CHEST

Update on Exhaled Nitric Oxide in Clinical Practice

Srinivas R. Mummadi, MD, FCCP; and Peter Y. Hahn, MD, FCCP

Asthma is characterized by chronic airway inflammation. Fractional exhaled nitric oxide (FENO) has emerged as a marker of T-helper cell type 2-mediated allergic airway inflammation. Recent studies suggest a role for FENO testing as a point-of-care tool in the management of patients with asthma. This Topics in Practice Management article reviews current coverage and reimbursement issues related to FENO testing and provides an overview of pertinent recent studies.

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Asthma is a heterogeneous disease characterized by chronic airway inflammation, variable airflow limitation, and airway hyperresponsiveness. It is increasingly recognized that asthma is a complex syndrome composed of recognizable demographic, clinical, and pathophysiologic clusters often referred to as asthma phenotypes.[1] In the era of personalized medicine, better recognition of these various phenotypes may help guide therapy for individual patients. Although the type of airway inflammation can differ between patients with asthma, T-helper cell type 2 (Th2)-driven allergic inflammation occurs in up to 80% of children and 50% of adults.[2] Allergic airway inflammation has been shown to increase with allergen exposure and is associated with worsened asthma control and increased rate of exacerbations. Allergic airway inflammation has also been shown to be very sensitive to inhaled corticosteroids (ICS). Measurement of fractional exhaled nitric oxide (FENO) is a noninvasive point-of-care test that accurately reflects allergic airway inflammation and may be helpful in identifying patients with corticosteroid-responsive airway inflammation and in the management of patients with asthma.[3]

Background

FENO levels increase during Th2 allergic inflammation and often correlate with eosinophilic inflammation in the airways.[3] Elevated FENO levels can help identify patients with allergic airway inflammation likely to respond to therapy with ICS (Table 1).[4] In allergic airway inflammation, mast cells and antigen-specific Th2 cells are activated, resulting in the production of cytokines, including IL-4, IL-5, and IL-13. IL-4 and IL-13 result in the upregulation of inducible nitric oxide synthase (iNOS) via the signal transducer and activator of transcription 6. The upregulation of iNOS results in the increased

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ABBREVIATIONS: FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; iNOS = inducible nitric oxide synthase; ppb = parts per billion; Th2 = T-helper cell type 2

AFFILIATIONS: From the Department of Pulmonary, Critical Care, and Sleep Medicine, Tuality Healthcare, Hillsboro, OR.

CORRESPONDENCE TO: Peter Y. Hahn, MD, FCCP, Tuality Healthcare, 364 SE 8th Ave, Ste 301, Hillsboro, OR 97123; e-mail: hahnpy@gmail.com

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TABLE 1] Factors Which Can Increase or Decrease FENO Levels

Increase	Decrease
Bronchodilator	Smoking
Airway infection	ICS therapy
Allergic rhinitis	Exercise
Nitrate-rich diet	Spirometric maneuvers
Height	Alcohol consumption
	Brochoconstriction
	Ciliary dyskinesia
	Pulmonary hypertension
	Cystic fibrosis

Adapted from Dweik et al[3] and Taylor et al.[4] ICS = inhaled corticosteroids; FENO = fractional exhaled nitric oxide.

production of FENO in airway epithelial cells.[5-7] This process is corticosteroid sensitive.

Previously, FENO was believed to be a marker specifically of eosinophilic airway inflammation. This assumption is reflected in the 2011 American Thoracic Society's guidelines for the use of FENO testing in clinical practice.[3] Recent studies, however, suggest that FENO more accurately is a broader marker of Th2-mediated allergic inflammation, which includes airway eosinophilia rather than eosinophilic inflammation only.[8,9] This finding was highlighted by studies investigating the use of anti-IL-5 (mepolizumab) and anti-IL-13 (lebrikizumab). In the mepolizumab study, FENO levels were unaffected in patients with asthma who received this drug, whereas blood and sputum eosinophil counts were significantly reduced.[9] In the lebrikizumab (anti-IL-13) study, patients who received lebrikizumab had a significant reduction in FENO levels, whereas peripheral blood eosinophil counts were unaffected, especially among patients with high baseline periostin levels.[8] Although increases in airway eosinophil counts and increases in FENO levels do occur concurrently, these studies suggest that the cytokines that regulate the induction of iNOS via signal transducer and activator of transcription 6 are separate from those regulating eosinophil traffic through the airways. This process may result in a disassociation between FENO levels and eosinophilic inflammation.

Recent evidence also suggests that levels of FENO may be influenced by ongoing systemic consumption of nitric oxide by systemic inflammatory pathways. Subgroup analyses of patients with severe asthma who exhibit evidence of systemic inflammation (eg, metabolic syndrome, diabetes, hypertension) revealed concomitantly low FENO levels but higher blood levels of the end products of nitric oxide consumption. It has been suggested that measured levels of FENO could thus represent a balance between airway production and systemic consumption.[10]

FENO and ICS Responsiveness

As a marker of Th2-mediated allergic airway inflammation, FENO can be useful as an indicator of ICS-responsive airway inflammation and in identifying airway inflammation that may not respond to corticosteroid treatment. Several studies have shown the superiority of FENO testing over spirometry, bronchodilator responsiveness, peak flow rates, and other conventional measures in predicting response to ICS.[11,12] Taylor summarized studies evaluating subjects with nonspecific respiratory symptoms and a variety of airway diseases and found high positive and negative predictive values of FENO in predicting response to ICS.[4] FENO levels may also have a role in distinguishing patients whose lack of asthma control is due to ICS noncompliance.[13]

The 2011 American Thoracic Society's guidelines advocate the clinical use of FENO testing in determining the likelihood of steroid responsiveness in patients with nonspecific respiratory symptoms. These guidelines recommend the use of cut points rather than reference values when interpreting FENO levels. A level $>$ 50 parts per billion (ppb) was believed to be a strong indicator that responsiveness to corticosteroids is likely, whereas response to ICS was believed to be unlikely with a level $<$ 25 ppb (Tables 2, 3).[3] FENO levels in nonasthmatic adults and children have recently been determined by using data from the National Health and Nutrition Examination Survey. According to this survey, the 95th percentile for FENO was 39 ppb in adults and 36 ppb in children (age $<$ 12 years). Values higher than these are considered indicative of allergic airway inflammation.[14]

FENO and Asthma Management

A number of studies have compared FENO-based asthma management algorithms with standard asthma management algorithms in adults and children.[15-17] These studies have produced conflicting results on whether FENO-guided management results in reduced exacerbation rates. A Cochrane systematic review in 2009 and a meta-analysis by Petsky et al[18,19] in 2012 reviewed these studies and concluded that the use of FENO testing in clinical practice could not be recommended and that future studies were needed.[18,19] The primary outcome of both the Cochrane review and the meta-analysis was the number of subjects who