Overview of Food Allergies

Michelle E. Conroy, MD
Instructor, Dept. of Medicine
Massachusetts General Hospital
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I have no professional conflicts of interest to disclose.
Food allergy is big…

Figure 3 Trend of three different diets (low carbohydrate diet, fat-free diet, and gluten-free diet), in the USA during the period 2004 to 2011. For the American general population, … and folks in the United States are impressionable!

*BMC Medicine* 2012, 10:13
Four out of every 100 children have a food allergy.

Figure 1. Percentage of children under age 18 years who had a reported food or digestive allergy in the past 12 months, by age, sex, and race and ethnicity group: United States, 2007

- Total: 3.9%
- Less than 5 years: 4.7%
- 5–17 years: 3.7%
- Male: 3.8%
- Female: 4.1%
- Non-Hispanic white: 4.1%
- Non-Hispanic black: 4.0%
- Hispanic: 3.1%

*Significantly different from children aged 5–17 years.
*Significantly different from non-Hispanic white and non-Hispanic black children.

SOURCE: CDC/NCHS, National Health Interview Survey.

Figure 4. Average number of hospital discharges per year among children under age 18 years with any diagnosis related to food allergy: United States, 1998–2006

- 1998–2000: 2,615
- 2004–2006: 9,537

*Statistically significant trend.

SOURCE: CDC/NCHS, National Health Interview Survey.
Incidence

**TABLE I. Estimated food allergy rates in North America**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Infant/child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Egg</td>
<td>1.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Peanut</td>
<td>1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>0.1%</td>
<td>2%</td>
</tr>
<tr>
<td>Wheat, soy</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sesame</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>5%</td>
<td>3% to 4%</td>
</tr>
</tbody>
</table>

Allergy 2005: 60 (Suppl. 79): 19–24
What does “Food allergy” mean?

- A **food allergy** is defined as an adverse health effect arising from a specific **immune response** that occurs **reproducibly** on exposure to a given food.

- A **food** is defined as any substance—whether processed, semiprocessed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements.

NIAID Guidelines, 2010
First things first…

**Toxic**
- Food poisoning

**Non-Toxic**

**Non-Immune Mediated**
- Lactase deficiency
- Reflux
- Sensitivities

**Immune-Mediated**

**IgE-Mediated**
- Eczema
- Urticaria
- Anaphylaxis

**Non-IgE-Mediated**
- Enterocolitis
- Proctocolitis
The importance of the history

- Allergy can almost always be diagnosed by a good history
  - Start with scan for “atopic background”
- Detailed account of “reactions”
  - What was eaten? (sounds simple…)
  - Amount/route of food ingestion/exposure
  - Timing after ingestion
  - Symptoms
  - Relieving factors
  - Recovery
  - Prior similar episodes
Non-immunologic mechanisms (mostly)-Sensitivities

Subjects with IBS-like symptoms according to the Rome II criteria and fulfilling the criteria for "gluten-sensitivity"

920 Patients eligible patient

Four weeks period of elimination diet and successive DBPC wheat challenge:

276 Suffered from wheat sensitivity or multiple food hypersensitivity, including wheat sensitivity

644 Not suffered from wheat sensitivity

Excluded

Four weeks period of elimination diet and successive DBPC cow’s milk protein challenge:

Group 1: 70 patients suffering from wheat sensitivity alone

Group 2: 206 patients suffering from multiple food hypersensitivity, including wheat sensitivity

Control groups: 50 irritable bowel syndrome patients, and 100 celiac disease patients

Overall symptoms

Bloating

Abdominal pain

Stools consistency

VAS (0-100 mm)

Weeks

Am J Gastroenterol 2012; 107:1898–1906
Mixed immunologic mechanisms - Eosinophilic esophagitis

Table 1: Symptoms reported by pediatric and adult patients with eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Chest pain or heartburn</td>
<td>Food impaction</td>
</tr>
<tr>
<td>Coughing</td>
<td>Retrosternal pain</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Food refusal (spits out food; throws food</td>
</tr>
<tr>
<td></td>
<td>away; self-limits food; fear of choking;</td>
</tr>
<tr>
<td></td>
<td>and picky eater)</td>
</tr>
<tr>
<td>Dysphagia (food sticking – especially meat,</td>
<td>Throat pain (itchy, scratchy, spicy, and</td>
</tr>
<tr>
<td>bread, pasta, and pills; ‘toy car’ in throat;</td>
<td>hot spit)</td>
</tr>
<tr>
<td>‘furball’ in throat; sticky saliva;</td>
<td></td>
</tr>
<tr>
<td>throat makes a clunking sound; food wads up;</td>
<td></td>
</tr>
<tr>
<td>holds food in mouth for 15 min before</td>
<td></td>
</tr>
<tr>
<td>swallowing; chews food finely; needs much</td>
<td></td>
</tr>
<tr>
<td>water to wash food down; and last one to</td>
<td></td>
</tr>
<tr>
<td>leave the table)</td>
<td></td>
</tr>
<tr>
<td>Food refusal (spits out food; throws food</td>
<td></td>
</tr>
<tr>
<td>away; self-limits food; fear of choking; and</td>
<td></td>
</tr>
<tr>
<td>picky eater)</td>
<td></td>
</tr>
<tr>
<td>Choking/gagging</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Regurgitation</td>
<td></td>
</tr>
<tr>
<td>Sleeping difficulty</td>
<td></td>
</tr>
<tr>
<td>Throat pain (itchy, scratchy, spicy, and hot</td>
<td></td>
</tr>
<tr>
<td>spit)</td>
<td></td>
</tr>
</tbody>
</table>

Allergy 2012; 67: 477–490
IgE mediated reactions - Anaphylaxis

Lancet 2008;371,9623:1538-1546
WHAT WAS EATEN?

Major allergenic foods (>90% of allergies)

- Milk
- Egg
- Soy
- Wheat
- Peanut
- Tree nuts
- Shellfish
- (sesame)
What happened??

Toxic
- Food poisoning

Non-Toxic

Non-Immune Mediated
- Lactase deficiency
- Reflux

Immune-Mediated

IgE-Mediated
- Anaphylaxis
- Urticaria
- Eczema (?)

Non-IgE-Mediated
- Enterocolitis
- Proctocolitis
- Eosinophilic gastroenteritis
What IgE does...

Mast cells immediately release:

- Histamine
- Heparin
- Proteases

ANAPHYLAXIS
What IgE does...

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

2. Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):

   - Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)
   - Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

So we go looking for it....
Skin prick testing

- **95% negative predictive value**
- **50% false positive rate**
- **Context/selection**
- **Immediate, visual results**
- **Blocked by common medications**
Skin prick testing

Measure presence of allergen specific IgE
Serum Specific Food Allergy Testing

Yields a quantitative value...
Serum Specific Food Allergy Testing

- Undetectable level has a LOW negative predictive value
  - If suspicious, confirm with skin testing
  - About 50% false positive rate
  - Interpretation can be difficult (i.e. need to wait at least 3-4 weeks post reaction to avoid false negative results)

The big issue: Age and allergen specific values
Food specific IgE levels

TABLE IV. Performance characteristics of 90% specificity diagnostic decision points generated in the retrospective study\textsuperscript{13} in diagnosing food allergy in 100 consecutive children and adolescents referred for evaluation of food hypersensitivity.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Decision point (kU\textsubscript{A}/L)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Efficiency</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>61</td>
<td>95</td>
<td>68</td>
<td>98</td>
<td>38</td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>57</td>
<td>94</td>
<td>69</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>57</td>
<td>100</td>
<td>84</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td>Fish</td>
<td>3</td>
<td>63</td>
<td>91</td>
<td>87</td>
<td>56</td>
<td>93</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>44</td>
<td>94</td>
<td>81</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>61</td>
<td>92</td>
<td>84</td>
<td>74</td>
<td>87</td>
</tr>
</tbody>
</table>

\textit{PPV}, Positive predictive value; \textit{NPV}, negative predictive value.
Food specific IgE levels

FIG 1. Probability of reacting to a food at a given IgE value.
Age specific values

<table>
<thead>
<tr>
<th>Food</th>
<th>Mean age 5 y, 50% react</th>
<th>Mean age 5 y, ~95% react</th>
<th>Age &lt;2 y, ~95% react</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg (kUa/L)</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Milk (kUa/L)</td>
<td>2</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Peanut (kUa/L)</td>
<td>2/5</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

J Allergy Clin Immunol 2001; 107: 891-6
Food specific IgE testing

- Recall: 50% false positive rate!!
  - *Critical* to test only for foods of high suspicion based on history
  - *Unless* you’re comfortable telling a patient to eat the food for which there is a “positive test”
# Helpful overview of foods

## Table 1. Natural History of Food Allergy and Cross-Reactivity between Common Food Allergies.

<table>
<thead>
<tr>
<th>Food</th>
<th>Usual Age at Onset</th>
<th>Cross-Reactivity</th>
<th>Usual Age at Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hen’s egg white</td>
<td>6–24 mo</td>
<td>Other avian eggs</td>
<td>7 yr (75% of cases resolve)*</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>6–12 mo</td>
<td>Goat’s milk, sheep’s milk, buffalo milk</td>
<td>5 yr (76% of cases resolve)*</td>
</tr>
<tr>
<td>Peanuts</td>
<td>6–24 mo</td>
<td>Other legumes, peas, lentils; coreactivity with tree nuts</td>
<td>Persistent (20% of cases resolve by 5 yr)</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>1–7 yr; in adults, onset occurs after cross-reactivity to birch pollen</td>
<td>Other tree nuts; coreactivity with peanuts</td>
<td>Persistent (9% of cases resolve after 5 yr)</td>
</tr>
<tr>
<td>Sesame seeds</td>
<td>6–36 mo</td>
<td>None known; coreactivity with peanuts</td>
<td>Persistent (20% of cases resolve by 7 yr)</td>
</tr>
<tr>
<td>Fish</td>
<td>Late childhood and adulthood</td>
<td>Other fish (low cross-reactivity with tuna and swordfish)</td>
<td>Persistent†</td>
</tr>
<tr>
<td>Shellfish</td>
<td>Adulthood (in 60% of patients with this allergy)</td>
<td>Other shellfish</td>
<td>Persistent</td>
</tr>
<tr>
<td>Wheat‡</td>
<td>6–24 mo</td>
<td>Other grains containing gluten</td>
<td>5 yr (80% of cases resolve)</td>
</tr>
<tr>
<td>Soybeans‡</td>
<td>6–24 mo</td>
<td>Other legumes</td>
<td>2 yr (67% of cases resolve)</td>
</tr>
<tr>
<td>Kiwi</td>
<td>Any age</td>
<td>Banana, avocado, latex</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apples, carrots, and peaches§</td>
<td>Late childhood and adulthood</td>
<td>Birch pollen, other fruits, nuts</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

More on cross reactivity

### Index Allergen
- **Legume**
  - peanut
- **Grain**
  - wheat
- **Tree Nut**
  - walnut
- **Fish**
  - salmon
- **Shellfish**
  - shrimp

### Risk of react to at least one
- **Other legumes**
  - beans
  - lentils
  - peas
- **Other grains**
  - barley
  - rye
- **Other tree nuts**
  - brazil
  - cashew
  - hazelnut
- **Other fish**
  - sole
  - swordfish
- **Other shellfish**
  - crab
  - lobster

### Risk of cross-reactivity
- **5%**
- **25%**
- **15-40%**
- **50%**
- **75%**
AVOIDANCE/RESTRICTION

- At the moment, the most accepted therapy
- Difficult!
- Give resources
- Anaphylaxis actions plan
- Please… (begging here)… prescribe Epi!!!
Risk for fatal anaphylaxis related to food

On review of 32 fatalities:

- Both sexes equally
- Adolescents and young adults
- Peanut and tree nut allergy caused 94% of these fatalities
- Asthma
- Delayed administration of epinephrine
  - 10% of these people had epinephrine with them
Future directions

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Immune rationale</th>
<th>Benefits</th>
<th>Observations to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard subcutaneous immunotherapy (native allergens)</td>
<td>Antigen presentation in nonmucosal site results in ( T_{H1} ) skewing</td>
<td>Proved for venom and respiratory allergy, possible benefit (pollen) for oral allergy syndrome</td>
<td>Primarily avoided for risk of anaphylaxis (eg, peanut)</td>
</tr>
<tr>
<td>Sublingual/OIT</td>
<td>Antigen presentation to mucosal site provides desensitization and might induce tolerance</td>
<td>Natural foods, reduced risk of systemic anaphylaxis compared with injections</td>
<td>Mounting evidence for desensitization and relative safety; unclear effect on tolerance</td>
</tr>
<tr>
<td>Modified protein vaccine</td>
<td>Reduced IgE activation by mutation of IgE-binding epitopes</td>
<td>A safer form of immunotherapy compared with injection of native protein</td>
<td>Murine models show promise, human studies are planned</td>
</tr>
<tr>
<td>Peptide vaccine (overlapping peptides)</td>
<td>Peptides are less likely to cross-link IgE, avoiding mast cell activation</td>
<td>No requirement for IgE epitope mapping/mutation</td>
<td>Limited</td>
</tr>
<tr>
<td>Conjugation of immune stimulatory sequences to allergens and additional adjuvant methods</td>
<td>Enhance ( T_{H2} ) response by activating innate immune receptors (using specific sequences or whole bacteria)</td>
<td>Increased efficacy, possibly improved safety</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Plasmid DNA-encoded vaccines</td>
<td>Endogenous production of allergen might result in tolerance</td>
<td>Possible 1-dose treatment</td>
<td>Murine models reveal strain-specific response</td>
</tr>
<tr>
<td>Anti-IgE antibodies</td>
<td>Targeted toward Fc portion of antibody, can inactivate IgE with reduced risk for activating mast cells</td>
<td>Not food specific Some response in eosinophilic gastroenteropathy (pilot study)</td>
<td>Preliminary study showed improved threshold overall but did not show uniform protection</td>
</tr>
<tr>
<td>Chinese herbal medicine</td>
<td>Mechanism unknown</td>
<td>Not food specific</td>
<td>Murine models show efficacy Human safety studies are underway</td>
</tr>
<tr>
<td>Cytokine/anti-cytokine (eg, anti-IL-5)</td>
<td>To interrupt inflammatory signals</td>
<td>Might allow directed interruption of inflammatory processes without need for food restriction</td>
<td>Preliminary study shows benefit for eosinophilic esophagitis.</td>
</tr>
</tbody>
</table>
Thank you for the invitation

Lots more to discuss…