Allergies and Asthma—Assessment and Control

H. David Stone, Jr., MD, FACAAI
Allergy, Asthma, & Sinus Center, P.C.
Florence, S.C.
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Intracellular Pathogens
Interleukin 12

TH0

Allergens
Interleukin 4

TH1

Interferon γ
Interleukin 2
Cell-mediated Immunity

TH2

Interleukin 2
Interleukin 5
Interleukin 13

Allergic Disease
Humoral Immunity

JAMA. 1997;278:1845.
Phase 1 – Sensitization

Allergen → Antigen-presenting cell → Processed allergen → CD4 T cell

B cell → Plasma cell → IgE antibodies
Phase 2 – Clinical Disease

Early Phase

Allergen

IgE antibodies

Mediator release

Mast cell

Blood vessels

Nerves

Glands

Sneezing

Itching

Rhinorrhea

Congestion

Late Phase

Late-phase reaction

Cellular infiltration

Eosinophils

Basophils

Monocytes

Lymphocytes

Priming

Hyperresponsiveness

Resolution

Complications

Irreversible Disease?

Overview of the Allergic Inflammatory Cascade in Patients with IgE-mediated Asthma

- B lymphocyte
- Allergic mediators
- Allergens
- Mast cells Basophils
- Allergic Exacerbation

γ-switch

Release of IgE

Allergic Inflammation: eosinophils and lymphocytes
Allergic Rhinitis

• CHRONIC Inflammatory Disease of the Upper Airway
  – 35 million Americans have allergic rhinitis–

• Prevalence in 20-30% of the population
  – Peak prevalence in children and young adults
  – 50% of patients have symptoms >4 months per year and 20% >9 months per year

• Productivity
  – 28 million days of restricted activity
  – 2 million lost school days
Asthma

- CHRONIC Inflammatory Disease of the Lower Airway
- Most common non-traumatic admission to children’s hospitals in the U.S.
- Greater 200,000 hospitalizations per year in U.S.
- Lifetime prevalence 7-9% in adults, 12-14% in children
Child and Adult Asthma Prevalence
United States, 1980-2007

- **Child**
- **Adult**

**Lifetime**

**Current**

**12-Month**

Source: National Health Interview Survey; CDC National Center for Health Statistics
Risk Factors for Wheezing at Age Three

- Passive smoke exposure (OR=2.1)
- Older siblings (OR=2.5)
- Allergic sensitization to food protein at 1 year of age (OR=2.0)
- At least one wheezing illness during infancy with RSV (OR=3.0), non-RV/RSV (OR=3.9), or Rhinovirus (OR=10)
Modified Asthma Predictive Index
Chang, et al, 2013

• Primary finding: >4 wheezing episodes/yr AND

• At least 1 major criteria: parental history of MD-diagnosed asthma; atopic dermatitis diagnosed by MD; allergic sensitization to at least one inhalant allergen; OR

• At least 2 minor criteria: wheezing unrelated to colds/URI; >4% eosinophils on CBC; or allergic sensitization to egg, milk, or peanut
Modified Asthma Predictive Index
Chang, et al, 2013

• Positive mAPI associated with a 67% incidence of asthma at age 6 in unselected patients, and 90% incidence in high-risk patients

• Negative mAPI associated with only an 8-10% risk of asthma in unselected patients and 28-30% incidence in high risk patients.
Rhinitis and Asthma

• High prevalence, high cost illnesses

• Both illnesses have a major effect of the sufferer’s quality of life

• Both illnesses have a strong association with allergy
Hypotheses for Links of Rhinitis and Asthma

Between 60-80% of patients with asthma have allergic rhinitis and many patients with allergic rhinitis have increased bronchial hyper-reactivity.

Common ciliated epithelium, similar inflammatory cell population and mediators.

Similar allergens are associated with both conditions.

Both have a familial link with atopy.

Possible pathophysiological mechanism: rhino-bronchial reflex.
# Markers of Severity/Risk in Asthma

<table>
<thead>
<tr>
<th>Subjective</th>
<th>Objective</th>
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</thead>
<tbody>
<tr>
<td>• Daytime symptoms</td>
<td>• Pulmonary Function Test/Spirometry</td>
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<tr>
<td>• Night-time symptoms</td>
<td>• FENO</td>
</tr>
<tr>
<td>• Activity Limitation</td>
<td>• Methacholine, Mannitol provocation</td>
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<tr>
<td>• Rescue Medication Use</td>
<td>• ER visits</td>
</tr>
<tr>
<td>• Perception of Control</td>
<td>• Exacerbations requiring PO or systemic steroids</td>
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<td>• Lost School Time</td>
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Evidence of Causal Role of Allergies in Asthma in Children

- Sensitization to indoor allergens and outdoor fungi increases the risk for asthma.
- The larger the size of the skin test reaction to house dust mite, the more sensitive the patient is to methacholine, a measure of bronchial hyper-reactivity.
- Severity of asthma is related to the level of allergen exposure.
- Reduction of allergen exposure improves asthma symptoms and reduces bronchial hyper-responsiveness.
Major triggers of Allergic Rhinitis and Asthma

- Pollens
- Molds
- House dust mites
- Animals (cat, dog, rodent)
- Insect aeroallergens (cockroaches)
Seasonal Pollens

- Wind-borne pollen (typically non-flowering plants)
- Smaller, more respirable particles are the most symptom-producing
- Highest on dry, windy days, and during the early morning hours
- Levels and duration of seasons may be affected by future climate changes
Pollen in South Carolina

• Tree pollen—late January/early February to the end of April

• Grass pollen—late April to late July/early August

• Weed pollen—summer weeds late May to October; Ragweed mid-August to early November

• Outdoor molds may peak in May and October as well, and behave like pollens
Mold Spore Exposure

**Outdoors**
- Some species prevalent on dry, windy days (Alt, Clado, Epic)
- Some types prevalent at night and on humid, rainy days (mushroom, puff, smut)
- High levels correlate with increased symptoms, medication use, morbidity/mortality

**Indoors**
- Prevalent in hot, humid climates (like S.C.)
- Incursion from outdoors
- Associated with indoor moisture, water damage
- Like dimly lit areas with increased moisture
- Most commonly found are Asp, Pen, as well as Alt, Clado, and Epic
House Dust

- Complex mixture of everything found in homes
- Impossible to standardize
- Variable quantities of many allergens: dust mites, cat, dog, mold, rodent, insect, food
- Human proteins: IgA, albumin
Dust Mites in Homes

• Mite growth is dependent on water content of air (>50% humidity) and temperature (65-80F)
• Mite population peaks in summer months and remain elevated into the fall and winter
• Mite particles settle out of air quickly, so airborne levels depend on disturbance in the room
Cat and Dog Allergen

• One major allergen: Fel d 1, produced in sebaceous and salivary glands of cats
• Source of major dog allergen is dander
• Most homes in the U.S. have measurable animal dander allergen even though there is no pet at home (this has also been found in schools and church nurseries)
• Higher measured levels correlate with increased risk of sensitization, especially cat
Household Insect Allergen

• Cockroaches are the major source of allergens, especially in inner cities
• May also include moths, crickets, ladybugs, beetles, etc.
• Also known to be occupational allergens
• Allergens from waste, saliva, and debris
• Large allergens, like dust mites, not easily detected in undisturbed air
# Respiratory Irritants/Pollution

## Outdoor Exposure
- Particulate Matter
- Diesel Exhaust
- Ozone
- Nitrogen oxides (NO$_2$)
- Sulfur oxides (SO$_2$)

## Indoor Exposure
- Environmental Tobacco Smoke
- Nitrogen oxides (NO$_2$)
- Formaldehyde
- Volatile Organic Chemicals from air fresheners, perfumes, etc.
- Endotoxins, Fungal toxins
- Home Dampness
Outdoor Dust Particles

• These are solids that are suspended in the air
• Particulate matter contains metal ions, silica, organic residues, hydrocarbons, and endotoxin
• Bioaerosols including pollens, fungal spores, animal proteins, soy dust and other plant proteins
Particulate Matter (PM$_{2.5}$, PM$_{10}$)

- Acute exposures to large and small particulate associated with increased asthma symptoms, reduced lung function, increased hospitalization, and increased medication use.
- Chronic exposure may be associated with increased bronchitis, reduced FVC in adults, and reduced growth of FEV1 in children.
- Specific traffic-associated particulate may be associated with asthma development (e.g. diesel exhaust particles enhance allergen-induced IgE).
Traffic and NO$_2$—Chronic Effects

- Higher exposure to truck traffic associated with increased respiratory sx, BHR, and sensitization to allergens; increases airway inflammation (PMN’s)
- Correlates with slow growth of FEV1 in children 10-18 y/o
- Increased asthma prevalence with proximity to freeways
- Derived from vehicle exhaust and other combustible fuels (gas/kerosene)
Ozone and Sulfur Dioxide

- Ozone is a secondary combustion product.
- Induces PMN infiltrate and inflammatory mediators.
- Ozone increases asthma symptoms, reduces pulmonary function, and enhances airway responsiveness to allergens.
- $\text{SO}_2$ shown to increase hospitalizations, increase bronchoconstriction, and reduce lung function.
Volatile Organic Chemicals

• Primary sources are water-based paints, cleaning products, air fresheners, adhesives, new carpeting, perfumes, and cosmetics

• Avoidance of these difficult, but involves:
  – Elimination of air fresheners and heavily perfumed cosmetics in the home
  – Use VOC’s only in well-ventilated areas
  – Use products with low VOC rating
### Environmental Tobacco Smoke

#### In Utero Exposure
- Impairs lung/airway development
- Increases risk of early childhood wheeze
- Increased risk of early childhood asthma
- Data regarding relation to allergen sensitization inconsistent

#### Post-natal exposure
- Irritant to respiratory mucosa
- Pro-inflammatory in the nasal and bronchial airway
- Increases BHR
- Increased risk of asthma exacerbation
Environmental Control: Pollen

Close windows, doors

Reduce outdoor exposure as practicality allows:
--When pollen counts are high (highest in early AM)

Avoid window/attic fans

--On sunny, windy days with low humidity

A/C on recirculate

Wear dust mask when working outdoors

Shower or bathe following exposure
Environmental Control Measures: Dust Mites

• Allergen-proof pillows, mattresses, box springs

• Wash bedclothes at 130 F
  Lower temperatures do not kill mites

• Avoid/cover quilts, comforters, and other dust collectors such as stuffed animals and throw pillows

• Cleaning of duct work and HEPA filter have no demonstrated value in removing dust mites
Environmental Control Measures: Dust Mites

- Vigorous methods necessary
- Simple furnishings without carpeting
  - Especially bedroom, family room, etc
  - Plastic, leather, wood are best
- Vacuum weekly with vacuum that has HEPA-filter or self-contained collection system
Environmental Control Measures: Molds

- Remain in closed environment as practicality allows
- A/C units, though helpful, can harbor mold
- Avoid lawn mowing, raking leaves, if practical (face masks can be of some value)
- Avoid/remedy dampness
- Minimize humidifier use (If used, keep very clean)
- Consider using a dehumidifier
- Completely remediate any water damaged areas
Avoidance Measures:
Cats and Dogs

• Removal of pet is the only clearly effective avoidance (may take 4-6 months to achieve a basal level)
• Pet washing only temporarily reduces allergen from shedding cats
• Aggressive cleaning of homes can reduce allergen levels
• Steam cleaning carpets did not seem more effective than regular cleaning
Avoidance Measures: Insects and Pests

• Stop inflow of pests and prevent reintroduction: seal cracks/holes, clean around dwelling

• Remove pests: poison/extermination, cleaning

• Remove sources of food and water for pests:
  – Remove food crumbs, stop leaking pipes/faucets
Outdoor pollution avoidance

- Watch out for high ozone/pollution alerts and limit time outdoors; especially in summer
- Avoid congested areas near highways, freeways
- Industrial emissions standards
- Efficient, lower-emission vehicles
Basic Indoor Irritant Control Strategies (would apply to workplace and school)

• Source management (reduce, substitute)
• Local exhaust
• Ventilation
• Exposure control
• Air cleaning/filtration
• Education
• EPA Indoor Air Quality Tools for Schools
• www.epa.gov/iaq/schools/actionkit_text.html
Environmental Tobacco Smoke Control

• Stopping smoking is the **ONLY reliably effective means of preventing smoke exposure**

• Increasing ventilation and air cleaning is technologically capable of reducing indoor smoke particle concentration, HOWEVER!!!

• EVIDENCE IS LACKING THAT VENTILATION AND FILTRATION REDUCE THE RISK OF ASTHMA DEVELOPMENT OR EXACERBATION
Principles of Asthma/Allergy Treatment

• Allergen Avoidance Measures
• Allergy/Asthma Medications
• Allergy-directed Immune modification
Goals of Asthma Therapy

• Prevent chronic troublesome symptoms
• Maintain normal or near-normal lung function
• Maintain normal physical activity
• Maintain quality of life
• Minimize side effects
• Prevent exacerbations
• Reduce hospitalizations/ER visits
• Prevent disease progression
Treatments Directed at Modifying Allergic Disease

Sub-cutaneous Immunotherapy (SCIT)

Omalizumab (Xolair)
Indications for Sub-Cutaneous Immunotherapy (SCIT)

- Patients whose symptoms are not adequately controlled by allergen avoidance and standard pharmacotherapy (FEV1 should be >65-70% at initiation)
- Patients who have nasal and bronchial symptoms
- Patients whose skin tests correlate with seasons/exposures
- Patients who would like to reduce the amount of medications they require for control
- Patients whose medications produce side-effects
Mechanisms of SCIT

- Inhibits allergen-induced late-phase inflammation in skin, nose, and lung
- Increases allergen-specific IgG, suppresses eosinophils
- Shifts TH2/TH1 balance back toward TH1
- Induces IL-10, increases T-regulatory cells (long-term effects)
- Reduces co-stimulatory inflammatory mediators
Benefits of SCIT

• Shown to reduce asthma symptoms and medication use during seasonal and perennial allergen exposure
• Reduces bronchial hyper-reactivity
• In children, studies suggest it reduces progression of allergic disease (fewer allergic patients with rhinitis developed asthma over 5 years on SCIT) and fewer new sensitizations occurred in asthmatic children on SCIT
Indications for Omalizumab

• Adults and children 12 and older with moderate to severe persistent asthma
• Symptoms not adequately controlled with inhaled corticosteroids
• Positive skin test or in vitro test to at least one perennial allergen (mite, pet, mold, cockroach)
• IgE should not typically exceed 700 IU/mL
• May be used concomitantly with SCIT
Mechanism of Action of Omalizumab

• Binds to, and forms immune complexes with, IgE
• Prevents IgE from binding to FcE receptor on mast cells and basophils
• Reduces serum IgE
• Down-regulates FcE receptors on several cell types
Benefits of Omalizumab

- Decreased early and late phase allergic inflammation
- Reduced symptoms and number of exacerbations
- Improvement in pulmonary function (FEV1)
- Increased the threshold of allergen required to produce broncho-constriction
The End

Questions???????