Novel Approaches to Steroid Resistance
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Lecture Objectives
1. Describe the current therapeutic approach for managing asthma.
2. Indicate circumstances where response to conventional therapy may be inadequate.
3. Identify opportunities to advance asthma care through novel treatment approaches.

Working Concepts
• Severe asthma is a complex phenotype of asthma with increased morbidity.
• A key feature is frequent and severe exacerbations.
• Mechanisms of disease severity are not fully established.

Potential New Treatments
• Tiotropium
• Anti-IgE in children less than 12 years
• Anti-IL-5
• Anti-IL-13
• Anti-IL4/13
• Re-evaluation of allergen immunotherapy

WHO definition
• Severe asthma is defined by the current level of clinical control and risks which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity. Severe asthma consists of three groups, each carrying different public health messages and challenges.
  – Untreated severe asthma
  – Difficult to treat asthma
  – Treatment resistant severe asthma
  Either controlled on high dose medication or not controlled on high dose medication

[Image of diagram showing disease pathology]
Unsupervised cluster analysis of 34 variables reveals 5 phenotypes of asthma in SARP adults

726 Adult Asthmatics in Cluster Analysis

Cluster 1 (n = 110)
Mild allergic asthma
FEV\textsubscript{1} 113%

Cluster 2 (n = 321)
Mild-to-moderate allergic asthma
FEV\textsubscript{1} 94%

Cluster 3 (n = 99)
Moderate-to-severe (older onset asthma)
FEV\textsubscript{1} 84%

Cluster 4 (n = 120)
Severe allergic asthma
FEV\textsubscript{1} 76%

Cluster 5 (n = 116)
Severe fixed airflow asthma (COPD like)
FEV\textsubscript{1} 58%

Moore WC et al., AJRCCM 2010; 181: 315-323.

Mechanisms

- Multiple
- Inflammatory pattern is not distinct
- Inflammatory mediators generated may lead to corticosteroid resistance (Th2)

Airway-Parenchymal Coupling

Favoring Airway Narrowing/Closure:
- Smooth muscle tone
- Luminal surface tension
- Airway wall thickening
- Intraluminal material

Opposing Airway Narrowing/Closure:
- Lung elastic recoil
- Airway wall stiffness

Biomarkers of Interest

- Exhaled nitric oxide
- Serum periostin
- Sputum eosinophils
- Blood eosinophils
- Urinary leukotrienes
- Exhaled breath condensates

Question: Interpretation on and off ongoing therapy?

Future Directions for Managing and Preventing Severe Asthma

- Introduction of new immunodulators directed primarily at TH2 pathways directed at IL5, IL13 and IL4/13.
- Identification of biomarkers and patient characteristics associated with response.
- Application of immunomodulators for prevention of exacerbations, progression and eventually onset of disease.