Optimal Assessment of Asthma Control in Clinical Practice: Is there a role for biomarkers?

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Disclosures:
• ACAAI, Immediate Past-President
• Clinical research:
  – Sunovion
  – Shionogi
  – Genetech
• Speakers bureau:
  – AstraZeneca
  – Novartis/Genetech

Learning Objectives
• Understand the challenges of monitoring asthma control.
• Patient perception factors complicate the measurement of control.
• Biomarkers of airway inflammation may be useful for monitoring asthma control.

How Should Control Be Measured in Asthma?

Asthma Control

- Utilization of Healthcare Resources
- Functional Status
- Daytime Symptoms
- Nighttime Awakenings
- Lung Function
- Missed Work and/or School
- Patient Self-Report of Control
- Use of a "Quick Relief" Inhaler and/or Nebulizer

Goal of Asthma Therapy: Achieve Control

Reduce Impairment
• Prevent chronic and troublesome symptoms
• Require infrequent use of reliever SABA (≤2 days/week)
• Maintain "near-normal" pulmonary function
• Maintain normal activity levels
• Meet patients’ expectations of, and satisfaction with, asthma care

Reduce Risk
• Prevent recurrent exacerbations
• Minimize need for emergency department visits or hospitalizations
• Prevent progressive loss of lung function
• Provide optimal pharmacotherapy, with minimal or no adverse effects
Factors Complicating Measures of Control: Variability

- Days per Week With Symptoms:
  - Patients Treated With Placebo
  - Patient 1
  - Patient 2

Factors Complicating Measures of Control: Poor Perception of Dyspnea (POD)

- 113 Asthmatics Evaluated
  - Breathe against 2-way valve load of 6-10, 10-20, and 30-cm H2O for 1 minute
  - Dyspnea defined as modified Borg scale versus 100 controls (normal = mean ± 1 SD)
  - POD
    - Low 29 (26%)
    - Normal 67 (59%)
    - High 17 (15%)
  - β2-Agonist use in 4 weeks
    - Low 1.7/day
    - Normal 2.4/day
    - High 4.1/day
  - Patients with asthma and a low POD had tendency toward
    - Older age
    - More females
    - Longer duration
    - More severe
  - Documented events over 2 years

Asthma Is a Chronic Inflammatory Disease: Pathophysiologic Changes

- Normal Architecture
- Disrupted Architecture

Challenges for the Allergist: Monitoring Asthma Control

- Evaluation of asthma control is a problem
  - No single best way to monitor
  - Should be using multiple measures
- Irregularity of airway reactivity and disease activity results in both inter-patient and intra-patient variability.
- Assessment of asthma control should not be based solely on individual single time-point measures, but rather on multiple parameters.
- Patient perception of asthma control doesn’t correlate with actual assessment.

Adapted from National Asthma Education and Prevention Program.
What Techniques Have Been Investigated to Assess Airway Inflammation in Asthma?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>- Invasive</td>
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<tr>
<td>Airway hyperresponsiveness (AHR)</td>
<td>- Time and labor intensive</td>
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<tr>
<td></td>
<td>- Corrosive effects are exhibited</td>
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<td></td>
<td>- Selection of bronchoconstrictive agents (β2 agonist, adenosine monophosphate, or mannitol)</td>
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<tr>
<td>Tracheal suction (TS)</td>
<td>- Rapid</td>
</tr>
<tr>
<td></td>
<td>- Expensive equipment</td>
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<tr>
<td></td>
<td>- Flow-dependent technique</td>
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<tr>
<td>Sputum eosinophils</td>
<td>- Tedious to perform</td>
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<tr>
<td></td>
<td>- Test not standardized</td>
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<tr>
<td></td>
<td>- Requires specialized lab</td>
</tr>
<tr>
<td>Exhaled breath condensate (EBC)</td>
<td>- Rapid</td>
</tr>
<tr>
<td></td>
<td>- Measurements not standardized</td>
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<tr>
<td>Eosinophilic Cationic Protein (ECP)</td>
<td>- Detected in a variety of body fluids</td>
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</table>

Roles of AHR and Biomarkers in the Control of Asthma

- **AHR**
  - Characteristic functional abnormality of asthma
  - Leads to variable airflow and intermittent symptoms in patients with asthma
- **Sputum eosinophils**
  - Possibly play a role in the release of growth factors and airway remodeling
  - May be a marker for future loss of control
- **FE_{NO}**
  - Elevated concentrations associated with inflammation in asthma
  - Several studies have demonstrated a relationship between asthma control and severity and FE_{NO}

Monitoring Asthma Inflammation: AHR

Summary of Sont et al study results:

- Patients treated by AHR strategy had a 1.8 fold lower rate of mild exacerbations vs patients using the reference strategy (using existing guidelines with respect to measuring symptoms and lung function).
- FEV1 improved to a greater extent in the AHR strategy.
- In the AHR strategy the average difference in ICS dose over the 2-year period had a median difference of 400 µg/day more in the AHR group
- There was a greater reduction of the subepithelial reticular layer in the AHR group.

Summary of Green study results:

- Patients in the sputum management group had significantly fewer severe asthma exacerbations than patients in the BTS group (35 vs 109, P=.01)
- In the sputum management study, there was no difference in mean ICS dose between groups overall.
- However, a subgroup analysis of patients with noneosinophilic inflammation revealed a mean difference of 1425 µg/day, with decreased ICS use in the sputum strategy group
- Therefore monitoring sputum eosinophils could help identify asthma patients with eosinophilic inflammation who are responsive to CS.

Monitoring Asthma Inflammation: Sputum Eosinophils

- **BTS Management Strategy**
- **Sputum Eosinophil Strategy**

Exacerbation Incidence (N=74)

<table>
<thead>
<tr>
<th>Number of Exacerbations</th>
<th>BTS Management Strategy</th>
<th>Sputum Eosinophil Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>16</td>
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<tr>
<td>26</td>
<td>26</td>
<td>23</td>
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<td>35</td>
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<td>31</td>
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<td>59</td>
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<td>56</td>
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<tr>
<td>75</td>
<td>75</td>
<td>72</td>
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<tr>
<td>93</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>169</td>
<td>169</td>
<td>166</td>
</tr>
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</table>

BTS = British Thoracic Society
Adapted from Green RH et al. Am J Respir Crit Care Med. 2002;165:1716-1721.

Limitations of Sputum Eosinophils as a marker for asthma severity

- Even though there is a relationship between number of eosinophils and asthma severity, there is much scatter.
- In the European Network for Understanding Mechanism of Severe Asthma (ENFUMOSA), eosinophils did not distinguish severe asthmatics from those well controlled on low or moderate doses of ICS.

**Monitoring Asthma Inflammation: **FeNO

- A biomarker that has been increasingly used in clinical practice, now has CPT billing code: 95012.
- May be useful to rule out a diagnosis of asthma in patients presenting with dyspnea
- Increased concentrations may be associated with insufficient asthma control
- May be useful to guide therapy and assess adherence with ICS
- May be useful to identify eosinophilic asthma phenotype.

**Sources for nitric oxide detected in exhaled air**

- Nobel Prize in Physiology or Medicine in 1998 awarded to Furchgott, Ignarro, & Murad for “discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system.”

**FeNO: Diagnostic Properties**

<table>
<thead>
<tr>
<th>FeNO (ppb)</th>
<th>Asthma (%)</th>
<th>Nonsensit (31-39) (%)</th>
<th>Predict Positive (%)</th>
<th>Predict Negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>57</td>
<td>97</td>
<td>85</td>
<td>69</td>
</tr>
<tr>
<td>≥28</td>
<td>20</td>
<td>97</td>
<td>93</td>
<td>73</td>
</tr>
</tbody>
</table>

- Asthma diagnosed by bronchodilator reversibility and/or bronchial hyperresponsiveness (shown above purple line)
- Comparison of FeNO with other diagnostic tests is shown at bottom.
**Summary of Smith et al study results:**

- This study enrolled 110 patients with chronic asthma on regular ICS therapy for 6 months. At the end of run-in, patients began receiving fluticasone 750 µg/day.
  - In phase 1, the dose was adjusted at each visit according to nitric oxide level (\( \text{FE}_{\text{NO}} \) group) or asthma control (control group).
  - In phase 2, a patient’s ICS dose could be increased according to the same protocol, but it could not be decreased.
- At the end of 12 months, patients in the \( \text{FE}_{\text{NO}} \) group had used significantly less ICS (mean=370 mcg) than those in the control group (mean=641 mcg) (\( P=.003 \)).
- There was a non-significant reduction (45.6%) in exacerbation rates in the \( \text{FE}_{\text{NO}} \) group.

**Summary of Shaw et al study results:**

- 118 patients with asthma were randomized to a single-blind trial of ICS therapy based on \( \text{FE}_{\text{NO}} \) measurements (n=58) or British Thoracic Society guidelines (n=60).
  - In the \( \text{FE}_{\text{NO}} \) group, the mean rate of exacerbations was 0.33 per patient per year (18 exacerbations among 12 subjects), compared with 0.42 in the control group (26 exacerbations among 19 subjects; \( P=.43 \)).
  - The \( \text{FE}_{\text{NO}} \) group used 11% more inhaled corticosteroid overall compared with the control group (not significant).
  - However, the final daily dose of ICS was significantly lower in the \( \text{FE}_{\text{NO}} \) group compared with control (557 versus 895 µg; \( P=.028 \)).

**Other potential biomarkers-Periostin**

- Periostin is a systemic biomarker of airway eosinophilia in asthma.
- Elevated periostin was found to correlate with three-gene bronchial epithelial Th2 signature in a subset of asthmatics.
- Elevated periostin levels associated with eosinophilic airway inflammation.

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*Other Studies Suggest That Use of a \( \text{FE}_{\text{NO}} \) Treatment Strategy Does Not Improve Outcomes*

<table>
<thead>
<tr>
<th>Time Elapsed (months)</th>
<th>No. of Exacerbations</th>
<th>BTS Treatment Strategy</th>
<th>( \text{FE}_{\text{NO}} ) Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>19 Patients, 26 Exacerbations Final ICS dose 895</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12 Patients, 18 Exacerbations Final ICS dose 557</td>
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<td></td>
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*Other potential biomarkers-Periostin*

- Periostin is a systemic biomarker of airway eosinophilia in asthma.
- Elevated periostin was found to correlate with three-gene bronchial epithelial Th2 signature in a subset of asthmatics.
- Elevated periostin levels associated with eosinophilic airway inflammation.
In High-Periostin group, FeNO fell from baseline mean = 37 by 34.4%.

In Low-Periostin group, FeNO fell from baseline mean = 25.3 by 4.3%.

Summary: Biomarkers have potential utility in the assessment of airway inflammation in patients with asthma and potential in helping to monitor control.

- AHR is time- and labor-intensive
  - Methacholine may be more useful for diagnosis
  - Mannitol has potential for assessing responsiveness to therapy
- Sputum eosinophils
  - Excellent research tool
  - Clinically useful in predicting exacerbations and ICS dose titration
- FeNO
  - Greatest ease of use
  - Useful for ruling out a diagnosis of asthma, and possibly for assessing ICS adherence
- Future biomarkers
  - Periostin
  - ?

Conclusions

- NAEPP guidelines recognize control as the goal of asthma management.
- At this time Expiratory Spirometry is an effective tool to monitor asthma control.
- Biomarkers use may be helpful in the future to help monitor control for asthma patients.