22nd World Allergy Congress

Food Allergy

Advances in Diagnosis

By:

Hugh A. Sampson, M.D.
Faculty Disclosures

- **FINANCIAL INTERESTS**
  I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount (including consulting fees, grants, honoraria, investments, etc.) or invest money 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>Advisory Board</td>
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<td>Food Allergy Initiative</td>
<td>Consultant</td>
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- **RESEARCH INTERESTS**
  I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

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<td>National Institutes of Health</td>
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</tbody>
</table>

- Patents – EMP-123 (recombinant protein vaccine) & FAHF-2 (herbal product)

Developing National Guidelines

- 3/2007 – AAAAI & FAAN initiative
- 3/2008 – NIAID agreed to sponsor a consortium of 34 professional organizations
  - Coordinating Committee members selected
  - RAND contracted: screened >12,000 titles & reviewed >1200 articles (1/88 – 9/09)
  - 5 expert panels formed: Definitions; Symptoms & Natural History; Diagnosis; Management; & Management of Food-induced Anaphylaxis
- 3/2010 – 60 day public comment period
  - 550 received & reviewed; modified Guidelines
- 12/6/2010 National Guidelines released
NIAID Diagnostic Guidelines

• #2 – Recommends detailed medical history to focus evaluation & physical exam useful to identify signs of FA, but neither can be considered diagnostic

• #4 – Recommends SPT to assist in identification of potential IgE-mediated food allergens, but alone SPT cannot be considered diagnostic

• #5 – Recommends not using intradermal skin tests

• #7 – Recommends food-specific IgE to assist in identification of potential IgE-mediated food allergens, but alone cannot be considered diagnostic

• #8 – Suggests that the atopy patch test not be used for routine evaluation of non-contact food allergy

• #10 – Suggests that elimination diets may be useful identifying food allergens, especially in non-IgE allergy

• #11 – Recommends using oral food challenges:
  - DBPCFC is the “gold standard”
  - Single-blind & Open challenges “diagnostic” if challenge negative or they elicit objective symptoms correlating with medical history plus supportive lab data

• #12 – Recommends not using the following: BHR* assays; lymph stimulation, food-specific IgG or IgG4, cytotoxicity assays, etc.
DIAGNOSING FOOD ALLERGY

- **History**: ~30% - 40% confirmed
- **Specific IgE or Skin Tests**: ~30% - 40% confirmed
- **Elimination Diets**: 0% - 40% confirmed

DBPCFC is the “GOLD STANDARD”

- Single-blind & open challenges may be diagnostic
- Time consuming, costly & poorly reimbursed
- Stress on the patient including the risk for an anaphylactic reaction

Tests for the Diagnosis of IgE-mediated Food Allergy

Correlation of the outcome of DBPCFC with
- food allergen-specific IgE concentrations in the serum; component-based assays
- Skin prick test wheal diameter

Development of diagnostic decision points that are 90% to 95% predictive of clinical reactivity

Prick Skin Testing
**Paradigm Shift in Interpretation**

- Tests were viewed as positive or negative
  - e.g., a 3 mm wheal is a positive test
- Tests now viewed as probability of reaction

**Predictive Value of PSTs**

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

- Wheat >100% PPV
- Milk ≥ 8 mm
- Egg ≥ 7 mm
- Peanut ≥ 8 mm


**PST Wheal Size & Reactivity**

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

- Children with positive challenges had PSTs > 5 mm
- 9 of 17 children with PST > 10 mm had a negative challenge

Features Affecting Skin Tests

- Extract – non-standardized; lot-to-lot variation
- Device used for prick/puncture
- Operator – pressure applied during application; precision of measurement
- Location of skin test – back > volar aspect of arm; mid- & upper-back > lower back; proximal forearm > distal forearm [3 cm/5 cm]
- Means of measuring wheal size
- No added value for intradermal testing

Bock et al. JACI 1978; 5:559-64

DIAGNOSING FOOD ALLERGY

- Development of in-vitro diagnostic tests for IgE-mediated food allergy

1. Predicting the outcome of oral challenge tests

Replacing oral food challenges

2. Predicting the long-term prognosis

Selecting children for whom immunotherapy would be of benefit in the future

Probability of Reacting to Egg

- Egg white

Retrospective study
n = 300

Prospective study
n = 100

Logit model using log(kU_A/L)

Sampson JACI 2001; 107:891-96.
### 95% Predictive Decision Levels

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Decision Pt (kU/l)</th>
<th>PPV</th>
<th>Sens.</th>
<th>Spec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg (≤ 2 yrs of age)</td>
<td>7</td>
<td>98%</td>
<td>61%</td>
<td>98%</td>
</tr>
<tr>
<td>Milk (≤ 1 yr of age)</td>
<td>15</td>
<td>95%</td>
<td>57%</td>
<td>94%</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>100%</td>
<td>57%</td>
<td>100%</td>
</tr>
<tr>
<td>Soy</td>
<td>30</td>
<td>73%</td>
<td>44%</td>
<td>94%</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74%</td>
<td>61%</td>
<td>92%</td>
</tr>
<tr>
<td>Tree nuts***</td>
<td>15</td>
<td>95%</td>
<td>----</td>
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### Age-related Probability of Reacting to Milk

861 oral food challenges performed in 969 children age range: 0.2 – 14.6 yrs


### Peanut-specific IgE

- Challenged 62 children with suspected peanut allergy

- 28% wrong diagnosis

- 25 patients with peanut-specific IgE > 15 kU/L

--- Boyer et al. personal communication
Diagnostic Decision Points

- Variations by age and atopy status.
- Equivocal areas [20th to 80th percentile]
- Decreasing IgE levels with food avoidance
- Not established for many foods, e.g. cereal grains, shell fish or tree nuts.
- For several foods, e.g. wheat and soy, the PPV of the diagnostic decision point are <75%

Epitope Diversity & Reactivity

Greater epitope diversity = more peanut-specific IgE molecules present on mast cells ➔ greater releasibility

Greater epitope diversity = more severe reactions

Component Resolved Diagnostics in Food Allergy

<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>Ara h 8</td>
<td>Ara h 9</td>
</tr>
<tr>
<td>Ara h 5</td>
<td>Cor a 1</td>
<td>Cor a 8</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 2</td>
<td>Gly m 4</td>
</tr>
<tr>
<td>Soybean</td>
<td>Gly m 3</td>
<td>Tri a 12</td>
</tr>
<tr>
<td>Wheat</td>
<td>Tri a 14</td>
<td>Tri a 14</td>
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</table>

Ana risk ➔

* Birch tree pollen, Timothy grass pollen for wheat
** Storage seed proteins, albumins and globulins
**Component Resolved Diagnostics 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
  
  Bindslev-Jensen C. et al.

- **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
  

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**Cross-reactivity in Testing**

<table>
<thead>
<tr>
<th>Food Allergy [cross-reactivity often &gt; 80%]</th>
<th>Prevalence of Allergy to &gt; 1 Food in Family</th>
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<tbody>
<tr>
<td>Fish</td>
<td>30 – 100%</td>
</tr>
<tr>
<td>Tree nut</td>
<td>15 – 40%</td>
</tr>
<tr>
<td>Grains (wheat, rye, barley, oat)</td>
<td>15%</td>
</tr>
<tr>
<td>Milk (cow, goat, sheep)</td>
<td>90%</td>
</tr>
<tr>
<td>Legumes [peanut, soy, pea, beans]</td>
<td>10%</td>
</tr>
<tr>
<td>Milk / Beef</td>
<td>10%</td>
</tr>
<tr>
<td>Egg / Chicken</td>
<td>10%</td>
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**Quantitative IgE Measurement Over Time as Monitoring Parameter**

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

Sampson, J Allergy Clin Immunol 2001
Skonick et al, J Allergy Clin Immunol 2001
Sampson, Curr Opin Allergy Clin Immunol 2002
Summary: Diagnostics

- PSTs and allergen-specific IgE both may be useful in the diagnosis & management of IgE-mediated food allergy, but alone without collaborating history are never sufficient.
- When interpreting results, must consider several factors:
  - Predictive value of test result
  - Strength of history
  - Age of patient & potential cross-reactivities
- When considering OFC, consider benefit of adding food & probability of passing.