Severe asthma

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Asthma in the US

• Affects 26 million Americans, including >7 million children
• $56 billion in healthcare costs + lost productivity at work/school
• *Prevalence continues to increase*

https://www.cdc.gov/asthma/most_recent_data.htm.
Severe asthma

• 5-10% of the population of adults with asthma (0.5% of US population).

• Not a uniform disease, but a description of asthma patients with high medical needs caused by a variety of pathophysiologic mechanisms.

• Often poorly controlled by the current standard of care

• Health care is associated with more than 50% of the total US costs associated with asthma, $28 billion per year.

• Health care costs per patient are higher than those for DM, stroke or COPD.
Definition of Severe Asthma (2014 ATS/ERS Guidelines)

• Asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or oral corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite treatment.

• Treatment with systemic CS for at least 50% of the previous year

When a diagnosis of asthma is confirmed and comorbidities have been addressed (misdiagnosis in 12-30%):

ERS/ATS Guidelines 2014
Advances over past 5 years

- Formulation of a standardized definition for severe asthma (ATS, ERS 2014)
- Evidence based treatment guidelines specifically for severe asthma
- Understanding of different phenotypic patterns and biomarkers
- Availability of novel targeted treatments.
### Estimating Severity: 2007 NHLBI Guidelines

<table>
<thead>
<tr>
<th>Severity assessment</th>
<th>Asthma severity</th>
<th>Treatment step</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
<td>Persistent</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2d/wk</td>
<td>&gt;2 d/wk but not daily</td>
</tr>
<tr>
<td></td>
<td>&gt;2 d/wk but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/mo</td>
<td>3-4x/mo.</td>
</tr>
<tr>
<td>SABA use</td>
<td>≤2 d/wk</td>
<td>&gt;2 d/wk, but not daily</td>
</tr>
<tr>
<td>Interference with ADL</td>
<td>None</td>
<td>Minor</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁ &gt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC normal</td>
</tr>
<tr>
<td>Treatment step</td>
<td>Step 1</td>
<td>Step 2</td>
</tr>
</tbody>
</table>

GINA guidelines

**Step 1**
- Consider low dose ICS

**Step 2**
- Low dose ICS
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline

**Step 3**
- Med/high dose ICS/LABA
- Add tiotropium
- Add low dose OCS

**Step 4**
- Med/high dose ICS/LABA
- Add tiotropium
- Add anti-IgE, anti-IL5

**Step 5**
- Refer for add-on treatment (e.g., tiotropium, anti-IgE, anti-IL5)

*Reliever:* As-needed short-acting beta₂-agonist (SABA)

*Prefered controller choice:* Other controller options

GINA 2017, Box 3-5, Step 1 (4/8)
Addition of tiotropium to ICS/LABA in poorly controlled asthma reduces exacerbations by 21%

Uncontrolled Asthma

- **Asthma symptoms that persist despite treatment**

- May be indicated by:
  - High/daily use of rescue medications (SABA)
  - Repeated need for oral corticosteroids
  - Frequent or severe exacerbations (ER/hospital visits for asthma)
  - Airflow limitation; FEV1 < 80% predicted

- May result from:
  - Resistance to therapies
  - Poor adherence
  - Inappropriate inhaler technique
  - Environmental factors
  - Comorbidities
### Uncontrolled Asthma

**GOAL Study (US)**[^1]

- After treatment intensification:
  - Total control achieved in only 19%-31% of patients
  - Well controlled asthma achieved in 50%-63% of patients

**Swedish database study**[^2]

- Poor asthma control in:
  - 28.2% of patients with mild-moderate asthma
  - 53.6% of patients with severe asthma

**Italian registry study**[^3]

- Patients with severe, uncontrolled asthma:
  - 60.6% female, 83.1% had allergic asthma
  - ~30% with late onset of asthma
  - In the last 12 months:
    - 55.7% had exacerbations
    - 9.7% had ED visits
    - 7.3% were hospitalized

Approach to Severe/Uncontrolled Asthma

- Accurate diagnosis and subtype
- Therapy
- Trigger control
- Comorbid conditions
- Education
  - Inhaler technique
  - Adherence

Asthma Care
Comorbidities in Asthma

Comorbidities are common and can affect asthma control

- Dutch survey of difficult-to-control asthma (N=914)\(^1\)
  - 92% of patients had ≥1 comorbidity
  - Comorbidities associated with older age, female gender, smoking history, and chronic prednisone use

- Analysis of the US National Health and Wellness Survey
  - Asthma patients with ≥1 allergic/asthma-related comorbidity (N = 1923)\(^2\)
  - 54.4% had very poorly or not well-controlled asthma
  - Patients with very poorly controlled asthma reported significantly greater decreases in quality of life, greater overall work impairment, and higher healthcare use (all p < 0.05)

Nasal mometasone does not improve asthma controlled in poorly controlled asthma with symptoms of rhinitis/sinusitis

<table>
<thead>
<tr>
<th></th>
<th>N*</th>
<th>Change from randomization (SE)</th>
<th>Difference in change from randomization (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mometasone</td>
<td>Placebo</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>cACT: Pediatric (ages 6-11)↑</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>82</td>
<td>1.81 (0.58)</td>
<td>2.69 (0.54)</td>
<td>-0.88 (-2.47 ,0.71)</td>
</tr>
<tr>
<td>Week 12</td>
<td>75</td>
<td>3.40 (0.61)</td>
<td>3.05 (0.71)</td>
<td>0.34 (-1.52 ,2.21)</td>
</tr>
<tr>
<td>Week 24</td>
<td>71</td>
<td>4.15 (0.64)</td>
<td>4.53 (0.65)</td>
<td>-0.38 (-2.19 ,1.44)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>ACT: Adolescent and adult (ages 12 and over)↑</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 4</td>
<td>277</td>
<td>1.89 (0.26)</td>
<td>1.75 (0.31)</td>
<td>0.14 (-0.66 ,0.94)</td>
</tr>
<tr>
<td>Week 12</td>
<td>262</td>
<td>2.69 (0.30)</td>
<td>2.25 (0.32)</td>
<td>0.44 (-0.43 ,1.31)</td>
</tr>
<tr>
<td>Week 24</td>
<td>248</td>
<td>2.95 (0.31)</td>
<td>2.44 (0.38)</td>
<td>0.51 (-0.46 ,1.48)</td>
</tr>
</tbody>
</table>

Dixon A, JACI 2014
PPI use does not improve asthma outcomes in patients with asymptomatic GER

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Asthma episodes - type 1</th>
<th>Exacerbation Components Peak flow, 30% drop</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Placebo</td>
<td>193</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>Placebo</td>
<td>193</td>
</tr>
<tr>
<td>#Events</td>
<td></td>
<td>201</td>
<td>224</td>
</tr>
<tr>
<td>Rate (events/person-year)</td>
<td></td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Rate (events/person-year)</td>
<td></td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Patients with ≥1 event, N(%)</td>
<td></td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Patients with ≥1 event, N(%)</td>
<td></td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Exacerbation Components Peak flow, 30% drop</td>
<td></td>
<td>141</td>
<td>180</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>141</td>
<td>180</td>
</tr>
<tr>
<td>Rate (events/person-year)</td>
<td></td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Rate (events/person-year)</td>
<td></td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Patients with ≥1 event, N (%)</td>
<td></td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Patients with ≥1 event, N (%)</td>
<td></td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Urgent Care</td>
<td></td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Urgent Care</td>
<td></td>
<td>53</td>
<td>51</td>
</tr>
</tbody>
</table>

Mastronarde J NEJM 2010
Evaluation of Severe Asthma

• First step is to confirm the diagnosis (pre and post spirometry), check adherence to conventional therapies and optimize treatment of coexisting conditions (rhinitis, sinusitis, GER).

• Assess environmental factors, allergy referral for those with skin test or RAST positive.

• Implement an adequate trial of therapy with high dose ICS and LABA, consider adding LAMA as well.

• Assess adherence and inhaler techniques since problems with these account for up to 50% of cases of uncontrolled asthma.
Phenotypes vs Endotypes

• Phenotypes:
  • Clinically observable characteristics of a disease
    • Examples: Allergic asthma, non-allergic asthma, obesity-related asthma, aspirin-sensitive asthma

• Endotypes:
  • Subtypes of a disease defined by intrinsic, distinct pathogenetic mechanisms
    • Examples: type 2 asthma, eosinophilic asthma, neutrophilic asthma
  • Two specific endotypes (T2 high and low) important to distinguish when considering biologic therapy.

Asthma Phenotypes in Clinical Practice

• Treatment of asthma is moving toward a personalized treatment strategy based on patient specific characteristics and endotype rather than disease severity alone.
• Asthma phenotypes may help clinicians identify “treatable traits”
• Particularly relevant in severe disease
• Widely available tests that may guide selection of therapy:
  • Blood eosinophils
  • Serum IgE
  • Fractional exhaled nitric oxide (FENO)
Asthma Phenotypes

**Early-onset allergic**
- Starts during childhood
- Positive allergy testing
- +/- eosinophils
- Strong FH

**Late-onset eosinophilic**
- Strong eosinophilic component
- Less atopic
- +/- obesity
- Female
- Reduced FEV1
- Nasal polyps
- Sinusitis
- AERC

**Late-onset neutrophilic**
- Fixed obstruction
- Reduced lung function
- Obesity
- +/- smoking

**Severe asthma**
- Non-inflammatory
- Associated with smooth muscle cell dysfunction
- Bronchial hyperresponsiveness
- Fixed obstruction

**Pauci-granulocytic**
- Non-inflammatory
Severe asthma phenotypes

Atopic
- Type 2 immune response
  - IgE
  - Eosinophilia
  - High or low FeNO
  - Early age of onset
  - Severe since childhood, or deterioration in adulthood

Nonatopic
- Type 2 immune response
  - Eosinophilia
  - High FeNO
  - Late age of onset
  - Severe from onset
- Mixed immune response
  - Eosinophilia
  - Neutrophilia
  - High FeNO
  - Granulomas
  - Late age of onset
  - Severe from onset
Airway inflammation- Type 2

• Type 2 inflammation: IL-4, IL-5, IL-13 cytokines are produced by Th2 cells but also by innate lymphoid cells.
• About 50% of severe asthmatics exhibit Type 2 inflammation.
• characterized by eosinophils and may be accompanied by atopy (atopy more common in childhood onset).
• In mild to moderate asthma, type 2 inflammation is common and resolves after treatment with glucocorticoids.
• In severe asthma, active type 2 inflammation exists despite high dose therapy with inhaled or oral corticosteroids.
• Sputum eosinophilia (T2 inflammation) is seen in more than half of patients with severe asthma and has been labeled GC resistant asthma.
Which of the following is an example of an endotype in asthma?

A. Allergic asthma
B. Eosinophilic asthma
C. Obesity-related asthma
D. Aspirin-sensitive asthma
Type 2 Asthma

- Associated biomarkers include FENO, serum IgE, periostin, and blood and sputum eosinophil levels
  - FENO, IgE, eosinophil tests available for clinical use

Effects of Type-2 Inflammation

Cytokine production

- IL-25, IL-33, TSLP

Signalling

- IgE-switched B cell
- IgE plasma cell
- IgE

Effects

- Mucus
- Smooth muscle hypertrophy
- Airway obstruction & hyperreactivity
- Fibrosis, remodelling

Exacerbations

Pollutants, viral infections, allergens

Which of the following tests can be used to identify type 2 asthma?

A. DLCO
B. Fractional excretion of nitric oxide
C. Sputum neutrophil count
D. Serum acute phase reactants
Phenotype targeted therapy – personalized medicine

- Biomarkers can help target therapies to the correct patients.

- Measurable type 2 biomarkers include FeNO, IgE and sputum/blood eosinophils.

- IgE and allergy skin or RAST testing are biomarkers for allergic asthma.

- mAb to IL-5 (mepolizumab, rezluzimab, benraluzimab) and IL-4/13 (dupilumab) were specifically developed for severe eosinophilic asthma (persistent blood eos despite treatment with ICS or oral steroids).

- Currently, no targeted treatments are available for non eosinophilic asthma.
Omalizumab

• Monoclonal Ab that binds to free IgE preventing binding of IgE to the high affinity receptor on mast cells and basophils. Approved for moderate to severe atopic asthma (2003)

• In adults, indicated for IgE > 30 or <700 KU/L (>1,300 in children aged 6 to 11 years) and at least one positive skin test or RAST. **Elevated IgE not necessary.**

• In those on ICS/LABA, reduces exac by 25-35%. FeNO >20ppb associated with better response and 50% reduction in exacerbations.

• Trial of 3-6 months to assess for clinical response; continue indefinitely if favorable response.

• Risk of anaphylaxis 0.1%
Omalizumab in severe allergic asthma inadequately controlled with ICS/LABA

25% fewer exacerbations with omalizumab compared with placebo

Hanania, Annals Internal Medicine 2011
## Omalizumab: Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanania et al. 2011¹</td>
<td>Patients with severe asthma inadequately controlled on ICS/LABA (N=850)</td>
<td>• Reduced rate of exacerbations (0.66 vs 0.88 per patient; P=0.006)</td>
</tr>
<tr>
<td>Busse et al. 2011²</td>
<td>Inner-city children, adolescents and young adults with persistent asthma (N=419)</td>
<td>• 24.5% reduction in number of days with asthma symptoms (from 1.96 to 1.48 per 2 weeks; P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduced proportion of subjects with ≥1 exacerbation from 48.8% to 30.3% (P&lt;0.001)</td>
</tr>
<tr>
<td>Humbert et al. 2005³</td>
<td>Patients with inadequately controlled asthma on ICS/LABA with reduced lung function and recent history of exacerbations (N=419)</td>
<td>• Reduced adjusted clinically significant exacerbation rate by 26% (P=0.042)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduced severe asthma exacerbation rate (0.24 vs 0.48; P=0.002)</td>
</tr>
</tbody>
</table>

Anti-IgE Therapy: Evidence Summary

• Efficacy of anti-IgE therapy in multiple studies, compared to placebo:
  
• *Improved* quality of life
• *Reduced* exacerbations
• *Reduced* emergency department visits
• *Reduced* hospitalizations
• *Reduced* corticosteroid requirements

IL-5 promotes eosinophil activation and survival
Blood eosinophil count correlates with increased exacerbations

Pavord, Lancet 2012
Anti-IL-5 Therapy

- Agents: IL-5 antibodies: mepolizumab, reslizumab,
- IL-5 receptor antibody: benralizumab
- Developed to treat eosinophilic asthma
- Efficacy in clinical trials:
  - In patients with blood eosinophils ≥150 (or ≥400) cells/mcL
    - Reduced exacerbations approx 50%
    - Reduced emergency department visits
    - Improved lung function
    - Reduced oral corticosteroid use (50%)

Benralizumab leads to reduction in oral steroid dose

Nair P NEJM 2017
Mepolizumab reduces exacerbations

- Mepolizumab 100 mg q4weeks vs placebo
- Reduced annualized rate of exacerbations by 32% vs placebo at week 24 (P=0.04)

Benralizumab effectiveness based on blood eosinophil count

Direct, rapid and near complete depletion of eosinophils

Fitzgerald; Lancet Resp Med 2018
## Anti-IL-5 Therapy: Clinical Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mepolizumab</strong></td>
<td>Ortega et al.(^1) (N=576)</td>
<td>• 53% lower exacerbation rate vs placebo (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Bel et al.(^2) (N=135)</td>
<td>• Zoster vaccine 4 weeks prior to initiation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduction in glucocorticoid dose 2.39-times more likely vs placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P=0.008)</td>
</tr>
<tr>
<td><strong>Reslizumab</strong></td>
<td>Castro et al.(^3) (N=953)</td>
<td>• Reduced exacerbation rate vs placebo (rate ratio 0.50 [study 1] and</td>
</tr>
<tr>
<td>Eo ≥ 400</td>
<td>Bjermer et al.(^4) (N=315)</td>
<td>0.41 [study 2]; both P&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Significantly improved FEV(_1) vs placebo (160 mL increase with 3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg/kg dose; P=0.0018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 3 cases of anaphylaxis, black box warning.</td>
</tr>
<tr>
<td><strong>Benralizumab</strong></td>
<td>Nair et al.(^5) (N=220)</td>
<td>• 75% reduction in median final glucocorticoid dose vs 25% reduction</td>
</tr>
<tr>
<td>Eo ≥ 150</td>
<td>Fitzgerald et al.(^6) (N=1306)</td>
<td>with placebo (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Ferguson et al.(^7) (N=351)</td>
<td>• Lower annual exacerbation rate vs placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rate 0.60 (q4weeks; P=0.0018), 0.66 (q8weeks; P=0.0188) vs. 0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(placebo):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 80 mL greater improvement in FEV(_1) vs placebo (P=0.04)</td>
</tr>
</tbody>
</table>

Anti-IL-4/IL-13 Therapy

IL-4 and IL-13 signal through 2 overlapping receptors each containing a different subunit of the IL-4 alpha receptor. Promote production of IgE and recruitment of inflammatory cells, stimulate goblet cell hyperplasia, modulates airway hyperresponsiveness and airway remodeling.

# Dupilumab: Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Castro et al. 2018¹ | Patients 12 years of age or older with uncontrolled asthma (N=1903)                | Significantly lower rates of severe asthma exacerbation than those who received placebo  
|                  | • Add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks | • 47.7% lower rate of severe asthma exacerbation among patients who received 200 mg dupilumab every 2 weeks than those who received placebo (P<0.001)  
|                  |                                                                                    | • Better lung function and asthma control                                 | 
|                  |                                                                                    | • Greater benefits were seen in patients with higher baseline levels of eosinophils | 

Dupilumab reduces exacerbations in patients with eosinophil count > 150

Dupilumab reduces oral steroid dose and improves lung function in eosinophilic asthma

### Current FDA-approved Targeted Therapies

<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Target</th>
<th>Dosing</th>
<th>Dosing calculation</th>
<th>Treatable traits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Subq q 2-4 weeks</td>
<td>IgE levels Weight</td>
<td>High IgE levels (30-700) + perennial allergens</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Subq q 4 weeks</td>
<td>100mg</td>
<td>Eosinophilic phenotype (&gt; 150 cells/mcL)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>IV q 4 weeks</td>
<td>Weight</td>
<td>Eosinophilic phenotype (&gt; 400 cells/mcL)</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5</td>
<td>Subq q 4 weeks x3, then q 8 weeks</td>
<td>30mg</td>
<td>Eosinophilic phenotype (&gt; 150 cells/mcL)</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4/ IL-13</td>
<td>Subq q 2 weeks</td>
<td>200mg or 300mg</td>
<td>Eosinophilic phenotype (&gt;150 cells/mcL)</td>
</tr>
</tbody>
</table>
Bronchial thermoplasty

• Radiofrequency ablation of airway smooth muscle during three outpatient administered bronchoscopic sessions.

• Increase in exacerbations during the treatment periods and a large placebo effect, but reduced exacerbations and symptoms in the subsequent year. The trial excluded patients with three or more exacerbations per year, FEV1 < 60% or CRS.

• Restrict to trials or registries.
Bronchial thermoplasty
-performed in bronchoscopy suite
-thermal energy to destroy bronchial smooth muscle cells in airways
-improves asthma quality of life, reduces exacerbations.
Thermoplasty improves asthma related quality of life
Azithromycin
Imatinib (KIT inhibitor) reduces airway hyper-responsiveness in severe asthma

KIT is a receptor for stem cell factor. Stem cell factor is increased in the serum of patients with asthma and correlates with asthma severity. Imatinib reduces mast cell number and serum tryptase level in CML.

TEZEPELUMAB (TSLP INHIBITOR) EFFECT ON ASTHMA

TSLP is central to regulation of T2 immunity, but many cell types relevant to asthma are activated by TSLP (mast cells, basophils, neutrophils).

Suspect VCD:

- Exercise induced dyspnea, recurrent episodes of shortness of breath
- Frequent ED visits
- No response to asthma treatment
- Psychiatric comorbidities
- Respiratory distress without desaturation
- Inspiratory stridor
- Frequent intubations
- Rapid onset/rapid recovery
- Voice changes
- FEF/FIF50 > 1
Evaluation for Vocal cord dysfunction

• Difficult to diagnose if tested during asymptomatic period
• Often coexists with asthma but often misdiagnosed as asthma
• If normal spirometry, can perform methacholine to r/o asthma (ATS guidelines recommend doing I/E loops as the methacholine may promote VCD).
• Visualization of VC through laryngoscopy is recommended, but diagnostic only in about 50% of patients not actively having symptoms. Can perform during exercise
• Treatment: laryngeal control treatment, very effective; breathing techniques to control VC, anti-anxiety; botulinum toxin injection to laryngeal muscle in refractory cases.
Case

• 65 year old woman, asthma onset age 55 years; much worse beginning three years ago.
• Multiple steroid tapers despite high dose ICS/LABA, montelukast; taking 7.5mg prednisone daily at time of initial visit unable to wean.
• Daily symptoms, trouble exercising, trouble sleeping due to cough, wheeze, SOB.
• IgE 768, Blood eosinophil count 552
• Exacerbations often begin with sneezing
• RAST with allergy to cat dander and cockroach
• No obvious triggers in her home or work
• FEV1 56% predicted
• Chest CT LLL atelectasis, scattered bronchiolitis
• Two episodes short lived rash, never biopsied
• Sinus CT shows moderate disease
All of the following are appropriate interventions EXCEPT?

A. Initiate omalizumab
B. Initiate anti-IL5 antibody
C. Allergen desensitization to cat and cockroach
D. Assess adherence
E. Review inhaler technique
Treatment

• Start omalizumab 375mg q2 weeks.
• After 6 months, able to wean off of prednisone.
• OK for 3 weeks, then recurrent wheeze and SOB, daily need for albuterol 2-3 times per day, wheeze on exam
• Eo count up from 552 to 1572.
• P-ANCA negative, ?Churg-Strauss without vasculitis
• Resume SLOW prednisone taper then maintain at 2.5mg daily
• Chest CT cylindrical LLL bronchiectasis, left lingular and RML atelectasis, b/l mild “tree in bud”
• Start mepolizumab 100mg daily (Shingrix vaccine). Doing well, pred stable at 2mg daily. Completely asymptomatic.
Another case

• 67 year old woman
• Lifelong asthma, very severe past 3 years, prednisone 10mg daily and still with symptoms.
• No allergy symptoms, RAST completely negative
• Continuous prednisone, unable to wean below 10mg daily prednisone, still with daily symptoms, interrupted sleep
• Multiple hospitalizations
• Moderate OVD on PFT
• Eo count ranges 110-440
• Start mepolizumab, no effect. Patient increasingly depressed.
• Empirically switch to reslizumab with marked improvement. Off prednisone for past 9 months.
Using Targeted Therapies in Practice

• Most patients with type 2 asthma can achieve good control with ICS/LABA
• About 5%-10% require additional treatment – targeted therapies
• Current biologics address type 2 inflammation only
• Before initiating targeted agents:
  • Identify asthma phenotype (if possible), eg, allergic asthma
  • Order appropriate testing, eg, serum IgE, eosinophils, FENO
• Choice of targeted agent based on features of asthma presentation and test results
  • Allergic asthma, anti-IgE or anti-IL5 or IL4/IL13
  • Eosinophilic asthma: anti-IL-5 or IL4/IL13
Summary

• Severe/uncontrolled asthma is difficult to treat
• Assess:
  • Adherence
  • Inhaler technique
  • Comorbidities
  • Environmental factors
• Asthma phenotypes/endotypes may inform treatment choices
• In appropriate patients, targeted therapies can reduce corticosteroid use, exacerbation rate, asthma symptoms and improve lung function and quality of life
• Use appropriate testing before selecting targeted therapy