Severe Asthma:
Definitions & Treatment Options

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Disclosure

None
Objectives

• Definition of severe asthma
• Pathogenesis
• Differential Diagnosis
• Treatment
Darryl’s Asthma

• 9 year old with asthma
  ➢ First admission age 7; now >1/year
  ➢ 4 ED visits/year
  ➢ Takes 4 different asthma medicines
  ➢ Multiple triggers
  ➢ Abnormal lung function, low FEV1

What else is going on with me?
• Lives with mom in inner city Cincinnati
• Spends weekends with dad, aunt and grandma
• Trouble getting medicines due to insurance changes
• Forgets to take medicines some days
• Apartment is very old, dusty and moldy

Is this severe asthma?
ATS-ERS* Severe Asthma

• The requirement for treatment with high-dose ICS** and a second controller medication (or systemic steroids>50% yr)
  – patients may or may not maintain asthma control, with this treatment regimen

• 5% of asthmatics are severe

• Severe asthma is heterogeneous

  *American Thoracic Society – European Respiratory Society
  ** inhaled corticosteroid

Severe Asthma

FIGURE 2. The WHO definition of severe asthma.

JACI 2010; 126:926-938
Definition of Uncontrolled Asthma

- At least one of the following:
  - 1) Poor symptom control:
    - ACQ consistently > 1.5, ACT < 20
  - 2) Frequent severe exacerbations:
    - 2 or more bursts of systemic CS in the previous year
  - 3) At least one hospitalization, ICU stay or mechanical ventilation in the previous year
  - 4) Airflow limitation (reduced FEV1, FEV1/FVC)
  - 5) Asthma that worsens on tapering medications
    - High dose ICS, oral steroid, biologic
Terminology

• Uncontrolled asthma
  – Frequent symptoms and/or exacerbations
  – Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

• Difficult-to-treat asthma
  – Asthma uncontrolled despite prescribing high dose controller treatment
  – Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

• Severe asthma (a retrospective definition)
  – asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased (Chung, ERJ 2014)
    i.e. relatively refractory to corticosteroids (rarely completely refractory)

GINA April 2019
Pathobiology of Severe Asthma

• Structural airway alterations
  – greater airway smooth muscle mass
  – increased reticular basement membrane thickening
  – epithelial damage, angiogenesis
• Occurs with/without mucosal eosinophilia
• May develop with age and asthma duration
Allergy 2008: 63: 533–541

J Allergy Clin Immunol 2012;129:974-82.)
Severe Asthma: Inflammatory Pathways

• IL-4/IL-13 pathways (T2 high)
  – Allergen associated, eosinophilic, high IgE
  – Periostin and MMP7 increased

• IL-5/IL-33 pathways
  – Innate Lymphoid cells (ILC2)
  – Non-atopic, late onset disease
  – Exacerbations: eosinophilia, Cys-LT
  – Resistant to ICS, responsive to systemic steroids, anti-IL-5

Severe Asthma: Pathways

- IL-17/IL-23 (T-2 low)
  - Sputum neutrophilia, variable airflow obstruction
  - Resistant to corticosteroids, responsive to macrolide antibiotics (?)

- Steroid Resistance
  - High IL-2, IL-4 reduces glucocorticoid binding affinity; elevated GRβ

- Others: PGD2, TSLP, IL-18, IFN-γ,
Characteristics of Severe Asthma

- High degree of atopy/allergic sensitization
- High IgE
- Eosinophilia (peripheral & sputum)
- Higher exhaled NO
- Lower lung function
  - Progressive loss of lung function
  - Air trapping
- Bronchodilator response
- Ethnicity/race

J Allergy Clin Immunol Pract 2017;5:901-8
## Heterogeneity of Severe Asthma

<table>
<thead>
<tr>
<th></th>
<th>Severe Cluster 3</th>
<th>Severe Cluster 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Co-morbid, difficult to treat</td>
<td>Refractory asthma, low lung function</td>
</tr>
<tr>
<td><strong>Asthma Onset</strong></td>
<td>Infancy</td>
<td>Toddler to preschool</td>
</tr>
<tr>
<td><strong>Aeroallergen sensitization</strong></td>
<td>High prevalence, multiple</td>
<td>High prevalence, multiple</td>
</tr>
<tr>
<td><strong>Lung Function</strong></td>
<td>Reversible obstruction</td>
<td>Partially reversible</td>
</tr>
<tr>
<td><strong>Asthma medications</strong></td>
<td>Multiple controllers, high dose ICS, <strong>daily OCS</strong></td>
<td>Multiple controllers, high dose ICS</td>
</tr>
<tr>
<td><strong>Utilization, past year</strong></td>
<td>Multiple OCS bursts, acute visits, hospitalization</td>
<td>Multiple OCS bursts, acute visits, hospitalization</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td>Sinusitis, GER, <strong>obesity</strong></td>
<td>Less frequent co-morbidities</td>
</tr>
</tbody>
</table>

*J Allergy Clin Immunol Pract 2017;5:901-8*)
Biomarkers: Severe Childhood Asthma

Cluster 3: 17%  
Cluster 4: 19%

Cluster 3: 33%  
Cluster 4: 23%

Cluster 3: 33%  
Cluster 4: 39%

Cluster 3: 17%  
Cluster 4: 39%

Blood eosinophils (%)  
Exhaled nitric oxide (ppb)
Asthma Phenotypes/Clusters in Inner City Children

J Allergy Clin Immunol 2016;138:1016-29.)
Conditions That Mimic Severe Asthma

- Vocal cord dysfunction
- Central airways obstruction/compression
  - Congenital malformations
  - Vascular ring
- Tracheobronchomalacia
- Recurrent (micro) aspiration, reflux, swallowing dysfunction
- Foreign body
- Primary ciliary dyskinesia
- Habit Cough
- Bronchiolitis obliterans
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immunodeficiency
- Connective tissue disease (EDS)
- Interstitial lung disease
- Congenital heart disease
- Carcinoid or other tumor
- Mediastinal mass, enlarged lymph nodes
Co-morbid Conditions in Severe Asthma

- Reflux, aspiration
- Rhinosinusitis
- Poor adherence
- Ongoing allergen/irritant exposure
- Obesity
- Obstructive sleep apnea
- Bronchiectasis
- Eosinophilic syndromes
- Allergic bronchopulmonary aspergillosis
- Fungal sensitization asthma
ADHERENCE

“Let’s try some role playing. I’ll be the elephant in the room and you address me.”
Question

• The proportion of patients who are non-adherent to prescribed doses of daily controller medications for asthma is approximately:
  – A) 10%
  – B) 20%
  – C) 50%
  – D) 80%
Correct Answer

- C: 50%
Adherence to Inhaled Steroids

Figure 1. Individual growth curve for fluticasone use.

Severe Asthma Management

- Confirm the diagnosis: Is it asthma?
- Identify co-morbidities
- Address adherence and proper med use
- Environmental exposures
  - Unrecognized allergen and irritant exposure
- Psychobehavioral issues: child and parent
- Shared decision making
Treatment Options for Severe Asthma

• High Dose ICS+LABA*, LTRA*
• Tiotropium
• Oral corticosteroids?
• Biologics
  – Omalizumab, Mepolizumab, Benralizumab, Dupilumab, (Reslizumab)
• Others: macrolide antibiotics, allergen immunotherapy, bronchial thermoplasty

*LABA: long acting beta-agonist
LTRA: leukotriene receptor antagonist
High Dose Corticosteroids

• Relative steroid resistance/insensitivity
  – 11% of children totally responsive (Sx, PFT, FeNO, BD response)
  – 43% obtained control with IM steroids
  – 30% of adults require oral steroids + ICS for control

• Associated with several co-morbidities
  – Obesity
  – Low vitamin D
  – Smoking
  – Persistent high allergen exposure
  – Low T2 phenotype
Heterogeneity of Steroid Response

B

Achieved control with Triamcinolone

Did not achieve control

IL1RN
TNFSF13B
CCR2
IL10RB
IL1A
C5
VEGFA
CCR6
CSF1
CCR5
AIMP1
IFNG
IL5
CCL3
IL17C

Magnitude of gene expression

min
avg
max

Control  Achieve Control  Control  Achieve Control

J Allergy Clin Immunol Pract 2017;5:410-9
Tiotropium in Children age 6-11 yr

All groups had similar improvement in ACQ

Question

• A 12 yo boy with severe asthma is being considered for biologic therapy. His FEV1 is 98% predicted and his weight is 85 kg. His peripheral eosinophil count is 325 cells/ul, IgE is 1500 IU (normal 0-450 IU) and he is allergic to eggs only.
Based on the data provided, which biologic is best suited for this patient?

- A) Omalizumab
- B) Reslizumab
- C) Benralizumab
- D) Tralokinumab
Correct Answer

• C: Benralizumab
Targeting IgE

(J Allergy Clin Immunol 2017;139:1411-21)
Targeting Cytokines

(J Allergy Clin Immunol 2017;139:1411-21)
<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>Mechanism of Action</th>
<th>Exacerbation</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair)</td>
<td>Anti IgE; prevents IgE binding to receptor on mast cells</td>
<td>Reduces by ~25- &gt;60%</td>
<td>Minimal or equivocal improvement</td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepolizumab (Nucala)</td>
<td>Anti-IL5; prevents IL5 binding to receptor</td>
<td>Reduces by ~50%</td>
<td>Inconsistent effect</td>
</tr>
<tr>
<td>6 yr +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benralizumab (Fasenra)</td>
<td>Anti-IL5 receptor; binds to IL5 receptor α; apoptosis of eos and basos</td>
<td>Reduces by 25-60%</td>
<td>Improves</td>
</tr>
<tr>
<td>12 yr +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupilumab (Dupixent)</td>
<td>Anti-IL4 receptor; blocks IL-4 and IL-13 signaling</td>
<td>Reduces by 50-70%</td>
<td>Improves</td>
</tr>
<tr>
<td>12 yr +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Biologic Therapy

• Omalizumab (anti-IgE)
  – sensitized to ≥ 1 perennial allergen
  – IgE 30- 1300 (1600) IU/ml (weight restrictions)
  – SC injection every 2-4 weeks
    • Black box warning for anaphylaxis

• Mepolizumab (anti IL-5)
  – 100 mg, SC every 4 weeks
  – Peripheral eos > 150/µl at screening or >300/µl in past 12 months
  – Anaphylaxis, zoster
Biologic Therapy

- Benralizumab (anti IL-5 receptor)
  - 30 mg SC q 4 weeks x 3, then Q 8 weeks
  - No eos requirement but better effect with higher eos (>300), FeNO

- Dupilimab (anti-IL4/13)
  - 400(600) mg SC x 1 then 200(300) mg q 2 weeks
  - Better effect with higher eos (>300), FeNO
  - Home administration
Omalizumab Effect on Asthma

Decrease in exacerbation rate with omalizumab compared with placebo

Pediatr Aller, Immunol, Pulm Volume:31(3), 2018
Mepolizumab in Eosinophilic Asthma

Asthma Exacerbations

Cumulative No.

Placebo

Mepolizumab 75 mg, intravenously

Mepolizumab 100 mg, subcutaneously

Week

**Dupilumab: Risk of Severe Asthma Exacerbations According to Baseline Blood Eosinophil Count and Baseline FE\textsubscript{NO}.**

### A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>0.52 (0.41–0.66)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥300 cells/mm(^3)</td>
<td>148 (Placebo) 264 (Dupilumab)</td>
<td>0.34 (0.24–0.48)</td>
</tr>
<tr>
<td>150 to &lt;300 cells/mm(^3)</td>
<td>84 (Placebo) 173 (Dupilumab)</td>
<td>0.64 (0.41–1.02)</td>
</tr>
<tr>
<td>&lt;150 cells/mm(^3)</td>
<td>85 (Placebo) 193 (Dupilumab)</td>
<td>0.93 (0.58–1.47)</td>
</tr>
<tr>
<td>FE\textsubscript{NO}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td>71 (Placebo) 119 (Dupilumab)</td>
<td>0.31 (0.18–0.52)</td>
</tr>
<tr>
<td>≥25 to &lt;50 ppb</td>
<td>91 (Placebo) 180 (Dupilumab)</td>
<td>0.39 (0.24–0.62)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td>149 (Placebo) 325 (Dupilumab)</td>
<td>0.75 (0.54–1.05)</td>
</tr>
</tbody>
</table>

### B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>0.54 (0.43–0.68)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥300 cells/mm(^3)</td>
<td>142 (Placebo) 277 (Dupilumab)</td>
<td>0.33 (0.23–0.45)</td>
</tr>
<tr>
<td>150 to &lt;300 cells/mm(^3)</td>
<td>95 (Placebo) 175 (Dupilumab)</td>
<td>0.56 (0.35–0.89)</td>
</tr>
<tr>
<td>&lt;150 cells/mm(^3)</td>
<td>83 (Placebo) 181 (Dupilumab)</td>
<td>1.15 (0.75–1.77)</td>
</tr>
<tr>
<td>FE\textsubscript{NO}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td>75 (Placebo) 124 (Dupilumab)</td>
<td>0.31 (0.19–0.49)</td>
</tr>
<tr>
<td>≥25 to &lt;50 ppb</td>
<td>97 (Placebo) 186 (Dupilumab)</td>
<td>0.44 (0.28–0.69)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td>144 (Placebo) 317 (Dupilumab)</td>
<td>0.79 (0.57–1.10)</td>
</tr>
</tbody>
</table>

Dupilumab: Change FEV₁ from Baseline over the 52-Week Intervention

## Currently Approved Biologics

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Explanations</th>
<th>Dosing and Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Reduce symptoms of allergic asthma, allergic rhino</td>
<td>10 mg subcutaneously every 4 weeks</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>0.016 mg/kg per IU of IgE for a 4-week period</td>
<td>375 mg in the United States; 150–600 mg in European Union*</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Anti-IL-5; blocks signaling of IL-4 and IL-13</td>
<td>30 mg subcutaneously every 4 weeks for three doses; followed by every 8 weeks subsequently</td>
</tr>
</tbody>
</table>

*Note: *Cost per year: ~$36,000*
Defining Response to Biologic Therapy

• Adequate response defined as:
  – at least 50% fewer asthma exacerbations needing systemic corticosteroids in those with >4 exacerbations in the previous 12 months or
  – clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control
Adherence Assessment in Biologic Therapy Decisions

- 30-day evaluation of patient on ICS/LABA with adherence monitoring
  - Adherence ≤ 70% Poor Control
    - Initiate education or other adherence intervention
  - Adherence ≥ 70% Poor Control
  - Adherence ≥ 70% Good Control
    - Consider biologic drug with follow-up as appropriate
    - Continue with ICS/LABA with follow-up as appropriate

Bender B. AJRCCM, Volume 199 (4):400-02; 2019
Macrolide Antibiotics

• Effective in other chronic respiratory disorders
• Anti-inflammatory effects on
  – PMN
  – Macrophages
  – Epithelium
  – Lymphocytes
• Antibacterial and anti-viral actions
• Possible effectiveness in certain phenotypes
• Cardiovascular risk

*Lancet Respir Med 2014 2: 657–70*
Azithromycin in Moderate-Severe Asthma

Lancet 2017; 390: 659–68
Other Potential Treatments

- Bronchial thermoplasty
  - possible trial in adolescents
- In Clinical trials: anti-PGD2, TSLP, probiotics
- Anti-fungal agents
  - Adjunct treatment for ABPA
  - fungal sensitization asthma; not recommended
- Theophylline
  - anti-inflammatory; Improves steroid sensitivity
- Allergen immunotherapy
  - Not safe/recommended in poorly controlled asthma
Summary

• Is it asthma?
• Is it severe?
  – therapy resistant or difficult to treat?
  – Severe co-morbidities or severe asthma?
• Identify and manage co-morbidities
  – Allergy, obesity, OSA, GER, VCD
• Assign a phenotype/endotype
  – Phenotype specific treatment
• Non-medical interventions: adherence