THE MEASUREMENT OF EXHALED NITRIC OXIDE AND ITS PLACE IN ASTHMA MANAGEMENT

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DISCLOSURE

• Advisory Board and/or Speakers Bureau for:
  Aerocrine
  ISTA
  McNeil
  Merck
  Sunovion
Objectives

• Discuss the challenges and unmet needs of asthma management

• Highlight the importance of monitoring airway inflammation for improved asthma control

• Address the role of fractional exhaled nitric oxide ($FE_{NO}$): a measurement of airway inflammation (“Inflammometry”)

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ASTHMA
CHALLENGES AND UNMET NEEDS
SUB-OPTIMAL OUTCOMES

• **PREVALENCE** RISING: YET ASTHMA UNDER-DIAGNOSED
  

• **SPIROMETRY**: Under utilized (Less than 25% of patients)
  
  Not sensitive enough to detect low grade inflammation

• **UNDER-TREATMENT and/or POOR ADHERENCE ⇒ POOR OUTCOMES**
  
  - **ASTHMA DEATHS**: US: (2002) 4,261
  
  - **DISEASE PROGRESSION**: LOSS OF LUNG FUNCTION (IN SOME)
    
    Recognition of small airways disease
  
  - **HEALTHCARE COSTS**: US >$20 Billion/Yr (2009)

• **QUESTIONS**
  
  A) IS CHOICE AND DOSE OF MEDICATION OPTIMAL?
  
  B) IMPROPER DIAGNOSIS ⇒ IMPROPER USE OF ICS ⇒ SIDE EFFECTS


Asthma Insight and Management (AIM) accessed at “Taking AIM at Asthma.com”2009
Airway Inflammation and Pathophysiology of Asthma

Environmental and genetic factors

Inflammation

Airway hyper-responsiveness

Reversible airway obstruction

Clinical symptoms (cough, wheezing, dyspnea)

What Defines Asthma Control?

• Measures based on **GUIDELINE RECOMMENDATIONS**
  
  **IMPAIRMEN**
  - Symptoms
  - $\beta_2$-agonist use
  - Pulmonary function

  **RISK**
  - Exacerbations
  - Irreversible airflow limitation
  - Medication side effects

• **INFLAMMATION?** Not presently a guideline recommendation!

  Should it not be?

NAEPP GUIDELINES 2007
Patients May Be Unable to Accurately Assess Their Disease Control

- Patients in 11 general practices (n=255)
  - Recorded asthma severity on a visual analog scale
  - Measured PEF up to 4 times daily for 14 consecutive days
- In 60% of patients there was no significant correlation between asthma symptom scores and PEF

Asthma Symptoms Correlate Poorly With Lung Function

ASTHMA HETEROGENEITY
All Asthma Does Not Behave The Same

- Eosinophilic vs. neutrophilic inflammation
- Propensity to develop fatal or near fatal asthma
- Atopic vs. non-atopic
- Response to medication:
  a) Corticosteroid sensitivity or resistance
  b) Leukotriene Modifier responsive
  c) β-receptor polymorphisms
- Development of irreversible airflow limitation (remodeling?)

THEREFORE:
- Markers needed to direct asthma management
  a) pharmacogenetics
  b) surrogate markers of inflammation
- Therapy must be individualized
- Markers needed to recognize suboptimal patient compliance/adherence!
Challenges and Opportunities

• Several underlying disorders can cause asthma-like symptoms. We have lacked an effective tool to measure underlying airway inflammation and its characteristics. A significant portion of patients diagnosed with asthma do not have asthma.

• Others with asthma may be undiagnosed as measures of lung function are not as sensitive as measures of inflammation

• Inhaled corticosteroids are the recommended and most widely used anti-inflammatory therapy in asthma, with a well-documented effect of reducing allergy-driven eosinophilic airway inflammation

• Major factors contributing to asthma morbidity and mortality include incorrect diagnosis and inadequate treatment. Poor adherence and drug delivery problems are also major contributing factors

• Measuring and controlling airway inflammation contributes to improved diagnosis, treatment and disease control
MEASURES OF AIRWAYS INFLAMMATION

OPTIONS

- **Measures based on DIRECT EVIDENCE OF INFLAMMATION**
  - Fiberoptic bronchoscopy with Endobronchial *Biopsy*
  - and/or bronchoalveolar lavage *Impractical*

- **Measures based on INDIRECT EVIDENCE OF INFLAMMATION**
  - Airways hyper-responsiveness (AHR) Methacholine challenge–PC$_{20}$

- **Measures based on INFLAMMATORY MARKERS**
  - Sputum induction for inflammatory cells (eosinophils)
  - Exhaled nitric oxide: FE$_{NO}$
  - Breath Condensates (pH, Leukotrienes, 8-Isoprostane)

NAEPP GUIDLEINES 2007
Airway Hyperreactivity (AHR)

Significant Reduction in Asthma Exacerbations in AHR vs. Reference Strategy (AMPUL Study Group)

1.8-fold decrease in exacerbation rate with the AHR strategy as compared with the reference strategy group ($P = .03$)

ICS titration in Adults
Higher ICS dose required!  

n=75 mild to moderate asthma

Biopsy findings after 2 years indicated that subjects treated according to AHR guidelines had significantly decreased reticular layer thickness compared to reference treatment subjects.

74 patients: Moderate to severe asthma
- **SPUTUM GP**: Anti-inflammatory dose adjustment according to inflammatory status (Maintain sputum eos < 3%)
- **BTS Group**: Dose-adjustment according to current British Thoracic Society guidelines

Results after 12 months:
- 35 severe exacerbations compared with 109, p=0.01
- 1 admission to hospital compared to 6/year, p=0.047
- Sputum eosinophil count 63% lower over 12 mosin sputum management group
- No difference in daily intake of corticosteroids

**Figure 3**: Cumulative asthma exacerbations in the BTS management group and the sputum management group

Green et al, Lancet 2002
NO Originates in the Airway Epithelium

- NO is an endogenous regulatory molecule widely distributed throughout the body
- NO synthesis is mediated by a family of enzymes, the NO synthases (NOS)
- Inducible NOS-derived NO is predominantly produced in the epithelial cells of the bronchial wall
- NO increases when there is asthmatic inflammation
- Epithelium is key source of exhaled NO seen in asthmatic patients

Normal epithelial cells
Minimal release of NO

Activated epithelial cells during inflammation
Predominant IL-4/IL13→STAT-6 and/or TNF α, IL 1 β, IFN γ→STAT-1) induced ↑ production of NO

Rationale for the Use of FE\textsubscript{NO} in the Management of Respiratory Disease

Significant Correlations Observed for:

- FE\textsubscript{NO} and eosinophilic airway inflammation (tissue>sputum)
- FE\textsubscript{NO} and Sputum eosinophils (best in mild/moderate asthma)
- FE\textsubscript{NO} and Major Basic Protein (Biopsy) in sub-epithelium even during remission in Atopic Asthma (sub-clinical inflammation!)
- FE\textsubscript{NO} and peripheral blood eosinophils
- FE\textsubscript{NO} and BAL eosinophils
- FE\textsubscript{NO} and airway hyper-responsiveness in steroid-naïve patients with mild asthma
- FE\textsubscript{NO} and Eosinophilic airway inflammation and steroid response

Association Between Exhaled NO and Eosinophilic Airway Inflammation (Sputum eosinophils)


<table>
<thead>
<tr>
<th>Exhaled NO concentration (ppb)</th>
<th>Sputum eosinophil count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.00</td>
</tr>
<tr>
<td>0.3</td>
<td>0.10</td>
</tr>
<tr>
<td>1</td>
<td>0.30</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>3.00</td>
</tr>
<tr>
<td>30</td>
<td>10.00</td>
</tr>
<tr>
<td>100</td>
<td>100.00</td>
</tr>
</tbody>
</table>

- **p < 0.001**
- \( R^2 = 0.26 \)

71% sensitivity 72% specificity

Correlation with 3% sp. eosinophils

3.3 ppb at 250 ml/sec

Sputum Eosinophils vs. Exhaled NO

**Sputum Eosinophil Induction**
- Inhalation of hypertonic saline (3-5%) for 12 to 30 minutes after albuterol inhalation
- Substantial time: Expectorate q 2 minutes x 30 minutes: Then 2 hour processing
- Technical Expertise to prepare and analyze sputum
- Some patients can’t perform (CAMP-77% successful)
- Potential Adverse effects: Bronchospasm

**Exhaled Nitric Oxide: FE\textsubscript{NO}**
- Requires only 5 to 10 minutes
- Little technical expertise
- Easy to perform for everyone (children as young as 4 years)
- Non invasive
- Reproducible (Exhalation at 50ml/sec)
- Surrogate marker of eosinophilic inflammation (over-simplification?)
Additional Factors Affecting $\text{FE}_{\text{NO}}$ Levels

- Airway viral infection (rhinovirus)
- Allergic rhinitis
- Nitrate-rich diet
- Bronchodilator
- Atopy
- Height

- Spirometric maneuvers
- Exercise
- Alcohol consumption
- Bronchoconstriction
- Ciliary dyskinesia

- Pulmonary hypertension
- Cystic fibrosis
- Smoking
- ICS therapy

Normal ranges of $\text{FE}_{\text{NO}}$ (at 50ml/sec)

- **Adults**: 2.6 to 28.8 ppb in men; 1.6 to 21.5 ppb in women

- **Children**: Upper limit is 15 ppb at age 4 and 25 ppb for adolescents

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**FE\textsubscript{NO} Measurement: An Important Tool for Physicians ("Inflammmometer")**

\textbf{FE\textsubscript{NO} measurement may help clinicians to}:
- Screen for Diagnosis of Asthma
- Differentiate asthma from other conditions
- Predict response to ICS therapy
- Monitor response to ICS and Guide and optimize ICS therapy
- Predict asthma relapse (Steroid holiday)
- Predict loss of control
- Rapidly identify noncompliance/adherence
- Monitor allergy avoidance regimen
**FE_{NO}** Is Superior to Lung Function in Early Detection Preschool Children With Probable Asthma

Receiver operating characteristics (ROC) of **FE_{NO}** and other lung function measures (Impulse oscillometry) in discriminating between children with probable asthma (n=96) and healthy controls (n=62)

- **FE_{NO}** ROC properties:
  - Sensitivity = 86%
  - Specificity = 92%

Cut point: 10ppb

Flow rate = 50ml/s
Ages 3.8-7.5 yrs.

Utility of Available Diagnostic Tests for Asthma

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak flow variability &gt; 20%</td>
<td>0</td>
<td>100</td>
<td>N/A</td>
<td>70</td>
</tr>
<tr>
<td>Peak flow increase 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>71</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>

- Both FENO and sputum eosinophils have significantly higher diagnostic accuracy than PFTs
- Asthma diagnosis ascertained by BHR and/or (+) Bronchodilator response
- FENO provides the added advantage of being noninvasive and easy to perform


*
Differential Diagnosis of Chronic Cough With $F_{E\text{NO}}$

- **C** = Healthy controls
- **NA** = Non-asthmatics with chronic cough
- **A** = Asthmatics with chronic cough
- **WA** = Asthmatics with wheezing or dyspnea;

At Cut point: 30 ppb (45 ml/sec)
Sensitivity 75%
Specificity 85%

Chatkin JM et al. *Am J Respir Crit Care Med.* 1999;159:1810-1813
**Influence of Gastro-Esophageal Reflux (GER) on $FE_{NO}$**

$FE_{NO}$ levels are lower in ATOPIC children with “asthma-like symptoms” and GER (n=12) as compared to asthmatic children (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Children with allergic asthma</th>
<th>Children with GER and allergic asthma like symptoms</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>&lt;sup&gt;a&lt;/sup&gt;, years</td>
<td>10.08 (1.56)</td>
<td>9.33 (1.30)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Blood eosinophil number</strong>&lt;sup&gt;b&lt;/sup&gt;, x1,000/μl</td>
<td>0.50 (0.35, 0.60)</td>
<td>0.41 (0.27, 0.69)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt;</strong>&lt;sup&gt;a&lt;/sup&gt;, % pred.</td>
<td>98 (13)</td>
<td>95 (14)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>FEF&lt;sub&gt;25–75%&lt;/sub&gt;</strong>&lt;sup&gt;a&lt;/sup&gt;, % pred.</td>
<td>106 (24)</td>
<td>97 (35)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>FVC</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95 (13)</td>
<td>96 (9)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

$FE_{NO}$ measured in the study population. The horizontal lines represent mean values.


**
Significant Response of $\text{FE}_{\text{NO}}$ to ICS Therapy - moderate/severe asthma

**Adults**
- N = 32

**Children**
- N = 33

$\text{NO}$ levels (ppb)
- Visit 1
- Visit 2

After 2 weeks ICS

$30\% -70\% \downarrow \text{FE}_{\text{NO}}$ correlated with asthma outcome measures but not with spirometry: Greater Sensitivity

Exhaled Nitric Oxide is one of the fastest biomarkers of inflammation
- Significant advantage when monitoring or titrating therapy

(FE_NO begins to fall within 3-5 days)

Bates CA and Silkoff PE. Exhaled nitric oxide in asthma: from bench to bedside. *J Allergy Clin Immunol.* 2003;111:256-262
**FE\textsubscript{NO} Can Predict Steroid Response**

Patients with Undiagnosed Respiratory Symptoms

FE\textsubscript{NO}>47 ppb greater response, all categories, regardless of diagnosis

### Steroid Response to FP 500 mcg/day x 4 weeks

<table>
<thead>
<tr>
<th>FE\textsubscript{NO} (ppb) by Tertiles</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;15</td>
<td>15-47</td>
<td>&gt;47</td>
<td>P</td>
</tr>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1}, %</td>
<td>1.7 (1.7)</td>
<td>2.1 (1.7)</td>
<td>15.9 (5.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean morning peak flow (over 7 days), %</td>
<td>1.2 (2.2)</td>
<td>1.9 (2.8)</td>
<td>17.5 (5.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>PC\textsubscript{20} AMP, doubling dose shift</td>
<td>0.4 (0.4)</td>
<td>0.4 (0.3)</td>
<td>4.3 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FE\textsubscript{NO}, ppb</td>
<td>-2.8 (1.4)</td>
<td>-2.6 (3.8)</td>
<td>-80.4 (18.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Children with Asthma:

$\text{FE}_{\text{NO}}$ Predicts/Records Response To 3 Month Therapy
ICS (FP) 100mcg BID vs. Montelukast 5 - 10mg hs

- Baseline $\text{FeNO} = 40 \text{ ppb}$
- After FP: $\text{FeNO} = 21 \text{ ppb}$
- After Montelukast $\text{FeNO} = 31 \text{ ppb}$
- $\text{FeNO}$ best predictor of ACDs and response indicator in discriminating drug response
- $\text{FeNO}$ helps identify children not on controllers who achieve better improvement in ACDs
  - Decrease in eNO correlates with
    - More asthma control days (ACDs)
    - Less use of rescue inhaler
    - Improved AM peak flows

CARE NETWORK $n = 144$ Ages 6 - 17
Zeiger et al. Response to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol* 2006; 117:45-52
Early Detection of Airway Inflammation Using \( \text{FE}_\text{NO} \) as a Marker


Symptom Free Patients

**With \( \uparrow \text{FE}_\text{NO} \): \( \uparrow \) BHR Histamine**

**With \( \uparrow \text{FE}_\text{NO} \): \( \uparrow \) BHR Histamine**

![Graph showing symptoms and FEV1 change](image-url)
Association of Allergen Avoidance With $F_{ENO}$ in Asthmatic Children


- **Exhaled NO (ppb)**
- **T0** – before admission to allergen-reduced residential home
- **T1** – day 15 after placement
- **T2** – 3 months after residential home placement
- **T3** – 14 days after return to sea level

P = 0.14

P = 0.0026

P = 0.004

Inhaled steroid withdrawal

N = 20

N = 20

N = 10

**Exhaled NO measurements in Clinical Practice**

**Symptoms during past 2-4 weeks**

Steroid-naive patient with ongoing or recent asthma-like symptoms:

- **Normal** $\text{FE}_{\text{NO}} < 25$ ppb adults, <20 ppb children
- **Intermediate or rising** $\text{FE}_{\text{NO}} 25-50$ ppb adults, 20-35 ppb children
- **High** $\text{FE}_{\text{NO}} > 50$ ppb adults, >35 ppb children

- **Unlikely to respond to steroid therapy**
- **Alternative diagnosis:** GERD, Vocal cord dysfunction, Anxiety-hyperventilation, Rhinosinusitis, Non-eosinophilic asthma (test airway function), Reactive airways disease, COPD, Bronchiectasis, Cardiac disease

- **May respond to steroid therapy**
- Investigate for allergen exposure
- Based on clinical judgment, consider initiating steroid therapy and monitor change in $\text{FE}_{\text{NO}}$

- **Highly likely to respond to steroid therapy**
- Investigate for allergen exposure
**FE\textsubscript{NO} Facilitates Early Identification of Noncompliance**

**FE\textsubscript{NO} increases with poor compliance: No significant change FEV\textsubscript{1}**

![Graph showing the relationship between FE\textsubscript{NO} and percent of compliance.](image)

- **Severe asthma**: $r = -0.76$, $p = 0.001$, $n = 30$
- **Moderate asthma**:

Predictive Value of High Fe\textsubscript{NO} in Poorly Controlled ICS Treated Asthma Patients (van Veen)

1. High Fe\textsubscript{NO} (>20 ppb) in difficult to treat and/or poorly controlled ICS treated asthma is predictive of accelerated decline in lung function particularly if FEV\textsubscript{1} is normal. Adult non-smokers n = 136

2. In these circumstances high FE\textsubscript{NO} might suggest:
   a) Sub-optimal steroid dose
   b) Poor patient compliance with medical regimen
   c) Steroid resistance: consider evaluating alternative anti-inflammatory regimen
   d) Continued exposure to allergen triggers$^2$

**FE_{NO} Predicts Asthma Relapse in Children With Clinical Asthma Remission after ICS Discontinued (Steroid Holiday)**

FE_{NO} levels higher than 49 ppb 4 weeks after steroid removal were highly indicative of asthma relapse.

Children (N=40, mean age 12.2 years) on a median dose of 400 mcg budesonide or equivalent (range 100 to 400).

FE_{NO} was measured before and at 2, 4, 12, and 24 weeks after withdrawal of steroids.

Sensitivity: 71%
Specificity: 93%

Flow rate = 50 mL/s

Predicting Loss of Control (LOC)

Mild to Moderate Asthma n=78
Taper ICS x 6 wks or LOC

↑Exhaled NO is as useful as
↑Sputum Eosinophils and
↑AHR (PD$_{15}$ Hypertonic Saline) in predicting LOC

Increase in FE$_{NO}$
>60% vs. baseline when controlled or > 33ppb

83% predictive of LOC
Targeting FeNO to Optimize Therapy

Personal Best vs. Reference Values

• Multiple factors affect FeNO ⇒
• Therefore, determining optimal therapy based on reference values is problematic even after factoring atopy, age, sex and smoking history.¹
• Some asthma patients may have higher than normal FeNO values despite good control. Therefore, normalizing FeNO with Rx may be unrealistic.²
• **Optimum FeNO levels** may be best established using Oral Steroid rather than ICS, as this best approximates predicted “normal” values by factoring out 
  a) improper ICS use 
  b) inadequate compliance or 
  c) poor small airway or alveolar deposition.¹
• When monitoring patients with asthma, interpreting FeNO values is best done using the patient’s **PERSONAL BEST** value as a reference point rather than predicted values.¹

1. Smith et al; JACI 2009;124;714-718
# Use of FeNO Measurements in Clinical Practice

**Patients diagnosed with Asthma and Treated with Anti-inflammatory Controller Medication**

## Symptomatic
- Unlikely to respond to increased ICS dose
- Consider alternative/comorbid diagnosis: GERD, chronic cough, VCD, anxiety-hyperventilated, bronchiectasis, primary ciliary dyskinesia, cardiac disease
- Address treatment adherence
  - Investigate ICS delivery problems
  - May benefit from increased ICS dose
  - Investigate and reduce allergen load
- Investigate ICS delivery problems
- Consider increasing ICS dose
- Investigate for and reduce allergen exposure

## Asymptomatic
- Adequate dosing and good adherence to prescribed therapy
- Consider reducing ICS dose**
- Potentially uncontrolled airway inflammation
  - Monitor changes in symptoms and FENO level
  - Do not reduce ICS unless patient remains asymptomatic with stable FENO level over time

<table>
<thead>
<tr>
<th>Normal FENO</th>
<th>Intermediate or rising FENO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 ppb adults</td>
<td>25-50 ppb adults</td>
</tr>
<tr>
<td>&lt;20 ppb children</td>
<td>20-35 ppb children</td>
</tr>
</tbody>
</table>

- Address uncontrolled airway inflammation and risk of exacerbations
- Do not reduce or withdraw ICS
- Investigate for and reduce allergen exposure

**Normal FENO**
- <25 ppb adults
- <20 ppb children

**High FENO**
- >50 ppb adults
- >35 ppb children
## Prospective Randomized Studies Evaluating the Role of FE\textsubscript{NO} to Guide ICS Dosing and Asthma Treatment

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Pijnenberg 2005 (n=85)</th>
<th>Smith 2005 (n=97)</th>
<th>Fritsch 2006 (n=47)</th>
<th>Shaw 2007 (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
</tr>
<tr>
<td><strong>1\textsuperscript{st} aim</strong></td>
<td>Total ICS dose</td>
<td>Exacerbations</td>
<td>FE\textsubscript{V1}</td>
<td>Severe Exac.</td>
</tr>
<tr>
<td><strong>FE\textsubscript{NO} Cut used (ppb)</strong></td>
<td>30</td>
<td>35</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>ICS dose same BHR better (p=.04)</td>
<td>Lower ICS dose</td>
<td>No differ FE\textsubscript{V1}, sx, rescue, exac.</td>
<td>No differ Exac (underpowered) (FE\textsubscript{NO} 12 vs 23)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Severe exacerbations FE\textsubscript{NO}: 8</td>
<td>Insignificant Exacerbations (minor and total)</td>
<td>Higher MEF</td>
<td>Final dose of steroids FE\textsubscript{NO}gp: 557 mcg/day</td>
</tr>
<tr>
<td></td>
<td>Symptom gp: 18</td>
<td>PFTs and sputum eos; same</td>
<td></td>
<td>Sx gp: 895 mcg/day</td>
</tr>
</tbody>
</table>

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Tailored Interventions Based on $\text{FE}_{\text{NO}}$ vs. Clinical Symptoms: Cochrane Review 2008

- Meta-analysis: 356 Adults and Children
- ICS dose titration $\text{FE}_{\text{NO}}$ vs. clinical symptoms with or without PFTs
- Beneficial in reducing ICS in adults, not children
- No difference in asthma outcomes (exacerbations, PFTs, $\text{FE}_{\text{NO}}$ symptom control)
- Note: similar findings by Szefler in inner city asthma patients (Lancet 2008) and de Jongste (Am J Respir Crit Care, 2009) telemonitoring in childhood asthma

**CONCLUDE:**

The role of utilizing $\text{FE}_{\text{NO}}$ to tailor the dose of ICS is currently uncertain; “This approach needs further work before it can be advocated in clinical practice”. (Merits further investigation!)

Petsky et al Cochrane Database Sys Rev, 2:CD006340
DRAWBACKS TO ICS TITRATION STUDIES

1. Varying cutpoints for FE\textsubscript{NO}
2. Varying symptom and PFT thresholds to adjust dose
3. LABA use (or not)
   All of above can affect overall ICS dose
4. Lack of uniform definition of exacerbations
5. No decrease in ICS dose for low FE\textsubscript{NO} levels in face of symptoms:

NOTE: Low values are highly predictive of:
   a) The absence of eosinophilic inflammation
   b) The absence of long term steroid requirements in children
   c) A low risk of deterioration of asthma control in adults.

Look for Comorbidities (GERD, CRS, VCD)
DRAWBACKS TO ICS TITRATION STUDIES (2)

• Failure to account for:
  1) All variables: i.e. age, height, atopy, ethnicity, gender
  2) Ongoing allergen exposure which could lead to steroid resistance
  3) Non-asthma conditions that could account for high \( \text{FE}_{\text{NO}} \) levels \( (\text{FE}_{\text{NO}} \text{ is non-specific}) \)
  4) Heterogeneity - Patients with:
     a) Inexplicable high “normal values”, and/or poor correlation between \( \text{FE}_{\text{NO}} \) and sputum eosinophils. (15% in Shaw)
     b) Low FeNO values and poor ICS response (Neutrophilic asthma or alternative diagnosis (i.e. GERD, VCD))
FeNO, Systemic Inflammation and Response to ICS in Severe COPD

- 60 ex-smokers: severe COPD (FEV1 1.07 L, 36% predicted)
- FP 500 mcg BID x 4 weeks
- ICS Responder \(\Rightarrow\) increase in FEV1 \(\geq\) or \(=\) 200 mL
- ICS Responders had higher baseline FE\(_{NO}\) levels compared with non-responders (46.5 ppb vs. 25 ppb)
- Baseline serum inflammatory markers (serum CRP, IL-6, and IL-8) did not differ between responders and non-responders.

CONCLUSION: In ex-smokers with severe COPD, FE\(_{NO}\) may be more closely associated with FEV1 responses to ICS than are standard markers of systemic inflammation,

Challenges and Opportunities

- Several underlying disorders can cause asthma-like symptoms. We have lacked an effective tool to measure underlying airway inflammation and its characteristics. A significant portion of patients diagnosed with asthma do not have asthma.

- Others with asthma may be undiagnosed as measures of lung function are not as sensitive as measures of inflammation.

- Inhaled corticosteroids are the recommended and most widely used anti-inflammatory therapy in asthma, with a well-documented effect of reducing allergy-driven eosinophilic airway inflammation.

- Major factors contributing to asthma morbidity and mortality include incorrect diagnosis and inadequate treatment. Poor adherence and drug delivery problems are also major contributing factors.

- Measuring and controlling airway inflammation contributes to improved diagnosis, treatment and disease control.
CONCLUSIONS
ASTHMA & FE\textsubscript{NO}

C) FeNo is the most practical surrogate marker of inflammation

1) Correlates with sputum, tissue and BAL eosinophilia and AHR
2) BUT: Simpler, non invasive, well tolerated
3) Increased in patients with asthma
4) reduced after ICS or other anti-inflammatory Rx
5) Produces immediate, accurate reproducible results
6) Suitable from age 4 to elderly
7) ATS and ERS standardized and FDA approved
8) CPT coded for 2007
SUMMARY: UTILITY OF FE\textsubscript{NO}

A SURROGATE MARKER OF EOSINOPHILIC AIRWAY INFLAMMATION: POTENTIAL TO IMPROVE ASTHMA OUTCOMES

- Asthma Screening
- Asthma diagnosis (in absence of airflow reversibility i.e. cough presentation)
- Agent selection: Predicting response to ICS and other therapies
- Evaluating response (or lack of response) to anti-inflammatory agents (ICS, LTRA, Anti-IgE)
- Monitoring adherence to Rx regimen
  - Anti-inflammatory medication
  - Allergen exposure or avoidance
- Predicting asthma flares (exacerbations, LOC)
- Confirmation of clinical remission
- ICS Dose titration accounting for inflammation:
  - a) optimal control
- Recognizing Absence of Eosinophilic asthma
- Recognizing Steroid Unresponsiveness

Asthma Screening

- Asthma diagnosis (in absence of airflow reversibility i.e. cough presentation)
- Agent selection: Predicting response to ICS and other therapies
- Evaluating response (or lack of response) to anti-inflammatory agents (ICS, LTRA, Anti-IgE)
- Monitoring adherence to Rx regimen
  - Anti-inflammatory medication
  - Allergen exposure or avoidance
- Predicting asthma flares (exacerbations, LOC)
- Confirmation of clinical remission
- ICS Dose titration accounting for inflammation:
  - a) optimal control
- Recognizing Absence of Eosinophilic asthma
- Recognizing Steroid Unresponsiveness
Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice

1. ATS and ERS standardized and FDA approved
2. Exhaled NO may be used as a surrogate marker for eosinophilic airway inflammation, and as such, be helpful in diagnosis and treatment decisions in asthma. Especially, exhaled NO may be used to evaluate the potential for response to corticosteroid treatment.
3. Exhaled NO may be used to predict the risk of future adverse events regardless of current clinical control.
4. With emerging work, the role of biomarkers is anticipated to be even more important in future guidelines, even overriding symptoms as the basis for treatment decisions.
THANK YOU
OPTIONAL CASE STUDIES
Case Study 1

Recognizing the Etiology of Cough and Institution of the Appropriate Treatment
6 Year-Old Girl With Chronic Dry Cough of 10 Weeks Duration

**History**
- Dry cough occurs almost daily, no present wheeze.
- Sight chest tightness and dyspnea with exertion.
- Nocturnal awakening several times a month with cough.
- History of “croup” with wheezing in past.
- URI’s several times a year associated with wheezing that improves with SABAs.
- No reported nasal symptoms or heartburn
- No prior history of food allergy or eczema (AD)

**Family History**
- Father and one sib have asthma
- Mother and another sib have Allergic rhinitis

**Medication History**
- OTC cough and cold medications, without benefit
6 year old girl (cont)

Physical Exam

• Well nourished girl, alert and cooperative who appears normal except for her intermittent coughing
• Nasal membranes pale but not swollen or wet, no discharge or post nasal drip
• No sinus tenderness
• Chest clear to auscultation: no wheezes rales or rhonchi
• No organomegaly or abdominal tenderness
Differential diagnosis might include

a) Asthma
b) Habit cough
c) GERD
d) Vocal cord dysfunction
e) Rhinosinusitis
f) All of the above
STUDY RESULTS

- Chest X-ray: normal, no hyperinflation, no infiltrates
- Peak flow: 100% of predicted
- Spirometry: within normal limits, Normal flow/volume loop
- **Exhaled NO**: 31 ppb (elevated)\(^1-5\)
- Sinus imaging: not indicated given absence of upper respiratory symptoms
- Skin tests (specific IgE): positive to dust mite


\*\*
Question 2
Which course of therapy is most appropriate?

A) Watch and wait approach; Reassurance, Instructions to call if symptoms worsen and make f/u visit in 1 month
B) Broad spectrum antibiotic for URI to cover atypical organisms such as mycoplasma or chlamydia
C) Albuterol MDI q4h PRN as monotherapy
D) Single entity controller asthma medication i.e. inhaled corticosteroid (ICS) or Leukotriene Receptor Antagonost (LTRA) along with albuterol MDI PRN and/or pre exercise.
E) Combination therapy with an ICS and Long Acting Beta Agonist (LABA) to control both exercise induced bronchospasm and cough due to airway inflammation
RESULTS OF THERAPEUTIC CHOICES

CHOICE A) Watch and Wait (Poor choice)

- 3 weeks later, mother still reports persistent cough increased by recent heavy dust exposure; wheezing is now observed
- She requests re-evaluation
- FeNO 37 ppb (still elevated)
- Alternative diagnosis and therapy indicated
RESULTS OF THERAPEUTIC CHOICES

CHOICE B) BROAD SPECTRUM ANTIBIOTIC (poor choice)

• Dry cough persists without change after completion of 2 week antibiotic course
• No fever, myalgia or discolored sputum,
• Mother returns for reevaluation and change in therapy
• FENO 31 ppb (still elevated)

• Elevated exhaled NO indicative of eosinophilic inflammation rather than neutrophilic inflammation associated with infection
RESULTS OF THERAPEUTIC CHOICES

CHOICE C) PRN ALBUTEROL MDI as sole therapy

(Poor Choice)

• Minimal decrease in daytime cough. Nocturnal awakening 3x/month
• Exercise induced cough prevented with albuterol MDI pre-treatment
• FeNO 30 (Still elevated) Initial impression of asthma was appropriate
• BUT: PRN albuterol only helpful in preventing EIB and controlling the bronchospastic aspect of cough and inadequate in controlling underlying bronchial inflammation as indicated by elevated exhaled NO level.
D) Daily ICS plus PRN Albuterol MDI (BEST Choice)

- Cough subsided, No further nocturnal awakening
- FeNO 7 ppb
- Mild Persistent Asthma is the most likely diagnosis\(^1\)
- Cough in an atopic child with elevated exhaled NO suggests atopic asthma despite normal peak flow and spirometry or impulse oscillometry\(^2\)
- Allergic asthma is likely because of sensitization to mite
- Maintenance asthma controller [ICS (preferred) or LTRA] is recommended\(^3-5\)

E) ICS +LABA  (Over-treatment: Poor Choice)

- Mother informed at Pharmacy that Insurance Company would not pay for a combination ICS/LABA drug for patient who had not tried and failed a single entity controller

- Mother would not pay for drug out of pocket and returned to office for alternative therapy

- Physician chastised by Quality Control HMO Director for prescribing a ICS/LABA for mild persistent asthma, when a less expensive single entity controller has been shown to be equally efficacious and less expensive!¹

**Exhaled NO measurements in Clinical Practice**

## Symptoms during past 2-4 weeks

**Steroid-naive patient with ongoing or recent asthma-like symptoms**

<table>
<thead>
<tr>
<th>FE\textsubscript{NO}</th>
<th>Unlikely to respond to steroid therapy</th>
<th>May respond to steroid therapy</th>
<th>Highly likely to respond to steroid therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FE\textsubscript{NO}</td>
<td>Unlikely to respond to steroid therapy</td>
<td>May respond to steroid therapy</td>
<td>Highly likely to respond to steroid therapy</td>
</tr>
<tr>
<td>Intermediate or rising FE\textsubscript{NO}</td>
<td>Unlikely to respond to steroid therapy</td>
<td>May respond to steroid therapy</td>
<td>Highly likely to respond to steroid therapy</td>
</tr>
<tr>
<td>High FE\textsubscript{NO}</td>
<td>Unlikely to respond to steroid therapy</td>
<td>May respond to steroid therapy</td>
<td>Highly likely to respond to steroid therapy</td>
</tr>
</tbody>
</table>

- **Normal FE\textsubscript{NO}**
  - \(<25\) ppb adults
  - \(<20\) ppb children

- **Intermediate or rising FE\textsubscript{NO}**
  - \(25-50\) ppb adults
  - \(20-35\) ppb children

- **High FE\textsubscript{NO}**
  - \(>50\) ppb adults
  - \(>35\) ppb children

- Unlikely to respond to steroid therapy
- Alternative diagnosis: GERD, Vocal cord dysfunction, Anxiety-hyperventilation, Rhinosinusitis, Non-eosinophilic asthma (test airway function), Reactive airways disease, COPD, Bronchiectasis, Cardiac disease
- May respond to steroid therapy
- Investigate for allergen exposure
- Based on clinical judgment, consider initiating steroid therapy and monitor change in FE\textsubscript{NO}
- Highly likely to respond to steroid therapy
- Investigate for allergen exposure

- Investigate for allergen exposure
- Based on clinical judgment, consider initiating steroid therapy and monitor change in FE\textsubscript{NO}
Fluticasone monotherapy achieves greater improvements in asthma control than PACT combination and montelukast as indicated by $\text{FE}_{\text{NO}}$ measurements.

Asthma control days stratified by $\text{FE}_{\text{NO}}$:

- $P = .0001$
- $P = 0.5$

FE\textsubscript{NO} Is Superior to Lung Function in Early Detection Preschool Children With Probable Asthma

Receiver operating characteristics (ROC) of FE\textsubscript{NO} and other lung function measures (Impulse oscillometry) in discriminating between children with probable asthma (n=96) and healthy controls (n=62)

FE\textsubscript{NO} ROC properties:
- Sensitivity=86%
- Specificity=92%

Flow rate = 50ml/s

Conclusion

- Determination of exhaled NO is a simple and noninvasive test and can be employed in children 4 and over. (Pre-school children may not be able to perform spirometry)
- Exhaled NO helps recognize underlying lung inflammation in children and may serve as a screening tool (Low FeNO has very high predictive value in ruling out eosinophilic airway inflammation).
- Elevated FeNO, even in the presence of normal spirometry suggests eosinophilic inflammation and warrants further evaluation and treatment: Elevated FeNO is predictive of (+) response to ICS
Exhaled NO measurements in Clinical Practice

### Symptoms during past 2-4 weeks

- Steroid-naive patient with ongoing or recent asthma-like symptoms

<table>
<thead>
<tr>
<th>Normal FE(_{NO}) &lt; 25 ppb adults</th>
<th>Intermediate or rising FE(_{NO}) 25-50 ppb adults</th>
<th>High FE(_{NO}) &gt; 50 ppb adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely to respond to steroid therapy</td>
<td>May respond to steroid therapy</td>
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<tr>
<td>Alternative diagnosis: GERD, Vocal cord dysfunction, Anxiety-hyperventilation, Rhinosinusitis, Non-eosinophilic asthma (test airway function), Reactive airways disease, COPD, Bronchiectasis, Cardiac disease</td>
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</tr>
<tr>
<td>Based on clinical judgment, consider initiating steroid therapy and monitor change in FE(_{NO})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- May respond to steroid therapy
- Investigate for allergen exposure
- Based on clinical judgment, consider initiating steroid therapy and monitor change in FE\(_{NO}\)
- High likely to respond to steroid therapy
- Investigate for allergen exposure
CASE 2

Adjusting medication to achieve asthma control
CASE 2
Loss of Control

- 29 year old man presents in late April for follow up evaluation of well controlled moderate persistent asthma.
- He also has a history of seasonal allergic rhinitis which usually flares in May and June.
- Prior skin tests: sensitivity to mite, trees and grass.
- ICS dose was tapered since February from 440mcg BID to 440 mcg once daily without difficulty.
  - Cough and wheeze <2 days/week
  - No nighttime awakenings
  - Exercise control with albuterol pre-treatment;
  - (otherwise albuterol MDI (SABA) rarely needed)
- Mild nasal symptoms: Minor Stuffiness
- No activity limitation
- ACT score=20 (controlled level)\(^1\)

**
• Wife smokes at home
• Lung function
  – FEV$_1$ 97% predicted, FEV$_1$/FVC 85%, FEF 25-75 (normal)
• Blood eosinophils=2.5% (normal)
• Exhaled NO: 38 ppb
• ***(FeNO on last visit in February was 20ppb)***

Therapeutic Options
Question 1: Select appropriate option

A) Maintain present regimen: If it ain’t broke don’t fix it
B) Add Intranasal Steroid (INS) and maintain present asthma regimen
C) Taper mometasone to 220 q hs as patient has normal lung function and minimal symptoms
D) Discontinue ICS because of normal lung function and good symptom control and add a Leukotriene Receptor Antagonist (LTRA) to control upper and lower airway symptoms
E) Add INS and either increase ICS to 220x2 BID or maintain ICS dose and add LABA
RESULTS at 3 week follow up

Choice A) If it aint broke!

- Nasal symptoms increase (tree/grass pollen season)
- Asthma symptoms increase (Loss of Control)
- Symptoms and SABA use almost daily
- Nocturnal awakening once a week
- Activities result in chest tightness and dyspnea
- Sneezing, rhinorrhea itching, stuffy
- FeNO ppb 50ppb
- ACT score 18
B) Add INS but maintain same ICS dose

At 3 week follow up:

- Nasal symptoms minimal
- Yet cough/wheeze 5 days a week
- SABA use 5 days a week
- Nocturnal awakening 3x month
- Some activity restriction
- ACT score 19
- FeNO 45 ppb
Choice C: Taper ICS Dose 220 mcg q.d

At 3 week follow up
- Symptoms: cough or wheeze 5 days/week with increase in upper respiratory sneezing and itching
- Spirometry: PEF 95%, FEV$_1$ 83%, FEV$_1$/FVC 78%
- ACT=17 (uncontrolled level)$^1$
- Exhaled NO: 64 ppb (elevated and increased)$^2,3$

• Assessment: increased impairment and uncontrolled status perhaps due to tapering of ICS during the spring grass pollen season
• Not an optimal choice given the elevated exhaled NO level and impending pollen season

Choice D: Discontinue ICS and add LTRA

- Symptoms daily cough, wheeze dyspnea, minimal nasal symptoms
- Nocturnal awakening
- Frequent SABA use
- Spirometry: PEF 80%, FEV₁ 79% FEV₁/FVC 75%
  - ACT=16 (uncontrolled level)¹
  - Exhaled NO: 70 ppb (elevated and increased)
- Assessment: increased impairment and uncontrolled status due to tapering off ICS during the spring grass pollen season
- Not an optimal choice given the elevated exhaled NO level and increased allergen exposure
Choice E: Increase ICS to 440 BID mcg BID or Add LABA BID or LTRA

- AT 3 week follow up:
  - Asthma symptoms < 2x week, good control
  - Lung function normal ACT 21, FeNO 18ppb
  - Minimal nasal symptoms
  - Optimal option given the presence of an elevated exhaled NO level at > 33ppb and increased > 60% over prior baseline due to tapering of ICS and recent increased exposure to allergen.
  - Will again try to taper ICS after pollen season and titrate monitoring FeNO as well as symptoms.

Predicting Loss of Control (LOC)

Mild to Moderate Asthma n=78
Taper ICS x 6 wks or LOC

↑Exhaled NO is as useful as
↑Sputum Eosinophils and
↑AHR (PD$_{15}$ Hypertonic Saline) in predicting LOC

Increase in FE$_{NO}$
>60% vs. baseline when controlled or > 33ppb
83% predictive of LOC

Exhaled NO, % Eosinophils, PD$_{15}$

Sensitivity vs. 1-Specificity

Lessons in ICS Tapering

- Consider elevated exhaled NO as possible warning of:
  - Ongoing inflammation
  - Subsequent worsening with tapering of ICS (even in situation of clinical control and normal lung function)\(^1,2\)
- Consider importance of temporal triggers:
  - Pollen seasons
  - Continued home smoke exposure may not allow tapering due to the existence of pertinent triggers
- Need multiple assessment parameters to appreciate more fully all the components that comprise the asthmatic:
  - Symptoms, lung function, inflammation, environment, and exacerbations
- These domains/factors appear somewhat independent of one another because their correlation is moderate to poor\(^3,4\)

Lessons in ICS Tapering (cont)

• Exhaled NO levels comprise an important domain separate from symptoms, lung function, exacerbations, and the environment\(^1\)
• Elevated exhaled NO levels, in the context of symptom control and normal lung function, may be an important indicator of impending asthma getting worse, particularly when maintenance-controlled medications are tapered\(^2,3\)
• Promote early follow-up and assess after tapered ICS and elevated exhaled NO levels are observed
• Tapered ICS may lead to increased asthma impairment, particularly in the presence of elevated exhaled NO and increased pollen exposure
• Impairment could be expected to worsen within a relatively short time period (weeks rather than months)\(^4,5\)

Conclusions

- Asthma heterogeneity makes management difficult
- Current asthma guidelines do not sufficiently emphasize the assessment of airway inflammation
- $\text{FE}_{\text{NO}}$ as a measure of eosinophilic inflammation
  - Is quick and easy to perform
  - Has clinical utility that is superior to AHR and induced sputum analysis
  - May be readily incorporated into routine pulmonary function test procedures to optimize care of asthma patients
- $\text{FE}_{\text{NO}}$ represents a significant advance in respiratory medicine
BURDEN OF ASTHMA
Recognizing an UNMET NEED
United States Data

- **PREVALENCE RISING: YET UNDER-DIAGNOSED**
- **POOR CONTROL ⇒ QUALITY OF LIFE (QOL)**
- **DISEASE PROGRESSION: LOSS OF LUNG FUNCTION (IN SOME)**
- **ASTHMA DEATHS**: 4261 (2002)
- **HEALTHCARE COSTS**: $20 Billion/Yr (2009)
  - **HOSPITALIZATIONS**: 1 MILLION (2009)
  - **ED VISITS**: 3 MILLION (2009)
  - **PHYSICIAN OFFICE VISITS**: 12.9 Million/Yr (2003)
  - **LOST WORKDAYS**: 8 Million/Yr
  - **LOST SCHOOL DAYS**: 11.8 Million/YY

NHLBI. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* No. 08-4051. 2007
Asthma Insight and Management (AIM) accessed at “Taking AIM at Asthma.com” 2009
**FE\textsubscript{NO} Measurements Provide a Method of Adjusting ICS Dose**

- 85 children (6-18 years age) allocated to FE\textsubscript{NO} group (n=39) or symptom group (n=46)
- 1 year of steroid titration on FE\textsubscript{NO} improved airway hyper responsiveness and inflammation and did not result in higher steroid doses


*Cut point = 30 ppb
Flow rate = 50 mL/s*
**FE_{NO}** Measurements Provide a Method of Adjusting ICS Dose

1. **Rate of exacerbations (no/patients/yr)**
   - Total: 1.2, 0.8, 0.2
   - Minor: 1.0, 0.6, 0.4
   - Major: 0.0
   - P = 0.27, P = 0.24, P = 0.91

2. **Fluticasone dose (µµµµg/day)**
   - Study entry: 500
   - End of phase 1: 750
   - End of phase 2 (final visit): 750
   - P = 0.36, P = 0.003, P = 0.003

Flow rate = 250 ml/s

Use of Exhaled Nitric Oxide to Guide Asthma Management – The Shaw Study

- One hundred eighteen asthmatics were randomized to a single-blind trial of ICS therapy based on either $F_{NO}$ measurements ($n=58$) or British Thoracic Society guidelines ($n=60$). The primary outcome was the number of severe asthma exacerbations.

- Authors concluded: *An asthma treatment strategy based on the measurement of $F_{NO}$ did not result in a larger reduction in asthma exacerbations or in the total amount of ICS therapy used over 12 months, when compared to current asthma guidelines.*

- Underpowered to prove that dose-titration based on $F_{NO}$ is not better than standard care

- Despite being underpowered a trend towards less exacerbations in the $F_{NO}$ group is observed

- Use of a very low cut point (26 ppb) may lead to poor correlation with sputum eosinophils

- The final dose of steroids used in the $F_{NO}$ group was significantly lower at study end (557 vs 895 µg/day).

\[ P=0.43 \]


\[ \text{Cut point} = 26 \text{ ppb} \]
\[ \text{Flow rate} = 50 \text{ mL/s} \]
NAEPP guidelines plus FeNO offers no further benefit as an indicator of control in the management of inner city asthma children vs. management by NAEPP guidelines alone!

- Patients included only if adherent during 3 week run in
- FeNO + NAEPP group raised ICS for high FeNO values
- ICS was not decreased with low FeNO and high symptoms
- As result, FeNO group used higher ICS doses
- Conventional management resulted in good control in most patients
- No difference in symptoms, asthma control days PFTs

  - **Exacerbations:** no statistical difference but:
    - Similar to the Smith and Shaw articles, there was a numerical reduction in the number of subjects that exacerbated as defined by having at least 1 burst of prednisone in the eNO group as compared to the controls (10% less subjects).

  - **Adherence:** no statistical difference but:
    - It was also shown that FeNO was numerically lower in patients with adherence levels better than 50% than in patients with adherence levels less than 50%.
Evaluation of Inflammation in Asthma

Monitor Airway Inflammation

- Fiberoptic bronchoscopy with endobronchial Biopsy (EBB) and/or bronchoalveolar lavage (BAL)
- Bronchoprovocation
  - Airway hyper responsiveness (AHR) measurement (methacholine, histamine, adenosine)
- Sputum eosinophil induction
- Fractional Exhaled nitric oxide ($FE_{NO}$)
- Exhaled Breath Condensates (pH, LTs, 8-isoprostane)

FE\textsubscript{NO} Can Help Distinguish ICS Responders from Non-Responders

Silkoff

- 24 patients with severe refractory asthma; mean oral steroid dosage 20 +/- 4 mg/day
- 17 healthy controls
- Measured FE\textsubscript{NO} and sputum eosinophils
- Patients with sputum eosinophilia had significantly higher FE\textsubscript{NO} than patients without sputum eosinophilia ($P<0.05$)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>FE\textsubscript{NO} (ppb)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOS pos</td>
<td>10</td>
<td>67.3 (25.6-102.9)</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>EOS neg</td>
<td>14</td>
<td>20.4 (10.5-34.1)</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Control</td>
<td>17</td>
<td>18.3 (13.3-31.2)</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>

Exhaled NO Indicates Poor Response to ICS Therapy in Non-eosinophilic Asthma

Alveolar NO in Adults With Asthma: Evidence of Distal Lung Inflammation


**NS:** Non-significant.

- **Steroid naive**
- **Inhaled steroid treated only**
- **Oral and inhaled steroid treated**

**Alveolar NO concentration ppb**

- Normal
- Mild-to-moderate asthma
- Refractory asthma

***p<0.001; NS: Non-significant.**
Case Vignette #2

An 8 year old African American girl is seen in the clinic for cough and wheeze

She has a 2 year history of gradually worsening cough

When she was younger she had cough and ‘wheeze’ that came during the winter months triggered by viral infections

They were typically treated with antibiotics, albuterol and oral steroids with relief of her s/o

She now has cough for which she takes albuterol about 2 times a week when she remembers to carry her inhaler; sometimes more if she plays a soccer game
Case Vignette #2

O/E: She has allergic shiners and boggy pale nasal turbinates. No wheezing/respiratory distress
Skin testing: Positive to grasses, weeds, and cockroach
PFT:  
  FVC 87% of predicted at 1.84 L  
  FEV1 was 81% of predicted at 1.60 L  
  FEV1/FVC ratio 0.87  
  FEF25-75% 71% predicted at 1.77 L/s  
  Flow-volume loop: normal
CHoices

a) 4 puffs of abuterol followed by post-bd spirometry
b) attribute s/o to allergies and add antiH1 +ICS
c) FENO assessment
d) peak flow monitoring at home
e) call her intermittent asthma based on h/o
f) call her persistent asthma and start controller medication
Case Vignette #2

I typically take this option in such a situation:

a) 4 puffs of abuterol followed by post-bd spirometry

Post bd spirometry:

PFT: 10% FEV1 post-bd change
22% change in FEF25-75%

CHOICES

a) peak flow monitoring at home
b) FENO assessment
c) call her intermittent asthma based on h/o
d) call her persistent asthma and start controller medication
e) attribute s/o to allergies and add antiH1 +ICS
f) methacholine challenge to r/o asthma (BHR)
g) order exercise challenge testing to diagnose asthma
Case Vignette #2

b) FENO assessment

Reasons to support decision?

| Asthma diagnosis       | 80% correct diagnosis in patients 8-75 years using cut-off of 20 ppb  
<table>
<thead>
<tr>
<th></th>
<th>80% correct diagnosis in patients 4-8 years using cut-off of 10 ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td>-when used in conjunction with other parameters</td>
<td></td>
</tr>
<tr>
<td>-in individuals who do not meet the criteria for reversibility</td>
<td></td>
</tr>
<tr>
<td>-normal values 5-20 ppb (upto 15 ppb in kids)</td>
<td></td>
</tr>
</tbody>
</table>
## Utility of Available Diagnostic Tests

### Sensitivity, Specificity, and Positive and Negative Predictive Values for Each of the Diagnostic Tests for Asthma

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak flow variation &gt;20%</td>
<td>0</td>
<td>100</td>
<td>NA</td>
<td>70</td>
</tr>
<tr>
<td>Peak flow increase 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>71</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>FENO₅₀ &gt;20 ppb</td>
<td>88</td>
<td>79</td>
<td>70</td>
<td>92</td>
</tr>
</tbody>
</table>

Figures for bronchodilator reversibility and bronchial hyper responsiveness to hypertonic saline are not given because both these parameters were used to diagnose asthma.

**Differential Assessment of Chronic Cough With $\text{FE}_{\text{NO}}$**

$\text{FE}_{\text{NO}}$ was measured in adults with chronic cough, known asthmatics and healthy controls. Patients with chronic cough and asthma had significantly higher $\text{FE}_{\text{NO}}$ values than non-asthmatics with chronic cough or healthy controls.

**Flow rate = 45mL/sec**

Her FENO was 50 ppb

CHOICES

a) attribute s/o to allergies and add antiH1 +ICS
b) peak flow monitoring at home to establish PEFR variability
c) consider her intermittent asthma based on h/o +FENO elevated due to atopy hence add antiH1 +ICS
d) consider her persistent asthma and start montelukast because she is mild persistent
e) consider her persistent asthma and start inhaled steroids
Case Vignette #2

Best option:

e) consider her persistent asthma with possible eosinophilic inflammation and start ICS

Reasons:

| Selection of therapeutic agent: prediction of response to ICS | FeNO >47 ppb is highly indicative of response in pts with non-specific symptoms. A median exhaled NO level of 54 ppb was the significant cut-point that recognized an FEV1 improvement ≥ 7.5% with ICS but not LTRA in children. An exhaled NO level >25 ppb at baseline was associated with an increased likelihood of a FEV1 improvement ≥ 7.5% (Odds Ratio = 2.8, p < 0.05). |

Fluticasone monotherapy achieves greater improvements in asthma control than PACT combination and montelukast as indicated by $\text{FE}_{\text{NO}}$ measurements.

**Asthma control days stratified by $\text{FE}_{\text{NO}}$**

- $P = 0.0001$
- $P = 0.5$

Use of $\text{FE}_{\text{NO}}$ in selection of therapeutic agent

- When $\text{FE}_{\text{NO}}$ is ↑, children and adolescents with mild-moderate persistent asthma may do better on ICS vs LTRA Rx based on recent studies\textsuperscript{1,2}
- Median exhaled NO level of 54 ppb demonstrated a significant cut-point by recognizing FEV\textsubscript{1} improvement >7.5% with ICS but not LTRA after 8 weeks of treatment\textsuperscript{1}
- Exhaled NO level >25 ppb at baseline is associated with increased likelihood of a FEV\textsubscript{1} improvement >7.5%\textsuperscript{1}
- Patients with lower levels of asthma impairment did as well on an ICS as on a LTRA\textsuperscript{1-4}

The predictive accuracy of $\text{FE}_{\text{NO}}$ to identify steroid response is significantly greater than other conventional predictors.

- Cut point for optimum predictive accuracy = 47 ppb
- Flow rate = 50 mL/sec
- Sensitivity = 82%
- Specificity = 91%

Case Vignette #2

On her return visit 4 weeks later, her FENO was 20 ppb

a) Step up her therapy by adding montelukast
b) Step up therapy by increasing ICS
c) Step up therapy by changing to ICS-LABA
d) Continue on the same regimen
e) Decrease her ICS dose
Case Vignette #2

Best option:

d) Continue on the same regimen

Reasons:

| Evaluation of response to ICS | A reduction of at least 20% in unstable patients indicates efficacy of anti-inflammatory treatment |
FE\textsubscript{NO} Measurements Provide a Method of Adjusting ICS Dose

Ninety seven asthma patients (12 to 75 yrs old) randomly assigned to have their ICS dose adjusted on the basis of either FE\textsubscript{NO} measurements or an algorithm based on conventional guidelines. Primary end point: frequency of exacerbations, secondary end point: mean daily dose of ICS.

Case Vignette #2

She returns 4 months later for a f/u. She says she is doing well and is taking her medications as prescribed. She has had no steroid bursts or ER visits. Her ACT score is 19 (even though she rated herself as well controlled=score 4). Her PFT shows no obstruction

**CHOICES**

a) Step down Rx since PFT is normal and she says she has been well controlled for 4 months

b) Continue ICS

c) Perform an FENO since her ACT indicates borderline control
Case Vignette #2

Best option:
c) do an FENO because her ACT is borderline

CHOICES

a) Attribute her FENO to the fall season and add allergy meds
b) Attribute her FENO to the fall season and step down since she is well controlled
c) Step up Rx by 1-2 steps
d) Consider exploring for non-adherence, inhaler device technique, insurance coverage issues
**Case Vignette #2**

**Best option:**

d) Consider exploring for non-adherence, inhaler device technique, insurance coverage issues

**Reasons:**

<table>
<thead>
<tr>
<th>Identification of non-adherence/non-compliance</th>
<th>Elevated FeNO levels (&gt; 35 ppb) in patients taking maintenance doses of ICS indicates that the patient is not prescribe adequate amounts, the right therapy, or they are not taking it correctly</th>
</tr>
</thead>
</table>

Positive Correlation Between Reduction in Exhaled NO and Compliance with Inhaled Budesonide (BUD)

FE\textsubscript{NO} Facilitates Early Identification of Noncompliance


\[ P = 0.0003 \]
\[ r^2 = 0.5863 \]
Case Vignette #2

However, if it is determined that she has been adherent and technique is correct,

Then Best option:

d) Step up Rx by 1-2 steps

Reasons:

<table>
<thead>
<tr>
<th>Predicting loss of control</th>
<th>If the FeNO level increases 60% between visits, this has a positive predictive value (PPV) of &gt; 80% of an imminent decrease in asthma control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction of asthma relapse</td>
<td>Pediatric: FeNO &gt; 35 ppb ;PPV: 53%; NPV: 91%</td>
</tr>
<tr>
<td></td>
<td>When asymptomatic children in clinical remission stopped taking steroids, FeNo &gt; 49 ppb 2-4 weeks later was an effective predictor of asthma relapse</td>
</tr>
</tbody>
</table>
A $\text{FE}_{\text{NO}}$ value of 49 ppb 4 weeks after discontinuation of ICS had the best combination of sensitivity (71%) and specificity (93%).

40 children of mean age 12.2 years on a median dose of 400 mg budesonide or equivalent (range 100-400).

$\text{FE}_{\text{NO}}$ was measured before and at 2, 4, 12, and 24 weeks after withdrawal of steroids.

Flow rate=50 mL/sec

Clinical Uses of $\text{FE}_{\text{NO}}$ Measurement in Asthma

$\text{FE}_{\text{NO}}$ measurement may help clinicians to

1. Differentiate asthma from other conditions
2. Selection of therapeutic agent: predict response to ICS therapy
3. Possible titration of ICS therapy
4. Predict loss of control and asthma relapse
5. Identify noncompliance