Evolving Paradigms: Food Allergy Treatment Options

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Disclosures

- Social Media Medical Editor – American Academy of Allergy, Asthma and Immunology
- Consultant – Before Brands, Kaleo, Novartis
- Associate Editor – Annals of Allergy, Asthma and Immunology
- Honoraria – ACAAI, AAP, AAAAI
- Non-financial:
  - Member – Joint Task Force on Practice Parameters for Allergy and Immunology
  - Member – Board of Regents, American College of Allergy, Asthma and Immunology
Objectives

• Prevent misdiagnosis of food allergy through proper use and interpretation of testing
• Discuss risks, benefits and expected outcomes associated with food allergen oral immunotherapy
Initial Thoughts…

• Food allergies are grossly over diagnosed and misdiagnosed
• Many families do not receive proper education to help them navigate risk
• While food allergies CAN be serious and life-threatening, they are also manageable
• A culture of FEAR has been created surrounding food allergies
A Growing Epidemic

PREVALENCE OF FOOD ALLERGY IN THE UNITED STATES*

5-8% of US children have a food allergy

- All races and income groups are affected

*Children <18 years of age; N=3339.
Definitions

- **Allergy**: An immunologic response to an allergen that results in reproducible symptoms with every exposure.
- **Intolerance**: A non-immunologic response to a substance (food) that causes gastrointestinal symptoms with exposure.
- **Sensitivity**: No agreed upon definition. Not an immune response. Often applied to a variety of symptoms without evidence to support use.
Risk Factors for Development of Food Allergy

- Eczema
- Asthma
- Environmental allergies
- Family history of allergies
Food Allergy Mad Libs

A _______ month/year old boy was eating ________ and within ________ minutes/hours, developed ________
IgE Mediated Food Allergy: The History IS the Test

- Reactions are objective, rapid onset and reproducible with every exposure to the offending food, no matter what form

- Typical symptoms:
  - Hives
  - Swelling
  - Vomiting
  - Runny nose/congestion
  - Wheezing
  - Hypotension
  - Anaphylaxis

![Top 8 Food Allergens]
- Fish
- Dairy
- Tree Nuts
- Soy
- Peanuts
- Shellfish
- Wheat
- Eggs
What Do You Want to Do Now?

- Strict avoidance of that food and all similar foods
- Order a food allergy panel
- Refer to an allergist
<table>
<thead>
<tr>
<th>ALLERGEN(S) INTERP.</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLERGEN: CAT DAND...</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: COCKROAC...</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: DOG DAND...</td>
<td>1.34</td>
</tr>
<tr>
<td>ALLERGEN: MITE FAR...</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: MITE PTE...</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: ALMONDS IGE</td>
<td>0.22</td>
</tr>
<tr>
<td>ALLERGEN: APPLE IGE</td>
<td></td>
</tr>
<tr>
<td>ALLERGEN: BANANA IGE</td>
<td>2.62</td>
</tr>
<tr>
<td>ALLERGEN: CASHEWS IGE</td>
<td>0.17</td>
</tr>
<tr>
<td>ALLERGEN: COD IGE</td>
<td>0.48</td>
</tr>
<tr>
<td>ALLERGEN: CRAB IGE</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: EGG WHIT...</td>
<td>4.97</td>
</tr>
<tr>
<td>ALLERGEN: LOBSTER IGE</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: MILK (CO...</td>
<td>1.06</td>
</tr>
<tr>
<td>ALLERGEN: PEANUT IGE</td>
<td>0.48</td>
</tr>
<tr>
<td>ALLERGEN: PECAN NU...</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: PISTACHI...</td>
<td>0.19</td>
</tr>
<tr>
<td>ALLERGEN: SALMON IGE</td>
<td>0.27</td>
</tr>
<tr>
<td>ALLERGEN: SCALLOP IGE</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: SHRIMP IGE</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>ALLERGEN: TUNA IGE</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Sensitization ≠ Allergy

- Sensitization
  - The detection of specific IgE toward an allergen through skin prick, intradermal, or serum specific IgE testing

- IgE mediated hypersensitivity
  - Characteristic clinical symptoms upon exposure to an allergen AND...
  - The detection of specific IgE toward that allergen
Diagnostic Testing

- Skin prick testing
  - Detects presence of specific IgE bound to cutaneous mast cells
  - Introduce small amount of allergen percutaneously – wheal/flare in 15 minutes
    - High negative predictive value
    - Low positive predictive value ~50%
Serum Specific IgE Testing

- Levels of IgE specific for food and/or inhalant allergens can be obtained through routine venipuncture
- Test offers convenience
- Commercial panels widely available and marketed as excellent screening tools

- Results reported in a range from 0.1 kU/L – 100 kU/L
  - Also reported as arbitrary classes (1 through 5)

- A big “!” will accompany any value reported > 0.10 kU/L
Pearls of Wisdom

• Both skin and blood testing have high **FALSE POSITIVE** rates
  • Many people without allergy will have positive tests
  • The best test is what happens upon exposure
  • Neither test tells us severity of reaction
  • “Shotgun” testing, or testing of patients without symptoms is not recommended for ANY reason
# Specific IgE Cutoff Points

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Decision Point (kU/L)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>98</td>
<td>38</td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>100</td>
<td>36</td>
</tr>
<tr>
<td>Fish</td>
<td>3</td>
<td>56</td>
<td>93</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
<td>87</td>
</tr>
</tbody>
</table>

## Cross-Reactivity: Clinical vs Testing

<table>
<thead>
<tr>
<th>Foods</th>
<th>Clinical Reactions</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut + Tree nuts</td>
<td>Low/none</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tree nuts + Other tree nuts</td>
<td>Pecan + walnut Cashew + pistachio</td>
<td>High</td>
</tr>
<tr>
<td>Fish + Shellfish</td>
<td>Low/none</td>
<td>Low/none</td>
</tr>
<tr>
<td>Fish + Other fish</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Shellfish + Other shellfish</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Peanut + soy</td>
<td>Low/none</td>
<td>High</td>
</tr>
<tr>
<td>Wheat + grains</td>
<td>Low/none</td>
<td>High</td>
</tr>
<tr>
<td>Cow’s milk + goat/sheep’s milk</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

## Aeroallergen Cross Reactivity

<table>
<thead>
<tr>
<th>Aeroallergen</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dust mite</td>
<td>Shellfish</td>
</tr>
<tr>
<td>Cockroach</td>
<td></td>
</tr>
<tr>
<td>Birch tree pollen</td>
<td>Peanut</td>
</tr>
<tr>
<td></td>
<td>Fruits</td>
</tr>
<tr>
<td></td>
<td>Soy</td>
</tr>
<tr>
<td>Grass pollen</td>
<td>Wheat</td>
</tr>
<tr>
<td>Tree pollen</td>
<td>Tree nuts</td>
</tr>
</tbody>
</table>

Peanut/Tree Nut Component Testing

- Predictive capabilities vary according to population background

<table>
<thead>
<tr>
<th>Nut</th>
<th>Antigens Associated with Clinical Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 1, 2, 3</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 9, Cor a 14</td>
</tr>
<tr>
<td>Cashew</td>
<td>Ana o 3</td>
</tr>
<tr>
<td>Walnut</td>
<td>Jug r 1</td>
</tr>
<tr>
<td>Pecan</td>
<td>Car I 1, Car I 2</td>
</tr>
<tr>
<td>Pistachio</td>
<td>Pis v 1, Pis v 2</td>
</tr>
</tbody>
</table>

The good physician treats the disease; the great physician treats the patient who has the disease.

~ William Osler
“Treat the patient, not the numbers”
An Ideal Food Allergy Test

Noninvasive
- Readily available
- Easy to use and interpret

Reliable
- High positive predictive value
- Low false positives

Clinically relevant
- Threshold dose
- Severity of reaction
Current Food Allergy Tests

Noninvasive
• Readily available
• Easy to use and interpret

Reliable
• LOW positive predictive value
• HIGH false positives

Clinically relevant
• Threshold dose
• Severity of reaction
Oral Food Challenges

Gold standard

Threshold
Severity
Clarification

Time consuming
Requires expertise
Potential for reactions

Benefits of Unsuccessful Challenge

- Quality of life improves after a challenge

Benefits of a Successful Challenge

• Life altering
• Improved quality of life
Non-IgE Mediated Food Allergy: Mostly Gastrointestinal

- Food protein induced enterocolitis syndrome
- Food protein induced allergic proctocolitis
- Food protein induced enteropathy
- Celiac disease
- Eosinophilic esophagitis
- Cow’s milk allergy induced iron deficiency anemia
Food Intolerance

- Difficulty with digestion
- Can be temporary or chronic
- Lactose intolerance
- FODMAPs

https://www.yogurtnutrition.com/lactose-intolerance-diagnostic/

https://www.wellworks.co.nz/author/ray/
Food Sensitivity

• There is no consensus definition of how to diagnose ‘food sensitivity’
• Symptoms of other conditions have been extrapolated (without evidence) to fit under the umbrella of ‘food sensitivity’
• This term has been used in numerous ways to support:
  • Unvalidated testing
  • Marketing
  • Products or services
Clinical Commentary Review

Unproven Diagnostic Tests for Adverse Reactions to Foods

John M. Kelso, MD  San Diego, Calif

Patients often seek opinions from allergists regarding unconventional testing for adverse reactions to foods. These tests include flow cytometry to measure the change in white blood cell volumes after incubation with foods, measurement of serum IgG or IgG₄ antibodies directed against foods, intradermal provocation-neutralization with food allergens, hair analysis, electrodermal testing, and applied kinesiology. In some cases, although the laboratory methods may be valid, there are no studies showing correlation with disease. In other cases, blinded, controlled studies have shown a lack of reproducibility and a lack of correlation with disease. Most of the tests lack biologic plausibility. By understanding the methodology of these tests and the lack of evidence supporting their utility, allergists can provide knowledgeable, evidence-based information to patients who inquire about them.

Kelso J. JACI:IP. 2018;6(2):362-365
What We Know About Food Allergy

- Education is lacking
- Self-management is hard to learn
- Accidental ingestion occurs
- Misdiagnosis is rampant
- Leading cause of ED visits for anaphylaxis
- Major life altering diagnosis
- Disparities exist

What We ALSO Know About Food Allergy

- Most people learn self management
- Can attend school, extracurricular activities
- Risk for severe reaction is low from trace amounts
- Can build confidence & skills
- Fatalities are very rare
- Airborne reactions are very rare
- Travel is safe
Successful Food Allergy Management

Communication
• Caregivers
• School personnel
• Peers
• Coaches
• Food handlers

Preparation
• Immediate access to epinephrine
• Address misconceptions surrounding epinephrine use

Education
• How to read food labels
• Signs/symptoms of anaphylaxis
• How to handle difficult situations

Addressing fears
Anyone Who Feels They Are Qualified to Diagnose Food Allergy Needs To:

- Avoid overdiagnosis
- Teach mitigation strategies
- Address risk
- Anticipate anxiety
- Provide ongoing support

Risk and Food Allergy

More Risk
- Lack of communication
- Not having epinephrine
- Accidental ingestion

Less Risk
- Trace amounts
- Casual exposure
Understanding Risk

Annual incidence of fatal anaphylaxis in an unselected population

- Fatal venom anaphylaxis
- Fatal drug anaphylaxis
- Fatal food anaphylaxis

Important Questions

• Do all foods pose the same risk for causing ANY reaction from ingestion of trace amounts?
• How often does ingestion of trace amounts cause severe allergic reactions?
• Does each individual with a certain food allergy carry the same risk for...
  • ANY reaction?
  • SEVERE reaction?
Controversies in Allergy

Managing Food Allergy When the Patient Is Not Highly Allergic

Scott H. Sicherer, MD, Elissa M. Abrams, MD, Anna Nowak-Wegrzyn, MD, PhD, and Jonathan O’B. Hourihane, FRCPI

New York, NY; Winnipeg, MB, Canada; Vancouver, BC, Canada; Olsztyn, Poland; and Dublin, Ireland
PATS – One 1.5 mg Dose To Find the Outliers

- 378 children with peanut allergy
  - (~50% ignore PAL)
- All in – one dose...what happens?

<table>
<thead>
<tr>
<th>% of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reaction</td>
</tr>
<tr>
<td>Subjective</td>
</tr>
<tr>
<td>Mild transient symptoms</td>
</tr>
<tr>
<td>Objective - likely related</td>
</tr>
</tbody>
</table>

Eliciting Dose for 50% of the population with each food allergy
May contain traces of ___ may be present due to methods used in manufacturing, this product occasionally contains ___

May Contain

Packed in an environment where ___ may be present.

Processed in the same facility

Not suitable for ___ allergy sufferers

Good manufacturing practices used to segregate ingredients in a facility that also processes allergens.
ALLERGEN STATEMENT

All products are produced in a facility which handles Wheat, Soy, Milk, Eggs, Peanuts and Tree Nuts.

Please eat your cookies, brownies or cake slices within 3-4 days or freeze them to enjoy later. They will stay delicious for up to 6 months!
Treatment

• Parents ask about something they read on Facebook…or heard from a neighbor…or saw a news story about
• What do you tell them about food allergy treatment?

☐ There is no treatment available
☐ Treatment allows children to eat their allergen
☐ Food allergies can be cured if treatment is started early
Evolution of Food Allergy Treatment
Desensitization Principles

Diagram showing the transition from allergy to tolerance through a desensitization food challenge process. The process includes:

- **Build-up phase**
  - Initial modified dose escalation
  - Weekly/bi-weekly dose escalation

- **Maintenance phase**

The diagram illustrates the dosing stages and phases, highlighting the progression towards tolerance.
**Allergic**

When the body’s immune system mistakenly responds to certain foods that it thinks are harmful.

**Desensitized**

An increase in reaction threshold to a food allergen while receiving months of continued, active therapy that may equal protection from accidental ingestion.

**Sustained Unresponsiveness**

After several years of therapy, a lack of clinical reaction to a food allergen after active therapy has been discontinued for a period of time. Has been seen in only subsets of treated subjects. Requires some level of continued allergen exposure.

**Tolerance**

A complete lack of clinical reactivity to an ingested food allergen, not depending on continued food allergen exposure.
Realistic Expectations

- No daily ingestion & still tolerate serving size
- Daily ingestion = serving size
- Daily ingestion > baseline & trace amounts

Some maintain tolerance after prolonged avoidance
Many achieve complete desensitization
Most achieve protective desensitization

<table>
<thead>
<tr>
<th>Food</th>
<th>Peanut Percentage</th>
<th>Egg Percentage</th>
<th>Milk Percentage</th>
<th>Wheat Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>73-90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td></td>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sesame</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazelnut</td>
<td>65%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sesame</td>
<td></td>
<td></td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td>Peanut</td>
<td>13-74%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>35-44%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>13%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Daily ingestion > baseline & trace amounts
Daily ingestion = serving size
No daily ingestion & still tolerate serving size

Realistic Risks

- Some need to discontinue
- Some have anaphylaxis
- Almost all have mild allergic reactions

Peanut: 13%
Egg: 18%
Wheat: 43%

16-17% vs 1.6-2.6% controls
Modifiable and Non-modifiable Risks of OIT

- **Patient**
  - Demographics: e.g. age, gender, pubertal stage
  - Allergy Characteristics: e.g. IgE profile
  - Atopic Comorbidity: e.g. allergic rhinitis, asthma
  - Host behaviours: e.g. patient compliance

- **Protocol**
  - Product Characteristics: e.g. heat modified vs raw allergen, food matrix
  - Dosing Characteristics: e.g. rush protocol vs extended updosing phase
  - Eligibility Criteria which may exclude higher risk patients

- **Cofactors**
  - Immune stimulation e.g. intercurrent infection
  - Environmental: e.g. pollen exposure
  - Exercise
  - Altered gut absorption

*Curr Treat Options Allergy 6, 164–174 (2019).*
AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators*
Up-Dosing Phase ~6 Months

Each Up-Dose Is Conducted at the Allergist’s Office at ~2 week intervals

Initial Escalation

- 0.5 mg
- 3 mg
- 6 mg
- 12 mg
- 20 mg
- 40 mg
- 80 mg
- 120 mg
- 160 mg
- 200 mg
- 240 mg
- 300 mg

Ongoing Maintenance

300 mg Sachets for At-Home Daily Maintenance Dosing

CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy

Entry Oral Food Challenges

• Misconceptions about safety/risk
• Can demonstrate symptoms with ingestion
• Can establish an idea of threshold dose
• Can remove fear of the unknown
• Can avoid unnecessary OIT in someone not allergic
• Can provide valuable information to influence medical decision making
Shared Decision Making

WE discuss evidence, options, risks

+ PATIENTS discuss preferences & values

+ WE help PATIENTS make decisions based upon “what matters most”
Help Families Prepare for Their OIT Journey

- Initial anxiety surrounding purposeful ingestion of known allergen
- Expected reactions and how to manage
  - Distinguish between OIT related symptoms vs anxiety vs comorbid conditions
- Time commitment
  - Up-dosing in office visits
  - Daily regimen at home
  - Scales, measurement of doses
FDA NEWS RELEASE

FDA approves first drug for treatment of peanut allergy for children

For Immediate Release: January 31, 2020

Palförzia
Peanut (Arachis hypogaea) Allergen Powder-dnfp
## Palforzia Protocol

**Table 1: Dosing Configuration for Initial Dose Escalation (Single Day Dose Escalation)**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Total Dose</th>
<th>Dose Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5 mg</td>
<td>One 0.5 mg capsule</td>
</tr>
<tr>
<td>B</td>
<td>1 mg</td>
<td>One 1 mg capsule</td>
</tr>
<tr>
<td>C</td>
<td>1.5 mg</td>
<td>One 0.5 mg capsule; One 1 mg capsule</td>
</tr>
<tr>
<td>D</td>
<td>3 mg</td>
<td>Three 1 mg capsules</td>
</tr>
<tr>
<td>E</td>
<td>6 mg</td>
<td>Six 1 mg capsules</td>
</tr>
</tbody>
</table>

Initial Dose Escalation supplied as a single card consisting of 5 blisters containing a total of 13 capsules.
## Palforziazia Protocol

### Table 2: Daily Dosing Configuration for Up-Dosing

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Total Daily Dose</th>
<th>Daily Dose Configuration</th>
<th>Dose Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 mg</td>
<td>Three 1 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6 mg</td>
<td>Six 1 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>12 mg</td>
<td>Two 1 mg capsules; One 10 mg capsule</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>20 mg</td>
<td>One 20 mg capsule</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>40 mg</td>
<td>Two 20 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>80 mg</td>
<td>Four 20 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>120 mg</td>
<td>One 20 mg capsule; One 100 mg capsule</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>160 mg</td>
<td>Three 20 mg capsules; One 100 mg capsule</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>200 mg</td>
<td>Two 100 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>240 mg</td>
<td>Two 20 mg capsules; Two 100 mg capsules</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>300 mg</td>
<td>One 300 mg sachet</td>
<td>2</td>
</tr>
</tbody>
</table>
Should We Start OIT in Infants?

- **Vickery et al**
  - 37 children 9-36 months to peanut maintenance 300 or 3000 mg/day
  - 81% desensitized to 5000 mg
  - 4 weeks sustained unresponsiveness after 29 months: 78% overall; no difference in daily maintenance

- **Martorell et al**
  - 60 children 24-36 months milk
  - After 12 months: 90% tolerated 200 mL vs 23% controls

- **Soller et al**
  - 270 children 0.75-5.9 yrs (median 1.9) peanut OIT; 90% reached 300-320 mg daily dose
  - 78% passed 4000 mg OFC at one year

Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study


Lancet 2022; 399: 359–71
12-24 months = 71%
24-36 months = 35%
36-48 months = 19%
Future (Soon?) Approaches

- Sublingual immunotherapy
- Epicutaneous immunotherapy (patch)
- Biologics
Conclusion

• Accurate diagnosis of food allergy requires careful consideration of the clinical history and knowledge of food allergy reactions
• Food allergy tests are misleading and must be interpreted in the proper context
• We need to help patients understand risk to guide their decisions for self-management