Asthma Phenotypes: Clinical Implications

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Definition of Phenotype

- The observable properties of an organism that are produced by the interaction of the genotype (genetic make-up) and the environment
- As applied to asthma, refers to subtypes of asthma, typically with unique triggers or symptoms
- Uncertain whether some asthma phenotypes are actually different diseases or just variations in a single disease
- Asthma phenotypes have implications for management

Asthma Phenotypes

- Allergic
- Non-allergic
- Aspirin Exacerbated Respiratory Disease (AERD)
- Infection-related
- Exercise-induced
- Cough-variant
- Obesity-associated
- Overlap with COPD

Information for each Phenotype

- Distinguishing Features
- Clinical Manifestations
- Targeted Therapy

Allergic Asthma: Question

- What is the ideal approach to identifying the Allergic Asthma phenotype?
  - A. History alone
  - B. Specific IgE alone
  - C. Correlation between history and specific IgE
  - D. None of the above

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Allergic Asthma

- Distinguishing Features
  - Specific IgE against mite, animal dander, cockroach, mold spores, or pollen
  - Ideally, correlation of specific IgE to
    - Seasonal variation
    - Symptoms in response to house dust, animals, mold exposure, or pollen

Allergic Asthma

- Clinical Manifestations
  - Most common phenotype in the general population of patients with asthma
  - Younger onset
  - More common in male patients
  - Associated with allergic rhinitis and atopic dermatitis (eczema)
  - Milder overall than non-allergic asthma, but substantial variability in severity

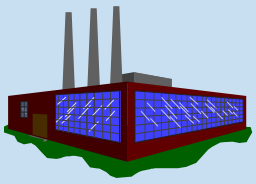
Allergic Asthma

- Targeted Therapy
  - Allergen avoidance
  - Immunotherapy
  - Omalizumab

What Is Allergen Immunotherapy?

Administer increasing doses of allergen to a sensitive individual

Increase tolerance for the particular allergen



Decrease symptoms

Immunotherapy Types

- Subcutaneous injections
  - Used for more than 100 years
  - Efficacy well-established
  - Can treat with multiple antigens
  - More inconvenient
  - More allergic reactions
- Oral (SLIT)
  - First products approved in 2014
  - May be somewhat less effective than SQ
  - Individual antigens (grass, ragweed, mite)
  - More convenient
  - Fewer allergic reactions

Omalizumab

- Mechanism
  - Antibody against IgE
  - Lowers specific IgE levels
- Use
  - Patients with allergic asthma
  - Uncontrolled by medium dose ICS + LABA and addressing triggers
  - Limited by expense and few long-term surveillance data

Non-allergic Asthma: Question

- Which of the following is NOT true in patients with Non-allergic Asthma?
  - A. Skin tests to common inhalant allergens are negative
  - B. Rhinitis is usually not associated
  - C. Age of onset is usually older than Allergic Asthma
  - D. It is more common in females

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Non-allergic Asthma

- Distinguishing Features
  - NO sensitization (RAST or skin test) to common allergens
    - Dust mite
    - Animal dander
    - Cockroach
    - Mold spores
    - Pollens
      - Tree
      - Grass
      - Weed

Non-allergic Asthma

- Clinical Manifestations
  - Older age of onset
  - More common in female patients
  - Typically more severe than allergic asthma
  - Non-allergic rhinitis may be associated
  - GERD may be associated

Non-allergic Asthma

- Targeted Therapy
  - Treatment of symptomatic GERD
  - No other targeted therapy (medications only)

Aspirin-Exacerbated Respiratory Disease (AERD): Question

- Which of the following is true regarding AERD?
  - A. It is often more severe than other phenotypes
  - B. It usually responds poorly to corticosteroids
  - C. Patients often also react to acetaminophen and COX-2 inhibitors
  - D. Aspirin desensitization has not been shown to be effective

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Aspirin-Exacerbated Respiratory Disease (AERD)

- Distinguishing Features
  - Increased nasal and/or chest symptoms within 1-3 hours after aspirin or other NSAIDs (COX-1 inhibitors)
  - COX-2 inhibitors are tolerated
  - Suggested by history
  - Ideally confirmed by challenge

Aspirin-Exacerbated Respiratory Disease (AERD)

- Clinical Manifestations
  - Adult onset
  - More common in women
  - Nasal polyps
  - Chronic rhinosinusitis
  - Generally more severe with decreased quality of life and increased exacerbations
  - Responds to corticosteroids but may be oral corticosteroid-dependent

Aspirin-Exacerbated Respiratory Disease (AERD)

- Targeted Therapy
  - Leukotriene modifiers (LTRA, zileuton)
  - Corticosteroids (often oral)
  - Aspirin desensitization
    - Should only be done with facilities and personnel able to treat severe reactions
    - Start with ¼ baby aspirin (20.25 mg)
    - Double dose at 90 minute intervals to 325 mg
    - When patient reacts, treat reaction and then repeat dose until dose is tolerated
    - Most individuals require two days to complete the procedure

Infection-related Asthma: Question

- Which of the following is true regarding Infection-related Asthma
  - A. It is usually triggered by viral rather than bacterial infections
  - B. It can be complicated by bacterial sinusitis or pneumonia
  - C. It can be treated with an increased dose inhaled-corticosteroids
  - D. All of the above

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Infection-related Asthma

- Distinguishing Features
  - Triggered by respiratory infections
    - Usually viral
    - Especially human rhinovirus
  - May be only trigger or one of several

Infection-related Asthma

- Clinical Manifestations
  - Symptoms of viral illness (nasal discharge, nasal obstruction, cough, and sore throat)
  - Increased asthma 1-2 days after symptoms of infection begin
  - Purulent discharge does not reliably differentiate viral from bacterial infection
  - Symptoms of sinusitis (post nasal drip, green mucus, sinus-distribution pain, reduced sense of smell) suggest bacterial infection
  - High index of suspicion for atypical organism and pneumonia

Infection-related Asthma

- Targeted Therapy
  - Begin or increase (at least four-fold) inhaled corticosteroids
  - Oral prednisone for severe exacerbation
  - Antibiotics for suspected sinusitis, atypical organism, or proven pneumonia

Exercise-induced Asthma: Question

- Which of the following is true regarding Exercise-induced Asthma
  - A. It is not usually associated with a change in pulmonary function
  - B. It usually does not respond to albuterol pre-treatment
  - C. It usually starts 5-10 minutes after exercise
  - D. None of the above

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Exercise-induced Asthma

- Distinguishing features
  - Asthma symptoms 5-10 minutes after exercise
  - Diagnosis confirmed by 10 % or more decrease in FEV_1 within 30 minutes after exercise in comparison with pre-exercise FEV_1

Exercise-induced Asthma

- Clinical features
  - May occur in patients with any phenotype
  - May be the only trigger for some patients
  - May develop in elite athletes with no prior history of asthma

Exercise-induced Asthma

- Targeted therapy
  - Albuterol prior to exercise
  - Optimize chronic therapy is patients with chronic asthma
  - Montelukast prophylaxis may help some patient not adequately controlled by albuterol prophylaxis

Cough-variant Asthma: Question

- Which of the following is *not* a typical characteristic feature of Cough-variant Asthma?
  - A. Abnormal pulmonary function
  - B. Positive methacholine challenge
  - C. Elevated FENO
  - D. Absence of substantial wheezing

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Cough-variant Asthma

- Distinguishing Features
  - Cough
  - Bronchial hyper-reactivity and/or eosinophilic airway inflammation
  - Absence of substantial wheezing, chest tightness, or dyspnea

Cough-variant Asthma

- Clinical Manifestations
  - Usually normal PFTs
  - Positive methacholine challenge and/or elevated fractional exhaled nitric oxide (FENO) in expired air
  - Response to asthma therapy

Methacholine challenge

- Baseline FEV_1
- Graded doses of inhaled methacholine followed by repeat FEV_1 after each dose
- Positive challenge (documents bronchial hyper-reactivity): 20 % decrease in FEV_1 from baseline
- Negative challenge: < 20 % decrease in FEV_1 at top dose

Fractional Exhaled Nitric Oxide (FENO)

- Measurement available in Allergy
- Nitric oxide is produced by the human lung and is present in the exhaled breath
- Elevated levels reflect eosinophilic airway inflammation
- Elevated levels are seen in patients with asthma, including cough-variant asthma

Cough-variant Asthma

- Targeted therapy
  - No specific therapy for this variant
  - Usual pharmacotherapy appropriate
  - Response to asthma therapy helps to confirm the diagnosis

Obesity-associated Asthma: Question

- Which of the following is true regarding Obesity-associated Asthma
  - A. It is more common in women
  - B. It is more common in non-allergic people
  - C. It has been shown to improve with weight loss
  - D. All of the above

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  - A. It is more common in women
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  - C. It has been shown to improve with weight loss
  - **D. All of the above**

Obesity-associated Asthma

- Distinguishing Features
  - BMI ≥ 30
  - Overweight or obesity may aggravate asthma of any phenotype

Obesity-associated Asthma

- Clinical Manifestations
  - More common in women
  - More common in non-atopic patients
  - May be poorly responsive to conventional therapy

Obesity-associated Asthma

- Targeted Therapy
  - Weight loss

Asthma/COPD Overlap Syndrome: Question

- Compared to pure asthma, patients with the Overlap Syndrome have
  - A. Less mucus production
  - B. More exacerbations
  - C. Better response to inhaled corticosteroids
  - D. All of the above

Asthma/COPD Overlap Syndrome: Answer

- Compared to pure asthma, patients with the Overlap Syndrome have
  - A. Less mucus production
  - **B. More exacerbations**
  - C. Better response to inhaled corticosteroids
  - D. All of the above

Asthma/COPD Overlap Syndrome

- Distinguishing features
  - Smoking history
  - FEV_1 < 70 % predicted after therapy

Asthma/COPD Overlap Syndrome

- Clinical Manifestations
  - Dyspnea on exertion after therapy
  - More cough and phlegm than pure asthma
  - Increased tendency to exacerbations compared to pure asthma or pure COPD
  - Less responsive to inhaled corticosteroids than pure asthma

Asthma/COPD Overlap Syndrome

- Targeted Therapy
  - Discontinue smoking
  - Consider pulmonary rehabilitation

Defining the Phenotype

- History
  - Age of onset of asthma
  - Rhinitis
    - Allergic
    - Nasal polyps
    - Sinus disease
  - Atopic dermatitis
  - Smoking
    - Past
    - Current
  - GERD

Defining the Phenotype

- Symptoms
  - Dyspnea
    - With other symptoms
    - On exertion after therapy
  - Chest cough
    - With other symptoms
    - Only symptom
    - With prominent mucus production

Defining the Phenotype

- Triggers
  - Seasonal variation
  - Allergens (house dust, animals, mold exposure, pollen)
  - Aspirin or other NSAID
  - Infection
    - Only trigger
    - One of several triggers
  - Exercise
    - Only trigger
    - One of several triggers

Defining the Phenotype

- Testing
  - BMI
  - Spirometry
  - Allergen-specific IgE
    - RAST
    - Skin tests
  - Methacholine challenge
  - FENO

Conclusions

- Asthma can be categorized into several phenotypes
- Asthma phenotypes have distinguishing features, characteristic clinical manifestations, and targeted therapy
- Asthma phenotypes may overlap
- Relationships of the phenotypes to different underlying pathogenetic mechanisms (endotypes) are not well-established
- Further research should better elucidate the mechanistic and clinical implications of asthma phenotypes