What's Better Skin Testing or RAST Testing: Interpreting IgE RAST Testing and Where Component RAST Testing Will Take Us

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Learning Objectives

- Review definition of IgE mediated allergies
- Review procedure for SPT
- Review IgE RAST procedure
- Discuss benefits and pitfalls of both methods of testing regarding food allergy
Disclosures

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Definitions

- Food allergies have gained considerable attention over recent years.
- IgE mediated food allergies are defined as an adverse health effect arising from a specific IgE mediated immune response that occurs reproducibly on exposure to a given food.
- This may be a possibly life-threatening condition that currently affects approximately 6–8% of children, and its incidence appears to be rising.
Introduction to testing

- The high incidence of food allergies in the pediatric population has increased the utilization of testing methods to evaluate the disease and diagnose potential at risk children.

- Two major testing methods have been available in the US:
  - Skin Prick Testing
  - Specific serum allergen testing

- Supervised oral food challenge remain the gold standard.
What is not appropriate

- As noted in many other resources we are focusing on allergic food allergy issues
- Inappropriate testing is as followed
  - IgG testing
  - Applied kinesiology
  - NAET testing
  - Electrodermal testing
  - Neutralization testing
  - Hair sampling analysis
  - Basophil/histamine release assays
Clinical question

- A parent arrives in your clinic with laboratories done by another physician stating that “My child has airborne and deadly allergies to peanuts.”
- The ImmunoCAP level is >100 ku/L
- The child has never eaten a peanut
- The child has severe head to toe atopic dermatitis
- Also the child’s total IgE level is 14,000 iu/L
10 minutes later

- While your medical assistant is getting the EMR to work, your second patient arrives.
- The parent states that the child just was in the ER for an anaphylactic reaction to peanuts and received epinephrine x 3. They are here for follow up.
- The ER doc obtained ImmunoCAP levels to peanut which was 0.37ku/L.
The last clinic patient

- Your last patient of the day arrives with testing results from their new allergist.
- The family tells you that the child is “Allergic to everything including all foods, yeast, molds, and gluten”.
- They show you the results which shows small 3mm wheals in the testing area but also reactivity to the negative control.
- You also notice and recall this child had a funny birthmark on your last exam.
This birthmark
Clinical Pearl

- IgE mediated food allergy to wheat can be a real entity, but “gluten allergy” is not what it seems.
- Other grains such as barley, oat, and rice can also trigger IgE mediated reactions.
- Amaranth and other ancient grains contain similar allergenic proteins as wheat.
- Many gluten-free foods often use pea or chickpea protein as substitute which can be problematic for peanut or legume allergic children.
- Wheat can be a common trigger food for EoE or gluten can be a trigger food for IgA gluten enteropathy or other intolerances.
What is this rash?
The most important test

- HISTORY
- HISTORY
- HISTORY

Both methods detect food-specific IgE antibodies, but having these antibodies does not necessarily indicate an associated clinical allergy.

- Individuals may be sensitized to the allergen (positive test) but may be able to tolerate ingestion of the food.

- Approximately 8% of the US population tests positive to peanut, but clearly the vast majority of these individuals tolerate this food. (Best estimates 0.5-1% have allergy)
SPT

- SPT is a procedure in which any of a variety of devices is used to prick or scratch the surface of the skin (percutaneous test), allowing food protein (commercial extract or a fresh form) to activate skin mast cells.

- This results in a wheal-and-flare response that can be measured within a few minutes.

- Typically intradermal testing is limited to very specific situations.

- A negative SPT is quite helpful in ruling out food allergy as it has >90% negative predictive value for many allergens.
What can go wrong?

- Test reagent quality
  - commercial extracts are prepared from raw peanut
  - home-made or fresh reagents for prick-prick testing
- Test device
- Pressure applied
- Timing when read
- Location of placement
  - upper back results in larger responses than volar aspect of the arm
- Patient factors
- Methods of measuring results
Reference SPT
PPV of SPT

- There is a general principle that a larger skin test is more likely to be correlated with clinical allergy.

- Sporik et al. found that an egg SPT >7 mm and peanut or milk SPT >8 mm had a 100% PPV.

- Hill et al. found these same SPT cutoff values in children >2 years old while those younger than 2 years old had 100% PPV cutoff of milk at 6 mm, egg at 5 mm, and peanut at 4 mm.
SPT predicts anaphylaxis

- Several older studies have noted that SPT still is a sensitive marker and may predict anaphylaxis
- SPT wheals that are >18mm are generally good indicators that an individual may experience an anaphylactic reaction to food allergy exposure
- At the same time, residual local mast cells can continue to react years after a food may be tolerated
- Rarely, SPT can trigger clinical reactions
Types of RAST

- There are three major assay systems for serum allergy IgE testing:
  - Phadia ImmunoCAP
  - Agilent Turbo-MP
  - Siemens Immulite 2000.
- The results from the three systems are not interchangeable.
Higher levels of food specific IgE correlate with increased risk of reaction to the foods, and decreases in food specific IgE are correlated with an increasing chance of tolerance or resolution of food allergy.

In a systematic review and meta-analysis, food specific IgE levels were found to be sensitive but not very specific in diagnosing IgE-mediated food allergy.
Interpreting RAST

- Limited studies suggest that among specific populations the chance of true allergy may be diagnosed by particular high ‘cutoff’ values.
- These highly diagnostic cutoffs (>95% PPV) have only been established for some of the more common food allergens ie milk, egg, nuts
- Additionally, the levels of food specific IgE do not reliably predict the severity of reaction or threshold that would trigger a reaction.
The famous graph
Mistakes in RAST

- Detection of food-specific IgE in individuals without clinical allergy upon ingestion of the food is more prevalent for fruits, vegetables, cereals, and nuts compared to animal-derived foods such as milk and egg.

- This is partially due to homologous proteins found both in plant-derived foods and pollens.

- Total IgE levels can also exacerbate findings.
Cross reactivity

- Homologous proteins among foods are another important pitfall of IgE testing.

- For example, peanut is a legume and >50% of individual with peanut allergy will have positive tests to other legumes including soy, pea, and others, and yet only about 5% with peanut allergy are clinically reactive to other beans.

- Persons with birch pollen allergy will generally test positive to hazelnut because birch-homologous proteins are present in the test; yet, if the sensitization is solely to the birch-related protein, clinical allergy is less likely.
## Peanut and Hazelnut Components

<table>
<thead>
<tr>
<th>Food</th>
<th>Allergen</th>
<th>Common name</th>
<th>Heat Stability</th>
<th>Clinical implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h1</td>
<td>Vicilin</td>
<td>Stable</td>
<td>Anaphylaxis</td>
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<tr>
<td></td>
<td>Ara h2</td>
<td>Conglutin</td>
<td>Stable</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Ara h3</td>
<td>Glycinin</td>
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<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Ara h6</td>
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<tr>
<td></td>
<td>Ara h8</td>
<td>Bet v 1 like</td>
<td>Unstable</td>
<td>Oral Allergy</td>
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<tr>
<td></td>
<td>Ara h9</td>
<td>NS lipid tran</td>
<td>Stable</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 1</td>
<td>Bet v1 like</td>
<td>Unstable</td>
<td>Local reactions</td>
</tr>
<tr>
<td></td>
<td>Cor a 8</td>
<td>Lipid trans protein</td>
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<td>Local and systemic rxn</td>
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<tr>
<td></td>
<td>Cor a 9</td>
<td>11s globulin</td>
<td>Stable</td>
<td>Systemic rxn</td>
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<tr>
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<td>Cor a 14</td>
<td>2s albumin</td>
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## Egg and Milk Components

<table>
<thead>
<tr>
<th>Food</th>
<th>Allergen</th>
<th>Common name</th>
<th>Heat stability</th>
<th>Clinical implication</th>
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<tbody>
<tr>
<td>Milk</td>
<td>Bos d 8</td>
<td>Casein</td>
<td>Stable</td>
<td>Major allergen in baked tolerance</td>
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<tr>
<td></td>
<td>Bos d 4</td>
<td>Alpha-lactoglobulin</td>
<td>Unstable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bos d 5</td>
<td>Beta-lactoglobulin</td>
<td>Unstable</td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>Gal d 1</td>
<td>Ovomucoid</td>
<td>Stable</td>
<td>Major allergen in baked tolerance</td>
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<tr>
<td></td>
<td>Gal d 2</td>
<td>Ovalbumin</td>
<td>Unstable</td>
<td>Most prominent egg white</td>
</tr>
<tr>
<td></td>
<td>Gal d 5</td>
<td>Alpha Livectin or chicken serum albumin</td>
<td>Unstable</td>
<td>Bird-egg syndrome</td>
</tr>
</tbody>
</table>
RAST Component Testing

- While standard food specific IgE levels test against all food proteins that are extracted in test production, component resolved diagnostics test against specified allergenic proteins from the food.

- This utilizes purified or recombinant allergens, which can identify the specific molecules to which patients are sensitized.

- Recombinant allergens are best utilized either when there is one primary isoform of the protein indicated in triggering the allergy or if the allergen is easily degraded in the extraction process.
A conceptual view

- **Primary proteins**: High risk for severe reaction
- **Cross-reactive proteins**: Low to moderate risk for severe reaction

**Legend**:
- :Birch pollen allergen
- :Ara h 8
- :Ara h 1, h 2, and h 3
- :Ara h 9
- :Peach allergen
Peanut testing

- The most commonly available component test in the US is for peanut, egg, and milk
- Several companies now provide access to this testing
- Some insurance companies do not yet cover component testing
- Over time, the hope is other components are available
Baked milk or egg?

- Component testing, specifically for baked egg products focuses on proteins such as ovomucoid which is the heat tolerate protein that can withstand baking or cooking.

- Utilizing this assay can assist in appropriate timing of introduction of baked egg containing goods.
Conclusions

- Although testing methods have improved over the past decade, there remains large gaps between testing methods and the gold standard of observed oral challenges.

- With new feeding guidelines and need for identification of high risk infants for food allergies, primary care providers need to be aware of testing limitations and advantages.

Niti Y. Chokshi & Scott H. Sicherer (2016) Interpreting IgE sensitization tests in food allergy, Expert Review of Clinical Immunology, 12:4, 389-403,
Some things to consider

- As a result of attending my lecture at the 2017 Practical Pediatrics CME course, I encourage you to make the following change in your practice:
  - There is no perfect test for determining food allergies
  - Observed oral challenges remain the gold standard
  - Understanding basic limitations of SPT and RAST testing can help clinicians triage high risk infants