EFFECTIVE ASTHMA MANAGEMENT IN PRIMARY CARE
Severity Assessment, Guidelines, and New Therapeutic Options

Bradley E. Chipps, MD, FAAP, FAAAAI, FAAAAI, FCCP
President-Elect, American College of Allergy, Asthma & Immunology
Medical Director, Capital Allergy & Respiratory Disease Center
Sacramento, CA

Educational Objectives
- Review methods used to assess asthma severity and control
- Review current guidelines for treating asthma
- Discuss phenotypes and endotypes in asthma and the use of biomarkers in clinical practice
- Examine the role of existing and potential future biologic agents in treating severe, refractory patients

Methods to Assess Severity and Control

Definition of Asthma
A chronic inflammatory disease of the airways with the following clinical features:
- Episodic and/or chronic symptoms of airway obstruction
- Bronchial hyperresponsiveness to triggers
- Evidence of at least partial reversibility of the airway obstruction
- Alternative diagnoses are excluded

Clinical Evaluation of Asthma
- History and physical examination
- Validated questionnaires to assess severity
- Pulmonary function (spirometry)
- Biomarkers
  - Blood eosinophil count
  - Exhaled nitric oxide
- Allergy testing

Asthma Control
Current Impairment and Future Risk

Current impairment
- Symptoms >2 day/week
- Rescue med >2 days/week
- Nighttime awakening >1 time/week
- FEV1 or PEF <80% predicted
- Decrease in normal activities

Future risk
- At least 2 exacerbations/year requiring oral corticosteroids (OCS)
- Need for urgent medical care, including ED visits or hospitalization
**Score**

- This test can help a parent determine if a child's breathing problems are not under control and when medical advice should be sought. Designed for children who:
  - Are under 5 years of age
  - Have a history of 2 or more episodes of wheezing, shortness of breath, or cough lasting more than 24 hours,  **AND**
  - Have been previously prescribed bronchodilator medicines, also known as quick-relief medications, for respiratory problems  **OR** have been diagnosed with asthma

- **Score 80**: Child's breathing problems may not be under control.
- **Score 90**: Child's breathing problems seem to be under control.

**Assessment of Asthma Control: Asthma Control Test (C-ACT)**

A longitudinal study of patients with asthma reported that C-ACT is reliable, valid, and responsive to changes in asthma control over time. In the clinical setting, the ACT should be a useful tool to aid physicians in identifying patients with uncontrolled asthma, facilitating their ability to follow patient progress with treatment.

**Are Most Patients With Asthma Well-Controlled?**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Percent with uncontrolled asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>TENOR¹</td>
<td>1,539</td>
<td>69.8</td>
</tr>
<tr>
<td>AIM²</td>
<td>2,500</td>
<td>70.8</td>
</tr>
<tr>
<td>CHOICE³</td>
<td>310</td>
<td>85.7</td>
</tr>
</tbody>
</table>


**Risk of Future Severe Asthma Event in Patients with Past Severe Asthma Event**

<table>
<thead>
<tr>
<th>Severe Asthma Event</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of severe exacerbation with history of recent exacerbation</td>
<td>6.33</td>
</tr>
<tr>
<td>Risk of OCS treatment with history of recent OCS treatment</td>
<td>3.91</td>
</tr>
</tbody>
</table>


**Important Factors Which Contribute to Poor Asthma Control**

- Rhinitis and sinusitis
- Gastroesophageal reflux disease
- Low vitamin D
- Obesity
- Obstructive sleep apnea
- Persistent lower respiratory tract infection
- Psychologic (anxiety, depression)
- Smoking
- Unabated environmental trigger
- Poor response to therapy

**Spirometry: An Important Test for Assessing Asthma**

- Low FEV1 is linked to lower quality of life and higher risk of exacerbations
- May not be able to accurately assess level of pulmonary function from symptoms and examination
- May be mastered by physician and office assistant
- Should be assessed at least once-yearly

---

**Global Initiative for Asthma. Global strategy for asthma management and prevention, 2017.**
Available at: [http://ginasthma.org/](http://ginasthma.org/).

---

**Pulmonary Function Test**

---

**Biomarkers and Asthma Pathogenesis**

- Biomarkers allow physicians to determine the primary pathogenetic pathway in a given patient
  - Th2 (Type 2) pathway
    - Presence of interleukins 4, 5, and 13
    - Elevated blood and sputum eosinophils
    - Present in 70% of asthma
  - Non-Th2 pathways
    - Inflammatory cells and cytokines poorly-characterized

---

**Epithelial Cells Play a Critical Role, as Well**

---

**Blood Eosinophils**

- Important identifier of Th2 (Type 2) pathophysiology
- Most widely accepted cut-off value separating "eosinophilic" and "non-eosinophilic" = 300/mcl
- Eosinophil count proportional to risk of asthma exacerbation
- May vary significantly over time
- Advantage = inexpensive and widely available

**Blood Eosinophil Counts and Risk of Asthma Exacerbations**

Claims database analysis examining eosinophil count and exacerbations requiring systemic CS or ER/hospital care

**Exhaled Nitric Oxide (FeNO)**

- Help identify eosinophilic asthma phenotype
- Diagnose steroid-responsive airway inflammation
- Help support asthma diagnosis and etiology of respiratory symptoms
- Disadvantage = requires specialized equipment

**Exhaled Nitric Oxide**

**Important Ways to Divide Asthma Into Subtypes**

**What is a phenotype?**

The outward manifestation of an individual’s genetics which is the result of an interaction with the environment and which may change over time in response to new environments

**What is an endotype?**

A phenotype of a disease state which has been well-characterized with respect to pathophysiologic mechanisms

**Separation of Asthma into Clinical Phenotypes**

- In past, asthma was characterized by the presence or absence of allergy without consideration of other characteristics
- Recent studies - unbiased hierarchical cluster analysis
  - Clinical characteristics (gender, age of onset, severity)
  - Physiology (lung function, airway hyperresponsiveness)
  - Triggers (allergens)
  - Sputum inflammatory cells (eosinophils, neutrophils)
- Sum total of characteristics are segregated into groups, with no single feature playing a predominant role in the classification
**EFFECTIVE ASTHMA MANAGEMENT IN PRIMARY CARE**

Severity Assessment, Guidelines, and New Therapeutic Options

---

### Tree Analysis

[Tree Analysis Image]

### Demographics and Clinical Characteristics of the SARP subjects

[Cluster Analysis Image]

### Common Endotypes of Severe Asthma

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Clinical/physiologic characteristics</th>
<th>Inflammatory phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset allergic</td>
<td>Frequent history of atopic dermatitis, usually have allergic rhinitis</td>
<td>Eosinophilic</td>
</tr>
<tr>
<td>Late-onset, minimally allergic</td>
<td>Frequent chronic rhinosinusitis/polyps; more severe obstruction; may have NSAID intolerance</td>
<td>Highly eosinophilic</td>
</tr>
<tr>
<td>Late-onset obese</td>
<td>Nonallergic, often with pulmonary restriction</td>
<td>Non-eosinophilic</td>
</tr>
<tr>
<td>Late-onset nonallergic</td>
<td>May have significant respiratory tract infection or GERD</td>
<td>Non-eosinophilic</td>
</tr>
</tbody>
</table>

### Current Guidelines for Treating Asthma

[GINA: Step-Guided Treatment Image]

### What Percent of Patients are Controlled with ICS and ICS/LABA?

<table>
<thead>
<tr>
<th>Stratum*</th>
<th>N</th>
<th>Well-controlled (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - FP</td>
<td>544</td>
<td>65</td>
</tr>
<tr>
<td>1 - FP-S</td>
<td>539</td>
<td>71</td>
</tr>
<tr>
<td>2 - FP</td>
<td>577</td>
<td>62</td>
</tr>
<tr>
<td>2 - FP-S</td>
<td>583</td>
<td>69</td>
</tr>
<tr>
<td>3 - FP</td>
<td>587</td>
<td>33</td>
</tr>
<tr>
<td>3 - FP-S</td>
<td>568</td>
<td>52</td>
</tr>
</tbody>
</table>

*Stratum 1 = no ICS
Stratum 2 = < 500 mcg ICS
Stratum 3 = 500-1000 mcg ICS

---

*Stratum 1 = no ICS
Stratum 2 = < 500 mcg ICS
Stratum 3 = 500-1000 mcg ICS
What is Effective for Asthma Beyond ICS/LABA?

- Leukotriene modifiers
  - Montelukast = leukotriene receptor antagonist
  - Zileuton = 5-lipoxygenase inhibitor
- Neither agent shown to have benefit added to ICS/LABA in DBPC trials, although may be helpful in patients with aspirin-exacerbated respiratory disease
- Long-acting muscarinic antagonists
  - Effective in conjunction with ICS (in place of LABA) or as 3rd-line therapy in addition to ICS/LABA

Effects of Tiotropium on FEV1 and Asthma Exacerbations

Biologic Agents in Asthma

- Unlike conventional inhaled and oral therapies for asthma, biologic agents are targeted at specific molecules responsible for asthma pathogenesis
- These biologic agents are typically formulated as monoclonal antibodies which are administered systemically

Existing and Future Biologic Agents in Treating Severe, Refractory Asthma

Biologic Agents Currently Available for Severe Asthma

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Main target</th>
<th>Class of agents</th>
<th>Specific compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>IgE</td>
<td>Anti-IgE</td>
<td>Omalizumab</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>Anti-IL5</td>
<td>Mepolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reslizumab</td>
</tr>
<tr>
<td>Late-onset with eosinophilia</td>
<td>Eosinophils</td>
<td>Anti-IL5</td>
<td>Mepolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reslizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Benralizumab*</td>
</tr>
</tbody>
</table>

*Submitted to FDA

Anti-IgE Antibody Therapy (Omalizumab) for Severe Allergic Asthma

- Humanized (95%) mAb against IgE – indicated in perennial allergic asthma
- Significant improvement of outcomes in patients receiving 3 controllers:
  - 25% less exacerbations in patient using maximal inhaled therapy
  - Improved asthma symptoms and AQLQ
  - Small improvements in lung function
- Overall response rate 50-60% - why not higher?
  - Absence of active inflammation
  - Insufficient dose of drug in some patients
  - Absence of relevant allergen exposure
  - Mechanisms other than IgE-mediated inflammation, e.g., infection, advanced remodeling

MEDX
MEDICAL EDUCATION EXCHANGE
EFFECTIVE ASTHMA MANAGEMENT IN PRIMARY CARE
Severity Assessment, Guidelines, and New Therapeutic Options

The Targets: IL-5 or Eosinophils (IL-5Rα)

Benralizumab

Mepolizumab Reslizumab

Eosinophil

• Raised levels present in 40% to 60% of asthmatics
• Release toxins that promote airway inflammation in asthmatic patients

IL-5

• Principal eosinophilic regulatory cytokine
• Involved in the maturation, differentiation, survival, and activation of eosinophils


Mepolizumab: The DREAM Study


Benralizumab and Exacerbations

By Eosinophil Status

≥ 200 cells/μL
≥ 300 cells/μL
≥ 400 cells/μL

By Baseline Eosinophil Level

Annual Exacerbation Rate

RR = 24%
P = .362

RR = 30%
P = .131*

RR = –30%
P = .327

RR = 57%
P = .015*

RR = 41%
P = .096*

RR = 43%
P = .049*

RR = –7%
P = .822

RR = 6%
P = .844

RR = 70%
P = .002*

RR = 57%
P = .024*

RR = 36%
P = .173

RR = –9%
P = .781

RR = 22%
P = .284

• In the LEos population, significant improvement was observed for the q2w regimens vs placebo, but not for the q4w regimens

• In the overall population, significant improvement was observed for all dupilumab dose regimens vs placebo

• In the LEos population, significant improvement was observed for the q2w regimens vs placebo, but not for the q4w regimens

Lung Function: % Change in FEV1


Dupilumab (Anti-IL-4/13Ralpha): A New Biologic Agent in Development for Severe Asthma


Tezepelumab (Anti-TSLP): A New Biologic Agent in Development for Severe Asthma

Case Studies

Case #1

- MP is a 45-year-old white male with a 3-year history of asthma, which has been worsening over the past year.
- Also has a 6-year history of chronic nasal congestion and postnasal drip with 2 sinus infections per year.
- Severe wheezing and rhinorrhea after taking ASA and other NSAIDs over the last 3 years.
- Asthma is a daily problem in spite of taking ICS/LABA and LAMA and intranasal corticosteroids for nasal/sinus symptoms.
- He has had 4 episodes of asthma exacerbation, 3 requiring OCS, during the past year.

Physical Examination

- Nose - bilateral nasal polyps
- Pharynx - mucopurulent secretions in posterior pharynx
- Chest - bilateral wheezing and decreased air exchange

Laboratory Values

- **PFT**
  - FVC: 88% predicted
  - FEV1: 62% predicted
  - FEV1/FVC: 0.60
  - 14% bronchodilator response
- FeNO = 62 ppb
- Absolute EOS = 454 cells/ml
- Total serum IgE = 42 IU/ml
- Allergy skin tests = borderline reactions to ragweed and elm tree pollens

Potential Therapies

- Leukotriene modifier, particularly zileuton (5-LO inhibitor)
- ASA desensitization and maintenance therapy
- Anti-IL-5 antibody therapy (mepolizumab or reslizumab)

Effectiveness of Various Medications in AERD

A survey analyzing patient observations of treatment effectiveness in those with AERD showed that aspirin was most beneficial, followed by a leukotriene receptor agonist and a combination of medicines. However, the majority of patients reported that no medication made a difference in symptoms. Despite ongoing medical therapy, the burden of disease remains high in these patients.
**EFFECTIVE ASTHMA MANAGEMENT IN PRIMARY CARE**

**Severity Assessment, Guidelines, and New Therapeutic Options**

---

**Long-term Aspirin Therapy**

- **Goal** = ASA 650 mg BID
- Reduces nasal congestion, anosmia, recurrent sinusitis
- Similar asthma control with less OCS
- Difficult to maintain long term due to gastritis

---

**Case #2**

- LS is a 36-year-old woman with asthma since age 8 years; has been worsening over past 2 years
- Also has had year-round nasal congestion, sneezing, and itchy eyes and nose since childhood with seasonal worsening in the spring and fall seasons for the same length of time
- Had flexural eczema in childhood, and now has frequent skin dryness and erythema over her neck and occasionally around her eyes
- Has been treated with medium-dose ICS/LABA and oral H1 antihistamine for past year but has continued to have some daily symptoms and had 3 asthma exacerbations in the past year requiring OCS
- Her home environment is noteworthy for a pet rabbit

---

**Physical Examination**

- Nose – pale, swollen inferior nasal turbinates and watery, clear secretions bilaterally
- Chest examination – clear
- Skin – mild erythema and papulation on her anterior neck

---

**Laboratory Values**

- **PFT**
  - FVC: 92% predicted
  - FEV1: 74% predicted
  - FEV1/FVC: 0.66
  - 20% bronchodilator response
- FeNO = 35 ppb
- Absolute EOS = 310 cell/mL
- Total serum IgE = 276 IU/mL
- Allergy skin tests = large reactions to Dermatophagoides pteronyssinus (dust mite) and Alternaria mold; negative to rabbit dander

---

**Potential Therapies**

- Leukotriene modifier, particularly montelukast
- LAMA
- Anti-IgE antibody therapy (omalizumab)

---

**Key Points to Improve Adherence**

- Use effective techniques to promote open communication
- Ask patient’s or parent’s concerns and goals for the visit
- Ask for any concerns patients or parents have about medicines (e.g. safety, impact, convenience, and cost)
- Assess patient’s and family’s perceptions of the severity level of the disease and how well it is controlled
- Assess level of family and social support
- Assess levels of stress, anxiety and depression
- Assess ability to adhere to a written asthma action plan
**Patient Education:**

**Expert Panel Recommendation - NAEPP**

- Clinicians teach patients and families the basic facts about asthma (especially the role of inflammation), need for each medicine, especially inhaled steroids, medication skills, and self-monitoring techniques (Evidence A)
- Provide all patients with a written asthma action plan:
  - Daily management
  - Recognize and handle worsening asthma
- Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B)
- Clinicians teach patients environmental control measures

**Summary**

- A significant proportion of patients with asthma have poorly controlled symptoms
- Asthma may be divided into a number of phenotypes and endotypes which is partly predicated upon inflammatory cell infiltration into the airways
- Patients with highly eosinophilic asthma are more likely to have more severe disease with recurrent exacerbations
- Current and future biologic therapies have targeted specific molecules (such as IgE and IL-5) and inhibition of these targets may reduce symptoms and exacerbations significantly
- Inhibition of IL-4 – IL-13 axis helps both atopic dermatitis and asthma

---

**Thank you!**