Take a Bite Out of Food Allergy

Melinda Braskett, MD
Keck School of Medicine at USC
Children’s Hospital Los Angeles
Gores Family Allergy Center

April 28, 2018
Acknowledgements

• No financial disclosures

• Slides courtesy of Ron Ferdman, MD, Moira Breslin, MD and Andy Saxon, MD
Today’s Objectives

• Describe impact & mechanisms of IgE “immediate” food allergy

• Understand evidence in support of early introduction of peanut

• Incorporate new practice guidelines for testing and early introduction of peanut in higher and lower risk infants

• Illuminate new and emerging therapies
Food allergy is common

- Estimates
  - 5 - 8% of young children or “2 in every classroom”
  - 2 - 4% of adolescents and adults
  - In US, up to 15 million affected & > 50,000 episodes of food anaphylaxis/year (but rates are rising!)

- Prevalence appears to be rising (sharply)
  - CDC interval increase of 50% (1997->2009) 3.4% -> 5.1% US (0-17y)

NCHS Data Brief 121: May 2013
Curr Opin Pediatr 2009 21:667–74
Pediatrics 2009 124:1549
Anaphylaxis is increasing

- Estimated btw 1.5%-5% in US and increasing worldwide

- Many not prepared (i.e. no epi autoinjector)

- Although anaphylaxis (allergic shock) appears to be increasing, rates of fatality are not increasing

J Allergy Clin Immunol 2014;133(2):461-7
J Allergy Clin Immunol 2007;120:878-84.
J Allergy Clin Immunol 2015;135:956-63
Increased prevalence & increased awareness

- Education of health-care providers and general public has led to increased screening, detection & reporting

- THEORIES explain increased food allergy prevalence
  - Hygiene Hypothesis
  - Delayed Introduction of Food
  - Form of food
  - Antibiotics, microbiome?
  - Genetically modified foods? (GMO)
Food allergies are immune responses

- Food allergies are reproducible
- Understanding pathways clarifies clinical picture
- Important to recognize what is not “allergic”

IgE to Food Protein

Food Protein
Food Intolerances are more common

- Miserable and not dangerous
- Don’t need or respond to epi or benadryl
- Real phenomenon but no reliable testing just reproducibility
  - IgG tests have no role in diagnosis of Food Allergy or food intolerance
- Patients feel need to be validated
<table>
<thead>
<tr>
<th></th>
<th>Classic Food Allergy</th>
<th>Food Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Examples</strong></td>
<td>Peanut</td>
<td>Lactose Intolerance, Migraines, Irritable Bowel Syndrome</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Immune reaction to structure of specific food</td>
<td>Usually unknown, some (lactose intolerance) due to low level of enzyme</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Most have hives or swelling, Can have breathing problems, vomiting, heart problems, fainting.</td>
<td>Variable, diarrhea, mood effects and headache are common</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>Can be life threatening</td>
<td>Not life threatening, but can be absolutely miserable</td>
</tr>
<tr>
<td><strong>Timeline</strong></td>
<td>Usually onset of trouble within minutes, can take up to 2 hours to develop</td>
<td>Variable, usually delayed</td>
</tr>
<tr>
<td><strong>Reproducible</strong></td>
<td>Intake of food (in the same form) always triggers reaction, although severity may differ</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Form of food</strong></td>
<td>Some baked forms can be tolerated especially for milk and egg</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Trace Amounts</strong></td>
<td>Can trigger severe reactions</td>
<td>Generally OK</td>
</tr>
<tr>
<td><strong>Avoidance</strong></td>
<td>Perfect, no problems</td>
<td>Better</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Avoidance, Antihistamines, Epinephrine (Adrenaline), Steroids</td>
<td>Treat the primary problem</td>
</tr>
</tbody>
</table>
Wide Spectrum of food allergy

**IgE-Mediated**

- Immediate hypersensitivity
- Oral allergy syndrome
- Allergic eosinophilic esophagitis
- Allergic eosinophilic gastroenteritis
- Food sensitive eczema

**Non-IgE Mediated**

- Food Protein Induced Enterocolitis Syndrome (FPIES)
- Dietary protein proctocolitis
- Celiac Disease*
Timeline of reaction is key

- IgE = Rapid or Immediate (onset usually <1h)

- Delayed (> 1-2h)
  - Eosinophilic Enteropathy (EGID, EoE)
  - Food protein induced enterocolitis (FPIES)
  - Allergic proctocolitis
  - Celiac Disease (not treated by allergists)
Rapid food allergies are dangerous

- 13y boy hx of avoiding peanut for eczema since infancy
  - Tries peanut and within minutes
    - has rapid swelling
    - vomiting within minutes
    - lump in throat
    - anxious
    - shortness of breath
IgE triggers classic food allergy

• Specific IgE response to a food protein
  • IgE, mast cells & eosinophils
  • T cells orchestrate inflammation
• Tiny amounts can cause reactions
• MAY be severe and even life-threatening
• MUST be differentiated from food intolerances
IgE “sees” the allergen

Protein

Guidance System

Amino acids (20)

Attachment to Bomb
Genetic Predisposition

Exposure

Sensitization

Re-exposure

Allergic “Sick”
Allergen + crosslinked IgE = Sick

- FcεRI-dependent activation
  - Degranulation
  - Histamine
  - Cytokines
    - TNFα, IL-6, IL-8
  - AA metabolites
    - LTC4, PGD2

Adapted from Kalnesnikoff and Galli, Nat Med, 11, 381 (2005)
IgE can trigger systemic reaction

Sensitisation

Dendritic cells → Peanut-specific T cells → Th2

IL-4
IL-5
IL-13

B cells → Peanut-specific IgE

Mast cells

FceRI

Allergic reaction

Systemic symptoms
- Airway obstruction
- Hives
- Low blood pressure
- Arrhythmia

Local symptoms
- Itching
- Swelling
- Nausea
- Vomiting
- Cramping
- Diarrhoea

Peanut allergens

Histamines
- Leukotrienes
- Cytokines
- Prostaglandins

Burks AW. Lancet 2008;371,9623:1538-1546
Detectable IgE does not imply FA

Testing overestimates food allergy

Cannot differentiate sensitization vs true allergy

- Skin prick test (ST) positive if > 3-4 mm
  - Excellent negative predictive value
  - Positive predictive value <50% without history

- Blood tests food specific IgE, formerly “RAST”
  published 95% probability of allergic reaction
  Peanut 14, Milk 15, Egg 7 kU/L (>2y)

Food Challenges are only definitive test

- May be open, single-blind, or double-blind placebo-controlled
- Must be used if the history and lab & skin tests results do not provide clear diagnosis
- Also provide monitoring and some information about threshold amount to trigger reaction
- Must be done with considerable caution
Peanut allergy is increasing rapidly

• The major cause of death in food-related anaphylaxis in the U.S.

• Peanut allergy has increased at an even greater rate than other food allergies in children
  – 1999 - 0.4%
  – 2010 - 1-3%

• Why??

Delayed introduction problematic

- **2000:** Higher risk infants (based on FHx) should delay introduction of “more allergenic” foods:
  - Milk - 1 yr; Egg - 2 yr; Nuts & Fish until 3 yr

- **2008:** No “convincing evidence” that delaying introduction of foods, beyond 4-6 months protective
  - Did not recommend early introduction of highly allergenic foods to prevent food allergy

- **2017:** New recommendations

Food allergy can be prevented

• **Primary prevention**
  – Prevent onset of IgE sensitization

• **Secondary prevention**
  – Prevent food allergy (reactivity) in IgE-sensitized individuals

• **Tertiary prevention**
  – Prevent clinical symptoms in individuals with established food allergies
Early introduction of peanuts → less food allergy

**Group 1**
Jewish children in Tel Aviv

- Peanut introduced per local customs
- Questionnaires & subset with testing/challenge
- 0.17% with peanut allergy

**Group 2**
Jewish children in London

- Peanut introduced per local customs
- Questionnaires & subset with testing/challenge
- 1.9% with peanut allergy

Genetically homozygous population in comparable urban environments

Differing cultural practices for peanut introduction

Israel: Start early
UK: Start late

RR of peanut allergy: 10x greater in UK

Early high dose effective in preventing peanut allergy high risk infants (LEAP)

• 640 high risk infants defined by eczema requiring prescription and/or egg allergy

• Infants randomized before 12m of age to high dose peanut consumption (2g protein =1 heaping tsp PB 3x/wk) or strict avoidance

• 80% reduction in prevalence peanut allergy at 5y in the early introduction group

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
  - 263 Were included in the ITT analysis
  - 18 Were excluded owing to inadequate adherence to treatment
  - 245 Were included in the per-protocol analysis
  - 266 Were included in the ITT analysis

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

58 Were in the SPT-positive cohort

- 51 Were assigned to peanut avoidance
  - 41 Consumed peanut protein
  - 51 Were included in the ITT analysis
  - 6 Had a positive baseline peanut challenge, did not consume peanut, and were included in the ITT analysis
  - 41 Were included in the per-protocol analysis

- 47 Were assigned to peanut consumption
  - 41 Were included in the ITT analysis
  - 2 Were excluded owing to inadequate adherence to treatment
INTENTION-TO-TREAT ANALYSIS

Skin Test Negative Cohort (N=530)
P<0.001

Avoidance Group 13.7%
Consumption Group 1.9%

Skin Test Positive Cohort (N=98)
P=0.004

Avoidance Group 35.3%
Consumption Group 10.6%

Both Cohorts (N=628)
P<0.001

Avoidance Group 17.2%
Consumption Group 3.2%

~80% reduction

PER-PROTOCOL ANALYSIS

Skin Test Negative Cohort (N=500)
P<0.001

Avoidance Group 13.9%
Consumption Group 0.4%

Skin Test Positive Cohort (N=89)
P<0.001

Avoidance Group 34.0%
Consumption Group 0.0%

Both Cohorts (N=589)
P<0.001

Avoidance Group 17.3%
Consumption Group 0.3%

We can prevent peanut allergy

• Early high dose is effective in preventing peanut allergy in high risk infants

• What about peanut allergy for lower risk infants?

• What about early introduction for other foods?

What does this mean to me and my patients?
We risk stratify for peanut allergy based on eczema

- **Category 1**
  - Significant eczema (persistent prescription medications) and/or confirmed egg allergy

- **Category 2**
  - Mild-moderate eczema

- **Category 3**
  - No Eczema

Eczema plays a role in sensitization
High Risk Infants need to be tested very early introduction encouraged (4-6m)

Togias A. J Allergy Clin Immunol. 2017;139:29
IgE tests for other foods less reliable, high false positive

- Serum IgE for peanut not preferred but can be faster than waiting for allergy skin test referral
- Use cut off of < 0.35 as negative for peanut
- Discouraged from sending food allergy IgE panels as poor positive predictive rate
New recommendations for introducing peanut

<table>
<thead>
<tr>
<th>Eczema</th>
<th>Age Introduction</th>
<th>Testing -&gt; Refer</th>
<th>Quality of Evidence</th>
<th>Observed Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Severe</td>
<td>4-6m</td>
<td>Yes</td>
<td>Moderate-High</td>
<td>Probably</td>
</tr>
<tr>
<td>Intermittent Mild/Moderate</td>
<td>6m</td>
<td>Not needed</td>
<td>Low</td>
<td>Possible</td>
</tr>
<tr>
<td>None</td>
<td>open</td>
<td>Not needed</td>
<td>Low</td>
<td>No</td>
</tr>
</tbody>
</table>

No clear recommendations for other foods

• Suggestions not to send other IgE tests, instead refer

• Less cooked form of egg $\rightarrow$ more allergenic
  – Baked egg least allergic form
  – Hard Boiled egg less allergic than scrambled or runny
  – Raw egg most allergenic

• Unknown if true for tree nuts, sesame, seeds
Early high dose also prevents peanut allergy in low risk infants less clear with other foods (EAT study)

- 1300 low risk infants (defined by lack of eczema)
- Infants randomized to receive early introduction to top allergenic foods at 3m (wheat, yogurt, egg, peanut, sesame)
- Significant findings in the per protocol group for peanut and egg but not the intention to treat analysis due to high drop out, and loss of power with multiple comparisons

EAT Study Design Overview
• ~1300 3m infants exclusively breast fed, low risk criteria
• Randomized to Standard or Early introduction
• Study Foods: milk (yogurt), peanut, egg (boiled), sesame, fish, wheat

Early Introduction
• Breast feed to 6m
• Skin test to all “study foods”
• + skin test → challenge
• At 3 months, start all

Standard Introduction
• Exclusive breast feed to 6m
• No food skin testing
• No “study foods” before 6m
• At 6 months, start any (pref)

Monitor until 3 years old
Prove any suspected food allergies with challenge

Intent to Treat
• All infants with data

Per Protocol Early
• From 3-6 m, eat 75% (3 g/wk) of 5/6 foods, for ≥ 5 wk

Per Protocol Std
• No study food < 6 m
• If milk formula from 3-6 m, must be <300 mL/day

based on: Perkin MR. NEJM. 2016; 374:1733.
Percent of Children with Food Allergy
Intention to Treat Group

Standard Introduction Group Early Introduction Group

Any Food Peanut Egg

P=0.32 P=0.11 P=0.17
7.1 5.6 3.7
2.5 1.2

Percent of Children with Food Allergy
Per Protocol Group

Standard Introduction Group Early Introduction Group

Any Food Peanut Egg

P=0.01 P=0.003 P=0.009
7.3 5.4 2.4
2.5 0 1.4

modified from: Perkin MR. NEJM. 2016; 374:1733.
Early introduction solids does not interfere with breast feeding

• Early introduction of complementary foods were not shown to interrupt breast feeding

• Infants were safely able to ingest foods even at 3m
  – but it wasn’t easy.
Data on maternal diet during pregnancy and breast feeding unclear

• Studies show conflicting results

• No clear recommendations
Practical tips for at home challenges

• Tip of the spoon, wait >10 minutes, then feed rest

• Goal 2g of peanut protein = 1 heaping tsp PB or 21 pieces of Bamba
  – Can mix PB or Bamba with warm water
  – Doesn’t have to be done all at once

• 1st attempt at home w/ adult who can focus on child for 2h

• Make sure child is well when introducing

• Keep in diet once introduced (LEAP study was 3x/week)

• Have benadryl and dose available
Low risk challenges can be also done at pediatrician's office

- Parental anxiety
- Parents unsure if had reaction
- Affected sibling
- Clinical intuition
- Monitor for 2h after
- Have benadryl dose (1.25mg/kg) and epinephrine available
We can prevent peanut allergy

- PRIMARY PREVENTION
  - New Role for pediatricians introduce before sensitized

- SECONDARY PREVENTION
  - Allergist challenges + skin or blood test but neg challenge

- TERTIARY PREVENTION
  - Oral immunotherapy (OIT) or desensitization
  - Research therapeutics
FA Immunotherapy increases threshold

- **Threshold** amount required to trigger a reaction
- **Desensitization** raises threshold of allergen needed to cause allergic rxn
  - dependent on regular allergen exposure
OIT protects from trace exposures

- Not a cure, does not replace epinephrine
- ~90% have adverse reactions --most mild
  - Up to 20% stop therapy due to adverse reactions
- Requires dose reduction for illness
- Long term safety, efficacy, adherence unknown
- Commercial product for peanut is in phase III

Stay Tuned: More to Come

• Patch—desensitization via epicutaneous IT
  – Phase 2 data w/ modest changes, less robust than OIT

• Nanoemulsion intranasal immunization (phase 1)
  – Switch to IgG response

• Chinese Herbs
  – No effect in phase 2, poor adherence
  – May be useful w/ OIT

• New biologics may be helpful in conjunction w/ OIT
  – Anti IL 4, IL13
  – Anti TSLP
  – Anti IL33
Thank you!
Photocredits

- Apple bite out
  04/26/18
- Nuts
  04/26/18
- Kid afraid of food
  GettyImages-81714805-56893c545f9b586a9e644491
  04/26/18
- FA vs FI
  04/26/18
- Time
  4/26/18
- Skin test 1
  4/26/18
- Skin test 2
  4/26/18
- 3m baby
  http://www.momjunction.com/articles/learning-activities-for-your-3-month-old-baby_0092253/#gref
- Kid eating
  http://5keysparenting.com/blog/2010/10/184/kid-eating/
  4/26/18
- Smile veg
  4/26/18
- Itch rash
  https://potomacpediatrics.com/eczema-itch-rashes/
  4/26/18