Asthma Phenotypes & Endotypes

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Definitions

- Phenotype
  - Observable characteristics without regard to underlying pathology
    - Clinical
    - Physiological
    - Biochemical
    - Response to treatment
  - Asthma phenotype results from interaction between genes and environment
    - Can change over time
    - Often overlap, making specific classification difficult
Definitions

- **Endotype**
  - Specific biological pathway that explains observable phenotypic characteristics
  - Defines an etiology and/or consistent pathophysiological mechanism
Early concepts
  ◦ Focus on duality: allergic (extrinsic) vs non–allergic (intrinsic)
    • Widely accepted, few physicians tried to determine subsets
  ◦ Single variable or trigger based
    • Exercise–induced
    • Obesity–related
    • Smoking–related
    • Allergens
    • Infection
    • Air pollution
    • Aspirin
    • Occupational
  ◦ Clinical symptom based
    • Early vs late onset
    • Exacerbation–prone
    • Asthma with fixed airway limitation
    • Cough–variant
Inflammatory Phenotypes
- 19th century eosinophilic vs non-eosinophilic
- Late 1990s & early 2000s increased research in cell types
  - 1999 Wenzel et al studied severe, corticosteroid-dependent asthma
    - Type 2–high phenotype with high levels of eosinophils
    - Type 2–low phenotype with low levels of eosinophils
  - 2006 Simpson determined 4 inflammatory subtypes:
    - Eosinophilic
    - Neutrophilic
    - Mixed granulocytic
    - Paucigranulocytic (absence of either eosinophilic or neutrophilic inflammatory pattern)
Hierarchical Cluster Analysis

- Clusters patients according to preselected variables
  - Age of onset
  - Atopy
  - Sex
  - Severity of obstruction
- 2008 UK: 16 variables, several clusters ID
- 2010 SARP sample: 32 core variables, 5 clusters ID
- 2 European cohorts: 4 clusters ID
  - 2 similar phenotypes identified
    - Early onset–allergic asthma
    - Late onset, mostly non–atopic women with high BMI
Severe Asthma Research Program (SARP) 2010

- Study of severe asthma (mild and moderate as controls)
- 9 US sites and 1 in UK
- Phenotypic characterizations
  - Questionnaires
  - Atopy
  - PFT
  - Blood tests
  - FeNO
Proposed Phenotypes & Endotypes

- $T_H^2$-Mediated Asthma
  - Early-Onset Allergic $T_H^2$ Asthma
    - Most studied phenotype, 50% of subjects
    - Most often begins childhood/adolescents
    - Hypersensitivity to environmental allergens
    - Strong correlation to other atopic disease
    - High level $T_H^2$ cytokines, inc total and specific IgE
    - Strong genetic component
    - Other biomarkers: FeNO, sputum eosinophils & serum periostin
    - Treatment: corticosteroids, biologics (anti-IgE, anti-IL5, anti-IL13)
Proposed Phenotypes & Endotypes

- $T_h^2$-Mediated Asthma
  - Late-Onset Persistent Eosinophilic Asthma
    - Recurrent exacerbations, marked eosinophilia, less atopy
    - Inflammation drivers unknown but unlikely allergic triggers
    - Decreased lung function compared to allergic asthma despite corticosteroid use
    - More severe with frequent exacerbations and poor control
    - Targeted anti–IL5 therapy
Proposed Phenotypes & Endotypes

- $T_{H2}$-Mediated Asthma
  - Late-Onset Persistent Eosinophilic Asthma
    - Subtype: Aspirin-Exacerbated Disease
      - Most often considered an endotype
      - Asthma, chronic rhinosinusitis with polyposis, and NSAID intolerance
      - Intense eosinophilic inflammation of nasal & bronchial tissues
      - Increased cysteiny1 leukotriene production
      - Benefit seen in some with use of cysteiny1 leukotriene receptor antagonist (montelukast) & 5-lipoxygenase inhibitors (zileuton)
Proposed Phenotypes & Endotypes

- $T_H^2$-Mediated Asthma
  - Allergic Bronchopulmonary Mycoses
    - Endotype characterized by a fungal hypersensitivity reaction, typically *Aspergillus fumigatus*
    - Association with cystic fibrosis, ? predisposed due to epithelial dysfunction
    - Clinical findings: bronchiectasis, mucus production, increased mold-specific IgE & IgG, eosinophilia, & obstructive lung function
    - Treatment: mainly systemic steroids and antifungal therapies, possibility for anti-IgE therapy
Proposed Phenotypes & Endotypes

- $T_H^2$–Mediated Asthma
  - Exercise–Induced Bronchospasm
    - Mild phenotype, likely at least partially $T_H^2$–mediated
    - Typically younger age onset, more commonly atopic athletes
    - Variable eosinophilic inflammation
    - Response to β–agonists and cysteinyi leukotriene receptor antagonist (montelukast)
Proposed Phenotypes & Endotypes

- Non-$T_H2$-Mediated Asthma
  - Neutrophilic Asthma
    - Airway neutrophilia can be associated with lower lung function, increased air trapping, & airway thickening
    - Sputum neutrophilia reported with severe and sudden-onset fatal asthma
    - Corticosteroids less effective, inhibit apoptosis promoting accumulation in the airway
    - Possible response to macrolide antibiotics
  - Paucigranulocytic Asthma
    - Corticosteroids less effective
    - Likely respond best to intensive bronchodilator therapy
    - No specific biologic therapy on horizon
Proposed Phenotypes & Endotypes

- Non-$T_H$2–Mediated Asthma
  - Extensive Remodeling Asthma
    - Accelerated decreased lung function and partial or irreversible obstruction
    - Profibrotic cytokines released from damaged epithelia result in fibroblast proliferation and activation
Biomarkers

Preferences
- Noninvasive
- Cost effective
- Clinically useful

Current & Potential
- Serum eosinophils
  - Easy to obtain, help stratify type-2 low or high phenotype
  - Neither sensitive or specific to asthma and no evidence of use in ICS adjustment to improve outcomes
- Sputum eosinophils
  - Correlate with airway inflammation, decreased FEV1 and increased bronchial hyperresponsiveness, and response to treatment
  - Difficult to obtain
- IgE
  - Easy to obtain, correlates with airway eosinophilic asthma and atopic asthma
  - Not specific for all asthma types
- FeNO
  - Easy to obtain, correlates with airway eosinophilic asthma and atopic asthma
  - Not specific to lower airway inflammation
- Periostin
  - Sensitive for eosinophilic and type 2-mediated inflammation in uncontrolled asthma
  - Not readily available and clinical utility as a measure of airway eosinophils unknown
Genetic and environmental interactions

- Smoking
  - Increased symptoms, accelerated decrease in lung function, corticosteroid response impairment
- Hormonal changes
- Infection
- Obesity
  - Possible phenotype: adult-onset, non-\(T_H2\), minimal atopy, female, symptomatic
  - Treatment with weight loss, possibly hormonal therapies
  - Study showing improved airway responsiveness to methacholine challenge after bariatric surgery
Treatment: IgE-blocking strategies

- FDA Approved
  - Omalizumab
    - Biomarkers
      - Antigen specific IgE
      - Improved response with higher FeNO and serum eosinophils >300 cells/uL
Treatment: IgE-blocking Strategies

- No longer in development
  - Quilizumab
    - Anti-M1 prime mAb depleting IgE-expressing B cells to block IgE production
    - Blocked early and late responses 30%, reduced serum IgE 40%
    - No therapeutic benefit in clinical field study
  - Lumiliximab
    - Anti-CD23 mAb, cross-links B cell CD23 to decrease IgE production
    - Decreased serum IgE by 40%
    - Failed clinical field trials
  - Ligelizumab
    - Anti-IgE mAb, 50–greater fold affinity compared to omalizumab
    - Inhibited skin test response, reduced IgE levels > omalizumab
    - No better effect than omalizumab in clinical field study
Treatment: IL-5-blocking Strategies

- FDA Approved
  - Mepolizumab
    - Reduced exacerbations by 53% (1.74 vs 0.83) & FEV1 increase ≈100ml in pivotal phase 3 trial
      - Possible greater benefit with eosinophil count >500
    - 80% reduction in exacerbations, FEV1 increase 132–222ml
    - Increased asthma QoL scores
    - Decreased ED visits and hospitalizations
    - Reduced corticosteroid dose >50%, with improved symptom score and reduced exacerbations
FDA Approved

- **Reslizumab**
  - Reduction in asthma exacerbation frequency (0.41 \& 0.5) in 2 phase III studies
  - Improved FEV1, QoL scores and asthma control parameters
  - Short-term study (16 week) >200ml increased FEV1

- **Benralizumab**
  - Greater benefit with higher eosinophil counts, reduction of exacerbations 45–51%
  - Improved FEV1 106–159ml
  - Improved symptom scores and QoL
  - Benefit seen at 4 weeks
In Clinical Trials

◦ Tralokinumab
  • Anti–IL–13 mAb
  • Trials with variable results, decreased exacerbations in patients with high periostin or DPP–4 levels

◦ Dupilumab
  • Anti–IL4Rα mAb, blocks both IL–4 and IL–13
  • Biweekly home administration with reduced exacerbations (0.27 vs 0.9) and pulmonary function regardless of blood eosinophil level, results better in >300 counts (0.2 vs 1.04)
  • Possible option for patients with lower eosinophil counts?

◦ AMG–157
  • Anti–TSLP mAb
  • Thymic stromal lymphopoietin (TSLP) promotes T_H2 inflammation
  • Clinical study with reduced allergen–induced early and late asthmatic response, blood and serum eosinophils, and FeNO
Treatment: $T_H^2$-Mediated Asthma

- No longer in development
  - Lebrikizumab
    - Anti-IL-13 mAb
    - Initial study showed improved FEV1, more so in patients with higher periostin levels
    - Phase 3 trials with mixed results, development stopped
What does this all mean for treating asthmatic patients?

**Traditional Guidance-Based Asthma Management**

- **Diagnosis**
- **Assessment of asthma severity**
  - Avoidance of triggers and management of comorbidities:
    - Laryngopharyngeal reflux
    - Subacute bacterial infection
    - Sinus disease
    - Sleep apnea
    - Vocal cord dysfunction
- **Stepwise approach to therapy:**
  - SABA, ICS alone, ICS + LABA, ICS + LTRA, oral corticosteroids, biologic therapy

**Personalized Approach to Asthma**

- **Diagnosis**
- **Determination of whether asthma is refractory**
- **Characterize subtype**

**Phenotype**
- Gender
- Age
- Obesity
- Ethnicity
- Smoking Hx

**Endotype**
- Blood biomarkers
  - IgE
  - Eosinophils
  - Periostin
  - Cytokines
- Sputum biomarkers
  - Eosinophils
  - Neutrophils
  - Cytokines
- Other
  - FeNO

**Genotype**

- **Assess comorbidities**
- **Tailored therapy**
Questions or Comments?
Resources