment.¹⁴ Each of these studies has its own set of limitations, but such variability in the literature highlights the complexity of this topic and the need for further large-scale clinical studies.

In the article titled Impact of Exhaled Nitric Oxide Measurements on Treatment Decisions in an Asthma Specialty Clinic published in this issue of the *Annals*, LaForce et al performed a single-center, single-visit study of 50 patients previously diagnosed as having asthma and examined the treatment decisions made by asthma specialists based on their estimates of airway inflammation using clinical examination, Asthma Control Test (ACT) scores, and spirometry. They then recorded how these treatment decisions changed once FeNO levels were revealed to the clinician.⁷ This study found poor correlation between clinical appraisal of airway inflammation and observed FeNO levels, with clinicians underestimating the degree of inflammation as estimated by FeNO measurements. Knowledge of FeNO levels affected treatment decisions made by the clinicians in the study for 36% of the study patients, with 20% of patients being prescribed an increased amount of anti-inflammatory treatment and 16% having a reduction or elimination of anti-inflammatory treatment. Of the patients with an increase in asthma medications based on physician knowledge of FeNO levels, half had ACT scores greater than 19 and forced expiratory volume in 1 second (FEV₁) values greater than 80, suggesting that FeNO identified a group of at-risk patients whose inflammation may have otherwise been missed. The authors concluded that these changes lead to lower estimated costs of asthma care.

In the face of well-controlled symptoms and normal lung function, a high FeNO may be evidence of uncontrolled inflammation and may be associated with increased risk of exacerbations and clinical deterioration.¹⁵ In a recent letter in the *Annals*, Chipps and colleagues describe a small-scale observational study of 40 patients with a clinical diagnosis of asthma and found a small group of patients with FEV₁ values greater than 90 and very high FeNO levels greater than 100 ppb, all of whom were corticosteroid naive or taking a low dose of ICSs.⁶ The authors suggest that these patients who appear “normal” based on ACT score and spirometry may in fact be at risk of an asthma exacerbation. In the group with FEV₁ values less than 90 treated with moderate doses of ICS, the authors postulate that persistent high FeNO levels may be due to poor adherence, poor inhaler technique, or continued exposure to allergen. The authors also cite recent evidence that suggests that a persistently elevated FeNO level greater than 100 ppb in ICS-treated patients may also reflect a highly reactive asthma phenotype with a more severe clinical course and encourage further research in this group of patients.

Emerging data regarding FeNO are important given the gaps in our knowledge regarding its utility and optimal use. However, both *Annals* studies are pilot, small-scale studies and thus should be interpreted with due caution. Several limitations exist in both studies and should be acknowledged in the hopes of sparking large-scale studies with similar robust clinical designs. Both studies included patients with a clinical diagnosis of asthma but no documentation of reversibility. This raises concern that patients may have had illnesses other than asthma, which may have been a confounding factor. There are significant methodologic limitations to the study by LaForce et al beyond a small sample size, such as convenience sampling and single-visit assessment. Of further concern is that the authors report that FeNO is a gold standard measure of inflammation and that treatment changes based on FeNO findings will necessarily result in improved outcomes. There was no measure of outcome, such as hospitalizations and mortality, to indicate that titration of controller therapy based on FeNO measurements led to improved asthma control. Therefore, any

predictions regarding projected future savings based on the assumption of improved asthma control and avoidance of exacerbations are at best speculative. In addition, the study tracked treatment decisions and changes made by a group of 4 allergists and 1 nurse practitioner; it is difficult to extrapolate based on the behaviors made by this one group of clinicians and anecdotal cases. The study by Chipps et al also did not document reversibility and may have captured patients with diseases other than asthma. Alternative diagnoses of asthma to consider with a high FeNO include eosinophilic bronchitis, Churg-Strauss syndrome, lupus, and recent intake of a nitrate rich diet among others (and with a low FeNO include vocal cord dysfunction, anxiety-hyperventilation, bronchiectasis, cardiac disease, and gastroesophageal reflux disease, among other factors).⁴ In addition, ICS treatment was not confirmed with adherence measures, but admittedly this was beyond the scope of this small-scale observational study.

Beyond flaws with study design, other concerns regarding FeNO exist that may limit interpretation and applicability of study findings. The American Thoracic Society clinical guidelines recommend using clinically significant cut points to interpret FeNO levels.⁴ However, many have suggested that a change in FeNO from a personal baseline may be a more useful measure of asthma control.⁵ A study by Jones et al¹⁶ found that when assessing loss of asthma control after ICS withdrawal, change from baseline FeNO level had a higher positive predictive value compared with an absolute value cutoff. In their critique of existing randomized clinical trials that use FeNO levels, Barnes et al suggest, “Perhaps the optimal way would be to determine the stable level for each individual by giving a short prednisone burst before the trial and use that in the algorithm. In other words, individual cut points are probably more effective than fixed cut points in addressing interindividual variability.”⁹ A new algorithm based on each individual’s “best” FeNO level and changes in FeNO may be useful but has not been rigorously studied to date. It is yet unclear whether achieving a “best” FeNO level is necessary for good asthma control.⁹ Furthermore, there are ethical considerations in giving systemic corticosteroids to nonstudy patients with asthma to optimize a laboratory measure without validation.

Another factor to consider in evaluating the utility of FeNO measurements is that asthma is a heterogeneous disease with several phenotypes, including eosinophilic, neutrophilic, mixed, and paucigranulocytic. FeNO measurements may help the physician differentiate between asthma phenotypes and guide therapeutic approaches. Measurement of FeNO appears to be helpful in determining whether there is eosinophilic inflammation, predicting corticosteroid responsiveness, and assessing the level of adherence. However, the exact context in which FeNO may be helpful (during exacerbations, recovery from exacerbations, and/or doing routine follow-up visits) is yet unclear. Given phenotypic differences, FeNO measurements may also not be an equally reliable and useful monitoring tool among all patients with asthma, and this needs to be considered in further research protocol designs.

Questions remain regarding the clinical efficacy and cost benefit of FeNO compared with other measures. Studies that directly compare asthma outcomes with FeNO measurements vs other measures are needed. The cost of implementing FeNO measurements in the office includes not just the cost of the device itself (typically several thousand dollars) but also the ongoing cost of sensors and filters and technician time to perform the measure. The cost itself may not be prohibitive; however, reimbursement is an issue, as is overall cost benefit of the procedure to the patient. In a recent Letter to the Editor in *The Journal of Allergy and Clinical Immunology: In Practice*, Crisp¹⁷ describes an Internet-based survey of allergists in the United States regarding use of FeNO, its usefulness, and barriers to implementation. Of the 638 respondents (representing a 12% response rate), 50% used FeNO measurements in their clinical practice. Study participants reported FeNO reimbursement

as the single greatest barrier to FeNO use (identified by 45% of study participants). Startup costs were identified as a problem by 78 respondents (13%). Despite concerns about reimbursement, 75% of FeNO users in the study reported reimbursement through billing insurance. FeNO tests are reimbursable through Medicare and increasingly through certain private insurers.

Despite significant enthusiasm regarding FeNO, it has fallen short of becoming the gold standard measure of airway inflammation that clinicians were hoping for. However, any expectation of finding a single gold standard tool may be unrealistic given the heterogeneity of asthma phenotypes. Although FeNO measurement is an imperfect tool, it is hopeful that FeNO or some other form of inflammetry may have a role in asthma care. The recent FeNO studies published in the *Annals* provide interesting information regarding the application of FeNO in routine clinical practice and the utility of this device in identifying possible high-risk populations. The value in discussing such preliminary data is that it will inspire further research with large-scale, well-designed randomized clinical studies with more precise characterization of asthma to shed light on the optimal use of this tool in clinical practice.

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