SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

The Big 8: Advances in Food Allergy Risk Assessment and Management

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Conflict of Interest Statement
Food Allergy Prevention and Treatment: Where We Stand

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Disclosures

- Member, Joint Task Force on Allergy Practice Parameters
- Member of Nutricia, DBV, Aimmune, Kaleo and Monsanto
  specialty advisory boards and has received honorarium
- Co-chair, Nestle international consensus panel on the use of
  hydrolyzed formula and received honorarium
- Member, CSACI Food Allergy in Schools Guideline Panel
- Member of the Medical Advisory team for the Allergy and
  Asthma Foundation of America and the International
  Association for Food Protein Enterocolitis (nonfinancial)
- Has received honorarium from Thermo Fisher, Symbiotix,
  Hybrid Health, ClinicalMind, Vindico, Before Brands,
  multiple state allergy societies for CME/non-CME
  presentations
- Consultant to Aimmune, Intrommune, Thermo Fisher
- Receiving support from K08-HS024599 (Agency for
  Healthcare Quality and Research)
- Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to
  Food committees
- Co-chair, AAAAI Primary Prevention of Food Allergy
  Working Group; Co-chair, AAAAI Oral Immunotherapy
  Office-based Practice Working Group
- Member ACAAI Annual Meeting Planning Committee,
  Chair, GI/Food Allergy Track chair; Chair, Food Allergy
  Committee
- ACAAI representative to consensus statement on interim
  consensus on early peanut introduction guidelines
- Member, NIAID Expert Panel on early introduction of
  peanut to prevent peanut allergy
- Associate Editor, Annals of Allergy, Asthma, and
  Immunology
- Editorial board: Allergy and Rhinology; Medscape
  Pediatrics; Infectious Diseases in Children
- Member, Scientific Advisory Council, National Peanut
  Board
- Member, EAACI Task Force on Nutrition and
  Immunomodulation
A Delicate Balance

Treating/curing food allergy vs Maximizing how we can live with food allergy

Choosing Treatment vs Avoidance

- Caregivers are faced with many decisions
  - May focus on the perceived benefit vs accidental death
  - May prefer to avoid therapy that becomes burdensome
  - May prefer to avoid costly therapy, or not care about cost
  - May have realistic or unrealistic expectations
  - May feel that doing "something" is better than avoidance
- Have to define their expectations and goals
- We can’t judge or prescribe—we are guides
- But, we must inform what would work best
  - If that is even possible!
Fast-tracked Approaches to Treatment

Oral and Epicutaneous Immunotherapy

OIT: What Do We Know?

- OIT involves slow medically supervised re-feeding of increasing doses of one’s allergen
- Many achieve some degree of desensitization
  - Threshold increased for most, but not all, but few develop sustained unresponsiveness
  - No indication of the duration of therapy, or how long the effects last
- Fairly equal effects were seen with milk, egg, peanut in ability to achieve desensitization
- Markers of allergen sensitivity diminish significantly
  - See shift in allergen-specific IgE > IgG4 and part of allergen recognized
- See variable effect of immune cell shut down
  - No consistent biomarker pattern shown, but are many targets of interest

“Typical” OIT Protocol

<table>
<thead>
<tr>
<th>Entry challenge</th>
<th>Rapid desensitization</th>
<th>Maintenance</th>
<th>Interim challenge</th>
<th>Maintenance</th>
<th>End of maintenance challenge</th>
<th>Continuation or discontinuation</th>
<th>End of study challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-study</td>
<td>Day 1</td>
<td>Can persist for a few months to 2 years</td>
<td>Variable duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Build to 12 mg-50 mg</td>
<td>Build up to ~300 mg-800 mg (varies), increase dose in office every 2 weeks</td>
<td>Placebo group crossover</td>
<td>? interrupt therapy, test sustained nonresponse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key Inclusion Criterion:
Tolerate ≤ 43 mg cumulative dose

Primary Endpoint:
Tolerate 1043 mg cumulative dose

- 90% were ages 4-17 years
- 72% had history of anaphylaxis
- 53% had asthma
- 66% with multiple food allergies
- 43% had peanut sIgE > 100 KU/L
- Median entry OFC challenge tolerance was 10mg (1/30th peanut)

PALISADES Entry Characteristics

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Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.airimmune.com publicly available slide deck
PALISADES Main Results

**Intention to treat population**

- NNT of 1.58 (ARR 63.2%) for primary endpoint
- NNT of 2.08 (ARR 48%) for secondary endpoint
- 44% with sIgE >100 kU/L tolerated 1000mg

**Per Protocol Population (“completers”)**

- NNT of 1.23 (ARR 82%) for primary endpoint
- NNT of 1.66 (ARR 60%) for secondary endpoint
- 58% sIgE > 100kU/L overall tolerated 1000mg

NNT in the 18-55y age group was 1.43, but placebo response was 15.4% (~3.5x the younger age group)

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**PALISADES End OFC Characteristics**

- Epinephrine Use
  - AR101 vs Placebo
  - Key Findings:
    1. Developed fewer moderate and severe symptoms;
    2. Required more peanut exposure for the onset of symptoms;
    3. Was more likely to complete the challenge;
    4. Needed less epinephrine

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*Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.immune.com publicly available slide deck.*
PALISADES Safety

- 9 SAE in 8 participants (2.2%), 1 SAE in placebo, no fatalities
- 4 events considered related
- 5 events led to discontinuation
- 1 case of anaphylaxis in early maintenance (high baseline sIgE)
- 1 case of EoE developed, patient withdrew
- 14.5% experienced investigator reported systemic hypersensitivity reactions, 98% of which were considered mild or moderate

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publicly available slide deck

PPOIT and 4-Year Outcomes

- Teng et al. demonstrated efficacy of 18 months of a novel peanut OIT + Lactobacillus Rhamnossus CGMCC combination in a 2015 double blind, randomized controlled study
- Initial effect demonstrated successful desensitization in 26/29 PPOIT patients and 2 week sustained unresponsiveness in 23/28 of these patients
- Probiotic dose the equivalent of “20 tubs” of yogurt/day!
- Now, following 48 of the original 56 participants for 4 years after discontinuation of OIT
- N=24 PPOIT and n=24 placebo patients followed after exit food challenge
- No set protocol for peanut ingestion in the PPOIT group
- At 4 years, both groups asked to discontinue peanut ingestion for 8 weeks and repeat challenge

PPOIT and 4-Year Outcomes

- Noted 16/24 PPOIT vs. 1/24 subjects were regularly ingesting peanut ad libitum (NNT 1.6)
- Half of the PPOIT subjects were eating >2g/week (46% 1x/wk, 29% 1-2x/wk, 17% 3x or more/wk, with 16/20 PPOIT subjects consuming peanut “regularly”, and 20/24 reporting no reactions since stopping PPOIT therapy
- N=27 agreed to the 8 week additional discontinuation. Of these 7/12 PPOIT vs. 1/15 placebo tolerated the challenge and resumed eating peanut (NNT=1.9)
- 7/12 who underwent PPOIT ate peanut ad lib for 4 years, then agreed to stop eating peanut for another 8 weeks demonstrated sustained unresponsiveness. This pattern mimics a non-allergic individual’s consumption!
- Study issues: no initial challenge for the 2015 study, some degree of drop out, small #’s
- The implications of this effect, if replicated, may completely change the game

Other Published Peanut OIT Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (mg)</th>
<th>Duration</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al</td>
<td>2009</td>
<td>Open label</td>
<td>29</td>
<td>1-16</td>
<td>1800</td>
<td>36 mo</td>
<td>93% passed 3.9-g peanut OFC</td>
</tr>
<tr>
<td>Blumchen et al</td>
<td>2010</td>
<td>Randomized open label</td>
<td>23</td>
<td>3-14</td>
<td>500</td>
<td>7-d Rush escalation, 8-wk maintenance period</td>
<td>64% reached maintenance of 500 mg of peanut</td>
</tr>
<tr>
<td>Varshney et al</td>
<td>2011</td>
<td>Randomized, placebo controlled</td>
<td>19</td>
<td>3-11</td>
<td>2000</td>
<td>48 wk</td>
<td>84% passed 5000-mg peanut OFC</td>
</tr>
<tr>
<td>Anagnostou et al</td>
<td>2011</td>
<td>Open label</td>
<td>22</td>
<td>4-18</td>
<td>800</td>
<td>32 wk</td>
<td>64% tolerated 6.6-g OFC</td>
</tr>
<tr>
<td>Anagnostou et al</td>
<td>2014</td>
<td>Randomized, controlled</td>
<td>39</td>
<td>7-16</td>
<td>800</td>
<td>26 wk</td>
<td>62% tolerated 1400-mg challenge</td>
</tr>
<tr>
<td>Vickery et al</td>
<td>2014</td>
<td>Open label</td>
<td>24</td>
<td>1-16</td>
<td>Up to 4000</td>
<td>Up to 5 y</td>
<td>50% SU to 5000-mg OFC after 4-wk avoidance</td>
</tr>
<tr>
<td>Narisety et al</td>
<td>2014</td>
<td>Randomized, placebo controlled</td>
<td>16</td>
<td>7-13</td>
<td>2000</td>
<td>12 mo</td>
<td>OIT &gt; SLIT in OFC threshold, low rate of SU</td>
</tr>
<tr>
<td>Factor et al</td>
<td>2012</td>
<td>Open, uncontrolled</td>
<td>93</td>
<td>5-18</td>
<td>450 (3 M&amp;M)</td>
<td>24 wk</td>
<td>90/100 pts able to tolerate 450 mg, showed improvement in pt FAQLQ score. Clinic-based study</td>
</tr>
<tr>
<td>Wasserman et al</td>
<td>2014</td>
<td>Open label</td>
<td>352</td>
<td>Median 5.9 y</td>
<td>415-8000</td>
<td>Variable, Weeks-ys</td>
<td>Real-life experience of 5 practices, 281/352 (80%) reached maintenance. 10% of pts required epi (36/352)</td>
</tr>
<tr>
<td>Tang et al</td>
<td>2015</td>
<td>Randomized, placebo controlled</td>
<td>62</td>
<td>1-10</td>
<td>2g with 2x10⁷ CFU L. rhamnosus</td>
<td>18 mo</td>
<td>23/28 (82.1%) vs 1/28 (3.6%) achieved SU at 2:5 wk post-discontinuation. 26/29 achieved desensitization.</td>
</tr>
<tr>
<td>Vickery et al</td>
<td>2016</td>
<td>Randomized, placebo controlled</td>
<td>40</td>
<td>9-36 mo</td>
<td>300 vs 3000</td>
<td>Up to 3 y</td>
<td>17/20 in 300-mg and 12/17 in 3000-mg arm achieved SU at 4 weeks (29/37 total)</td>
</tr>
</tbody>
</table>
Published Egg and Milk OIT Studies

### TABLE II. Egg OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (g)</th>
<th>Duration (mo)</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchanan et al 2007</td>
<td>2007</td>
<td>Open label</td>
<td>7</td>
<td>1.16</td>
<td>0.3</td>
<td>24</td>
<td>57% Passed 8 g OIT</td>
</tr>
<tr>
<td>Vickeray et al 2010</td>
<td>2010</td>
<td>Open label</td>
<td>8</td>
<td>3.13</td>
<td>0.3-3.6</td>
<td>18.50</td>
<td>75% Passed OIT 1 mo after stopping OIT</td>
</tr>
<tr>
<td>Burks et al 2012</td>
<td>2012</td>
<td>Randomized, placebo controlled</td>
<td>40</td>
<td>5.11</td>
<td>1.6</td>
<td>22</td>
<td>75% Passed 10g OIT but SU in only 28% at 6-8 wk later</td>
</tr>
</tbody>
</table>

### TABLE III. Milk OIT studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>Subject age (y)</th>
<th>Maintenance dose (g)</th>
<th>Duration</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglio et al 2006</td>
<td>2006</td>
<td>Open label</td>
<td>21</td>
<td>6-10</td>
<td>200 mL</td>
<td>6 mo</td>
<td>72% Desensitization to 200 mL of cow’s milk daily</td>
</tr>
<tr>
<td>Longo et al 2008</td>
<td>2008</td>
<td>Randomized, open label</td>
<td>30</td>
<td>5-17</td>
<td>150 mL</td>
<td>3 wk</td>
<td>Median OIT threshold increased from 40 to 5,140 mg after OIT</td>
</tr>
<tr>
<td>Sreliuk et al 2008</td>
<td>2008</td>
<td>Randomized, placebo controlled</td>
<td>13</td>
<td>6-17</td>
<td>500 mg</td>
<td>25 wk</td>
<td>Median OIT threshold of 1,000 mg (with 33% tolerating 16,000 mg)</td>
</tr>
<tr>
<td>Nartey et al 2009</td>
<td>2009</td>
<td>Open label (follow-up)</td>
<td>13</td>
<td>6-16</td>
<td>500-4,000 mg</td>
<td>3-17 mo</td>
<td>Median OIT threshold of 1,000 mg (with 33% tolerating 16,000 mg)</td>
</tr>
<tr>
<td>Pajon et al 2010</td>
<td>2010</td>
<td>Randomized, placebo controlled</td>
<td>15</td>
<td>4-10</td>
<td>200 mL</td>
<td>18 wk</td>
<td>68% Desensitization to 200 mL of cow’s milk</td>
</tr>
<tr>
<td>Mutterli et al 2011</td>
<td>2011</td>
<td>Randomized, placebo controlled</td>
<td>30</td>
<td>2-3</td>
<td>200 mL</td>
<td>1 y</td>
<td>99% Showing complete desensitization</td>
</tr>
<tr>
<td>Keet et al 2012</td>
<td>2012</td>
<td>Randomized, placebo controlled</td>
<td>70</td>
<td>6-17</td>
<td>1,000-2,000 mg</td>
<td>60 wk</td>
<td>70% Desensitized to 8-g OIT; SU in 40% after 6 wk</td>
</tr>
<tr>
<td>Wood et al 2015</td>
<td>2015</td>
<td>Omniflumab OIT, open-label OIT</td>
<td>57</td>
<td>7-32</td>
<td>3,300 mg</td>
<td>24 mo</td>
<td>80% Desensitized to 10-g OIT; SU in 42% after 8 wk</td>
</tr>
</tbody>
</table>

Predicting Symptoms from OIT

Incidence rate ratios of the influence of baseline characteristics on the prevalence of AEs, overall and during the buildup and maintenance phases of OIT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall AEs</th>
<th>Buildup AEs</th>
<th>Maintenance AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>P value</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Sex (female compared with male)</td>
<td>0.7 (0.4-1.2)</td>
<td>.24</td>
<td>0.6 (0.3-1.0)</td>
</tr>
<tr>
<td>Age (per 1-y increase)</td>
<td>1.0 (0.9-1.1)</td>
<td>.89</td>
<td>1.1 (0.9-1.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.9 (0.5-1.4)</td>
<td>.55</td>
<td>0.6 (0.4-1.1)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1.2 (0.6-2.2)</td>
<td>.59</td>
<td>1.2 (0.6-2.3)</td>
</tr>
<tr>
<td>AR</td>
<td>2.9 (1.6-5.0)</td>
<td>&lt;.001*</td>
<td>2.1 (1.2-3.8)</td>
</tr>
<tr>
<td>Peanut SPT wheal size (per 5-mm increase)</td>
<td>1.4 (1.1-1.7)</td>
<td>.005*</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>Log peanut IgE (per log increase)</td>
<td>0.9 (0.7-1.0)</td>
<td>.14</td>
<td>0.9 (0.7-1.0)</td>
</tr>
</tbody>
</table>
Predicting Symptoms from OIT

A

Antihistamines
Albuterol
Steroids

Emergency Department

Number of AEs
No Epinephrine

0 50 100 150 200 250

B

Cough
Moderate
Severe
Wheeze
Moderate
Severe
Hives
Severe
Abd Pain
Moderate
Severe
Vomiting
Moderate
Severe

Number of AEs
No Epinephrine

0 10 20 30 40

FIG 4. Frequencies of AEs resulting in epinephrine use. Patterns of use of epinephrine concurrently with administration of antihistamines, albuterol, oral corticosteroids, or an ED visit (A), and in response to specific symptoms (cough, wheeze, hives, abdominal [Abd] pain, or vomiting) (B). Overlap of AEs with 2 or more given symptoms (ex: cough and wheeze) may be present.

EPIT—Where Do We Stand?

- DBV Viaskin MILES and PEPITES in Phase 2/3
- Far fewer published data vs OIT
  - Early data note that 70% had a 10-fold dose increase, no serious AEs
  - MILES data noted all AEs associated with site urticaria/redness
  - Milk EPIT induced T_{reg}s protect from anaphylaxis in adoptive transfer
  - Higher numbers of T_{reg}s were produced in EPIT vs OIT, persisted after EPIT stopped
  - EPIT was not associated with EoE in murine models vs OIT
- Phase III peanut trial showed significant effect for 250mcg patch with good safety
- Phase II milk trial showed significant effect for 250mcg patch also with good safety

PEPITES Design

356 peanut allergic children
33 centers in US, Canada, Austria, Germany, Iceland

Study Population
- Highly allergic patients ages 6-11
  - \( > 0.7 \text{ kU/L peanut-specific IgE} \) and \( \geq 6 \text{ mm MDST} \) wheal
- Reactor dose at \( M0 \leq 300 \text{ mg peanut protein} \) (i.e., approximate 1 peanut)

Efficacy Endpoints
- Treatment responder definition:
  - Assessed using DBPCFC**
  - For subjects with a M0 ED*** < 10 mg: responder if ED \( \geq 300 \text{ mg} \) at M12
  - For subjects with a M0 ED > 10 mg: responder if ED \( \geq 1,000 \text{ mg} \) at M12

Key secondary endpoints:
- CBQ*** changes in peanut skin and skinG4

Baseline
- 1 mg
- 3 mg
- 10 mg
- 30 mg
- 100 mg
- 300 mg

Month 12*
- 1 mg
- 3 mg
- 10 mg
- 30 mg
- 100 mg
- 300 mg
- 1,000 mg
- 2,000 mg

OFC protocol

PEPITES Entry Characteristics

356 Patients Randomized
- Active: 238
- Placebo: 118

Peanut Eliciting Dose (mg)
- Median: 100
- Mean: ~140

Medical History of Patients
- Asthma: 169 (47.5%)
- Eczema/Atopic Dermatitis: 218 (61.2%)
- Allergic Rhinitis: 199 (55.9%)
- Polyallergic: 305 (85.7%)

PEPITES Main Results

Response rate was statistically significant, but 15% lower bound of the 95% CI proposed in the SAP submitted to FDA was not reached

<table>
<thead>
<tr>
<th>Response Rate (ITT)</th>
<th>% of Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=118</td>
<td>13.6%</td>
</tr>
<tr>
<td>Vialskin Peanut 250 μg N=238</td>
<td>35.3%</td>
</tr>
</tbody>
</table>

Δ = 21.7%  
p = 0.000001

NNT 4.6 (ARR 21.7%)

LCL 12.4  
UCL 25.8

Differentiated Safety Profile

- Favorable tolerability and compliance observed
- 1.1% dropout due to treatment emergent adverse events (TEAEs)
- Most commonly reported adverse events were application site reactions, which were generally mild to moderate
- Mean patient compliance above 95%


PEPITES Change in Reactive Dose

CRD After 12 Months (Mean and Median, ITT)*

Mean = 361 mg
Median = 144

Mean = 905.7 mg
Median = 444

ps <0.001

Mean = 500 mg

Mean = 1,000 mg

Placebo n = 118
Vialskin Peanut 250 μg n = 238

**Longer Term Outcomes: VIPES Study**

- Unlike in OIT, changes in EPIT may occur over a longer horizon
- Data on mean CRD and response improved through year 2 and 3 of study

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**MILES Entry Criteria and Design**

- **Study Population**
  - Children (3-12) and adolescents (12-17)
  - Highly sensitive to milk (≥ 10 kU/L, milk-specific ≥6 and ≥ 6 mm Hg** for ≥ 6 mm Hg
  - Reactive dose at baseline (≤ 30 mg cow’s milk protein (CMP) or ≤ 0.4 mL of cow’s milk)

- **Efficacy Endpoints**
  - Treatment responder definition at M12:
    - ≥ 10-fold increase in CRD** and at least 144 mg of CMP
    - OR CRD ≥ 1,444 mg
  - Key secondary endpoints:
    - Change from baseline in IgE, IgG4

- **198 patients randomized**
  - 152 Children (2-11)
  - 46 Adolescents (12-17)

- **CRD of Cow’s Milk**
  - Mean
    - Children: 216.3 mg
    - Adolescents: 222.0 mg
  - Median
    - Children: 144 mg
    - Adolescents: 144 mg

- **Medical history of patients**
  - Asthma: 139 (70.2)
  - Atopic Dermatitis: 139 (70.2)
  - Allergic Rhinitis: 144 (72.7)
  - Polyallergic: 170 (89.9)

- **Mean Cow’s Milk sIgE**
  - Children: 135.2 kU/L
  - Adolescents: 127.9 kU/L
MILES Phase II Results

For the 300ug dose, NNT was 3.93 (ARR 25.4%)
Unclear why response at 300ug was optimal
High placebo rate likely reflects difficulty of treating an allergen that has a favorable natural history


What Motivates Parents to Seek Therapy

Study Features
- 45 minute semi-structured interviews transcribed verbatim
- 22 patients interviewed (6 OIT, 16 EPIT)
- Questions probed caregiver motivations/goals for therapy, treatment expectations and trade-offs, family lifestyle, and emotions surrounding life with peanut allergy.

Summary of Key Themes

<table>
<thead>
<tr>
<th>Theme</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theme 1</td>
<td>Peanut allergy therapy only needs to provided minimal protection with minimal risks</td>
</tr>
<tr>
<td></td>
<td>a. Desire for a buffer</td>
</tr>
<tr>
<td></td>
<td>b. Understanding that therapy wasn’t a cure.</td>
</tr>
<tr>
<td>Theme 2</td>
<td>How the buffer translates to meaningful impact on quality of life</td>
</tr>
<tr>
<td></td>
<td>a. Decreasing reaction severity</td>
</tr>
<tr>
<td></td>
<td>b. Enhancing social activity</td>
</tr>
<tr>
<td>Theme 3</td>
<td>Helping others by advancing science</td>
</tr>
</tbody>
</table>

Caregiver definitions of what a “buffer” represents, with example quotes

**Barrier Objective**

- Sample Quotation
  - The child would tolerate ingestion of a higher amount of total peanut protein than their pre-therapy baseline (which was measured as a primary outcome for both the OIT and EPIT trials)
  - “We'd like him to be bite proof.”
- The child would have less severe symptoms resulting from ingestion than at pre-therapy baseline;
  - “So my goal and his goal is that if there’s ever accidental exposure…that it’s not gonna end up landing him in the emergency room…It’s just if we could just curb the reactions a little bit and minimize the likelihood of them that’s kind of our goal.”
  - “We’d like him to be able to accidentally ingest his allergen and not have anaphylaxis. And that would be, if we could get there I would consider that a success.”
- Any resulting allergic reaction to peanut would take longer to manifest and peak (a “slower reaction”), allowing for more time for someone to assess the child and administer treatment
  - “We’ve got a chance if he gets exposed that it doesn’t mean he’s going to die. It means we see the symptoms, we catch them quick enough, and hopefully everything will be okay.”
- Favorable safety, tolerability and compliance
  - Overall discontinuation rate of 4.5%
  - 1.5% dropout due to adverse events
  - Most adverse events were related to application site, and were mild to moderate
  - No SAEs or epinephrine use related to treatment
  - Treatment adherence was high, with a mean patient compliance > 95%
Drivers of Food Allergy Quality of Life

The Facts

- 8% prevalence among children
  - No known cure or treatment
  - Some allergies are lifelong
- Reaction severity is poorly predictable
- Accidental reactions from trace amounts may occur
- Associated with anxiety and stress
- High cost to society
  - $24.88/year ($4,184/patient/year)

The Burdens

- Fear of accidental reaction, and persistent vigilance toward prevention
- Fear of hidden ingredients
- Fear of being able to treat a reaction
- Burden of no cure for the disease
- Burden of food avoidance/label reading
- Limitation of activity/travel
- Social stigma/inclusion and interactions
- Bullying
- Empowerment (or lack thereof)

QoL is Different Between Populations

- There is no "singular" food allergic population—this is quite segmented
- Each segment of this population feels this burden differentially
- Total and domain specific QoL worse in self-reported population
- Noted also for anaphylaxis, epinephrine use, and by allergen (milk/egg worse than peanut/tree nut)
- Why would we expect attitudes and preferences for treatment to be any less segmented?

Ward CA and Greenhawt MJ. J Allergy Clin Immunol Pract 2016; 4: 257-64.e3
QoL as an OIT Outcome Measure

- Limited patient reported outcomes from OIT
  - Stanford group: Significant improvement vs. baseline over time (24m), all domains/times, more change in older pts or those undergoing >4 food OIT (both multi-food and omalizumab trials)
  - Factor et al: QoL noted to significantly improve after reaching 450mg maintenance dose
  - Anagnostou et al (STOP II trial): QoL scores noted to improve after OIT to 800mg peanut maintenance dose
  - Epstein Rigbi et al: selected QoL domains improve during buildup to maintenance in some, though some with good baseline QOL deteriorated and some with poor baseline QOL improved

- Being assessed in current OIT and EPIT trials, but using a parent proxy index, or only assessing older child’s impression. Not assessing caregiver impact

QoL and Treatment: Needs Assessment

- Understand what contributes to poor QoL so we know what we are modifying
  - Weight/importance of child vs. caregiver QoL with respect to treatment
  - Bark worse than the bite--disease perception vs. reality must be better aligned

- Understand heterogeneity in QoL
  - Determine effect of MD knowledge, practice variation

- Integration of QoL as a clinical outcome
  - Is it QoL that changes, or their self-efficacy, or something else
  - Parent proxy child QoL is not the same as the child’s QoL, or the parent QoL.
  - Must move towards developing more specific interventions and tools to improve QoL
The Evolving Saga of Prevention Advice

**Pre-2000’s**
- You want to know what to avoid or include in your baby’s diet to prevent what?
- We don’t have any advice for that!

**2000**
- Delayed introduction of these highly allergenic foods in infants at high risk for allergic disease, to prevent development of future allergy
  - Cow’s milk until age 1 year, egg until age 2 years, peanuts, tree nuts, and fish until age 3 years

**2008**
- No convincing evidence for delaying the introduction of specific highly allergenic foods, but no specific guidelines on when and how to introduce the highly allergenic foods listed above.

**2010-14**
- Emerging data suggest the delayed introduction of complementary foods may increase the risk of food allergy, asthma, or eczema, and the early introduction of allergenic foods may prevent these outcomes.

• But, since 2008, 7 major studies have been performed that provide us much better data....

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### Table: Key Studies and Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Full Title</th>
<th>Study Type</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAP (UK)</td>
<td>Learning Early About Peanut Allergy</td>
<td>Non-blinded RCT (n=640)</td>
<td>High-risk infants</td>
<td>Thrice weekly consumption of 2g of peanut protein vs delayed avoidance of peanut after randomization at 4-11 months, through 60 months of life</td>
<td>IgE-mediated peanut allergy based on OFC at month 60</td>
<td>ITT analysis showed prevalence of peanut allergy 13.7% in the consumption group (p=0.001)</td>
</tr>
<tr>
<td>EAT (UK)</td>
<td>Enquiring About Tolerance</td>
<td>Non-blinded RCT (n=1303)</td>
<td>Standard risk: kids until severe eczema</td>
<td>Early introduction group (EIG) introduced 2g of protein twice weekly at 3 months of peanut, cooked egg, cow’s milk, sesame, whitefish, wheat Standard introduction group (SIG) at 6 months of above 6 foods</td>
<td>IgE-mediated food allergy to 1 or 3 years of age based n OFC</td>
<td>ITT analysis showed no difference in food allergy between EIG vs SIG PP analysis showed significantly less prevalence of peanut allergy (p=0.003) and egg allergy (p=0.009) in EIG vs SIG</td>
</tr>
<tr>
<td>STAR (Australia)</td>
<td>Solids Timing for Allergy Reduction</td>
<td>Blinded RPCT (n=86)</td>
<td>High-risk infants with moderate to severe eczema</td>
<td>Daily consumption of egg vs placebo powder from 4-8 months 0.9 g raw whole egg powder daily (0.4 g protein/day) Cooked egg at 8 months</td>
<td>IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC</td>
<td>Study terminated early: 1/3 of patients reacted to egg at entry OFC At 12 months, 33% had egg allergy in egg group vs 51% in control (not significant)</td>
</tr>
<tr>
<td>STEP (Australia)</td>
<td>Starting Time for Egg Protein</td>
<td>Blinded RPCT (n=820)</td>
<td>Intermediate risk: Infants with 1st degree relative with atopy Infants: neg egg SPT</td>
<td>Daily consumption of egg vs placebo powder from 4-6.5 months 0.9 g raw whole egg powder daily (0.4 g protein/day)</td>
<td>IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC</td>
<td>No significant differences in egg allergy between groups No anaphylactic reactions at initial egg intro</td>
</tr>
<tr>
<td>BEAT (Australia)</td>
<td>Beating Egg Allergy Trial</td>
<td>Blinded RPCT (n=319)</td>
<td>Intermediate risk: Infants with 1st degree relative with atopy Infants: neg egg SPT</td>
<td>Daily consumption of egg vs placebo powder at 4 months 350 mg protein daily raw whole egg powder Cooked egg at 8 months</td>
<td>Sensitization to egg by SPT at 12 months of age</td>
<td>Subjects in egg group vs placebo had significantly less egg sensitization (10.7% vs 20.5%, p=0.03) No harm with egg intro</td>
</tr>
<tr>
<td>HEAP (Germany)</td>
<td>Hens Egg Allergy Prevention</td>
<td>Blinded RPCT (n=406)</td>
<td>Normal risk general population Infants with IgE &lt;0.35 kU/L at enrollment</td>
<td>Thrice weekly 2.5 g egg protein from 4-6 months of age until 12 months</td>
<td>Sensitization to egg based on egg IgE &gt;0.35 kU/L at 12 months of age</td>
<td>No evidence of preventing egg sensitization or allergy High rate of anaphylaxis at egg introduction at entry</td>
</tr>
<tr>
<td>PETIT (Japan)</td>
<td>Preventing egg allergy in infants with AD</td>
<td>Blinded RCT (n=121)</td>
<td>High-risk infants with atopic dermatitis</td>
<td>Daily consumption of 50 mg heated egg from 6-9 months Daily consumption of 250 mg heated egg from 9-12 months</td>
<td>IgE-mediated egg allergy at 12 months of age based on OFC</td>
<td>Prevalence of egg allergy 37.7% in placebo vs 8.3% in egg group (p&lt;0.0013) No SAEs</td>
</tr>
</tbody>
</table>
### Pooled Data of Early Introduction Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Events, n</th>
<th>Total, n</th>
<th>Late Events, n</th>
<th>Total, n</th>
<th>Food Allergy</th>
<th>RR</th>
<th>95% Cl</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome = Egg Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perkin 2016</td>
<td>21</td>
<td>569</td>
<td>32</td>
<td>596</td>
<td></td>
<td>0.69</td>
<td>[0.40, 1.18]</td>
<td>30.9%</td>
</tr>
<tr>
<td>Natsume 2016</td>
<td>5</td>
<td>60</td>
<td>23</td>
<td>61</td>
<td></td>
<td>0.22</td>
<td>[0.09, 0.54]</td>
<td>16.7%</td>
</tr>
<tr>
<td>Tan 2016</td>
<td>8</td>
<td>130</td>
<td>13</td>
<td>124</td>
<td></td>
<td>0.59</td>
<td>[0.25, 1.37]</td>
<td>18.2%</td>
</tr>
<tr>
<td>Bellach 2015</td>
<td>2</td>
<td>142</td>
<td>1</td>
<td>156</td>
<td></td>
<td>2.20</td>
<td>[0.20, 23.97]</td>
<td>3.1%</td>
</tr>
<tr>
<td>Palmer 2013</td>
<td>14</td>
<td>42</td>
<td>18</td>
<td>35</td>
<td></td>
<td>0.65</td>
<td>[0.38, 1.11]</td>
<td>31.1%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>943</td>
<td>972</td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>[0.36, 0.87]</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Heterogeneity: P=35.8%, P=0.1829*

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Events, n</th>
<th>Total, n</th>
<th>Late Events, n</th>
<th>Total, n</th>
<th>Food Allergy</th>
<th>RR</th>
<th>95% Cl</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome = Peanut Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perkin 2016</td>
<td>7</td>
<td>571</td>
<td>15</td>
<td>597</td>
<td></td>
<td>0.49</td>
<td>[0.20, 1.19]</td>
<td>45%</td>
</tr>
<tr>
<td>Du Toit 2015</td>
<td>10</td>
<td>312</td>
<td>54</td>
<td>313</td>
<td></td>
<td>0.19</td>
<td>[0.10, 0.36]</td>
<td>95%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>883</td>
<td>910</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
<td>[0.11, 0.74]</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Heterogeneity: P=66.1%, P=0.0857*

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Events, n</th>
<th>Total, n</th>
<th>Late Events, n</th>
<th>Total, n</th>
<th>Food Allergy</th>
<th>RR</th>
<th>95% Cl</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome = Milk Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perkin 2016</td>
<td>3</td>
<td>569</td>
<td>4</td>
<td>597</td>
<td></td>
<td>0.79</td>
<td>[0.18, 3.50]</td>
<td>32.7%</td>
</tr>
<tr>
<td>Lowe 2011</td>
<td>6</td>
<td>193</td>
<td>8</td>
<td>191</td>
<td></td>
<td>0.74</td>
<td>[0.26, 2.10]</td>
<td>67.3%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>762</td>
<td>788</td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
<td>[0.32, 1.78]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

*Heterogeneity: P=10%, P=0.3469*

---

### So What Do These Data Suggest?

- UK Food Standards sponsored a recent evidence review
  --16,289 titles screened, 51 studies identified

- “Moderate certainty evidence” from 5 egg trials for protective benefit of early egg introduction at 4-6 months
  --44% lower risk, prevents 24 cases of allergy per 1000 children

- “Moderate certainty evidence” from 2 trials for protective benefit for early peanut introduction
  --71% lower risk, prevents 18 cases of allergy per 1000 children
LEAP Results Influence on NIAID Policy

The study effect, in plain English........  Negative skin test  Positive skin test  Total
Feed this many infants peanuts to prevent one case of peanut allergy 8.5 4 7.1

Take home messages
• This worked very well—there was clear benefit for early introduction vs. avoidance, good NNT is <10
• This worked even if you had a positive skin test, showing it halted an allergy-in-progress
• The effect was not temporary—even after not eating peanut for a year, in each group there were only 3 new cases of peanut allergy (LEAP-On study)

NIAID Peanut Prevention Addendum

<table>
<thead>
<tr>
<th>Addendum Guideline</th>
<th>Infant Criteria</th>
<th>Recommendations</th>
<th>Earliest Recommended Age of Peanut Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe eczema, egg allergy or both</td>
<td>Strongly consider evaluation by sIgE and/or SPT, and if necessary an oral food challenge. Based on test results, introduce peanut containing foods</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Timing of introduction is age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>
Comparing NIAID vs. Other Guidelines

Australia/New Zealand (ASCIA)  
- When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breast-feeding.
- All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products in the first year of life. This includes infants at high risk of allergy.
- Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.
- No specific screening, testing, evaluation recommendations prior to introduction.

UK Department of Health  
- Exclusive breastfeeding for around the first six months of life.
- Foods containing peanut and hen’s egg need not be differentiated from other complementary foods and should be introduced in an age-appropriate form from around six months of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child.
- The deliberate exclusion of peanut or hen’s egg beyond six to twelve months of age may increase the risk of allergy.
- Once introduced, and where tolerated, these foods should be part of the infant’s usual diet, to suit both the individual child and family.
- Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

Primary Prevention with Other Foods  
- **EAT study:** Weak but significant effects for egg and peanut only in per protocol. No effect for any other allergen, shows non-inferiority  
  - 68% unable to follow protocol in the early intro group. Influenced by perceived sx, nonwhite race, poor caregiver QoL, eczema. Adherence: milk 85%, peanut 62%, fish 60%, sesame 51%, egg 43%
- **Milk:**
  - Katz et al Israeli observational birth-cohort of 13,019 infants. 1 yr cumulative incidence of milk allergy 0.5% (66/13,019), but 0.05% (introduction < 14d) vs. 1.75% (105-194d) (OR 19.3)
  - Onizawa et al. Japanese retrospective case-control study of 51 milk allergic vs 102 controls and 32 egg allergic children. 69% of the CMA children had milk in the first month of life versus 88% in the non-CMA infants (OR 4.57)
- **Fish:**
  - Finnish cohort has suggested fish consumption in 1st year associated with reduced risk of rhinitis, eczema, asthma, and food/pollen sensitization at 4y (RR=0.76)
The Role of Dietary Diversity

- Timing of solid food introduction may not be the only factor promoting tolerance
  - Diverse exposure to a variety of foods in early childhood may be equally as important
- Roduit et al: diversity of commonly eaten food in Swiss infants in 1st year of life showed protective association against asthma, eczema and food allergy at age 6
- Nwaru et al: diversity of commonly eaten food in Finnish infants at 3 mo showed protective association against risk of "atopic sensitization" including foods at age 5
- Maslin et al: in infants with eczema, a more diverse diet in first year of life prevented challenge proven food allergy at age 3
- Perkin et al: both cohorts exposed to 5 foods between 3-6 mo or 6-9mo, very low rates of food allergy developed overall
- No interventional trial done to show potential causal effects, however

Conclusions

- Multiple potential approaches to treating food allergy may exist
- None have long-term efficacy
- Quality of life as a treatment outcome is still being defined
- Entering into a therapy is a very complex decision
- Key is to understand the caregiver goals for seeking therapy
- Prevention strategies for early allergen introduction expected to help decrease the ultimate number of food allergic individuals
- Early introduction may not be the only important dietary factor associated with prevention