Differentiating Difficult to Control vs. Severe Asthma

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HPI: 38 year old female with severe persistent asthma on chronic oral steroid therapy p/w increasing SOB and worsening wheezing.

Asthma history
Diagnosed with asthma at age 13
30-40 hospitalizations for asthma throughout her life
Endotracheal intubation X 1 for status asthmaticus
Chronic steroid dependence since 2003
Has been treated for contributing diseases
— GERD, Allergic rhinitis (h/o nasal polyps)

Current status:
— Daily symptoms of shortness and wheezing, limited activity
— Use of rescue inhalers 6-8x/day
— Adherent with her medical regimen
— Treated with omalizumab for six years with reduction but not resolution of exacerbations
**Past Medical History:**

1. Severe Persistent Asthma
2. Allergic rhinitis
3. GERD
4. Fibromyalgia
5. Major Depressive Disorder

**Allergies:**
ASA - causes rash and wheezing

**Medications:**

1. Methylprednisolone 16 mg daily
2. Fluticasone/Salmeterol 500/50 mcg inhalation b.i.d.
3. Montelukast 10 mg daily
4. DuoNeb as needed
5. Albuterol INH 3-4 times daily
6. Omeprazole 20 mg twice daily
7. Loratadine 10 mg daily
8. Fluticasone Nasal 1 puff twice daily
9. Calcium/Vitamin D
10. Alendronate 70 mg weekly
11. Xolair 300 mg SQ q 2 weeks

**Social History:**
Married with 3 children and husband, 2 dogs, outside cats, office work with no exposures, non-smoker.

**Family History:**
Mother with asthma and atopic dermatitis

**Physical Exam:**
Pulmonary - prolonged expiration with moderate air movement and diffuse expiratory wheezing.
Pulmonary Function Testing:

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref</th>
<th>Best</th>
<th>% Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>3.05</td>
<td>2.40</td>
<td>78%</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.65</td>
<td>1.27</td>
<td>48%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>86</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>FEF 25-75%</td>
<td>3.28</td>
<td>0.58</td>
<td>18%</td>
</tr>
<tr>
<td>PEF</td>
<td>5.78</td>
<td>2.89</td>
<td>50%</td>
</tr>
<tr>
<td>MVV</td>
<td>109</td>
<td>45</td>
<td>41%</td>
</tr>
</tbody>
</table>

What is Asthma?

Asthma is a chronic disease characterized by recurrent episodes of:
- wheezing,
- shortness of breath, and
- cough 2o to reversible airflow obstruction.

Bronchial Hyperresponsiveness & Airway Inflammation are hallmarks of asthma.

Definition of Severe Asthma > age 6
(ATS/ERS Guidelines; ERJ 2014;43:343)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.
Assessing Asthma Control in Patients ≥12 Years of Age

### Components of Control

#### Classification of Asthma Control (Youths 12 years of age and adults)

<table>
<thead>
<tr>
<th>Symptom Impairment</th>
<th>Well-Controlled</th>
<th>Not Well-Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-Controlled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Limitation</td>
<td>1 day/week</td>
<td>1-2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>None</td>
<td>Rare</td>
<td>Extensive</td>
</tr>
<tr>
<td>Medication usage</td>
<td>None</td>
<td>Rare</td>
<td>Extensive</td>
</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>90% predicted</td>
<td>60-80% predicted</td>
<td>&lt;60% predicted</td>
</tr>
<tr>
<td><strong>Not Well-Controlled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Limitation</td>
<td>2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>Frequently</td>
<td>1-3x/month</td>
<td>4x/week</td>
</tr>
<tr>
<td>Medication usage</td>
<td>Several times per day</td>
<td>&gt;2 days/week</td>
<td>4x/week</td>
</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>60-80% predicted</td>
<td>40-60% predicted</td>
<td>&lt;40% predicted</td>
</tr>
<tr>
<td><strong>Very Poorly Controlled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Limitation</td>
<td>&gt;2 days/week</td>
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</tr>
<tr>
<td>FEV1 or peak flow</td>
<td>&lt;60% predicted</td>
<td>&lt;40% predicted</td>
<td>&lt;40% predicted</td>
</tr>
</tbody>
</table>

### Risk Factors

- Evaluation requires long-term follow-up care.
- Treatment-related adverse effects vary in intensity. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.
- Medication side effects vary in intensity. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.

### Stepwise Approach for Managing Asthma in Patients ≥12 Years of Age

#### Step 1
- Preferred: SABA PRN
- Alternative: Cromolyn, Nedocromil, LTRA, or Theophylline

#### Step 2
- Preferred: Low-dose ICS
- Alternative: Medium-dose ICS or Low-dose ICS + LABA

#### Step 3
- Preferred: Medium-dose ICS + LABA
- Alternative: Medium-dose ICS + LTRA, Theophylline, or Zileuton

#### Step 4
- Preferred: Medium-dose ICS + LABA
- Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

#### Step 5
- Preferred: High-dose ICS + LABA
- Alternative: High-dose ICS + LABA + oral corticosteroid

#### Step 6
- Preferred: High-dose ICS + LABA + oral corticosteroid
- Alternative: Consider Omalizumab for patients who have allergies

### Challenges with Definition

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

- Inherent in the definition of severe asthma is the exclusion of individuals who present with “difficult” asthma in whom appropriate diagnosis and/or treatment of confounders vastly improves their current condition.
- Therefore, it is recommended that patients presenting with “difficult asthma” have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months.
- Thus, severe asthma according to the ATS/ERS definition only includes patients with refractory asthma and those in whom treatment of comorbidities such as severe sinus disease or obesity remains incomplete.
**Contribution of Asthma Control to Definition of Severe Asthma**

ERS/ATS Severe Asthma Guidelines (ERJ 2014;43:343)

Uncontrolled asthma defined as at least one of the following:
1) Poor symptom control: ACQ consistently > 1.5, ACT < 20 or “not well controlled” by NAEPP/GINA guidelines
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids (> 3 days each) in the previous year
3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

**Poor Control vs Severe Asthma**

- Evidence of any one of these four criteria while on current high-dose therapy identifies the patient as having “severe asthma”.
- Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma.
- Fulfillment of this definition predicts a high degree of future risk both from the disease itself (exacerbations and loss of lung function), as well as from side-effects of the medications.

**Approach to Management/Contributing Factors/Co-Morbid Conditions**

- Examine for concomitant medical disorders, i.e. sinusitis/rhinitis, nasal polyps – 75-80% prevalence
- Obstructive Sleep Apnea
- Vocal Cord Dysfunction
- GERD - acid and non-acid reflux – 60-80% prevalence
- Obesity
- Steroid insensitivity – can be affected by co-morbidities or asthma itself
Approach to Management/Contributing Factors/Co-Morbid Conditions

- Atopy/Environmental exposures
- Ongoing smoking vs. Asthma/COPD overlap
- Alternative diagnoses
- Psychological factors – Anxiety/Depression – 25-49% prevalence
- Non-adherence
- Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, ACE inhibitors

Diagnoses Masquerading as Asthma in Adults

- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (e.g. angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis

Diagnoses Masquerading as Asthma in Adults

- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg–Strauss syndrome
Diagnoses Masquerading as Asthma in Children

- Dysfunctional breathing/vocal cord dysfunction
- Bronchiolitis
- Recurrent (micro)aspiration, reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression

Diagnoses Masquerading as Asthma in Children

- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumor
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease
- Foreign Body

Key Concepts

- Control: Significant activity of known disease
- If control poor on high dose medication, likely to have severe asthma
- Difficult asthma can suggest asthma or another diagnosis worsened by key co-morbid conditions
We have now moved to defining phenotypes of this heterogeneous disease

**Clinical:**
- Fixed obstruction
- Obese
- Adult onset
- Exacerbation prone
- Treatment resistant

**Pathologic:**
- Eosinophilic
- Non-eosinophilic
- Pauci-granulocytic

**Triggers**
- Occupational
- Aspirin
- Exercise
- Menses

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**Severe Asthma Clusters**

- **Cluster 1:** early onset, atopic, nl lung fxn ≤ 2 controllers, minimal healthcare utilization
- **Cluster 2:** early onset, atopic, > 2 controllers, nl lung fxn, significant health care utilization
- **Cluster 3:** adult onset, obese woman with low lung fxn, high medication requirement and healthcare utilization
- **Cluster 4:** early onset, atopic, severe obstruction with some reversibility (FEV1: 57% to 76% pred), high healthcare utilization
- **Cluster 5:** early onset, severe obstruction, 66% atopic; less reversibility (FEV1: 43% to 58%), high health care utilization

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Moore et al. AJRCCM 2010;181:315-223
Phenotype to Endotype?

- Phenotype suggests a clustering of characteristics, but may not describe underlying pathobiology that create these characteristics
- Endotype: underlying biologic or pathobiologic mechanism

Phenotypes to Endotypes

Pathological Phenotypes: Can they determine therapeutic choices?

- Eosinophilic/TH2 (IL-4, IL-5 and IL-13)
- Non-eosinophilic (sputum eos < 2%, or peripheral blood eos < 200/µl)
Biomarkers to identify the type 2 asthma phenotype

- Sputum eosinophils
- Exhaled nitric oxide
- Circulating eosinophils
- Periostin
- IgE
- Allergen skin testing
- Eosinophil Peroxidase?

Once we have identified a potential phenotype, what choices do we have?

How Does Omalizumab Compare With New Biologics In Similar Patients?

Effect of omalizumab based on type 2 inflammatory biomarkers

*Baseline reduction in eosinophil count to 60% of baseline.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>n</th>
<th>P-value 60% Baseline Reduction</th>
<th>P-value 30% Baseline Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>303</td>
<td>P=0.045</td>
<td>P=0.031</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>383</td>
<td>P=0.54</td>
<td>P=0.025</td>
</tr>
<tr>
<td>Periostin</td>
<td>414</td>
<td>P=0.026</td>
<td>P=0.604</td>
</tr>
<tr>
<td></td>
<td>279</td>
<td>P=0.54</td>
<td>P=0.604</td>
</tr>
</tbody>
</table>

*Omalizumab vs. placebo.
Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids.


Mepolizumab (anti-IL-5) in Severe, Eosinophilic Asthma (Pavord et al. Lancet 2012;380:651)

Reslizumab for Poorly Controlled Eosinophilic Asthma

- 106 patients randomized to reslizumab 3 mg/kg vs. placebo (IV dosing at weeks 0, 4, 8, and 12)
- Sputum eosinophil count reduced by 95.4% in reslizumab group vs. 38.7% in placebo group (P=0.0068)
- Mean change in FEV1 was -0.08 in the placebo group versus +0.18 in reslizumab group (P=0.0023)
- Exacerbations reduced (P=0.08)
- Greater change from baseline in patients with nasal polyps -1.0 vs. -0.1 with placebo (P=0.012)
Treatment options for the non-eosinophilic phenotype

- Macrolides
- Tiotropium – perhaps agnostic?
- Bronchial thermoplasty

Conclusions

- Severe asthma is a spectrum of disease, with different pathologic and clinical phenotypes.
- Determining the presence of difficult to control asthma is important as it can be driven by co-morbid conditions that require attention
- Individualizing therapy in asthma to achieve control, decreased exacerbations and high quality of life is the ultimate goal for our patients.