The Changing Approach to Food Allergy

September 15, 2017
Dr. Stacy K. Silvers, MD
Objectives

• Identify the signs and symptoms of a classic IgE-mediated food reaction
• Have a basic understanding of testing used to diagnose food allergy
  o Food-specific serum IgE testing
  o Percutaneous / skin prick testing
• Have an understanding of the new NIAID guidelines for early food introduction in infants
• Overview of developing food allergy treatments
Adverse Reactions to Food vs. Food Allergy

Adverse Reactions to Food
- “Food intolerance” or “sensitivity”
- Non-immunologic
- Typically not consistent or are very dose-dependent

Intolerance (nonallergic hypersensitivity)
- Lactose intolerance

Pharmacologic
- Caffeine (jitteriness or migraine)

Toxins
- Food poisoning

Masqueraders of food allergy
- Gustatory rhinitis, scombroid fish poisoning
Types of Food Allergy

**IgE-mediated**
- Acute urticaria
- Acute angioedema
- Pollen-food syndrome
- Generalized anaphylaxis
- Food-dependent exercise-induced anaphylaxis
- Delayed food-induced anaphylaxis to meats

**Mixed IgE and non-IgE mediated**
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis
- Atopic Dermatitis

**Non-IgE mediated**
- Celiac disease
- Dermatitis herpetiformis
- Food-induced pulmonary hemosiderosis (Heiner syndrome)
- Food protein-induced enterocolitis syndrome (FPIES)
- Food protein-induced proctocolitis
- Allergic contact dermatitis
IgE-Mediated Food Allergy

Allergens cross-link IgE that is bound to mast cells and basophils. This leads to the release of pre-formed mediators, such as histamine.

Symptoms consist of:
- Urticaria
- Angioedema
- Bronchospasm
- Nausea/vomiting/diarrhea
- Hypotension

Symptoms typically develop quickly.
First exposure to allergen

Second exposure to allergen
Prevalence

Food Allergy does seem to be increasing
- More ED visits, more admissions
- Greater in Western Countries

In the US:
- 2.5-8% of infants and children have food allergies (5.9 million individuals)
  - About 1 in 13 children
- 2-3.5% of adults have food allergies (15 million individuals)

Very different from public perception
- Up to 35% of Americans report food allergy!

## Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Observation (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Increased risks for siblings, HLA, specific genes</td>
</tr>
<tr>
<td>Sex</td>
<td>Increased risk for boys, possibly women</td>
</tr>
<tr>
<td>Associated atopic disease</td>
<td>Atopic dermatitis, comorbid food allergies</td>
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<tr>
<td></td>
<td>Asthma for increased severity of reactions</td>
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<tr>
<td>Exposure route</td>
<td>Theory that lack of ingestion exposure during period of environmental exposure may increase risk</td>
</tr>
<tr>
<td>Maternal ingestion</td>
<td>Controversy about maternal ingestion of allergen during pregnancy/lactation being risk factor</td>
</tr>
<tr>
<td>Infant ingestion of allergen</td>
<td>Recent studies supporting earlier ingestion of allergen as protective</td>
</tr>
<tr>
<td></td>
<td>Frequency, dose may be a factor</td>
</tr>
<tr>
<td>Dietary constituents</td>
<td>Fatty acid profile may be risk/protective</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>May be protective</td>
</tr>
<tr>
<td>Obesity</td>
<td>May be risk factor (inflammatory state)</td>
</tr>
<tr>
<td>Hygiene hypothesis</td>
<td>Increased risk for cesarian section, antibiotics</td>
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<tr>
<td></td>
<td>Reduced risk more siblings, child care, pets, rural/farm</td>
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<tr>
<td>Race/ethnicity</td>
<td>Nonwhite may be risk</td>
</tr>
<tr>
<td>Geography/diet</td>
<td>Pollen exposure may drive differences</td>
</tr>
<tr>
<td></td>
<td>Dietary differences (eg, roasted peanut compared with boiled)</td>
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</tbody>
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*Sicherer, J Allergy Clin Immunol. 2011;127:594-602*
# Common Foods

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
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<tbody>
<tr>
<td>Milk</td>
<td>2.2-3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Egg</td>
<td>0.8 – 1.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Peanut</td>
<td>0.6 – 2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tree Nuts</td>
<td>0.4 – 1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fish</td>
<td>0.2 – 0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>0.5 – 1.4%</td>
<td>2%</td>
</tr>
<tr>
<td>Wheat</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Soy</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Rate of allergy resolution varies according to the food, the patient’s age, and other factors. Most individuals will develop tolerance to milk, egg, wheat, and soy.

- **Milk**
  - 19% at age 4 years, 64% at age 12 years, and 79% by age 16 years

- **Egg**
  - Similar to milk

- **Wheat**
  - 29% by age 4 years and 65% by age 12 years

- **Soy**
  - 25% by age 4 years and 69% by age 10 years

Peanut, Tree nut, Fish and Shellfish are more likely to persist.
- Up to 20% become tolerant to peanut
- 10% for tree nuts
MILK ALLERGY RESOLUTION PROBABILITY
OVER TIME

To be used for young (less than 15 months old) patients with their presenting (greater than 3 months of age) values; for PST use Milk wheal size minus Saline control wheal size.

Milk IgE: 0.5 KUA/L
Milk PST: 8 MM
Atopic Dermatitis Status: 0= None or Mild  1= Moderate or Severe

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EGG ALLERGY RESOLUTION PROBABILITY OVER TIME

Egg IgE: 12 KUA/L
Presenting reaction: • Skin Only • Flare of Atopic Dermatitis • Flare of Systemic Reaction

% Resolved

Age (Years)
Diagnosis

**HISTORY**
- Are symptoms consistent with an IgE-mediated response?
- What food is implicated and is it a common food allergen?
- Timing of symptoms in relation to food ingestion.
- How quickly did symptoms resolve?
- What treatment was given, if any?
- Has the same food been ingested since then? How frequently was it consumed before the incident?

**Food Allergy Testing**
- A POSITIVE TEST IS NOT ENOUGH TO CONFIRM FOOD ALLERGY
- Testing should be focused on foods suspected of provoking the reaction
- Test results alone should not be considered diagnostic of food allergy
- In general, avoid sending panels
- In most cases, allergy testing does not predict the severity of reactions and do not help determine how much food a person can eat without having a reaction
Diagnosis

Percutaneous/skin prick testing

• Safe, can be performed in-office (essentially any age), quick and effective
• Results are interpreted by comparing the skin response with negative (e.g., saline) and/or positive (e.g., histamine) controls.
• A positive SPT response will produce a wheal-and-flare reaction within 10 to 20 minutes
• An SPT response is considered positive if the wheal has a mean diameter 3 mm or larger than the negative control

Estimated sensitivity and specificity of 85% and 74%, positive likelihood ratio of 3.3

Relatively high NPV
• Useful in ruling out IgE-mediated food allergy
Allergic Reaction
Diagnosis

Food-specific Serum IgE Testing

- Measure of the serum IgE that is directed against specific foods
- Also helpful and frequently used
- sIgE testing is particularly useful when
  - SPTs cannot be performed due to concurrent antihistamine use
  - Moderate-to-severe skin disease (atopic dermatitis)
  - Dermatographism
- Predictive thresholds for peanut, egg, milk, fish, soy, and wheat have been established.
- Generally, higher sIgE levels are more likely to be associated with clinical reactivity, but the predictive value of sIgE levels varies across patient populations and might be related to the patient’s age, time since last ingestion of the suspected food allergen, and other underlying disorders.
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>slgE (ImmunoCap)</th>
<th>SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s Milk</td>
<td>≥15 (≥5 if &lt;1 yo)</td>
<td>≥8</td>
</tr>
<tr>
<td>Egg</td>
<td>≥7 (≥2 if &lt;2 yo)</td>
<td>≥7</td>
</tr>
<tr>
<td>Peanut</td>
<td>≥14</td>
<td>≥8</td>
</tr>
<tr>
<td>Fish</td>
<td>≥20</td>
<td></td>
</tr>
<tr>
<td>Walnut</td>
<td>≥18.5</td>
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</table>

### ~95% Positive OFC

<table>
<thead>
<tr>
<th>Test</th>
<th>slgE (ImmunoCap)</th>
<th>SPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy</td>
<td>≥30</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>≥26</td>
<td></td>
</tr>
</tbody>
</table>

### ~73-74% Positive OFC
Component Resolved Diagnostic Testing

• Typically not necessary for routine evaluation.
• Available for peanut, tree nuts, milk and egg
• Helps to further identify patients that are at risk for a systemic reaction. Particularly peanut.
• Gives an idea of severity of symptoms in specific cases.
• For milk (casein) and egg (ovomucoid), may help identify those patients that would be a good candidate for a baked challenge.
Component Resolved Diagnostic Testing

• Identify serum IgE directed against specific proteins, rather than whole allergen

• Peanut:
  • Ara H 1, 2, 3 are most common peanut allergen associated with clinical reactivity.
  • These are stable proteins, resistant to heat and peptic digestion.
  • Ara H 8 is a PR-10 protein, similar to Bet v 1 (a birch tree pollen protein).
    • This is heat labile and is associated with pollen-food allergy syndrome rather than anaphylaxis.
  • May be helpful in someone that has been avoiding peanut only secondary to a positive allergy test or in those with very mild symptoms.
Food Challenge

Various types
- open (unmasked)
- single-blind with or without placebo
- double-blind, placebo-controlled (Gold Standard)

Should be performed by an provider experience in the interpretation of challenges and the treatment of anaphylaxis

In general, graded dosing is recommended

Used to establish a diagnosis or determine if a patient has developed tolerance to a food that had previously caused allergic reactions.
Possible Prevention of Food Allergy

Atopic Dermatitis
• Moderate to severe AD increases risk of food allergy

Route of exposure
• Cutaneous exposure of food allergen rather than oral exposure is the cause of allergic sensitization
  • Household peanut consumption (Fox et al) and peanut oil (Avon Longitudinal Study)

Timing of exposure
• Early introduction vs delayed introduction
• LEAP trial
Dual-allergen-exposure hypothesis
Dual-allergen-exposure hypothesis

• “Explains the association between severe eczema in infancy and the of food allergies”

• “Explains the different rates of food allergies in different parts of the world”

• “Prompt intensive treatment of eczema in early infancy will decrease inflammation in the skin, reduce skin permeability, and prevent allergic sensitization to foods”

• “Early introduction of allergenic foods to the infant's diet (in the first 6 months of life) can reduce the development of food allergies through oral tolerance induction”
Early Food Introduction

2000 American Academy of Pediatric recommendations
• Solid foods should not be introduced into the diet of a high-risk infant until 6 months
  o Dairy products at 1 year
  o Egg at 2 years
  o Peanuts, tree nuts, and fish at 3 years

2008 AAP recommendations
• “little evidence that delaying the timing of the introduction of complementary foods beyond 4 to 6 months of age prevents atopic disease... Potentially allergenic foods may be introduced at this time as well.”
Early Food Introduction

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team

Followed 640 infants 4-11 months of age with

- Severe Eczema
- Egg Allergy
- Or Both
Early Food Introduction

Stratified into two cohorts based on results of a skin-prick test for peanut allergy

• SPT that is negative vs positive

Participants assigned to avoid or ingest dietary peanut (at least 6g of protein/wk) until 5yo

Primary outcome: % of participants with peanut allergy as determined by oral food challenge

Both Cohorts (N=628)

P<0.001

80% decrease
LEAP-On

All participants were told to avoid peanut for 1 year
• Primary outcome: % of participants with peanut allergy at 72 months of age

88.5% (556/628) eligible participants from LEAP were enrolled in LEAP-On

There was a 74% relative reduction in prevalence of peanut allergy

A 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy.
2017 NIAID Guidelines

Severe eczema
or
Egg allergy
or
Both

**Peanut sIgE**

- <0.35
  - Risk of reaction low. Over 90% will have (-) SPT to peanut.
  - Options:
    - a) Introduce peanut at home
    - b) Supervised feeding in the office (based on provider/parental preference)
  - Refer to specialist for consultation/SPT protocol

- ≥0.35

**Peanut Skin Prick Test**

- 0-2 mm
  - Risk of reaction low (95% will not have peanut allergy).
  - Options:
    - a) Introduce peanut at home
    - b) Supervised feeding in the office (based on provider/parental preference)

- 3-7 mm
  - Risk of reaction varies from moderate to high.
  - Options:
    - a) Supervised feeding in office
    - b) Graded OFC in a specialized facility

- ≥8 mm
  - Infant probably allergic to peanut.
  - Continue evaluation and management by a specialist

MyPeanut™ & MyPeanut with Tree Nuts™
“A Revolution in Prevention”

- MyPeanut™ for 4 months of age and up
- MyPeanut with Tree Nuts™ for 6 months and up
- Designed by allergists who understand pediatric immunity
- Based on studies endorsed by the American Academy of Asthma, Allergy, and Immunology
- Consistent with guidelines put forth by the National Institutes of Health and National Allergy Societies
- Made with Organic Apples and Nuts for your little one
Food Allergy Management

Allergen Avoidance
• In a 2 year period, up to 50% of peanut-allergic patients will have an accidental ingestion
• 75% in a 10-year period
• Maybe more common in those <5 years.

Label reading

Monitoring for cross-contamination

Dietary supplementation may be necessary

Epinephrine autoinjectors and a written Food Allergy Action Plan should be readily available at all times

Precautions at daycare/school
Food Allergy Management

• Food Allergy Research and Education: www.foodallergy.org
• Consortium on Food Allergy Research: www.cofargroup.org
• Asthma and Allergy Foundation of America: www.aafa.org
• American Academy of Allergy, Asthma and Immunology: www.aaaai.org
• American College of Allergy, Asthma and Immunology: www.acaai.org
• Kids with Food Allergies: www.kidswithfoodallergies.org
• AllergyReady.com
• Centers for Disease Control and Prevention: www.cdc.gov/healthyyouth/foodallergies
• National Institute of Allergy and Infectious Diseases: www.niaid.nih.gov/topics/foodallergy
Food Allergy Treatment

EPIT (peanut patch)
- DBV Technology

Sublingual immunotherapy

Oral Immunotherapy
- With or without omalizumab
EPIT-Viaskin

• DBRPC study comparing placebo (n=24), Viaskin Peanut 100 μg (n=24), and Viaskin Peanut 250 μg (n=25)

• Primary outcome after 52 weeks - passing a 5044-mg protein oral food challenge (~4 teaspoons peanut butter) –OR- achieving a 10-fold or greater increase in successfully consumed dose from baseline

• Treatment success was achieved in 3 (12%) placebo, 11 (46%) VP100, and 12 (48%) VP250 (P = .005 and P = .003, respectively, compared with placebo; VP100 vs VP250, P = .48).
  o No patients tolerated the 5044 mg protein oral food challenge dose in the active arms.

• Median change in successfully consumed doses were 0, 43, and 130 mg of protein in the placebo, VP100, and VP250 groups, respectively (placebo vs VP100, P = .014; placebo vs VP250, P = .003)
EPIT VIPES
Unpublished data
• An additional year (24 months of therapy) increased success to 70%
• Success defined as 10-fold increase in tolerated amount of peanut protein –OR- were able to consume 1000mg of peanut protein.

Phase III trials underway, primarily focusing on young children.
• PEPITES
• REALISE

Trials for milk and egg are underway as well
Sublingual Immunotherapy

• DBRPC study comparing sublingual and oral immunotherapy.

• Children (7-13 years old) with peanut allergy were randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT. Doses were escalated to 3.7mg/day (SLIT) or 2000mg/day (OIT), and subjects were re-challenged after 6 and 12 months of maintenance. After unblinding, therapy was modified per protocol to offer an additional 6 months of therapy.

• N=21, but 5 discontinued therapy during the blinded phase.

• Remaining 16 all had a >10-fold increase in challenge threshold after 12 months.

• Increase was greater in the active OIT group (141-fold versus 22-fold, P=0.01).

• Skin tests and peanut-specific IgE and IgG4 changes were found, with overall greater effects with OIT.

• Adverse reactions were generally mild but more common with OIT (P<0.001), including moderate reactions and doses requiring medication.

In the 9 SLIT subjects, the median cumulative dose increased
• After 6 months, baseline cumulative dose increased from 21mg to 496mg
• There was no further increase in cumulative dose after 12 months of therapy

In the 7 OIT subjects completing maintenance, threshold doses increased even further
• After 6 months, baseline cumulative dose increased from 21mg to 7246mg
• There was no further increase in cumulative dose after 12 months of therapy

Active SLIT showed a 14-fold increase
Active OIT showed a 141-fold increase
The proportion of doses with adverse reactions was significantly higher in the OIT group (43% versus 9% of doses, p<0.001)

- Most reactions were mild, although a small percentage were moderate in severity (3.4% versus 1.3%, p<0.001)

Antihistamines were used to treat symptoms in 40.9% of OIT doses versus 23.1% of SLIT doses (p<0.001).

β₂-gonists were also used for a significantly higher percentage of doses in the OIT group (1.9% versus 0.3%, p<0.001).

Five doses of epinephrine were required to treat systemic reactions in 4 subjects in the active OIT group, one during dose build up and four during maintenance.
Oral Immunotherapy in Infants and Toddlers

40 children aged 9 to 36 months with suspected or known peanut allergy.

Eligible subjects were randomized to receive E-OIT at goal *maintenance* doses of 300 or 3000 mg/d in a double-blinded fashion.

The primary end point: sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy (4-SU), was assessed by double-blinded, placebo-controlled food challenge either upon achieving 4 prespecified criteria, or after 3 maintenance years.
Oral Immunotherapy

All subjects underwent OIT up to 3000mg of peanut protein.

They then were given 3000mg or 300mg of peanut protein daily in the maintenance phase.

At the end of maintenance, subjects were instructed to stop all peanut consumption. A challenge was then performed 4 weeks after peanut avoidance.

30 of 37 (81%) overall were desensitized at the end of treatment (low-dose, 17 of 20 [85%]; high-dose, 13 of 17 [76%]).

A total of 29 of 37 (78%) achieved 4-SU (low-dose, 17 of 20 [85%]; high-dose, 12 of 17 [71%])

In the per-protocol analysis, the rate of desensitization was 30 of 32 (94%), with 29 of 32 (91%) achieving 4-SU (low-dose, 17 of 19 [89%]; high-dose, 12 of 13 [92%]).
Oral Immunotherapy

No treatment-related, protocol-defined severe AEs, hospitalizations, or deaths. Overall, 95% of the subjects were affected by AEs that were likely related to OIT. A total of 85% of these AEs were mild, with 15% considered moderate and none severe.

Overall, 25% of events (47% of subjects) required treatment, with the vast majority being antihistamines only.

No epinephrine was administered during a dose escalation visit, and once at home following a dose reaction.
Take Home Points

• Know what IgE-mediated food reactions are.
• Testing will not confirm food allergy without a good history
• Avoid sending large food allergy panels
• Food Challenges are under utilized
• Early food introduction in high-risk will decrease the food allergy epidemic. Follow the new NIAID guidelines.
• Avoidance of the food allergen remains the recommendation for patients
• However, food allergy treatment is near/here.
Questions?

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