Allergies and Asthma

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Unprecedented Patient Results
Learning Objectives

1) Understand the key role that allergies play in asthma

2) Understand that treatment of allergies is part of the asthma treatment guidelines

3) Treating allergies will often reduce disease burden and cost of asthma
What is asthma?

Asthma is a chronic inflammatory disorder of the airways.

Features of asthma include inflammatory cell infiltration:

- Neutrophils (fatal asthma exacerbations; occupational asthma; smokers)
- Eosinophils (associated with allergies)
- Mast cell activation (associated with allergies)
- Epithelial cell injury (may be due to allergens, toxins, or inflammation)

Inflammation leads to symptoms, hyperresponsiveness, and disease chronicity.

Gene-by-environment interactions are important to the expression of asthma.

Atopy, the genetic predisposition for the development allergies, is the strongest identifiable predisposing factor for developing asthma.

Viral respiratory infections are an important causes of asthma exacerbation.
Inflammation

Airway Hyperresponsiveness

Airway Obstruction

Clinical Symptoms
Overview of IgE-Mediated Asthma Inflammatory Cascade

- B cell
- T cell
- IL-4, IL-13, IgE production
- Mast cell
- Activated B cell (plasma cell)
- Allergen cross-linking
- FcεRI
- Mediator release
- Airway wall

Data from a stratified cluster sample of 2657 patients from white non–Mexican-American households in which the association of self-reported asthma with serum IgE levels and skin-test reactivity to allergens was investigated. Blood samples were obtained from subjects, and serum IgE levels were measured.

The risk for allergic asthma starts with relatively low IgE levels.

Do patients with allergic rhinitis have pathophysiologic risk factors for developing asthma?
Patients With Allergic Rhinitis Alone Have Abnormalities Of The Lower Airways

- Pathologic abnormalities
  - Eosinophilic inflammation
  - Basement membrane thickening

- Bronchial hyperresponsiveness to nonspecific stimuli
Bronchial Inflammation In Patients With Isolated Allergic Rhinitis vs. Asthmatics

Comparative Histopathology Of Allergic Rhinitis (AR) vs. AR/Asthma

- Biopsy studies of nasal and bronchial tissue
- Difficult to distinguish AR/asthma from isolated AR on basis of:
  - Nasal or bronchial eosinophils
  - Nasal or bronchial mast cells
  - Bronchial basement membrane thickening
  - Serum IL-5 or eotaxin levels

Braunstahl et al, Clin Exp Allergy, 2002;33:579-87
Correlation Between Nasal And Bronchial Eosinophils In Asthmatics

\( r = 0.851, P < .001 \)

(n = 11)
What’s the Risk of a Patient with Allergic Rhinitis Developing Asthma?
Frequent Association of Upper and Lower Airway Disease

- Involvement of upper airway is very common in patients with asthma

- Of 478 patients w/ asthma, 99% of adults and 93% of adolescents reported concomitant AR

- In patients with allergic rhinitis, asthma present in 19% - 40%

Allergic Rhinitis Symptoms Are Ubiquitous in Asthma

ADOLESCENT ASTHMA STUDY
n = 125
88.8%
rhinitis symptoms

ADULT ASTHMA DATABASE
n = 348
94.3%
rhinitis symptoms

COLLABORATIVE STUDIES FOR THE GENETICS OF ASTHMA
n = 168
85.1%
rhinitis symptoms
Patients With AR + Comorbid Conditions

AR As A Risk Factor For The Development Of Asthma Incidence of Asthma Over An 8-Year Period

OR: 46.5

Linneberg et al. Allergy 2002;57:1048

% of subjects

pollen
animal
mite

OR: 8.2
OR: 18.9

no rhinitis at baseline
rhinitis at baseline
Will Treatment Of Allergic Rhinitis Result In Improvements In Lower Airway Disease?
Number of topical and oral rhinitis treatments have been evaluated in patients with both allergic rhinitis and mild asthma.

All classes have been demonstrated to reduce lower airway symptoms.

Variable effects on objective parameters (i.e., pulmonary function and BHR).
How Does an Antihistamine-Decongestant Affect Asthma?

Mean Change From Baseline In Asthma Sx Severity Score

Effect Of Cetirizine On Asthma Symptoms In Patients With SAR And Mild Asthma


![Graph showing the effect of Cetirizine on asthma symptoms. The graph compares the total asthma score between Placebo (n = 93) and Cetirizine (10 mg/d) (n = 93). *P<0.05*]
Effect Of Loratadine+Pseudoephedrine On FEV1 in SAR & Mild Asthma

4 studies have examined effects of nasal steroids on nonspecific BHR: beclomethasone 2, fluticasone 1, triamcinolone 1

3 of 4 studies demonstrated statistically significant improvements in BHR with 2 to 4 wks of use

None of studies demonstrated improvements in pulmonary function (FEV1, PEFR)
Asthma Pathophysiology

before

Smooth muscle dysfunction

Airway inflammation

Airway remodeling

after

Bronchoconstriction

Edema

Bronchospasm

Before

10 Min After Ag Challenge

Airway Morphology in Asthma

- Goblet cell hyperplasia
- Increased permeability/microvascular leakage
- Mucus
- Collagen deposition
- Epithelial damage
- Increased smooth muscle mass
- Inflammatory cell infiltration
- Angiogenesis

The Soaring Cost of a Simple Breath

The Centers for Disease Control and Prevention puts the annual cost of asthma in the United States at more than $56 billion, including millions of potentially avoidable hospital visits and more than 3,300 deaths, many involving patients who skimped on medicines or did without.
NHLBI: Asthma Control Assessment (Adults and Youths ≥12 Years of Age)

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Well Controlled</th>
<th>Not Well Controlled</th>
<th>Very Poorly Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>1x-3x/week</td>
<td>≥4x/week</td>
</tr>
<tr>
<td>Interfering with normal activity</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td><strong>Short-acting β₂-agonist use for symptom control (not prevention of EIB)</strong></td>
<td>≤2 days/week</td>
<td>&gt;2 days/week</td>
<td>Several times per day</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
<td>60%-80% predicted/ personal best</td>
<td>&lt;60% predicted/ personal best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75*</td>
<td>≥1.5</td>
<td>N/A</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
<td>16-19</td>
<td>≤15</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations† requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
<td>≥2/year (see notes)</td>
<td>Consider severity and interval since last exacerbation</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td></td>
<td>Evaluation requires long-term follow-up care</td>
<td></td>
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<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
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</table>

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ATAQ = Asthma Therapy Assessment Questionnaire; EIB = exercise-induced bronchospasm; FEV₁ = forced expiratory volume. *ACQ values of 0.76 to 1.4 are indeterminate regarding well-controlled asthma. †Exacerbations of asthma are episodes of progressive worsening in symptoms and reductions in lung function that interfere with the ability to perform usual activities unless quick-relief therapy, such as SABA and additional corticosteroid treatment, is used. NHLBI. J Allergy Clin Immunol. 2007;120:S94.
### Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults

#### Intermittent Asthma

Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

<table>
<thead>
<tr>
<th>Step 1 Preferred:</th>
<th>Step 2 Preferred:</th>
<th>Step 3 Preferred:</th>
<th>Step 4 Preferred:</th>
<th>Step 5 Preferred:</th>
<th>Step 6 Preferred:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA PRN</td>
<td>Low-dose ICS</td>
<td>Medium-dose ICS + LABA</td>
<td>High-dose ICS + LABA</td>
<td>High-dose ICS + LABA + oral corticosteroid</td>
<td></td>
</tr>
<tr>
<td>Cromolyn, LTRA,</td>
<td>Medium-dose ICS +either LTRA, Theophylline, or Zileuton</td>
<td>AND</td>
<td>AND</td>
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<tr>
<td>Nedocromil, or</td>
<td></td>
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<tr>
<td>Theophylline</td>
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Each step: Patient education, environmental control, and management of comorbidities. Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

*The safety and efficacy of omalizumab used concomitantly with long-acting beta₂-agonists have not been established.
†Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.
NHLBI. *J Allergy Clin Immunol.* 2007;120:S94.