FOOD ALLERGY: AN UPDATE

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Disclosures

• FARE, Clinical Network Grant
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• Aimmune, Principal Investigator
• DBV, Principal Investigator
Objectives

• Discuss the evolving field of food allergy and recent lessons from the literature
• Discuss recently updated food allergy guidelines
• Describe investigational food allergy treatments
• Discuss the psychosocial impact of food allergy
• Identify resources for children with food allergy
Food Allergy: Perception vs Reality

• Public perception of food allergy:
  • 25 – 30%

• Prevalence of IgE-mediated food allergy¹:
  • 7.6% of children - 1 in 12
  • 42% reported ≥1 severe FA
  • 19% ≥1 FA-related ED visit in the past year
  • 41% had a current epinephrine auto-injector

- ¹Gupta et al, Pediatrics, 2018
**Food Allergy: Immunologic Spectrum**

**IgE-mediated (most common)**
- Anaphylaxis
- Pollen-food allergy syndrome (oral allergy syndrome)
- Urticaria
- Morbilliform rash, flushing
- Immediate GI sx
- Upper and lower respiratory sx (not in isolation)

- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis

**Non-IgE Mediated (cell-mediated)**
- Food-protein colitis
- Protein-induced enteropathy
- Food-protein enterocolitis syndrome (FPIES)
- Eosinophilic colitis
- Dermatitis herpetiformis
- Contact dermatitis

- Sampson H. J Allergy Clin Immunol, 2004
IgE-mediated Food Allergy: Key Features

- **Timing**
  - Usually within 10-15 min
  - 90% within 2 hours

- **Reproducibility**

- **Duration**
  - Symptoms usually resolve in hours
    - Exception - biphasic reaction
  - **Not** chronic respiratory symptoms
  - **Not** chronic urticaria
8 Foods Cause > 90% of Food Allergy

- Milk
- Egg
- Wheat
- Soy
- Peanut
- Tree nuts
- Fish
- Shellfish
Max, age 8

My tummy hurts
Food Allergy Testing Dilemmas

Max has been going to the school nurse’s office 2-3 times per week due to belly pain.

• Scenario 1: Mom asks for allergy testing.

• Scenario 2: Mom brings in outside testing.
Food-specific IgE Testing (ImmunoCAP)

Scenario 1: Mom asks for allergy testing.
- Must be guided by history
- Highest utility - confirming IgE-mediated symptoms
  - NPV 90-95%, PPV <50%
  - “Positive” test ≠ food allergy
  - “Class” designation is useless; use published cut-offs
- Food allergy testing not indicated
Food-specific IgE Panels

284 patients with food allergy panel testing
  - Only 1/3 had history warranting food allergy evaluation
  - Most common indications: AR, mild AD, idiopathic urticaria

Very low PPV

Almost 90% of individuals avoiding a food due to panel testing were able to reintroduce at least 1 food

Food IgE panels are not recommended
  - Often result in misdiagnosis, unnecessary dietary changes, direct and indirect costs, and anxiety

Unproven/Disproven Diagnostic Testing

Scenario 2: Mom brings in outside testing.

- ALCAT test (Cell Science Systems, Fla) – flow cytometry
- Food IgG testing
  - Reputable test platform, incorrect application
  - Measures normal immunologic response, not chronic inflammatory pathway
  - IgG₄ marker of food desensitization
- Provocation-neutralization testing – intradermal testing
- Applied kinesiology

- Most lack biologic plausibility
- None has been shown to correlate with disease

- Kelso, JACI In Prac, 2018
Food Allergy Testing Dilemmas

• Let the history and physical be your guide

• Employ firm and clear counseling with families

• Heed the risks of food allergy mis/over-diagnosis
Toby, age 5 months

“Should we introduce peanut?”
Avoidance

Early Introduction

- LEAP
- LEAP-On
- EAT
- NIAID

- Du Toit et al, NEJM 2015
- Du Toit et al, NEJM 2016
- Perkin, JACI 2016
- Togias et al, JACI 2017
Learning Early about Peanut Allergy (LEAP) Trial

- 640 high-risk children
  - Eczema or egg allergy → 20% likelihood of developing peanut allergy
  - Excluded those at highest risk (SPT>4mm)
- Enrolled at 4-10 months of age and assigned to peanut avoidance or regular consumption

- At age 5, 70% reduction in peanut allergy in those assigned to peanut consumption
- After 1 year of avoidance, no increase in prevalence of peanut allergy

- Du Toit et al, NEJM 2015
- Du Toit et al, NEJM 2016
Toby, age 5 months

- Severe atopic dermatitis involving face and body
- Treated with mometasone 0.1% ointment, wet wraps
- Breastfed and growing well
- Sibling with food allergy
# NIAID Addendum Guidelines for Prevention of Peanut Allergy

<table>
<thead>
<tr>
<th>Infant criteria</th>
<th>Recommendations</th>
<th>Age of peanut introduction</th>
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<tbody>
<tr>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider allergy testing +/- supervised challenge</td>
<td>4-6 months</td>
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<tr>
<td>Mild-to-moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family and cultural practices</td>
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</table>
Severe eczema
or
Egg allergy
or
Both

**Peanut sIgE**

- **<0.35**
  - Risk of reaction low. Over 90% will have (-) SPT to peanut.
  - Options:
    a) Introduce peanut at home
    b) Supervised feeding in the office
    (based on provider/parental preference)

- **≥0.35**
  - Refer to specialist for consultation/SPT protocol

**Peanut Skin Prick Test**

- **0-2 mm**
  - Risk of reaction low (95% will not have peanut allergy).
  - Options:
    a) Introduce peanut at home
    b) Supervised feeding in the office
    (based on provider/parental preference)

- **3-7 mm**
  - Risk of reaction varies from moderate to high.
  - Options:
    a) Supervised feeding in office
    b) Graded OFC in a specialized facility

- **≥8 mm**
  - Infant probably allergic to peanut.
  - Continue evaluation and management by a specialist

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* 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.
Risk Stratification: Serum Testing
Food Allergy Prevention: A Global Perspective

USA/Canada (2017)
Risk-stratify, skin/serum testing in severe eczema/egg allergy

UK (2017, 2018)
Wean at 6 mo, peanut treated as other foods, consider referral/testing if high-risk but weigh against delay

Japan (2016)
Wean at 5-6 mo, exclude no foods

Europe (2014*)
No need to delay intro of complementary foods beyond 4 mo

Australia (2017)
All children, intro peanut at 6 mo (4-12 mo), no testing guidance, ingestion home/supervised

- Fisher et al, JACI In Prac, 2019
Nuances of Translating Trials into Practice

• Geographic/cultural differences

• Screening may promote safety but has logistic and financial challenges

• Focus on identifying children “at risk” may miss substantial portion who develop peanut allergy and do not meet criteria

• Broad-based public health messages are often more effective
  • Must account for parental willingness

- Fisher et al. JACI In Prac, 2019
Food Allergy Prevention

WE NEED YOU

TO HELP PREVENT FOOD ALLERGY!
Current Best Practice

- Risk stratify early – NIAID algorithm
- Judiciously utilize testing when appropriate
- Consult Allergy when needed
Toby successfully introduces peanut.

Will eating peanut worsen his eczema?
Allergy Prevention: Learning from LEAP

- LEAP participants aged 60 and 72 months
- High and increasing rate of food and airborne allergy
  - 76% had ≥1 allergic disease at 60 months of age
  - No differences between LEAP groups

- Good news
  - Significant resolution of eczema
  - Significant resolution of sensitization to egg and milk
  - Not affected by peanut consumption

- du Toit, et al. JACI, 2018
AD Severity Bands (SCORAD) Over Time

- du Toit, et al. JACI, 2018
Mom plans to continue breastfeeding.

Should I eat peanut?
Evidence demonstrates benefit:

• Exclusive breastfeeding x 3-4 months decreases AD in first 2 years

• Early introduction of peanut may prevent peanut allergy
No evidence or known benefit for food allergy/atopy prevention:

- Maternal dietary restrictions during pregnancy or lactation
- Role of exclusive breastfeeding beyond 3-4 months
- Use of hydrolyzed formula
- Delaying intro of allergenic foods beyond 4-6 months
What is the root cause of Toby’s eczema?
AD and Food Allergy

In a relationship
Engaged
Married
✓ It’s complicated
AD Pathophysiology: Multifactorial

AD and Food Allergy: Perception vs Reality

• Parental perception of food allergy in AD is high: 55%\textsuperscript{1}

• Rarely is food allergy the primary cause of AD

• More often, FA and AD are co-expressed

• Adequate therapy for AD may alleviate concerns \textsuperscript{2}
  - Decreased food allergy concerns after 3 months of therapy with tacrolimus

• Early AD may promote food allergy and development of other atopic disease\(^1\) or could cluster with these conditions due to shared genetic loci and environmental triggers\(^2\)

“Atopic march is imminent once skin manifestations evident.”

- \(^1\) Czarnowicki, JACI 2017
- \(^2\) Paller, JACI 2019
AD and Food Allergy

- Approximately 30% of children under age 5 with refractory moderate-to-severe eczema have allergy to 1 or more foods\(^1\)
  - Cow’s milk, egg, peanut, soy, wheat
- Correlated with AD severity, younger age of onset, increased need for medical therapy \(^2,3,4\)
- Rarely linked in older children and adults

\(^3\) Martin et al. Clin Exp Allergy, 2015.
AD and Food Allergy

- Food allergy should be considered in 2 settings:
  - IgE-mediated allergic symptoms
  - Children under age 5 with moderate-to-severe eczema not responding to treatment
    - IgE-mediated symptoms with foods
    - Non-IgE mediated symptoms with foods
      - Delayed onset and very difficult to distinguish from typical waxing/waning of eczema
      - History of flares with food ingestion generally unreliable

- NIAID Food Allergy Guidelines, JACI 2010
Limitations of Food Allergy Testing in AD

- Seldom identify the sole/primary trigger of atopic dermatitis

- Specific IgE may not be clinically relevant in setting of high total IgE/AD
  - Predictive cut-offs established in studies of immediate reactivity
  - Sensitization may not correlate with symptoms
  - Nuanced approach to test interpretation

- Food patch testing not recommended

Elimination Diets

- Potential benefits¹
  - No overall benefit for general milk or egg avoidance
  - Beneficial in children 11-17 months with suspected egg allergy and positive egg IgE – 50% response rate

- Risks
  - Detract focus from AD skin care regimen
  - Impact nutrition/growth, particularly with milk elimination
  - Incite development of IgE-mediated allergy²
  - Post-LEAP era: increase risk of IgE-mediated food allergy with avoidance/delayed introduction

² Chang, et al. JACI In Prac, 2015
Oral Food Challenges in AD

• Retrospective chart review of 125 children with AD
  • Excluded those with anaphylaxis/IgE-mediated food allergy
• 89% (325 of 364) of OFC were negative
  • No immediate reaction nor delayed eczematous flare
• Vast majority of foods that had been restricted were returned to diet

• In the absence of anaphylaxis, serum food-specific IgE testing cannot be used to determine the need for an elimination diet, especially in children with AD

Lucas, age 5

Lucas had a reaction at a birthday party and went to the ER.
Food Allergy Treatment: Current Standard of Care

• Accurate diagnosis
  • Allergy referral

• Allergen avoidance

• Patient/caregiver education

• Early use of epinephrine auto-injector
Food Allergy Investigational Treatments: First Generation

- Food immunotherapy
  - Not FDA-approved
  - Various routes, doses, side effect profiles
  - Aim to reduce severity of symptoms with accidental ingestion = desensitization
  - Also being studied in conjunction with biologics
AR101 Peanut Oral Immunotherapy (OIT): Phase 3 RCT

- 551 subjects, 496 aged 4-17 years with challenge-proven peanut allergy
- Randomized 3:1 to active treatment or placebo
- Supervised dose escalation, daily home dosing, 24-week maintenance phase – total 12 months
- End-of-trial food challenge

- Vickery et al, N Engl J Med, 2018
**AR101 Peanut OIT: Phase 3 RCT**

67.2% treatment group vs 4% placebo group tolerated ≥600 mg peanut protein dose

- Vickery et al, N Engl J Med, 2018
AR101 Peanut OIT: Phase 3 RCT

• Subjects receiving treatment had lower severity of symptoms during the exit food challenge and lower epinephrine use

• Safety profile
  • Adverse events occurred in nearly all subjects
  • 5.6% serious or severe AE
    • No deaths or life-threatening events
  • 14% active vs 6.5% placebo required epinephrine
  • 11.6% withdrew due to AE
    • 6.5% due to GI symptoms

- Vickery et al, N Engl J Med, 2018
Peanut Epicutaneous Immunotherapy (EPIT): Phase 3 RCT

- 356 children aged 4-11 years with challenge-proven peanut allergy
- Randomized 2:1 to daily treatment with peanut patch containing 250 mcg of peanut protein or placebo for 12 months
- End-of-trial food challenge

- Fleischer et al, JAMA, 2019
Peanut Epicutaneous Immunotherapy (EPIT): Phase 3 RCT

- 35.3% of active treatment vs 13.6% placebo responded to treatment
  - 21.7% difference in response rate
  - Did not meet predefined lower bound of CI threshold

- Patch site reactions - 95.4% active and 89% placebo
- No discontinuation due to GI side effects
- 3.4% of active treatment subjects had anaphylaxis related by some degree to treatment – all mild-mod
  - 6 received epinephrine

- Fleischer et al, JAMA, 2019
PACE – Clarifying the Evidence

- Meta-analysis – RCT peanut oral immunotherapy vs no oral immunotherapy
  - 12 trials, n=1041 subjects, median age 8.7 years

- Outcomes – anaphylaxis, allergic or adverse reaction, epinephrine use, quality of life

- Chu et al, Lancet, 2019
PACE – Clarifying the Evidence

• Compared with avoidance, oral immunotherapy:
  • Increased anaphylaxis risk – risk ratio 3.12 (95% CI 1.76-5.55)
    • OIT 22% per year vs baseline 7% per year
  • Increased anaphylaxis frequency – incidence rate ratio 2.72 (95% CI 1.57-4.72)
  • Increased epinephrine use – RR 2.21 (1.27-3.83)
  • Increased serious adverse events and non-anaphylactic reactions

• Increased likelihood of passing supervised challenge – RR 12.4 (95% CI 6.8-22.6) – surrogate for preventing out-of-clinic reactions
• Low certainty evidence that OIT does not improve QoL

- Chu et al, Lancet, 2019
PACE – Clarifying the Evidence

- Peanut OIT increases allergic and anaphylactic reactions over avoidance or placebo
- Peanut OIT effectively induces desensitization, though variable and rarely complete

- Mechanistic but not clinical efficacy
- Favor avoidance over treatment with OIT
- Further investigation needed
  - Better surrogate measure of treatment efficacy than OFC
  - Safer treatment options

- Chu et al, Lancet, 2019
Further Study Needed

- Are “controlled” allergic reactions with OIT preferred to unexpected allergic reactions with accidental exposure?

- What reduction in threshold of sensitivity confers meaningful protection?

- What patients would benefit most from treatment?

- How long does any protective benefit last?
Food Allergy Investigational Treatments: Next Generation

- Therapeutic approaches targeting immunologic pathways
  - Omalizumab recently granted Breakthrough Therapy Designation – monotherapy or in combination with multifood OIT
  - mAB anti-IL-33 in phase 2 studies investigating impact on oral peanut challenges in adults
  - Dupilumab + peanut OIT trials

- Vickery et al. JACI In Prac, 2019.
Lucas has become increasingly anxious around food, worried about another reaction.
Psychosocial Impact of Food Allergy

- Must address psychosocial impact of food allergy
  - Quality of life
  - Anxiety
  - Economic burden
  - Bullying
  - Common misconceptions/fears regarding casual exposure\(^1\)
    - Ingestion is primary route for reaction
    - Peanut not aerosolized and does not remain airborne
    - Casual contact results in no or localized reaction

\(^1\) Venter et al, JACI In Prac 2019
Food Allergen Casual Contact

- Skin contact and inhalation of peanut often feared

- 30 children with peanut allergy, median peanut IgE >100
  - 19 reported history of contact/inhalation reactions

- DBPC contact and inhalation exposures to peanut butter
  - None experienced a systemic reaction

- Ingestion most relevant in systemic reactions
  - Inhalation possible with foods that have been aerosolized
    ex: cooking fish, steaming milk

- Sicherer, JACI, 2003
TOUCH Study: Reducing Food Allergy Anxiety

- RCT of education + behavioral intervention (touch allergen) vs verbal education alone

- 60 patients with pn/tn allergy and parents
  - 35% reported reactions from casual exposure

- Both education and education + behavioral intervention resulted in decreased patient- and parent-reported anxiety

- Incorporate short verbal education script when counseling patients

- Weinberger T, et al, JACI In Prac, 2019
Psychosocial Impact of Food Allergy

- Discuss high- vs low-risk situations
- Address parental and patient fears
- Ask about bullying
- Utilize testing, food challenges
- Team-based approach including psychologist, dietitian, child life, speech/feeding therapy
Lucas is starting kindergarten this fall.

What do we need to do to prepare?
Management of Food Allergy in School

- Identification of students at risk – diagnosis
  - ED follow-up
  - Allergy referral
- Written Anaphylaxis Action Plan
- Epinephrine auto-injectors
- Individualized Health Plan/504 Plan PRN

- Resources – FARE website, CDC “School Guidelines for Managing Students with Food Allergies”
Management of Food Allergy in School

- Texas SB66 – stock epinephrine in schools

- AISD Experience – all epi administered 2015-2017
  - 68% unassigned epinephrine
  - 22% in persons without history of allergy
  - 45% in persons with known allergy but no assigned epinephrine
    - Adolescents over-represented
  - Food was trigger for nearly 50% of reactions treated
  - Closing the gaps

- Neupert, Cherian, Varshney. JACI In Prac, 2019
J.J., age 7 months

JJ vomited until he emptied his stomach
FPIES Consensus Guidelines

- Non-IgE-mediated food allergy
- 15% progress to hemodynamic instability/shock-like picture → medical emergency
- Challenging diagnosis with wide differential and no biomarkers
- Limited, if any, role of allergy testing
  - Weak ability to predict more protracted course – milk

- Nowak-Wegrzyn, JACI 2017
FPIES Consensus Guidelines: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Major criterion:</th>
<th>Minor criteria:</th>
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<tbody>
<tr>
<td>Vomiting in the 1- to 4-h period after ingestion of</td>
<td>1. A second (or more) episode of repetitive vomiting</td>
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<tr>
<td>the suspect food and absence of classic IgE-</td>
<td>after eating the</td>
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<tr>
<td>mediated allergic skin or respiratory symptoms</td>
<td>same suspect food</td>
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<td>2. Repetitive</td>
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<td>vomiting episode 1-4 h after eating a different food</td>
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<td>3. Extreme</td>
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<td>lethargy with any</td>
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<td>suspected reaction</td>
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<td>4. Marked</td>
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<td>pallor with any</td>
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<td>suspected reaction</td>
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<td>5. Need for emergency department visit with any</td>
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<td>suspected reaction</td>
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<td>6. Need for</td>
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<td>intravenous fluid</td>
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<td>support with any</td>
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<td>suspected reaction</td>
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<td>7. Diarrhea in 24 h (usually 5-10 h)</td>
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<td>8. Hypotension</td>
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<td></td>
<td>9. Hypothermia</td>
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Major criterion + ≥3 minor criteria

- Nowak-Wegrzyn, JACI 2017
FPIES Consensus Guidelines

- **Common triggers**
  - Milk, soy in formula-fed infants
  - Grains (rice, oat), legumes, poultry

- **Treatment**
  - Removal of allergen – patient, not generally mother
  - Recognition/treatment of symptoms
    - Fluid resuscitation, ER evaluation, IV steroids?, ondansetron
  - **Dietary guidance**
  - Feeding therapy

- Nowak-Wegrzyn, JACI 2017
Lily, 9 months

Is it safe for Lily to receive the flu shot?
Influenza Vaccine and Egg Allergy

• Annual influenza vaccination – most effective means of protection
• Almost 1/3 of children with egg allergy have asthma
• Because most influenza vaccines grown in embryonated chicken eggs, they were contraindicated in those with egg allergy until recently

- Greenhawt, Annals 2017
Influenza Vaccine and Egg Allergy

- Flu shot skin testing
- Choose specific vaccine based on ovalbumin content
- Flu shot divided or graded dosing
- Specific medical setting
- Specific waiting period
- Egg allergy severity
- Standard precautions
Influenza Vaccine and Egg Allergy

Large number of studies have confirmed safety
  • Included those with hx anaphylaxis
  • Low rates of minor reactions in egg-allergic recipients, no greater than non-egg allergic
  • All current vaccines have ovalbumin content <1 mcg/dose

- Greenhawt, Annals 2017
Influenza vaccine and egg allergy

- Pediatricians can administer the influenza vaccine to all children with egg allergy
  - Endorsed by AAP and CDC
  - Remove question from screening forms
  - Standard precautions
    - 15 minute observation
    - Ability to respond to rare acute hypersensitivity reactions
- Allergist
  - Family preference/anxiety
  - Allergic reaction to influenza vaccine/vaccine component
    - Testing/graded challenge
Thank you!

¿What if soy milk is just regular milk introducing itself in Spanish?