Allergy Evaluation—What it all Means & Role of Allergist

Sai R. Nimmagadda, M.D.
Associated Allergists and Asthma Specialists Ltd.

Clinical Assistant Professor
Of Pediatrics
Northwestern University
Chicago, Illinois
Objectives of Presentation

- Discuss the different options for allergy evaluation.
  - Skin tests
  - Immunocap Testing
- Understand the results of Allergy testing in various allergic diseases.
- Briefly Understand what an Allergist Does
Common Allergic Diseases Seen in the Primary Care Office

- Atopic Dermatitis/Eczema
- Food Allergy
- Allergic Rhinitis
- Allergic Asthma
- Allergic GI Diseases
Factors that Influence Allergies Development and Expression

Host Factors

- Genetic
  - Atopy
  - Airway hyperresponsiveness
- Gender
- Obesity

Environmental Factors

- Indoor allergens
- Outdoor allergens
- Occupational sensitizers
- Tobacco smoke
- Air Pollution
- Respiratory Infections
- Diet
Why Perform Allergy Testing?

– Confirm Allergens and answer specific questions.
  • Am I allergic to my dog?
  • Do I have a milk allergy?
  • Have I outgrown my allergy?
  • Do I need medications?
  • Am I penicillin allergic?
  • Do I have a bee sting allergy
Tests Performed in the Diagnostic Allergy Laboratory

- Allergen-specific IgE (over 200 allergen extracts)
  - Pollen (weeds, grasses, trees),
  - Epidermal, dust mites, molds,
  - Foods,
  - Venoms,
  - Drugs,
  - Occupational allergens (e.g., natural rubber latex)
- Total Serum IgE (anti-IgE; ABPA)
- Multi-allergen screen for IgE antibody
Diagnostic Allergy Testing
Serological Confirmation of Sensitization
History of RAST Testing

- RAST (radioallergosorbent test) invented and marketed in 1974
- The suspected allergen is bound to an insoluble material and the patient's serum is added
- If the serum contains antibodies to the allergen, those antibodies will bind to the allergen
- Radiolabeled anti-human IgE antibody is added where it binds to those IgE antibodies already bound to the insoluble material
- The unbound anti-human IgE antibodies are washed away.
- The amount of radioactivity is proportional to the serum IgE for the allergen
In 1989, Pharmacia Diagnostics AB replaced RAST with a superior test named the ImmunoCAP Specific IgE blood test.

- Also described as CAP RAST or CAP.
- In 2013 Component ImmunoCAP available for Peanut.
- 2015 for Tree Nut Component ImmunoCAP.
<table>
<thead>
<tr>
<th>IgE Class</th>
<th>KU/L</th>
<th>% Response</th>
<th>Level of IgE Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>&lt; or = 70</td>
<td>Absent/undetectable</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.70</td>
<td>71-110</td>
<td>Low Level</td>
</tr>
<tr>
<td>2</td>
<td>0.71-3.50</td>
<td>111-220</td>
<td>Moderate Level</td>
</tr>
<tr>
<td>3</td>
<td>3.51-17.5</td>
<td>221-600</td>
<td>High Level</td>
</tr>
<tr>
<td>4</td>
<td>17.6-50</td>
<td>601-2000</td>
<td>Very High Level</td>
</tr>
<tr>
<td>5</td>
<td>51-100</td>
<td>2001-6000</td>
<td>Very High Level</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>&gt; 6000</td>
<td>Very High Level</td>
</tr>
</tbody>
</table>
Skin Test
Confirmation of Sensitization
Allergy Skin Testing

• Skin testing remains the central test to confirm allergic sensitivity when it can be performed ¹
• Skin testing is fast (15-30 minutes), safe, sensitive and involves minimally invasive procedures which can be cost effective
• When performed correctly, skin testing is reproducible
• Skin testing has demonstrated good correlation with results of nasal challenge² and bronchial challenges ³
• Results of skin test should always be used as an adjunct to the clinical history and physical examination when making the diagnosis of allergic disease

¹. Oppenheimer et al, Ann Allergy 2006;S1:6-12
Skin Testing

Photographs courtesy of Dr. Ed Philpot.
Interpretation of Test Results

• The wheal & flare should be recorded in millimeters.
• 3 mm is considered the cut-off for positive, but may overestimate clinical allergy!
• All results should be compared to the negative and positive control.
• If negative control is positive the patient has dermographism, and entire test is invalid.
• If histamine control is negative, the results are probably being inhibited by antihistamines (Patients do forget!)
• Remember that sensitivity (positive skin prick tests) does not mean clinical reactivity or allergy.
COMPARISON OF SKIN TESTING AND SEROLOGY?
### Allergen-Specific IgE

**In vitro (lab) and In-Vivo (skin tests)**

<table>
<thead>
<tr>
<th></th>
<th><strong>In-vitro</strong></th>
<th><strong>In-vivo</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE Antibody</strong></td>
<td>High sensitivity*</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>High specificity*</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>High reproducibility</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Quantitative results in kIU/L^</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WHO Standard calibrated</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Quality assurance test program</td>
<td>Yes</td>
</tr>
<tr>
<td>Can be used independently of pharmaceutical treatment</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Can be used independently of patient skin status</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Time factor</strong></td>
<td>1-7 days</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td><strong>Cost factor</strong></td>
<td>more expensive</td>
<td>inexpensive</td>
</tr>
<tr>
<td><strong>Usefulness in motivating patients</strong></td>
<td>obscure</td>
<td>dramatic</td>
</tr>
</tbody>
</table>

*Results may vary between specific bioassays

^Although all are expressed with same units, cannot compare results between different bioassays
Food Allergy Evaluation
Why can’t you test my child to everything???
When to Test/What to Test

IgE associated clinical disorder? (Is testing for food allergy appropriate?)

Determination of potential triggers
- Requires careful history, consideration of epidemiology, pathophysiology
- Foods tolerated (should not be tested)
- Foods not often ingested, more likely triggers
- Foods commonly associated with severe reactions:
  - Peanut, nuts from trees, fish, shellfish, seeds
  - Common allergens for children with moderate-severe atopic dermatitis:
    - Egg, milk, wheat, soy

Selection of serological or skin tests
- Select tests to confirm/exclude suspicions
- Avoid “panels” of food allergens
- Avoid testing tolerated foods

Alternative tests/advice

No

Yes
Office Based Evaluation of Food Allergy

• Primary Care Professional
  – Clinical history (symptoms, food, reaction consistency, alternative explanations, determination if likely IgE mediated)
  – Physical examination
  – Serological tests for food-specific IgE

• Allergist
  – Clinical history and physical examination
  – Serum and/or skin prick tests for food-specific IgE antibodies
  – Diagnostic elimination diets
  – Physician-supervised oral food challenges
Pathogenesis: Allergens

• Adults
  - Nuts, peanuts, fish, shellfish, eggs
• Children
  - Eggs, peanuts, milk, soy, fish, wheat
• Societal eating patterns influence development of specific food hypersensitivities
  – Boiled peanuts in Asian cultures,
  – Lack of Peanut Consumption in Sweden
Diagnostic Laboratory Techniques
IgE-Mediated Food Hypersensitivity

• Prick skin tests: Positive tests are “suggestive”
  - Wheal diameter 3 mm > negative control
  - Positive predictive accuracy: < 50%
  - Negative predictive accuracy: > 90%
• Intradermal skin tests: Too non-specific
• IgE RAST: In good lab is similar to skin test
  - Positive: 3+ to 6+ in 6+ scoring system
Food-specific IgE concentrations predictive of clinical reactivity (adapted from Sampson HA)

- **Diagnostic Decision Point**

<table>
<thead>
<tr>
<th>Allergen</th>
<th>[kUA/L]</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>61</td>
<td>95</td>
<td>98</td>
<td>38</td>
</tr>
<tr>
<td>- Infants &lt; 2 yrs</td>
<td>2</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>57</td>
<td>94</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>- Infants &lt; 2 yrs</td>
<td>5</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>57</td>
<td>100</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>44</td>
<td>94</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>61</td>
<td>92</td>
<td>74</td>
<td>87</td>
</tr>
<tr>
<td>Tree nuts*</td>
<td>~15</td>
<td>~95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic Decision Point

Value of the Immuno Cap Assay for Peanut Protein

- kU/L
- Percentage of positive reactions

Graph showing the relationship between kU/L and the percentage of positive reactions.
Sample Case

• Connor age 3 with a history of multiple food allergies and recent anaphylaxis to unknown food at a party. Drinks milk with no problem, No exposure to Peanuts or tree nuts, shrimp etc.

• Cap Rast
  – Milk            Class II    2.5 kU/L
  – Peanut          Class III   7.5 kU/L
  – Cashew          Class IV    22.7 kU/L
  – Walnuts         Class III   13.2 kU/L
  – Shrimp          Class I     0.70 kU/L
Treatment of Food Allergy

• Strict avoidance - teach patients to read labels
• Avoidance of the specific 1 or 2 foods proven to cause the allergy symptom
• Re-challenge at intervals to determine loss of sensitivity
• Re-challenge should be performed in a medical setting if there is any possibility of severe reaction
When to Re-challenge?

- Are skin tests predictive of positive food challenges?
  - Study performed in 467 children suspected of food allergy
    - 555 food challenges
    - Positive in 55% of the patients, negative in 37% and inconclusive in 8%
  - Challenges were ALWAYS positive when the skin test diameter was >8mm for milk, >7mm for egg, and >8mm for peanut
Food-specific IgE concentrations predictive of clinical reactivity (adapted from Sampson HA)

- **Diagnostic Decision Point**

<table>
<thead>
<tr>
<th>Allergen</th>
<th>[kUA/L]</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>61</td>
<td>95</td>
<td>98</td>
<td>38</td>
</tr>
<tr>
<td>- Infants &lt; 2 yrs</td>
<td>2</td>
<td></td>
<td></td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>57</td>
<td>94</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>- Infants &lt; 2 yrs</td>
<td>5</td>
<td></td>
<td></td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>57</td>
<td>100</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>44</td>
<td>94</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>61</td>
<td>92</td>
<td>74</td>
<td>87</td>
</tr>
<tr>
<td>Tree nuts*</td>
<td>~15</td>
<td></td>
<td></td>
<td>~95</td>
<td></td>
</tr>
</tbody>
</table>
When to Re-challenge?

• Milk and soy allergy in infants
  – Every 6-12 months depending on initial reactions and intervening period

• Peanuts and tree nuts
  – Depending on exposure and history at 3-5 years of age. ONLY IN A CONTROLLED SETTING

• Eggs
  – Challenge eggs in baked goods at 2-3 years of age
  – Eggs as such at 4-5 years of age
Component Immuno-Cap

• Specific proteins now may be isolated and tested.
  – Proflins
  – PR-10 Proteins
  – LTP Proteins
  – Storage Proteins
Managing Allergies in School - Reaction

• EpiPen policy
  - It is not sufficient to have an EpiPen in a cabinet or drawer in the classroom. It must be on the child whenever he/she leaves the classroom (recess, gym, bathroom, field trips etc…) – designated hanging spot for an EpiPouch to be taken when leaving the classroom.

• Illinois EpiPen guidelines
  - EpiPens should be carried at all times by a person with severe allergies, because it is not enough to have one nearby.

• In the event of a reaction:
  - Administer EpiPen immediately - even mild allergy symptoms can rapidly progress to a life-threatening situation
  - Call 911

• Everyone who has been treated with epinephrine must be taken to hospital immediately for evaluation because the symptoms may recur and further injections may be required.

---

**Increasing risk of systemic reactions**

<table>
<thead>
<tr>
<th></th>
<th>Profilin</th>
<th>PR-10 protein</th>
<th>LTP</th>
<th>Storage Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEANUT</td>
<td>Profilin</td>
<td>Ara h 8</td>
<td>Ara h 9</td>
<td>Ara h 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ara h 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ara h 3</td>
</tr>
<tr>
<td>HAZEL NUT</td>
<td>Profilin</td>
<td>Cor a 1</td>
<td>Cor a 8</td>
<td>Cor a 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cor a 14</td>
</tr>
<tr>
<td>WALNUT</td>
<td>Profilin</td>
<td></td>
<td>Jug r 3</td>
<td>Jug r 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAZIL NUT</td>
<td>Profilin</td>
<td></td>
<td></td>
<td>Ber e 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASHEW NUT</td>
<td>Profilin</td>
<td></td>
<td></td>
<td>Ana o 3</td>
</tr>
</tbody>
</table>
Management: Dietary Elimination

- Hidden ingredients in restaurants/homes (peanut in sauces, egg rolls)
- Labeling issues ("spices", changes, errors)
- Cross contamination (shared equipment)

Seeking assistance
- Food allergy specialist
- Registered dietitian: (www.eatright.org)
- Food Allergy & Anaphylaxis Network (www.foodallergy.org; 800-929-4040) and local support groups

---

**Peanut (f13)**

- **Ara h 1 + Ara h 2 + Ara h 3**
  - (f422)
  - (f423)
  - (f424)
  - Storage proteins
  - Stable to heat and digestion
  - Associated with severe reactions

- **Ara h 9 (f427)**
  - Lipid transfer protein (LTP)
  - Stable to heat and digestion
  - Associated with both severe and local reactions
  - Associated with allergy to peach and peach related fruits

- **Ara h 8 (f352)**
  - PR-10 Protein
  - Labile to heat and digestion
  - Associated with local reactions
  - Associated with allergy to birch and birch related tree pollens
Role of Allergy Testing in Atopic Dermatitis

• Skin Testing Preferred
  – Can see positive reaction and can grade ST’s

• Immunocap Testing:
  – Unknown decision points
  – Do not run food allergy testing as a screening tool.
    • Many false positives and no “decision points”
Sample Case

Devin age 18 months with AD. No prior hx of anaphylactic reactions to foods

- Milk: Class III 3.2 kU/L
- Egg: Class IV 17.6 kU/L
- Soy: Class I 0.40 kU/L
- Peanut: Class III 4.2 kU/L
Atopic Dermatitis - Food Allergy

- 40-50% of patients with severe AD have food allergy as a major trigger
- Food allergy in 20-25% with less severe AD
- Egg allergy is most common, followed by milk, peanut, soy, wheat, and fish
- These 6 foods account for 80-90% of food sensitivities in AD
- 36% react to one food, 26% to 2 foods, 18% to 3 foods, 10% to 4 foods, 10% to 5 or more foods
Gastrointestinal Food Hypersensitivity

IgE-Mediated
Immediate GI hypersensitivity
Oral allergy syndrome
Allergic eosinophilic esophagitis
Allergic eosinophilic gastritis
Allergic eosino-gastroenteritis

Non-IgE-Mediated
Enterocolitis syndrome
Dietary protein proctitis
Celiac Disease
Role of Allergy Testing in EoE

- Skin Tests not specific enough
  - Skin tests are “suggestive” of sensitization
    - Positive results- Diet directed
  - Six foods-Implicated in EoE
    - Milk, Wheat, Soy, Egg, Nuts, Fish and Shellfish.
    - Six food Elimination Diet
  - Undefined role of ImmunoCAP in EoE no “decision points”
  - Atopic Patch Testing- Some clinical benefit in EoE
Figure 1

EoE: ≥15 eosinophils per HPF despite acid blockade

Aeroallergen Testing: PST
Food Testing: PST
consider APT

Institute Therapy

Elimination Diet
Empiric: 6 Food Elimination
Directed: PST, APT Based

Food Reintroduction

Histologic/EGD/Symptom Response
Histologic/EGD Failure

Topical Corticosteroids
Fluticasone BID

Budesonide + Sucralose/Maltodextrin QD/BID

Repeat EGD with Biopsy

Maintenance

Elemental Formula
Systemic corticosteroids
Biologics
Role of Allergy Testing - Asthma and Allergic Rhinitis

- Skin Prick Testing
  - Still the most useful tool for evaluation
  - Correlates to “Clinical Sensitivity”
  - Clinical challenges with Nasal and Bronchial provocation

- Immunocap Testing
  - Again no clinical “decision points”. Not correlating with clinical sensitivity
Common Asthma Intradermal Skin Testing Antigens

- Mold
- Dust mites
- Pollens
- Cockroach
- Animals
- Feathers
What is an allergist/immunologist?
An allergist/immunologist is a physician certified in either internal medicine or pediatrics, who has completed an additional two years of training in allergy and immunology at an accredited training program and passed the examination given by the American Board of Allergy and Immunology (ABAI).
The allergist/immunologist is uniquely trained in:
• Allergy testing (skin, in-vitro)
• History-allergy test correlation
• Bronchoprovocation testing (e.g. exercise, methacholine)
• Environmental control instructions
• Inhalant immunotherapy
• Immunomodulator therapy (e.g. anti-IgE, IVIG)
• Venom immunotherapy
• Food and drug challenges
• Drug desensitization
• Evaluation of immune competence
• Education (disease, medications, monitoring)
• Management of chronic or recurrent conditions where allergy is not always identified: rhinosinusitis, conjunctivitis, asthma, cough, urticaria/angioedema, eczema, anaphylaxis
Summary

• Depending on the diagnosis allergy testing results are variable
• Skin tests useful for evaluation of most allergic conditions.
• ImmunoCAP for foods has “decision points” but variable for other allergic conditions.
Questions ???