Assessment of Pulmonary Function and Non-Invasive Measures of Inflammation in Children with Asthma

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Asthma is a Complex Disease with Multiple Dimensions that Must Be Evaluated and Managed

- Exacerbations
- Lung Function Impairment
- Symptoms
- FeNO
- Quality of Life (ACT, cACT)
- Atopy & Eosinophilic Inflammation
Complex & Poorly Understood Relationship Between Symptoms, QOL, Lung Function, Exacerbations, Atopy/Eosinophilic Inflammation
Why Perform Lung Function Tests and Assess Airway Inflammation?

- Asthma is the most common chronic disease in children and acute exacerbations account for a large number of ED visits and hospitalizations.
- Yet, it is often under-diagnosed & under-treated as it is a relapsing and remitting disease that is almost always diagnosed clinically.
- Objective monitoring of lung function and inflammation underutilized or unavailable yet…
  - We monitor daily blood sugar for diabetes, ECGs for heart disease, serial blood pressure measures for hypertension, cholesterol levels in hypercholesterolemia, but we do not routinely measure lung function or inflammation in asthma!
Why is Objective Monitoring of Asthma Important?

• Important in establishing the diagnosis.
• Provides objective evidence for the nature and severity of asthma.
• Useful in monitoring the progression of asthma both acutely and over time.
• Useful in assessing the response to intervention.
• But there are limitations to all of the available tests.
Available Pulmonary Function Tests

• Peak Expiratory Flow
• **Spirometry**
  • Body Box Plethysmography
  • Bronchial Challenges
    – Methacholine Challenge
    – Exercise Challenge
• Impulse Oscillometry
• Non-invasive Measures of Inflammation
  – Sputum Induction for Eosinophils
  – Exhaled Nitric oxide (FeNO)
Peak Expiratory Flow Measurement

- Easy to perform, portable, and inexpensive.
- Useful for home monitoring of asthma control.
- Measures flow through the largest airways during the first $1/10^{th}$ of a second during a forced exhalation.
  - It is almost always the least impaired lung function measure.
- Serial PEF measures are no longer recommended.
- Technique:
  1. Perform test standing.
  2. Do 3 consecutive forced expiratory efforts, record highest value.
  3. Perform twice daily (pre/post bronchodilator therapy) when optimizing asthma control and during illnesses.
Serial PEF Measures in a 5 yo Child with Asthma. Was the Prednisone Burst of Sufficient Duration?

Trend more important than value
Establish baseline when stable
Zones based on personal best
  » Green zone 80-100% of best
    • patient doing well, no changes required
  » Yellow zone 60-80% of best
    • moderate airflow obstruction, medications may need intensified
  » Red zone <60% of personal best
    • severe obstruction, requires immediate attention

1 to 2 prednisone burst given, 3=patient admitted with status asthmaticus
PEF Values in an 8 y.o. Asthmatic. What’s Wrong With This Picture?

1-2: Note there is no change in AM & PM PEF rates for 6 days!
* Suspect spurious values
3: Apparent very rapid worsening of PEF values requiring admission for status asthmaticus
Deterioration of AM & PM PEFs Do Not Precede Worsening Symptoms

Spirometry

• More difficult to perform & until recently not portable
  – Takes ≥5 minutes, requires well trained technician
  – Requires forced expiration for 3 to 6 seconds
  – Minimum age ~5 years old

• More sensitive than PER

• Can measure flow from the large to small airways based on the parameter evaluated.

• Can distinguish 2 major types of lung disease:
  – Obstructive lung disease
  – Restrictive lung disease
Flow is related to resistance. The smaller the airway, the greater the magnitude of change in resistance during AW constriction.

Resistance = \( \frac{1}{r^4} \)

Flow = \( \frac{P}{R} \)

As resistance increases, flow decreases.

2 mm reduction in radius =

- 15x increase in resistance
- 7.5x increase in resistance

2 mm reduction in radius:

- 1/5th
- 1/15th
- 1/38th
- 1/75th
Large-Sized Air-Tube Function.
Least affected in children with asthma
\( \text{FEV}_1 = \)

Mid-Sized Air-Tube Function.
Will be more affected than the \( \text{FEV}_1 \)
\( \text{FEV}_1/\text{FVC} \) Ratio =

Small Air-Tube Function.
Always the earliest to be affected & most severely affected in children with asthma
\( \text{FEF}_{25-75} = \)

Airway Inflammation test
\( \text{FeNO} = \)

Asthma is a disease of the air tubes, not the lung tissue. Constriction can be caused by muscle spasm +/- swelling.
Spirometry: Always evaluate the flow-volume and volume-time curves first.

1. Note the difference in exhalation time pre- vs. post-albuterol
2. Note the concavity of the expiratory flow volume loop
3. Note the significant but incomplete reversal of airflow limitation with albuterol
12 y.o. male with severe asthma. AM Spirometry on Day 1

Asthma severity can be determined by assessing either the FEV₁ or FEV₁/FVC ratio (*2007 NHLBI Asthma Guidelines).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-albuterol</th>
<th>Post-albuterol</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>*FVC (% pred)</td>
<td>110</td>
<td>117</td>
<td>6%</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>73</td>
<td>95</td>
<td>30%</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>61</td>
<td>75</td>
<td>23%</td>
</tr>
<tr>
<td>PEF (% pred)</td>
<td>83</td>
<td>116</td>
<td>40%</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (% pred)</td>
<td>30</td>
<td>56</td>
<td>88%</td>
</tr>
</tbody>
</table>

**Notes:**
- FEV₁ >80%
- FEV₁/FVC >80%
- Mild Persistent: 60-80%
- Mod. Persistent: 75-80%
- Severe Persistent: <60
Severe 12 yo asthmatic male. Spirometry on Day 10 after observed therapy & avoidance of perennial aeroallergens

- Note the consistency and reproducibility of the 3 efforts.
- Also note minor scalloping of his inspiratory flow volume loops
- Lastly, his PEF is well above the predicted value, yet has some AF limitation
### Spirometry on Day 10

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effort 1 (best)</th>
<th>% predicted</th>
<th>Effort 2</th>
<th>Effort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>2.43</td>
<td>110</td>
<td>2.46</td>
<td>2.42</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.94</td>
<td>97</td>
<td>1.91</td>
<td>1.83</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>80%</td>
<td></td>
<td>77%</td>
<td>76%</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>4.77</td>
<td>108</td>
<td>4.95</td>
<td>5.15</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (l/s)</td>
<td>1.73</td>
<td>69</td>
<td>1.52</td>
<td>1.39</td>
</tr>
</tbody>
</table>

His lung function has nearly completely normalized with mild small airways obstruction remaining (FEV₁, FEF₂₅-₇₅).
Obstructive Pulmonary Diseases Are By Far the Most Common Type Lung Disease in children

- FEV$_1$, FEV$_1$/FVC decreased:
  - Mild obstruction: FEV$_1$ = 70-100% of predicted
  - Moderate obstruction: FEV$_1$ = 50-69% of predicted
  - Severe obstruction: FEV$_1$ ≤ 50% of predicted
- Diseases characterized by obstruction on expiration:
  - Asthma: accounts for >90% of all cases in children
  - Cystic fibrosis
  - Chronic lung disease of prematurity
  - Emphysema / chronic obstructive pulmonary disease
When well (1 to 2): pre/post FEV₁ values similar, with little airflow obstruction (90-110%).

When ill with URI (2 to 3): variability increases significantly (pre-β agonist values range from 35 to 98% predicted)

In addition, there is a much larger increase in FEV₁ post-albuterol when ill.
1. Note the large difference in AM vs. PM values. PM FEV$_1$ values are better & have less variability ranging from 75-110% predicted.

2. AM values are worse, have greater variability ranging from 38 to 105% of predicted.

3. Significant diurnal variability, is a sign of very poorly controlled asthma.

3. This child eventually required a prednisone burst.
Serial FEV$_1$ Demonstrating Rapid Response to Prednisone Therapy

Pre-β-Agonist FEV$_1$ (%)

Days

Prednisone

20 bid

20 qd
Obstructive Pulmonary Diseases

- Diseases characterized by obstruction on inspiration:
  - Vocal cord dysfunction
    » Common, most often noted in adolescent females with asthma, “Type A” personality, athletic.
    » Trouble “getting air in”, poor response to albuterol and other asthma medications.
  - Tracheal stenosis- very rare.
  - Bilateral vocal cord paralysis- very rare.
What is Wrong with These Flow Volume Loops? & Is this Asthma?

- FVC 85% predicted
- FEV\(_1\) 82% predicted
- FEV\(_1\)/FVC 84%

The FEV\(_1\) is decreased, but the FEV\(_1\)/FVC ratio is normal. Expiratory loop is normal. Inspiratory loop is truncated. This patient has vocal cord dysfunction (VCD)- a masquerader of asthma.
Normal Mid-Inspiratory Glottis

Closed Mid-Inspiratory Vocal Cord Adduction

Mid-Inspiratory Vocal Cord Adduction with Posterior Chinking

Mid-Inspiratory Prolapse of Periglottic Structures into Glottic Airway
Children With Asthma Will Often Have Normal FEV\textsubscript{1} Values When Well

- Although the FEV\textsubscript{1} is considered the “gold standard”, it is not a very useful measure in children with asthma as most stable asthmatic children will have normal FEV1 values.

- The FEV\textsubscript{1}/FVC ratio and FEF\textsubscript{25-75} are more sensitive measures of airflow limitation.

- The FEF\textsubscript{25-75} is always the first & the most impaired measure.
  - Reduced FEF\textsubscript{25-75} values in children with asthma increased the risk for persistence of asthma into adulthood.
  - Association remained significant among children with normal FEV\textsubscript{1} suggesting it was independent from the effects of large airways.
  - FEF\textsubscript{25-75} was also associated with increased AHR and asthma exacerbations.

FEV\textsubscript{1} Is Associated With Risk of Asthma Attacks in a Pediatric Population

Proportion of Observations Reporting an Asthma Attack Over Subsequent Year

Yet...Only a Fraction of Exacerbations Occurred Among Children with Compromised Lung Function

Children with an FEV\(_1\) <60% had a 70% chance of exacerbating, while those with FEV1>80% had a ~25% of exacerbating. But only 0.8% of all exacerbations occurred in children with FEV\(_1\) values <60% of predicted.

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Fuhlbrigge et al., J Allergy Clin Immunol 2001;107:61-67
Histogram of FEV1 Values Among Asthmatics: Children vs. Adults evaluated at NJH

>85,000 measures from 2,740 children and 12,844 adults

The FEF$^{25-75}$ is a More Sensitive Measure of Airflow Obstruction than the FEV$_1$ in Children with Asthma.

>24,000 measures from 2740 children over 5 years

Frequency Distribution of FEV$_1$ in Stable vs. Stable Asthmatic Children on Inhaled Steroids

- Spirometry from 301 children 5-17 yrs with chronic asthma from 1/02-12/04 evaluated.
- All children on inhaled GC therapy
- Those with no symptoms & good adherence = Stable
- Those with active symptoms ± poor adherence = Unstable

De Jong et al., J Allergy Clin Immunol 2006;118:280-282
Restrictive Pulmonary Diseases

- Both FVC & FEV₁ decreased; FEV₁/FVC ratio is normal or above normal
- Rare in children, more common in adults
- Examples: idiopathic pulmonary fibrosis, sarcoidosis
- End-stage CF and ABPA (initially obstructive diseases, but become restrictive in advanced stages of the disease)
The Effect of Acute and Chronic Asthma on Lung Volumes

TLC total lung capacity, RV=Residual Volume, FRC=Functional Residual Volume
IRV=Inspiratory Reserve Volume, ERV=Expiratory Reserve Volume, TV=Tidal Volume
VC=Vital Capacity; FEV1=Forced Expiratory Volume in Second
Complete PFTs in Child with Severe Asthma

<table>
<thead>
<tr>
<th></th>
<th>pre-BA</th>
<th>post-BA</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>4.7</td>
<td>109%</td>
<td>4.9</td>
</tr>
<tr>
<td>TGV</td>
<td>2.2</td>
<td>108%</td>
<td>1.9</td>
</tr>
<tr>
<td>RV</td>
<td>1.3</td>
<td>195%</td>
<td>1.3</td>
</tr>
<tr>
<td>FVC</td>
<td>3.2</td>
<td>102%</td>
<td>2.3</td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>1.6</td>
<td>59%</td>
<td>2.1</td>
</tr>
<tr>
<td>Ratio</td>
<td>50%</td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td>R(_{aw})</td>
<td>7.0</td>
<td>203%</td>
<td>5.6</td>
</tr>
<tr>
<td>S(_{gaw})</td>
<td>0.06</td>
<td>45%</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Measures of Bronchial or Airway Hyperresponsiveness (BHR or AHR)

- BHR is a cardinal feature of asthma. It is the component of asthma that causes the airways to be more reactive than they should. This reactivity results in bronchospasm following exercise, allergen exposure, and during viral URIs.
- There is an intrinsic and extrinsic component:
  - Underlying defect causing airways to be hyper-reactive, likely not treatable.
  - Inflammation results in heightened BHR and can be treated with steroids.
- BHR can measured by methacholine (MCh) challenge
  - Rarely used outside of research studies.
  - Medications that decrease BHR are the most effective controller agents.
A methacholine challenge is considered positive if the PC$_{20}$ is $\leq$ 8 mg/ml.

- Non-asthmatic, no BHR; PC$_{20}$ >25 mg/ml
- Asthmatic, mild BHR; PC$_{20}$ 3.05 mg/ml
- Asthmatic, moderate BHR; PC$_{20}$ 0.38 mg/ml
- Asthmatic, severe BHR; PC$_{20}$ 0.04 mg/ml

With increasing methacholine concentrations, a plateau effect occurs limiting further bronchospasm in most asthmatics.

With increasing concentrations of methacholine there is unlimited AW narrowing. She is at high risk for life-threatening asthma.
Other Measures of BHR: Exercise Challenge Studies

• Exercise Challenge
  – Most asthmatics will develop bronchospasm if they exercise vigorously enough. The phenomena is termed exercise-induced bronchospasm or asthma (EIB/EIA).
  – EIB typically occurs after (5-10 min), not during exercise.
  – 2 types of tests:
    » exercise “free run” test mimics real life, less control.
    » exercise treadmill test controlled environment. A positive test is a 12-15% drop in FEV\(_1\) or PEFR with exercise.
  – Can be performed with/without albuterol pre-treatment
Bronchospasm usually occurs following exercise. It can be attenuated with inhaled steroid therapy over time.


18/22 (82%) had EIA at baseline. After 2 months 59% had EIA & after 8 months 55% had EIA.

28% fall in PEF 3 min post-exercise.
Exercise challenge without albuterol pre-treatment in a child with suspected VCD

Laryngoscopy Report

- Exercise challenge stopped at 4 minutes due to difficulty breathing. Laryngoscopy attempted, but unsuccessful in visualizing vocal cords. Patient had cough and throat clearing.
- On exam patient’s O₂ saturation ranged from 88 to mid-90’s with poor air exchange, and diffuse expiratory wheeze that persisted after 4 puffs of albuterol. No obvious stridor. Aeration and wheeze improved after second 4 puffs of albuterol.
- “Although vocal cords were not visualized, patient had clinical symptoms suspicious for VCD.”

- The flow-volume loops demonstrated significant scooping of expiratory loops with normal appearing inspiratory flow volume loops.
- Patient had a 48% drop in FEV₁ & a 63% drop in her FEF₂₅-₇₅ that only improved after 8 actuations of albuterol.
Exercise challenge with pre-treatment was performed to determine if severe EIB could be blocked.

Exercise challenge with *albuterol/ipratropium pretreatment

- This child had severe EIB, not VCD! Work-up revealed patient to have severe, labile asthma. EIB occurred during (not following) exercise.
- Repeat challenge performed with pre-treatment. Spirometry was performed immediately and 5, 10 min after exercise, if reversal not required sooner.
- Patient had a dyspnea score of 6 (score ≥5 severe dyspnea), yet her lungs were clear during & after the challenge.
- Immediately after exercise, her FEV$_1$ and FEF$_{25-75}$ increased modestly with a fall to baseline 10 minutes after exercise (note how large her FEV$_1$ and FEF$_{25-75}$ values were with albuterol/ipratropium pretreatment.)
Non-invasive measures of inflammation: Why Measure Exhaled Nitric Oxide (FeNO)?
Non-invasive measures of inflammation: Why Measure Exhaled Nitric Oxide (FeNO)?

- Asthma is a chronic disease characterized by airway inflammation. FEV\textsubscript{1} & bronchial challenges are at best indirectly associated with airway inflammation. As FeNO is a non-invasive measure of inflammation, it can help in:
  - (1) detecting of eosinophilic/atopic airway inflammation,
  - (2) diagnosing asthma
  - (3) determining the likelihood of steroid responsiveness,
  - (4) monitoring of airway inflammation to determine the need for steroid therapy,
  - (5) Unmasking otherwise unsuspected non-adherence to steroid therapy.
  - (6) predicting subsequent asthma exacerbations

FeNO & sputum EOS compared against spirometry, response to beta-agonist & oral GC in diagnosing asthma.

47 suspected asthmatics enrolled. 17/47 (36%) had asthma 2\(^{\circ}\) \(\beta\)-agonist response or positive a methacholine challenge.

**Asthma vs. non-asthma:** FeNO 52 vs. 15 ppb, FEV\(_1\) 90% vs. 110%

<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>FEV(_1) improvement with steroid &gt;15%</td>
<td>12</td>
<td>100</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>FEV(_1) &lt;80% predicted</td>
<td>29</td>
<td>100</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>FEV(_1)/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 is Significantly Elevated in Asthma

- FeNO levels were significantly increased in both asthma groups
- FeNO levels significantly higher in patients with allergic asthma versus patients with non-allergic asthma

FeNO Distinguishes Asthma From Other Allergic Conditions

- Asthma diagnosis:
  - FEV\(_1\) increase of >12% predicted and >200 mL or PC\(_{20}\) histamine ≤8 mg/mL
- FeNO = 27 ppb considered optimal cut point for asthma diagnosis
  - PPV = 86%
  - NPV = 87%

AR= allergic rhinitis; NAR= nonallergic rhinitis; PC\(_{20}\) = concentration provoking 20% decrease in FEV\(_1\).

CC: Nasal Allergies

HPI: 12 y.o. male with long history of nasal allergies. Increasing nasal congestion, runny nose, sneezing with nasal throat & eye pruritis for 4 months. Post-nasal drip, throat clearing and cough occurring several times/day attributed to postnasal drip.

PMH: Peanut allergy. Eczema as an infant. Wheezing illness as an infant requiring hospitalization, no longer wheezes and asthma has never been diagnosed.

Medications:

- Loratadine 10 mg daily,
- Nasal saline irrigations
- Intranasal fluticasone prescribed, but rarely used.
Spirometry is Normal in a Male with Nasal Allergies and Cough:

**Parameter**  
9/25  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*FVC (%)</td>
<td>98</td>
</tr>
<tr>
<td>FEV1(%)</td>
<td>93</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>80</td>
</tr>
<tr>
<td>FEF25-75 (%)</td>
<td>83</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td><strong>202</strong></td>
</tr>
<tr>
<td>Serum IgE</td>
<td>153</td>
</tr>
<tr>
<td>Circulating eosinophils</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Percent of predicted  
**Normal range 10-20 ppb

Skin Testing to Aeroallergens:  
**Seasonal:** ash, cottonwood, elm, juniper, maple, aspen, pine, Bermuda, Kentucky blue, Timothy, kochia, ragweed, Russian thistle, sagebrush, Alternaria.  
**Perennial:** dust mites, dog & cat dander.
What Could be the Cause of this Child’s Cough??

What are the most common causes of chronic cough?

1. Post-infectious (pertussis, mycoplasma, viral)
2. Rhinosinusitis with post-nasal drip
3. Gastroesophageal Reflux
4. Asthma
Asthma diagnosed based upon:
1. Current symptoms (daily cough)
2. History of eczema
3. History of recurrent wheeze in the past
4. Elevated FeNO

Plan:
1. NHLBI Asthma Guidelines recommend low dose inhaled steroid therapy for mild persistent asthma.
   - Fluticasone (44 mcg/puff) 2 puffs BID.
2. Albuterol 2 puffs with spacer as needed up to every 4 hr for cough, wheeze, SOB and prior to vigorous activity.
An Elevated FeNO in Asthmatics Predicts Response to Inhaled Steroid Therapy

- Determine likelihood of individual patient response to anti-inflammatory agents, including ICS, & biologics
- Guide changes in dosing of anti-inflammatory medications
  - Step-down or step-up dosing or discontinuation of anti-inflammatory medications

Follow-up visit 3 weeks later: Low dose Flovent Resulted in an Improvement in Symptoms.

- Since last visit, the cough has vanished.
- Significant improvement in the child’s activity level.
- He even won a swimming meet for the 1st time ever!

<table>
<thead>
<tr>
<th>Parameter</th>
<th>9/25</th>
<th>10/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>*FVC (%)</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>FEV₁(%)</td>
<td>93</td>
<td>101</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ (%)</td>
<td>83</td>
<td>123</td>
</tr>
<tr>
<td>**eNO (ppb)</td>
<td>202</td>
<td>39</td>
</tr>
</tbody>
</table>

*Percent of predicted; **Normal range 10-20 ppb
Exhaled Nitric Oxide: A Predictor Of Inhaled Steroid Response

• Comprehensive study evaluated the predictive accuracy of FeNO to other conventional measures to identify response, using several different response parameters.
• 52 subjects with suspected asthma studied in a single-blind, fixed-sequence PC-controlled trial of inhaled fluticasone for 4 weeks.
• Comparisons of predictive accuracy were made between FeNO & other conventional predictors

### TABLE 2. PREDICTORS AND OUTCOME MEASUREMENTS FOR STEROID RESPONSE

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Measures at Baseline Used to Predict Response to Fluticasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>FEV₁ % predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁ bronchodilator response</td>
</tr>
<tr>
<td></td>
<td>PD₂₀ methacholine</td>
</tr>
<tr>
<td></td>
<td>Diurnal peak flow variation (amplitude % mean, over last 7 d of run-in)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Measures of Response to FP Endpoint</th>
<th>Cut point for significant response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Improvement in FEV₁</td>
<td>&gt; 12%</td>
<td>ATS (17)</td>
</tr>
<tr>
<td>B. Improvement in mean morning peak flow (over 7 d)</td>
<td>&gt; 15%</td>
<td>GINA (18)</td>
</tr>
<tr>
<td>C. Reduction in composite symptom score</td>
<td>&gt; 1 point</td>
<td>—</td>
</tr>
<tr>
<td>D. Improvement in PC₂₀ AMP</td>
<td>&gt; 2 doubling dose shift</td>
<td>ERS (19)</td>
</tr>
</tbody>
</table>

FeNO Was the Best Predictor Response to a Number of Response Outcomes

<table>
<thead>
<tr>
<th>Steroid Response Endpoint</th>
<th>Predictors</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, increase of ≥ 12%</td>
<td>BD reversibility &gt; 12%</td>
<td>8</td>
<td>95</td>
<td>33</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 80% predicted</td>
<td>17</td>
<td>88</td>
<td>29</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>PD&lt;sub&gt;20&lt;/sub&gt; methacholine &lt; 8 μmol</td>
<td>58</td>
<td>69</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>PEFR variation &gt; 20%</td>
<td>0</td>
<td>97</td>
<td>NA</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>FeNO &gt; 47 ppb</td>
<td>67</td>
<td>78</td>
<td>47</td>
<td>89</td>
</tr>
<tr>
<td>Mean morning peak flow, increase of ≥ 15%</td>
<td>BD reversibility &gt; 12%</td>
<td>18</td>
<td>98</td>
<td>67</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 80% predicted</td>
<td>36</td>
<td>93</td>
<td>57</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>PD&lt;sub&gt;20&lt;/sub&gt; methacholine &lt; 8 μmol</td>
<td>55</td>
<td>68</td>
<td>32</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>PEFR variation &gt; 20%</td>
<td>9</td>
<td>100</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>FeNO &gt; 47 ppb</td>
<td>82</td>
<td>81</td>
<td>53</td>
<td>94</td>
</tr>
<tr>
<td>Composite symptom score, reduction of ≥ 1 point</td>
<td>BD reversibility &gt; 12%</td>
<td>7</td>
<td>95</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 80% predicted</td>
<td>7</td>
<td>84</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>PD&lt;sub&gt;20&lt;/sub&gt; methacholine &lt; 8 μmol</td>
<td>29</td>
<td>60</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>PEFR variation &gt; 20%</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>FeNO &gt; 47 ppb</td>
<td>43</td>
<td>71</td>
<td>35</td>
<td>77</td>
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<tr>
<td>PC&lt;sub&gt;20&lt;/sub&gt; AMP, increase of 2 doubling doses or more</td>
<td>BD reversibility &gt; 12%</td>
<td>18</td>
<td>100</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 80% predicted</td>
<td>24</td>
<td>91</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>PD&lt;sub&gt;20&lt;/sub&gt; methacholine &lt; 8 μmol</td>
<td>82</td>
<td>85</td>
<td>74</td>
<td>90</td>
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<td>PEFR variation &gt; 20%</td>
<td>6</td>
<td>100</td>
<td>100</td>
<td>69</td>
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<tr>
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<td>FeNO &gt; 47 ppb</td>
<td>82</td>
<td>91</td>
<td>82</td>
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</table>

Patients with Elevated FeNO Levels Had the Greatest Improvements in FEV$_1$, PEF, Symptoms Scores & PC$_{20}$

- Inhaled steroid response was greatest in patients in the highest FeNO tertile (>47 ppb) for each endpoint.
- Predictive values for FeNO were higher than those of the other baseline predictors including FEV$_1$, PC$_{20}$, βAR, PEF variability

βAR=beta-agonist response

Role of Spirometry & eNO to Predict Exacerbations in Treated Asthmatics

- Complementary roles of FEV₁ & eNO to predict exacerbations of asthma were investigated.
- 44 adults (FEV₁ 70%) on fluticasone/salmeterol combination 250 (mcg/puff) 1 puff bid followed x 18 mo.

Gelb et al., Chest 2006;129:1492-1499.
Kaplan-Meier Curve for Time to First Exacerbation Stratified by FEV\textsubscript{1} & eNO

- Independent of baseline FEV\textsubscript{1}, an eNO ≥ 28 ppb increased RR for exacerbation by 3.4-fold
- Independent of baseline eNO, FEV\textsubscript{1} ≤ 76% increased RR by 1.7-fold

Gelb et al., Chest 2006;129:1492-1499.
Clinical Use of Noninvasive Measurements of Airway Inflammation in Steroid Reduction in Children*

- 40 children with stable asthma on inhaled GC therapy had their iGC dose halved every 8 weeks if clinically indicated.
- Median age 12 yr, inhaled glucocorticoid dose 400 mcg/d, FEV₁ 88.5% of predicted, sputum eosinophil 2%, FeNO 21.5 ppb
- Sputum induction, assessment of BHR, eNO, & exhaled breath condensates performed at each visit to predict success or failure of steroid dose reduction.

Increasing FeNO Levels Predict Asthma Worsening During Treatment Withdrawal

75% tolerated ≥1 iGC dose reduction, 30% were completely weaned off, while 38% lost asthma control.

Treatment reduction successful in all children without sputum eosinophils at baseline.

Predictors of failed reduction:
- FeNO >22 ppb OR 6.3
- Sputum eosinophils OR 1.38
- No other parameter including EBC, BHR were predictive