A LEAP FORWARD IN FOOD ALLERGY PREVENTION

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• Consulting honorarium from Horizon Pharma

Objectives
• 1. Describe the risk factors, clinical presentation, laboratory & skin testing findings of peanut allergy.
• 2. Discuss the pathophysiology of peanut allergy and role of oral tolerance in prevention.
• 3. Select the appropriate preventive therapies for at risk patients.
Outline

- Peanut History
- Peanut Prevalence
- AAP Recommendations
- LEAP Study
- LEAP-ON Study and other interventions
- Conclusions

1500 BC
Peanuts used in South America/Mexico

1700s AD
Africans introduce it to N. America

1900s AD
Boil weevil decimates cotton, Dr. GW Carver suggests peanuts

1800s AD
First commercial crops in Virginia

1600s AD
Europeans arrive and spread it to Asia and Africa

1990s AD
Peanut allergy rates rising

http://nationalpeanutboard.org

Peanut allergy (PA) prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for definition</th>
<th>Method</th>
<th>Survey year</th>
<th>Prevalence per 1000 US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor et al.</td>
<td>Self-reported allergy and reactions</td>
<td>Telephone survey</td>
<td>2006</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>MAVIS 2005-2006</td>
<td>Clinical allergy based on skin tests (2)</td>
<td>Nationally representative survey</td>
<td>2005-2006</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>MAVIS 2006-2006</td>
<td>Peanut allergy ( &lt; 3 ) yrs</td>
<td>Nationally representative survey</td>
<td>2006-2006</td>
<td>1.8 (95% CI 1.5-2.2)</td>
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<td>MAVIS 2007-2007</td>
<td>Self-reported allergy ( &lt; 6 ) yrs</td>
<td>Nationally representative survey</td>
<td>2007-2008</td>
<td>1.8 (95% CI 1.5-2.2)</td>
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<tr>
<td>Editor et al.</td>
<td>Self-reported allergy and reactions</td>
<td>Telephone survey</td>
<td>2008</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>MAVIS 2008-2009</td>
<td>Self-reported allergy ( &lt; 6 ) yrs</td>
<td>Nationally representative survey</td>
<td>2008-2009</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>MAVIS 2009-2010</td>
<td>Self-reported allergy ( &lt; 6 ) yrs</td>
<td>Nationally representative survey</td>
<td>2009-2010</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>Baylor University Study ( 8 )</td>
<td>Self-reported allergy</td>
<td>Mail survey</td>
<td>2009-2010</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
<tr>
<td>Ziman et al.</td>
<td>Self-reported allergy and reaction history</td>
<td>Electronic survey</td>
<td>2009-2010</td>
<td>1.8 (95% CI 1.5-2.2)</td>
</tr>
</tbody>
</table>


[Additional content not included in the image]
Audience Question

• Question 5: True or False:
  A blood or skin allergy test alone can diagnose a food allergy.
  • True
  • False

Project Viva

TABLE II. Prevalence of peanut allergy among school-age children in a US observational birth cohort not selected for any disease (N = 616)

<table>
<thead>
<tr>
<th>Criteria for definition</th>
<th>No.</th>
<th>Prevalence percent (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported reaction and symptoms</td>
<td>27</td>
<td>4.6 (2.9-6.3)</td>
</tr>
<tr>
<td>Clinical food allergy based on sIgE criteria†</td>
<td>31</td>
<td>5.0 (3.5-7.1)</td>
</tr>
<tr>
<td>Peanut sIgE ≥ 0.35 kU/L and prescribed epinephrine auto-injector</td>
<td>29</td>
<td>4.9 (3.2-6.7)</td>
</tr>
<tr>
<td>Peanut sIgE ≥ 14 kU/L†</td>
<td>18</td>
<td>2.9 (1.6-4.3)</td>
</tr>
<tr>
<td>Peanut sIgE ≥ 14 kU/L and prescribed epinephrine auto-injector</td>
<td>12</td>
<td>2.0 (0.9-3.2)</td>
</tr>
</tbody>
</table>

Why do we care?

• Food allergy is the leading cause of anaphylaxis treated in ERs each year
  • 30,000 anaphylactic reactions
  • 2000 hospitalizations
  • 200 deaths
  • Allergies to peanuts and tree nuts account for the majority of fatal and near-fatal
• 90% US households consume peanuts
  • Found in many products
    • Amounts in Precautionary Allergy Labeling (0.0% to 32.4%)
    • US #3 producer in the world behind China and India


2000 AAP Recommendations

- Infants at high risk for developing allergy. . . Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:
  - a) Breastfeeding mothers should continue breastfeeding for the first year of life or longer. . . Mothers should eliminate peanuts and tree nuts (eg, almonds, walnuts, etc) and consider eliminating eggs, cow’s milk, fish, and perhaps other foods from their diets while nursing. Solid foods . . . introduced . . . until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
  - b) No maternal dietary restrictions during pregnancy are necessary with the possible exception of excluding peanuts;

2008 AAP Recommendations

- Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease . . .
- . . . there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease.
- Additional studies are needed to document the long-term effect of dietary interventions . . .

Why didn’t it work?

- Skin sensitization?
  - Eczema and PA correlated
  - Peanut based oils in breast creams and other skin care products
  - Presence of peanut in dust (bed and kitchen)
    - Norwegian adolescents
    - German households
    - Mouse models of cutaneous sensitization
- Lack of oral tolerance?
  - Mouse models with Ovalbumin, Peanut or β-lactoglobulin administration
  - Human study of oral exposure to nickel (braces) prior to ear piercing showed lower rates of sensitization
  - Early egg introduction study in eczema infants
Worldwide differences

- Study of ~4000 children each in Tel Aviv, Israeli and North London, UK Jewish children (recent immigrants)
- Use of Food Allergy Questionnaire
  - Peanut Allergy definition was self report of symptoms within 2 hours of ingestion
  - Subgroup evaluated by sIgE or SPT (95% PPV) or positive Oral food challenge
- Use of Food Frequency Questionnaire
  - Asked when do you introduce foods on weaning
- Peanut Allergy Prevalence: 0.17% Israel vs 1.8% UK (Peanuts)
  - High risk infants: 0.79% vs 6.46%


Higher rates in UK vs Israel

**Table:** The ratio of the risk of food allergies in the UK compared with Israel

<table>
<thead>
<tr>
<th></th>
<th>Peanut</th>
<th>Breastfeeding</th>
<th>Tree nuts</th>
<th>Sunflower</th>
<th>Sesame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>RR 16.6</td>
<td>RR 21.4</td>
<td>RR 10.8</td>
<td>RR 7.1</td>
<td>RR 20.0</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>RR 16.6</td>
<td>RR 21.4</td>
<td>RR 10.8</td>
<td>RR 7.1</td>
<td>RR 20.0</td>
</tr>
</tbody>
</table>

- 47 of 81 of PA clinically evaluated; 36 (77%) confirmed PA, rest were tolerant
- Adjust for this and worst case scenario then RR 5.4 (2.4-12.2)

Food introduction
Bamba
- 25% of the Israeli snack market
  - Product since 1964
  - Roasted peanut butter flavored puffed maize
- Similar Ara H 1, 2, & 3 content as roasted peanut butter from UK
- 2 grams of peanut protein per 17 grams of Bamba

Learning Early About Peanut Allergy (LEAP) Study
- A randomized controlled trial in high risk infants that aims to determine which is the best strategy for the prevention of PA
  - Early introduction of peanut into the diet
  - Complete avoidance
- Recruitment focused on
  - (1) child health professionals such as dermatologists, allergists, and specialist nurses
  - (2) a study flyer posted to parents of young infants in the United Kingdom
  - (3) other avenues, such as written and electronic media and word of mouth

High Risk Population
- Eczema risk factor
  - (1) frequent need for treatment with topical corticosteroids or calcineurin inhibitors
  - (2) parental description of “a very bad rash in joints and creases” or “a very bad itchy, dry, oozing, or crusted rash,”
  - (3) a severe SCORAD grade (>40) by a clinician
- Egg allergy risk factor
  - (1) an SPT-induced wheal diameter of 6mm or greater with raw hen’s egg white and no history of previous egg tolerance
  - (2) an SPT-induced wheal diameter of 3 mm or greater with pasteurized hen’s egg white with a history of an allergic reaction to egg
Baseline Testing

- SPTs
  - Egg, Peanut, cow’s milk, sesame, soya
- Specific IgE
  - Peanut, Egg, Cow’s milk, sesame, brazil nut, hazelnut, cashew, almond, walnut
- SCORAD score

[Flowchart images]

- Enrolled in LEAP?
  - Yes
  - 542 Group II SPT - negative
  - Group III SPT - positive
  - 640
  - No
Black race, egg allergy or eczema are significantly associated with peanut sensitization assessed by sIgE

Egg allergy or eczema are significantly associated with SPT also

### Table 1. Baseline characteristics for the LEAP screening study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (mean, SD)</td>
<td>7.4 (1.8)</td>
<td>7.1 (2.0)</td>
<td>7.0 (1.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Latino race</td>
<td>48.9% (25)</td>
<td>47.0% (12)</td>
<td>49.6% (41)</td>
<td>0.59</td>
</tr>
<tr>
<td>Female</td>
<td>52.1% (10)</td>
<td>57.5% (10)</td>
<td>52.1% (10)</td>
<td>0.59</td>
</tr>
<tr>
<td>White</td>
<td>47.9% (9)</td>
<td>42.5% (8)</td>
<td>47.9% (9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Black</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.9% (0)</td>
<td>7.5% (0)</td>
<td>8.9% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Other</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Family history of peanut allergy</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>History of peanut allergy</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>SPT-positive花生 (n, %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Nut sensitivity</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Food sensitivity</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

### Table 2. OR estimates (95% CI) for prediction of peanut-specific sIgE comparing 0.15 kUA/L or greater to less than 0.15 kUA/L

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for all variables except peanut SPT response</th>
<th>Adjusted for all variables including peanut SPT response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race</td>
<td>4.2 (1.1-15.2)</td>
<td>4.9 (1.5-16.2)</td>
<td>4.9 (1.5-16.2)</td>
</tr>
<tr>
<td>Female</td>
<td>1.4 (0.4-4.9)</td>
<td>1.5 (0.4-5.3)</td>
<td>1.5 (0.4-5.3)</td>
</tr>
<tr>
<td>White</td>
<td>1.6 (0.3-8.6)</td>
<td>1.6 (0.3-8.6)</td>
<td>1.6 (0.3-8.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.2 (1.1-15.2)</td>
<td>4.9 (1.5-16.2)</td>
<td>4.9 (1.5-16.2)</td>
</tr>
<tr>
<td>SPT-positive花生 (n, %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nut sensitivity</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>History of peanut allergy</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

- Black race, egg allergy or eczema are significantly associated with peanut sensitization assessed by sIgE
- Egg allergy or eczema are significantly associated with SPT also

### Table 3. OR estimates (95% CI) for prediction of skin test-inducible wheal size in models comparing 1.5 mm or greater than 0.6 mm wheals without 0.6 mm wheals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for all variables except peanut SPT response</th>
<th>Adjusted for all variables including peanut SPT response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race</td>
<td>3.9 (0.7-14.6)</td>
<td>4.0 (0.7-14.6)</td>
<td>4.0 (0.7-14.6)</td>
</tr>
<tr>
<td>Female</td>
<td>1.1 (0.2-3.0)</td>
<td>1.1 (0.2-3.0)</td>
<td>1.1 (0.2-3.0)</td>
</tr>
<tr>
<td>White</td>
<td>2.6 (0.8-7.3)</td>
<td>2.6 (0.8-7.3)</td>
<td>2.6 (0.8-7.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.9 (0.7-14.6)</td>
<td>4.0 (0.7-14.6)</td>
<td>4.0 (0.7-14.6)</td>
</tr>
<tr>
<td>SPT-positive花生 (n, %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nut sensitivity</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>History of peanut allergy</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>
LEAP Study Population

• Inclusion Criteria
  • Ages ≥4 to <11 months old who have had solids successfully introduced into their diet.
  • Egg allergy, severe eczema, or both.
• Exclusion Criteria
  • Chronic illness, except for eczema or recurrent wheeze.
  • SPT >4 mm in the presence of a negative saline control.
  • Previous or current consumption of peanut protein >0.2g
  • Investigator-suspected allergy
  • Diagnosis of persistent asthma.
  • Liver, renal or hematologic abnormalities
  • 640 infants (2006-2009), randomized
  • Oral Food Challenge at 5 years of age

Study Protocol

• SPT testing done for primary (0mm) vs secondary intervention
• Randomized to either consumption or avoidance
  • OPEN Label Consumption Arm:
    • At least 2 g of peanut protein 3 times per week until 60 months of age
• Primary Endpoint
  • The proportion of participants with peanut allergy at 60 months of age by DBPCFC or Open Challenge.
• Secondary Endpoints
  • Aeroallergen sensitization and incidence of allergic rhinitis and asthma at 30 and 60 months of age
  • At 60 months of age other food challenges.
  • Incidence of adverse events and laboratory abnormalities
  • Results of cellular and humoral assessments of immune response related to the development of allergy or tolerance to specific allergens.

Demographics
Primary Intervention Outcomes

- Avoidance: 13.7%  
- Consumption: 1.9%  
- 11.8% (3.4-20.3%)  
- 86% reduction

Secondary Intervention Outcomes

- Avoidance: 35.3%  
- Consumption: 10.6%  
- 24.7% (4.9-43.3%)  
- 70% reduction
Outcomes of Peanut Consumption

• 4 of the 7 who had positive OFC at baseline had one at 60 months
• 6 of the 9 peanut consumption group who discontinued treatment had positive OFC at 60 months
  • Stopped between 6m to 39m of age due to eczema or Type 1 Hypersensitivity reactions
  • 6m required IM Epinephrine at home
  • 1 patient stopped due to FPIES reaction
• 10 total patients in Peanut consumption group had peanut allergy
  • 4 were positive at baseline
  • 6 stopped consuming because of intolerance

### Table S3. Primary and Secondary Prevention for Different Levels of Sensitization

<table>
<thead>
<tr>
<th></th>
<th>Peanut Avoidance</th>
<th>Peanut Consumption</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Allergic</td>
<td>172 (94.9%)</td>
<td>155 (99.4%)</td>
<td>327 (98.1%)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Allergic</td>
<td>11 (6.0%)</td>
<td>2 (1.6%)</td>
<td>13 (3.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Prevention Group</strong></td>
<td></td>
<td></td>
<td></td>
<td>-0.0001*</td>
</tr>
<tr>
<td>Not Allergic</td>
<td>87 (95.9%)</td>
<td>110 (95.2%)</td>
<td>197 (94.4%)</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td>4 (4.1%)</td>
<td>5 (4.8%)</td>
<td>9 (5.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>SPT-Negative &amp; IgE Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td>-0.0001*</td>
</tr>
<tr>
<td>Not Allergic</td>
<td>94 (96.4%)</td>
<td>97 (97.2%)</td>
<td>191 (97.3%)</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td>25 (25.5%)</td>
<td>2 (2.2%)</td>
<td>27 (27.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>SPT-Positive &amp; IgE Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
</tr>
<tr>
<td>Not Allergic</td>
<td>22 (92.9%)</td>
<td>24 (92.9%)</td>
<td>46 (93.7%)</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td>15 (60.0%)</td>
<td>13 (60.0%)</td>
<td>28 (60.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>SPT-Positive &amp; IgE Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.1599*</td>
</tr>
<tr>
<td>Not Allergic</td>
<td>11 (78.6%)</td>
<td>10 (78.6%)</td>
<td>21 (78.6%)</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td>3 (21.4%)</td>
<td>3 (21.4%)</td>
<td>6 (21.4%)</td>
<td></td>
</tr>
</tbody>
</table>

### SPT Wheal Size

- SPT Wheal Size
- Graph showing distribution of SPT Wheal Size
IgG, IgG4, and Ratio

Adverse events

- Peanut consumption group
  - URIs
  - Viral skin infections
  - Gastroenteritis
  - Urticaria
  - Conjunctivitis
- 7 positive challenges at baseline required oral antihistamines or glucorticoid
- 57 with positive oral food challenges
  - 9 required IM Epinephrine
Criticisms

- No placebo arm
- Compliance not confirmed throughout study
- 92% Adherence
  - But highly motivated family (2/3 self-enrolled)
- HIGHLY sensitized group or Low Risk group (e.g. Group IV and I)
  - No idea if Bamba would prevent Peanut Allergy

Audience Question

- Question 6: True or False:
  Peanut Oil has allergenic properties.
- True
- False

LEAP-ON study

- At the end of the primary trial, patients instructed to avoid peanuts for 12 months
- Primary outcome: OFC to peanut at the end of the 12-month period
- RESULTS:
  - 550 participants (98.9%) had complete primary-outcome data.
  - Peanut-avoidance group (18.6% [52 of 280 participants] )
  - Peanut-consumption group (4.8% [13 of 270], P<0.001).
  - 3 new cases of allergy developed in each group
  - Prevalence in allergy in the consumption group
    - 3.6% [10 of 274 participants] at 60 months
  - 4.8% [13 of 270] at 72 months, P=0.25
- CONCLUSIONS:
  - Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy. Longer-term effects are not known.
  
Early Introduction of Allergenic Foods

- 1303 exclusively breast-fed infants at 3 months of age randomly assigned to
  - Early introduction of six allergenic foods (peanut, cooked egg, cow’s milk, sesame, whitefish, and wheat; early-introduction group)
  - 2g of protein twice weekly
  - Or current practice recommended exclusive breast-feeding to approximately 6 months of age
- Outcomes: Food allergy to one or more of the six foods between 1 year and 3 years of age challenge proven
- Safety:
  - No episodes of anaphylaxis with home introduction
  - Adherence was poor


Results

CONCLUSIONS
The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis.

The trial did show the efficacy of early introduction of allergenic foods in an per protocol analysis.

No higher rates of food allergy in intervention group.

Conclusions

- Early introduction of peanuts for at risk infants leads to decreased prevalence of peanut allergy.
- Regular consumption was not necessary to retain the effect.

- Early introduction of peanuts and eggs in not at risk infants leads to decreased prevalence of food allergy.
- The same may hold true for other allergenic foods though compliance remains an issue.

- Early introduction of allergenic foods does NOT increase risk of developing food allergy.
Practical Implementation in Your Practice

• At 4 month or 6 month visit (earlier the better)
  • If severe eczema, egg allergy or both
    • Send serum specific IgE testing to peanut only
      • If negative (<0.35 ku/L) then allow home introduction
        - Peanut butter (2 teaspoons) OR peanut flour (1 teaspoon) mixed in 1-2 oz. of formula or fruit/vegetable purees
      • If positive (>0.35 ku/L) then refer to specialist for office challenge to peanut based on level
  • If no severe eczema or egg allergy
    • Encourage early introduction of allergenic foods (age appropriate forms) freely into the diet

Main Papers

• J Allergy Clin Immunol 2008;122:984.
• J Allergy Clin Immunol 2013;131:135-43.

References

• http://nationalpeanutboard.org