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

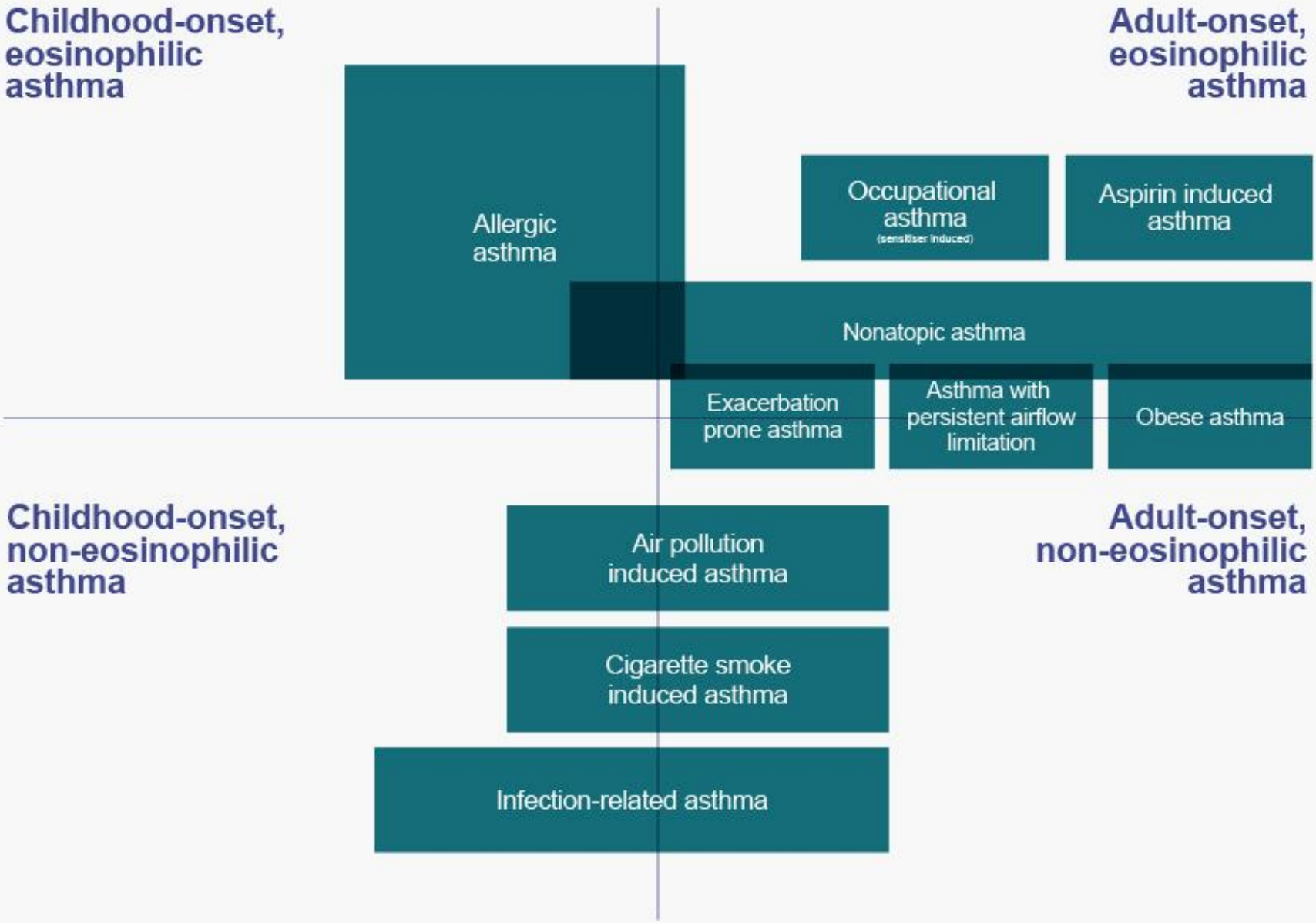
- Endotype
  - Specific biological pathway that explains observable phenotypic characteristics
  - Defines an etiology and/or consistent pathophysiological mechanism

Classifications of Phenotypes

- 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

Early Classifications

- 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)


Childhood-onset, eosinophilic asthma
Adult-onset, eosinophilic asthma
Allergic asthma
Occupational asthma
(sensitiser induced)
Aspirin induced asthma
Nonatopic asthma
Exacerbation prone asthma
Asthma with persistent airflow limitation
Obese asthma
Childhood-onset, non-eosinophilic asthma
Adult-onset, non-eosinophilic asthma
Air pollution induced asthma
Cigarette smoke induced asthma
Infection-related asthma

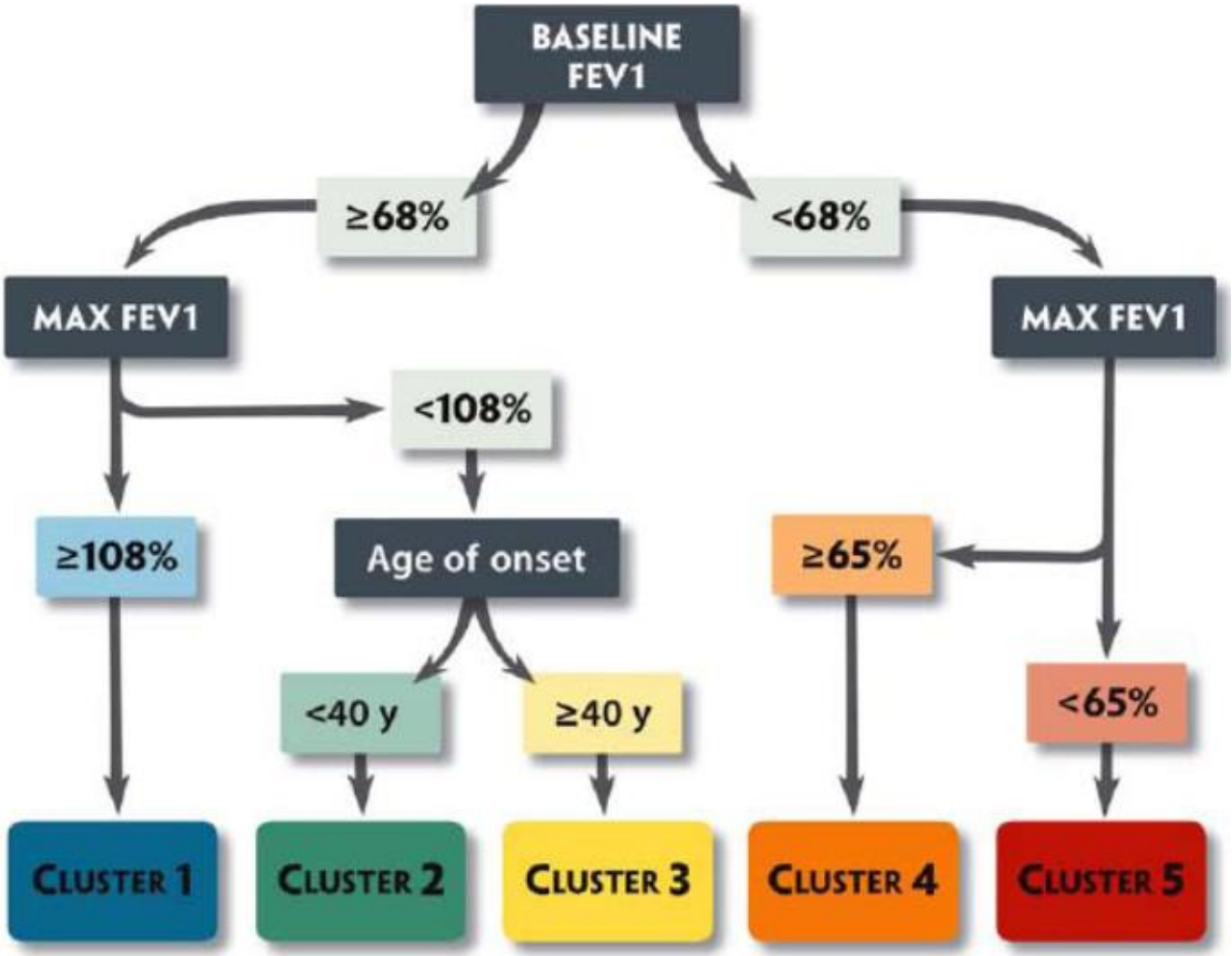
New Approaches

- 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

Newer Approaches

- 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

SARP Cluster Analysis



Proposed Phenotypes & Endotypes

- T_H2-Mediated Asthma
  - Early-Onset Allergic T_H2 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_H2 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_H2-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 cysteinyl leukotriene production
      - Benefit seen in some with use of cysteinyl leukotriene receptor anatagonist (montelukast) & 5-lipoxygenase inhibitors (zileuton)

Proposed Phenotypes & Endotypes

- T_H2-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_H2-Mediated Asthma
  - Exercise-Induced Bronchospasm
    - Mild phenotype, likely at least partially T_H2-mediated
    - Typically younger age onset, more commonly atopic athletes
    - Variable eosinophilic inflammation
    - Response to B-agonists and cysteinyl leukotriene receptor anatagonist (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_H2-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

Confounders to Phenotype

- 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

Treatment: IL-5-blocking Strategies

- 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

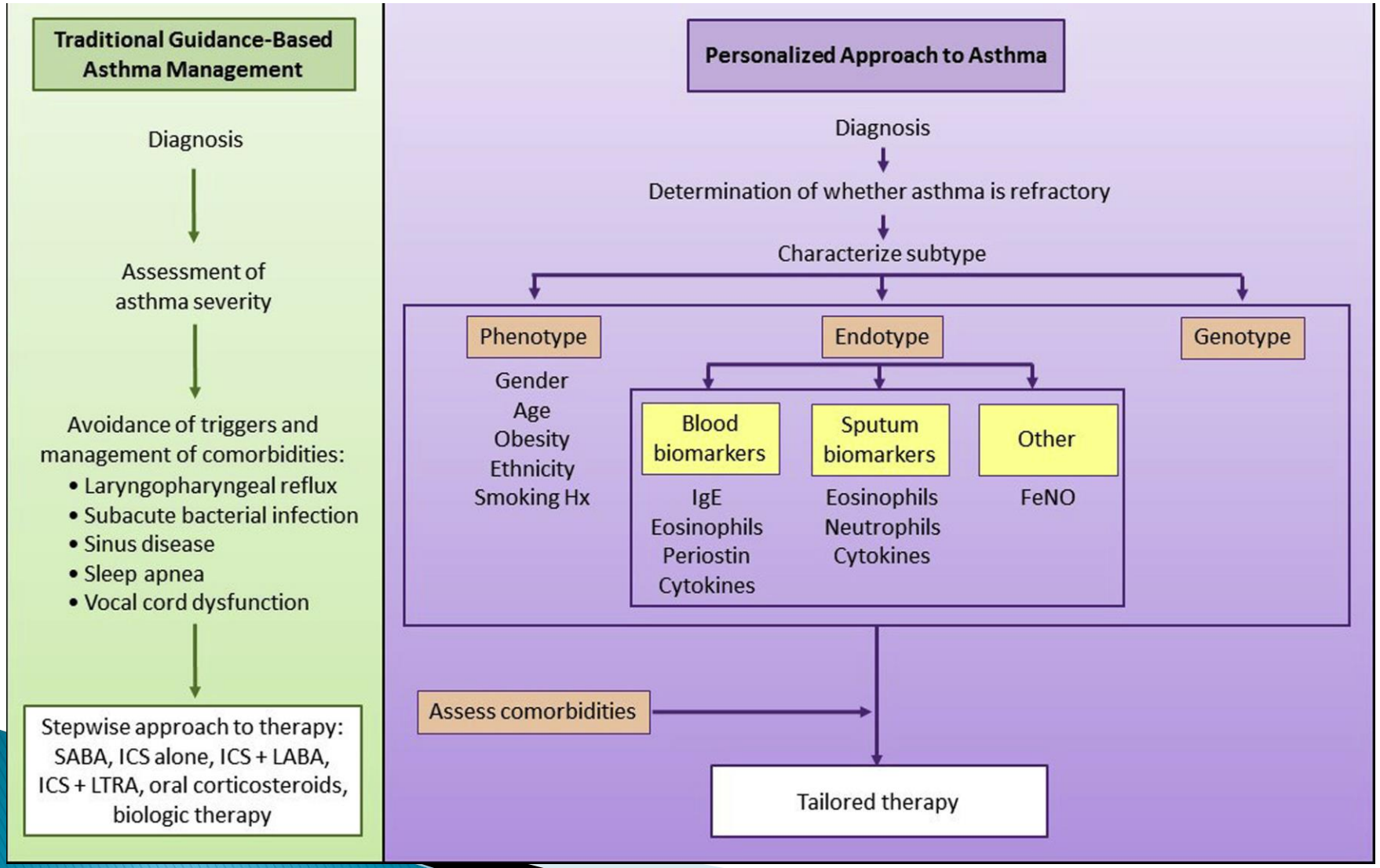
Treatment: T_H2-Mediated Asthma

- 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_H2-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?



Questions or Comments?

Resources

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