Clinical Benefits of FeNO Monitoring in Asthma

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Objectives

- Nitric Oxide
- Inflammation in Asthma
- Phenotyping Personalized Medicine
- Aids in the diagnosis of th2 allergic inflammation
- Instrument for optimizing the dose of inhaled corticosteroids (ICS)
- Non-Adherence to medication (ICS) / Improper Medication Technique
- Outcomes Data
- Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic
- Clinical Utility of FeNO testing
Fractional Exhaled Nitric Oxide — (FeNO)
What is Nitric Oxide (NO)?

• NO is present in virtually all mammalian organ systems, including the human lung

• Present in the exhaled breath of all humans

• 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

• The functions and effects of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator
  • Neonatal respiratory distress syndrome
  • Health/Fitness supplements

2011 ATS FeNO Guidelines on Interpretation
Fractional Exhaled Nitric Oxide — (FeNO)

ASTHMA AND INFLAMMATION
Asthma Facts

- Asthma cost the US $56 Billion dollars a year****
- 1 in 11 children have asthma*
- 1 in 12 adults have asthma*
- 1 in 5 children with asthma went to an emergency department for asthma-related care****
- 479,000 hospitalizations a year****
- 1.6 million emergency room visits a year w/asthma as primary diagnosis **
- 10.5 million physician office visits a year w/asthma as primary diagnosis***

Source: U.S. Centers for Disease Control and Prevention

* 2010, ** 2013, *** 2012, **** 2009

11 People a Day Die from Asthma

*CDC
Asthma Heterogeneity

• Complex genetic disorder with heterogeneous phenotype
  • Largely attributed to interactions among many genes and between these genes and the environment
  
• Variability in underlying inflammation, clinical symptoms, natural history, and response to treatment
  • Variability contributes to suboptimal diagnosis and therapeutic control
  • Environment
  • Access to healthcare
  • Specialists vs primary care
  • Co-morbidities

Inflammation in Asthma

NHLBI, EPR 3, 2007

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.

GINA - 2017

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing...
Guideline Recommendations for Stepwise Treatment of Asthma

**Interruption of Asthma**

- **Step 1**
  - Preferred: SABA PRN

- **Step 2**
  - Preferred: Low-dose ICS + LABA
  - Alternative: Cromolyn, LT, neomycin, or theophylline

- **Step 3**
  - Preferred: Low-dose ICS + LABA
  - Alternative: Medium-dose ICS + either LT, theophylline, or zileuton

- **Step 4**
  - Preferred: Medium-dose ICS + LABA
  - Alternative: Consider omalizumab for patients who have allergies

- **Step 5**
  - Preferred: High-dose ICS + LABA + oral corticosteroid
  - AND: Consider omalizumab for patients who have allergies

- **Step 6**
  - Preferred: High-dose ICS + LABA + oral corticosteroid
  - AND: Consider omalizumab for patients who have allergies

Each Step: Patient education, environmental control, and management of comorbidities.

Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-relief Medication for All Patients • SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed • Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.
Current Assessment of Asthma Management

- Assessment of symptoms / history
- Assessment of lung function
- Assessment of AHR
- Symptoms are not predictive of response to ICS
- Lung function can be misleading, especially in children
  - Quality control is a major issue
  - Lung function can be normal in patients with severe asthma
- Measurement of AHR
  - Expensive
  - Technically difficult
  - Non-specific

Hasn’t changed in >20 years
Tools Used in the Clinical Assessment of Asthma

Clinical Symptoms: ACT, AQLQ, etc

Airway Hyperresponsiveness (AHR): Bronchodilator testing, Methacholine challenge, etc

Airway Obstruction: Spirometry, PEF, etc
Tools to Assess Inflammation

**INVASIVE**
- Bronchoscopy
- Bronchial wash
- BAL
- Biopsy
  - Sputum investigation
  - Sputum Eosinophils*

**NONINVASIVE**
- Total IgE
- Blood eosinophils
- NO in exhaled air

BAL, bronchoalveolar lavage; NO, nitric oxide.
Goal of Therapy: Control of Asthma

Reduce Impairment

• Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion).

• Require infrequent use (≤2 days a week) of inhaled SABA for quick relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]).

• Maintain (near) normal pulmonary function.

• Maintain normal activity levels (including exercise and other physical activity and attendance at school or work).

• Meet patients’ and families’ expectations of and satisfaction with asthma care.

Reduce Risk

• Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations.

• Prevent loss of lung function; for children, prevent reduced lung growth.

• Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.

ADAPTED FROM NHLBI EPR3 2007
Fractional Exhaled Nitric Oxide — (FeNO)
Cluster Phenotyping By Degree Of Th2 Inflammation

- Two distinct molecular phenotypes:
  - Therapy targeting Th2 cytokines only benefits Th2-driven phenotypes
  - Non-Th2-driven asthma does not respond well to current therapies including ICS

Asthma Phenotypes: Not All Asthma is Th2 Inflammation!

80% of Ped Asthma is Allergic Driven
Mahr et al. Allergy Asthma Proc 34. 2013

50-60 % of Adult Asthma is Allergic Driven
Asthma Inflammation and Pathophysiology

Environmental factors

Acute inflammation

Proinflammatory mediators

Th2/Th1

cytokines (eg, IL-13, TNF-α)

Environmental factors and inflammatory products

AIRWAY MICROENVIRONMENT

INFLAMMATION

Airway effects

Bronchospasm

Acute inflammation

Persistent inflammation

Remodeling

MUCUS

INITIATION

AMPLIFICATION

PROPAGATION

SMOOTH MUSCLE

BLOOD VESSELS

Nitric Oxide (NO) Production

- NO endogenous regulatory molecule
- Synthesis regulated by family of enzymes—NO synthases (NOS)
- Inducible NOS-derived NO is predominantly produced in bronchial wall epithelial cells
- Exhaled NO levels increase during Th2 (allergic) inflammation—often correlate with eosinophilic inflammation

**Diagram:**

*Healthy* vs *Asthma* mechanism:
- Healthy: IFN-γ (Homeostatic, source unknown) → NO → Soluble mediator → Healthy
- Asthma: Air pollution (oxidative stress) → NO → INOS → AP-1 → Mucus, AHR → IL-4/IL-13 → IL-6

**Key:**
- AP, activator protein; iNOS, inducible nitric oxide synthase; IL, interleukin; IFN-γ, interferon-gamma; STAT, signal transducer and activator of transcription.

**References:**
Fractional Exhaled Nitric Oxide — (FeNO)

AIDS IN THE DIAGNOSIS OF TH2 ALLERGIC INFLAMMATION
Elevated FeNO Distinguishes Asthma From Other Allergic Conditions

Figure from Cordeiro et al. With permission. AR, allergic rhinitis; NAR, nonallergic rhinitis; Cordeiro et al. Allergy Asthma Proc. 2011;32(2):119-126.
Diagnostic Accuracy of FeNO, Blood Eosinophils, Total IgE And Their Combinations To Identify Sputum Eosinophils

ROC Characteristics for FeNO, Blood Eosinophils, IgE and combinations

Fractional Exhaled Nitric Oxide — (FeNO)

INSTRUMENT FOR OPTIMIZING THE DOSE OF INHALED CORTICOSTEROIDS (ICS)
Significantly Better Than FEV$_1$

FeNO Measurement Predicts ICS Responsiveness

In patients with nonspecific symptoms, a FeNO value of > 47 ppb is highly indicative of corticosteroid responsiveness.

FeNO measurement was significantly better than FEV$_1$ bronchodilator for predicting response to inhaled fluticasone propionate ($P < 0.01$).

52 patients referred by their family practitioners to the hospital with persistent, previously undiagnosed respiratory symptoms.

FeNO Testing to Support an Asthma Diagnosis

- Bronchodilator reversibility and/or AHR was used to establish asthma diagnosis in study (47 patients with symptoms suggestive of asthma, 17 were subsequently diagnosed with asthma)
- Both FeNO and sputum eosinophils had significantly higher diagnostic accuracy than lung function tests
- FeNO testing provides added advantage of being noninvasive and easy to perform

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak flow improvement with steroid &gt;15%</td>
<td>24</td>
<td>100</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>FEV₁ improvement with steroid &gt;15%</td>
<td>12</td>
<td>100</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>FEV₁ &lt;80% predicted</td>
<td>29</td>
<td>100</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>FEV₁/FVC &lt;70%</td>
<td>35</td>
<td>100</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>Sputum eosinophils &gt;3%</td>
<td>86</td>
<td>88</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>FeNO &gt;20 ppb</td>
<td>88</td>
<td>79</td>
<td>70</td>
<td>92</td>
</tr>
</tbody>
</table>

FeNO measurements provide the physician with means of evaluating asthma patients' response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. Not all patients with asthma will have an elevated FeNO level. FeNO levels should be interpreted in the clinical context.
Fractional Exhaled Nitric Oxide — (FeNO)

NON-ADHERENCE/TECHNIQUE TO MEDICATION (ICS)
Lack of Improvement in Medication Adherence in Asthma

- Adherence improvement strategies have included patient education, motivational interviewing, adherence feedback, provider communication skill training, and use of mobile communication technology.
- Collectively, most interventions had a positive but modest impact on adherence that was not sustainable long term.
- A sample of 9 studies conducted between 1996 and 2015 using objective measures of adherence indicate no overall change in adherence rates over 2 decades.
Asthma Patients do not Use Medication Inhalers Correctly

- High prevalence (90%) of inhaler technique errors (>1 error) across all devices.
- More than 20% of the patients demonstrated at least 4 errors when using their controller inhalers.

### TABLE II. The 12 most common DPI Diskus errors recorded in the iHARP study\(^{22}\)

1. Did not slide cover fully open
2. Dose lost after preparation because of holding downward
3. Shook inhaler device after dose preparation
4. Did not breathe out to empty lungs
5. Exhaled into the inhaler before inhalation
6. Did not put Diskus in mouth and seal lips around mouthpiece
7. Did not have head tilted such that chin is slightly upward
8. Insufficient inhalation effort (inhalation is not fast, forceful from the start, and as long as possible)
9. Did not inhale through mouth
10. No breath-hold follow inhalation (or holds breath for <3 s)
11. Patient had expired inhaler or empty inhaler
12. After inhalation did not replace cover

*Braido, JACI IP 2016*
Percent of Correct, Acceptable, Poor Inhaler Tests

Correct or acceptable inhaler technique over course of 40 years has remained below 50%
FeNO but Not FEV\textsubscript{1} Was Associated with ICS Non-Adherence

- Patients followed for 2.5yrs; total of 53 visits
- Mean FeNO levels were significantly reduced in patients with good ICS adherence
- FEV\textsubscript{1} levels were not substantially different among adherence groups
- Adherence determined by calculating number of doses taken per day/doses prescribed x 100. Good, moderate, and poor adherence defined as >75% adherence, 50% to 75% adherence, or <50% adherence to prescribed medication, respectively.

Fractional Exhaled Nitric Oxide — (FeNO)

OUTCOMES DATA
Cochrane: FeNO-based Management Reduces Exacerbation Rates

<table>
<thead>
<tr>
<th>Population</th>
<th>Meta-Analysis Design</th>
<th>Odds Ratio for Reducing Exacerbations Using FeNO vs. Symptoms-based Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult¹</td>
<td>7 Studies, 1700 Randomized Subjects, 1546 Completed Study</td>
<td>OR 0.60 (95% CI 0.43-0.84); NNTB in one year = 12 (95% CI 8-32)</td>
</tr>
<tr>
<td>Pediatric²</td>
<td>9 Studies, 1426 Randomized Subjects, 1370 Completed Study</td>
<td>OR 0.63 (95% CI 0.49-0.83)</td>
</tr>
</tbody>
</table>

- Conclusions: Tailoring asthma medications based on FeNO levels (compared with primarily on clinical symptoms) decreases the frequency of asthma exacerbations.
- The rate of exacerbations (number of exacerbations per 52 weeks) was significantly reduced by at least 40% by incorporating FeNO into asthma management.
- Number needed to treat to benefit (NNTB) over 52 weeks was clinically relevant and very low (12 in adults, 9 in children)

Real World Experience with Use of FeNO-LaForce Study

- Treatment decision-making study to evaluate the impact of FeNO testing on asthma management (physician assessment of inflammation, dosing and cost savings)
- Treatment decisions were altered (step up, step down, add-on) in 36% of subjects when FeNO was used in conjunction with standard clinical assessment, ACT, and spirometry

LaForce et al Annals Allergy Asthma Immun 2014
Fractional Exhaled Nitric Oxide — (FeNO)

Helps to identify asthmatics who are possible candidates for treatment with a biologic
Severe Asthma vs Difficult to Control Asthma

**Severe refractory asthma** is characterized by difficulty to achieve disease control despite high dose inhaled steroids plus long acting beta agonists (LABAs) or oral corticosteroids (OCS).

**Difficult to control asthma** can be attributed to factors other than asthma itself such as: Non adherence, Poor inhaler technique, Comorbidities

- **5 - 10%** of 26 million Americans suffering from asthma experience severe disease
- Approximately **1/2 of direct asthma costs** related to care of patients with severe disease ($56 billion total, $28 billion for severe asthma)
- Patients with uncontrolled severe asthma incur up to **3x cost** compared to controlled severe asthma ($21 billion)
- Pharmaceuticals represent the single largest expenditure for asthma care

Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic

- A small minority of asthma patients cannot achieve control of their disease with traditional therapies and are considered for treatment with biologic therapy.  
  
- Decision making in these patients is difficult; FeNO helps to confirm ICS failures, non-adherence/compliance and identifies patients that have persistent airway inflammation despite optimization on current therapy.

- Baseline measurement of FeNO identifies patients with persistent inflammation and who will benefit most from a biologic such as omalizumab.

- FeNO identifies patients likely (and unlikely) to respond to Xolair® (omalizumab)


Mean percent reduction (95% CI) in protocol-defined asthma exacerbation rate in the low- and high-biomarker subgroups (baseline fractional exhaled nitric oxide [FeNO], peripheral blood eosinophils, and serum periostin).

<table>
<thead>
<tr>
<th></th>
<th>Low FeNO at baseline</th>
<th>High FeNO at baseline</th>
<th>Low eosinophils at baseline</th>
<th>High eosinophils at baseline</th>
<th>Low periostin at baseline</th>
<th>High periostin at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>0.60</td>
<td>0.50</td>
<td>0.65</td>
<td>0.70</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.71</td>
<td>1.07</td>
<td>0.72</td>
<td>1.03</td>
<td>0.72</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Fractional Exhaled Nitric Oxide — (FeNO)

CLINICAL UTILITY OF FENO TESTING
Clinical Interpretation of FeNO Measurements (2011 ATS)

- Use of cut points rather than reference values
- Account for age as a factor in children <12 years old
- Clinical context in which FeNO is obtained should be taken into account and reported*
- When monitoring patients, clinically significant increase determined as
  - >20% significant change for levels >50 ppb
  - >10 ppb significant change for levels <50 ppb
- Decrease of >20% in an elevated FeNO level, which often occurs 2 to 6 weeks after initiation of anti-inflammatory therapy, supports that treatment was successful for reduction of inflammation

*Includes date, time of day, age, sex, ethnicity, height, weight, smoking status, reasons for test, prior diagnosis if known, whether patient was using ICS or oral steroids at time of testing, and number of measurements made. Dweik et al. Am J Respir Crit Care Med. 2011;184(5):602-615.
Clinical Guide to Interpretation of FeNO Levels and Airway Inflammation in Asthma

Parts per billion (ppb) of NO in exhaled air

- 300: Maximum measurement with NIOX
- 50: Cut point indicating high Th-2 (ICS-responsive) inflammation (35 for children)
- 25: Cut point indicating low Th-2 (ICS-responsive) inflammation (20 for children)
- 5: Minimum measurement with NIOX

Additional Factors Affecting FeNO Levels

- Airway infection (viral)
- Allergic rhinitis
- Atopy
- Nitrate-rich diet
- Acute Bronchodilator
- Spirometric maneuvers that cause bronchospasm
- Smoking
- Acute Bronchoconstriction
- Alcohol consumption
- Exercise

Effects generally not clinically significant

# Effect of Drug Therapy on FeNO Levels

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect on FeNO</th>
<th>Mechanism of Action</th>
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| Corticosteroids              | Marked Decrease    | Less IL4/IL13 release  
|                               |                    | Less STAT 6 Activation in epithelium  
|                               |                    | Less iNOS Expression in epithelium                                                  |
| LTRA                          | Slight Decrease    | Reduces eos  
|                               |                    | Slight less IL13 release                                                           |
| Anti-IgE                      | Decrease           | Blocks Th2/mast cell activation  
|                               |                    | Less IL4/IL13 release                                                               |
| Anti IL4/IL13                 | Decrease           | Reduces STAT 6 Activation in epithelium                                              |
| Anti IL5                      | No Effect          |                                                                                     |
| Anti TNF-x                    | No Effect          |                                                                                     |
| Methylxanthines (theophylline, | No Effect          |                                                                                     |
| caffeine, etc)                |                    |                                                                                     |
Guideline Support
Guideline Support

Key Findings
1. Depending on the FeNO cutoff, the likelihood of having asthma in people ages 5 years and older increases by 2.8 to 7.0 times given a positive FeNO test result.
2. FeNO results can predict which patients will respond to inhaled corticosteroid therapy.
3. Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations. [https://www.ahrq.gov/](https://www.ahrq.gov/)

NICE
Initial treatment and objective tests for acute symptoms at presentation
1.1.5 Treat people immediately if they are acutely unwell at presentation, and perform objective tests for asthma (for example, fractional exhaled nitric oxide [FeNO], spirometry and peak flow variability) if the equipment is available and testing will not compromise treatment of the acute episode. [https://www.nice.org.uk/](https://www.nice.org.uk/)
Summary

• Aids in the Diagnosis of Asthma and Identifies Patients with T2 Allergic Inflammatory Phenotype
• Instrument for Optimizing the Dose of Inhaled Corticosteroids (ICS)
• Uncovers Non Adherence to ICS
• Reduces the Likelihood of Exacerbations in Patients at Risk for Future Events
• Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic