Prevention of Food Allergy

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**Disclosures**

During the past 2 years, I **have/had** an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation(s).

<table>
<thead>
<tr>
<th>Financial Interest/Affiliation</th>
<th>Name of Company(s)</th>
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<tbody>
<tr>
<td>Grant/research support</td>
<td>Aimmune Therapeutics</td>
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<td>DBV Technologies</td>
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<tr>
<td>Membership on an advisory panel, standing</td>
<td>Medical Advisory Board for the Food Allergy &amp; Anaphylaxis Connection Team (FAACT);</td>
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<tr>
<td>committee, or board of directors</td>
<td>Clinical Advisory Board for Food Allergy Research &amp; Education (FARE);</td>
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<td>Medical Advisory Council for the National Peanut Board</td>
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<tr>
<td>Other financial or material interest</td>
<td>Royalties: UpToDate; Speaker: Nutricia, Abbott; Consultant: INSYS Therapeutics,</td>
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<tr>
<td></td>
<td>Intrommune Therapeutics, DBV Technologies, AllerGenis, DOTS Technology, Aravax</td>
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Learning Objectives

• Review the advancement in identification of risk factors for the development of food allergy over the last several decades

• Identify which risk factors are modifiable and how any interventions may affect patient management for prevention of food allergy
Risk Factors for Food Allergy

**PRENATAL**
- Genetic Factors
- Family History of Allergy
- Fetal Epigenetic Modification Through Maternal Exposure
- Parents’ Country of Birth
- Maternal Diet During Pregnancy
- Maternal Folate Level

**PERINATAL**
- Gut Microbiota
- Route of Delivery
- Antibiotic Use
- Animal Exposure

**POSTNATAL**
- Maternal Diet During Lactation
- Duration of Breastfeeding
- Atopic Dermatitis and Cutaneous Exposure to Food Allergens
- Introduction of Allergenic Foods
- Age at First Introduction of Foods
- Vitamin D

PRENATAL FACTORS
Genetics: Family History

High risk: at least one first-degree relative (parent or sibling) with an allergic condition (AD, asthma, AR, or food allergy)

<table>
<thead>
<tr>
<th>Family history</th>
<th>No parent with allergies</th>
<th>1 parent with allergies</th>
<th>2 parents with allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Babies who develop allergies</td>
<td>15%</td>
<td>20-40%</td>
<td>60-80%</td>
</tr>
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EXL BM et al. Nutrition 2001; 17:642-51
Genetics: Family History – Is All Risk Equivalent?

Asthma – on ICS
Allergic rhinitis – S/P SCIT
Eczema as child

Kjellman NI. Acta Paediatr Scand 1977
Exl BM and Fritsche R. Nutrition 2001

Asthma – on ICS
Allergic rhinitis – on SCIT

Kjellman NI. Acta Paediatr Scand 1977
Exl BM and Fritsche R. Nutrition 2001
Proposed Risk Gradient of Food Allergy Development Among Infants

- Severe Eczema
- Other Food Allergy
- Mild to Moderate Eczema
- Family History of Atopy
- Sibling with Peanut Allergy
- General Population Infant
Country of Birth, Migration, and FA Risk

Children born in Australia to Asian-born mothers (aOR 2.67, 95% CI 2.28–3.27) were more likely to have nut allergy than non-Asian children, while children born in Asia who subsequently migrated to Australia were at decreased risk of nut allergy (aOR 0.1, 95% CI 0.03–0.31).

Conclusion: Migration from Asia after the early infant period appears protective for the development of nut allergy.
Maternal Avoidance During Pregnancy

Restriction of maternal diet during pregnancy, to avoid highly allergenic foods, does not work and may be harmful.


AAAAI and EAACI, therefore, state that there is no substantial evidence at present to recommend that women modify their diets during pregnancy.
PERINATAL FACTORS
Influence of the Microbiome in Food Allergy: Human Studies

• **Mode of infant delivery**: C-section has been shown to delay gut microbiome development and result in colonization of gut microbiota similar to the skin; this may increase the risk of sensitization to food allergens, but studies with OFC-proven food allergy have shown mixed results.

• **Farming and animal exposure**: presence of a dog in the home was inversely associated with egg allergy diagnosis at 1 year of age in the only OFC-confirmed study (HealthNuts).

• **Antibiotic exposure**: in one study, prenatal and postnatal antibiotic exposure was associated with an increased risk of cow’s milk allergy, but other studies have not shown a statistically significant association.

• **Breastfeeding vs. bottle feeding**: there are microbiota differences depending on feeding form, but differences in extent/duration of breastfeeding and reliance on sensitization of food allergy make conclusions difficult.

A Healthy Gut or a “Diverse” Gut?

**Problem:** We are far from understanding what constitutes a “healthy gut” microbiome, making interpretation of “different” microbiomes difficult.

- Raises the question: Is it the diverse population or particular organisms (or combinations) within that population? And does a diverse population indicate positive outcome?

**Conclusion:** Before we can study possibly modify altering the microbiome for prevention of food allergy, we need to define what is a healthy microbiome.

Matricardi P. Clin Exp Immunol. 2010
POSTNATAL FACTORS
Avoidance Diets During Lactation

Maternal avoidance diets of highly allergenic foods during lactation do not work based on current data, and may even be harmful.

AAAAI And EAACI , therefore, state that there is no substantial evidence at present to recommend that women modify their diets during pregnancy.
Breastfeeding

- Exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age to:
  - Possibly reduce the incidence of atopic dermatitis for children <age 2 years
  - Reduce early onset wheezing <age 4 years
  - Reduce the incidence of cow’s milk allergy (CMA) but not food allergy in general in the first 2 years of life

- The effects of breastfeeding on allergic rhinitis are not clear at this time.

- There is no need to avoid allergens during breastfeeding

- Caveat: these recommendations are based on limited evidence from observational studies that were small, non-randomized, not prospective, and many performed several decades ago

- However, RCTs of breastfeeding will not be performed due to ethical reasons

<table>
<thead>
<tr>
<th>Maternal diet factor</th>
<th>During lactation</th>
</tr>
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<tbody>
<tr>
<td>Prebiotics</td>
<td>No recommendations due to insufficient evidence</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Use recommended for reduced atopic dermatitis/eczema outcomes</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>No recommendation at present</td>
</tr>
<tr>
<td>Food allergen elimination/alteration</td>
<td>Not recommended due to insufficient evidence</td>
</tr>
<tr>
<td>Healthy diet</td>
<td>No current studies</td>
</tr>
</tbody>
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Currently there is no clearly positive recommendation from scientific societies to use pre- or probiotics for prevention of food allergy, allergic rhinitis, and asthma.
Timing of Introduction of Complementary Foods and Atopic Dermatitis
You want to know what to avoid or include in your baby's diet to prevent what now?

We don’t have any advice for that!

<table>
<thead>
<tr>
<th>Pre-2000’s</th>
<th>2000</th>
<th>2008</th>
<th>2010-14</th>
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<tbody>
<tr>
<td>Mothers should eliminate peanut and tree nuts and consider eliminating egg, cow’s milk, fish and perhaps other foods from their diets while breastfeeding. 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.</td>
<td>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.</td>
<td>Emerging data from observational studies suggest the delayed introduction of complementary foods may increase the risk of food allergy, and the early introduction of allergenic foods may prevent development of them.</td>
<td></td>
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- Delayed introduction beyond 4-6 months is not recommended
- This is a passive, not an active recommendation
2017 Introduction

Some patients?
For how long?
M, T, W, Th, F, Sa, Su?
Once, 1m, 6m, 3y, 5y, life??

Every child??
What type of peanut?
Some patients?
LEAP Screening and Protocol

Eligibility
- Infants age 4-11 months with either or both:
  - Moderate to severe eczema (SCORAD >40 or parental self-report) OR
  - Egg allergy

Screening
- All participants underwent peanut skin testing prior to study entry
- If ≥5mm, excluded (felt to already be “likely” peanut allergic)

Randomization
- Stratified by 0mm vs. 1-4mm skin test size, randomized within each group to consume (2g, 3x week x 60m) vs. avoid peanut
- All initial peanut consumption done under Allergist supervision

Assessment and Challenge
- Food frequency and household ambient peanut dust levels assessed through 60m.
- Multiple interval visits
- All subjects underwent in office peanut challenge at age 5y
LEAP Outcome: Intention-to-Treat Analysis

SPT-Negative Cohort (N=530)

Risk Reduction: 86% Relative
11.8% Absolute
NNT 8.5

SPT-Positive Cohort (N=98)

Risk Reduction: 70% Relative
24.7% Absolute
NNT 4

Both Cohorts (N=628)

Overall Risk Reduction: 81% Relative
14% Absolute
What was included in these new guidelines:

**Guidelines**

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

- Discussion of risk strategies for infants at low, medium, and high risk
- Recommendations on who and how to test prior to introduction
- Recommendations for methods of introduction
- Recipes for introducing to infants

What was NOT included in these guidelines:

- No recommendations regarding introduction of other allergenic foods
- No recommendations for infants with food allergies other than egg or siblings of peanut-allergic children
- No data from parents or from primary care providers regarding what they want or are willing/able to do with respect to peanut introduction at home/office
Caregiver Preferences for Early Peanut Introduction

- Nationally-representative survey of 2,000 pregnant and caregivers of children <12 months querying support for peanut introduction before 6 months of life.
- Only 31% expressed willingness to introduce peanut before 6 months of life, and 40% expressed willingness to introduce peanut only after 11 months of life.
- 60% reported willingness to introduce egg before 8 months of life.
- Only 49% reported willingness to allow their child to undergo pre-introduction skin testing and 54% willingness to allow their child to undergo an oral challenge before 11 months of life.

Greenhawt et al Ann Allergy Asthma Immunol 2018
# Summary of Addendum Guidelines

<table>
<thead>
<tr>
<th>Addendum Guideline</th>
<th>Infant Criteria</th>
<th>Recommendations</th>
<th>Earliest Age of Peanut Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider evaluation with peanut-specific IgE and/or skin prick test 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>Age-appropriate and in accordance with family preferences and cultural practices</td>
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</tbody>
</table>
To minimize a delay in peanut introduction for children who may test negative, testing for peanut-specific IgE may be the preferred initial approach in certain healthcare settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.
What About Other Foods?

Does the evidence support policy changes?
The EAT Study hypothesis: introduction of six allergenic foods (dairy, egg, peanut, sesame, fish, wheat) into the diet of infants from 3 months of age vs 6 months, alongside continued breastfeeding, results in a reduced prevalence of food allergies by 3 years of age.

Randomized controlled study – general population:

- Group 1: followed present UK government weaning advice i.e. aim for exclusive breastfeeding until six months
- Group 2: six allergenic foods from 3 months of age alongside continued breastfeeding, having been screened to check for pre-existing food allergy
  - Aim was that by 5 months all participants in the early introduction group would have each of the 6 allergenic foods twice weekly

Early introduction of all 6 foods was not easily achieved (overall 42.8%)

- Cow’s milk 85%, wheat 100% (introduced last)
- Peanut 61.9%, fish 60%
- Sesame 50.7%, egg 43.1%

Trial’s intention was that breastfeeding for both groups should remain an important source of nutrition until at least 6 months of age.

Perkin et al. NEJM 2016
Clinical Reactivity – EAT Trial

**Peanut**

- **Intention-to-Treat (N=1168)**
  - P=0.11
  - ARR 2.5%
  - NNT: 40

- **Peanut Per-Protocol (N=806)**
  - P=0.009

- **Adjusted Peanut Per-Protocol (N=806)**
  - P=0.000

**Egg**

- **Intention-to-Treat (N=1165)**
  - P=0.17
  - ARR 4.1%
  - NNT: 20

- **Egg Per-Protocol (N=711)**
  - P=0.008

- **Adjusted Egg Per-Protocol (N=709)**
  - P=0.02
EAT Trial - Summary

• Likely no harm from introducing any of these foods to infants at 3 months of age due to absence of effects on breastfeeding rates
• Effects on egg and peanut allergy have limited clinical significance given a NNT of 20 and 40 patients, respectively.
• Significant non-compliance with ingestion of all 6 allergenic foods
• What was effect of concomitant breastfeeding on results?
<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Full Title</th>
<th>Study Type (Sample size)</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| STAR (Australia) | Solids Timing for Allergy Reduction | Blinded RPCT (n=86) | **High-risk** infants with moderate to severe eczema | • **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 | **IgE-mediated egg allergy** at 12 months based on positive SPT and egg OFC | • 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) |
| STEP (Australia) | Starting Time for Egg Protein | Blinded RPCT (n=820) | **Intermediate risk:**  
• atopic moms (allergic disease + positive envir SPT)  
• Infants: no allergic dz | • **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)** | **IgE-mediated egg allergy** at 12 months based on positive SPT and egg OFC | • No significant differences in egg allergy between groups  
• No anaphylactic reactions at initial egg intro |
| BEAT (Australia) | Beating Egg Allergy Trial | Blinded RPCT (n=319) | **Intermediate risk:**  
• Infants with 1st degree relative with atopy  
• Infants: neg egg SPT | • **Daily consumption of egg** vs placebo powder at 4 months  
• **350 mg protein daily** raw whole egg powder  
• Cooked egg at 8 months | **Sensitization to egg** by SPT at 12 months of age | • Subjects in egg group vs placebo had significantly less egg sensitization (10.7% vs 20.5%, p=0.03)  
• No harm with egg intro |
| HEAP (Germany) | Hens Egg Allergy Prevention | Blinded RPCT (n=406) | **Normal risk** general population  
• Infants with IgE <0.35 kU/L at enrollment | • **Thrice weekly 2.5 g egg protein** from 4-6 months of age until 12 months | **Sensitization to egg** based on egg IgE >0.35 kU/L at 12 months of age | • No evidence of preventing egg sensitization or allergy  
• High rate of anaphylaxis at egg introduction at entry |
| PETIT (Japan) | Prevention egg allergy in infants with AD | Blinded RCT (n=121) | **High-risk** infants with atopic dermatitis  
• Concomitant treatment of AD | • **Daily consumption of 50 mg** heated egg from 6-9 months  
• **Daily consumption of 250 mg** heated egg from 9-12 months | **IgE-mediated egg allergy** at 12 months of age based on OFC | • Prevalence of egg allergy 37.7% in placebo vs 8.3% in egg group (p=0.0013)  
• No SAEs |
Moderate certainty evidence from 5 trials for protective benefit of early egg introduction (4 raw, 1 cooked)
--RR 0.56, I^2=36%; P=0.009; ARR 24 cases per 1000

Moderate certainty evidence from 2 trials for protective benefit for early peanut introduction
--RR 0.29, I^2=66%; P=0.009; ARR 18 cases per 1000
Increased Food Diversity and Allergic Diseases

- Diversity scores for food introduction calculated by focusing on foods eaten by 80% of infants:
  1. Major foods introduced in 1st year of life (veggies or fruits, cereals, bread, meat, cake and yogurt)
  2. All food items introduced 1st year of life: any cow’s milk, yogurt, other milk product, eggs, nuts, vegetables or fruits, cereals, bread, meat, fish, soy, margarine, butter, cake, and chocolate

**Conclusions:** Infants exposed to an increased diversity of complementary foods within the 1st year of life have a reduced risk of food allergy.
Does AD Cause Food Allergy?

Recent systematic review: 66 studies – no meta-analysis due to marked heterogeneity of study designs, participants and diagnostic criteria

- Only 49 (74%) used doctor’s diagnosis of AD, validated AD diagnostic criteria, or both
- Only 26 (39%) use OFCs to determine FA status
- In population-based studies: likelihood of food sensitization up to 6x higher in patients with AD at 3 months of age
- 16 studies suggested FA associated with more severe AD phenotype
- 6 studies showed that earlier onset AD or increased AD persistence particularly associated with FA
- **Significant limitations**: study design, diagnoses of AD/FA, selection bias of subjects reporting to study centers, reverse causality

Tsakok T, et al. JACI 2016
Can We Identify Infants around Birth at Higher Risk for AD?

- TEWL measured at 3 time points: day 2 of life and at 2 and 6 months
- Infants were FLG genotyped
- Screening for AD done at 6 and 12 months of age
- Skin testing at age 2 years; positive SPT patients not regularly eating or tolerating the food were offered OFCs

- The odds ratio of having FA at 2 years, with day 2 TEWL in the top quartile versus the bottom quartile, was 18.7 (95% CI, 7.13-49.3; P < .0001
Can We Prevent AD and then Prevent FA?

- 118 infants at high risk for AD: parent or sibling with AD
- Emulsion-type moisturizer applied daily for weeks 1-32 of life vs petroleum jelly PRN in control group
- Diagnosis of AD made by dermatologist blinded to therapy
- Mean daily amount of emulsion-type moisturizer applied in treatment group = 7.86 + 4.34 g vs 0.101 + 0.286 g petroleum jelly in control group
- Cox regression analysis showed the risk of AD to be significantly lower in the intervention group (hazard ratio, 0.48; 95% CI, 0.27-0.86).
- Sensitization to egg was not significantly different between the group

**Barrier Enhancement for Eczema Prevention (BEEP) Trial** underway in UK: RCT of emollient daily for 1st year vs standard skin care in 1400 high risk infants (first-degree relative with physician diagnosed eczema, AR, or asthma)

Outcome: blinded, physician-diagnosed eczema at age 2 years

Horimukai K, et al. JACI 2014
US Addendum Peanut Guidelines

- **Addendum 1**: Infants with severe eczema, egg allergy or both should have introduction of age-appropriate peanut-containing food as early as 4 to 6 months of age to reduce the risk of peanut allergy.

- **Addendum 2**: Infants with mild to moderate eczema should have introduction of age-appropriate peanut-containing food around 6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy.

- **Addendum 3**: Infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, and in accordance with family preferences and cultural practices.

United Kingdom

- 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.**

Australia and New Zealand

- 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.**
What can you tell parents to do to decrease the risk of food allergies:
- Recommend Moms eat a healthy, diverse diet
- Have babies born by vaginal delivery; if not, do vaginal seeding?
- Breastfeed for a variety of benefits
- Have a farm (at least a dog) in your house
- Start using a moisturizer on your baby daily
- Introduce a variety of healthy, diverse foods, including all major allergens, starting around 6 months of age, but within the first year of life
- Consider sending infants with early-onset or difficult to control, moderate to severe eczema or an existing food allergy to an allergist for evaluation prior to introduction of peanut or other high-risk allergens
Revised Prevention Guidelines: 2019

• North American consensus: Joint AAAAI, ACAAI, and CSACI guidelines

• What criteria define an infant at high risk for allergy?

• Recommendations for introduction of peanut and egg, but also other allergenic foods

• Role of dietary diversity

• How to implement these recommendations, including practical feeding advice

• Cost-effectiveness analysis of any screening prior to introduction
Thank you