Clinical Implications of Asthma Phenotypes

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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, although not perfectly defined, have implications for management
Endotype

• A subtype of a condition, which is defined by a distinct functional or pathobiological mechanism

• Two main endotypes in asthma
  • Th2 (eosinophilic)
  • Non-Th2

• A single phenotype may have more than one endotype
  • Non-allergic asthma may be Th2 or Non-Th2

• A single endotype may contribute to more than one phenotype
  • Th2 endotypes contribute to allergic asthma, one type of non-allergic asthma, and AERD

• Endotype identification may further facilitate “personalized medicine”
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
Allergic Asthma: Answer

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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
House Dust Mite Avoidance

- Wash all bedding, blankets, comforters, mattress pads and sheets in hot water (>120 degree F) at least every two weeks.

- Get water-proof dust covers for the mattress and all pillows. These can be obtained from mail order allergy supply houses.

- Do not humidify your house, and if you live near the beach consider getting a dehumidifier for the bedroom.

- Use dust mask if you need to vacuum and consider vacuum cleaner with HEPA filter.
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
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
Non-allergic Asthma: Answer

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
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
  • May be Th2 or non-Th2 endotype
    • May or may not have peripheral eosinophilia (at least ≥ 150 cells/microliter)
    • May or may not have elevated fractional exhaled nitric oxide (FENO)
Fractional Exhaled Nitric Oxide (FENO)

- Exhaled breath measurement available in Allergy and Pulmonary
- Measures nitric oxide that is produced by the human lung
- Elevated levels reflect eosinophilic airway inflammation
- Elevated levels are seen in patients with Th2 endotype of asthma
- Elevated levels suggest likely response to inhaled corticosteroids
Non-allergic Asthma

• Targeted Therapy
  • Treatment of symptomatic GERD
  • Interleukin-5 (IL-5) antagonists for Th2 endotype
  • Macrolides, theophylline, roflumilast for non-Th2 endotype
IL-5 Antagonists

• IL-5 is the major cytokine responsible for the growth, differentiation, recruitment, and activation of eosinophils.

• IL-5 antagonists are monoclonal antibodies that reduce the production and survival of eosinophils by preventing IL-5 from binding to its receptors.

• Three now approved
  • Benralizumab
  • Mepolizumab
  • Reslizumab
## Comparison of IL-5 Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Benralizumab</td>
<td>≥ 12</td>
<td>30 mg</td>
<td>SQ</td>
<td>Every 4 weeks X 3, then every 8 weeks</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>≥ 12</td>
<td>100 mg</td>
<td>SQ</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>≥ 18</td>
<td>3 mg/kg</td>
<td>IV</td>
<td>Every 4 weeks</td>
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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)
  • 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

• Biologic therapy (Th2 endotype)
  • Omalizumab
  • IL-5 Antagonists
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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  • D. All of the above
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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  • D. None of the above
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. Response to asthma therapy
  • D. Absence of substantial wheezing
Cough-variant Asthma: Answer

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

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

• Clinical Manifestations
  • Usually normal PFTs
  • Positive methacholine challenge
  • May or may not exhibit elevated fractional exhaled nitric oxide (FENO)
  • 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
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
Obesity-associated Asthma: Answer

- 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
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
  - GERD may be associated
Obesity-associated Asthma

• Targeted Therapy
  • Weight loss
  • Treatment of symptomatic GERD
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
  - ICS/LABA combination therapy
  - Tiotropium
  - Consider pulmonary rehabilitation
Defining the Phenotype

• History
  • Age of onset of asthma
  • Rhinitis
    • Allergic or non-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
    • Blood tests (RAST)
    • Skin tests
  • Methacholine challenge
  • Peripheral eosinophil count (endotype)
  • FENO (endotype)
Conclusions

• Asthma can be categorized into several phenotypes (and two main endotypes)
• Asthma phenotypes have distinguishing features, characteristic clinical manifestations, and targeted therapy
• Asthma phenotypes may overlap
• Asthma phenotype (and endotype) classification can contribute to more targeted therapy
• Further research should better elucidate the mechanistic and clinical implications of asthma phenotypes and lead to even more successful personalized therapy