An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels ($F_{ENO}$) for Clinical Applications

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Background: Measurement of fractional nitric oxide (NO) concentration in exhaled breath ($F_{ENO}$) is a quantitative, noninvasive, simple, and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. While $F_{ENO}$ measurement has been standardized, there is currently no reference guideline for practicing health care providers to guide them in the appropriate use and interpretation of $F_{ENO}$ in clinical practice.

Purpose: To develop evidence-based guidelines for the interpretation of $F_{ENO}$ measurements that incorporate evidence that has accumulated over the past decade.

Methods: We created a multidisciplinary committee with expertise in the clinical care, clinical science, or basic science of airway disease and/or NO. The committee identified important clinical questions, synthesized the evidence, and formulated recommendations. Recommendations were developed using pragmatic systematic reviews of the literature and the GRADE approach.

Results: The evidence related to the use of $F_{ENO}$ measurements is reviewed and clinical practice recommendations are provided.

Conclusions: In the setting of chronic inflammatory airway disease including asthma, conventional tests such as FEV1 reversibility or provocation tests are only indirectly associated with airway inflammation. $F_{ENO}$ offers added advantages for patient care including, but not limited to (1) detecting of eosinophilic airway inflammation, (2) determining the likelihood of corticosteroid responsiveness, (3) monitoring of airway inflammation to determine the potential need for corticosteroid, and (4) unmasking of otherwise unsuspected non-adherence to corticosteroid therapy.

Keywords: nitric oxide; asthma; inflammation; airway disease; exhaled breath; clinical application

EXECUTIVE SUMMARY

Nitric oxide (NO) is now recognized as a biological mediator in animals and humans. NO is produced by the human lung and is present in the exhaled breath. It has been implicated in the pathophysiology of lung diseases, including asthma. The measurement of exhaled NO has been standardized for clinical use. Numerous studies have provided evidence regarding the applications of NO measurements in clinical practice, together with the performance characteristics and the strengths and weaknesses of the test. Based on this evidence, this Clinical Practice Guideline is designed to guide clinicians as to how exhaled NO measurements should be used and interpreted.

EVIDENCE QUALITY AND RECOMMENDATIONS

These recommendations may vary with respect to the particular target population. Where this is the case, this has been included
in the recommendation. If not stated, then the recommendation applies to patients with asthma.

- We recommend the use of $\text{FENO}$ in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of $\text{FENO}$ in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that $\text{FENO}$ may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).
- We suggest the use of cut points rather than reference values when interpreting $\text{FENO}$ levels (weak recommendation, low quality of evidence).
- We recommend accounting for age as a factor affecting $\text{FENO}$ in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend that low $\text{FENO}$ less than 25 ppb ($< 20$ ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that $\text{FENO}$ greater than 50 ppb ($> 35$ ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of $\text{FENO}$ (strong recommendation, moderate quality of evidence).
- We recommend the use of $\text{FENO}$ in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).
- We suggest using the following values to determine a significant increase in $\text{FENO}$: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next (weak recommendation, low quality of evidence).
- We suggest using a reduction of at least 20% in $\text{FENO}$ for values over 50 ppb or more than 10 ppb for values lower than 50 ppb as the cut point to indicate a significant response to antiinflammatory therapy (weak recommendation, low quality of evidence).

Conclusion: Advances in technology and standardization have made $\text{FENO}$ measurement simple, permitting its use as a biomarker that adds a new dimension to the traditional clinical tools in the assessment and management of airways diseases. These guidelines for interpretation of $\text{FENO}$ measurements are meant to enhance their clinical utility, but more work is still needed to better define the use of $\text{FENO}$ in different clinical settings.

INTRODUCTION

NO has long been known as an atmospheric pollutant present in vehicle exhaust emissions and cigarette smoke, and more recently its clinical importance as a biological mediator in animals and humans has been recognized (1, 2). NO is present in virtually all mammalian organ systems and is produced by the human lung. It is present in the exhaled breath of all humans (3). NO is recognized to play key roles in virtually all aspects of lung biology and has been implicated in the pathophysiology of lung diseases, including asthma (4). The functions and effects of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator (3). Patients with asthma have high levels of NO in their exhaled breath and high levels of inducible nitric oxide synthase (NOS2) enzyme expression in the epithelial cells of their airways, suggesting a role for NO in asthma pathogenesis (5). NO is a highly reactive molecule/free radical and may have oxidant properties directly or in the form of the more noxious peroxynitrite. These properties give NO its bactericidal and cytotoxic effects and may participate in host defense by mediating antimicrobial activity and cytotoxicity for tumor cells (4). The exact pathophysiological role of NO in the airways and lungs is complex (4, 6–8). On the one hand, it may act as a proinflammatory mediator predisposing to the development of airway hyperresponsiveness (AHR) (4, 9). On the other, under physiological conditions NO acts as a weak mediator of smooth muscle relaxation, and protects against AHR (4, 10). In exhaled air, NO appears to originate in the airway epithelium (5, 11–15), as a result of NOS2 up-regulation which occurs with inflammation (5, 12, 13, 16). Thus, exhaled NO may be regarded as an indirect marker for up-regulation of airway inflammation.

The field of exhaled NO measurement has developed remarkably over the last 15 years. The use of chemiluminescence analyzers allowed for the detection of NO in exhaled breath in the early 1990s (17). Patients with asthma were found to have high $\text{FENO}$ in their exhaled breath (18–20) that decreased in response to treatment with corticosteroids (21). This quickly prompted the evaluation of $\text{FENO}$ as a potential noninvasive method to diagnose asthma and monitor the response to antiinflammatory therapy.

Advantages for $\text{FENO}$ include the noninvasive nature of the test, ease of repeat measurements, and the relatively easy use in patients with severe airflow obstruction where other techniques are difficult to perform (22). By providing information about airway inflammation (23, 24), $\text{FENO}$ adds a new dimension to the traditional clinical tools (history, physical exam, and lung function tests).

Before $\text{FENO}$ could become useful as a clinical tool, several issues needed to be addressed (25). In particular, the methods and equipment for measuring $\text{FENO}$ needed to be standardized (26, 27). Large population studies were needed to determine effect of confounding factors and provide the normal range or useful cutoff points of $\text{FENO}$ levels (22, 25). Most of these issues have either already been addressed or are currently under investigation, allowing $\text{FENO}$ measurement to make the transition from research into the clinical arena. Last, but not least, interpretative strategies need to be devised and put in place for the different potential uses and applications (28). The purpose of this document is to address this last requirement.

Wherever possible, the recommendations are based on published material, including abstracts, as referenced, but they are supplemented by nonsystematic observations of experts in the field. The guidelines are provided with the clear understanding that this will be a rapidly evolving area and that periodic updating will be required.

METHODS

Committee Composition, Meetings, and Document Preparation

The project Chair (R.A.D.) assembled a group of international experts in exhaled nitric oxide. Their expertise was in clinical
care, clinical research, or basic science in the area of asthma and/or nitric oxide (five pulmonologists [R.A.D., S.C.E., A.C.O., A.L.P., D.R.T.], an allergist [P.B.B.], two physiologists [C.G.I., J.O.L.], and one pediatric pulmonologist [M.W.L.]). The outline of the Report was proposed by the Chair and modified and agreed upon following input from all Committee members. The Committee was divided into subgroups, each was assigned a specific section, and preliminary drafts were developed. Three face-to-face meetings and nine teleconferences were held. The outline and the drafts were reviewed, and evidence-based recommendations were discussed and finalized by consensus. Committee members disclosed all potential conflicts of interest. All disclosed conflicts of interests were reported to the Chair of the Ethics and Conflict of Interest Committee of the ATS. These were reviewed in detail, and members with perceived conflicts abstained from the discussion of specific questions related to their conflicts of interest. Furthermore, members were reminded to consider their own and other members’ potential conflicts of interest during the meetings. The Chair (R.A.D.) integrated the draft sections and composed the entire document into a preliminary document that was circulated among the committee members for further input. The revised document incorporated the comments and input from all Committee members.

Document Structure
This document is structured to provide an evidence-based review of the current state of knowledge regarding the application and interpretation of FENO measurements in clinical practice. The recommendations regarding interpretive strategy were organized around specific questions according to the GRADE approach to assessing the quality of the evidence (Summary Table E1 in Appendix in online supplement) (29, 30). Relevant section topics and questions were identified by the Committee. Committee members were asked to review the current evidence by independently completing a pragmatic systematic review of the literature using PubMed and OVID. Each Committee member was asked to assess the identified literature relevant to his/her section, and decide about inclusion of individual articles. MEDLINE searches from 1993 to December 2008 were performed by Committee members, with periodic updates during document development and finalization. Searching the literature before 1993 was not done systematically since the discovery of nitric oxide in asthma was first reported in 1993. The search was augmented by searches of Committee member files. The literature search was limited to all relevant studies including randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies published in the English language. Sections that did not yield specific recommendations were written after a thorough review of the available literature in a narrative review format.

Quality of Evidence and Strength of Recommendations
The quality of evidence was determined according to the ATS GRADE criteria (30). For each question, the Committee graded the quality of the evidence available (high, moderate, low, or very low), and made a recommendation for or against. Recommendations were decided by consensus. Recommendations were either “strong” or “weak.” The strength of a recommendation reflects the extent to which one can, across the range of patients for whom the recommendation is intended, be confident that desirable effects outweigh undesirable effects (30). Consensus on the recommendations was reached among all the members of the Committee. The strength of a recommendation has important implications for patients, clinicians, and policy makers (30).

Strong recommendation.
- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action
- Policy makers: The recommendation can be adopted as a policy in most situations

Weak recommendation.
- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with the patient’s own values
- Policy makers: There is a need for substantial debate and involvement of stakeholders

Why Should a FENO Test Be Obtained?
Common reasons for measuring FENO.
- To assist in assessing the etiology of respiratory symptoms
- To help identify the eosinophilic asthma phenotype
- To assess potential response or failure to respond to antiinflammatory agents, notably inhaled corticosteroids (ICS)
- To establish a baseline FENO during clinical stability for subsequent monitoring of chronic persistent asthma
- To guide changes in doses of antiinflammatory medications: step-down dosing, step-up dosing, or discontinuation of antiinflammatory medications
- To assist in the evaluation of adherence to antiinflammatory medications
- To assess whether airway inflammation is contributing to poor asthma control particularly in the presence of other contributors (e.g., rhinosinusitis, anxiety, gastro-esophageal reflux, obesity, or continued allergen exposure).

Can FENO Be Used to Diagnose Asthma?
Asthma is a clinical diagnosis and there is no single diagnostic test for the disease. The background pathology of asthma is often but not always due to eosinophilic airway inflammation. The two are not synonymous. This is extremely important in the interpretation of FENO measurements. It is often claimed that FENO is a diagnostic test for asthma, but in cases of asthma not due to airway eosinophilia, FENO may be low. Similarly, the value of exhaled FENO as a predictor of steroid responsiveness is high even in the absence of induced sputum eosinophils (31).

Recommendations:
- We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that FENO may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).

FENO is associated with eosinophilic airway inflammation. There are several inflammatory phenotypes in asthma most commonly described as eosinophilic, neutrophilic, mixed, and paucigranulocytic (32). Determination of the subtype may help a physician...
decide which therapies to select or stop (33–35). Given the long-established relationship between eosinophilic inflammation and steroid responsiveness in airways disease, the finding that FeNO correlates with eosinophilic inflammation suggests its use as an indirect indicator not only of eosinophilic inflammation, but more importantly of the potential for steroid responsiveness (36–42).

There is little evidence directly demonstrating that eosinophilic airway inflammation increases FeNO by increasing NOS2 expression or activity (43). However, eosinophilic airway inflammation may affect FeNO indirectly through NOS2 or via NOS2 expression or activity (43). Thus NO production is to some extent independent of eosinophilic airway inflammation. Eosinophils can be measured in sputum, bronchoalveolar lavage, and biopsies. There are also reports of correlation between FeNO and blood eosinophils (44–46). Warke and coworkers reported that in bronchoalveolar lavage fluid the correlation between eosinophils and FeNO was 0.78 (P < 0.001) (40). Payne and colleagues reported that the correlation between FeNO and eosinophils in bronchial biopsies was 0.54 (P = 0.03) (47), but in contrast Lim and coworkers were unable to find a significant correlation in the biopsies (48). In induced sputum, the correlation between FeNO levels and eosinophils ranges from 0.35 (n = 25, P = 0.09) (36) to 0.48 (n = 35, P = 0.003) (49) to 0.62 (n = 78, P < 0.001) (50). In the largest study to date (n = 566), the correlation was of a similar order (0.59, P < 0.001) (39). In this last study, FeNO of 36 ppb (at a flow rate of 50 ml/s) had a sensitivity and specificity for sputum eosinophilia of more than 3% (the cut point deemed by the authors to be clinically significant) of 78% and 72%, respectively. In the study by Shaw and colleagues, a FeNO of less than 26 ppb had a negative predictive value of 85% for sputum eosinophilia less than 3% (51). Similarly, Porsbjerg and coworkers have reported that with FeNO less than 27 ppb, it is unlikely that sputum eosinophils will be greater than 1% (52). Thus a low FeNO is of value in determining the absence of eosinophilic, and, by inference, the likely absence of steroid-responsive airway inflammation.

These limited correlations reflect the fact that whereas sputum eosinophilia is always abnormal, exhaled nitric oxide is present even in health with its distribution skewed to the right. It is also necessary to bear in mind that negative and positive predictive values are limited in their generalizability, given that they depend on the prevalence of the condition in the tested population. Importantly, two studies have shown that the relationship between FeNO levels and airway eosinophilia is independent of the diagnosis of asthma as reported in patients with chronic obstructive pulmonary disease (COPD) (53), and with eosinophilic bronchitis (54). Furthermore, NO and NO metabolites in the airway (e.g., peroxynitrite) alter the REDOX balance in the airways, may cause inflammation, and are in some part steroid sensitive. Thus NO production is to some extent independent of eosinophilic inflammation (4).

FeNO predicts likelihood of corticosteroid responsiveness. Treatment response in asthma is heterogeneous (55). Not all patients respond to corticosteroids and an important reason to use FeNO is to help decide who might benefit from steroid treatment, and who should try other medications (e.g., leukotriene modifiers). FeNO may also be used to determine patients in whom steroid therapy may be safely withdrawn. FeNO has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or AHR to methacholine (56–58). The optimum cut point in the study by Smith and coworkers (56), was 47 ppb, with a negative predictive value of 89% for the change in FEV1 with inhaled steroids. The predictive values were similar for alternative endpoints. Even when patients do not demonstrate sputum eosinophilia, FeNO is highly predictive of steroid response (at a cut point of 33 ppb) (31). These data are consistent with studies in which high FeNO (> 47 ppb) predicts the likelihood of loss of control when inhaled steroids are reduced or withdrawn in children with a confirmed diagnosis of asthma (59). Conversely, low FeNO (< 22 ppb) predicts the likelihood of successful reduction or withdrawal of inhaled steroids (positive predictive value, 92%) (60). Again, these outcomes may differ somewhat depending on the target population: for the most part these data are derived from patients with mild to moderate asthma. In summary, depending on the prevalence of eosinophilic airway inflammation in the target population, FeNO measurements may provide a signal that is helpful in identifying patients with asthma-like symptoms who are likely to benefit (or not) from corticosteroid treatment.

FeNO can support a diagnosis of asthma. The diagnosis of asthma is well defined, and the background pathology is often but not always due to eosinophilic airway inflammation. Early studies in populations comprising mainly patients with eosinophilic asthma explored the performance characteristics of FeNO as a diagnostic test. The predictive values for FeNO (usually at cut points of > 25 ppb) were shown to be sufficiently robust for it to be used in this context (23, 61, 62). Further, the predictive values for FeNO are higher than for conventional measurements such as peak flows and spirometry (23), and similar to those associated with bronchial challenge tests (62). However, in general, in patients presenting with variable cough, wheeze, and shortness of breath, an increased FeNO provides supportive rather than conclusive evidence for an asthma diagnosis. As stated, the limitations to the diagnostic role of FeNO arise principally because airway inflammation in asthma is heterogeneous and is not always associated with increased FeNO (e.g., neutrophilic airway inflammation). Similarly, in patients who have already been treated with inhaled steroids, the test may be falsely negative. Thus, the importance of FeNO lies in its potential to identify steroid responsiveness, rather than the exact clinical diagnosis. This information is much more clinically relevant because it enables the clinician to bypass an empirical “trial of steroids” or unnecessary long-term corticosteroid treatment.

FeNO may predict AHR. Irrespective of the specific underlying inflammatory signal which FeNO represents, measurements appear to reflect the dynamic interrelationships between the response to allergen or other triggers and evolving eosinophilic airway inflammation/AHR (4, 7, 8, 63). Serial FeNO levels increase progressively in response to allergen exposure and the advent of airway symptoms (63). Because of the practical difficulties involved in measuring AHR, especially in children, it was initially thought that FeNO might be used as a surrogate marker for AHR. The relationship between NO metabolism and AHR in asthma is complex (64). When FeNO was used to predict the presence of AHR, the studies reveal inconsistent relationships and correlations are generally low. The clinical interpretation of FeNO in relation to AHR is even more problematic in subjects who are taking ICS (9, 65) and with long-standing as opposed to recently developed asthma (66). This is demonstrated in studies designed to evaluate pathophysiological relationships in clinical asthma using factor analysis: AHR, airway inflammation, and FeNO belong to different domains (66–68). However, in one study FeNO has been used as a surrogate for AHR testing to support the diagnosis of asthma in children, and the data appear to support its use in this limited context (62).

Is There a Normal FeNO Value? This section will discuss the normal ranges of FeNO. We will also discuss the important clinical cut points and the rationale for selecting these cut points to be used in the interpretation of an
Normal Values versus Relevant Cut Points for FENO

This section will discuss the normal ranges of FENO and what are the important clinical cut points to be used in the interpretation of an elevated or reduced FENO value. It is important to choose the appropriate cut point in relation to the clinical setting and question. While this section and the accompanying tables (see Tables 3–5) focus on asthma and airway diseases/inflammation, other causes of high and low FENO levels are listed in the Appendix in the online supplement.

We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age (strong recommendation, high quality of evidence).

Confounding factors that may affect FENO

As discussed in the Appendix in the online supplement, FENO values can be affected by several factors, including measurement technique, exhalation flow rate, nasal NO contamination, the NO analyzer used (74), age, height, smoking, and antiinflammatory medications. A number of recent publications have reported reference values for FENO in adults (69, 75–79) (Table 1) and children (76, 80–83). There are important differences between these studies with regard to the size of the examined population, as well as the range of statistical variables that have been included or excluded, limiting their value (76, 77, 80–83). Factors affecting population FENO levels may be due to one or more variables including genetics, age, sex, atopy, weight and height, current smoking, and diet. The importance of current smoking and atopic status is generally agreed upon (28), but there are inconsistencies between the studies regarding which other factors ought to be accounted for when deriving and applying reference values (Table 1). More detailed information on these biological sources of variability is provided in the Appendix in the online supplement.

Thus, in our present state of knowledge the problems of multiple confounding factors and overlap between normal populations and populations with asthma preclude the routine application of reference values in the clinical setting. The Committee felt that it is more relevant to identify clinically meaningful cut points rather than reference values to interpret FENO levels as outlined below, keeping in mind that very few of these cut points are well validated. At any one time, however, the most important consideration is whether or not the patient has current respiratory symptoms or a prior diagnosis of airways disease; that is, the...
interpretation of FeNO levels should be determined in individual patients with reference to the context in which the measurement is being obtained.

What Are the Clinically Significant Cut Points for FeNO?

It is important to choose the appropriate cut point in relation to the clinical setting and question. In this section, we discuss the rationale for selecting these cut points (see Tables 3–5). While this section and the accompanying tables focus on asthma and airway diseases/inflammation, other causes of high and low FeNO levels are listed in the Appendix in the online supplement.

Recommendations:

We recommend that low FeNO (< 25 ppb [< 20 ppb in children]) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).

We recommend that FeNO > 50 ppb (> 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).

We recommend that FeNO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously with reference to the clinical context (strong recommendation, low quality of evidence).

Low FeNO (< 25 ppb in adults; 20 ppb in children). In a symptomatic adult patient with a FeNO of less than 25 ppb (20 ppb in children), eosinophilic airway inflammation is unlikely. This cut point is based on evidence from a number of sources including the study by Shaw and colleagues (51) and Porsbjerg and coworkers (52), studies investigating the role of FeNO measurements to diagnose asthma (23, 70–72), and studies designed to optimize ICS use (56, 60). The differential diagnosis for symptomatic patients with a low FeNO is given in Table 3. In patients presenting with nonspecific respiratory symptoms, low FeNO levels are associated with a high likelihood of response to inhaled or oral steroid therapy.

High FeNO (> 50 ppb in adults, 35 ppb in children). High FeNO is likely to indicate significant airway eosinophilia. It is also likely to indicate that a symptomatic patient has steroid-responsive airways inflammation (56, 57, 85, 86). The clinically significant cut point of 50 ppb is based on the results of pragmatic studies. However, this is a general guide and may vary slightly in individual patients. Symptomatic steroid-naïve patients with high FeNO are more likely to exhibit responsiveness to inhaled steroid therapy, irrespective of the diagnostic label (e.g., asthma or nonasthma), with an optimum cut point of 47 ppb (56). In asymptomatic patients with stable asthma, the likelihood of relapse following withdrawal of ICS therapy is greatest in patients whose FeNO increases to above 49 ppb during the 4 weeks after

### TABLE 1. STUDIES OF ONLINE FRACTION OF EXHALED NITRIC OXIDE VALUES AT EXHALATION FLOW RATE OF 50 ml/s IN HEALTHY SUBJECTS

<table>
<thead>
<tr>
<th>Author and Reference</th>
<th>N</th>
<th>Groups for which Reference Values Are Given</th>
<th>“Normal Values” (ppb)</th>
<th>Analyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairtonov 2003 (75)</td>
<td>59</td>
<td>Mixed population of adults and children aged 4–71 yr</td>
<td>Mean 16.3 ppb, ULN 33.</td>
<td>NIOX (Aerocrine AB, Stockholm, Sweden)</td>
</tr>
<tr>
<td>Buchvald 2005 (76)</td>
<td>405</td>
<td>Data also available by age stratification</td>
<td>Mean 9.7 ppb, Upper 95% CI: 25.2</td>
<td>NIOX (Aerocrine AB, Stockholm, Sweden)</td>
</tr>
<tr>
<td>Olivieri 2006 (77)</td>
<td>204</td>
<td>Male, nonsmoker, nonasthmatic</td>
<td>4.5–20.6</td>
<td>(CLD88, Ecomedics, Switzerland)</td>
</tr>
<tr>
<td>Olin 2007 (69)</td>
<td>3,376</td>
<td>Random population</td>
<td>(note: values quoted are 90% confidence interval)</td>
<td>See Table 2 NIOX (Aerocrine AB, Stockholm, Sweden)</td>
</tr>
<tr>
<td>Travers 2007 (78)</td>
<td>3,500</td>
<td>Male, nonsmoker, nonasthmatic</td>
<td>9.5–47.4</td>
<td>NIOX (Aerocrine AB, Stockholm, Sweden)</td>
</tr>
<tr>
<td>Buchvald 2005 (76)</td>
<td>405</td>
<td>Male, smoker, nonasthmatic</td>
<td>7.5–38.4</td>
<td></td>
</tr>
<tr>
<td>Olin 2007 (69)</td>
<td>3,376</td>
<td>Female, nonsmoker, nonasthmatic</td>
<td>8.8–44.6</td>
<td></td>
</tr>
<tr>
<td>Travers 2007 (78)</td>
<td>3,500</td>
<td>Female, smoker, nonasthmatic</td>
<td>5.9–30.5</td>
<td></td>
</tr>
<tr>
<td>Buchvald 2005 (76)</td>
<td>405</td>
<td>Female, smoker, atopic</td>
<td>6.9–36.4</td>
<td></td>
</tr>
<tr>
<td>Olivieri 2006 (77)</td>
<td>204</td>
<td>Male, nonsmoker, atopic</td>
<td>19.5</td>
<td>(NOA 280, Sievers, Boulder, CO)</td>
</tr>
<tr>
<td>Olin 2007 (69)</td>
<td>3,376</td>
<td>Male, nonsmoker, atopic</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>Travers 2007 (78)</td>
<td>3,500</td>
<td>Male, smoker, atopic</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Buchvald 2005 (76)</td>
<td>405</td>
<td>Male, smoker, atopic, 165 cm</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Olin 2007 (69)</td>
<td>3,376</td>
<td>Female, nonsmoker, atopic</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Travers 2007 (78)</td>
<td>3,500</td>
<td>Female, smoker, nonasthmatic</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>Buchvald 2005 (76)</td>
<td>405</td>
<td>Female, smoker, nonasthmatic, 160 cm</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Olin 2007 (69)</td>
<td>3,376</td>
<td>Female, smoker, atopic, 160 cm</td>
<td>14.7</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2. FRACTION OF EXHALED NITRIC OXIDE 95% UPPER LIMITS, STRATIFIED FOR SEX AND ATOPY, ACCORDING TO HEIGHT AND AGE AMONG 1,131 HEALTHY LIFELONG NEVER-SMOKING SUBJECTS

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Age 25–49 yr</th>
<th>Age 50–75 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>150–159</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>160–169</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>170–179</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>180–189</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>190–199</td>
<td>—</td>
<td>42</td>
</tr>
<tr>
<td>150–159</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>160–169</td>
<td>36</td>
<td>63</td>
</tr>
<tr>
<td>170–179</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>180–189</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>190–199</td>
<td>—</td>
<td>50</td>
</tr>
</tbody>
</table>

Data taken from Reference 69.
TABLE 3. LOW FENO (< 25 ppb [< 20 ppb IN CHILDREN]): IMPLIES NONEOSINOPHILIC OR NO AIRWAY INFLAMMATION*

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a symptomatic patient (chronic cough and/or wheeze and/or shortness of breath for &gt; 6 wk) presenting for the first time, the patient is unlikely to benefit from a trial of inhaled corticosteroid treatment, possible etiologies:</td>
</tr>
<tr>
<td>Other pulmonary/airway causes:</td>
</tr>
<tr>
<td>- Rhinosinusitis</td>
</tr>
<tr>
<td>- Noneosinophilic asthma</td>
</tr>
<tr>
<td>- Reactive airways dysfunction syndrome</td>
</tr>
<tr>
<td>- COPD</td>
</tr>
<tr>
<td>- Bronchiectasis</td>
</tr>
<tr>
<td>- Cystic fibrosis, primary ciliary dyskinesia</td>
</tr>
<tr>
<td>- Extended post-viral bronchial hyperresponsiveness syndrome</td>
</tr>
<tr>
<td>- Vocal cord dysfunction</td>
</tr>
<tr>
<td>Nonpulmonary/airway causes:</td>
</tr>
<tr>
<td>- Anxiety-hyperventilation</td>
</tr>
<tr>
<td>- Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>- Cardiac disease/pulmonary hypertension/pulmonary embolism</td>
</tr>
<tr>
<td>Confounding factors:</td>
</tr>
<tr>
<td>- Smoking</td>
</tr>
<tr>
<td>- Obesity</td>
</tr>
</tbody>
</table>

Monitoring

In a symptomatic patient with an established diagnosis of asthma, possible etiologies:

Asthma:
- Noneosinophilic asthma (probably steroid unresponsive)

Additional or alternative diagnosis?
- Vocal cord dysfunction
- Anxiety-hyperventilation
- Bronchiectasis,
- Cardiac disease,
- Rhinosinusitis,
- Gastroesophageal reflux disease

In an asymptomatic patient with an established diagnosis of asthma: Implies adequate dosing and good adherence to antiinflammatory therapy.

Inhaled corticosteroid dose may possibly be reduced (repeat FENO 4 wk later to confirm this judgment; if it remains low then relapse is unlikely).

**Definition of abbreviation:** COPD = chronic obstructive pulmonary disease; FENO = fraction of exhaled nitric oxide.

*The interpretation of FENO is an adjunct measure to history, physical exam, and lung function assessment.

For intermediate FENO levels (in the range 25–50 ppb [20–35 ppb in children]), refer to Table 5.

steroid withdrawal (59). The differential diagnosis for high FENO is shown in Table 4.

Intermediate FENO (between 25 ppb and 50 ppb in adults; 20–35 ppb in children). The above data indicate that for FENO values between 25 and 50 ppb, cautious interpretation is required. The weight placed on an FENO result within this range will depend on whether the test is being used diagnostically in a symptomatic steroid-naive subject, or whether the patient’s FENO has increased or decreased from a previous value by what is deemed to be a clinically significant amount in a patient who is being monitored over time.

**Recommendation**

We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO (strong recommendation, moderate quality of evidence).

**Persistently high FENO (> 50 ppb in adults, 35 ppb in children).** In a patient with ongoing asthma, symptoms may occur despite apparently adequate antiinflammatory treatment (87). In the collective experience of the Committee, a common cause of persistently high FENO is poor adherence to ICS therapy. Other explanations could be poor inhaled drug delivery or continued exposure to allergen (7, 8).

Continuing or increasing exposure to aeroallergens to which a patient is sensitized may result in a rise in FENO, or the persistence of an elevated FENO. The magnitude of the effect may be sufficient for FENO levels to increase beyond the cut point of 50 ppb, and in some patients may occur even in the absence of respiratory symptoms (88–91). More recent evidence suggests that persistent high FENO in corticosteroid-treated individuals with asthma may also reflect a highly reactive asthma phenotype, and such patients need to be managed with caution (35). However, if the patient is asymptomatic and has a high FENO, then no change in treatment is required. There is a small group of patients whose FENO remains high despite good asthma control. This probably results from the fact that more than one factor (i.e., not just eosinophilic airway inflammation) is responsible for the elevated FENO. Another explanation may be that the high exhaled NO is derived from constitutive NOS sources which are steroid insensitive. Thus, levels greater than 50 ppb in a well-treated asymptomatic patient may be “normal” for that specific patient.

**Can FENO Be Used to Monitor Airway Inflammation?**

The change in FENO value following corticosteroid intervention may be more valid than the absolute FENO value. The definition of a clinically significant change in FENO, however, remains to be established.

**Recommendations**

We recommend the use of FENO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).

TABLE 4. HIGH FENO (> 50 ppb [> 35 ppb IN CHILDREN]) OR RISING FENO (> 40% CHANGE FROM PREVIOUSLY STABLE LEVELS): IMPLIES UNCONTROLLED OR DETERIORATING EOSINOPHILIC AIRWAY INFLAMMATION*

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a symptomatic patient (chronic cough and/or wheeze and/or shortness of breath during past &gt; 6 wk) presenting for the first time, possible etiologies:</td>
</tr>
<tr>
<td>Atopic asthma</td>
</tr>
<tr>
<td>Eosinophilic bronchitis</td>
</tr>
<tr>
<td>COPD with mixed inflammatory phenotype</td>
</tr>
<tr>
<td>That the patient is likely to benefit from a trial of inhaled corticosteroid treatment</td>
</tr>
</tbody>
</table>

Monitoring

In a symptomatic patient with an established diagnosis of asthma, possible etiologies:

High persistent allergen exposure

Inhaled corticosteroid delivery problems:
- Poor adherence
- Poor inhaler technique
- Proximal drug deposition, with untreated distal airway/alveolar inflammation

Inadequate inhaled corticosteroid dose:
- Likely to respond to increased inhaled corticosteroid dose OR prednisone
- Rarely: truly steroid resistant asthma (a trial of systemic steroid will confirm this; FENO will remain high)
- Rarely: Churg Strauss syndrome, pulmonary eosinophilia

In an asymptomatic patient:

No change in inhaled corticosteroid dosing, but refer to FENO trend over time in individual patient

Withdrawing inhaled corticosteroid is likely to be followed by relapse

An increase in therapy is indicated as some patients are asymptomatic, but the high FENO could be a risk factor for an upcoming exacerbation.

“High” FENO may be normal in a certain percent of the population (Figure 1).

**Definition of abbreviation:** FENO = fraction of exhaled nitric oxide.

*The interpretation of FENO is an adjunct measure to history, physical exam, and lung function assessment.

For intermediate FENO levels in the range 25–50 ppb [20–35 ppb in children], refer to Table 5.

For intermediate FENO levels (in the range 25–50 ppb [20–35 ppb in children]), refer to Table 5.
We suggest using the following values to determine a significant increase in FENO: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next (weak recommendation, low quality of evidence).

We suggest using a reduction of at least 20% in FENO for values over 50 ppb or more than 10 ppb as the cut point to indicate a significant response to antiinflammatory therapy (weak recommendation, low quality of evidence).

Monitoring Airway Inflammation in Asthma

Serial measurements obtained when patients’ asthma is both stable and unstable allows each patient to act as his/her own control when assessing subsequent measurements and as a result “personal best” can be used (92). The same cut points used in detecting airway inflammation apply when monitoring patients with asthma. In asymptomatic individuals, including patients with well-controlled asthma, low FENO suggests that ICS dose could be reduced or even that ICS treatment may be withdrawn altogether. In a study of children with stable asthma, withdrawal of ICS did not result in symptom relapse when FENO remained consistently low (optimum cut point 22 ppb) when measured 2 to 4 weeks after treatment withdrawal (60). In symptomatic patients with low FENO, strategies other than increasing the ICS dose should be pursued. Thus, FENO values which are either high or low are informative as to the etiology of current symptoms particularly in patients with difficult asthma. Sequential measurements may be important in determining trends. The relatively rapid change in FENO in response to ICS is thought to add to its utility in monitoring adherence to and response to such therapy (93). However, as a predictor of asthma control, FENO is no better than more conventional lung function tests (51, 87, 94, 95). The predictive values of a single measurement of FENO for loss of asthma control are insufficiently sensitive or specific to justify its use for this specific purpose (51, 94, 95).

Minimally Important Differences, and Prognostic Significance of FENO

The within-subject coefficient of variation for FENO in healthy subjects is approximately 10%, or up to 4 ppb (75, 96). The variation increases to approximately 20% in patients with asthma (75, 96, 97). Since a change of 20% could be due to the variation in the FENO measurement, the Committee recommends a change of at least 20% to indicate a significant rise or fall in FENO over time or following an intervention. However, there are very few data that clarify what constitutes a clinically important change in individual patients. In one study, FENO levels were 50% higher during acute asthma compared with when stability was restored (98). Data obtained from steroid withdrawal studies show that the mean increase in FENO associated with the advent of loss of control ranges from 16 ppb (99) to 25 ppb (50), the latter representing a 60% increase from baseline. However, the range of the increase in FENO between stability and loss of control is high (up to 141 ppb) (50). More recently, Michils and colleagues have reported that the transition from good control to poorly controlled asthma is likely to be associated with a rise in FENO of 40% or greater (100). An acute rise (over 12–24 h) in FENO may occur after infection or exposure to an allergen to which the patient is sensitized. The magnitude of the rise may be as high as 150 ppb.

### TABLE 5. GENERAL OUTLINE FOR FENO INTERPRETATION: SYMPTOMS REFER TO COUGH AND/OR WHEEZE AND/OR SHORTNESS OF BREATH*

<table>
<thead>
<tr>
<th>FENO (&lt;25 ppb)</th>
<th>FENO 25–50 ppb</th>
<th>FENO &gt; 50 ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;20 ppb in children)</td>
<td>(20–35 ppb in children)</td>
<td>(&gt;35 ppb in children)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Diagnosis</strong></td>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>Symptoms present during</td>
<td>Persistent allergen exposure</td>
<td>Persistent allergen exposure</td>
</tr>
<tr>
<td>past 6 wk</td>
<td>Inadequate ICS dose</td>
<td>Poor adherence</td>
</tr>
<tr>
<td>Alternative diagnoses</td>
<td>Poor adherence</td>
<td>Steroid resistance</td>
</tr>
<tr>
<td>Unlikely to benefit from ICS</td>
<td>Steroid resistance</td>
<td>Risk for exacerbation</td>
</tr>
<tr>
<td>Monitoring (in Patients with Diagnosed Asthma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms present</td>
<td>Adequate ICS dose</td>
<td>Adequate ICS dose</td>
</tr>
<tr>
<td>Possible alternative diagnoses</td>
<td>Good adherence</td>
<td>Good adherence</td>
</tr>
<tr>
<td>Unlikely to benefit from increase in ICS</td>
<td>Monitor change in FENO</td>
<td>Monitor change in FENO</td>
</tr>
<tr>
<td>Symptoms absent</td>
<td>Good adherence</td>
<td>Good adherence</td>
</tr>
<tr>
<td>Adequate ICS dose</td>
<td>Monitor change in FENO</td>
<td>Monitor change in FENO</td>
</tr>
<tr>
<td>Good adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS taper</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The interpretation of FENO is an adjunct measure to history, physical exam, and lung function assessment. See text and Tables 3 and 4 for other details.
recent study, investigators aimed to evaluate the accuracy of baseline \( F_{\text{ENO}} \) to recognize individuals with difficult-to-treat asthma who have the potential to achieve control with a guideline-based stepwise strategy (105). One hundred two consecutive patients with suboptimal asthma control underwent stepwise increase in the treatment with maximal inhaled corticosteroids for 1 month. Then, those who remained uncontrolled received oral corticosteroids for an additional month. With this approach, 53 patients (52%) gained control. A \( F_{\text{ENO}} \) cut point greater than or equal to 30 ppb demonstrated a sensitivity of 88% and a specificity of 91% for the identification of responsive individuals with asthma, and a value less than or equal to 30 ppb had a negative predictive value for steroid response of 92% (105). Thus, incorporating optimal design features into future \( F_{\text{ENO}} \) studies should help in obtaining a better estimate of the value of \( F_{\text{ENO}} \)-guided asthma therapy (104). Otherwise, a study is unlikely to detect a positive result in favor of one decision-making algorithm versus the other, even if one truly exists.

How Should a \( F_{\text{ENO}} \) Measurement Be Interpreted and Reported?

1. **Assure proper methodology: follow ATS/ERS guidelines.** ATS/ERS guidelines for the measurement of \( F_{\text{ENO}} \) have been published and are the current standard (26, 27). These guidelines should be followed carefully to obtain accurate and reproducible measurements. These guidelines should be used in conjunction with FDA-approved instructions for the use of specific nitric oxide analyzers. As additional instruments using different technologies to measure \( F_{\text{ENO}} \) become available, these guidelines as well as the scope of FDA endorsements are likely to change.

2. **Determine the reason for the test and the type of subject being tested: does the patient have asthma-like symptoms OR an already established diagnosis of asthma?** The interpretation of \( F_{\text{ENO}} \) begins with whether a patient’s symptoms are nonspecific and as yet undiagnosed, or whether they have a confirmed diagnosis of asthma. This upfront distinction between the diagnostic and monitoring uses of \( F_{\text{ENO}} \) allows for a more appropriate interpretation of the results as outlined in Table 5. Other factors to take into account include whether the subject is a smoker or is on antiinflammatory medications, as well as his/her height and age.

3. **Interpretation of \( F_{\text{ENO}} \) measurement: clinically relevant cut points.** The purpose of measuring \( F_{\text{ENO}} \) is to determine whether the value is within normal limits, high, or low. In addition, when monitoring over time, one must be able to determine when a significant change (increase) has taken place. After correct measurement, and with reference to factors which may be affecting the measurement (e.g., current smoking), interpretation can be made as follows (see also Table 5):

- \(< 25\text{ppb} (<20\text{ppb in children}): \text{cosinophilic inflammation and responsiveness to ICS (post-bronchodilator FEV}_1) \text{is unlikely.}\)
- \(> 50\text{ppb} (>35\text{ppb in children}): \text{cosinophilic inflammation is likely; responsiveness to ICS (post-bronchodilator FEV}_1) \text{is likely.}\)
- \(\text{Values between 25ppb and 50ppb (20–35ppb in children) must be interpreted cautiously with reference to the clinical context.}\)
- \(\text{An increase of} > 20\% \text{and more than 25ppb (20ppb in children) may be significant but there are wide inter-individual differences.}\)
- \(\text{A minimally important decrease of the FENO value is defined as a difference larger than} 20\% \text{for values over} 50\text{ppb or more than} 10\text{ppb for values lower than} 50\text{ppb from one visit to the next. A reduction of an elevated FENO of more than} 20\% \text{that often occurs 2–6 wk after initiation of anti-inflammatory therapy supports that the treatment was successful in reduction of inflammation.}\)

4. **Minimum reporting requirements for \( F_{\text{ENO}} \).** When reporting \( F_{\text{ENO}} \) results, a minimum information set should be included. This should include but not be limited to: date, time of the day, age, sex, ethnicity, height, smoking status, reason for the test, and prior diagnosis (if known), and whether or not the patient was using inhaled or oral corticosteroids at the time of testing. The format of the reporting should include the device used to make the measurement, the number of measurements made, and the flow rate (currently approved FDA devices use 50 ml/s flow rate). One can choose to include all measurements performed or just the mean value. Results of previous testing (if available) should be included. A listing of the relevant cut point values is usually helpful.

Other Situations in which \( F_{\text{ENO}} \) May Be Useful

These are emerging areas for the use of \( F_{\text{ENO}} \) in the clinical setting, but there is not enough literature to provide specific guidelines for their application (106).

**COPD.** The exact role of exhaled nitric oxide measurements in patients with established COPD remains to be defined. In a significant number of patients, an overlap syndrome comprising features of both asthma and COPD is found (53). The airway inflammatory cell infiltrate may be mixed, including eosinophilic inflammation. Studies show that, at least in the short term, the response to corticosteroids is likely to be greater in patients with COPD who also have sputum eosinophilia (107, 108) or elevated \( F_{\text{ENO}} \) (109). This raises the possibility that \( F_{\text{ENO}} \) measurements might be used in predicting steroid responsiveness in COPD. In a small group of 19 patients, Zietkowksi and coworkers reported a significant correlation between baseline \( F_{\text{ENO}} \) and ΔFEV1 after 2 months with inhaled budesonide 800μg/day (108). de Laurentiis and colleagues (110) reported greater \( F_{\text{ENO}} \) variability in patients with COPD who subsequently develop exacerbations. More recently baseline \( F_{\text{ENO}} \) was found to be a predictor for changes in airflow obstruction, but not improvements in functional exercise capacity or health-related quality of life, with corticosteroid therapy (56). There is also some early evidence that a raised \( F_{\text{ENO}} \) predicts FEV1 response to ICS in COPD (111, 112).

**Pulmonary hypertension.** \( NO \) is one of the important pathophysiological mediators of pulmonary hypertension (113, 114). It is important to point out, however, that while \( NO \) is the most recognized product of NOS, it is not the only one and an activity that is inhibited by NOS inhibition is not necessarily caused by NO (115–119). In the case of pulmonary hypertension for example, NO concentrations 1,000 times higher than those produced by NOS endogenously (normally present in the airways) are required for therapy, and pulmonary hypertension can be treated by nitrogen oxides such as ethyl nitrite that do not produce any nitric oxide at all (119). Thus in this sphere, we use NO to refer to NOS activity, recognizing that NO is a biomarker for NOS activity without always being the effector molecule. In addition to vasodilatation, NO regulates endothelial cell proliferation and angiogenesis, and maintains overall vascular health (121, 122). Interestingly, patients with pulmonary hypertension have low levels of \( F_{\text{ENO}} \) (123). Although this is a far more complex issue than the simple lack of a vasodilator (124), giving NO therapeutically seems to work well (125). Therapies that target the NO pathway have revolutionized the treatment of this disease, including the widely used phosphodiesterase type 5 (PDE5) inhibitors, which prevent the breakdown of the NO effector molecule 3′,5′-cyclic guanosine monophosphate (cGMP), thus prolonging NO effects on tissues (122). The NO deficiency state in patients with pulmonary hypertension also improves with other therapies that do not directly target the...
NO pathway like prostacyclins and endothelin receptor antagonists (125, 126). This seems also to have a prognostic significance, with improved survival in patients who respond to therapy with higher $F_{ENO}$ levels compared with those who do not change their $F_{ENO}$ levels in response to therapy (127). The low $F_{ENO}$ levels in patients with pulmonary hypertension and the improvement with effective therapies suggest that monitoring NO levels over time may be a useful noninvasive marker to evaluate response to or failure of medical therapy in these patients (127).

Cystic fibrosis and nasal NO measurements. Continuous and high production of NO takes place in the human nose and paranasal sinuses (128, 129), and this NO is readily measurable by noninvasive techniques (130). It has been shown that the nasal NO levels are altered in several respiratory disorders—including primary ciliary dyskinesia (PCD) (129), cystic fibrosis (CF) (131, 132), and allergic rhinitis (133, 134), and this has led to the proposal that nasal NO may be clinically useful in diagnosis and monitoring of these diseases. The levels of nasal NO are uniformly extremely low in patients with PCD, and the sensitivity and specificity of the test in this setting is excellent (135–139). The low levels of NO in CF are related to the absence of NOS2 expression in the airway epithelium, which supports the concept of NOS2 contribution to much of the NO detectable in exhaled breath (140–142). There is now abundant evidence that NO levels in CF are affected by a variety of other pathways as well. In addition to NOS2, determinants of exhaled NO in CF include arginase activity (143), superoxide levels (144), S-nitrosothiol metabolism (145), and denitrification pathways/prokaryotic nitrogen oxide metabolism (146, 147). Thus, these various determinants are all important when it comes to clinical interpretation $F_{ENO}$ in CF. As such, response to arginase, response to antioxidants, response to inhaled nitrosothiols, and response to antimicrobial therapy might potentially be monitored in CF, to some extent, by monitoring $F_{ENO}$. Although $F_{ENO}$ is low in PCD, the diagnostic accuracy is considerably greater for a nasal NO test. Therefore this test is attractive for screening for PCD, prior to confirmatory testing (e.g., biopsies with analysis of ciliary structure). In contrast to $F_{ENO}$, a single standardized procedure has not yet been defined for measuring nasal NO. Until this has been agreed upon, nasal NO levels are not yet recommended in routine clinical practice.

In summary, the use of $F_{ENO}$ in COPD and pulmonary hypertension and the use of nasal NO in diagnosis and monitoring of other respiratory disorders (e.g., allergic rhinitis, sinusitis, nasal polyposis, CF) are potentially of interest, but more research is needed before we know how clinically useful these tests can be for these disorders.

Conclusions and Future Directions

Advances in technology and standardization have made $F_{ENO}$ measurements simple, permitting their use as a biomarker in the assessment of inflammatory airways diseases. It is widely acknowledged that asthma is a heterogeneous disease with a variety of underlying pathophysiological abnormalities. $F_{ENO}$ plays a role in identifying these different phenotypes (4, 7, 8, 34, 35, 148). Measurements are easily performed in different settings and may be used in diagnosis and monitoring. Large population studies have identified various confounders that affect $F_{ENO}$ including age, sex, and height, among others. Consistent observations indicate that atopic individuals have higher $F_{ENO}$ levels while smokers tend to have lower $F_{ENO}$ levels (69, 76–78). Reference values have been derived from large population studies, but in practice they have limited application. Rather, evidence-based cut points that are shown to have diagnostic significance appear to be more relevant. When monitoring individual patients with asthma and assessing their treatment requirements, achieving “personal best” rather than “normal” values is more helpful. In many patients, changes in $F_{ENO}$ in relation to a baseline when clinically stable may be even more relevant. $F_{ENO}$ values of themselves do not justify a diagnosis or change in treatment. Rather, they need to be interpreted in relation to the clinical context as discussed in this Guideline. They may be particularly useful in understanding patients with asthma in whom more than one factor is contributing to respiratory symptoms (e.g., obesity, anxiety) and for whom clinical decision making is difficult. Another potential use of $F_{ENO}$ might be during inhalation challenge testing. That is, as with spirometry, giving an allergen inhalation challenge while measuring changes in $F_{ENO}$ before and after the challenge. This may be potentially useful in the assessment of occupational asthma (149, 150).

Although these guidelines for interpretation of $F_{ENO}$ measurements will enhance their clinical utility, we need to continue to investigate how to interpret $F_{ENO}$ measurements in different clinical settings. Inclusion of $F_{ENO}$ as an endpoint in clinical trials would be very helpful in understanding the role of $F_{ENO}$ in monitoring response to therapy (151). Furthermore, $F_{ENO}$ measurement in large population-based studies like the National Health and Nutrition Examination Survey (NHANES) would provide more information on normative values (152). Thus, the guidelines provided here will need to be periodically updated with regard to new developments in this rapidly evolving field.

This official Clinical Practice Guideline was prepared by an ad hoc committee of the Assembly on Allergy, Immunology and Inflammation (Alli).

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References


