FOOD ALLERGY UPDATES

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Disclosures

- **Speakers Bureau**
  - AstraZeneca
  - Sanofi Genzyme & Regeneron

- **Advisory Boards**
  - AstraZeneca
  - Genentech
  - Whole & Free Foods, Inc.
  - Food Allergy & Anaphylaxis Connection Team (FAACT)
Objectives

1. Recognize how to appropriately diagnose and evaluate patients with food allergies.
2. Distinguish the benefits and limitations of food allergy testing.
3. Determine which patients referred to them for diagnosis of food allergy require an oral challenge to confirm or refute the same.
4. Summarize the various therapies currently available for food immunotherapy.
Impact of food allergy diagnosis

- Risk of anaphylaxis just one of many concerns

- Financial Burden
  - Annual U.S. Direct Medical Costs: $24.8 billion overall; $4,184 per child
  - Clinician visits, ER visits, hospitalizations
  - Specialty foods and diets
  - Lost productivity due to time off work

- Nutritional Deficiencies
  - Broad panel food testing leads to unnecessary avoidance of multiple foods
  - Poor weight gain and/or poor food choices due to limited options

- Sibling Effect
  - Entire family often practices avoidance even if they don’t have a food allergy
Impact of food allergy diagnosis

- Quality of life
- Social & Psychological Consequences
  - Creating a safe environment for food allergic children can be isolating
    - avoiding sleep-overs and birthday parties
    - avoiding airplanes and sporting events
  - Hypervigilance can instill excessive amounts of anxiety and fear
    - Often spills over into other areas of life
  - Validated QOL surveys before & after OFCs show significant change
    - Irrespective of the outcome (for both child and parents)
Back to Basics

- Oral immunotherapy (OIT) is the culmination of a comprehensive, thoughtful, and time-intensive evaluation with collaborative input from the patient and/or parents.

- Choosing appropriate candidates for OIT is more complicated than it may seem.

- First step is performing a proper evaluation with detailed food allergy history and select testing based on clinical reactivity.
Evaluation

- History and physical examination
  - *clinical history is critical* in the diagnosis of food allergy
  - *used to determine subsequent testing and interpretation of results*
- Prick/puncture skin testing
- In vitro testing
- Elimination diets
- Oral food challenges (OFC)
Testing advantages & pitfalls

- Patient-specific factors can modulate the probability of clinical allergy of a given sIgE result
- Component testing can improve the accuracy of food allergy diagnosis
  - Particularly for peanut allergy where Ara h2 is a strong predictor of disease
  - High IgE levels to Gal d1 (ovomucoid) and Bos d8 (casein)
  - Associated with more persistent allergy
  - Increased reactivity to both heated and concentrated forms of egg and milk

Important point:
validated cutoffs are reliable when applied to a similar patient population to the one where they were developed

Testing advantages and pitfalls

- SPT to foods has high NPV but overall PPV of only ~50%
- Many patients come to office with positive testing but no h/o reaction
  - *i.e. broad panel food testing in moderate-severe eczema or chronic urticaria*

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
<th>Laboratory Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IgE</td>
<td>3873 IU/mL</td>
<td>Hazelnut</td>
<td>10.2 kU/L</td>
</tr>
<tr>
<td>Egg white</td>
<td>45.3 kU/L</td>
<td>Cashew</td>
<td>14.9 kU/L</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>35.9 kU/L</td>
<td>Pistachio</td>
<td>12 kU/L</td>
</tr>
<tr>
<td>Peanut</td>
<td>14.3 kU/L</td>
<td>Walnut</td>
<td>10.8 kU/L</td>
</tr>
<tr>
<td>Almond</td>
<td>6.6 kU/L</td>
<td>Pecan</td>
<td>12.5 kU/L</td>
</tr>
</tbody>
</table>

Testing methods

- Larger SPT wheal size (>8mm) or higher food-sIgE levels are associated with persistent food allergy
  - SPT and sIgE appear sensitive although not specific for diagnosing FA
- Rate of change can help predict likelihood that food allergy has resolved
- Testing methods being investigated for diagnosis, monitoring for tolerance:
  - IgE epitope specificity
  - Component-resolved diagnostics
  - IgE/IgG4 ratio
  - Cellular-based assays
  - Basophil activation test
  - Specific IgA and IgA2 levels

Identify biomarkers that can predict therapeutic outcomes and monitor treatment responses in OIT

- OFCs are laborious and not without risk: more accurately diagnose food allergies, reduce the need for OFCs

- BAT proved to be superior to other diagnostic tests in discriminating between peanut allergy and tolerance, particularly in difficult cases, and reduced the need for OFCs
  - *Reduced number of required OFCs by 2/3*
  - *Useful in cases in which specialists could not accurately diagnose peanut allergy with SPT and sIgE to peanut and to Arah2*
  - *Using a 2-step diagnostic approach in which BAT was performed only after equivocal SPT or Arah2-sIgE, BAT had a major effect (97% reduction) on the number of OFCs required*

Sustained successful peanut OIT associated with low basophil activation and peanut-specific IgE

- Clinical tolerance diminishes over time on discontinuation or low-dose maintenance
- OIT significantly decreases basophil activation, peanut sIgE, Ara h 1, Ara h 2, and Ara h 3 IgE levels, and sIgE/total IgE, but increases sIgG4/sIgE.
  - Participants who became reactive to 4 g of peanut 13 weeks off active OIT exhibited higher peanut-induced basophil activation ex vivo and higher peanut sIgE levels and sIgE/total IgE, but lower sIgG4/sIgE
  - Substantial suppression of basophil activation was required to maintain long-term clinical tolerance after peanut OIT
- These values can help to predict treatment outcomes; differentiate transient desensitization vs sustained unresponsiveness after OIT

OFCs: gold standard for diagnosing food allergy

- **Underutilized** in clinical practice
- Not prudent or necessary if patient has unequivocal, convincing history of clinical reactivity and positive specific IgE testing (SPT or serum sIgE)
- Patient’s history should take priority over laboratory findings

Results of specific IgE testing should not be interpreted as absolute indications or contraindications for conducting an OFC
Reasons to perform OFCs

- Identify food that caused the allergic reaction for the initial diagnosis
- Monitor for resolution of food allergy
- Assessing the status of tolerance to cross-reactive foods
  - Tree nuts in peanut allergy (35% will react to at least one TN)
  - Non-crustacean shellfish (mollusks) in crustacean shellfish allergy
- Relieve parental or patient anxiety
- Determine if patient is a candidate for oral immunotherapy (OIT)
Requires ingestion of meal-sized portion of tested food prepared in usual state

Some rely too heavily on results of SPT/serum sIgE when deciding which patients should undergo OFC

- Large proportion of patients have intermediate values
- Limited predictive power for which patients are likely to pass

Food allergy is still an art as much as a science

- Experience and clinical judgement matter!

Ultimately current testing modalities are inadequate
Guidelines to predict when OFC is unnecessary

- Sampson et al published 2 studies that proposed 90% and 95% PPVs for milk, egg, and peanut IgE levels and 50% to 75% PPVs for soy and wheat IgE levels.
  - Helps determine when sIgE level is so high that a challenge is unnecessary

<table>
<thead>
<tr>
<th></th>
<th>Egg</th>
<th>Milk</th>
<th>Peanut</th>
<th>Fish</th>
<th>Soy</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive if ≥ (no challenge necessary)</td>
<td>7</td>
<td>15</td>
<td>14</td>
<td>20</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Possibly reactive (physician challenge)</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Unlikely reactive if &lt; (home challenge)</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Need more accurate tests to predict the likelihood of passing an OFC

When will patients fail OFC...

**IgE levels associated with a 50% and 95% PPV for clinical allergy**

<table>
<thead>
<tr>
<th>Food allergen</th>
<th>50% positive predictive value</th>
<th>95% positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, if investigated</td>
<td>Specific IgE level (kUA/L)</td>
<td>Age, if investigated</td>
</tr>
<tr>
<td>Milk</td>
<td>2&lt;sup&gt;37&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Egg</td>
<td>2&lt;sup&gt;37&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Peanut</td>
<td>2&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Wheat</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Soy</td>
<td>&gt;1</td>
<td>20&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>—</td>
<td>20-30&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NA: Not available/applicable.

Specific IgE levels associated with a 50% positive predictive value and a 95% positive predictive value for clinical allergy. In general, we use the 50% positive predictive value to guide the timing of an oral food challenge to assess for resolution, but caution should always be exercised in considering when to perform a food challenge. See text for additional details.

*These are published values for uncooked milk and lightly cooked egg. Higher levels can be used when considering assessing for resolution to extensively heated milk and egg.

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**Table I: Examples of diagnostic cutoffs with 95% PPV and 50% NPV for specific IgE to food allergen extracts**

<table>
<thead>
<tr>
<th>Approximate predictive value</th>
<th>Cow’s milk</th>
<th>Egg</th>
<th>Peanut</th>
<th>Fish</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% PPV</td>
<td>32 kU/L</td>
<td>7 kU/L</td>
<td>15 kU/L</td>
<td>20 kU/L</td>
</tr>
<tr>
<td>50% NPV</td>
<td>2 kU/L</td>
<td>2 kU/L</td>
<td>2 kU/L&lt;sup&gt;*&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>NA</td>
<td>—</td>
<td>—</td>
<td>5 kU/L&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

NPV: Negative predictive value; PPV: positive predictive value.

- The 50% PPV cutoff is different depending on the previous history of reaction; 2 kU/L if the patient reports a reaction and <5 kU/L if the patient has never had an allergic reaction to peanut in the past.
# Factors affecting accuracy of testing

<table>
<thead>
<tr>
<th>Peanut challenges by specific IgE cutoff level (n=169)</th>
<th>&lt;0.35 kUA/L</th>
<th>0.36 - 2 kUA/L</th>
<th>2 – 4.9 kUA/L</th>
<th>&gt;5 kUA/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear history of previous reaction (n=110)</td>
<td>29/38 (76%) passed</td>
<td>17/38 (44%) passed</td>
<td>11/27 (40%) passed</td>
<td>0/7 (0%) passed</td>
</tr>
<tr>
<td>Unclear history or positive test response only (n=59)</td>
<td>15/17 (88%) passed</td>
<td>15/21 (71%) passed</td>
<td>4/12 (33%) passed</td>
<td>7/9 (77%) passed</td>
</tr>
</tbody>
</table>

Out of 173 peanut challenges, 59% passed
Median for those who passed 0.5 kUA/L
Median for those who failed 1.9 kUA/L

Guidelines to predict the likelihood of passing an OFC

- Perry et al. performed a retrospective chart review of 604 food challenges in 391 children

<table>
<thead>
<tr>
<th>Food</th>
<th>Cutoff sIgE level at which a 50% pass rate could be expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2 kUA/L</td>
</tr>
<tr>
<td>Egg</td>
<td>2 kUA/L</td>
</tr>
<tr>
<td>Peanut</td>
<td>2 kUA/L</td>
</tr>
<tr>
<td></td>
<td>5 kUA/L without a clear history of reaction</td>
</tr>
</tbody>
</table>

Data was less clear for wheat and soy

- Suggests 50% pass rate as the ideal circumstance for performing an OFC
  - *Data should be used to make individual decisions for each patient based on personal preferences and clinical history*

SCAMP is an attempt to improve sIgE and SPT thresholds for Food Challenges. Triage safely into either a low- or high-intensity care setting for OFC.
### Factors Modulating the Interpretation of Allergy Test Results

<table>
<thead>
<tr>
<th>Factors identified in the clinical history</th>
<th>Effect on the probability of clinical allergy for a given specific IgE level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported immediate allergic reaction to the specific food</td>
<td>A history of reacting to the tested food supports the clinical relevance of detected IgE.</td>
</tr>
<tr>
<td>(Younger) Age</td>
<td>Lower levels of allergen-specific IgE have increased clinical relevance in young children.</td>
</tr>
<tr>
<td>(Black) Ethnicity</td>
<td>Black race is associated with higher levels of allergen-specific IgE with decreased clinical relevance.</td>
</tr>
<tr>
<td>Atopic eczema</td>
<td>Polyclonal IgE response can be non-allergen-specific and thus decrease clinical relevance of a given specific IgE level.</td>
</tr>
<tr>
<td>Concomitant inhalant allergies</td>
<td>Pollen sensitization can cause false-positive results of specific IgE to plant food extracts.</td>
</tr>
<tr>
<td>Atopic population</td>
<td>Positive predictive value of a given specific IgE level increases with the increase in the prevalence of the disease in the population.</td>
</tr>
<tr>
<td>Geographical Location</td>
<td>Variable</td>
</tr>
</tbody>
</table>

These factors affect the pretest probability and therefore influence the resulting post-test probability.
<table>
<thead>
<tr>
<th>Factors</th>
<th>Effect on the decision to perform an OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of an allergic reaction</td>
<td>A previous history of a reaction to the specific food increases the chance of reacting during the OFC.</td>
</tr>
<tr>
<td>Recent exposure to the food</td>
<td>A recent allergic reaction or the consumption of age-appropriate amount of the food precludes the OFC.</td>
</tr>
<tr>
<td>(Low) specific IgE levels</td>
<td>Current low level of food-specific IgE and &gt;50% decline within the last year indicate lower likelihood of a positive OFC.</td>
</tr>
<tr>
<td>Importance of the food</td>
<td>The importance of the food to the child's diet and social life and her or his willingness to eat the food regularly in the case of a negative challenge favor performing an OFC.</td>
</tr>
<tr>
<td>Resources available</td>
<td>The resources available may limit the number of OFCs offered to patients.</td>
</tr>
<tr>
<td>Patient preferences</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Patient may wish to undergo an OFC or not and her or his preferences need to be taken into account.</td>
</tr>
</tbody>
</table>

The decision to perform an OFC is made when the probability of a systemic reaction is sufficient for there to be concern and low enough that the OFC is likely to be passed. The arrows indicate the effect on the decision to perform an OFC: the arrow pointing up means weighing pro and the arrow pointing down means weighing con performing an OFC.

AAAAl AFRC Workgroup Report: Oral food challenge practices among allergists in the United States

Justin Greiwe, John Oppenheimer, David Fleischer, J. Andrew Bird, Jacqueline Pongracic, & Matthew Greenhawt

- Distributed to both ACAAI and AAAAI members (~10% response rate)
- Based on food allergy survey published by Pongracic et al in 2012
- Updated to reflect recent advances in food allergy and knowledge gaps that were not addressed in previous survey, such as OFCs in infants
Highlights from Survey

- 92% feel there’s a need to perform OFC in clinical practice
- Open (non-blinded) challenges method of choice

Top 3 perceived barriers to performing OFCs

<table>
<thead>
<tr>
<th>2009</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of time</td>
<td>1. Lack of time</td>
</tr>
<tr>
<td>2. Reimbursement</td>
<td>2. Lack of staff</td>
</tr>
<tr>
<td>3. Risk of adverse events</td>
<td>3. Lack of office space</td>
</tr>
</tbody>
</table>

- 58% generally perform 1 to 5 OFCs per month
- 82% obtain written informed consent
Highlights from Survey: Training & Safety

- **Poor Fellowship Training:**
  - 56% of respondents performed <10 OFCs in their entire fellowship
  - **29% performed no OFC**
    - ACGME requirements: recent fellowship graduates expected to participate in minimum of 5 OFCs

- **Safety**
  - One known OFC related fatality in U.S. since description of modern OFC procedure was published in 1976
    - One fatality outside U.S. as part of an OIT entry challenge
  - **Top priority among allergists offering OFCs however...**
    - Only 60% reported having a standardized protocol for stopping challenges and treating reactions
    - Only 56% had emergency medicine ready and available

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Highlights from Survey: Infant OFCs

- 79% encourage caregivers of infants to incorporate peanut into diet
- 50% followed recommendations for skin testing high-risk infants
- 38% routinely perform in-office open feeding for high-risk infants for the purposes of early peanut introduction
  - 36% did not provide this resource at all
- 25% less willing to provide OFCs in the office after recent food challenge fatality
  - willingness inversely proportional to number of OFCs provided per month

As defined in the National Institutes of Allergy and Infectious Diseases addendum guidelines

Insights from Survey

- Since initial workgroup report 10 years ago some improvements in OFCs have been made
- Lack of training and experience continues to be a major issue
- **Hesitancy in challenging infants**
- Concern that obtaining written consent prior to OFC is not universal, especially with recent fatality
- More targeted efforts recommended
  - *Expanding OFC fellowship training opportunities observing higher risk challenges*
  - *Increase comfort among allergists performing challenges, especially in infants*
Coaching parents and children after failed challenge

- Use failed challenge as teaching point both during and after reaction
- Our responsibility as allergists to reduce anxiety and fear
- Instill healthy respect for foods without crippling parents and children
- Food allergy does not have to define the patient

Confidence not Fear

Empowerment not Despair
Coaching parents and children after passed challenge

- Advised to incorporate tested food into diet on a regular basis to maintain tolerance
  - failure to incorporate challenged food into diet regularly linked to recurrence of food allergy

- ~25%-30% of previously allergic patients continue a food avoidance diet despite negative challenge
  - peanut and TNs most common

- Reasons for not consuming food regularly
  - child disliking the food
  - fear of a reaction
  - food not being a routine part of the family’s diet

- Importance of post-challenge counseling and dietary guidance
  - address potential barriers to food introduction
  - should patients continue to carry their autoinjector at least a year after a negative OFC?

<table>
<thead>
<tr>
<th>Case Example</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year-old coming in for OIT evaluation</td>
<td></td>
</tr>
<tr>
<td>12-month-old with a history of moderate/severe atopic dermatitis here for interpretation of recent serum sIgE testing</td>
<td></td>
</tr>
<tr>
<td>3-year-old referred for multiple food allergies on a restricted diet</td>
<td></td>
</tr>
</tbody>
</table>
Patient: OIT evaluation

- Noone et al. performed retrospective review of challenges performed in higher risk group (highly atopic)
  - 1/3 had h/o anaphylaxis requiring epinephrine

- Reactions for screening OFCs tend to be more severe and require more aggressive treatment
  - Reactions that required epinephrine: **39.2%**

- Screening OFCs did **NOT** have higher rates of requiring multiple epinephrine doses or biphasic reactions

- Clinics should **NOT** offer OIT if hesitant to provide OFCs at any age

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Specific cutoffs in food-triggered AD are not known

Exacerbations of skin disease do in fact occur in relation to food ingestions
  - Occurrence not as prevalent as is often perceived by the community
  - Dietary elimination may put children at risk for developing an IgE-mediated food allergy

Be more aggressive about offering OFCs in patients with moderate to severe AD and elevated total IgE levels

Patient: Rare food allergy

- Occurrence of any reaction or anaphylaxis after OFCs to less commonly challenged foods is 18.8%
  - Much lower than reactions observed during OFCs to peanut, egg, milk, and wheat at CHOP: 45%
- Pass rate for rare foods in these studies is around 80% overall
  - 73% for grains
  - 94% for fruits and veg
- Strict/unproven food elimination diets lead to poor weight gain, malnutrition, picky eating
- Most common FAs have not changed in the last 3 decades

FOOD ALLERGY THERAPIES
As food allergy rates and awareness increase, demand for disease-modifying therapies has intensified.

Therapies Currently Being Studied

- Oral immunotherapy (OIT)
  - Private practice OIT
  - Palforzia (formally known as AR101)
  - OIT with anti-IgE (omalizumab)
- Subcutaneous immunotherapy
- Patch (epicutaneous) immunotherapy
- Sublingual immunotherapy
- Peanut vaccine
- Anti-IgE (omalizumab) solo treatment for multiple food allergies
- Food allergy herbal formula-2 (FAHF-2)
- Etokimab (anti–IL-33 biologic)
Subcutaneous Peanut Immunotherapy

- Initially attempted years ago in two separate studies, showed good efficacy (Oppenheimer et al. 1992, Nelson et al. 1997)

- Study terminated early due to fatal reaction following formulation error in pharmacy
  - accidental administration of maintenance dose of peanut to placebo-treated
  - lead to fatal anaphylaxis

- High rate of systemic reactions (13.3–39%) made this form of treatment unacceptable for routine use

Epicutaneous Peanut IT (Viaskin® Peanut)

- Based on epicutaneous immunotherapy, or EPIT®
  - *DBV’s method of delivering biologically active compounds to the immune system through intact skin*
  - *Ongoing clinical trials of Viaskin Peanut and Viaskin Milk*
    - preclinical development of Viaskin Egg
    - human proof-of-concept clinical study of Viaskin Milk for the treatment of EoE
- After 3 years, **83.3%** were able to tolerate more peanut protein
  - *compared to 53.6% after 1st year of trial*
Epicutaneous Peanut IT (Viaskin® Peanut)

- At study entry, median cumulative reactive dose was 44mg of peanut protein. After 3 years reactive dose increased to 1,440mg (~6 peanuts)
- Compliance was >95%, no serious adverse events reported (dropout rate 2.3%)
- Resubmitted a BLA for their Viaskin Peanut therapy in August 2019
  - submission addresses additional data needed on manufacturing procedures and quality controls
  - DBV voluntarily withdrew its prior BLA submission in Dec 2018
Peanut Sublingual IT

- Kim et al. evaluated 37/48 subjects who completed 3 to 5 years of peanut SLIT
- 67% (32/48) successfully consuming 750 mg or more during DBPCFCs
- 25% (12/48) passed the 5000-mg DBPCFC without clinical symptoms
  - 10 of these 12 demonstrating sustained unresponsiveness after 2 to 4 weeks
- Side effects reported with 4.8% of doses
  - transient oropharyngeal itch most common
- Extended-therapy peanut SLIT provided clinically meaningful desensitization in the majority of children
  - balanced with ease of administration and a favorable safety profile

Peanut Vaccine

■ Phase 1 trial of EMP-123
  - rectally administered vaccine containing modified Ara h1, Ara h2 and Ara h3 (heat/phenol-killed, Escherichia coli-encapsulated, recombinant modified peanut proteins)
  - vaccine failed to induce tolerance to dominant peanut proteins, 50% unable to complete
  - no significant changes were detected in peanut-specific IgE and IgG4
  - overall vaccine not efficacious or safe, frequent adverse reactions including severe allergic reactions in 20%

■ Aravax’s PVX108

■ HAL Allergy’s HAL-MPE1

Intradermal & Subcutaneous Immunotherapy Vaccines

- **Aravax’s PVX108**: Australian biotechnology company

- Positive Phase I data evaluating the safety and tolerability of PVX108 (peptide IT)
  - *peptides don’t activate the kinds of cells responsible for extreme reactions*

- May be a more specifically targeted form of therapy that moves beyond desensitization
  - *more convenient (does not have to be taken daily) and with potentially less risk*

- **HAL Allergy’s HAL-MPE1**: natural peanut allergen extract that has been chemically modified to limit allergenicity
  - *adsorbed to aluminium hydroxide to enhance the tolerogenic immune response*

Bindseil-Jensen, Carsten et al. SCIT-treatment With a Chemically Modified, Aluminum Hydroxide Adsorbed Peanut Extract (HAL-MPE1) Was Generally Safe And Well Tolerated And Showed Immunological Changes In Peanut Allergic Patients. Journal of Allergy and Clinical Immunology, Volume 139, Issue 2, AB191
Dampen the Immune Response

- Food immunotherapy can cause significant side effects leading to drop out
- One possible way to get patients to stay with program is to dampen immune system before getting dose of allergen
- Two options:
  - Anti-IgE monoclonal antibody: Omalizumab
    - approved for asthma and chronic urticaria
    - inhibits IgE which is typically elevated in people who have severe allergic reactions
  - Food Allergy Herbal Formula-2 (FAHF-2)
    - combines medicinal herbs: reduces allergies, inflammation, and GI problems
    - in clinical trials: thought to work on a similar principle as monoclonal antibody drugs
1. Omalizumab monotherapy

2. Omalizumab + OIT

- Given during up-dosing phase of single and multi-allergen OIT has been studied for milk and peanut
  - intended to reduce side effects and/or go faster

- Data from 7 studies evaluating safety and efficacy generally indicate improved safety and time to maintenance
  - no increase in efficacy compared with OIT alone

- Some preliminary evidence of efficacy using omalizumab as monotherapy

- Recently granted breakthrough therapy designation by FDA
  - with and without multi-food OIT in upcoming multicenter study

Food Allergy Herbal Formula-2 (FAHF-2)

- Traditional Chinese medicine (TCM) has been used to treat various diseases for thousands of years
- FAHF-2 is a 9-herb formula developed using TCM principles
- Efficacy for improving tolerance to food allergens has not been demonstrated
- Poor adherence given large number of capsules required
- Major advantage: therapy is nonspecific, could theoretically be used to treat individuals with multiple food allergies if efficacy can be demonstrated

**Etokimab (anti–IL-33 biologic)**

- 6-week placebo-controlled phase 2a study evaluated safety and the ability of a single dose of etokimab to desensitize peanut-allergic adults
- Participants received either etokimab (n = 15) or blinded placebo (n = 5)
  - Clinical tests included oral food challenges (cumulative 275mg protein) and skin prick tests at days 15 and 45
- 73% and 57% increases in the tolerated threshold allergen dose of the active treatment group (day 15 and 45, respectively), but saw 0% in the placebo group on either of the 2 days.
- IL-4, IL-5, IL-9, IL-13, and ST2 levels in CD4+ T cells were reduced in the active vs. placebo arm upon peanut-induced T cell activation
- Peanut-specific IgE was reduced in active vs. placebo (P = 0.014 at day 15)
  - With OIT IgE decreases are seen typically after 12 months of treatment. Intriguing to see this level of change after 15 days
- Single dose of etokimab could have the potential to desensitize peanut-allergic participants and possibly reduce atopy-related adverse events

Oral Immunotherapy

- OIT has generated the most interest, press, and research attention over the last decade
- A lot has changed over this time period
Timeline of OIT Trials

Modern OIT in clinical practice is only recently gaining traction, but concept of oral desensitization is not new

- **1908**: Schofield desensitized 13yr old boy with h/o egg anaphylaxis by starting at a 1/10,000 dose followed by gradual increases over 6 months, eventually leading to negative challenge

- **1990s**: desensitization to peanut via subcutaneous route reported unacceptably high rates of anaphylaxis (one fatality)

- **2006**: two case reports of successful desensitization to peanut using OIT

- **2009**: first clinical trial of peanut OIT. Induced clinical desensitization to peanut safely and with minimal side effects

- **2011**: Food Allergy Research & Education (FARE) helped found a company that would become known as Aimmune
Protocol for OIT Administration

Protocols vary considerably but follow a similar pattern

solution $\rightarrow$ natural form

(capsule $\rightarrow$)

- Initial Rapid Dose Escalation (~6 hours)
  - Build-up Phase (6-12 months)
    - Maintenance Phase
Palforzia

- Will be the first FDA-approved treatment for peanut allergy

- Comes in the form of a powder that parents mix into foods like apple sauce, yogurt, and pudding once per day

  - after dose escalation period (~6 months), patient continues daily therapeutic dose to maintain desensitization
Standardized, pharmaceutical-grade

- Employs Good Manufacturing Processes (GMP)
  - Ensures product is consistently produced and controlled according to industry-recognized quality standards
  - All allergists will be using the identical formulation

- Phase 3 PALISADE trial of the drug in 554 patients aged 4-17
  - Of the 79.6% of those that completed the trial:
    - 96.3% tolerated a 300-mg dose of peanut protein in the exit food challenge
    - 84.5% tolerated a 600-mg dose
    - 63.2% tolerated a 1000-mg dose

Selecting Appropriate OIT Candidates

■ Confirm IgE-mediated food allergy before starting OIT

■ Good Candidates:
  - *Failed an OFC*
  - *Recent history of severe reaction*
  - *High and unchanged sIgE levels/skin prick wheals over time*
  - *Poor QoL due to avoidance*
  - *Safety concerns from parents and/or child*

■ If there is any doubt regarding clinical reactivity, OFC is indicated
Majority Experience Significant QOL Improvement with OIT

OIT patients may experience
- reduced anxiety
- increased social engagement
- reduced fear of accidental exposure
- reduced psychosocial burden associated with food allergy diagnosis

- Opposite is true when patients experience frequent adverse reactions

- 2019 systematic review and meta-analysis of 12 trials (n=1041; median age across trials 8-7 years)
  - available peanut OIT regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo

Safety Concerns and OIT

- **Pre-screen** patients before starting OIT to mitigate risks:
  - Evaluate atopic status
  - Maximize control of allergic rhinitis and atopic dermatitis
  - **Asthma screening**: PFT pre/post bronchodilator and FeNO if available
  - Exclude patients with uncontrolled asthma or h/o eosinophilic esophagitis (EoE)
    - relationship between OIT and EoE continues to be examined
Reactions to OIT

Most participants experience adverse events during OIT, most are benign
- oropharynx itching
- mild GI discomfort

Almost every trial to date has documented one or more severe reactions requiring epinephrine

Severe reactions most often reported in office with up-dose
some reactions at home with maintenance doses for various reasons
OIT and EoE

- Repetitive oral administration of allergens to atopic individuals mimics exposures thought to trigger EoE

- Typical rates of “new-onset” EoE diagnosed during OIT range from 2-5% but are likely higher
  - Many patients drop out of OIT with GI symptoms before being referred for endoscopy
  - Study patients not routinely scoped prior to treatment, and rarely during treatment

- Remains unknown whether OIT-associated EoE is specifically caused by the OIT allergen, becomes unmasked during OIT, or develops concurrently
Eosinophilic Esophagitis Like Oral Immunotherapy Related Syndrome (ELORS)

- Comprises a recognizable syndrome affecting some OIT patients
- Characteristic presentation of vomiting with or without epigastric abdominal pain or nausea occurring 2-6 hours after OIT doses
  - accompanied by increased peripheral blood eosinophilia
- In many patients, ELORS resolves after 2-3 months of OIT dose reduction and successful desensitization can ultimately be achieved
- ELORS substantially limits OIT for some patients

Silvers, Stacy K. et al. Eosinophilic Esophagitis Like Oral Immunotherapy Related Syndrome (ELORS). Journal of Allergy and Clinical Immunology, Volume 139, Issue 2, AB134
Screening, Education, & Close Monitoring

- The relationship between food OIT, GI side effects, and EoE deserves future study
- More invasive surveillance may be necessary
- Long term follow up is critical, especially in those who withdraw
- Importance of educating potential OIT subjects about the risk of developing EoE
- Proactively screen for concerning symptoms prior to starting OIT and follow closely:
  - dysphagia, chest tightness, abdominal pain, heartburn, vomiting, regurgitation, weight loss/poor growth; “reflux”; ask about family history
- Low threshold for starting an EoE evaluation
Increased likelihood of reactions to OIT

- Concurrent viral illness
- Undiagnosed or sub-optimally controlled asthma
- Administering dose on an empty stomach
- Physical exertion after dosing
- Dosing during menses
- NSAIDs
- Sleep deprivation/stress
- Likely others – e.g. still have “unexplained” cases

OIT Failure: causes of dropout from OIT both during and after completion (10-20% of cases)

- Persistence of chronic symptoms, especially chronic abdominal pain and/or vomiting
  - Prophylactic probiotics, H2 blockers, spacing out dosing, altering dosing protocol
- Taste aversion
- Epinephrine-treated reactions
- Severe anxiety
  - Psychiatry/psychology consultation
- Poor adherence and/or inconvenience
- Development of EoE
The OIT Debate Continues

TO USE

Utilization in private practice has dramatically increased and demand for treatment continues to grow
- Growing number of board-certified allergists around the country currently offering food OIT
- Drastic improvement in QOL has been demonstrated for both parents and patients
- OIT efficacy is higher compared with SLIT and EPIT

NOT TO USE

Some experts believe that OIT is still not ready for routine clinical practice despite all the progress made
- Risks of adverse reactions
- Lack of long-term safety data
- Lack of standardization in private practice
- Higher rate of systemic adverse events compared with SLIT and EPIT
- Billing codes are not standardized or currently available
More Questions than Answers

1. How long must a patient avoid a food for a sustained unresponsiveness challenge to be truly predictive?
2. How does sustained unresponsiveness compare to naturally acquired tolerance to a food at the cellular and molecular immunological level?
3. How long do I have to continue maintenance?
4. Do I have to take my dose every day?

- After more than 100 years of experience, we know SCIT often must be individualized
  - there are some clearly wrong ways to do SCIT but there are many acceptable variations of the right way