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Abbreviations

ABPA – allergic bronchopulmonary aspergillosis

ACT – Asthma Control Test

BHR – bronchial hyperresponsiveness

BPD – bronchopulmonary dysplasia

cACT – Childhood Asthma Control Test

COPD – Chronic obstructive lung disease

CF – cystic fibrosis

FE_{NO} - fraction of exhaled nitric oxide

FEF₂₅₋₇₅ - volume of air expired during 25 to 75 percent of an exhalation

FEV₁ - forced expiratory volume in 1 second

FVC – forced vital capacity

GERD – gastroesophageal reflux disease

GC – glucocorticoid

ICS - inhaled corticosteroid

NO – nitric oxide

NOS – nitric oxide synthase

PEF - peak expiratory flow

PCD - primary ciliary dyskinesia

STAT-signal transducer and activator of transcription.

TLC – total lung capacity

VCD – vocal cord dysfunction

Introduction

Exhaled nitric oxide was initially used in clinical research, as the analyzer was large and costly, but with the development of cheaper, portable units, it is now being used in the management of asthma in specialty care settings. Nitric oxide (NO) is measured in exhaled breath in parts per billion (ppb) and is measured as the fraction of exhaled nitric oxide or FeNO. Airway NO is constitutively expressed in small quantities (<20 ppb) by inducible NOS (iNOS) in the airway epithelium via iNOS induction by interferon-gamma and STAT-1. In asthma, allergen exposure results in IL-4 and IL-13 expression, which, acting through STAT-6, induces iNOS resulting in significant increases in NO. This brief commentary will highlight the utility of FeNO in the diagnosis, management and treatment of asthma.

Practical Aspects

FeNO is measured by inhaling to TLC, followed by exhalation at a steady flow rate for 6 to 10 seconds. The procedure takes only minutes to perform and just one successful effort is required. Children > 5 years can perform this test if the exhalation time is 6 seconds. FeNO is flow dependent, as a result the standard flow rate is 50 mL/second. FeNO levels rise in childhood due to increased airway size as children grow. FeNO levels are elevated allergic/eosinophilic-driven lung diseases including asthma, ABPA, COPD with an eosinophilic component, and eosinophilic bronchitis. Levels are low or normal in neutrophil-mediated diseases including COPD, BPD, alpha-1-antitrypsin deficiency, PCD, and CF, in addition to chronic cough, GERD and VCD. The ATS (1) has recommended that cut points, rather than reference ranges, be used when interpreting

FeNO levels. Levels of <25 in adults (<20 children) are considered low; intermediate levels are 25-50 in adults (20-35 children), while high levels are >50 in adults (>35 ppb children).

FeNO is an Indicator of Allergic Inflammation

As FeNO correlates with serum IgE and increases during allergen exposure, it measures allergic airway inflammation, mediated via allergen-driven IL-4 and IL-13 effects on the airway epithelia. FeNO has been thought to measure eosinophilic inflammation, as FeNO and sputum eosinophils are correlated (r values ranging from 0.26 to 0.6), but with the development of drugs that target either eosinophilic (IL-5 driven) or allergic inflammation (IL-4 and IL-13 driven), FeNO should be considered a marker of allergic inflammation, while eosinophilia should be considered a marker of eosinophilic inflammation.

Sputum eosinophils were compared to FeNO in a large cohort of asthmatic children. Both correlated with atopy, circulating eosinophil counts, β -agonist reversibility, and BHR. FeNO was preferred over sputum induction as only 63% of subjects were able to perform the procedure twice, bronchospasm occurred in 8% during sputum induction, and a considerable amount of time and technical expertise was required, while FeNO was easily and quickly measured (2). Similar findings have been reported in adult asthmatics.

Clinical Applications of Exhaled Nitric Oxide

Diagnostic Test for Asthma. FeNO can aid in the diagnosis of asthma. Standard diagnostic tests (methacholine reactivity and β -agonist responsiveness), are rarely used in primary care where most patients receive the diagnosis of asthma based solely on clinical criteria. Specialists routinely measure beta-agonist responsiveness to diagnose asthma, but it is not a sensitive measure in children with asthma. FeNO is both highly sensitive and specific for asthma diagnosis in both children and adults with sensitivities ranging from 0.79 to 0.86 and specificities ranging from 0.85 to 0.89. Due to its ease of use, FeNO could aid in diagnosis of asthma in both specialty practices and in primary care.

Indicator of Asthma Severity and Control. FeNO correlates with BHR, β -agonist response, diminished FEV₁/FVC ratio and FEF₂₅₋₇₅, *but not FEV₁*, need for rescue albuterol, and symptoms. FeNO also correlates with the Childhood Asthma Control Test (cACT) in children not yet on controller therapy. Although good symptom control could be achieved following institution of therapy, many children had elevated FeNO levels suggesting that symptoms and inflammation are distinct features of asthma (3).

Predictor of Response to Glucocorticoid Therapy. As up to 45% of asthmatics fail to benefit from inhaled corticosteroid (ICS) therapy, FeNO can help predict responders to ICS therapy. Multiple studies in children and adults have demonstrated elevated FeNO levels predict a favorable response to ICS. Baseline FeNO levels are superior to baseline FEV₁, beta-agonist responsiveness, and BHR in predicting response to ICS therapy as measured by improvements in morning PEF, FEV₁, symptoms and BHR.

136

137 **Predictor of Asthma Relapse During ICS Reduction.** Multiple studies have
138 demonstrated that an elevated FeNO at baseline, or increasing FeNO levels during ICS
139 reduction, accurately predict asthma relapse. This is an important application, as a major
140 goal is to use lowest ICS dose required to maintain asthma control, especially in children
141 where there is the potential for adverse effects.

142

143 **Predictor of Asthma Exacerbations.** Diminished lung function and elevated
144 FeNO levels are independently associated with risk of having an asthma exacerbation.
145 Patients with FeNO in the highest quartile (≥ 72 ppb) vs. those in the lowest quartile (15
146 ppb) at baseline had a higher risk of requiring frequent albuterol (>7 canisters of
147 albuterol, RR 2.4) and higher risk having an asthma exacerbation (RR 1.5) in the
148 subsequent year (4).

149

150 **Marker of Severe Asthma.** There was initial concern that FeNO would not be
151 useful in the management of severe asthma, as iNOS can be suppressed by oral steroids.
152 This was not the case, as 50% of severe steroid dependent asthmatics studied had
153 elevated FeNO levels (5). FeNO can also identify a group of asthmatics with a more
154 reactive, high-risk risk phenotype. Patients with high FeNO levels had greater BHR,
155 higher circulating and sputum eosinophils, were atopic, had air-trapping, and were more
156 likely to have had a past ICU admission compared to subjects with low FeNO (6).

157

Predictor of Response to Biologic Agents. Mepolizumab, an anti-IL5 antibody, reduces exacerbations in patients with severe eosinophilic asthma. Although an elevated FeNO value (>50 ppb) was an entry criteria, mepolizumab had no effect on FeNO levels, while dramatically reducing eosinophils, and eosinophil counts (not FeNO), were correlated to exacerbation frequency (7). Lebrikizumab, an anti-IL13 antibody, improved lung function in patients with high periostin or FeNO levels (measures of allergic inflammation), and both fell following lebrikizumab therapy (8). Eosinophilic asthmatics treated with dupilumab, anti-IL4/13 receptor antibody, had fewer exacerbations, improved lung function and reduced symptoms. FeNO levels were elevated at baseline, fell significantly during therapy, while dupilumab had no effect on circulating blood eosinophils (9). Lastly, omalizumab-treated patients with elevated FeNO levels had a two-fold greater reduction in exacerbations than patients with low FeNO levels, yet FeNO levels were unaffected by omalizumab (10).

Limitations

Asthma is a complex disease, and single measures, can not be used to assess, manage and treat this disease. FeNO is no exception. FeNO is not a useful tool in non-atopic asthma. It cannot be easily performed in young children. It adds costs to the care of asthmatics and studies demonstrating its cost effectiveness are lacking. Lastly, controversy persists as to whether monitoring FeNO provides better asthma outcomes than the guidelines approach to managing asthma.

Summary

181 FeNO can be an important tool in the management of asthma. Asthma guidelines
182 should define its application, so that it can be more readily applied in the primary care
183 setting, where the majority of asthma patients are managed.

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185

186 **Figure Legend.** Concept diagram summarizing the mechanisms and clinical application
187 of exhaled nitric oxide.
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220 Figure: See PowerPoint Slide

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Figure Legend. FeNO is produced as a consequence of allergic inflammation mediated via IL-13 and IL-4 expression. Allergic inflammation is involved in both the initiation and maintenance of airway inflammation seen in asthma, while less is known regarding eosinophilic inflammation plays. As FeNO is a direct measure of local airway inflammation, it is a good marker of inflammation in asthma, and as a result, has significant clinical utility. It's levels fall with dupilumab (inhibition of both IL-4 and IL-13), while mepolizumab (inhibition of IL-5) has no effect on FeNO, suggesting that these two forms of inflammation are not closely linked.

Abbreviations

STAT= signal transducer and activator of transcription

JAK= Janus kinase

IL= interleukin

TH2= T helper type 2 cell

mAB= monoclonal antibody

AW= airway

iNOS= inducible nitric oxide synthase

GC= glucocorticoid

LPR= late phase asthmatic response

AHR= airways hyperresponsiveness

NO= nitric oxide

FeNO= fraction of exhaled nitric oxide

Figure 1

