Allergy and Asthma

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Allergy, Asthma and Immunology
Associates of South Texas
The Role of the Mast Cell in Chronic Inflammation Due to Allergen Exposure in Allergic Asthma

**SENSITIZATION**
- Priming of the immune system prior to development of symptoms upon allergen exposure
- T Cell Differentiation
- IL-4, IL-13
- DC
- FcεRI
- B Cell
- Activated B Cell
- IgE

**LYMPH NODE**
- Airway Inflammation
- Airflow Obstruction
- Airway Hyperresponsiveness
- Mucus Hypersecretion

**EARLY-PHASE RESPONSE**
- Cross-linking of surface-bound IgE causes mast cells to degranulate and release inflammatory mediators
- Bronchospasm
- Edema
- Airflow Obstruction
- Mucus Production
- Recruitment of Inflammatory Cells Leading to the Late-Phase Response

**LATE-PHASE RESPONSE**
- Activated mast cells and T\(_{h2}\) cells secrete mediators that cause airway inflammation and recruitment of eosinophils
- Perennial exposure to allergens contributes to a positive feedback loop resulting in chronic airway inflammation

Objectives

• Characterize asthma based on phenotypes
• Define how atopy influences asthma development in children and adults
• Define diagnostic options to define IgE mediated influences on asthma
• Consider immunotherapy to modify outcomes in IgE mediated asthma
• Utilize phenotypes in defining best treatment options for patients with moderate to severe persistent asthma
Defining Asthma by Phenotypes

- Phenotype – expression of genotype as influenced by environment – clusters of characteristics used to define asthma

- Review of pubmed.gov reveals numerous articles adding “phenotypes” to the reasons for asthma – ever expanding playing field

- NHLBI multi-organization collaboration in 2011 defined the following phenotypes
  - One size does not fit all – interrelate
Asthma Phenotypes

• Define 9 phenotypes in 3 general categories:
  - Trigger-induced asthma
    1. Allergic
    2. Non-allergic
    3. Aspirin-exacerbated respiratory disease (AERD)
  4. Infection
  5. Exercise-induced
Asthma Phenotypes

- Clinical presentation of asthma
  6. Pre-asthma wheezing in infants
     - Episodic (viral) wheeze
     - Multi-trigger wheezing
  1. Exacerbation-prone asthma
  2. Asthma associated with apparent irreversible airflow limitation
- Inflammatory markers of asthma
  1. Eosinophilic and neutrophilic asthma
Atopy and the Allergic Response in Asthmatics
What is “Atopy”

• Essentially, atopy defines the tendency for a person to develop allergic (IgE mediated) disease

• IgE is the main culprit in provoking allergic or Type 2 mediated asthma and rhinitis

• IgE is made from B lymphocytes that are instructed by Type 2 converted T lymphocytes to produce IgE specific for one allergen
The Role of the Mast Cell in Chronic Inflammation Due to Allergen Exposure in Allergic Asthma

**SENSITIZATION**

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- T Cell Differentiation
- IL-4, IL-13

**EARLY-PHASE RESPONSE**

- Cross-linking of surface-bound IgE causes mast cells to degranulate and release inflammatory mediators
- Histamine, Leukotrienes, Prostaglandins, Other Mediators (IL-8, CCL2)

**LATE-PHASE RESPONSE**

- Activated mast cells and T\(_\text{h}2\) cells secrete mediators that cause airway inflammation and recruitment of eosinophils

**AIRWAY LUMEN**

- Allergen
- Damaged Epithelium Due to Inflammation

**LYMPH NODE**

- B Cell, Activated B Cell
- Migration of DCs
- Peptide MHC Class II, TCR

**AIRWAY WALL**

- Activated B Cell
- Mast Cell
- IL-5, IL-13, IL-4, IL-13
- Recruitment and Activation of Eosinophils
- Inflammatory Mediators, Cytokines

**Mucus**

- Airway Inflammation, Airflow Obstruction, Airway Hyperresponsiveness, Mucus Hypersecretion

**Perennial exposure to allergens contributes to a positive feedback loop resulting in chronic airway inflammation**
What Happens with IgE

- Each mast cell is covered with thousands of IgE molecules – most specific for different allergens
- Cross-linking by an allergen of two adjacent IgE molecules “fires” the mast cell to release its inflammatory mediators
- Mediators such as LTD$_4$ are chemotactic for eosinophils and LTB are chemotactic for neutrophils
Leukotriene Production in Allergy

Minutes to hours

Nuclear Mast Cell Membrane

Phospholipase A₂

Arachidonic Acid

5 L O F L A P

LTC₄ synthase

Epoxide hydrolase

Dipeptidyl hydrolases

LTD₄

Cytosol Mast Cell Membrane

LTC₄

LTE₄
The Result

• Histamine and leukotrienes provoke bronchospasm and eosinophil chemotaxis
• Mast cell mediators IL4 and IL13 provoke perpetuation of the allergic response
• Eosinophil derived toxins cause breakdown of columnar epithelial layers
• Mucus hypersecretion from goblet cells add to the mess and blockage of airways
• Inevitable scarring of inner airways leads to changes in inflammatory cell mix with steroid resistant neutrophils
The Role of the Mast Cell in Chronic Inflammation Due to Allergen Exposure in Allergic Asthma

**SENSITIZATION**

Primning of the immune system prior to development of symptoms upon allergen exposure.

- **1.** Allergen
- **2.** T Cell
- **3.** B Cell
- **4.** Activated B Cell
- **5.** Peptide MHC Class II
- **6.** TCR
- **7.** DC
- **8.** Migration of DCs
- **9.** IL-4
- **10.** IL-13
- **11.** IL-4
- **12.** FcεRI
- **13.** IgE

**EARLY-PHASE RESPONSE**

Cross-linking of surface-bound IgE causes mast cells to degranulate and release inflammatory mediators.

- **1.** Bronchospasm
- **2.** Edema
- **3.** Airflow Obstruction
- **4.** Mucus Production

**LYMPH NODE**

- **1.** Mast Cell
- **2.** Histamine
- **3.** Leukotrienes
- **4.** Prostaglandins
- **5.** Other Mediators (IL-8, CCL2)

**LATE-PHASE RESPONSE**

Activated mast cells and T\(_2\) cells secrete mediators that cause airway inflammation and recruitment of eosinophils.

- **1.** Airway Inflammation
- **2.** Airflow Obstruction
- **3.** Airway Hyperresponsiveness
- **4.** Mucus Hypersecretion

**AIRWAY WALL**

- **1.** Airway Obstruction
- **2.** Mucus Hypersecretion

Perennial exposure to allergens contributes to a positive feedback loop resulting in chronic airway inflammation.
• Prescribing a medication to suppress the allergic response should quell the reaction

It’s Not That Easy

• The allergic response begins in early childhood for most children who develop asthma
• Those children grow into adults with asthma remissions occur during adolescence but you don’t “outgrow your immune response”
• Must start early to modify the immune response
Rate of Decline in FEV$_1$

Has Any Therapy Reduced the Decline in Airflow with Time?

• Allergen Immunotherapy?
  When to start? Can immunotherapy be started for infants at risk?

• Chemotherapy?
  • Prednisone, inhaled corticosteroids, muscarinic antagonists, LTRAs?

• Monoclonal antibodies?
  • Too soon to tell but not likely
  • $$$$$$
So Why Is Consideration of Allergy Important in Diagnosis and Management of Asthma?
Risk of Asthma in Those with Atopy

% Patients with Eczema before Age 2

Asthma Predictive Index

History of greater than 4 wheezing episodes in one year (one - physician documented) PLUS

• One major criteria:  
  – Parent with asthma  
  – Atopic dermatitis

  OR

• Two minor criteria:  
  • Food sensitivity (milk, egg or peanuts)

If +, then 65% likelihood of developing asthma  
If -, then 95% likelihood of NOT developing asthma
Importance of Identifying Sensitivities to Aeroallergens
The Role of the Mast Cell in Chronic Inflammation Due to Allergen Exposure in Allergic Asthma

1. **SENSITIZATION**
   - Priming of the immune system prior to development of symptoms upon allergen exposure.
   - Peptide MHC Class II
   - TCR
   - DC
   - T Cell
   - IL-4
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   - B Cell
   - Activated B Cell

2. **EARLY-PHASE RESPONSE**
   - Cross-linking of surface-bound IgE causes mast cells to degranulate and release inflammatory mediators.
   - Bronchospasm
   - Edema
   - Airflow Obstruction
   - Mucus Production
   - Histamine
   - Leukotrienes
   - Prostaglandins
   - Other Mediators (IL-8, CCL2)

3. **LATE-PHASE RESPONSE**
   - Recruitment of inflammatory cells leading to the late-phase response.
   - IL-5
   - IL-13
   - IL-4
   - IL-13
   - Activated B Cell

4. **AIRWAY WALL**
   - Airway inflammation
   - Airflow obstruction
   - Airway hyperresponsiveness
   - Mucus hypersecretion

Activated mast cells and T_{h}2 cells secrete mediators that cause airway inflammation and recruitment of eosinophils.

Perennial exposure to allergens contributes to a positive feedback loop resulting in chronic airway inflammation.
Exposure to Dust Mites and Asthma

- Children exposed to high level of dust mite antigen at age 1 year were likely to have developed atopic asthma by age 11 yr
  
  Sporik R et al NEJM 1990; 323: 502-7

- Environmental controls for dust mite exposure often incomplete considering presence of dust mite antigen in carpeting and parent’s bedding
Dust Mites and Asthma

Asthma development in children

Lung function in adult asthmatics


Custovic et al, JACI 1996;98:64-72
Bed Covers for Adults with Asthma

**Methods:** Randomized double blind placebo controlled study of allergen impermeable mattress covers.

**Results:**
- Mite allergen lower for the active than placebo group at 6, but not 12 months.

**Conclusion:** Mattress covers alone are not sufficient to control asthma symptoms in allergic adults.

How ‘Bout Them Animals?

• Study of the development of asthma and atopy in children raised with cats and/or dogs
  – Boys raised with animals present since birth were less likely to develop allergies (as measured by prick skin testing) to those animals compared to girls
  – Methacholine sensitivity improved in boys but not girls
    • However, girls were less likely to develop sensitivities to indoor aeroallergens and atopy overall if raised with animals
  – Significance only achieved if 2 or more animals in house

Ownby D et al JAMA 2002; 288: 963-72
Cat Allergen and Asthma Morbidity in Adult Women Who Own Indoor Cats

<table>
<thead>
<tr>
<th>Steroid Use</th>
<th>ER Visit</th>
<th>Wheeze, No Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR</td>
<td>Adjusted OR</td>
</tr>
<tr>
<td>Low exp. or not sens.</td>
<td>1.0 (1.2-6.4)</td>
<td>1.0 (1.2-6.2)</td>
</tr>
<tr>
<td>High exp. and sens.</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Cat Allergen in Home Declines Slowly After Pet Removal

Fel d 1 content in the dust from homes after removal of a cat
Wood et al JACI 83:730,1989
Effect of Pet Removal on Asthma Morbidity

- Prospective observational study of 20 asthmatic pet allergic adults
- 10 elected to remove pets, 10 kept pets
- Followed for ≥ 1 year
- 5/10 - * 0/10 on ICS in removal group
- 6/10 - * 9/10 on ICS in keeping group

## Cockroach Allergen Exposure
### Risk Factors for High Blag 1 Levels

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of dwelling</strong></td>
<td></td>
</tr>
<tr>
<td>Detached</td>
<td>Reference</td>
</tr>
<tr>
<td>High rise apartment</td>
<td>70.0 (16.6-295.9)</td>
</tr>
<tr>
<td><strong>No of units in building</strong></td>
<td></td>
</tr>
<tr>
<td>Single family</td>
<td>Reference</td>
</tr>
<tr>
<td>Multifamily</td>
<td>4.89 (1.87-12.8)</td>
</tr>
<tr>
<td><strong>Construction year</strong></td>
<td></td>
</tr>
<tr>
<td>1978-1998</td>
<td>Reference</td>
</tr>
<tr>
<td>pre-1940</td>
<td>3.29 (0.87-12.4)</td>
</tr>
<tr>
<td><strong>Urbanization</strong></td>
<td></td>
</tr>
<tr>
<td>population &lt; 1 million</td>
<td>Reference</td>
</tr>
<tr>
<td>population &gt; 1 million</td>
<td>3.15 (1.06-9.37)</td>
</tr>
<tr>
<td><strong>Household income</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; $60,000</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; $20,000</td>
<td>12.1 (2.05-71.7)</td>
</tr>
</tbody>
</table>

Cohn et al., Environmental Health Perspectives, 114: 522-526, 2006
Cockroach Allergen Exposure and Asthma Morbidity in Inner City Children

- Hospitalizations:  
  - $p=0.001$  
  - $p<0.001$

- Unscheduled Medical Visits:  
  - $p<0.001$

- Change in Care Giver’s Plans:  
  - $p=0.006$

- Days With Changed Plans in Past Year:
  - neg skin test, low allergen exposure
  - neg skin test, high allergen exposure*
  - pos skin test, low allergen exposure
  - pos skin test, high allergen exposure*

* Blag 1 > 8 U/gram

Association Between Spore Peaks and Asthma Hospitalizations in Kansas City

• First documented by Salvaggio 1971

ER Visits vs Spores per Cubic Meter of Air

Spores and ER Visits display a significant correlation, with spikes in both occurring during certain dates.
The Atopic March

- Prevalence of AD peaks at 20% at age 1 and declines to 5% by age 22
- Prevalence of wheezing increased from 5% at age 1 to 40% by age 22 years
- Early sensitization to foods in 1st year of life (odds ratio 12.3) or aeroallergens (OR 4.6) by year 2 increased risk of asthma by adulthood

Allergy Testing
Participants ≥1 year (n = 9440) were tested for serum specific-IgE to a panel of inhalant and food allergens.

- Prevalence of allergen sensitivities to 19 allergens in the participants ≥ 6 years (N=7268)

Diagnostic Algorithm for the Assessment of Human Allergic Disease

Clinical History & Physical Examination

- Perform Diagnostic test for Specific IgE (skin test/In-vitro test)

  - Are there symptoms with exposure?
    - No
      - Not allergic to that exposure
    - Yes
      - Uncertain

  - Positive Test?
    - Yes
      - Consider provocation challenge
        - IgE-mediated Reaction Confirmed
    - No
      - Not allergic to that exposure

- Non IgE-mediated Reaction
What Goals Do You Want to Accomplish by Performing Allergy Testing?

- Desiring “an idea” as to whether or not a baby or young child is atopic
  - ImmunoCAP based on age
    - Foods for infants with AD – most likely egg, milk, wheat, soy, peanut, tree nut, fish
    - Children < 3 years – with AD -> above foods plus dust mites, animal danders, mold screen
    - Children < 3 years w/o AD – mites, dander, mold
    - Children > 3 years – perennial and major seasonal aeroallergens (cedar, elm, oak, bermuda, timothy, ragweed, pigweed)
What Goals Do You Want to Accomplish by Performing Allergy Testing?

• More definitive identification of allergens in children > 2 years
  – Skin testing by ABAI certified allergist
  – If PCP ask yourself how comfortable you will be in explaining the results to patient or parent
    • Testing tools available from manufacturers – MultiTEST, GreerPiks, Duo-Tip, Comforten, etc
    • Recognition of false positives in dermatographic patients
    • Reasons for falsely negative testing (meds, age)
How Does Immunotherapy Work?
Does it Matter Where the Antigen is Administered?

Subcutaneous
- Administered in one or more injections quickly
  - “Depot” allows for tissue dendritic cells to access and uptake
  - Other inflammatory cells infiltrate (late phase response) – Optimal dosages defined for standardized allergens
  - Rare fatalities reported

Sublingual
- Must be held under tongue for 1 to 2 minutes to be effective
  - Langerhans cells uptake by pinocytosis smaller peptide fragments
  - Larger dosages required
  - Dilutional effect of multi-allergens may effect response
  - No benefit for hymenoptera
  - No fatal reactions reported (yet) – a few category IV’s
Bottom Line SCIT

Effective when ideal (high dose) maintenance concentrations achieved
– At maintenance, monthly dosing intervals make SCIT cost effective
– Effective dosage achieved per dose and not cumulative dosing
– Promotes development of T regulatory cells that produce IL-10 and TGF-beta responsible for shifting naïve T cells away from T2 pathway
– Rare risk of anaphylaxis
Effectiveness of SLIT

• Extensive reviews of most studies document
  – Best benefits (e.g., symptom scores, medication usage) start in second year / season of use despite pre-seasonal rush / rapid updosing
  – Initial rise in allergen-specific IgE seen in the first year followed by gradual decline in subsequent years of use
  – Studies are small with high (upwards of 25%) drop-out rates in both active and placebo arms
Bottom Line SLIT

• Effective alternative to SCIT
• Safer than SCIT – no fatalities reported
  – Bronchospasm reported frequently – caution with subsequent dosing
• As with SCIT, effective dosing only at high dosages and dosages taken daily to QOD
  – Unlike SCIT, dosing intervals cannot be increased
    – Unlike SCIT, multi-antigen in one vial may reduce effectiveness
  – Unlike SCIT, SLIT drops not FDA approved
Why Immunotherapy?

Only Therapy Available to Change Immune Response Longterm
Prevention of new sensitivities after HDM immunotherapy in children

Des Roches A. et at. JACI 1997;99:450-53
ospective study with 205 children, 6 and 14 years mean age 10.7), with AR to birch and/or grass to determine if specific immunotherapy can prevent the development of asthma.

Development of Asthma

Control

Immunotherapy

3 years 5 years

Birch Pollen Induced Asthma

102 mcg per year of birch extract for 3.5 years

Significant declines in symptom scores (p<0.001) compared to baseline year (2000)

Marogna M et al JACI 2005; 115: 1184-1188
Stepwise management, SLIT as an add-on option for some patients

REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV₁ is 70% predicted
- Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

SLIT: sublingual immunotherapy
Other Therapeutic Options
For Both Allergic and Non-Allergic Asthma Phenotypes
## Table 1. Biologic Agents in Asthma and Potential Biomarkers

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Biologic Agents Approved or in Trials</th>
<th>Biomarkers Predicting Response to Therapy</th>
<th>Biomarkers Modulated by Therapy</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Omalizumab</td>
<td>$F_{\text{ENO}}$ Blood eosinophils</td>
<td>$F_{\text{ENO}}$ Sputum eosinophils</td>
<td>Hanania et al., 2013 (63)</td>
</tr>
<tr>
<td>IL-4/IL-13</td>
<td>Pitrakinra (competitive antagonist)</td>
<td>$F_{\text{ENO}}$ Periostin</td>
<td></td>
<td>Wenzel et al., 2007 (81)</td>
</tr>
<tr>
<td></td>
<td>Dupilumab (receptor antibody)</td>
<td>$F_{\text{ENO}}$ Sputum eosinophils</td>
<td></td>
<td>Wenzel et al., 2013 (60)</td>
</tr>
<tr>
<td>IL-13</td>
<td>Lebrikizumab</td>
<td>$F_{\text{ENO}}$ Blood eosinophils</td>
<td></td>
<td>Corren et al., 2011 (61)</td>
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<tr>
<td></td>
<td>Tralokinomab</td>
<td>$F_{\text{ENO}}$ Periostin</td>
<td></td>
<td>Piper et al., 2013 (62)</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab</td>
<td>$F_{\text{ENO}}$ Eosinophils</td>
<td></td>
<td>Flood-Page et al., 2007 (25)</td>
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<tr>
<td></td>
<td>Reslizumab</td>
<td>Sputum IL-13 (periostin surrogate)</td>
<td></td>
<td>Haldar et al., 2009 (57)</td>
</tr>
<tr>
<td></td>
<td>Benralizumab</td>
<td>Sputum eosinophils</td>
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<td>Pavord et al., 2012 (58)</td>
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<tr>
<td></td>
<td></td>
<td>Blood eosinophils</td>
<td></td>
<td>Bel et al., 2014 (59)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nair et al., 2009 (66)</td>
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<td></td>
<td></td>
<td>Ortega et al., 2014 (74)</td>
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<td></td>
<td></td>
<td>Castro et al., 2011 (75)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Castro et al., 2014 (76)</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: $F_{\text{ENO}} = $ fractional exhaled nitric oxide.*
Bottom Line

- One size does not fit all – PHENOTYPES
- Asthma is dynamic and complex
- The immune response (allergic or not) changes the playing field such that we are in a constant guessing mode
  - Allergy to cat dander may not respond solely to home environmental controls due to dander elsewhere
  - Viral infections provoke a different immune response that may complicate the original picture
Bottom Line

• Identification of children at risk of asthma allows for earlier intervention
  – Children with atopic dermatitis
  – Children with asthmatic parent

• Accurate allergy testing for defining control measures and potential immunotherapy
  – SCIT currently approved by FDA
  – SLIT more convenient if done correctly