Food Allergy Testing

Ronald M. Ferdman, M.D., M.Ed.
Children’s Hospital Los Angeles
Division of Clinical Immunology and Allergy

Disclosure

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• I do not intend to discuss an unapproved / investigative use of a commercial product / device in my presentation.

Learning Objectives

After completion of this activity, participants will be able to:

• Recognize the importance of accurate food allergy testing in children
• List the variables that influence the interpretation of food allergy blood tests
• Recognize unproven methods for food allergy testing
From 1997-2007, the prevalence of reported food allergy increased 18% among children under age 18 years.

CDC / NCHS, National Health Interview Survey

<table>
<thead>
<tr>
<th>Year</th>
<th>Discharges per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998-2000</td>
<td>2,615</td>
</tr>
<tr>
<td>2001-2003</td>
<td>4,115</td>
</tr>
<tr>
<td>2004-2006</td>
<td>9,347</td>
</tr>
</tbody>
</table>


Overestimation of Food Allergies

- **Perceived:**
  - 12-30% of parents believe their children have at least one food allergy
  - 13-33% of adults believe they have food allergies

- **Actual:**
  - 3 - 8% of children <3 - 6 years have verifiable food allergies
  - 2 - 4% of general population have verifiable food allergies
  - May be higher in selected groups
  - Atopic dermatitis (eczema) ~30-50%+


Quality of Life in Families with Food Allergy

- **Children** with food allergies report worse QOL scores compared to those with irritable bowel synd., rheumatologic diseases, & diabetes
  - In general, the most affected scores are in social (especially social interaction), emotional (e.g. fear) and psychosocial (e.g. anxiety) scales
  - But also “bodily pain”, “general health” & “vitality”

- **Parents** of food-allergic children also report worse scores on QOL surveys

Bullying Due to Food Allergies

- Of 353 respondents (parents and kids) 24% reported being bullied, teased or harassed due to their food allergies
  - Verbal
  - Physical: allergen thrown at them, their food purposely contaminated with allergen


Costs of Food Allergies

- 2007: Economic burden of allergic reactions cause by foods ~ $½ billion
  - $307 million direct costs
  - $203 million indirect costs

- Amazon.com (per oz of powder ~2014)
  - Milk / soy intact protein formula ~$1.08/oz
  - Extensively hydrolyzed formula ~$1.80/oz
  - Amino acid formula ~$2.60/oz


Nutritional Consequences

- Failure to thrive
- Macronutrient deficiencies
  - Protein (kwashiorkor)
- Micronutrient deficiencies
  - Calcium with rickets & hypocalcemic sz’s
  - Iron deficiency with anemia, zinc
  - Multiple vitamins- D, B-complex, E
- Electrolyte abnormalities

Importance of Accurate Food Allergy Testing in Children

- The frequency and severity of food allergic reactions is truly increasing
  - But...the frequency of food allergies are also over-estimated by patients
- Food allergies have a significant negative impact on children / families
- Food allergies have significant economic costs for individuals and the system
- May have significant nutritional consequences

Accurate Food Allergy Testing in Children

- Impact of false positive diagnosis:
  - Unnecessary negative psychosocial, financial & nutritional consequences
- Impact of false negative diagnosis:
  - Ongoing risk for exposure to food and potential serious allergic reactions or worsening chronic disease

How To Diagnose Food Allergies

- History and physical exam
- Specific food tests
  - Blood tests (IgE and non-IgE)
  - Skin testing (prick and patch)
- Food challenges
- Unproven testing methods

How To Diagnose Food Allergies

• History and physical exam
• Specific food tests
  – Blood tests (IgE and non-IgE)
  – Skin testing (prick and patch)
• Food challenges
• Unproven testing methods


Know Your Foods

Eight foods account for 90% of all food allergic reactions

Egg     Milk     Soy     Wheat     Peanut     Tree Nuts     Seafood     Shellfish

• More common in children
• More common in adults

• Rarely necessary to tests for other foods
• Tests have highest predictive value for these foods

Know Your Diseases

Often Associated With Food Allergies

• Urticaria - acute
• Anaphylaxis
• Atopic dermatitis
• Eosinophilic esophagitis and gastroenteritis
• FPIE
• Oral allergy syndrome
History Suggestive of Food Allergy

- Immediate onset of symptoms
  - Usually minutes, occasionally hours
  - Rarely several hours-days (certain GI, eczema)
- Multiple systems (respiratory, skin, GI)
  - Isolated single system can occur
- Happens each time food is eaten in same form
- Does not occur if food is not eaten
- Very small amounts can trigger symptoms
- Responsive to allergy therapy

History Not Suggestive of Food Allergy

- Delayed onset of symptoms
  - Day or days
- Prolonged duration (days to weeks)
- Only occurs with large quantities of food, or “cumulative” effect over days
- Occurs even when food is not eaten
- Doesn’t occur each time food is eaten
  - In same “form” (low-heat vs high-heat)
- Atypical symptoms (‘hyper’, bruising, fever, etc)

How Common are Delayed Onset of Symptoms?

With few exceptions, most food allergy symptoms present quickly after food is eaten

Respiratory
- Rhinitis
- Conjunctivitis
- Wheeze/cough

Gastrointestinal
- N/V/D
- Pain
- Hematochezia
- Irritability
- Food refusal
- Weight loss

Cutaneous
- Eczema
- Itch
- Angioedema
- Urticaria

* = more likely than others in group to present later, but still more common overall to present early
**Benefits of a Comprehensive Food Allergy History**

- Can be "diagnostic" in some cases
  - Symptom + food diary
- Guide specific food tests
- Confirm the validity of food tests

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**Not all adverse reactions to foods are allergic reactions**

**ADVERSE REACTIONS TO FOODS**

- Immune Mediated
  - IgE
  - Non-IgE or Mixed
  - Celiac disease
  - Food protein colitis
  - Eosinophilic enteritis
  - Contact dermatitis
- Non-immune Mediated
  - Metabolic
  - Pharmacologic
  - Toxic
  - Idiopathic
  - Host Related
    - Gastroesophageal reflux
    - Malabsorption
    - Psychological

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**Food Allergy Physical Exam**

- No specific physical findings
  - Except for non-specific acute allergic (urticaria, angioedema, eczema, etc)
- Mostly used to assess for signs of underlying non-allergic disease
  - Overall nutritional status
Diagnostic Tests

- IgE testing
  - Skin prick testing
  - Blood food-specific IgE
- Oral Challenge
- Non-IgE testing
  - Patch testing
  - Basophil release
- Unproven Techniques

Skin Testing

- Rapid and safe assessment of food-specific IgE
- Skin prick testing (SPT)
  - “Scratch” tests → antiquated method
  - Intradermal (ID) food tests not recommended
    - ID tests are still performed selectively for aeroallergens, medications and venoms, but not for foods
  - Scoring: size (mm) of wheal (less so flare)
- “Prick-Prick” testing useful for fresh food testing (especially fruits and vegetables)
  - Prick food - then prick patient
- Blocked by H1-antagonists
Blood IgE Testing

- “RAST” often used as “generic” name of blood allergy test for specific IgE
- Many proprietary tests available
  - ImmunoCAP® - has most clinical studies correlating with oral food challenges
  - Immulite®
  - Turbo RAST®
- Score (ImmunoCAP): <0.35 kU/L ⟷ >100 kU/L
  - Other scales for different brands
- Not affected by H1-blockers

Food-Specific IgE Testing (not a very good test)

- Positive test indicates “sensitivity” (presence of IgE against food), but not necessarily “reactivity” (clinical reaction to food)
  - Many people have detectable IgE to foods, but have absolutely no symptoms
  - Seen with all other antigens (venom, medications, aeroallergens…)
- Can NOT make the diagnosis of food allergy based solely on an elevated IgE

Food-Specific IgE Testing (not a very good test)

- Sensitivity of IgE tests is generally high
  - Very good at showing what patient is NOT allergic to (high negative predictive value (NPV))
  - Skin test NPV (~90%) > blood IgE NPV (~75-90%)
- Specificity for “random” screen IgE tests is low
  - Low positive predictive value (PPV) ~<50%
- Specificity & PPV of test improves when using “targeted” testing guided by clinical history.
  - Dependent on level of IgE, specific food, clinical hx
  - PPV may be as high as >95%
General Interpretation of Food Tests

- General perception
  - The more positive the test (bigger size skin test, high value of blood IgE) → the more severe the food allergy

- More accurate perception
  - The more positive the test (bigger size skin test, high value of blood IgE) → the more likely the patient is allergic to the food

Interpretation of Food-Specific IgE Blood Tests

- Level of IgE
- Specific food
- Age of child
- Underlying disease
- Clinical history
- Preparation of the food (milk, egg)

Predicting Clinical Reactivity Based on Specific IgE Level

Matoney J.K. J Allergy Clin Immunol 2008;122:1497

ImmuNoCAP IgE Level (KU/L)
Predictive Values for CAP RAST for Children with Suspected Food Allergy

<table>
<thead>
<tr>
<th>Food Protein</th>
<th>90% Spec. (kUA/L)</th>
<th>PPV%</th>
<th>95% NPV (kUA/L)</th>
<th>90% NPV (kUA/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7 (2*)</td>
<td>98</td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>Milk</td>
<td>15 (5*)</td>
<td>95</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>95</td>
<td>Best NPV = 85% @ 0.35</td>
<td>Best NPV = 85% @ 0.35</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>100</td>
<td>0.9</td>
<td>5</td>
</tr>
<tr>
<td>Soy</td>
<td>30</td>
<td>73</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

* = ≤ 2 year old


Milk & Egg Specific IgE Influence of Age

<table>
<thead>
<tr>
<th>IgE concentration (kU/L)</th>
<th>Probability</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.35</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td>100</td>
<td>1.2</td>
</tr>
</tbody>
</table>


Predictive Values for CAP RAST for Children with Atopic Dermatitis

<table>
<thead>
<tr>
<th>Food Protein</th>
<th>95% PPV (kUA/L)</th>
<th>90% PPV (kUA/L)</th>
<th>95% NPV (kUA/L)</th>
<th>90% NPV (kUA/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>6</td>
<td>2</td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>Milk</td>
<td>32</td>
<td>23</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>Peanut</td>
<td>15</td>
<td>9</td>
<td>Best NPV = 85% @ 0.35</td>
<td>Best NPV = 85% @ 0.35</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>9.5</td>
<td>0.9</td>
<td>5</td>
</tr>
<tr>
<td>Soy</td>
<td>Best PPV = 50% @ 0.05</td>
<td>-</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Wheat</td>
<td>Best PPV = 75% @ 0.05</td>
<td>-</td>
<td>5</td>
<td>79</td>
</tr>
</tbody>
</table>

Influence of Clinical History

<table>
<thead>
<tr>
<th>IgE (kU/L)</th>
<th>Total</th>
<th>Failed Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35</td>
<td>38</td>
<td>24%</td>
</tr>
<tr>
<td>0.36 – 1.9</td>
<td>38</td>
<td>56%</td>
</tr>
<tr>
<td>2 – 4.9</td>
<td>27</td>
<td>60%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>7</td>
<td>100%</td>
</tr>
</tbody>
</table>


You Can’t Un-Fry an Egg

- 100 children (2.1-17.3 yrs) with milk allergy
- Challenged with extensively heated milk products
  - ≥350°F for ≥30 minutes
  - 75% tolerated heated milk

- 117 children (1.6-18.6 yrs) with egg allergy
- Challenged with extensively heated egg products
  - 54% tolerated heated egg


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Which is Better
Skin Test or Blood Test?

Summary ROC Curves for the Diagnosis of All Food Allergies, Cow’s Milk Allergy, and Hen’s Egg Allergy Comparing SPT With sIgE Testing

• In most cases, when properly chosen and interpreted, they have similar validity

Schneider Chafen JJ. JAMA. 2010;303:1848-56.

What Foods?

• Should generally avoid testing for large “random” food panels
  – Should be driven by medical history
• Should generally avoid testing for foods that are currently being tolerated
• 90% of childhood food allergies
  – Milk, eggs, peanut, wheat, soy
• 90% of adult food allergies
  – Shellfish, peanuts, tree nuts, seafood

<table>
<thead>
<tr>
<th>ALLERGY TO:</th>
<th>RELATED FOOD</th>
<th>APPROXIMATE RATE OF SENSITIVITY</th>
<th>APPROXIMATE CLINICAL REACTION RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Other legumes (beans + soybean)</td>
<td>19-79%</td>
<td>3-5%</td>
</tr>
<tr>
<td>A Tree Nut</td>
<td>Other tree nuts</td>
<td>92%</td>
<td>12-37%, Higher for: walnut-pecan-almond-hazelnut cashew-pistachio</td>
</tr>
<tr>
<td>A Tree Nut</td>
<td>Peanut</td>
<td>59-86%</td>
<td>33%</td>
</tr>
<tr>
<td>Codfish</td>
<td>Another fish</td>
<td>5-100%</td>
<td>30-85%</td>
</tr>
<tr>
<td>Shrimp</td>
<td>Other crustacea</td>
<td>50-100%</td>
<td>38%</td>
</tr>
<tr>
<td>Crustacea</td>
<td>Mollusk</td>
<td>47%</td>
<td>14%</td>
</tr>
<tr>
<td>Crustacea</td>
<td>Other mollusks</td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>Wheat</td>
<td>Another grain</td>
<td>47-85%</td>
<td>20% [eczema]</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>Goat / sheep milk Mare’s milk</td>
<td>20-100%</td>
<td>90%</td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>Other eggs</td>
<td></td>
<td>Common (90%)</td>
</tr>
</tbody>
</table>

Oral Food Challenge

- Gold standard for diagnosis of food allergy
  - Double blind placebo controlled (DBPCFC)
  - Open challenge, single blind
- When history and testing are inconclusive
  - Test for “outgrowing” of certain food allergies
- In properly selected patients, risk is low
  - Should be done under adequate supervision
  - Home “challenge -- de-challenge” diets, for very low risk

ANA

- A 10 year old boy presents with a fever
- Chemistry panel: ANA 1:80
  - Normal lab cut-off = <1:40
- You make the diagnosis of lupus and prescribe methotrexate
- 5-20% of the general population have a positive ANA
- Need more than a test result alone to make the diagnosis of lupus

Kavanagh A. Arch Pathol Lab Med. 2000;26:71-81

IgG4

- 10 year old boy presents with abdominal pain
- IgG4 to milk, wheat, egg, beef, soy and chicken are elevated
- You advise elimination of all these foods from his diet
- Can detect IgG to foods in up to >80% of the population (increases with exposure)
- Most studies show IgG4 increases as children begin to outgrow allergy

Unproven Methods for Food Allergy Testing

• “Valid” test, but not to diagnose allergy
  – IgG (especially IgG4) tests
  – Basophil histamine release (research)

• Non-standardized or unproven
  – Lymphocyte stimulation / cytotoxic tests
  – Mediator release assay (LEAP)
  – Electrodemal testing (Vega)
  – Provocation/neutralization
  – Facial thermography

Milk

• Not a homogenous liquid
• Proteins, fats & carbohydrates
• Collection of several proteins
  – α-lactalbumin
  – β-lactoglobulin
  – Caseins (α-s1, α-s2, β, 6)
  – Serum albumin
  – Transferrin
  – Lactoferrin
  – others

Building a Better Allergy Test
Component-Resolved Testing

• Most allergens have more than one epitope
• Some may bind IgE, others may bind IgG
• Some bind with very high avidity, others with low
• Some are resistant to acid hydrolysis, others not
• Some are resistant to heating, others not
• Some may cross react with other allergens, others not
Conventional vs Component Testing

• Conventional ‘RAST’ (or skin test)
  – Extract - mixture of multiple proteins, some allergenic and some not
• Component-resolved diagnostics (CRD)
  – Multiple individual proteins (chosen for clinical relevance) either isolated from natural source or produced recombinantly
  – Microarray chip

<table>
<thead>
<tr>
<th>Conventional RAST</th>
<th>Component-Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive if:</td>
<td>Sensitized</td>
</tr>
<tr>
<td>IgE 1</td>
<td>No clinical reaction</td>
</tr>
<tr>
<td>OR</td>
<td>(“false positive”)</td>
</tr>
<tr>
<td>IgE 2</td>
<td>Allergic</td>
</tr>
<tr>
<td>OR</td>
<td>High risk anaphylaxis</td>
</tr>
<tr>
<td>IgE 3</td>
<td>Cross react with other foods</td>
</tr>
<tr>
<td>OR</td>
<td>Allergic</td>
</tr>
<tr>
<td>IgE 4</td>
<td>Likely to outgrow</td>
</tr>
<tr>
<td>detected</td>
<td>Allergic</td>
</tr>
<tr>
<td></td>
<td>Likely to tolerate heated food</td>
</tr>
</tbody>
</table>

Overview of the allergic proteins in peanut (Arachis hypogaea)

<table>
<thead>
<tr>
<th>No</th>
<th>Name</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ara h 1</td>
<td>vicilin family of storage proteins</td>
</tr>
<tr>
<td>2</td>
<td>Ara h 2</td>
<td>conglutinin, 2S albumin, seed storage protein</td>
</tr>
<tr>
<td>3</td>
<td>Ara h 3</td>
<td>profilin</td>
</tr>
<tr>
<td>4</td>
<td>Ara h 4</td>
<td>like Ara h 2</td>
</tr>
<tr>
<td>5</td>
<td>Ara h 5</td>
<td>conglutinin, 2S albumin, seed storage protein</td>
</tr>
<tr>
<td>6</td>
<td>Ara h 6</td>
<td>PR 10 (Bet v 1) family</td>
</tr>
<tr>
<td>7</td>
<td>Ara h 7</td>
<td>lipid transfer protein</td>
</tr>
<tr>
<td>8</td>
<td>Ara h 8</td>
<td>oleosin</td>
</tr>
<tr>
<td>9</td>
<td>Ara h 9</td>
<td>oleosin</td>
</tr>
<tr>
<td>10</td>
<td>Ara h 10</td>
<td>oleosin</td>
</tr>
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<td>Ara h 1, Ara h 2, Ara h 3/4</td>
</tr>
<tr>
<td>2S albumin seed storage protein</td>
<td>Ara h 5</td>
</tr>
<tr>
<td>Glycinin</td>
<td>Ara h 2, Ara h 3/4</td>
</tr>
<tr>
<td>Oleosin</td>
<td>Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11</td>
</tr>
<tr>
<td>Lipid transfer protein</td>
<td>Ara h 10</td>
</tr>
</tbody>
</table>

Food Testing Summary

- There is a significant impact on many levels for families with true food allergies, as well as with falsely identified or missed food allergies.
- Food allergy testing should be guided by history:
  - Should generally not test for random panel of foods, or for foods that are being tolerated.
- Tests for food-specific IgE (skin or blood) are the only validated test in the majority of clinical contexts.
- Food allergy-specific IgE blood tests should be interpreted in context of validated predictive values and clinical scenarios.
- Multiple non-IgE food “allergy” tests are available which have unproven and disproven validity.

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