Dr. Letz has declared that he does not have a financial interest or other relationship with any manufacturer(s) of any commercial product or apparent conflict of interest related to the content of this presentation. He further states that he will not be discussing the uses of any unapproved / unlabeled drugs or devices.

Disclosures

Objectives

- At the end of the presentation attendees will be able to describe factors critical to the success of treating food allergies in primary care.
- At the end of the presentation attendees will be able to discuss the benefits/Drawbacks of performing allergy testing and implementing skin testing in the primary care setting.
- At the end of the presentation attendees will be able to describe the benefits/Drawbacks of immunotherapy and implementing immunotherapy in primary care.
Why? People Die
No Current Treatment
Incorrectly Diagnosed

Food Allergy: Outline
- Definitions
- Pathophysiology
- Signs and Symptoms
- New Guidelines
- Food Allergy-Induced Diseases
- Prevalence and Natural History
- Diagnosis and Management
- Prevention
**Definition**

A food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.

**Prevalence**

- Perception by public: 20-25%
- Confirmed allergy (oral challenge)
  - Adults: 1-2%
  - Infants/Children: 6-8% (~2/4 million births)
One in 12 kids in the United States may have a food allergy, according to new findings based on an online survey. The study, published June 20th in Pediatrics, also showed that more than one third of those kids had severe allergies, and that allergies were more common in minority kids.

- Dye/preservative allergy (rare)
- Specific Allergens
  - Milk (infants): 2.5%
  - Peanut/nuts in general population: 1.1%

**Food Allergy Prevalence in Specific Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Food Allergy Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>35-55%</td>
</tr>
<tr>
<td>Oral allergy syndrome</td>
<td>25-75% in pollen allergic</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>37% in children (rare in adults)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>20% in acute (rare in chronic)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5-6% in asthmatic or food allergic children</td>
</tr>
<tr>
<td>Chronic rhinitis</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Definitions: Immune-mediated Adverse Reactions to Food

- **IgE-Mediated**:
  - Oral Allergy Syndrome
  - Anaphylaxis
  - Urticaria
  - Eosinophilic esophagitis
  - Eosinophilic gastritis
  - Eosinophilic gastroenteritis
  - Atopic dermatitis

- **Non-IgE Mediated**:
  - Protein-Induced Enterocolitis
  - Protein-Induced Enteropathy
  - Eosinophilic proctitis
  - Dermatitis herpetiformis

Pathophysiology: Allergens

- Proteins (not fat / carbohydrate)
  - 10-70 kD glycoproteins
  - Heat resistant, acid stable, small glycoproteins
- Major allergenic foods (>85% of allergy)
  - Children: milk, egg, soy, wheat and as in adults
  - Adults: peanut, nuts, shellfish, fish
- Single food allergy, then have 11% chance of multiple food allergies
- Characterization of epitopes underway
  - Linear vs conformational epitopes
  - B-cell vs T-cell epitopes

Pathophysiology: Immune Mechanisms

- Protein digestion (IgA)
- Antigen processing
- Some Ag enters blood
- Mast cell
- Histamine
- APC
- B cell
- T cell
- TNF-α
- IL-5
- Non-IgE-Mediated
- IgE-Mediated
- IgE-receptor
<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Natural History**

- Dependent on food & immunopathogenesis
- ~ 85% CM, egg, wheat, soy allergy remit by 3 yrs
  - Declining/low levels of specific-IgE predictive
  - IgE binding to conformational epitopes predictive
- Allergy to peanut, nuts, seafood typically persist
- Non-IgE-mediated GI allergy
  - Infant forms resolve 1-3 years

Most children with FA will tolerate milk, egg, soy, and wheat; far fewer will eventually tolerate tree nuts and peanut.

FA is associated with severe asthma.

AD and FA are highly associated.

FHx of atopy and the presence of AD are risk factors

The factor most commonly identified with the most severe reactions is the coexistence of asthma.
Oral Allergy Syndrome

- Oral pruritus, rapid onset, IgE-mediated, rarely progressive
- Usually fresh fruits and vegetables
- Heat labile: cooked forms, no reaction
- Cause: cross reactive proteins pollen/food

<table>
<thead>
<tr>
<th>Pollen</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birch</td>
<td>Apple, apricot, carrot, cherry, kiwi, plum</td>
</tr>
<tr>
<td>Ragweed</td>
<td>Banana, cucumber, melon, watermelon</td>
</tr>
<tr>
<td>Grass</td>
<td>Cherry, peach, potato, tomato</td>
</tr>
</tbody>
</table>

Disorders Not Proven to be Related to Food Allergy

- Migraines
- Behavioral / Developmental disorders
- Arthritis
- Seizures
- Inflammatory bowel disease
- ADHD

Prevalence of Clinical Cross Reactivity Among Food “Families”

<table>
<thead>
<tr>
<th>Food Allergy</th>
<th>Prevalence of Allergy to &gt; 1 Food in Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>30% - 100%</td>
</tr>
<tr>
<td>Tree Nut</td>
<td>15% - 40%</td>
</tr>
<tr>
<td>Grain</td>
<td>25%</td>
</tr>
<tr>
<td>Legume</td>
<td>5%</td>
</tr>
<tr>
<td>Any</td>
<td>11%</td>
</tr>
</tbody>
</table>
Diagnosis: History / Physical

- History: symptoms, timing, reproducibility
  - Acute reactions vs chronic disease
- Diet details / symptom diary
  - Specific causal food(s)
  - "Hidden" ingredient(s)
- Physical examination: evaluate disease severity
- Identify general mechanism
  - Allergy vs intolerance
  - IgE versus non-IgE mediated

Diagnosis

- When should FA be suspected:
  1. In individuals presenting with anaphylaxis
  2. Young children with certain conditions such as AD, EoE
  3. Adults with EoE
- History alone cannot be considered diagnostic nor physical exam
- 50-90% of presumed FAs are not allergies

Diagnosis

Methods to identify causative food

The EP recommends performing an SPT to assist in identification of foods

The routine use of measuring total serum IgE should not be used

Elimination of one or a few specific foods from the diet may be useful

The double-blind placebo-controlled food challenge is the gold standard however a single-blind or an open food challenge may be considered diagnostic

The EP recommends not using allergen specific IgG testing nor a # of other modalities
Diagnosis: Laboratory Evaluation

- Suspect IgE-mediated
  - Finger stick screen
  - Prick skin tests (fresh extract if oral allergy)
  - "RAST" (or Immuno-CAP assay)
    - immunofluorescent | radioallergosorbent
- Suspect non-IgE-mediated
  - Consider biopsy of gut, skin
- Suspect non-allergic, consider:
  - Breath hydrogen
  - Sweat test
  - Endoscopy

Interpretation of Laboratory Tests

- Positive prick test or RAST
  - Indicates presence of IgE antibody NOT clinical reactivity
- Negative prick test or RAST
  - Essentially excludes IgE antibody (>95%)
- ID skin test with food
  - Risk of systemic reaction & not predictive
  - Contraindicated
- Unproven/experimental tests
  - Provocation/neutralization, cytotoxic tests, applied kinesiology, hair analysis, IgG4
# Recommended Interpretation of Food Allergen-Specific IgE levels (kU/L)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Egg</th>
<th>Milk</th>
<th>Peanut</th>
<th>Fish</th>
<th>Soy</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive if &gt;</td>
<td>7</td>
<td>15</td>
<td>14</td>
<td>20</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Possibly reactive (provider challenge)</td>
<td></td>
<td></td>
<td>30</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely reactive if &lt; (home challenge)</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
</tbody>
</table>


# Diagnosis: Elimination Diets and Food Challenges

- Elimination diets (1 to 6 weeks)
  - Eliminate suspected food(s), or
  - Prescribe limited “eat only” diet, or
  - Elemental diet
- Oral challenge testing (NP supervised, ER meds available)
  - Open
  - Single-blind
  - Double-blind, placebo-controlled (DBPCFC)

# Diagnostic Approach: IgE-Mediated Allergy

- Test for specific-IgE antibody
  - Negative: reintroduce food*
  - Positive: start elimination diet
- Elimination diet
  - No resolution: reintroduce food*
  - Resolution
    - Open / single-blind challenges to “screen”
    - DBPCFC for equivocal open challenges

* Unless convincing history warrants supervised challenge.
Diagnostic Approach: Non-IgE-Mediated Disease

- Includes disease with unknown mechanisms
- Food additive allergy
- Elimination diets (may need elemental diet)
- Oral Challenges
  - Timing/dose/approach individualized for disorder
  - Enterocolitis syndrome can elicit shock
  - Enteropathy / eosinophilic gastroenteritis may need prolonged feedings to develop symptoms
- DBPCFCs preferred
- May require ancillary testing (endoscopy / biopsy)

Management

Individuals with documented IgE-mediated FA should avoid ingesting their specific allergen or allergens

Products with precautionary labeling should be avoided

Whether testing is done annually or at other intervals depends on the food in question, age, and history

No medications currently recommended to prevent

Treatment: Dietary Elimination

- Hidden ingredients (peanut in sauces or egg rolls)
- Labeling issues ("spices", changes, errors)
- Cross contamination (shared equipment)
- "Code words" ("Natural flavor" may be CMP)
- Seeking assistance
  - Registered dietitian: (www.eatright.org)
  - Food Allergy Network (www.foodallergy.org)
### Treatment: Follow-Up

- Re-evaluate for tolerance periodically
- Interval and decision to re-challenge:
  - Type of food allergy
  - Severity of previous symptoms
  - Allergen
- Ancillary testing
  - Skin prick test/RAST may remain positive
  - Reduced concentration food specific-IgE encouraging

### Managing at risk individuals

- Children <5 with moderate AD considered for milk, egg, wheat, soy, and peanut testing
- Does not recommend restricting maternal diet during pregnancy or lactation
- Recommends that all infants be exclusively breast fed until 4-6 months
- Does not recommend using soy formula instead of milk
- Hydrolyzed formula may be considered a strategy for preventing FA in at-risk infants who are not exclusively breast fed
- Introduction of solid foods should not be delayed beyond 4-6 months

### Acute Reactions

- Epinephrine is the first-line treatment in all cases of anaphylaxis
- The use of antihistamines is the most common reason reported for not giving epi and may place a patient at significant risk for progression toward a life threatening reaction.
- Allergy action plan
Anaphylaxis Is Not Rare
Prevalence of generalized allergic reaction*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insect sting</td>
<td>3% of adults</td>
</tr>
<tr>
<td>Food</td>
<td>1-3% of children</td>
</tr>
<tr>
<td>Drug</td>
<td>1% of adults</td>
</tr>
<tr>
<td>RCM</td>
<td>0.1% of cases</td>
</tr>
<tr>
<td>Immuno Tx</td>
<td>3% of patients</td>
</tr>
<tr>
<td>Latex</td>
<td>1% of adults</td>
</tr>
<tr>
<td>All causes</td>
<td>5% of adults</td>
</tr>
</tbody>
</table>

*urticaria / angioedema / dyspnea / hypotension

Anaphylaxis / Anaphylaxis Syndromes

- Food-induced anaphylaxis
  - Rapid-onset
  - Multi-organ system involvement
  - Potentially fatal
  - Any food, highest risk:
    - peanut, nut, seafood, sesame
- Food-associated, exercise-induced
  - Associated with a particular food
  - Associated with eating any food
Fatal Food Anaphylaxis

- **Frequency:** ~ 150 deaths/year
- **Risk:**
  - Underlying asthma — Delayed epinephrine
  - Symptom denial — Previous severe reaction
- **History:** known allergic food
- **Key foods:** peanut / nuts / shellfish
- **Biphasic reaction** (observe 4 hr prior to d/c from ER)

Immunizations

- **Immunizations with egg allergic individuals**
  - MMR and MMRV should be given
  - There are different approaches to giving influenza vaccine
  - Yellow fever and rabies vaccine should not be given

Future Allergy Therapies

- Recombinant anti-IgE antibody (Stanford)
- Gene (naked DNA) immunization with CPG repeats (Johns Hopkins)
- Sublingual Immunotherapy (Stanford)
- Oral Immunotherapy (Stanford)
- Hypo-allergenic formulas (Stanford)
- Probiotics (UCSF)
Reasons for Allergy Referral

- Identification of causative food
- Institution of elimination diet
- Education on food avoidance
- Development of action plan
- Prevention of other allergies
- Food challenges

Summary

- History and physical paramount
- IgE & non-IgE mediated conditions exist
- Diagnosis by elimination and challenge
- Avoidance/education/preparation for emergencies are current therapies
- Periodic re-challenge to monitor tolerance as indicated by history, allergen, and level of food specific-IgE

Questions

THE 3 STAGES OF MAN
### Example: Milk Elimination

Artificial butter flavor, butter, butter fat, buttermilk, casein, caseinates (sodium, calcium, etc.), cheese, cream, cottage cheese, curds, custard, Half&Half®, hydrolysates (casein, milk, whey), lactalbumin, lactose, milk (derivatives, protein, solids, malted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized, protein concentrate), yogurt. MAY contain milk: brown sugar flavoring, natural flavoring, chocolate, caramel flavoring, high protein flour, margarine.

* It is common to have a reaction to a hidden ingredient to rather than to have an allergic reaction to a previously tolerated food.

### Substitute Infant Formulas

- Soy (confirm soy IgE negative)
  - <15% soy allergy among IgE-CMA
  - ~50% soy allergy among non-IgE CMA
- Cow’s milk protein hydrolysates
  - >90% tolerance in IgE-CMA
- Partial hydrolysates
  - Not hypoallergenic!
- Elemental amino acid-based formulas
  - Lack allergenicity

*エピネフリンは、反応に対する薬物の選択です。
**自己管理用エピネフリンは、すぐに利用可能です。
**患者を訓練：症状/技術
**抗ヒスタミン：次療法
**緊急計画：書面
**学校、配偶者、看護師、成年兄弟/友人
**緊急識別ブレスレット

### Treatment: Emergency Medications

- Epinephrine: drug of choice for reactions
  - Self-administered epinephrine readily available
  - Train patients: indications/technique
- Antihistamines: secondary therapy
- Emergency plan in writing
  - Schools, spouses, caregivers, mature sibs/friends
- Emergency identification bracelet

* CMA=cow’s milk allergy
Incidence and/or Severity of Anaphylaxis

- Risk Factor
  - Age (over age 45 yrs)
  - Gender (more common in males)
  - Time elapsed since last reaction

Anaphylaxis Diagnosis

- Clinical Features
  - Cutaneous and respiratory findings in 60% of subjects
  - N=1217, retrospective studies
  - Serum Tryptase (mast cell degranulation marker) measurable up to 6 hours

Pediatric Gastrointestinal Syndromes

<table>
<thead>
<tr>
<th>Age Onset</th>
<th>Enterocolitis</th>
<th>Enteropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Infant/Toddler</td>
<td>Newborn</td>
</tr>
<tr>
<td>Newborn</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>12-24 mo</th>
<th>12-24 mo</th>
<th>9</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Failure to thrive</th>
<th>Malabsorption</th>
<th>Bloody stools</th>
</tr>
</thead>
<tbody>
<tr>
<td>stools</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villous atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>Self limited</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-IgE-mediated, typically milk and soy induced
Spectrum may include colic, constipation and occult GI blood loss
### GI Syndromes of Children/Adults

- Celiac Disease (Gluten-sensitive enteropathy)
  - Anti-gliadin IgG, anti-endomysial IgG, IgA
  - Villus atrophy, malabsorption, pain, associated CA
- Eosinophilic esophagitis, gastritis, gastroenteritis
  - Eosinophilic infiltration
  - Poor growth, pain, vomit, diarrhea, reflux
  - Multiple food allergy, IgE and non-IgE-mediated
  - May affect varying regions of gut
- Gastrointestinal Anaphylaxis
  - Acute vomit/diarrhea, IgE-mediated