ALLERGIES ARE A LOW PROFILE HIGH IMPACT DISEASE.

MASOOD AHMAD, M.D.
What Is a Food Allergy?

• A food allergy is a medical condition in which exposure to a food triggers an IgE mediated immune response. The response results in reproducible symptoms with every exposure.

• Non IgE mediated immune reactions also occur, after ingestion, including cows milk protein induced enterocolitis, food protein induced enterocolitis, eosinophilic esophagitis.

• Non immunological food intolerance to foods, like lactose intolerance and non-celiac gluten sensitivity.
How common is IgE mediated food allergy?

• Food allergy is a term used by both patients and physicians to describe any adverse reaction to food as allergy.

• About, 34% of parents or individuals think they have food allergy

• Thus about 22% avoid food because it may “contain” allergen

• Direct and indirect societal costs relating to pediatric food allergy in the United States have been estimated at nearly 25 billion USD.
How Many People Have Food Allergies?

Researchers estimate that up to 15 million Americans have food allergies, including 5.9 million children under age 18.

That’s 1 in 13 children, or roughly two in every classroom.

About 30 percent of children with food allergies are allergic to more than one food.

Food Allergies Are on the Rise

The Centers for Disease Control & Prevention reports that the prevalence of food allergy in children increased by 50 percent between 1997 and 2011.

Between 1997 and 2008, the prevalence of peanut or tree nut allergy appears to have more than tripled in U.S. children.
Source: FARE
DIRECT AND INDIRECT COST OF FOOD ALLERGIES

Food allergy impacts, 4-8% (5.9 million) of children in the United States (US). Forty percent of food-allergic children have experienced at least one severe reaction.

Direct and indirect societal costs relating to pediatric food allergy in the United States have been estimated at nearly 25 billion USD.

The mean annual total household costs (direct + indirect costs) were higher in families with a food-allergic child (about $5,050 USD) or adolescent (about $6,100 USD), compared to those without staple food allergy.

JACI; Feb 2013, v131, Issue 2.
Food Allergy Reactions Are Serious and Can Be Life-Threatening.

Every three minutes, a food allergy reaction sends someone to the emergency room.

Each year in the U.S., 200,000 people require emergency medical care for allergic reactions to food.

Childhood hospitalizations for food allergy tripled between the late 1990s and the mid-2000s.

About 40 percent of children with food allergies have experienced a severe allergic reaction such as anaphylaxis.

Source: FARE
Food Allergy Impacts Quality of Life:

Food allergy limits a major life activity and may qualify an individual for protection under the Americans with Disabilities Act of 1990 (ADA) and Section 504 of the Rehabilitation Act of 1973.

About 1 in 3 children with food allergy reports being bullied as a result.

Source: FARE
Who Is at Greatest Risk?
Compared to children who don’t have food allergy, children with food allergy are two to four times as likely to have other allergic conditions, such as asthma or eczema.

Delaying introduction of allergenic foods does not provide protection against food allergy. In fact, feeding peanut foods early and often to babies with egg allergy or eczema dramatically reduces their risk of developing peanut allergy.

While most food allergies arise in childhood, at least 15 percent of food allergies are first diagnosed in adulthood.

Approximately 20-25 percent of epinephrine administrations in schools involve individuals whose allergy was unknown at the time of the reaction.

Source: FARE
HOW DO WE DIAGNOSE FOOD ALLERGY?

• So far the most common way to diagnose allergy is,
• History
• Skin prick testing
• RAST testing.
• This testing involves using all proteins in the allergen to determine the reaction, which gives information of allergic sensitization.
2) Blood tests:
Blood tests for food allergy involve analysis of the patient’s blood, or blood serum.

3) RAST (radioallergosorbent test):
The RAST uses radioactive or enzyme markers to detect levels of IgE antibodies in the blood.
PROBLEM WITH THE CURRENT TESTING.

• Currently we use the testing proteins as a mixture, which have many components, some of them are proteins that are very labile and very unstable and they get denatured with heat, and digestion, thus unless they are exposed in raw form, they will not cause an allergic reaction.

• Then there are other proteins that are stable to both heat and digestion and are more likely to cause an allergic reaction.

• SO,
Increasing risk of allergic symptom

Labile protein
- Low amount

Stable protein
- High amount

Risk

Profilin

PR-10

LTP

Storage Proteins

Ara h 8

Ara h 9

Ara h 1

Ara h 2

Ara h 3
Profilins are small proteins:

in the cytoplasm of nucleated cells and they are involved in the function of the intracellular fibrils of the cells.

Plant profilins are described as minor allergens in most pollen species and plant food allergens.

Show great homology and cross-reactivity even between distantly related species
Summary PR-10 proteins (Bet v 1 homologues)

Heat labile proteins, primarily localized to the pulp of the fruit. Cooked and processed foods are often tolerated.

Often associated with local symptoms such as oral allergy syndrome (OAS).

Commonly related to allergic reactions to fruit and vegetables.
Summary nsLTPs (non sp. Lipid transfer proteins) (PR-14 proteins)

Proteins stable to heat and digestion, primarily localized to the peel of the fruit/vegetable

Allergic Reactions also to cooked and processed foods

Often associated with systemic and more severe reactions in addition to, Oral Allergy Syndrome (OAS)

Commonly related to allergic reactions to fruit and vegetables.
Storage proteins:

Proteins stable to heat and digestion, primarily localized to the seed/nut/kernel

Reactions also to cooked and processed foods

Sensitization is regarded as an important risk marker for severe systemic reactions

Cross-reactivity is often seen to unrelated nuts and seeds and seems to increase with age
CCD:

CCD-reactive carbohydrate determinants are seldom associated with clinical symptoms but may cause demonstrable or even severe reactions in a small minority of patients. Since these determinants function as foreign epitopes in humans they can be highly immunogenic and will give rise to antibodies such as IgE.
Most common food allergies in the US

• Cows milk, egg, soy, wheat, peanuts, tree nuts finned fish and shellfish account for more than 90% of all IgE mediated food allergy reactions.

• In children, eggs, cows milk, and peanut allergies are the most common.

• In adults, peanuts, tree nuts and sea food allergies are most common.

• Some seeds like sesame and mustard seeds are slowly becoming another major allergen.
SO,

• If we know more about all the components in an allergen would it help us better diagnose food allergy?
• Lets test the hypothesis.
CRD OR Components resolved diagnostics.

• Instead of using crude allergen extracts consisting of a mixture of allergenic and non-allergenic components,
• CRD uses pure allergen proteins, produced by purification from natural allergen sources or recombinant expression of allergen-encoding complementary DNA.
• Component resolved data facilitate more precise diagnosis of allergic diseases and identify sensitizations attributable to cross-reactivity.
The component Bos d 8 (casein) is resistant to heat denaturation, and is associated with a higher anaphylactic risk in milk-allergic children.

Bos d 4 (α-lactalbumin) and Bos d 5 (β-lactoglobulin) sensitivities are generally mild and are likely to be outgrown. Because Bos d 4 and Bos d 5 are susceptible to heat denaturation, 75% of children with cow’s milk allergy can tolerate baked milk even though they are at high risk of reacting to fresh milk.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Protein</th>
<th>Allergen name</th>
<th>Concentration (g/l)</th>
<th>Total proteins (%)</th>
<th>Molecular weight (kDa)</th>
<th>Amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caseins</td>
<td></td>
<td></td>
<td>~30</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bos d 8</td>
<td></td>
<td>12-15</td>
<td>29</td>
<td>26.8</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-4</td>
<td>6</td>
<td>26.2</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9-11</td>
<td>27</td>
<td>24.0</td>
<td>209</td>
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<td></td>
<td></td>
<td></td>
<td>~1</td>
<td>1</td>
<td>26.8</td>
<td>180</td>
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<td></td>
<td></td>
<td></td>
<td>3-4</td>
<td>5</td>
<td>23.2</td>
<td>5.1-5.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>~5.0</td>
<td>20</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-2</td>
<td>2</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>~0.5</td>
<td>1</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Whey</td>
<td></td>
<td></td>
<td>~0.09</td>
<td>Traces</td>
<td>~0.1</td>
<td></td>
</tr>
</tbody>
</table>

Caseins= 80% of total protein
β lactoglobulin (β-LG) not present in human milk
Egg (Gallus domesticus)

Allergen component in egg white *Gal d 1, 2, 3, 4*

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Common name</th>
<th>Constituent (%</th>
<th>Mw (kDa)</th>
<th>Carbohydrate (%)</th>
<th>IgE binding activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Gal d 1</em></td>
<td>Ovomucoid</td>
<td>11</td>
<td>28</td>
<td>25</td>
<td>Stable</td>
</tr>
<tr>
<td><em>Gal d 2</em></td>
<td>Ovomucin</td>
<td>54</td>
<td>45</td>
<td>3</td>
<td>Unstable</td>
</tr>
<tr>
<td><em>Gal d 3</em></td>
<td>Ovotransferrin/ovomucin</td>
<td>12</td>
<td>766</td>
<td>2.6</td>
<td>Unstable</td>
</tr>
<tr>
<td><em>Gal d 4</em></td>
<td>Lysozyme</td>
<td>3.4</td>
<td>14.3</td>
<td>0</td>
<td>Unstable</td>
</tr>
</tbody>
</table>

* Of total egg white proteins.

<table>
<thead>
<tr>
<th>Components</th>
<th>White</th>
<th>Yolk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovalbumin (or <em>Gal d 2</em>) (~54%)</td>
<td>Serum albumin protein or α-livetin (Gal d 5)</td>
<td></td>
</tr>
<tr>
<td>Ovomucoid (or <em>Gal d 1</em>) (~11%)</td>
<td>β-Livetin (α2 glycoprotein)</td>
<td></td>
</tr>
<tr>
<td>Ovotransferrin (or <em>Gal d 3</em>) (~12%)</td>
<td>γ-Livetin (IgY)</td>
<td></td>
</tr>
<tr>
<td>Ovomucin (~3.5%)</td>
<td></td>
<td>Yolk glycoprotein 42 (Gal d 6)</td>
</tr>
<tr>
<td>Lysozyme (or <em>Gal d 4</em>) (~3.4%)</td>
<td></td>
<td>Vitellins</td>
</tr>
<tr>
<td>Ovoglobulin G2 (~4%)</td>
<td></td>
<td>Phosvitins</td>
</tr>
<tr>
<td>Ovoglobulin G3 (~4%)</td>
<td></td>
<td>Protease and protease inhibitors</td>
</tr>
<tr>
<td>Ovoinhibitor (~1.5%)</td>
<td></td>
<td>Other enzymes</td>
</tr>
<tr>
<td>Ovoglobulin protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovomacroglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avidin/cystatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Gal d 5* alpha-livetin (serum chicken albumin)
Food allergens

Peanut

- Ara h1,2,3 (storage proteins) → genuine peanut reaction
- Ara h 8 (PR-10, Bet v 1-homologue) → milder or local symptoms
- LTP (Ara h 9) → southern Europe, prevalent sensitizing allergen → systemic and more severe reactions
  - Further studies in other geographical regions
- Profilin or CCD sensitization → no or local oral symptoms → heated peanuts may be tolerated

Fig. 1: Peanut allergens identified to date. The size of

bold letters: Allergens are available for diagnosis using specific IgE.

World Allergy Organization Journal 2013, 6:17
Seafood allergy: Allergens

*Tropomyosin* is the major shellfish *thermostable* allergen and is responsible for cross-reactivity between members of the shellfish family, particularly within the crustacean family.

• Newly described allergens and subtle differences in the structures of tropomyosin among different species of shellfish could account for the discrepancy between in vitro cross-antigenicity and clinical cross-allergenicity in patients who may be sensitized to certain allergens, yet not manifest clinical reactivity on ingestion of these cross-reactive items.


**Crustaceae**

Allergen is mostly Tropomyosin, a protein responsible for muscle contractions

Main Allergen(s): Shrimp (*Pen a 1*), Crabs (*Cha f 1*), Crawfish (*Pan s 1*), Lobster (*Hom a 1*), Oyster (*Cra g 1, Cra g 2*), Squid (*Tod p 14*)

High probability of cross-reactivity between different seafoods
Food allergens

Hazelnut

- Cor a 1 (PR-10) → local reactions like OAS
- Cor a 8 (LTP), storage proteins (Cor a 9, Cor a 14) → severe symptoms
- Profilin (Cor a 2) or CCD alone → no or local oral symptoms
  → heated hazelnuts may be tolerated.
# Plant Food Allergens

<table>
<thead>
<tr>
<th>Pollen cross-reactive components*</th>
<th>LTP</th>
<th>Pollen non-cross-reactive components**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td></td>
<td>Ara h 1: Ara h 2, Ara h 3</td>
</tr>
<tr>
<td>Peanut</td>
<td>Ara h 8</td>
<td>Ara h 9, Ara h 6: Ara h 7</td>
</tr>
<tr>
<td>Peanut</td>
<td>Ara h 5</td>
<td></td>
</tr>
<tr>
<td>Hazelnut</td>
<td></td>
<td>Cor a 9</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 1</td>
<td>Cor a 11</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 2</td>
<td></td>
</tr>
<tr>
<td>Soybean</td>
<td></td>
<td>Gly m 5</td>
</tr>
<tr>
<td>Soybean</td>
<td>Gly m 4</td>
<td>Gly m 6</td>
</tr>
<tr>
<td>Soybean</td>
<td>Gly m 3</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td></td>
<td>Tri a 19 (ω-5 gliadin)</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 12</td>
<td>Tri a 21 - alfa gliadin</td>
</tr>
<tr>
<td>Wheat</td>
<td></td>
<td>Tri a 26 - HMW glutenin</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 14</td>
<td>Tri a 28 - AAI dimer 0.19</td>
</tr>
</tbody>
</table>

*PRP-10 Profilin*  
*Ana risk*

*Birch tree pollen, Timothy grass pollen for wheat  
** Storage seed proteins, albumins and globulins
Case one

• A 14 years old boy is seen in your office for possible peanut allergy. He has a history of facial hives and lip swelling after eating peanuts at 2 years of age and has had no further exposure to the peanuts. He does report having spring time allergies symptoms.

• His peanut SPT is positive and he has total peanut IgE of 13kuA/L.

• Can this pt. be safely challenged in the office?
Components to peanuts results

Peanut components test results are,
Ara h1 0.1KUA/L, Ara h2 0.1KUA/L, Ara h3, 0.1KUA/L, Ara h8, 12.1KUA/L, and Ara h9 less than 0.1KUA/L.

NOW can this pt. be safely tested by OFC in office?
Thus

• In this case based on information from the component testing we can Safely do an oral food challenge, OFC, which is the gold standard.
Bronchial Asthma

• NEW DISCOVERIES IN AN OLD DISEASE.
• ASTHMA PHENOTYPES
• ASTHMA ENDOTYPES OR GENOTYPES
• NEW TREATMENT OPTIONS.
How common is asthma in the USA

- According to the Centers for Disease Control and Prevention (CDC), 1 in 13 people have asthma.¹
- About 25 million Americans have asthma. This is 7.6 percent of adults and 8.4 percent of children. Asthma has been increasing since the early 1980s in all age, sex and racial groups.²
- Asthma is more common in adult women than adult men.³
- African-Americans in the U.S. die from asthma at a higher rate than people of other races or ethnicities.³
- More than 11.5 million people with asthma, including nearly 3 million children, report having had one or more asthma episodes or attacks in 2015.⁴
- Asthma is the leading chronic disease in children.⁵
- Asthma is more common in children than adults.¹
- Asthma is more common in boys than girls.⁴
- Currently, there are about 6 million children under the age of 18 with asthma.⁶
- In 2015, 1 in 12 children had asthma.⁷
- It is the top reason for missed school days. In 2013, about 13.8 million missed school days were reported due to asthma.

What Does Asthma Cost in the United States?

Researchers think the yearly cost of asthma in the United States is around $56 billion (2007)
The direct costs make up almost $50.1 billion.

Hospital stays are the largest part of that cost. Indirect costs make up $5.9 billion. This includes lost pay from sickness or death and lost work output from missed school or work days.

In 2009, researchers found that the direct cost of asthma is about $3,259 per person each year. For adults, asthma is the top reason those with asthma miss work and don’t perform as well at work. Sufferers miss about 14 million work days each year. This equals about $2 billion of asthma indirect costs.

In children 5 to 17, asthma is one of the top reasons they miss school. This causes more than 10.5 million missed school days per year.

In 2008, more than half of children and one-third of adults missed school because of their asthma. Children with asthma miss 2.48 more days of school each year than children without asthma. Adults who make $75,000 a year or less are more likely to have asthma compared to those with higher yearly salaries.

Severe asthma prevalence in us

• Severe asthma is characterized by a difficulty to achieve disease control despite high-intensity treatment. Current estimates of the prevalence of severe asthma are between 5 and 10% of all asthma patients.

• So if total number of asthmatics are about 25 million, then about 1.2 to 2.5 million asthmatics have very severe refractory asthma.
The Cost of Severe Asthma

Annual Cost by Asthma Severity

Cost/Patient/Year

Mild
Moderate
Severe

$2,200
$4,800
$12,800

Increased Healthcare Utilization
ER Visits
Hospitalizations

Cost of Asthma Hospitalization

![Graph showing the cost of asthma hospitalization from 2000 to 2010. The graph compares the mean cost per hospital stay for asthma between children (aged 2-17 years) and adults (aged 18 years and older). The cost for children shows a steady increase from $3,200 in 2000 to $3,600 in 2010. The cost for adults shows a similar trend, starting at $5,300 in 2000 and reaching $6,600 in 2010.]}
It is now recognized that the term “asthma” actually represents a heterogeneous collection of respiratory diseases with distinct phenotypes originating from the complex interplay between individual genetic and environmental factors.

A newly proposed approach to asthma classification is based on “endotypes” that represent specific cellular patterns along with clinical characteristics within each patient subgroup.
ALLERGIC ASTHMATIC INFLAMMATION:

Many inflammatory cells are recruited to asthmatic airways or are activated in situ. These include mast cells, macrophages, eosinophils, T lymphocytes, dendritic cells, basophils, neutrophils, and platelets.

Airway epithelial cells, smooth muscle cells, endothelial cells, and fibroblasts are all capable of synthesizing and releasing inflammatory mediators.

Indeed, these cells may become the major sources of inflammatory mediators in the airway, and this may explain how asthmatic inflammation persists even in the absence of activating stimuli.
PHENOTYPES OF ASTHMA

Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program

Moore et al AJRCCM 2010
Based on SARP, several types of asthma phenotypes were identified.
Genotypes or endotypes of Asthma

• Term endotype was proposed in 2008 to think about the molecular heterogeneity of asthma.

• Endotype is a distinct subtype of asthma defined by pathobiological mechanisms, it differs from Phenotype, that accounts observable characters of the disease.

• Benefit of defining asthma based on genotypes is that, logically, it will help finding treatments based on the causative molecular mechanisms.

• Major endotype of asthma is TH2 high asthma (IL 4, 5, 13).

• Other subtype is TH2 low asthma.
Sub-types of asthma

- What subtype of asthma someone will have depends upon the, dominant gene expression, in the lungs.
- TH2 (T-helper cells type2) dominant asthma;
  - Over expression of IL-4,5,9,13 and GMCSF
  - Over expression of master gene regulators, IL-25, 1L,33 and TSLP, with increased IL-13 and increased levels of periostin.

- NON-TH2 type asthma;
  - Increased expression of IL-1b gene expression
  - Increased expression of TNFa-NFb expression
  - Increased TH 17 cellular infiltrate elaborating IL-17
  - TLR gene expression alteration, with neutrophilic infiltration.
  - Paucigranulocytic asthma, mostly a smooth muscle disorder.
Allergens, viruses, air pollution

Lower airways epithelial cells

Alveolar macrophages/ lung dendritic cells

Th2 asthma

Failed: anti-IL-1β, -IL-4, -IL-17, -TNFα

High periostin
High eosinophils

Eosinophilic inflammation

Anti-IL-5, anti-IL-13, ICS

Non-Th2 asthma

Failed: anti-IL-1β, -CXCL-8, -TNFα,

High neutrophils

Neutrophilic inflammation

Anti-CXCL2 and others?
Nonspecific immunosuppression:
- **Corticosteroids**

Corticosteroids are effective across all three diseases, but toxicity precludes widespread and long-term use.

**IL-5-specific blockers:**
- **Mepolizumab** (GSK)
- **Reslizumab** (Teva)
- **Benralizumab** (AZ)

Mepolizumab is effective in asthma (in subgroup with high eosinophils); effective in CSwNP; not effective in AD.

**IL-4-specific blockers:**
- **Altrakincept** (Immunex)
- **Pascolizumab** (GSK)

**Dual IL-4 and IL-13-specific blockers:**
- **Pitrakinra** (Aerovance)
- **AMG317** (Amgen)
- **Dupilumab** (Regeneron/Sanofi)

Dupilumab is effective across all three diseases.

**IL-13-specific blockers:**
- **Tralokinumab** (AZ)
- **Anrufinumab** (Pfizer)
- **Lebrikizumab** (Roche)

Lebrikizumab is effective in asthma (T_{H2} high subgroup).

**IgE-specific mAbs:**
- **Omalizumab** (Novartis/Genentech)

Omalizumab is effective in allergic asthma and asthmatics with co-morbid CSwNP; not effective in AD.

**MHC class II TCR**

**Eosinophil**

**B cell**

**IgE**

**FceRI**

**Mast cell**

**Histamine**

**Antihistamines**

**Nature Reviews | Drug Discovery**
Conclusion

• One of the major challenges of respiratory medicine is the management of patients with severe asthma. Identifying a specific endotype may have profound implications on advanced targeted therapy selection and intern clinical outcomes.

• It should be acknowledged that the mere presence of a particular gene, protein or a cell do not necessarily make them a therapeutic target or disease biomarker.

• Persistence of a particular cell type or cytokine and their temporal association with exacerbation and resolution provide strong evidence to support a causative role.

• A consensus as to how to best identify asthma endotypes and what therapy to use for a given endotype is now required.
THE END

THANKS.