Prevention (& Treatment) of Food Allergy

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02/02/18

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The Problem: Food Allergy

- Affects 3 -6% of children worldwide \(^1\),\(^2\)
  - US: 8% peanut allergic \(^3\)
- Significant morbidities, fatalities rare \(^4\)
- Negatively affect QOL of the patients and families \(^5\)
- Can pose a significant financial burden \(^6\)

3. Gupta, RS et al Pediatric 2011;128:9-17

Risk Factors for the Development of Food Allergy

- Family history of atopy
- Male sex
- Ethnicity
- Atopic dermatitis
- Genetic polymorphisms (epigenetics)

Prevalence of Food Allergy is Increasing

WHY?
Hypotheses for the Development of Food Allergy

Development of Food Allergy: Non-modifiable factors

- Genetics
  - Family history of food allergy
    - 7 fold increase in peanut allergy (PA) if a parent or sibling has PA
  - Twin studies
    - Monozygotic twins have an 82 - 87% hereditable incidence of PA (asthma 87%, eczema 74%)


Development of Food Allergy: Non-modifiable factors

- Race
  - Mixed results depending on methodology
  - All self reported (telephone or written surveys)
  - Random or National
  - Food allergy in general or a specific food allergy
  - Sensitization is more frequent

Development of Food Allergy:
Modifiable factors

- Window of opportunity
- Primary prevention (before sensitization)
  - Sensitization occurs post-uterine
  - Skin testing not as sensitive as blood testing in infants
  - Sensitization occurs early
  - Short window for primary prevention (early infancy)
- Secondary prevention (after food allergy specific IgE is present “sensitization”)
  - Before clinical reactivity
  - More realistic


Development of Food Allergy:
Modifiable factors

- Transcutaneous sensitization
- Clinical data: Skin barrier dysfunction
- Pre-clinical data
- Clinical data: Environmental allergen exposure

Development of Food Allergy:
Modifiable factors

- Transcutaneous sensitization
- Clinical data: Skin barrier dysfunction
  - there is a preceding history of AD in the majority of children with PA
  - TEWL (Transepidermal water loss)
    - measure of decreased skin barrier effect
    - increased at both lesional and nonlesional skin sites in AD
    - also in pre-AD at high risk for atopy
    - also facilitates allergen penetration and subsequent sensitization.

Development of Food Allergy:
Modifiable factors

- TEWL correlates with skin dryness, it is possible to identify reduced skin barrier function in patients with no history or clinical evidence of AD.
- use of “wet wipes” and more frequent washing of babies known to influence skin integrity and permeability
- skin permeability to foreign proteins has changed.
- Studies (2, small) suggest
  - regular application of emollients from birth
  - reduces the risk of AD development
  - might thus affect FA
Development of Food Allergy: Modifiable factors

- Transcutaneous sensitization
- Clinical data: Skin barrier dysfunction
- Pre-clinical data summary
  - is allergen specific
  - the IgE response is exclusive to the allergen that is applied
  - ONLY to abraded skin.
- Clinical data: Environmental allergen exposure

Environmental allergen exposure

- Household peanut consumption correlates with PA
- Can measure significant levels of food allergen in vacuumed house dust
- High levels of peanut in dust correlates with peanut sensitization in AD children
- Increased risk of PA in children with FLG-null mutation with high levels of peanut in dust from playrooms
- Indicates transcutaneous sensitization to environmental peanut allergen can occur via inflamed and impaired skin barrier.


Dietary factors

- Maternal Diet
  - No impact on development of AD/FA/PA whether consumed during pregnancy or breast feeding
  - (remember, post partum total household levels are important)

Infant Diet: General measures

- Breast feeding
  - May be good for other things, but not preventing atopy or FA.
- Modified infant formula
  - no evidence to support feeding with a hydrolyzed formula for the prevention of allergy compared with exclusive breast-feeding.
  - high-risk infants unable to be exclusively breast-fed
    - limited evidence prolonged feeding with a hydrolyzed formula reduced infant and childhood allergy and infant cow’s milk allergy (compared with cow’s milk formula).
Development of Food Allergy: Modifiable factors

- Dietary factors
- Infant diet: allergen specific measures
- Allergen avoidance
- 165 children randomized
  - Avoiding common food allergens in mothers during 3rd trimester and children after birth x 3 years
  - Cow’s milk sensitization & AD reduced at age 2
  - Not FA, sensitization, total IgE or atopic disease by age 7.
- 120 infants, breast fed or hydrolyzed formula
  - restricted diet in mothers and children + house dust mite avoidance
  - Age 8, decreased asthma, AD, rhinitis & atopy.
  - Not powered for FA


Other Dietary Factors

- Vit D
- Other vitamin supplements
- Prebiotics
- Probiotics
- Fatty acids
- Antioxidants
- No good data, some safety concerns

Other Factors

Epigenetics

- Epigenetics: changes in gene function in relation to environmental influences
- Markers of these epigenetic changes include DNA methylation and histone modification
  - forkheadbox P3 (FOXP3): example of DNA methylation from pollution correlates with asthma in children via impairment of T-reg function
  - Can be influenced by nutrition, the intrauterine environment, and lifestyle factors, pollution, stress etc.
- Methylation biomarkers outperformed allergen sIgE and SPT responses for predicting OFC outcomes
- FA status correct predicting: 79.2%

Hope for epigenetics:
- the identification of modifiable trigger factors will guide the development of strategies for the prevention of FA.
Modifiable Dietary Factors
Infant Diet: Allergen Specific Measures

- Allergen specific introduction: Observational studies
- LISA (Lifestyle-Immune System-Allergy) birth cohort study
  - n = 2073
  - delayed solid food introduction past 4–6 months
  - not protective of developing food sensitization at age 6 years
  - was associated with greater food sensitization


- More limited food diversity in the first 6 months of life:
  - associated with development of allergic rhinitis at 5 years
- Limited diversity in the first 12 months:
  - Associated with risk of developing asthma, allergic rhinitis, eczema, and wheeze


- Reduced diversity of foods introduced within the first year of life
  - none to three vs. six or more foods
- Associated with higher risk of
  - food sensitization at age 4.5 and 6 years
  - physician-diagnosed food allergy at age 6 years

Modifiable Dietary Factors
Infant Diet: Allergen Specific Measures

- Allergen specific introduction: Randomized trials
- LEAP study (“Learning Early About Peanut”)
  - 640 high risk infants (severe eczema and/or egg allergy); 4 – 11 months
  - PST –; or weakly +
  - (7 of 319 reacted to peanut challenge at baseline; not severe, no epi)
  - Study group: ate peanut protein 3X/week (minimum) (24 g peanuts; 3 teaspoons peanut butter)
  - Control group avoided peanut for 60 months
  - Controls: 17.2% + peanut challenge at 60 months
  - Peanut group: 3.2% (80% relative risk reduction)
  - 6/319 developed PA during the study
- Consensus statements now recommending early introduction of peanut in high-risk infants with negative skin tests
  - (NIAID, AAP, AAD, AAAAI, ACAAI, AAFP)


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Modifiable Dietary Factors
Infant Diet: Allergen Specific Measures

- Allergen specific introduction: Randomized trials
- EAT study (Enquiring About Tolerance)
  - 1,303 breast fed 3 month old infants, general population
  - Introduced peanut, cooked egg, cow’s milk, sesame, white fish and wheat once a week vs. exclusive breast feeding to 6 months
    - Adherence only 42%
  - ITT (Intent To Treat) analysis (entire study group)
    - No difference in overall incidence of FA at age 3 (7.1% vs. 5.6%; p=.32)
  - Per protocol analysis (adherent group only)
    - Any food allergy: 7.3 vs. 2.4 (p<0.01)
    - Peanut alone: 2.5 vs. 0 (p<0.003)
    - Egg alone: 5.5 vs 1.4 (p<0.009)


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Modifiable Dietary Factors
Infant Diet: Allergen Specific Measures

- Allergen specific introduction: Randomized trials
- LEAP – ON study
  - 12 month extension of LEAP
  - No peanut ingestion x 12 months then rechallenge
  - 74% reduction in PA in those who had consumed vs. those avoiding


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Are the LEAP Dietary Interventions Allergen Specific?

- Peanut, tree nuts, and sesame contain highly conserved homologous seed storage proteins
- cross-sensitization to these antigens may explain the co-occurrence of allergy to these foods.
- Since the consumption peanut in early life protects against the development of PA, would it also protect against the development of these other related FAs?
Dietary Factors
Infant Diet: Allergen Specific Measures

- Allergen specific introduction: Randomized trials
- Egg
  - five RCTs
    - STAR, STEP, BEAT (Australia) no benefit
    - HEAP (Germany) made things worse
    - PETIT (Japan) showed dramatic benefit
- Problems different entry criteria, timing of introduction, amount of egg consumed, type of egg consumed
- What if this had happened with the LEAP trial?
  - We’d be in a HEAP of trouble

Conclusions

- Large proportion of the allergy burden is inherited
- Genetic predisposition alone cannot explain the disturbing increase in FA
- Epigenetic modifications (changes in gene function in relation to environmental influences) provide evidence to explain the mechanisms underlying the development of FA
- Sensitization and FA can occur early in infancy, so interventions must begin early as well
- Use of dietary interventions in high risk pregnant and/or lactating women for the prevention of FA is weak, inconsistent and might compromise both maternal and fetal nutrition

Conclusions (cont.)

- It is not certain whether exclusive breastfeeding for any length of time offers protection against FA
- In high-risk infants, who are not exclusively breast-fed, use of hydrolyzed formula might offer weak protection against allergic disease and generally limited to the development of AD.
- Other dietary manipulations (Vit D, other vitamin supplements, fatty acids, prebiotics, probiotics, antioxidants) cannot be recommended (and may have safety concerns)

Addendum Guidelines for the Prevention of Peanut Allergy in the United States
Report of the NIAID-Sponsored Expert Panel
January 2017

- Recommendation #1: The EP recommends that infants with severe eczema, egg allergy, or both have introduction of age-appropriate peanut-containing food as early as 4 to 6 months of age to reduce the risk of peanut allergy.
- Other solid foods should be introduced before peanut containing foods to show that the infant is developmentally ready.
- The EP recommends that evaluation with peanut-specific IgE (peanut sIgE) measurement, SPTs, or both be strongly considered before introduction of peanut to determine if peanut should be introduced
Addendum Guidelines for the Prevention of Peanut Allergy in the United States
Report of the NIAID-Sponsored Expert Panel
January 2017

- Recommendation #2: The EP suggests that 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.
- Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready.
- The EP recommends that infants in this category may have dietary peanut introduced at home without an in-office evaluation.

Recent FDA Position

- Sept 2017: FDA approved a qualified claim:
  - “For most infants with severe eczema and/or egg allergy who are already eating solid foods, introducing foods containing ground peanuts between 4 and 10 months of age and continuing consumption may reduce the risk of developing peanut allergy by 5 years of age.”
- Caveats:
  - “Based on a single study”.
  - Not an “authorized” claim (requires rigorous data)

Conclusions (cont.)

- Numerous questions remain about how to implement early food introduction, and which groups of infants should be targeted.
- The paradigm has shifted from recommending avoidance of common food allergens in infancy, to consideration of early consumption strategies to prevent allergy development.
Peanut Treatment for Prevention of PA

- How to introduce peanut to babies
  - NOT whole peanuts: choking hazard
  - Peanut butter (possible choking hazard so dilute with hot water, breast milk, infant formula, or pureed fruit into a puree)
  - Add peanut powder/protein to pureed baby food or finger food
  - Commercially available products: all organic, preservative free
    - Bamba a baked snack containing 50% peanut + vitamins & iron
      - 25% of Israeli snack market
      - 90% of Israeli households purchase regularly
  - My Peanut (formerly First Nuts) peanut powder mixed in apple sauce; stand alone product
    - My Peanut + Tree Nut Mix also available
  - Simply Peanut (peanut protein + "essential vitamins") add to bottles
  - Hello, peanut! (organic peanut + sprouted oat flakes) add to whatever baby is eating
    - graded dose increase first week; then maintenance

Treatment for Peanut Allergy

- Viaskin (DVB technologies):
  - Peanut patch
    - Successful phase 2 trial
    - Failed to meet primary endpoint in phase 3 trial
    - Likely inadequate dosing in patch

- Sublingual immunotherapy (SLIT)
  - FDA approved
    - grass (Grastek, Oralair)
    - ragweed (Ragwitek)
    - dust mite (Odactra)
  - Peanut SLIT failed
    - likely secondary to inadequate dosing possible via sublingual administration

- Oral Immunotherapy (OIT):
  - AR101: Aimmune Therapeutics oral peanut immunotherapy
    - Phase 2 trial ¹: 0.5 ug up dose to 300 ug over 6 months
      - 20% drop out during the 6 month dose build-up
        - mostly due to GI side effects)
    - Among the rest, after 6 months of maintenance
      - 79% tolerated 300 mg (2 peanuts) 443 total cumulative dose
      - 62% 600 mg (2 peanuts) 1043 total cumulative dose
      - vs. 19% and 0% in the control group (p<.0001)
    - Pivotal phase 3 trials were to be completed by end of 2017 results should be forthcoming in first quarter of 2018

### Treatment for Peanut Allergy

- **Peanut OIT:**
  - Prior, smaller, investigator initiated, studies demonstrated similar results: “desensitization”
  - Must continue to eat regularly to maintain “desensitized state”
- Only a few developed “tolerance”
  - May choose to eat “ad lib” or not
- Desensitization alone would allow for some sense of safety for patients/parents

### Treatment for Egg Allergy

#### Scripps Approach

1. If the parent/patient with an allergy to egg in any or all forms or of any severity wishes to avoid all egg, we do not discourage this approach.
2. We allow persons to continue to eat egg in more processed forms than what triggered their reaction(s) if they have eaten egg in these forms regularly and in the recent past:
   - patients who reacted to lightly cooked egg (eg, scrambled egg, French toast), but have a history of tolerating extensively heated egg (eg, muffins, waffles).
   - we generally suggest that these patients avoid more intermediate forms of cooked egg, such as meatballs/meatloaf, breaded foods, casseroles, custard, mayonnaise, and hard-boiled egg.
   - it is possible that a patient may have a reaction due to ingestion of a larger amount of egg or more lightly cooked egg than usual (eg, normally tolerates egg in muffins, but has a reaction when blueberries are used in the muffins and the batter does not cook completely around the blueberries).

#### Extensively heated egg (EHE)

- Several studies have indicated that 66 to 88 percent of individuals with egg allergy can tolerate EHE or baked forms of egg
- The potential benefits of including EHE in the diet:
  - Improvements in quality of life.
  - Tolerance to extensively heated egg is a good prognostic factor for the development of tolerance to less heated forms of egg.
  - May accelerate the development of tolerance.
- However, consumption of extensively heated egg may also increase the risk of a reaction:
  - May be due to inconsistencies in the amount of egg in baked products
  - Leads to greater exposure
  - May be due to incomplete cooking leading to exposure to lightly cooked egg.


### Treatment for Egg Allergy (cont.)

3. Patients who have reacted to intermediately cooked or extensively heated egg avoid all forms of egg.
4. An oral challenge to extensively heated egg may be performed by an allergy specialist if a patient is not currently eating egg in this form but the patient (or parents of the patient) wishes to introduce it into the diet:
   - Caution is needed severe reactions can occur from this type of OFC.
   - >80 percent chance that baked egg will be tolerated if egg-specific IgE is <2 kUA/L
   - >10 kUA/L suggests an increased likelihood of reacting to baked egg.
   - 100 percent negative predictive values when mean wheal diameters were <3 mm for three different forms of extensively heated egg (cake, frittata, and boiled egg)

Treatment for Egg Allergy

- OIT for egg allergy
- Need is? As most children outgrow
- Desensitization is often successful (as with other foods)
  - 55% after 10 months
  - 75% after 22 months
- Tolerance still elusive
  - 28% successful at 2 months post desens (24 months)


Treatment for Food Allergy

- SubCutaneous Immunotherapy (SCIT):
  - “Allergy shots”
- Demonstrated efficacy > 100 years
  - Aeroallergens: pollens, furry animals, dust mite, mold
  - Venoms: bee, wasp, hornet, yellow jacket
- Why not foods?
  - NIH sponsored multicenter study 1990’s
  - Death at major US med center
  - Trial halted
  - interim analysis +
  - Considered “too dangerous” besides the death, increased incidence of systemic reaction (but “rush” protocol – like venoms. Why?)
- RAS always did & does (& it works & is safe)
  - Surprised?: Not

IntraLymphatic ImmunoTherapy (ILIT)

- Shown to work for grass pollen & cat
- Why not food?
- Scripps Trial
- 3 PA patients
  - 2 + DBPCFC
  - 1 with high levels sIge peanut (PST & invitro)
    - 95% confidence would react to OFC
- 3 ILIT injections one month apart (inguinal ln)
  - Each of the three had (one or two) systemic reaction during ILIT
  - Repeat DBPCFC in one month
- Preliminary results:
  - One patient eats peanut ad lib
  - One patient eats peanut ad lib with mid GI upset/stomach pain
  - Third patient to undergo oral challenge in a few weeks.

Conclusions
(Bottom Lines)

- Do not withhold solid food from infants in hope of preventing food allergy: data says this will backfire
- Recommend to parents of infants with egg allergy &/or severe eczema to introduce peanut early *
  - Only after testing for peanut sIgeE or PST’s
- Recommend to parents of infants with mild/moderate eczema to introduce peanut early *
  - Can be introduced without any prior testing, in the home
- Do feel free to encourage parents to introduce peanut and other solid foods as early as 4-6 months of age (only after tolerating at least one other solid food)
  - May or may not help prevention of food allergy, but no down side
- Caveats: * 4 – 6 months (only after tolerating at least one other solid food) to reduce development of PA
Conclusions
(Bottom Lines)

- Egg allergic child
  - Consider referral to allergist
    - History
    - PST's/sIgE
    - Baked egg challenge
    - Baked egg “OIT”
    - Follow-up

- Peanut allergic child
  - Consider referral to allergist
    - History
    - PST's/sIgE
    - Peanut component testing (sIgE to ara h2)
    - Oral peanut challenge
    - Referral to research center
Post test questions

1. Current recommendations to parents include the use of dietary interventions in high risk pregnant and/or lactating women for the prevention of food allergy.
   Is this statement a) True or b) False?

2. Exclusive breastfeeding for a 3-6 month length of time offers protection against food allergy.
   Is this statement a) True or b) False?

3. Which of the following supplements has been shown to be effective in preventing food allergy:
   a) Vit D multivitamin
   b) fatty acid, prebiotics
   c) probiotics
   d) antioxidants
   e) all the above
   f) none of the above

4. Current recommendations are to withhold solid food from infants in hope of preventing food allergy.
   Is this statement a) True or b) False

5. Current recommendations, within certain parameters are for parents of infants with egg allergy &/or severe eczema to introduce peanut early.
   Is this statement a) True or b) False

6. Current recommendations, within certain parameters are for parents of infants with mild/mild eczema to introduce peanut early.
   Is this statement a) True or b) False

See reverse for answers.
Answers:

1. b) False

2. b) False

3. f) None of the above

4. b) False

5. a) True

6. a) True