Food Allergies: Going Nuts Over Nuts? 
An update on Infant Feeding Guidelines, 
Food Allergies, and Eczema

Elena E. Perez, MD/PhD
PBPS Meeting
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CME Objectives

• Comprehend the latest landmark studies on peanut allergy and the allergic mechanisms that will support future food allergy guidelines.

• Review the new recommendations for introduction of allergenic foods to babies

• Discuss the new approaches to treatment with oral immunotherapy
Outline

• Epidemiology/background

• Prevention: Early Introduction of allergenic foods
  o Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel (2017)
  o Studies that led to new recommendations:
    • LEAP study (NEJM 2015)
    • LEAP on study (NEJM 2016)
    • EAT Study (NEJM 2016)
    • Issues with new recommendations

• Treatment: avoidance vs. desensitization
  o Anaphylaxis
  o SLIT
  o OIT – 2000mg oral maintenance/6000mg protection
  o Aimmune 300mg oral maintenance/1000mg protection
  o DBV-"Peanut Patch” 250ug/1000mg protection
Background and Epidemiology
Food Allergies (and Eczema)

• among the most common chronic non-communicable diseases in children in many countries worldwide¹

• increasing in both developed and developing countries in the last 10–15 years¹ (20y)

• increased burden in infants and preschool children¹

• “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food”²

²NIAID expert panel, Guidelines for Diagnosis and Management of Food Allergy in the US. JACI 2010 Dec
Adverse Reactions to Food

Adverse Food Reactions

Immunologic

IgE-Mediated

- Systemic (Anaphylaxis)
- Oral Allergy Syndrome
- Immediate gastrointestinal allergy
- Asthma/rhinitis
- Urticaria
- Morbilliform rashes and flushing
- Contact urticaria

Eosinophilic esophagitis (EoE)
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis

Non-IgE Mediated

Cell-Mediated

- Food Protein-Induced Enterocolitis
- Food Protein-Induced Enteropathy
- Food Protein-Induced Proctocolitis
- Dermatitis herpetiformis
- Contact dermatitis

“Gell and Coombs Type I Hypersensitivity”

Type 1 Hypersensitivity Reaction

Food protein antigen → IgE → Mast cell → Histamine

Urticaria
Angioedema
Anaphylaxis

“Minutes to hours”

Local involvement (Oropharynx and or GI tract symptoms):
• Itching, tingling lips, palate, tongue, or throat
• Swelling lips or tongue
• Hoarseness, tightness in throat
• Nausea/vomiting/Diarrhea
• Colic/abdominal cramping

May involve other organ systems and become generalized anaphylaxis:
• Skin: urticaria/angioedema, AD, flushing, pruritis
• Airways: chest tightness, wheezing, dyspnea
• Pharynx: tightness, dysphonia, tongue swelling, vocal cord edema
• Nose: congestion, itching, rhinorrhea, sneezing
• Eyes: Ocular itching, tearing
• Systemic: hypotension, LOC

Side note: What isn’t food allergy?

- Lactose intolerance (lactase deficiency) is not food allergy.
- Unusual susceptibility to pharmacologic substances in foods (caffeine, tyramine) is not food allergy.
- Celiac disease is not food allergy.
Prevalence of Food Allergy

• Appears to be increasing, but difficult to assess
  o Self-reported in adults ~15%,
  o studies using more stringent criteria, ~4% of children and 1% of adults.
• European Anaphylaxis Registry (Jul 2007-Mar 2015):
  o 1300/1970 (66%) of reports of anaphylaxis (<18yo) were triggered by foods.
  o Age specific differences:
    • cow’s milk and hen’s egg most common < 2 yo,
    • hazelnut and cashew most common in school-aged children,
    • peanut common in all age groups.
  o ICU admissions and fatal reactions occurred in 26 (1.3%) patients
  o hospital-based emergency use of IM epinephrine increased from 12% to 25% from 2011-2014.

## Prevalence of Food Allergy in Specific Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Food allergy prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>35-55%</td>
</tr>
<tr>
<td>Oral allergy syndrome</td>
<td>25-75% (with pollen allergy)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>37% in children (rare in adults)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>20% in acute (rare in chronic)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5-6%</td>
</tr>
<tr>
<td>Chronic rhinitis</td>
<td>rare</td>
</tr>
</tbody>
</table>
Peanut allergy

• prevalence among children in Western countries has doubled in the past 10 years \(^1\)-\(^3\)
• becoming apparent in Africa and Asia \(^4\)-\(^5\)
• leading cause of anaphylaxis and death due to food allergy \(^6\)
• substantial psychosocial and economic burdens on patients and their families \(^6\)
• develops early in life and is rarely outgrown \(^7\)-\(^9\)

## Prevalence of Peanut Allergy in US School-age Children

<table>
<thead>
<tr>
<th>Definition of peanut allergy</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported</td>
<td>4.6</td>
</tr>
<tr>
<td>laboratory-based results</td>
<td>5</td>
</tr>
<tr>
<td>laboratory results + prescribed epinephrine auto-injector</td>
<td>4.9</td>
</tr>
<tr>
<td>laboratory-based peanut sensitization level (greater than the 90% specificity decision point) and prescribed epinephrine auto-injector</td>
<td>2</td>
</tr>
</tbody>
</table>

Risk Factors for Food Allergy

• Genetic susceptibility\(^1\)
  o 64% concordance among monozygotic twins vs dizygotic twins (7%)

• Age of food introduction\(^2\)
  o Higher rates in kids than adults
  o Early introduction may be protective (lower incidence of peanut allergy in Israel vs UK)

• Lack of oral exposure with concomitant cutaneous exposure\(^3\)

• Gut barrier function
  o Gastric pH\(^4\)
  o Commensal bacteria\(^5\)
  o Vitamin D deficiency\(^6\)

Food Allergy Testing

- **History**
  - IgE mediated or non-IgE mediated?
  - Possible foods involved
  - Timing/type of reaction

- **SPT (skin prick test)**
  - alone cannot be considered diagnostic of FA
  - safe & useful for identifying foods potentially provoking IgE-mediated reactions
  - Low specificity, low PPV for the clinical diagnosis of FA (may lead to over diagnosis)
  - High sensitivity, high NPV (95%)

- should not comprise large general panels of food allergens

- diagnostic tests for non-allergic disorders may be needed
In Vitro Testing

Total serum IgE + Secondary labeled anti IgE antibody

Allergen bound to solid matrix

$\text{kJU/L}$

Less sensitive than skin prick test, in general panels should not be performed without consideration of history (irrelevant +s). Many patients have sIgE without clinical food allergy!
Serum Tests for Food allergy

- presence of sIgE: allergic sensitization, not necessarily clinical allergy

- ↑ quantity of sIgE, the higher the probability of an allergic reaction on oral challenge
  - (predictive values varied from study to study)

- undetectable sIgE levels occasionally occur in patients with IgE-mediated FA (false negative)
  - If history is highly suggestive, further evaluation (oral food challenge) is necessary
# IgE and SPT cut-offs predicting reaction in OFC

<table>
<thead>
<tr>
<th>Food</th>
<th>&gt;50% react</th>
<th>&gt;95% react</th>
<th>&gt;95% react (≤2 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>$sIgE = 2\text{kIU/L}$ (clear history)</td>
<td>$sIgE = 13-14\text{kIU/L}$</td>
<td>SPT = 4mm wheal</td>
</tr>
<tr>
<td></td>
<td>$sIgE = 5\text{kIU/L}$ (unclear history)</td>
<td>SPT = 8mm wheal</td>
<td></td>
</tr>
</tbody>
</table>

## Table 1
Predictive values of specific IgE and prickle skin testing for selected food allergens.

<table>
<thead>
<tr>
<th>Food</th>
<th>&gt;50% react</th>
<th>&gt;95% react</th>
<th>&gt;95% react (≤2 years of age)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>$sIgE = 2\text{kIU/L}$</td>
<td>$sIgE = 15\text{kIU/L}$</td>
<td>$sIgE = 5\text{kIU/L}$</td>
<td>(Garcia-Ara et al., 2001; Perry et al., 2004b; Sampson, 2001) (Hill et al., 2004)</td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>$sIgE = 2\text{kIU/L}$</td>
<td>$sIgE = 7\text{kIU/L}$</td>
<td>$sIgE = 2\text{kIU/L}$</td>
<td>(Perry et al., 2004b; Sampson, 2001; Boyano Martinez et al., 2001) (Hill et al., 2004)</td>
</tr>
<tr>
<td>Peanut</td>
<td>$sIgE = 2\text{kIU/L}$ (clear history)</td>
<td>$sIgE = 13-14\text{kIU/L}$</td>
<td>$sIgE = 5\text{kIU/L}$</td>
<td>(Perry et al., 2004b; Sampson, 2001; Maloney et al., 2008) (Hill et al., 2004)</td>
</tr>
<tr>
<td>Peanut</td>
<td>$sIgE = 5\text{kIU/L}$ (unclear history)</td>
<td>SPT = 8mm wheal</td>
<td>SPT = 4mm wheal</td>
<td>(Sampson, 2001)</td>
</tr>
<tr>
<td>Fish</td>
<td>$sIgE = 2\text{kIU/L}$</td>
<td>20 kIU/L</td>
<td>18.5 kIU/L</td>
<td>(Maloney et al., 2008)</td>
</tr>
</tbody>
</table>

$sIgE$, food specific IgE level; SPT, skin prick test.
Component Testing

- pinpoints sensitization to specific allergen components (proteins)
- Associated with risk of allergic reaction
- differentiates between symptoms caused by cross-reactive proteins vs primary, species-specific proteins.
- commercially available for peanuts, cow’s milk, and hen’s egg
- Available commercially

Clin Exp Allergy. 2004 Apr;34(4):583-90. Relevance of Ara h1, Ara h2 and Ara h3 in peanut-allergic patients, as determined by immunoglobulin E Western blotting, basophil-histamine release and intracutaneous testing: Ara h2 is the most important peanut allergen. Koppelman SJ, et al.
Component testing—Arachis hypogaea (peanut)

**TABLE III. Allergenic proteins in peanut**

<table>
<thead>
<tr>
<th>Allergenic protein</th>
<th>Plant family</th>
<th>Clinical implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara h 1</td>
<td>Vicilin [7S globulin]</td>
<td>Correlated with reactivity</td>
</tr>
<tr>
<td>Ara h 2</td>
<td>Conglutin [2S albumin]</td>
<td>Best correlation with reactivity/severity</td>
</tr>
<tr>
<td>Ara h 5</td>
<td>Profilin [Bet v 2-like]</td>
<td>Not correlated with reactivity</td>
</tr>
<tr>
<td>Ara h 6</td>
<td>Conglutin [Ara h 2 homologue]</td>
<td>Correlated with reactivity</td>
</tr>
<tr>
<td>Ara h 7</td>
<td>Conglutin</td>
<td></td>
</tr>
<tr>
<td>Ara h 8</td>
<td>Bet v 1-like</td>
<td>Not correlated with significant reactivity</td>
</tr>
<tr>
<td>Ara h 9</td>
<td>Nonspecific lipid transfer protein</td>
<td>Correlated with reactivity in some studies (see text)</td>
</tr>
<tr>
<td>Ara H 10, 11</td>
<td>Oleosin</td>
<td></td>
</tr>
</tbody>
</table>

Ara h 5 and Ara h 8 (birch pollen homologues) are not usually associated with severe allergy


**Summary Statement 24:** Component-resolved diagnostic testing to food allergens can be considered, as in the case of peanut sensitivity, but it is not routinely recommended even with peanut sensitivity because the clinical utility of component testing has not been fully elucidated. [Strength of recommendation: Weak; C Evidence]

Management of Food Allergy

• Elimination of offending foods from diet
  o Symptomatic reactivity to food allergens often lost over time
    (except for peanuts, tree nuts, shellfish and fish)
• Retest yearly in childhood to know when to challenge (if outgrowing)
• Ensure nutritional needs are being met
  o (elemental/aa vs. peptide formulas)
  o Nutrition consult
• Education / Counseling
• Anaphylaxis Emergency Action Plan
  o Epinephrine autoinjector, home and school
• Prevention:
  o early introduction of allergenic foods? NEJM 2015
  o Probiotics? Australian study
• Emerging treatments: desensitization
Natural History of Peanut Allergy

- Allergies to peanuts, tree nuts, seafoods, and seeds typically persist

- ~20% of cases of peanut allergy resolve by age 5 years.

Prognostic factors include:
  - PST <6mm
  - ≥2 years avoidance
  - History of mild reaction
  - Few other atopic diseases
  - Low levels of peanut-specific IgE
  - Rarely re-develop allergy: role for regular ingestion?
Integrated Model for Patient and Family Centered Care of Patient with Food Allergy

**Diagnosis**
- Clinical History
- Testing (SPT, IgE, CRD, BAT)
- Diagnostic OFCs
- Evidence Based Guidelines
- National/International Position Statements

**Management**
- Evidence Based Guidelines
- Food Allergy Action Plan
- Nutritional Support
- Training and Education
- Online Resources
- Advocacy Groups
- Psychological Support

**Patient**

**Family**

**Allergist**
- Oral immunotherapy
- Sublingual Immunotherapy
- Epicutaneous immunotherapy
- Anti-IgE, Monoclonal Antibodies
- Combined approaches

Consensus guidelines for early peanut introduction
- Engagement of professional organizations, advocacy groups for dissemination of guidelines
- Nutritional support and counseling for early introduction

Prevention through early introduction
Significant Paradigm Shift in Management of Food Allergy

Delayed introduction of allergenic foods, (such as peanut), into the diets of infants and toddlers

to current consensus recommendations for early peanut introduction to prevent peanut allergy
Evaluation and Prevention of Peanut Allergy
What do we know?

Peanut sIgE has been shown to increase over the first 5 years of life

LEAP trial - Early peanut introduction and relative risk reduction in the prevalence of peanut allergy:

a) 86% relative risk reduction - Negative baseline SPT
b) 70% relative risk reduction - Positive baseline SPT

Expert panel recommendation: Introduction of peanut to infants 4-6 months of age with severe eczema, egg allergy or both to reduce the risk for peanut allergy

Approach for evaluation of children with severe eczema and/or egg allergy before peanut introduction

- To minimize a delay in peanut introduction, testing for specific IgE may be preferred initial approach. Food allergy panel test not recommended due to poor PPV.

Togias et al. Ann Allergy Asthma Immunol; 2017; 118: 166-173
New dietary guidelines for early peanut introduction depends on 3 risk categories:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: severe eczema, egg allergy or both</td>
<td>Perform allergy test, and if appropriate introduce as early as 4-6mo</td>
</tr>
<tr>
<td>Mild to moderate eczema</td>
<td>No testing required, introduce around 6m to decrease risk of peanut allergy</td>
</tr>
<tr>
<td>Low-risk: no eczema or food allergy</td>
<td>Ad lib dietary peanut introduction together with other complimentary foods</td>
</tr>
</tbody>
</table>

Practical Considerations for Implementation at a Population Level—Editorial

• compelling evidence for early peanut introduction in high-risk infants but no convincing evidence from RCTs to support the recommendations for lower-risk groups

• Factors that might hinder broad implementation:
  o complex risk stratification
  o resource-intensive screening process
  o narrow 4- to 6-month window.

• ‘‘screening creep’’—possible unintended consequence
  o infants who are not in a high-risk category undergo screening because of parental anxiety or over diagnosis of eczema, leading to delays in introduction while navigating the screening & challenge process

• removal of a clinically tolerated food in the presence of a positive allergy test may lead to loss of tolerance and development of food allergy instead.

LEAP Study: Learning Early about Peanut

**Hypothesis:** regular consumption of peanut containing products starting in infancy would promote a protective immune response and dietary tolerance to peanut.

**Conclusion:** showed a 5-to-1 (80%) reduction in the development of peanut allergy after 5 years of exposure vs. avoidance.
LEAP Study

• **Objective:** To determine which strategy (peanut consumption vs. avoidance) is most effective in preventing the development of peanut allergy in infants at *high risk*

• **Method:**
  o randomly assigned 640 (4m-11m) infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age.
  o assigned to separate study cohorts on the basis of pre-existing sensitivity to peanut extract, (skin-prick test)
    • no measurable wheal after testing
    • wheal measuring 1 to 4 mm in diameter.

• **Primary outcome:** proportion of participants with peanut allergy at 60 months of age.
## LEAP Study Results

<table>
<thead>
<tr>
<th></th>
<th>Skin test negative cohort</th>
<th>Skin test positive cohort (4mm or less)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention to treat</strong></td>
<td>n=530</td>
<td>n=98</td>
</tr>
<tr>
<td><strong>avoidance group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>consumption group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>prevalence of peanut allergy at 60m</strong></td>
<td>13.70%</td>
<td>35.30%</td>
</tr>
<tr>
<td><strong>SPT neg cohort</strong></td>
<td>absolute difference in risk of 11.8 percentage points (95%[CI], 3.4 to 20.3; P&lt;0.001) represents an <strong>86.1% relative reduction</strong> in the prevalence of peanut allergy</td>
<td></td>
</tr>
<tr>
<td><strong>SPT pos cohort</strong></td>
<td>the absolute difference in risk of 24.7 percentage points (95% CI, 4.9 to 43.3; P = 0.004) represents a <strong>70.0% relative reduction</strong> in the prevalence of peanut allergy</td>
<td></td>
</tr>
<tr>
<td><strong>consumption group</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*consumption group*: fed at least 6 g of peanut protein per week, distributed in three or more meals per `week, until they reached 60 months of age
LEAP Study Results

- no significant between-group difference in the incidence of serious adverse events.
- Increases in peanut-specific IgG4 antibody occurred mostly in the consumption group (tolerance)
- a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody (allergy)
- A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.
The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.
Question: Does the rate of peanut allergy remain low after 12 months of peanut avoidance?

Method: asked all the participants to avoid peanuts for 12 months. (both groups)

primary outcome: % of participants with peanut allergy at the end of the 12-month period, (72 mos)
LEAP-On Results*

<table>
<thead>
<tr>
<th></th>
<th>Avoidance</th>
<th>Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy to peanut</td>
<td>18.6% (52/280)</td>
<td>4.8% (13/270)</td>
</tr>
<tr>
<td>after 12mos avoidance</td>
<td>at 72m</td>
<td></td>
</tr>
</tbody>
</table>

- Peanut allergy more prevalent among original peanut-avoidance group than in the peanut-consumption group
- Fewer participants in the peanut-consumption had high levels of Ara h2 specific IgE and peanut-specific IgE
- Peanut-consumption group continued to have a higher peanut-specific IgG4 and a higher peanut-specific IgG4:IgE ratio.

*remember these are high risk infants from the LEAP study, who had eczema or egg allergy or both, who tested negative to peanut or slightly positive. (>4mm wheal excluded)
Prevalence of Peanut Allergy in LEAP and LEAP On

LEAP study

LEAP-On study
Avoidance
Consumption

Arah2 IgE
Peanut IgE
Skin test

Biomarkers over 60m and 72m in LEAP and LEAP On

Avoidance
Consumption

IgG4
IgG4:IgE
Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants (EAT Study: "Enquiring About Tolerance")

**Question:** does early introduction of allergenic foods in the diet of breast-fed infants protect against the development of food allergy?

**Methods:** 1303 exclusively breast-fed 3mo infants (not pre-selected for atopic risk), randomly assigned to the early introduction of six allergenic foods (peanut, cooked egg, cow’s milk, sesame, whitefish, and wheat = early-introduction group) or to the current practice in UK of exclusive breast-feeding to 6 months of age (standard-introduction group)

**Primary outcome:** Food allergy to one or more of the 6 foods at 1y and 3y

# EAT Study Result Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence of Food Allergy to 1 or more of 6 foods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT: Standard introduction</strong></td>
<td>7.1% (42/495)</td>
</tr>
<tr>
<td><strong>ITT: Early introduction</strong></td>
<td>5.6% (32/567)</td>
</tr>
<tr>
<td><strong>Per Protocol: Standard</strong></td>
<td>ANY 7.3% Peanut 2.5% Egg 5.5%</td>
</tr>
<tr>
<td><strong>Per Protocol: Early</strong></td>
<td>ANY 2.4% Peanut 0% Egg 1.4%</td>
</tr>
</tbody>
</table>

No significant effects with respect to milk, sesame, fish or wheat

Order of introduction: cow’s milk (yogurt) then (in random order) peanut, cooked (boiled) hen’s egg, sesame, and whitefish; wheat was introduced last
EAT Study

• No efficacy of early introduction of allergenic foods in an intention-to-treat analysis. (poor adherence?)

• raised question: is prevention of food allergy by early introduction of multiple allergenic foods is dose-dependent?
  o (eating >2 g/wk assoc with lower peanut and egg allergy).

• highlighted difficulty of early introduction of all foods (negatively affected the results?)
  o -- low rate of per-protocol adherence in the early-introduction group

• per protocol analysis done with subjects ingesting at least 3g/week, adherence ~75% rec dose
  o (saw significant differences with reanalysis)
Studies supported early introduction of both peanut and heated egg protein to prevent food allergy to specific allergens.

Rate of food introduction after negative challenge?

- (small study) -- Assessment of the overall rate of food introduction after a negative OFC in pediatric patients:
  - 20% of children did not incorporate the food into their diet regularly,
    - fear of a reaction, disliking the food, or the food not being a routine part of the family’s diet.
  - Peanuts and tree nuts were the most common allergens (60%) that were not incorporated regularly into the diet despite a negative OFC result.

- ?? If not incorporated after negative challenge, what is risk of recurrence?? -- Need more research

Treatment: Avoidance or Desensitization?
Anaphylaxis in Avoidance

- **top 3 causes:** **food (29.9%), venom (26.4%), and medications (13.3%)** (Cleveland clinic study)
  - Venom most common in adults. Foods most common in kids.
  - **Children:** peanuts (32.0%), tree nuts (22.7%), milk (17.2%), and eggs (16.4%)
  - **Adults:** shellfish (34.4%), tree nuts (20.0%), and peanuts (12.2%)

- **annual recurrence rate 17.6% (food most common cause of recurrences (84.6%).** (Canadian study of 292 children at 2 tertiary hospitals and 1 general hospital ED with anaphylaxis)

- **epinephrine** for the acute treatment dose: **0.01 mg/kg IM**
  - 0.3 mg for ≥30 kg
  - 0.15 mg for 15–30 kg
  - 0.1 mg for 7–15 kg

- **AAP and Canadian Pediatric Society recommend switching most children from 0.15 to 0.30 mg when bodyweight >25 kg**

Yue et al. Journal of Asthma and Allergy 2018:11 111–120
Anaphylaxis in Avoidance

• Most rxns occur after ingestion of foods thought safe.
• accidental exposure to peanuts by children with peanut allergy occurs in as many as 11.9% of patients each year.
  o 71% of exposures resulted in moderate-to-severe reactions (5y f/u study in 1411 kids).
  o 20% of kids who experienced a reaction received epinephrine.
• peanut ingestion blamed for 20/32 episodes of fatal-food-associated anaphylaxis. (2001 study)
• available epinephrine autoinjector is often not used when its is indicated.
• → increased interest in alternative approaches to treating food allergies including OIT

Wasserman et al. J ALLERGY CLIN IMMUNOL PRACT JANUARY/FEBRUARY 2014
Management

• “Standard of care”: strict avoidance and epinephrine, anaphylaxis management plan in case of accidental exposure
• epinephrine continues to be vastly under prescribed and underused by health care providers and patients.
• Address quality of life issues and anxiety surrounding food allergies

• New options
  o EPIT: Peanut patch (DBV) – applying for FDA approval
  o OIT: peanut capsule (Aimmune) – applying for FDA approval
  o OIT: peanut flour/peanuts (available in some private practices for >10y, 80-90% success rates)
  o SLIT
  o Other
Therapeutic Approaches to IgE-mediated Food Allergy: Desensitization

- clinical trials
- sublingual immunotherapy (SLIT)
- epicutaneous immunotherapy (EPIT)
- oral immunotherapy (OIT)
- monoclonal IgE (omalizumab)
- other immunomodulatory approaches under investigation
SLIT

• moderate treatment response
• low side effect profile limited predominantly to oral mucosal symptoms
• Additional studies are necessary to realize full utility in clinical care
• Some doctors use SLIT before OIT (SLIT uses smaller doses than OIT)
EPIT: Mechanism of action

- targets specific epidermal dendritic cells, (Langerhans cells) which capture antigens and migrate to the lymph node → activate specific regulatory T cells (Tregs) → down-regulate the Th2-oriented (allergic) reaction.
- Avoiding bloodstream may result in a favorable safety and tolerability profile for patient

https://www.dbv-technologies.com/viaskin-platform/
Two Phase III long-term studies in children ages four to 11 are ongoing. Phase III trial in patients one to three years of age is ongoing (Milk and egg are next). DBV's Viaskin Peanut has obtained Fast Track and Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA) for the treatment of peanut allergy in children.

https://www.dbv-technologies.com/pipeline/viaskin-peanut/
EPIT: Peanut patch -- dose finding study

• Viaskin Phase II: age 6y-55, +OFC, N=221
• 3 doses randomized 50, 100, 250mcg/d vs placebo x12m then 2y open label treatment
• Primary endpoint: % responders (ED>10times increase from baseline OFC or >1000mg peanut protein) at 12m
• Observed in 250-mcg patch group compared with the placebo group (50%vs 25%, P.01) but not in other groups.
• Interaction by age group was significant only for the 250-mcg Peanut patch (P5.04), with significance reached in the 6- to 11-year-old age group (P.008) compared to placebo and no differences noted in the adolescent/adult age group

EPIT—dose finding study

- mean cumulative *reactive* dose at 12m:
  - 250-mcg Viaskin Peanut patch → 1117.8 mg (~4+peanuts)
  - placebo → 469.3 mg
- AEs noted: mostly mild reactions at patch site
- overall 12mo adherence: 97.6%.
- Subset continued on 250-mcg open-label dosing, followed by OFCs at 12 and 24 months, with response rates of 59.7% and 64.5% respectively
- safety of Viaskin Peanut dosing and some level of desensitization noted in younger subjects.
- phase 3 trial was initiated in children aged 4 to 11 years using the 250-μg peanut patch

Oral Immunotherapy (OIT): Review

• Supported by an extensive body of literature
• References date back to 1905
• Desensitization in a majority of treated subjects
• Sustained unresponsiveness (SU), after a period of cessation of therapy (subset)
• performed in select private practices using diluted foods for ~15yrs
  o (tailored to patients based on protocols for single or multiple foods)
• gaining traction due to high success rates (85-90%)
• Clinical trials for standardized protocol using pharmaceutical approach underway
• NOT A CURE (yet?)
### Traditional OIT for peanut

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose (mg peanut protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

10 gradually increasing doses

2mg

Weekly dose increases using peanut flour solution until transition to peanut fragments, then whole nuts until 4 peanut or 8 peanut equivalent (standardized by weight). About 6 months then maintenance every day.

2-hour rest period after dosing at home, allergies, asthma, illness under control.

Also available for tree nuts, seeds, egg, milk, wheat, other less common foods,

(Usually allergies to common foods are outgrown)
Anaphylaxis in “Traditional” OIT

- Retrospective chart review, 5 centers, peanut OIT
  - 352 treated patients received 240,351 doses of peanut, peanut butter, or peanut flour
  - 95 rxns were treated with epinephrine (0.4/1000 doses)
  - 57 rxns req epi occurred during 79,726 escalation doses (reaction rate 0.7 per 1000 doses).
  - 38 rxns req epi occurred during 160625 maintenance doses (reaction rate 0.2 per 1000 doses)

- 85% patients achieved the target maintenance dose
- Peanut OIT carries a risk of systemic reactions but those rxns were recognized and treated promptly.
- Peanut OIT risk of reaction higher but comparable to 0.1% with high dose SCIT
Aimmune OIT--Phase II

- RPCMT, 8 centers, 55 subjects (4y-26y), +OFC to 143mg or less of peanut protein
- Randomized 300mg peanut protein vs placebo
- 20wk, 34wks→? If tolerated 443mg at exit
  - 79% tolerated 443mg or greater
  - 62% tolerated 1043mg peanut protein (4peanuts)
  - Vs. 19% and 0% placebo
- AEs: GI sxds most common reported in 66% of the AR101 group and 27% of the placebo group,
- Study withdrawal of 21% of treated subjects

### Intent-to-Treat Efficacy:
Percent of Patients Tolerating Each Dose in Exit DBPCFC¹

<table>
<thead>
<tr>
<th>Dose</th>
<th>AR101 (n=372)</th>
<th>Placebo (n=124)</th>
<th>95% CI difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>76.6%</td>
<td>8.1%</td>
<td>(58.6–78.5%)</td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>600 mg</td>
<td>67.2%</td>
<td>4.0%</td>
<td>(53.0–73.3%)</td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>1000 mg</td>
<td>50.3%</td>
<td>2.4%</td>
<td>(38.0–57.7%)</td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>

¹ Ages 4–17

### Completer Efficacy:
Percent of Patients Tolerating Each Dose in Exit DBPCFC¹

<table>
<thead>
<tr>
<th>Dose</th>
<th>AR101 (n=296)</th>
<th>Placebo (n=116)</th>
<th>95% CI difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>96.3%</td>
<td>8.6%</td>
<td>(78.0–97.3%)</td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>600 mg</td>
<td>84.5%</td>
<td>4.3%</td>
<td>(69.7–90.6%)</td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>1000 mg</td>
<td>63.2%</td>
<td>2.6%</td>
<td>(49.9–71.3%)</td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>

¹ Ages 4–17
Discontinuation Aimmune

<table>
<thead>
<tr>
<th></th>
<th>AR101 (n=372)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Total discontinuations regardless of causality</td>
<td>20.4% 76</td>
</tr>
<tr>
<td>Discontinuations not related to adverse events</td>
<td>8.0% 30</td>
</tr>
<tr>
<td>Discontinuations related to adverse events</td>
<td>12.4% 46</td>
</tr>
<tr>
<td>• Gastrointestinal$^2$</td>
<td>6.7% 25</td>
</tr>
<tr>
<td>• Systemic hypersensitivity reactions$^3$</td>
<td>2.7% 10</td>
</tr>
<tr>
<td>• Respiratory system</td>
<td>1.1% 4</td>
</tr>
<tr>
<td>• Cutaneous</td>
<td>0.8% 3</td>
</tr>
<tr>
<td>• Other$^4$</td>
<td>1.1% 4</td>
</tr>
</tbody>
</table>
# OIT: Aimmune Pipeline

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>PRE-IND</th>
<th>PHASE 1/2*</th>
<th>PHASE 3</th>
<th>APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR101 (PEANUT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR201 (EGG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR301 (WALNUT)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Because our treatment product candidates are based on foods that have not shown toxicology issues except in their functions as allergens, we have not been required to and at this time do not anticipate conducting Phase 1 clinical trials.*

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# A Standardized Protocol with Precise Oral Dosing

- **Initial Escalation**
- **Up-Dosing**
- **Ongoing Maintenance**

Early oral immunotherapy (E-OIT) in peanut-allergic preschool children is safe and highly effective

RDBCT of low- and high dose peanut early intervention OIT (E-OIT) among recently diagnosed peanut-allergic children aged 9 to 36 mo. Vs. control group of untreated peanut-allergic patients

- **Study population:** 37 enrolled, (average 28 mo, pslgE 14.4 kU\(_A\)/L, wheal 11.5mm, entry OFC cumulative eliciting dose 21mg

- **Block randomized 1:1 E-OIT maintenance dose** - Low dose (300 mg/d), high dose (3000mg/d)

- **Matched standard controls:** 154 peanut allergic patients, pediatric allergy clinic database at Johns Hopkins, pslgE 21

- **Food challenge assessments:**
  a) After 3y maintenance OR 12 months maintenance, pslgE <15, wheal <8mm
  b) Two 5 gram peanut protein exit DBPCFC end of treatment AND 4 weeks after stopping OIT to assess sustained unresponsiveness

E-OIT Results

- E-OIT median psIgE declined 1.6 kU$_A$/L, Controls increased to 57.4 kU$_A$/L
- Overall 78% of subjects receiving E-OIT demonstrated SU, median 2.5 years
- 300mg/day as effective as 3000mg/day – safety profile, dietary reintroduction
- Ad lib Peanut introduction in the diet: Controls 4%, Peanut E-OIT 78%

changes in patient quality of life during oral immunotherapy for food allergy

--patients with impaired QoL at baseline improved significantly despite the burdensome demands of therapy

--Pre-OIT reaction severity affects quality of life in both preschool and school-aged food-allergic children

--a lower maximal tolerated dose during OIT induction is associated with worse indices of quality of life primarily in children aged 6-12 years.

--some patients with acceptable QoL at baseline had deterioration because of the demands associated with OIT.

Summary

- OIT, EPIT, and SLIT, hold promise but also have associated risks
- Further investigation is needed to address existing knowledge gaps:
  - Optimal dose, duration, maintenance regimen, long-term outcomes, predictors of response, cost-effectiveness, and psychosocial effects
- Need to maximize efficacy,
- Need to minimize risk, and develop individualized approaches for future clinical application.
Thank you!

Allergy Associates of the Palm Beaches

561-626-2006