Changes in Infant Feeding Guidelines to Prevent Food Allergies: Reviewing the LEAP, LEAP-ON, and EAT Studies and How Early Dietary Interventions Play Role

Harvey L. Leo, MD
Associate Research Scientist
University of Michigan School of Public Health
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Learning Objectives

- Review evidence supporting relationship of timing of foods (peanut) and risk of food allergy development
- Review and evaluate findings of the LEAP study
- Discuss policy changes and impact on complimentary food introduction in infants
- Consider impacts of “prevention” strategies given current research environment
Rise of Food Allergy

1Statistically significant trend.
SOURCE: CDC/NCHS, National Health Interview Survey.
The Evolution of a Prevention Strategy

- Pre-2000’s: NADA
- 2000: Mothers should eliminate nuts and consider avoiding milk, egg, and fish while breastfeeding.
  - Delayed introduction of highly allergenic foods in high risk children to prevent food allergy
  - Avoid Cow’s milk until 1 year, egg until 2 years, and nuts until 3 years
- 2008: No convincing evidence for delayed introduction and no specific guideline recommendations
  - Do not delay introduction of allergenic foods
  - Maybe use of partially hydrolyzed formulas delays eczema outbreak
Now the big change

2010-2014: Emerging data from both observational studies suggest that delayed introduction of complimentary foods may increase the risk of food allergy and that early avoidance in infants may increase risk for food allergy development later in life.
Peanuts in house?

Skin vs mouth

- Skin exposure through disrupted membranes could explain the increased risk in light of attempted avoidance through oral mechanism.

Bamba

- Lack et al noted that English children of Jewish descent had significantly higher prevalence of peanut allergy compared to Israeli children.
- Traditionally Bamba, a peanut flour puff, is an early complimentary food in infants.
- This is complete contrast to avoidance recommendations at the time.
But is not so easy

- This issue leaves many questions:
  - How much?
  - When?
  - When is too soon?
  - How long to try it?
  - What if we are wrong? What’s anaphylaxis or not?
  - All infants or only some?
Exposure to Allergen after weaning

- 79% of Irish infants weaned 17-26 weeks
- In first 6 weeks, infants ate:
  - Milk 61%
  - Wheat 63%
  - Soy 42%
  - Egg 10%
  - Fish 8%
  - Peanut 0.5%

- In 2010 UK mothers, 45% of mothers of 8-10 mo infants reported feeding foods
  - 8% given peanut
  - 12% given egg
  - 11% given dairy
  - 8% given fish

Odonovan SM et al. Public Health Nutr 2015
McAndrew F. Infant Feeding Survey 2010 Leeds UK
Exposure after weaning

- In Canada, survey of pediatricians and dietitians noted
  - Pediatricians are less aware than dietitians of current food recommendations that no benefit in delaying allergenic foods beyond 4-6 months
  - Similar pattern seen in US, particularly with peanuts
Why LEAP?

- This randomized trial of peanut consumption in infants at risk for peanut allergy” demonstrated a successful 11% to 25% absolute reduction in the risk of peanut allergy in high-risk infants (and a relative risk reduction of up to 80%) if peanut was introduced between 4 and 11 months of age.

- Limited to high risk children and may or may not be generalizable to broader population
The LEAP protocol

834 Participants were screened for LEAP study

194 Were excluded
- 76 Had SPT >4 mm
- 118 Did not have severe eczema

640 Underwent randomization

542 Were in the SPT-negative cohort
- 270 Were assigned to peanut avoidance
  - 7 Had missing data on outcomes
  - 4 Withdrew voluntarily
  - 2 Could not be evaluated by means of diagnostic algorithm
  - 1 Had other reason
  - 188 Were excluded
    - Owing to inadequate adherence to treatment
    - 18 Were excluded
      - Owing to inadequate adherence to treatment
      - 11 Were excluded
        - Owing to inadequate adherence to treatment
        - 111 Were included
          - In the ITT analysis
          - 253 Were included in the per-protocol analysis

272 Were assigned to peanut consumption
- 273 Consumed peanut protein
  - 5 Had missing data on outcomes
  - 2 Withdrew voluntarily
  - 1 Was lost to follow-up
  - 2 Had other reasons
  - 246 Were included
    - In the ITT analysis
    - 250 Were included in the per-protocol analysis

98 Were in the SPT-positive cohort
- 42 Were assigned to peanut avoidance
  - 41 Consumed peanut protein
    - 11 Were included
      - In the ITT analysis
      - 39 Were included in the per-protocol analysis

- 51 Were assigned to peanut consumption
  - 50 Were included
    - In the ITT analysis
    - 39 Were included in the per-protocol analysis
Early peanuts good?

LEAP primary Outcomes

Less allergic overall?

- Throughout protocols, no evidence of fatalities, and few anaphylactic reactions
- However, there were some incidences of food reactions within protocols, none requiring hospitalization or significant intervention
- So maybe it’s overall safe?

2015;372:803-813
LEAP Race Outcome

If we apply the data

Whole population: n=1000

Low risk: No early onset eczema and no egg allergy
HealthNuts data: 84% (n=840)
  No intervention

HealthNuts data: 0.8% peanut allergic
Cases: n=7

High risk: Early onset eczema (≤6mths) treated with topical steroids and/or egg allergy
HealthNuts data: 16% (n=160)
  Skin prick test screening to peanut +/- intervention (introduction of peanut at 4-11 months)

SPT >4mm No intervention
LEAP data: 10.6% (n=17)²

SPT 0-4mm: Intervention
LEAP data: 89% (n=142)
17% allergic without intervention*
Predicted cases: n=24

HealthNuts data: 80% peanut allergic
Predicted cases: n=14

LEAP data: 3% allergic with intervention*
Cases: n=4
Cases prevented: n=20
LEAP-ON

- Long term implications of LEAP policy were studied.

- If continued for 5 years, cessation of ingestion appeared to continue tolerance in older children.

- 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.
EAT Study

- 1303 exclusively breast-fed infants who were 3 months of age and randomly assigned them 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 recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard-introduction group).

- The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age.
EAT trial results

• This trial did not show efficacy of early introduction of allergenic foods versus standard introduction in an intention-to-treat analysis.

• There was a nonsignificant 20% lower relative risk of food allergy in the early-introduction group than in the standard-introduction group.

• In the per protocol analysis, there was a significant 67% lower relative risk of food allergy overall in the early introduction group.

• Unexpectedly, in the per protocol analysis, significantly lower relative risks of peanut allergy and egg allergy were observed in the early introduction group than in the standard introduction group.
EAT results

A One or More Foods
- Standard introduction (N=1305)
- Early introduction (N=567)
- Intention to Treat (N=1162)
- Per Protocol (Overall) (N=736)
- Adjusted Per Protocol (Overall) (N=727)

B Peanut
- Standard introduction (N=1305)
- Early introduction (N=567)
- Intention to Treat (N=1162)
- Per Protocol (Peanut) (N=835)
- Adjusted Per Protocol (Peanut) (N=825)

C Egg
- Standard introduction (N=1305)
- Early introduction (N=567)
- Intention to Treat (N=1162)
- Per Protocol (Egg) (N=740)
- Adjusted Per Protocol (Egg) (N=730)

D Raw Egg White
- Standard introduction (N=1305)
- Early introduction (N=567)
- Intention to Treat (N=1162)
- Per Protocol (Egg) (N=740)
- Adjusted Per Protocol (Egg) (N=730)
EAT Study

- Dose–Response Analysis of the Relationship between Mean Weekly Dose of Peanut or Egg Protein Consumed and Allergy or Positive Result on Skin-Prick Testing to Peanut, Egg, and Raw Egg White

- The prevalence of both food allergy and positive skin-prick test diminishes with increasing levels of mean weekly consumption
Non-White EAT

- The rates of food allergy were higher among nonwhite participants than among whites and higher among participants with eczema at enrollment than among those without eczema.

- Adherence to the trial protocol was significantly lower among participants in the early introduction group who were nonwhite and was lower (but not significantly) among those who had eczema than among the rest of the standard-introduction group.

- This may reflect differences in phenotype or confounding factors to affect adherence ie egg flaring AD and not food allergy reactions.
It’s not so easy

Points to consider from the EAT trial

- Compliance is pretty good with diet
- Some groups did not adhere and why??
- Good long term follow up
- Looks to be safe (low risk of fatalities?)
- No impact on outcome of dietary intervention
- Non-statistical obs. Reduced rate food allergy in intervention group vs full avoidance
- Results may not fully be generalizable if implemented in populations
Infants considered at “high risk” as defined by the LEAP study criteria:

Egg allergy: Children with either:
1. A SPT wheal diameter $>6$ mm from exposure to raw hen’s egg white and no history of previous egg tolerance
OR
2. A SPT wheal diameter $>3$ mm from exposure to pasteurized hen’s egg white and allergic symptoms related to exposure to hen’s egg

Severe eczema: An eczematous rash that:
1. Requires application of topical creams, ointments, or both containing corticosteroids or calcineurin inhibitors and that, if the participant is $<6$ months of age, lasted for at least 12 of 30 days on 2 occasions or, if the participant is $>6$ months of age, lasted for at least 12 of 30 days on 2 occasions in the last 6 months
OR
2. Is currently or was previously graded $>40$ by using the modified SCORAD evaluation

Example of SPT method used in the LEAP trial

- SPTs to peanut extract should be performed in the presence of a negative control and a positive histamine control.
- SPTs should be performed in duplicate, and the maximum wheal diameter of the 2 SPT responses should be calculated and rounded up to the greatest whole millimeter. Of note, in the LEAP trial measurement of IgE to peanut resulted in considerably higher rates of sensitization compared with skin testing, which could lead to numerous unnecessary oral peanut challenges.
Examples of Peanut products

• Smooth peanut butter (1 teaspoon) mixed with milk or with mashed or pureed fruit

• Bamba snack* (Osem; approximately two thirds of a 1-oz (25 g) bag; 21 sticks of Bamba)
  — For young infants (<7 months), softened with 20 to 30 mL water or milk and mixed with milk or with mashed or pureed fruit or vegetables

• Peanut soup

• Finely ground peanuts mixed into other foods, such as yogurt

*Other foods more customary to particular nations/cultures can be substituted.

Whole peanut is not recommended for introduction because this is a choking hazard in children less than 4 years of age.
NIAID Guidelines 2016

- Expert Panel recommends that infants with severe eczema, egg allergy, or both receive age appropriate peanut containing foods as early as 4-6 months to reduce risk of peanut allergy.

- The Expert Panel recommends that evaluation with peanut specific IgE or SPT be strongly considered before introduction of peanut to be determined if peanut should be introduced, and if so, the preferred method of introduction.
The Expert Panel suggests that infants with mild to moderate eczema should receive age appropriate peanut containing foods around 6 months of age.

The Expert Panel recommends that infants in this category may have dietary peanut introduced at home without an in office evaluation.
The Expert Panel recommends that infants without eczema or any food allergy have age appropriate peanut containing foods freely introduced in the diet, together with other complimentary foods, and in accordance with family preferences and cultural practices.
The Practical

- The window and timing appears to be pretty small
- Per both observation and current studies support that implementing by 4-9 months of age is ideal
- Looks relatively safe with few significant reactions and no fatalities
  - But is this generalizable to wide population? Does this only work for peanut? What about other nuts? Other foods?
- As previously noted, many things can change in a month
- If testing occurs, then implementation of protocol should happen within a few days/week.
The Practical Implementation

- How can parents and clinicians identify true reactivity vs normal behavior or food refusal
- How do we message the confounders
  - Penicillin/Amoxicillin reactions vs true drug allergy prevalence
  - Foods triggering AD
  - Foods triggering FPIES?
  - Foods triggering contact dermatitis?
  - The “fussy” baby and “anxious” parent
    - 50 formulas to choose from
Who sees the specialist

- There are true service limitations
- Do all kids see an allergist and get tested?
- Should PCPs be screening? How to interpret screening?
- What will families expect
- What if you miss it?
Failed LEAP kids

- Rabinovitch et al. responded to broad implementation of the LEAP study
  - In the LEAP study 1 (0.37%) of 272 children with negative skin test responses who were randomized to the peanut consumption group failed the initial food challenge
  - Although this is a relatively small percentage, it is not negligible, considering the potential widespread use of primary prevention
  - In addition, because more than 70% of these children were white, this rate might not accurately reflect the risk in children of different ethnicity and racial origin
The Policy Implications

- Can and should be implement such broad policy based on only 2-3 well designed studies? Do we need to replicate studies?
- How generalizable are these studies given the limited phenotypes and ideal conditions?
- How is this different that the historic approaches to feeding and how policy was initially implemented in the past?
- Is this all overkill for a relatively small population of fatality vs high morbidity and quality of life impact?
Things to think about

- What is the overall fatality risk of food anaphylaxis?
  - Despite the hype it’s rare (and not to discount trauma of fatalities)
  - Is this like screening for sudden death in HS athletes? Does everyone need an ECHO?

- Is too much purposeful intervention a bad thing?

- Is food allergy a biomarker for high risk asthma and morbidity? If so, is this the reason for preventative strategies?

- Are there other biological factors and phenotypes that cannot be influenced by dietary prevention strategies? ie Fillagrin deficiency, microbiome impacts, acetaminophen in pregnancy?

- When should preventative strategies start ie in utero, early infancy, community based?
Pain relief in pregnancy and C-sections

- Evidence supports that acetaminophen use in pregnancy could increase atopic presentations in infants. This only adds to evidence suggesting that in utero and peri-partum environment are additional factors that affect food allergy development.

Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study

Maria C. Magnus,1* Øystein Karstad,1 Siri E. Håberg,1 Per Nafstad,1,2 George Davey Smith3 and Wenche Nystad1

1Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway,
2Department of Community Medicine, University of Oslo, Oslo, Norway and 3MRC Integrative Epidemiology Unit at the University of Bristol, School of Social and Community Medicine, Bristol, UK

Mode of delivery and development of atopic disease during the first 2 years of life
How to we apply this in high risk communities?

- If we are serving a population of high risk individuals
  - African American
  - Low SES
  - High genetic risk for atopy

- Should we implement policy
  - WIC—cover peanut butter and high risk foods early
  - Allow for peanuts in Headstart again? Vs Nut Free schools?
  - How do we balance risk for true anaphylaxis
Summary

- Current data and growing consensus supports the early introduction of "allergenic" complimentary foods as early and consistently as possibly to decrease risk of food allergy development.
- There are truly high risk groups that may still have poor outcomes that need to be identified.
- Pediatricians and PCPs should be prepared for unexpected reactions when giving guidance.
- Specialists are still needed for complex cases, but PCPs will take the burden.
- Early intervention may have significant impacts in populations based morbidity with relative low risk of mortality which should be considered in policy decisions.
Final thoughts

- As a result of attending my lecture at the 2017 Practical Pediatrics CME course, I encourage you to
  - Be aware of upcoming guidelines from the AAP and NIAID Expert Panel on Feeding High Risk Atopic Infants
  - Consider the appropriate criteria for referral to allergy
  - Know risk factors for food allergy development in children
  - Be aware of limitations in data on current food allergy recommendations