A CHILD WITH FOOD ALLERGY: DIAGNOSIS & MANAGEMENT

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Faculty Disclosures

- **FINANCIAL INTERESTS**
  I have disclosed below information about all organizations and commercial interests, other than my employer, which may create or be perceived as a conflict of interest.

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>Allertein Therapeutics, LLC</td>
<td>Consultant, Minority Stockholder</td>
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<tr>
<td>University of Nebraska</td>
<td>Consultant</td>
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<tr>
<td>Food Allergy Initiative</td>
<td>Consultant</td>
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<td>Danone Research</td>
<td>Scientific Advisory Board</td>
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- **RESEARCH INTERESTS**
  I have disclosed below information about all organizations which support research projects for which I serve as an investigator.

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<td>National Institutes of Health</td>
<td>Grantee</td>
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<td>Food Allergy Initiative</td>
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- **Patents** – EMP-123 (recombinant protein vaccine) & FAHF-2 (herbal product)
Guideline 2: *Medical history and physical examination*

- **Medical History:** EP recommends utilizing a detailed medical history to help focus the evaluation of a FA. Although the medical history often provides evidence for the type of food allergic reaction and the potential causative food(s) involved, history alone cannot be considered diagnostic of food allergy.

- **Physical Examination:** EP recommends performing a focused physical examination of the patient, which may provide signs consistent with an allergic reaction or disorder often associated with FA.
Diagnosing Food Allergy

Critical questions should include the following:

- What are the symptoms of concern?
- What food precipitated the symptoms? more than once?
- What quantity of food was ingested?
- Was the food in a baked (extensively heated) or native form?
- When did symptoms occur in relation to food exposure?
- Can the food be eaten without these symptoms occurring?
- Were other factors involved such as exercise, alcohol, or use of aspirin or NSAIDS?
- Have the symptoms been present at times other than after exposure to a given food?
- What treatment was given and how long did the symptoms last?
Diagnosing Food Allergy

- **Guideline 4: EP recommends performing a skin prick test**
  
  (SPT) to assist in the identification of foods that may be provoking IgE-mediated food allergic reactions, but the SPT alone **cannot** be considered diagnostic of food allergy.

- SPTs effectively detect the presence of food-specific IgE antibodies (sIgE). Studies suggest that the larger the mean wheal diameter provoked, the more likely that a food allergen will be of clinical relevance.
Predictive Value of PSTs

Comparison of PST results & the outcome of 120 oral milk challenges - 37% positive

Wheal > 95% PPV
- Milk ≥ 8 mm
- Egg ≥ 7 mm
- Peanut ≥ 8 mm

64 of 140 children evaluated for peanut allergy had a + PST - 18 of the 64 had positive peanut challenge

<table>
<thead>
<tr>
<th>Suggestive history</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>Questionable history</td>
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<td>Negative history</td>
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</table>

- Children with positive challenges had PSTs $\geq 5$ mm
- 12 of 23 children with PST $\geq 8$ mm had a negative challenge
- With an unclear history of reactivity, need oral food challenge or further testing

Diagnosing Food Allergy

- Guideline 5: EP recommends that *intra-dermal testing* not be used to make a diagnosis of FA.

- Guideline 6: EP recommends that the routine use of measuring total serum IgE not be used to make a diagnosis of FA.
Guideline 7: EP recommends allergen-specific IgE (sIgE) tests for identifying foods that potentially provoke IgE-mediated food allergic reactions, but alone these tests are not diagnostic of FA.

Fluorescence-labeled antibody assays have comparable sensitivity to that of SPTs, and the absolute levels of sIgE may directly correlate with the likelihood of clinical reactivity.
Probability of Reacting to Food

Sampson *JACI* 2001; 107:891-96.
Check Brands/Labs May Vary

- Watch out for different “units” (classes, counts, ASM, kIU/L)
- Watch for different brands when comparing results
- Correlations possible

Wood RA Ann Allergy Asthma Immunol 2007;99:34-41
Hamilton RG Ann Allergy Asthma Immunol 2011;107:139-44
Challenged 62 patients with suspected peanut allergy.

- Of 25 patients with PN-IgE > 15 kU/L, 7 had negative challenge.
- Of 37 patients with PN-IgE < 15 kU/L, 16 had a positive challenge.

With unclear history, need oral food challenge.

# Component Resolved Diagnostics in Food Allergy

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

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

**Anaphylaxis risk**

- PRP-10
- Profilin
Component Resolved Diagnostics (CRD) in Food Allergy

- Ara h 2 > 1.63 kU/L → 123/123 positive challenge
  - Ara h 2 < 1.63 kU/L → 52/82 positive challenge
  - Ara h 2 level does not predict threshold dose

- Poor correlation between fruit & hazelnut IgE & reaction

- Sensitization to Bet v 1 homologues, Pru av 1/Mal d 1/Cor a 1, is a risk factor for OAS

- Sensitization to LTPs, Pru av 3/Mal d 3/Cor a 8/Jug r 3, is a risk factor for systemic reactions to cherry/apple/hazelnut/walnut (30% - 50%)
  - sensitization to Cor a 9 is a risk factor for systemic reaction, especially in children

Beyer *JACI* 2002; 110:517.
# Cross-reactivity in Testing

## Food Allergy [cross-reactivity often > 80%]

<table>
<thead>
<tr>
<th>Food</th>
<th>Prevalence of Reactivity to &gt; 1 Food in Family</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fish</strong></td>
<td>30 – 100%</td>
</tr>
<tr>
<td><strong>Tree nut</strong></td>
<td>15 – 40%</td>
</tr>
<tr>
<td><strong>Grains</strong> [wheat, rye, barley, oat]</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Milk</strong> [cow, goat, sheep]</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Legumes</strong> [peanut, soy, pea, beans]</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Milk / Beef</strong></td>
<td></td>
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<tr>
<td><strong>Egg / Chicken</strong></td>
<td></td>
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</tbody>
</table>
Quantitative IgE Measurement Over Time as Monitoring Parameter

- Studies support concept that IgE levels can be monitored to assist in determining when it may be worthwhile rechallenging a patient with food allergy:
  - Egg < 1.5 kU$_A$/l
  - Milk < 7 kU$_A$/l
  - Peanut < 2 kU$_A$/l
Diagnosing Food Allergy

Prior Probability & Likelihood Ratios

\[ LR(+) = \frac{\text{sens}}{1 - \text{spec}} \]

- Must estimate pre-test probability (history, prior tests)
- Use simple, additional tests with (hopefully) strong predictive accuracy
- Decide upon further testing that may be definitive but more costly/risky/invasive
Example 1

5 year old with 4 acute episodes of urticaria and angioedema to egg, last episode 1 week before evaluation.

Egg CAP IgE <0.35

Conclusion: Probably true egg allergy, ? OFC versus another test?
Example 1- continued

5 year old with 4 acute episodes of urticaria and angioedema to egg, last episode 1 week before evaluation.

Egg PST= 8 mm wheal

Conclusion: True egg allergy, no further evaluation
Example 2

15 year old with oral pruritus & throat tightness after eating a candy with peanut butter center

PST 10 mm wheal
Peanut - IgE 17 kU\textsubscript{A}/L

Conclusion: Peanut allergy (?)
Example 2 – continued

15 yr old with no previous history of reaction to peanut

PST 10 mm wheal

Components:
- Ara h 2 <0.35 kU/L
- Ara h 8 23 kU/L

Conclusion: Probable Bet v 1-related OAS
Diagnosing Food Allergy

- **Guideline 11:** EP recommends using *oral food challenges* for diagnosing FA.

- The DBPCFC is the “gold standard”

- Single-blind & open food challenge may be considered diagnostic in clinical settings when
  - food challenges elicit no symptoms (i.e. negative challenge)
  - there are objective symptoms (i.e. positive challenge) that correlate with medical history and are supported by laboratory tests.
Managing Food Allergies

- **Recommendation 20**: Patients with documented FA should avoid ingesting their specific allergen or allergens.
  - EP recognizes that allergen avoidance is a strategy that is unproven in randomized controlled trials. However, allergen avoidance is currently the safest strategy for managing food allergy.

- **Recommendation 25**: Avoiding potentially allergenic foods is not recommended as a means of managing AD, EoE, or asthma in patients without documented or proven food allergy.
Managing Food Allergies

- **Recommendation 31:** There are no medications recommended to prevent future IgE-mediated food allergic reactions.

- **Suggestion 33:** It is not suggested that patients at risk for developing food allergy limit exposure to potential, non-food allergens.

- **Recommendation 34:** Using allergen-specific immunotherapy to treat FA is **not** recommended for clinical practice settings.
Diagnosing & Managing Food Allergy

- The diagnosis of food allergy requires a careful medical history, supportive laboratory data, and often an OFC

- SPTs and allergen-specific IgE levels are not diagnostic of food allergy
  - there is insufficient evidence to indicate that component- or epitope-based assays are more predictive of food allergies

- The OFC remains the “gold standard” for diagnosing food allergy

- Elimination diets remain the standard of care for treatment of food allergy
Role of OIT in Clinical Care

- Guideline 28: The EP does **not** recommend using allergen specific immunotherapy to treat IgE-mediated food allergy.
  - “additional safety and efficacy data are needed before such treatment can be recommended”

- FDA – OIT is not approved for use in the treatment of food allergy
  - all approved drugs require FDA approved Phase I, II & III trials prior to approval for general use
  - no Phase III trial for OIT has yet to be approved

- Insurance companies will not compensate for OIT
  - cannot bill insurance for OIT; patient must pay out of pocket
Historical Perspective

- First case report of OIT was in 1908 – scattered case reports for next few decades, but OIT was basically discontinued WHY? Schofield AT. *Lancet* 1908; 1:716-17.

- More than 100 published studies (case reports and uncontrolled studies) demonstrated efficacy of WBE for prevention of anaphylaxis in insect sting allergy – WBE shown to be no more effective than placebo; only venom showed significant protection [Hunt KJ et al. *NEJM* 1978]

- To date, we lack prospective, well-controlled, blinded, multi-center trials of peanut OIT in patients with documented food allergy & well-defined end-points
# Peanut OIT: A Systematic Review

<table>
<thead>
<tr>
<th>Trials (All case series)</th>
<th>Number of participants</th>
<th>Age (yrs)</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumchen et al <em>JACI</em> 2010</td>
<td>6</td>
<td>3 – 10 [5.7]</td>
<td>DBPCFC</td>
<td>Crushed PN (up to 0.5 g)</td>
<td>Change in threshold dose</td>
</tr>
<tr>
<td>Clark et al <em>Allergy</em> 2009</td>
<td>4</td>
<td>9 – 13 [12.5]</td>
<td>History + ↑ PN-IgE or PST</td>
<td>Peanut flour (800 mg)</td>
<td>Threshold dose</td>
</tr>
<tr>
<td>Jones et al <em>JACI</em> 2009</td>
<td>39</td>
<td>1 – 9.3 [4.8]</td>
<td>History + ↑ PN-IgE or PST</td>
<td>Peanut flour</td>
<td>Threshold dose</td>
</tr>
<tr>
<td>Buchanan et al <em>JACI</em> 2005*</td>
<td>7</td>
<td>Mean – 4.4</td>
<td>History + ↑ PN-IgE</td>
<td>No details</td>
<td>Change in threshold dose</td>
</tr>
<tr>
<td>Nash et al <em>JACI</em> 2008*</td>
<td>13</td>
<td>No details</td>
<td>History + ↑ PN-IgE or PST</td>
<td>Peanut flour</td>
<td>Tolerate 7.8 gm of peanut</td>
</tr>
<tr>
<td>Wasserman et al; <em>JACI</em> 2010*</td>
<td>&gt;16</td>
<td>No details</td>
<td>History + ↑ PN-IgE or PST</td>
<td>No details</td>
<td>Tolerate ≥ 1 peanut</td>
</tr>
</tbody>
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## Peanut OIT: A Systematic Review + Two Additional Studies

<table>
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<tr>
<th>Trials</th>
<th>Number of participants</th>
<th>Age (yrs)</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anagnostou et al; <em>CEA</em> 2011</td>
<td>22</td>
<td>4 – 18</td>
<td>DBPCFC (up to 100 mg)</td>
<td>Peanut flour (800 mg)</td>
<td>6.6 gm protein (0.83 mg x 8)</td>
</tr>
<tr>
<td>Varshney et al <em>JACI</em> 2011</td>
<td>28</td>
<td>2 – 11</td>
<td>History + ↑ PN-IgE or PST</td>
<td>Peanut flour (up to 4 gm)</td>
<td>5 gm flour (↑ing doses)</td>
</tr>
<tr>
<td><strong>TOTAL SUBJECTS</strong></td>
<td><strong>135</strong></td>
<td><strong>1 – 18</strong></td>
<td><strong>2 OF 8 CONFIRMED PN Allergy by DBPCFC</strong></td>
<td>PEANUT FLOUR OR CRUSHED PEANUT</td>
<td>VARIABLE</td>
</tr>
</tbody>
</table>

- 4 published case series & 1 controlled trial with 99 subjects, < 30% confirmed peanut allergic with variable interventions reporting variable outcomes

Sampson HA. *JACI-IP* 2013; 1:15-19
Unknowns of Oral Immunotherapy

- Which patients to select - ~20% can’t tolerate OIT
- Dosing regimen & optimal maintenance dose
- Appropriate length of therapy
- What should be considered success?
  - desensitization: how much is enough?
  - tolerance: can it be achieved? In everyone?
- Variables that lead to “breakthrough” reactions
  - concurrent illness; suboptimal control of asthma;
  - timing of dose with food ingestion; physical exertion after dosing; dosing during menses;
  - dosing during pollen seasons; OTHERS?

Sampson HA. *JACI-IP* 2013; 1:15-19
Unknowns of Oral Immunotherapy

- GI symptoms are common and often the leading cause of subjects discontinuing therapy
- Eosinophilic esophagitis – at least 6 OIT studies have reported the development of EoE is patients
  - prevalence to EoE unknown because OIT D/Ced, symptoms clear & subjects not further evaluated
  - In one report, 39/75 (52%) patients developed new GI symptoms (e.g., vomiting, dysphagia, abdominal pain, diarrhea)
  - 3 subjects discontinued therapy, 4 (10%) were diagnosed with EoE by endoscopy and biopsy

Wasserman RL et al. JACI 2011; 127[2], AB28

- At least 10% - 20% of subjects develop EoE on OIT

Sampson HA. JACI-IP 2013; 1:15-19
OIT Trials: Are Controls Necessary

- 45 patients: 24 milk- & 21 egg- allergic; median age: 2.5 yrs

25 Subjects treated

- Non-responder – 9 (36%)
- Partial responder – 4 (16%)
- Responder w/intake – 3 (12%)
- Responder – 9 (36% tolerance)

Elimination Diet Control – 20 (35% tolerance)

Overall 20% of PN-allergic patients “outgrow” their peanut allergy

Staden U et al. Allergy 2007; 62:1261-69
“Do Good, or Do No Harm”

• Safety paramount – virtually all of the studies in academic centers are under FDA IND oversight
  - Rigorous controls but adverse reactions in all subjects; epinephrine required in <5% of subjects

• Office-based practice (published abstr) – 6/16 (38%) of patients required epinephrine
  - 9/28 (32%) were not able to continue on the treatment
  - Much higher rate than seen in research-based trials

• Quality of Life: emotional toll on patients & families
  - much 2° to medical community saying patients could die
  - chances in a 2 y/o – less than being struck by lightening
  - likely that <15% of peanut allergic patients ever experience a life-threatening reaction

Sampson HA. JACI-IP 2013; 1:15-19
Evidence Base for OIT

- Preliminary evidence for peanut OIT is encouraging, but...
  - evidence from “small case series conducted in highly motivated, selected, carefully monitored patients”
  - “different protocols of administration tested”
  - “…preliminary results from studies at potentially high risk of bias…[OIT] should not be taken-up in routine clinical settings. Reports that a few clinicians in the United States have taken this leap is very worrisome.”

  Editorial in the BMJ (Sheikh et al. 2010)

  - only 1 study of PN OIT (19 treated subjects) evaluable

  - Milk OIT – 5 studies considered evaluable
  - small #s of patients; quality of evidence is generally low

Sampson HA. JACI-IP 2013; 1:15-19