Preventing Food Allergy:
LEAPing Forward, Looking Back

Pennsylvania Allergy & Asthma Association
Annual Meeting

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Disclosures

- Member, Joint Task Force on Allergy Practice Parameters
- Member of Nutricia specialty advisory board and have received honorarium from Nutricia for lectures
- Member of the medical advisory team for Kids With Food Allergies Foundation and the International Association for Food Protein Enterocolitis (non-financial)
- Former member Thermo Fishery Advisory Board regarding Allergen Component Testing and have received honorarium for speaking
- Have received honorarium from Gerber/Nestle and Adams Pharmaceuticals
- Consultant to Canadian Transport Agency, Aimimmune, Intrumune
- Receiving support from 1-K08-HS024599-01 (AHRQ, start date 4/15/16)
- Received support from NIH grants #2K22TR004334 & UL1RR024986, private foundation (while at U of M)
- Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food, Health Technologies and Joint Task Force on Quality Improvement Measures Committees
- Member ACAAI Conferences On-Line Allergy, Abstract, Practice Improvement, and Adverse Reaction to Food committees
- AAAAI/ACAAI advisor to CDC-ACIP on Egg Allergy/Influenza Vaccine Safety
- 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
- Former officer and legislative advocacy liaison Michigan Allergy and Asthma Society (2010-2015)
- Have testified to Michigan State Legislature on behalf of Michigan State Medical Society and Michigan Allergy and Asthma Society
- Member, Scientific Advisory Council, National Peanut Board
- Former Medical Advisory Chair/member, Food Allergy and Anaphylaxis Connection Team
Learning Objectives

• Review the evidence supporting a relationship between timing of peanut introduction and the risk of peanut allergy development
• Review and understand the recent LEAP study data
• Discuss the implications related to making changes to the peanut introduction policy
• Discuss the evidence supporting similar changes for other foods

Guidance to Prevent Food Allergy

Year 2000 Early Feeding Guidance

• Dietary avoidance of certain antigens in pregnancy
• Selected avoidance of certain foods while breastfeeding to prevent eczema and asthma
• Use of partially hydrolyzed whey formula
• Delay solid food introduction until 6 months
• Delay introduction of high risk allergens until age 3y

All were felt to reduced risk of food allergy!
An “Epidemic” Rise of Disease

Food Allergy Reported Prevalence According to NHIS Data, 1997-2011


An Evolution of Prevention

Pre-2000’s
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!

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.

2012
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 them.

- WHO recommends exclusive breastfeeding x 6mo, but not for allergy prevention
- 2008 recommendation is passive, not active
Can food allergy be prevented?

The LEAP Study and Peanut Allergy Prevention

What Makes Peanut So Special

• Peanut allergy a growing public health problem
• Prevalence between 1-3%, varies by country
  --Milk and egg allergy more prevalent, however
• Prevalence may have doubled in a 10 yr period
• < 20% develop tolerance
• 2000 AAP feeding guidelines suggest delaying introduction of peanut until age 3 to deter risk of developing peanut allergy

A Ray of Light?

- 2008 DuToit et al: UK babies avoiding peanut until age 3 were 10 times more likely to develop peanut allergy than Israeli babies fed Bamba before 9 mo
- Was not an RCT but findings were provocative
  --Could timing of introduction promote primary prevention?
- Learning Early About Peanut Allergy Study started
  --RCT of early vs. delayed peanut introduction in infants at “high-risk” for peanut allergy
  --Use of Bamba or peanut butter as vehicle

Learning Early About Peanut Allergy (LEAP)

- Open label single center RCT
- Trial of early (4-11m) vs. delayed (60m) peanut introduction
- Inclusion Criteria
  1) Age 4-11 months at screening
  2) Having either or both
     a) Severe eczema
        --Frequent topical corticosteroids/calcineurin inhibitor use
        --“a very bad rash in joints and creases” or “a very bad itchy, dry, oozing, or crusted rash” reported by parent
        --SCORAD grade (≥40)
     b) Egg allergy
  3) Screening peanut allergy skin test < 5mm
Screening and Protocol

Screening
• All participants underwent peanut skin testing
• 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

Defining the Effect Studied

• Primary prevention: preventing peanut allergy from developing in the skin test - person who has no baseline exposure to peanut
• Secondary prevention: preventing progression of allergy (from sensitization to reactivity) in the skin test + but non-reactive person at baseline with no known peanut exposure
Results

LEAP Study: NNT Analysis

<table>
<thead>
<tr>
<th></th>
<th>Skin test negative</th>
<th>Skin test positive</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>8.5</td>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>Per protocol</td>
<td>7.4</td>
<td>2.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Imputed ITT</td>
<td>10.4</td>
<td>4</td>
<td>8.3</td>
</tr>
</tbody>
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- The treatment effect is heterogeneous
- Study showed evidence of both primary and secondary prevention
- Benefit was far greater within the sensitized group
- Unknown effect among the not-at-risk or >4mm sensitized
- How can we assess the health and economic benefits of a single policy with a heterogeneous treatment effect?
Adverse Event Plot

- No fatalities
- No difference in rates of hospitalization/SAE
- Consumption AE rates higher for URI, skin infection, gastro, urticaria, conjunctivitis
- AE rate not different based on sensitization


Challenge Failures

- 7 infants failed challenge at first ingestion
- 57 children failed the 60m challenge
  -- 9 consumption vs. 48 avoidance failures
  -- 9 required epinephrine, 14 had cardiorespiratory symptoms
- 9 kids in consumption group discontinued due to reported reactions

Constructive Criticisms

• No placebo group or low risk group comparison
• 5mm skin test cut off chosen—arbitrary
• No control group to test necessity of skin testing
• Single center, referral population
• Participation bias? >96% retention at 5yr
• Weak “high risk” criteria
• Dose/duration of exposure not tested
• Unknown effect of partial adherence or long-term outcomes after discontinuation

What Else Was Learned

• Challenge and skin test feasible in 4-11mo old
• Rate of significant reactions not very high
• Early sensitization occurs in some without oral exposure
• Skin test negative kids can react
• New model for BAT which predicts reactivity
• Environmental distribution and FLG risk

Justifying Conclusions

• “The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.”

• AGREE, BUT SECONDARY EFFECT MUCH GREATER THAN PRIMARY

• UNSURE THEY WERE AS “HIGH RISK” AS BILLED

• HOW MANY > 4MM WOULD HAVE HAD BENEFIT?

Looking Before You LEAP:

Changing policy for early complementary feeding to prevent peanut allergy development
LEAP NEJM Editorial

- Recommended “immediate” implementation
- Screen all “high-risk” children 4-8mo
  --if skin test -, start 2g thrice weekly
  --if skin test 1-4mm, challenge in the office
  --if skin test ≥ 5mm, do not introduce
- Children considered at “high risk” for peanut allergy not otherwise defined beyond LEAP criteria


Measure Twice, Cut Once

- Danger in implementing findings from a single study
- Duty to replicate?
- Issue of generalizability to US
  --Referral center vs. population-level
  --Should still work, but with same effect size?
  --Is screening even necessary?
  --What is skin testing cut off point? What was missed benefit?
- Issue of Allergist supply/access and utilization
- Issue of compliance—provider and parent

Are we playing LEAPfrog with a unicorn?
**Current Early Feeding Policy**

- 2008 AAP and 2013 AAAAI guidance *already advises* against delayed introduction of foods beyond 4-6 mo if standard risk
- Recommendation is passive, not active
- Reversed guidelines urging delay issued in 2000
- Both AAP and AAAAI recommend allergist evaluation prior to highly allergenic food introduction in patients with hx food allergy or moderate-to-severe atopic dermatitis
- Guidance is based on available data from observational studies suggesting favorable benefit for early introduction of food, and the promise of several RCTs investigating these questions

**Mission Impossible?**

- ~4,000,000 US children under the age of 1
- 20% have eczema, and 2% have egg allergy
- Only 10% of the 5,500 US allergists perform >1 challenge per week

- Between 20,000-800,000 infants to be seen in 5mo window
- Is this reimbursable or cost effective?
- What would happen to access for other diagnoses?
- How many providers or parents would comply?
Long Term Unknowns

• Are duration and doses the right targets?
• What is outcome after discontinuing?
• What about partial compliance?
• What about other foods, other evidence?
• Has the “high-risk” child really been identified?
• Have the variable costs of the procedure been determined?
  Should we really be altering policy yet?

“Official” Policy

• Interim guidelines formulated by an international consortium (US, Canada, Europe, Japan, Israel, and World Allergy Organization as well as AAP and Society for Pediatric Dermatology)
• Restricted to peanut only
• Expert panel met at NIAID on June 16 to start process for a “final” document (GRADE analysis)
• Official addendum to 2010 NIAID food allergy guidelines anticipated Summer/Fall 2016
Interim Consensus

• There is now strong scientific supporting early introduction of peanut-containing products into the diet of “high-risk” infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent, since delaying may be associated with an increased risk of developing peanut allergy.

• Infants with early-onset atopic disease, such as severe eczema or egg allergy in the first 4-6 months of life may benefit from evaluation by an allergist or physician trained in management of allergic diseases to assist in implementing these suggestions regarding the appropriateness of early peanut introduction.

• Evaluation of such patients may consist of performing peanut skin testing and/or in-office observed peanut ingestion, as they deem appropriate after discussion with the family, especially for those with evidence of a positive peanut skin test.

• The study does not address use of alternative doses of peanut protein, minimal length of treatment necessary to induce the tolerogenic effect, or potential risks of prematurely stopping or sporadic feeding of peanut.

Revising the NIAID Guidelines

• Expert panel recommending 3 addendum

• Addendum 1: infants with severe eczema, egg allergy or both have introduction of age-appropriate peanut-containing food as early as 4-6 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 as early as 4-6 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 as early as 4 to 6 months of age, together with other solid foods, and in accordance with family preferences and cultural practices.
Redefined Risk Criteria

- **Severe eczema** is defined as persistent or frequently recurring eczema covering ≥10% of body surface area with typical morphology and distribution as assessed by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors or other anti-inflammatory agents despite appropriate use of emollients.

- **Egg allergy** is defined as a skin prick test wheal diameter of 3 mm or greater with egg white extract in an infant with a history of an allergic reaction to egg or who has failed an egg oral food challenge.

- A **specialist** is defined as a health care provider with the training and experience to perform and interpret skin prick testing and oral food challenges; and know and manage their risks.

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NIAID Guideline Algorithm
Medicinal Peanut Introduction?

- Are data strong enough to suggest a policy?
- Have all stakeholders “bought in” & who benefits?
- How will the knowledge translate?
- What are the health and economic benefits?
- Should expectations for success be tempered?
  -- TIPS Study: 7% introduce solids by 4mo, 13% by 6 mo
  -- Wheat (8.7m), egg (11.2m), fish (13.4m), peanut/tree nut (20-22m)
  -- Asian race, maternal hx food allergy associated w/delay


Latest Data
LEAP ON—Does this Help?

• Aim to test effect of discontinuation
  -- 1 year follow-up at the end of the original 5 year LEAP study
  -- Both consumption and avoidance group avoided peanut

• 3 new cases of peanut allergy in each arm

• Shows effect was not transient desensitization

• Question of applicability
  -- Does not address partial adherence/discontinuation at younger ages
  -- Does not address long term outcomes of shorter periods of adherence

EAT: Evidence in Low Risk Kids?

• Enquiring About Tolerance study
  -- Early introduction of allergens in breastfed infants at 3mo vs 6mo
  -- Infants were not considered “high-risk” as in LEAP study
  -- Milk 1st, then egg, fish, sesame, wheat, peanut in random order
  -- Assessed rates of allergy development between 1-3 years in 1303 children

• 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%

• No significant differences between groups
  -- Concern for limited power, drop out
  -- Best case scenario shows approaches non-inferior
Conclusions

- Early introduction of peanut may have distinct protective effects
- Unclear if this has been definitively proven
- Policy change is coming, but unclear how to best implement such change
- Trade-offs associated with these changes need to be better defined
- More data for other foods forthcoming
Food Allergy: Is there an Answer?

Thanks!

The view from the Food Challenge Unit, Children’s Hospital Colorado