REVIEW

Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates

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KEYWORDS
Exhaled nitric oxide; Asthma; Airway inflammation; Corticosteroid responsiveness; Asthma exacerbation rates

Summary
Until recently, no point-of-care tool was available for assessing the underlying airway inflammation associated with asthma. Fractional exhaled nitric oxide (FeNO) emerged in the last decade as an important biomarker for asthma assessment and management. Evidence also indicates that FeNO is most accurately classified as a marker of T-helper cell type 2 (Th2)-mediated airway inflammation with a high positive and negative predictive value for identifying corticosteroid-responsive airway inflammation.

This manuscript evaluates the evidence for FeNO as a predictor of Th2-mediated corticosteroid-responsive airway inflammation and presents the results of a meta-analysis of three adult studies comparing asthma exacerbation rates with FeNO-based versus clinically-based asthma management algorithms, one of which was not included in a 2012 Cochrane meta-analysis. The primary purpose of the updated meta-analysis was to evaluate asthma exacerbation rates. The results demonstrate that the rate of exacerbations was significantly reduced in favor of FeNO-based asthma management (mean treatment difference $\bar{Z} = 0.27; 95\% CI [0.42, 0.12]$ as was the relative rate of asthma exacerbations (relative rate $Z = 0.57; 95\% CI [0.41, 0.80]$).

In summary, FeNO has value for identifying patients with airway inflammation who will and will not respond to corticosteroids. Importantly, the use of FeNO in conjunction with clinical parameters is associated with significantly lower asthma exacerbation rates compared with asthma...
managed using clinical parameters alone. Together these data indicate that FeNO testing has an important role in the assessment and management of adult asthma. Further studies will continue to define the exact role of FeNO testing in adult asthma.

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Introduction

The prevalence of asthma in the United States (US) now exceeds 8%, and the proportion of asthmatics grew by 15% in the last decade.1 Not surprisingly, the economic burden of asthma is also substantial, estimated for 2007 at $56 billion in direct medical costs and loss of productivity.2 These facts underscore the need for more effective ways to both assess and manage asthma.

It is noteworthy that there have been important changes in both asthma treatments and asthma guidelines in the past decade. While the annual death rate for asthma in the US has declined over the past 15 years,3 the hoped-for impact of these asthma treatment and asthma guideline changes on asthma morbidity have not been realized. For example, the Asthma in America Survey, which was conducted in 1998, demonstrated that the need for acute care (hospitalization, emergency department visits or other acute care visits) was common and occurred in approximately 36% of survey respondents.4 When a similar survey, the Asthma Insight and Management Survey, was conducted in 2009, it was found that the need for acute care remained unchanged, occurring in approximately 34% of adult survey respondents.4

The reasons for the persistently high levels of asthma morbidity are multi-factorial and may include, among others, failure to implement published asthma guidelines, poor adherence to prescribed medications, differences between specialist versus primary care management, and regional differences in access to health care.4 However, it is also important to note that while routinely available tests for the evaluation of asthma such as the Asthma Control Test and spirometry provide some information about asthma control, they provide no information about underlying airway inflammation, the central pathophysiologic feature of asthma. This has a number of practical consequences including both over and under diagnosis of asthma.5,6 In addition, without an objective way to assess airway inflammation, decisions on which medications to prescribe to individual patients are often subjective.

Recently, point-of-care measurement of allergic airway inflammation via assessment of fractional exhaled nitric oxide (FeNO) has become available. While the measurement of FeNO bridges important gaps in asthma assessment and management, questions remain about its meaning as a marker of airway inflammation and its exact role in the assessment and management of asthma. The purpose of this paper, therefore, is 3-fold: (1) to evaluate the scientific and clinical evidence for FeNO as a marker of T-helper cells type 2 (Th2) inflammation; (2) to evaluate the positive and negative predictive value of FeNO for identifying corticosteroid-responsive airway inflammation; and (3) to present the results of an updated meta-analysis evaluating asthma exacerbation rates with FeNO-based versus clinically-based asthma management algorithms.

FeNO as a marker of Th2-mediated airway inflammation

Asthma is a heterogeneous, chronic disease characterized by two fundamental and interrelated abnormalities: airway inflammation and airway hyper-responsiveness. The airway inflammation and hyper-responsiveness associated with asthma can be triggered by exercise and numerous exogenous factors such as allergens, infections, cigarette smoke and other irritants. In allergic asthma, which is the
underlying cause of asthma for up to 80% of children and approximately 50% of adults,7–9 airway inflammation results from the activation of mast cells and antigen-specific Th2 cells, resulting in the production of cytokines, including interleukin (IL)-4, IL-5 and IL-13.10 In turn, IL-4 and IL-13 cause epithelial inducible nitric oxide synthase (iNOS) expression to be upregulated via signal transducer and activator of transcription (STAT)-6, a process which is corticosteroid sensitive.11 Thus, exhaled NO is a direct signal of the Th2-mediated, pro-inflammatory cytokine mechanisms of central importance in the pathophysiology of allergic airway inflammation.

The 2011 American Thoracic Society (ATS) guideline for the use of FeNO in clinical practice characterized FeNO as a marker of eosinophilic airway inflammation.12 However, recent clinical information suggests that FeNO production is more accurately defined as a marker of Th2-mediated inflammation, which often includes airway eosinophilia, rather than eosinophilic inflammation per se. The dissociation between FeNO and eosinophilic inflammation was highlighted by the results of recent studies with anti-IL-5 and anti-IL13. In the first study, systemic treatment with mepolizumab, an anti-IL-5 monoclonal antibody, was shown to significantly reduce blood and sputum eosinophil counts, but it had no effect on FeNO levels.13

In the second study, systemic treatment with lebrikizumab, an anti-IL-13 monoclonal antibody, had no effect on peripheral blood eosinophils but was associated with significant reductions in FeNO levels, especially among subjects with high baseline peribronchial eosinostisis.14 Additionally, treatment with anti-IL-13 was associated with significant improvements in FEV1 in the overall population and a 60% reduction in exacerbation rate compared with placebo (p = 0.03) among the subgroup of patients defined as the high-Th2 subgroup. Hence, while increases in airway eosinophil and increases in FeNO often occur concurrently, the cytokines that regulate induction of iNOS via STAT-6 are separate from those regulating eosinophil traffic through the airways in asthma, with the result that FeNO and eosinophilic inflammation may be dissociated.

Albeit airway inflammation is central to the pathophysiology of asthma, it is recognized that the type, extent and severity of inflammation is not uniform and varies among patients with asthma. Specifically, asthma patients differ with respect to clinical characteristics, underlying airway inflammation cell type, and response to inhaled corticosteroid (ICS) treatment.15 For example, the presence of Th2-mediated airway inflammation, eosinophilia, elevated FeNO levels, and responsiveness to ICS is common in both pediatric and adult asthma. However, some asthma patients have airway inflammation that is characterized by airway neutrophilia and lower FeNO levels. Such patients are often less responsive to ICS.16,17 Nonetheless, at least one study has reported that FeNO levels can help predict ICS response even among patients with neutrophilic asthma in whom airway eosinophilia is absent.18 Importantly, traditional parameters such as symptoms and lung function are not able to distinguish these patients, while biomarkers such as FeNO can help distinguish patients with corticosteroid-responsive asthma from those whose asthma is unlikely to be corticosteroid responsive.

Exhaled nitric oxide and the assessment of corticosteroid-responsive airway inflammation

FeNO has been shown to be useful as an adjunct to traditional methods for the assessment of patients with suspected but undiagnosed asthma. In this regard, FeNO levels have been shown to correlate well with sputum eosinophils,19–21 blood eosinophils,22 serum eosinophil cationic protein,22 and immunoglobulin E levels.23 However, FeNO, a marker of Th2-mediated airway inflammation, is particularly useful as an indicator of ICS-responsive airway inflammation and, perhaps more importantly, for identifying airway inflammation that will not respond to corticosteroids. These principles are reflected in the 2011 ATS guidelines, which recommended the use of normal ranges and clinical cut points when interpreting FeNO values. Specifically, the ATS guidelines suggest that a FeNO less than 25 ppb (<20 ppb in children) is a strong indicator that responsiveness to corticosteroids is unlikely, while a FeNO greater than 50 ppb (>35 ppb in children) is a strong indicator that responsiveness to corticosteroids is likely.12

While not directly related to the FeNO cut points that have been defined for patients with established asthma, FeNO levels in non-asthmatic children and adults have recently been evaluated using data from the National Health and Nutrition Examination survey (NHANES) 2007–2010 data set. From this data set, the 95th percentile for FeNO was determined to be 39 ppb (ages 12–80 years) and 36 ppb (ages <12 years), and FeNO levels above these values are indicative of airway inflammation.24 Importantly, the authors found that predictive equations did not adequately explain the variation observed in FeNO in the general population. This observation provides further support for the recommendation of the ATS that clinical cut points rather than predictive equations be used when interpreting FeNO values.

The robust evidence for the positive and negative predictive value (PPV, NPV) of FeNO for identifying corticosteroid-responsive Th2 airway inflammation was reviewed recently by Taylor,25 who summarized studies evaluating subjects with various airway diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD], chronic cough) and varying prior asthma medication histories (e.g., steroid-naive asthma, severe asthma on ICS). These studies (Table 1) demonstrate three key points: (1) FeNO has greater value for predicting ICS responsiveness than conventional measures such as peak flow rates, spirometry, and bronchodilator responsiveness4,26,27; (2) the PPV of FeNO for assessing asthma and identifying ICS non-responsiveness is very high across the asthma studies (91–95%) at cut points of FeNO that generally range from 20 to 30 ppb26–32; and (3) the PPV of FeNO for assessing asthma and identifying ICS responsiveness is also high across asthma studies (79–82%) when the FeNO cut point is 47 ppb or higher.25–29

The PPV and NPV of FeNO for ICS responsiveness is further supported by results of bronchial hyper-responsiveness (BHR) studies. BHR can be assessed using direct stimuli such as MCH or using indirect stimuli such as mannitol or adenosine monophosphate (AMP). AMP and mannitol cause release of inflammatory mediators from inflammatory cells and the respiratory epithelium that, in turn, cause
A diagnosis of non-atopic asthma (often ‘neutrophilic’) may still be made if the patient has relevant symptoms, abnormal spirometry, and steroid naïve. The performance characteristics of FeNO in this context were similar to those of induced sputum eosinophil counts, and better than that the PPV of FeNO for identifying a PC20 to MCH of 47 ppb had a PPV of 88% for identifying a PC20 to MCH of >46 ppb.35 Importantly, the authors indicated that in subjects with a FeNO cut point of 47 ppb than those without BHR to mannitol had substantially higher FeNO levels (47 ppb) than those without BHR to indirect stimuli such as AMP and mannitol. It can thus be anticipated that FeNO can be helpful in assessing asthma and ICS responsiveness. For example, Schleich et al. demonstrated a FeNO > 34 ppb had a PPV of 88% for identifying a PC20 to MCH of <16 mg/ml.34 Similarly, Schneider et al. found that the PPV of FeNO for identifying a PC20 to MCH of <16 mg/ml was 80% when the FeNO level was >46 ppb.35 Importantly, the authors indicated that in subjects with non-specific respiratory symptoms whose FeNO is <12 ppb, asthma can effectively be excluded and that bronchoprovocation tests are unnecessary.

Exhaled nitric oxide and asthma management

Because FeNO levels predict ICS responsiveness, and, more importantly, lack of ICS responsiveness, the ATS guidelines recommend using FeNO in monitoring airway inflammation in patients with established asthma.12 Nonetheless, when interpreting FeNO levels, factors that can confound FeNO levels need to be considered.12,36 These include acute viral airway infection and allergic rhinitis, both of which may elevate FeNO levels.11,12,36 Notably, chronic rhinosinusitis may be associated with elevated FeNO levels that may not be responsive to corticosteroid administration.36–38 Moreover, FeNO levels are reduced by smoking11 but may be increased by eating.12 Patients should thus refrain from eating and drinking for 1 h before FeNO testing as a nitrate-rich diet may increase FeNO levels. Additionally, FeNO should be measured before spirometry and bronchodilator administration as both may affect FeNO levels, though the effect is small.12,39

With these caveats in mind, the number of studies comparing FeNO-based asthma management algorithms with standard asthma management algorithms in adults and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected data indicating the performance characteristics for baseline measurements of exhaled nitric oxide FeNO as a predictor of different clinical outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication/clinical outcome of interest</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>Diagnosis of asthma in patients with chronic non-specific respiratory symptoms</td>
<td>88 (20 ppb)</td>
</tr>
<tr>
<td>Diagnosis of asthma in patients with chronic cough</td>
<td>75 (30 ppb)</td>
</tr>
<tr>
<td>Diagnosis of asthma in patients with chronic cough</td>
<td>88 (40 ppb)</td>
</tr>
<tr>
<td>Steroid responsiveness (non-specific respiratory symptoms)</td>
<td>86 (32 ppb)</td>
</tr>
<tr>
<td>Steroid responsiveness (non-specific respiratory symptoms)</td>
<td>82 (47 ppb)</td>
</tr>
<tr>
<td>Steroid responsiveness (cough)</td>
<td>NA</td>
</tr>
<tr>
<td>Steroid responsiveness (COPD)</td>
<td>29 (50 ppb)</td>
</tr>
<tr>
<td>Prediction of likely steroid response in patients with ‘difficult asthma’ already taking ICS</td>
<td>88 (30 ppb)</td>
</tr>
<tr>
<td>BOS in lung transplantation</td>
<td>94 (20 ppb)</td>
</tr>
</tbody>
</table>

In general, and similar to d-dimer and pro-BNP, FeNO is a better negative predictor when values are low/normal (<25 ppb in adults, <20 ppb in children) than it is a positive predictor when values are high. Thus it may be better used to exclude rather than include the outcome in question. The data quoted in the table are for the single optimum cut point (figures in parentheses) unless data for additional (low and high) cutpoints were available in the papers cited.

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* A diagnosis of non-atopic asthma (often ‘neutrophilic’) may still be made if the patient has relevant symptoms, abnormal spirometry and/or airway hyper-responsiveness but a low/normal FeNO.

** The performance characteristics of FeNO in this context were similar to those of induced sputum eosinophil counts, and better than spirometry and peak flow variability. See Smith et al. (2004).26

* Patients assessed at first presentation, and steroid naïve.

* The endpoint was reduction in AHR, i.e. an increase in PC20/AMP of >2 doubling doses.

* The endpoint was improvement in FEV₁ of >0.21.

* The endpoint was reduction in exacerbation rates. Respiratory Medicine (2013), http://dx.doi.org/10.1016/j.rmed.2013.02.018
children has been relatively limited. Petsky et al. published a meta-analysis of studies evaluating FeNO or FeNO and sputum eosinophils for the management of patients with asthma in 2012. Based on the meta-analysis results, the authors concluded that the use of FeNO in clinical practice cannot be recommended and that future studies are needed.

In evaluating the conclusions of these papers, it must be noted that the algorithm study by Powell et al., published in 2011, was not included in either publication. The Powell study was a randomized controlled trial of up to 6 months duration in which 220 pregnant women with asthma were randomly assigned to a FeNO-based management group (n = 111) or a clinical management group (n = 109). This study showed a significantly lower exacerbation rate in the FeNO group (0.288 exacerbations per pregnancy) compared with the group managed using clinical parameters alone (0.615 exacerbations per pregnancy; P = 0.001).

The primary outcome of both the Cochrane systematic review and the Petsky meta-analysis was the number of participants who had asthma exacerbations during follow-up. Fig. 1 shows the results for the number of exacerbations from the original Cochrane meta-analysis. Of note, the number of subjects with asthma exacerbations was numerically lower for subjects managed using FeNO compared with subjects managed using clinical parameters alone for all of the studies except for the Smith study.

In considering these data, it must be recognized that the number of patients having asthma exacerbations is not the most appropriate endpoint for assessing exacerbations, as it does not take into consideration subjects who may have multiple exacerbations during the course of a study. In this regard, the time to first asthma exacerbation and/or asthma exacerbation rates are considered by the NIH to be the most appropriate outcomes for assessing asthma exacerbations. For this reason, the data from FeNO studies conducted in adults (the Shaw and Smith studies from the original meta-analysis plus the Powell study) have been analyzed for the endpoint of asthma exacerbation rates. The analysis was conducted using the standard approach that was used in the Cochrane meta-analysis. This analysis demonstrates that the rate of exacerbations was substantially reduced in favor of the FeNO-based asthma management strategy (−0.27 [−0.42, −0.12]) (Fig. 2). Moreover, when the data is expressed as a relative rate, the rate of asthma exacerbations was more than 40% lower with the FeNO-based asthma management strategy compared with the control asthma management strategy (0.57 [0.41, 0.80]) (Fig. 3).

As with all treatments or treatment approaches used in patients with asthma (children and adults), it is important to consider the risk:benefit ratio. For a comparison of FeNO-guided asthma management with asthma managed using clinical parameters alone, the corticosteroid requirements for each management strategy must be assessed. ICS dose at the end of the study for the FeNO and control strategies was similar or lower for all of the algorithm studies except for the study by Szefler et al. The study by Szefler et al., however, did not permit non-compliant subjects to be randomized, and the subjects had high levels of asthma control at randomization. Additionally, FeNO levels could be used to increase ICS dose even when asthma was otherwise controlled, but the ICS dose could not be reduced when FeNO levels were low unless every other asthma parameter was also controlled. Thus it is not surprising that ICS doses were higher in the FeNO group. In other studies in children and adults where requirements for high medication compliance and control were not study entry requirements, ICS doses were either similar for the FeNO and control strategies or were lower in favor of the FeNO strategy.

Figure 1 Number of subjects who had ≥1 exacerbation over the study period in adult algorithm-based clinical trials using exhaled nitric oxide (FeNO) levels versus traditional methods for asthma management. Reprinted from Ref. 41. ©2012, with permission from the BMJ Publishing Group.
Finally, although published after the 2012 Petsky meta-analysis,41 one additional study in adults has recently been published. Specifically, Calhoun et al. conducted a study in which the following treatment approaches were compared: physician-based management, biomarker-based management using FeNO and symptom-based management (i.e., when a patient had symptoms, he/she received a dose of an ICS as well as a short-acting beta agonist).49 There was no difference in time to treatment failure among the three groups. However, this finding is potentially related to the very mild cohort included in this study. The patients evaluated had very well controlled asthma as evidenced by the fact that approximately 40% of subjects required no ICS at any given clinic visit. As such it is not surprising that a biomarker such as FeNO, which identifies inflammation that might be discordant from symptoms, was not of benefit.

In summary, studies comparing FeNO to usual clinical management of asthma generally indicate that exacerbation rates are reduced while ICS requirements are generally neutral. The preponderance of data thus indicates that the risk:benefit ratio is positive for FeNO and indicate that FeNO testing has an important role in the assessment and management of adult asthma. Further studies will continue to define the exact role of FeNO testing in adult asthma.

Additional uses for exhaled nitric oxide in the management of inflammatory airway diseases

A thorough review of the clinical applications of FeNO testing has recently been published.25 Nonetheless, three additional areas where FeNO testing is particularly relevant are the identification of “at risk” patients, assessing corticosteroid adherence/compliance, and the assessment of airway inflammation in patients with COPD or the overlap syndrome.

Identification of ‘at-risk’ patients

A number of recent studies have examined the role for FeNO in identifying patients at risk for future impairment, such as the development of an asthma exacerbation. Zeiger et al., in a cross-sectional study of 304 patients with established asthma, demonstrated that the likelihood of having $\geq 7$ short-acting beta-agonist canisters dispensed or

<table>
<thead>
<tr>
<th>Study</th>
<th>FeNO Strategy</th>
<th>Control Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. Patients</td>
<td>Exacerbation Rate</td>
<td>Total No. Patients</td>
</tr>
<tr>
<td>Shaw 2007</td>
<td>0.33</td>
<td>0.42</td>
</tr>
<tr>
<td>Smith 2005</td>
<td>0.49</td>
<td>0.9</td>
</tr>
<tr>
<td>Powell 2011</td>
<td>0.288</td>
<td>0.615</td>
</tr>
<tr>
<td>Combined</td>
<td>0.31</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Figure 2 Rate of asthma exacerbations (number of exacerbations per patient over the study period) in adult algorithm-based clinical trials using exhaled nitric oxide (FeNO) levels versus traditional methods for asthma management. Data from the study by Powell et al. have been added to data from adult studies included in the original Petsky et al. meta-analysis (i.e., Shaw et al. and Smith et al.). DerSimonian and Laird random effects model used for the meta-analysis. Test for heterogeneity: $Q = 2.2$ with $p = 0.33$ and $I^2 = 9.7\%$, indicating little if any evidence of heterogeneity.

Figure 3 Relative rate of asthma exacerbations (number of exacerbations per patient over the study period) in adult algorithm-based clinical trials using exhaled nitric oxide (FeNO) levels versus traditional methods for asthma management. Data from the study by Powell et al. have been added to data from adult studies included in the original Petsky et al. meta-analysis (i.e., Shaw et al. and Smith et al.). DerSimonian and Laird random effects model used for the meta-analysis. Test for heterogeneity: $Q = 1.6$ with $p = 0.46$ and $I^2 = 0\%$, indicating no evidence of heterogeneity.

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FeNO < ICS.52,53 It is important to note, however, that changes in asthma control following a reduction in, or cessation of, ICS use are generally useful in identifying patients who will develop a loss of corticosteroid responsiveness.7 Studies in both adults and children have shown that FeNO is a strong correlation between FeNO levels and compliance to budesonide. In another study conducted in 30 children treated with or without budesonide. This study also showed that FeNO, but not conventional lung function tests, were able to differentiate between children with asthma exacerbation.51 Among 53 patients followed for a period of 18 months, no subject with an FEV1 < 76% predicted and a FeNO > 28 ppb developed an asthma exacerbation, whereas 85% of subjects with an FEV1 ≤ 76% predicted and a FeNO ≥ 28 ppb developed an asthma exacerbation.51 Moreover, studies in both adults and children have shown that FeNO is useful in identifying patients who will develop a loss of asthma control following a reduction in, or cessation of, ICS.52,53 It is important to note, however, that changes in FeNO levels may not be as useful as changes in sputum eosinophils for predicting loss of asthma control following reduction/cessation of ICS use.54,55 Additional studies in this area are clearly needed. However, the available data generally suggests that FeNO is useful in identifying patients at risk for future impairment or for developing loss of asthma control during reduction/cessation of ICS treatment.

Assessment of corticosteroid treatment compliance

In addition to being an indicator of corticosteroid-responsive Th2 airway inflammation, FeNO is also useful for assessing adherence with corticosteroid therapy in patients with established asthma. This was first identified more than a decade ago by Beck-Ripp and colleagues, who evaluated FeNO levels in children in a placebo-controlled study following sequential changes in budesonide.56 The authors demonstrated that FeNO, but not conventional lung function tests, were able to differentiate between children treated with or without budesonide. This study also showed a strong correlation between FeNO levels and compliance to budesonide. In another study conducted in 30 children 7–17 years of age with persistent asthma, a significant correlation between FeNO levels and corticosteroid compliance was demonstrated (r = −0.76, p = 0.001).57 This type of information is critical to asthma treatment decision making in practice. It has been established that corticosteroid compliance rates are, on average, below 50% (range 20–73%).58 Thus, FeNO can help distinguish patients whose lack of asthma control is due to corticosteroid non-compliance and help avoid overuse of more costly and unnecessary asthma medications.

Table 2 Mean ICS dose in patients managed with a FeNO strategy compared with clinical management.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>FeNO strategy</th>
<th>Control strategy</th>
<th>Mean diff. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ICS dose</td>
<td>Mean ICS dose</td>
<td>FeNO strategy — control</td>
</tr>
<tr>
<td></td>
<td>Total no.</td>
<td>Total no.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>patients</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>557</td>
<td>895</td>
<td>−338.0 (−676.6, −0.4)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>51</td>
<td>13.8%</td>
</tr>
<tr>
<td>Smith</td>
<td>740</td>
<td>1282</td>
<td>−542.0 (−847.9, −236.1)</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>48</td>
<td>14.7%</td>
</tr>
<tr>
<td>Powell</td>
<td>738.9</td>
<td>631.6</td>
<td>107.30 (−69.2, 283.8)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>76</td>
<td>18.7%</td>
</tr>
<tr>
<td>Combined</td>
<td>170</td>
<td>175</td>
<td>−242.0 (−671.0, 186.8)</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>47.2%</td>
<td></td>
</tr>
<tr>
<td>Peds</td>
<td>474.67</td>
<td>444.37</td>
<td>30.3 (−166.7, 227.3)</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>71</td>
<td>18.1%</td>
</tr>
<tr>
<td>de Jong</td>
<td>935.4</td>
<td>910.4</td>
<td>25.0 (−259.2, 309.2)</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>46</td>
<td>15.4%</td>
</tr>
<tr>
<td>Pijnenburg</td>
<td>1120</td>
<td>880</td>
<td>240.0 (86.9, 393.1)</td>
</tr>
<tr>
<td></td>
<td>276</td>
<td>270</td>
<td>19.3%</td>
</tr>
<tr>
<td>Szeffler</td>
<td>390</td>
<td>387</td>
<td>121.9 (−32.2, 276.0)</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>52.8%</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>560</td>
<td>562</td>
<td>−50.7 (−259.4, 158.0)</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

>2 courses of oral corticosteroids for asthma exacerbations in the follow-up year was 2.26 and 3.26 times more frequent, respectively, for subjects whose FeNO values were >300% predicted.59 Similarly, Gelb et al. showed that the combined use of FeNO and FEV1 was useful for identifying patients at risk for future development of an asthma exacerbation.51 Among 53 patients followed for a period of 18 months, no subject with an FEV1 > 76% predicted and a FeNO < 28 ppb had an asthma exacerbation, whereas 85% of subjects with an FEV1 ≤ 76% predicted and a FeNO ≥ 28 ppb developed an asthma exacerbation.51 Moreover, studies in both adults and children have shown that FeNO is useful in identifying patients who will develop a loss of asthma control following a reduction in, or cessation of, ICS.52,53 It is important to note, however, that changes in FeNO levels may not be as useful as changes in sputum eosinophils for predicting loss of asthma control following reduction/cessation of ICS use. Additional studies in this area are clearly needed. However, the available data generally suggests that FeNO is useful in identifying patients at risk for future impairment or for developing loss of asthma control during reduction/cessation of ICS treatment.

Assessment of airway inflammation in patients with COPD or the overlap syndrome

Asthma can coexist with COPD, particularly in older adults, a condition labeled the overlap syndrome. In data from NHANES (1988–1994) and the UK General Practice Research Database (1998), Soriano et al. determined that a concomitant diagnosis of asthma and COPD may be found in as many as 50% of patients aged ≥50 years,59 although other studies have estimated the incidence to be in the range of 20–30%.60,61 It is considered likely that some asthmatics develop COPD in addition to asthma as they age due to the cumulative harmful effects of cigarette smoking.62 In contrast to patients with the overlap syndrome, patients who have chronic bronchitis and/or emphysema, which is almost always caused by smoking, are characterized by airflow obstruction that is often irreversible and airway inflammation that is often not Th2-mediated.51

It is important to note that no ICS is currently approved for use as a monotherapy for COPD in the US. Moreover, while several ICS/long-acting beta agonist combination products have been approved for use in COPD, the incidence of ICS-related morbidity such as osteoporosis and pneumonia are increased in COPD patients treated with ICS-containing products.63–65 It is in this context that FeNO may help identify patients with allergic airway inflammation who will have a beneficial response to treatment with an ICS and those who will not.66–69 Along these lines, Antus et al. demonstrated a significant correlation between FeNO levels and improvements in FEV1 in patients with COPD exacerbations following treatment with systemic
corticosteroids and bronchodilators. Similarly, Kunisaki et al. found a significant difference in FeNO levels among COPD patients who did versus did not respond to a 4-week trial of ICS with a $\geq 200$ ml increase in FEV$_1$ (46.5 ppb versus 25 ppb). While additional studies are needed, FeNO has potential as a tool to help identify those patients with COPD or the overlap syndrome for whom the risk:benefit ratio for treatment with an ICS-containing product will be positive.

**Conclusion**

In summary, asthma is a costly and burdensome disease, and there is need for effective ways to both identify those who will benefit from corticosteroid treatment and those who will not. Until recently, there has been no point-of-care tool for use in assessing the underlying airway inflammation associated with asthma. However FeNO testing has emerged as a non-invasive, inexpensive, reliable indicator of corticosteroid-responsive Th2-mediated inflammation for use in the assessment and management of asthma.

Does FeNO assist clinicians in treatment decision making such as initiating or increasing ICS therapy, and can these decisions have a beneficial impact on asthma outcomes? Taking into account the accumulated evidence, including the data from new analyses in this paper, the answer to both questions is "yes."

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**Conflict of interest**

Dr. Donohue is a principal investigator on an Aerocrine research grant to the University of North Carolina and a consultant for Aerocrine. Dr. Donohue is also a consultant for GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and Novartis and on the Speakers Bureau for Boehringer Ingelheim. Dr. Jain is a member of the Speaker’s Bureau for GlaxoSmithKline, Novartis, and Abbott Laboratories and a consultant for Aerocrine.

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Utility of exhaled nitric oxide in adult asthma


