Food Allergy Update
What’s New in 2016

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Disclosures

Speaker’s Bureau- Meda Pharmaceuticals
Outline

- Prevalence of food allergies
- Differential diagnosis
- Anaphylaxis and management
- Specific food allergy disorders
- Making an accurate diagnosis of food allergies
- Risk factors and prevention
- Oral immunotherapy and novel treatments for food allergy

Food Allergies: Statistics

- Approx. 8% of children and 5% of adults in the US have food allergies
- Prevalence and severity are increasing
- According to CDC, food allergies increased by almost 20% in US in past 2 decades
- 3 million allergic (> 1%) to peanuts in US
- Food-allergic reactions leading cause of emergency department visits for anaphylaxis

Food Allergens

Children
- Milk
- Egg
- Peanut
- Soybean
- Wheat
- Tree nuts
- Fish
- Shellfish

Adults
- Peanut
- Tree nuts
- Fish
- Shellfish
- Fruits/vegetables in OAS
Differential Diagnosis: Non-Immune Mediated Adverse Food Reactions

- **Toxic/Pharmacologic**
  - Food poisoning
  - Scombroid fish poisoning
  - Ciguatera fish poisoning
  - Histamine
  - Tyramine
  - Caffeine

Differential Diagnosis: Non-Immune Mediated Adverse Food Reactions

- **Non-Toxic/Intolerance**
  - Lactase deficiency
  - Fructose intolerance
  - Galactosemia
  - Pancreatic insufficiency
  - Gallbladder/Liver disease
  - Panic/Anxiety
  - Depression, anorexia, bulimia
  - Hiatal hernia; GERD
  - Gustatory rhinitis
  - Auriculotemporal syndrome

Food Allergy: Immune System-mediated Adverse Food Reaction

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<th>IgE</th>
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<td>• ATOPIC DERMATITIS</td>
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<td>• ANGIOEDEMA</td>
<td>• EOSINOPHILIC GASTRO-INTESTINAL DISORDERS</td>
<td>• CELIAC DISEASE</td>
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<td>• VOMITING</td>
<td>• CONTACT DERMATITIS</td>
<td>• DERMATITIS HERPETIFORMIS</td>
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<td>• ANAPHYLAXIS</td>
<td>• FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS</td>
<td>• HEINER’S SYNDROME</td>
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<td>• ORAL ALLERGY SYNDROME</td>
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Food Anaphylaxis

- Definition: an acute systemic allergic reaction that is potentially fatal
- The opposite of prophylaxis “without or against protection”
- Onset of symptoms seconds to minutes (up to 2 hrs) following ingestion
- Prior reactions may have been milder
- Very unpredictable in its clinical presentation and outcome
1. Impending doom sensation
2. Metallic taste in mouth
3. Uterine contraction
4. Pruritus in unusual places (scrotum, vagina, ear)

**Patterns of Anaphylaxis**

- Uniphasic
  - Rapid onset, symptoms resolve within hours of treatment

- Biphasic
  - Symptoms resolve after treatment but return between 1 and 72 hours later (usually 1-3 hours)

- Protracted
  - Symptoms do not resolve with treatment and may last >24 hours
Uniphasic Anaphylaxis

Antigen Exposure

Initial Symptoms

Time

Treatment

Biphasic Anaphylaxis

Antigen Exposure

Initial Symptoms

Second-Phase Symptoms

Time

Treatment

Classic Model

New Evidence

1-8 hours

1-72 hours

Protrated Anaphylaxis

Antigen Exposure

Initial Symptoms

Time

Possibly >24 hours
Other Triggers of Anaphylaxis

- Medications
  - Antibiotics
  - Aspirin and other NSAIDs
  - Any drug can
- Diagnostic agents
  - Contrast media (IVP dyes)
- Allergen immunotherapy
- Blood transfusions
- Insect Stings
- Idiopathic-no known cause

Overview of Anaphylactic Triggers

Emergency Management

- Prompt recognition of symptoms
- Intramuscular epinephrine
  - Self-injectable device
  - EpiPen Jr / Auvi Q Jr: 0.15 mg, under 50 lbs
  - EpiPen / Auvi Q: 0.3 mg, over 50 lbs
- Oral antihistamines (Secondary therapy)
  - Eg. diphenhydramine, 1-1.5 mg/kg/dose
- Mandatory: Emergency Dept.
- >4 hour observation period
  - Potential for biphasic reaction
Treatment: Epinephrine

- Treats all symptoms of anaphylaxis and prevents progression of reaction (antihistamines DO NOT)
- IM inject. in lateral thigh produces most rapid rise in blood level
- Children treated w/Epi for food anaphylaxis before ED arrival were at much lower risk for hospitalization than if delayed until after seen in ED
- Up to 20% of time, more than one dose needed so it is strongly recommended to keep multiple doses

IM vs SQ Epinephrine

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<th>Time to C_{max} after injection (minutes)</th>
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<td>2 minutes</td>
<td>2</td>
<td>34</td>
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<tr>
<td>14 (5 – 120) minutes</td>
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<td>p &lt; 0.05</td>
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Additional Treatment of Anaphylaxis

- Supplemental oxygen
- Fluid replacement (10-20 cc/kg)
- H-1 antagonists (eg. Diphenhydramine) and H-2 antagonists (eg. Ranitidine)
- Corticosteroids-but no proven benefit
- Observe for 4-24 hrs after initial symptoms have subsided
- Severe cases: IV epinephrine, vasopressors
Exercise-induced Anaphylaxis (EIA)

- Exercise alone can trigger anaphylaxis
- It is different from exercise-induced asthma where wheezing, shortness of breath occur in an asthmatic
- Symptoms of EIA may include itching, hives, swelling, breathing difficulty, dizziness, fall in blood pressure, loss of consciousness
- It can be episodic, fatalities reported

Case Presentation

- 14 year old female with no significant past medical history
- Began training for high school varsity basketball team
- 15 minutes into practice, she developed diffuse hives and difficulty breathing
- Reports eating granola bar 1 hour prior to practice; has eaten granola bars for several years with no reaction
- No new exposures, no new foods, no new medications

Food-dependent Exercise-induced Anaphylaxis (FDEIA)

- Requires food ingestion followed by exercise to occur
- Anaphylaxis occurs when patient exercises within 2 to 4 hours of ingesting a food (peanut/tree nuts, wheat, celery, shellfish have been reported)
- Severity increased with co-administration of alcohol and NSAIDs/ aspirin
- Twice as common in women, especially young women, 60% of cases in individuals <30 years of age
- Management: Identifying specific foods, if possible, and avoiding exercise for 4 hrs after eating
Case Presentation

• 12 year old male with allergic rhinitis seen in clinic for “new” food allergies
• Has year-round allergies, that noticeably worsen in spring and are mildly worse in fall
• Reports itchy mouth and throat with fresh peaches, cherries, and some nuts
• Symptoms worse during Springtime
• No hives, no respiratory symptoms, no GI distress

Oral Allergy Syndrome
(Pollen-food allergy syndrome)

• Contact IgE-mediated reaction in the oropharyngeal mucosa, onset < 5 minutes
• Caused by raw fruits or vegetables, nuts, cooked foods well-tolerated
• Cross-reactive allergens in pollen and plant foods (primary sensitization to pollen/airborne allergens then reaction to food ingestion/plant proteins)
• Rare cases may progress to systemic reactions

Case Presentation

• 8 year old male with history of asthma
• Awoken at midnight with diffuse hives and mild wheeze
• Recalls eating hot dog for dinner and an ice cream sandwich for dessert around 6 pm
• Watched a movie after dinner and went to bed immediately after
• Reports a few tick bites during summer, which took one month to fully heal
What is happening?

• This condition usually is associated with bites by the Lone Star Tick
• This can result in antibodies to a carbohydrate called alpha-gal
• When that person ingests mammalian meat antibodies to alpha gal can cause an allergic reaction, even anaphylaxis

Typical History

• Reactions are delayed (~3-6 hours) after ingesting red meat
• Hives and swelling can be severe (often during night)
• Progressive: begins with itching, then urticaria, then systemic symptoms (GI, decreased BP)
• Skin prick test tests to commercial extracts of these meats are usually negative
• Blood test to alpha-gal is positive
• Frequently missed (and called idiopathic anaphylaxis)
Eosinophilic Esophagitis

- Disease of esophagus which may be triggered by foods (and possibly environmental allergens)
- Presents with epigastric abdominal pain, difficulty swallowing or food impaction
- Identification of food triggers using standard allergy testing is challenging
- Treatment: swallowing inhaled steroids, anti-reflux medication and elimination diets

Food Allergy Diagnosis

- History
  - Food ingested
  - Timing of symptoms, acute reaction versus chronic disease
  - Co-ingestion of aspirin, alcohol, viral infection, fever, menstruation
  - Association with exercise
    - Eczema and asthma
- Diagnosis
  - Prick skin testing
  - Serum food-specific IgE
  - Oral food challenges - “Gold Standard”

Diagnosis Evaluation

- Suspect IgE-mediated (allergy)
  - Prick skin tests
  - ImmunoCAP/RAST test (IgE levels in blood)
  - Neither test is BETTER
- Suspect non-IgE-mediated (skin/blood tests not helpful)
  - Allergic gastrointestinal conditions
  - Elimination diets may be helpful
- Suspect not allergic, consider: lactose intolerance, toxic reactions, celiac disease (gluten-sensitivity)
Skin Testing

• Provide rapid screening for sensitivity to allergens
• Less discomfort and cost compared to blood tests—may need to skin test with fresh foods
• A lot of ‘false-positives’ in children with eczema—oral food challenges helpful
• Size of skin test may be helpful in predicting likelihood of reacting
• Negative skin tests strongly suggest the absence of IgE-mediated allergy

Blood Tests for Foods

• ImmunoCAP/RAST test measure specific IgE antibody levels to different foods in the blood
• Can be helpful when child has eczema or is on antihistamines
• Are helpful in predicting likelihood of an allergic reaction
• High levels less likely to outgrow allergy

Oral Food Challenges (OFC)

• Physician supervised
  – Open
  – Single-blind
  – Double-blind, placebo controlled
• Negative
  – Reintroduce food
• Positive
  – Avoidance
  – Should we eliminate those foods if eaten?
  – Awareness of cross-contamination
Oral Food Challenges

- Decision to perform an OFC
  - No recent reactions (past 6-12 months)
  - No severe anaphylaxis in past 24 months
  - Skin tests/serum food IgE negative or significantly decreased from previous evaluation

Why are food allergies more common?

- Nobody really knows why
- Maybe the hygiene hypothesis-the ‘cleaner’ we have become, more allergies
- Gastrointestinal bacteria – good vs bad bacteria – can probiotics help?
- Delaying introduction of high allergy foods
- Low Vitamin D levels

Vitamin D Hypothesis

- Higher rates of egg and peanut allergy in regions further from the equator
- Move to someplace warm and sunny!
  - Food anaphylaxis more common in northern US
- Adequate levels of vitamin D protective against food allergy
- Maternal intake of vitamin D during pregnancy may be associated with decrease risk
Primary Prevention-Learning Early About Peanut Allergy (LEAP)

- 640 infants aged 4-11 months of age
- 2 groups: negative skin test to PN and those with small < 4 mm skin test to PN
- Peanut group fed 2 grams of PN 3 times/week for 60 months starting in infancy
- At 5 years old group eating peanuts 80x less likely to have a peanut allergy!

Caution regarding LEAP

- LEAP Study conclusion- Early peanut introduction significantly reduces allergy risk
- Selected population-severe eczema, egg allergy
- Excluded infants already allergic to peanut
- Importance of seeing an allergist first
- Caution in generalizing or making recommendations for ALL infants/children

Leap-On study

- Extension of Leap Study
- To see if patients who had consumed peanut in primary trial would remain protected if stopped eating PN for 12 mo.
- Peanut allergy did not develop in these patients after 1 year of no consumption
- So, 4 years of eating peanuts was enough to prevent allergy
Natural History

• Milk, egg, wheat, and soy allergy
  – >50% resolve by school age
  – But, milk/egg allergy have been lasting longer often into 2nd decade
  If high blood levels, less likely to outgrow

• Peanut, tree nuts, fish, shellfish
  – Usually lifelong
  – 20% of young children outgrow peanut, 9% outgrow tree nut allergy

What’s in Practice Parameters

• Be aware of cross reacting foods- pecan/walnut, cashew/pistachio, ALL mammalian milk eg goat’s milk, fish, shellfish
• Latex allergy-caution with bananas, avocado, kiwi, chestnuts
• Encourage exclusive breastfeeding x 4-6 months
• Early introduction of potentially allergic foods may prevent allergies

Practice Parameters-DON’Ts

• Food allergy/additive avoidance in ADD/ADHD
• Food allergy testing for chronic hives
• Asthmatics routinely avoiding sulfites
• Avoiding IVP dye in shellfish allergy
• Allergen testing for IgG, hair analysis, provocation/neutralization, applied kinesiology
• General allergy blood test ‘screening’ for food allergies
Food Allergy Treatment

- Allergen avoidance has been the mainstay of prevention and management
- Conventional immunotherapy (shots) many side effects, risky, not an option for food allergies
- Periodic evaluations are recommended every 6-12 months, especially for children who may outgrow their food allergy
- Oral immunotherapy is efficacious and has been shown in studies and practice to be safe and effective

Avoidance Management Strategy (AMS)

- Food allergy guidelines-recommendations: strict avoidance and treatment of systemic reactions with injectable epinephrine (AMS)
- AMS creates burdens for many affected children and their families
- Difficulty of implementing AMS in schools and social environments
- Despite present management, many families have suboptimal knowledge of how to avoid and treat food allergy emergencies

Realistic concerns over AMS

- Accidental exposure to PN occurs in many allergic children in 5 year period, (hidden allergens or cross-contamination)
- >70% resulted in moderate to severe reactions
- Auto-injectors not carried when prescribed
- Available epinephrine auto-injectors often not used when indicated
- Highest risk population: teenagers and young adults (refusal to carry and unsafe behavior)
Oral Immunotherapy (OIT)

History of OIT
- First report on oral desensitization in 1908 (to egg)
- Encouraging results from case reports over the years
- Over past 2 decades clinical studies showed impressive results for OIT (efficacy and safety)
  - Peanut: Duke/Arkansas
  - Milk: Johns Hopkins

Assessing Efficacy of PN OIT: STOP II Phase 2 Study
- Randomized placebo controlled study of 100 peanut allergic patients age 7-16 years
- Confirmed PN allergy with double-blinded food challenges
- Chose a target desensitizing dose of 800 mg daily (4-5 peanuts daily)
- 91% of treated patients could tolerate top dose
- Approx. 60% could tolerate 10 peanuts in a challenge (those that could not had mild Sx)
- Adverse affects minor/ epinephrine given once
  Anagnostou Lancet 2014
OIT in Private Practice Setting

- More private practices in US performing OIT
- Protocols and procedures vary as well as target doses (unstandardized)
- Explosion of social media sites and blogs advocating OIT, eg. “Private Practice OIT”
- Still not recommended as ready for private practice use at this time by many in academic community
- Concerns: long-term effectiveness, safety and cost-effectiveness of OIT

Food Allergies and Quality of Life (QOL)

- Parents of PN allergic children reported that their children had disruption in daily activities and impairment in normal social interactions
- Disease specific measures impaired (such as emotional impact, food-related anxiety, fear of anaphylaxis, social and dietary limitations)
- Children with peanut allergy reported a lower health related QOL than children with diabetes
- Taken together food allergies shown to have major adverse effects on QOL
New England Food Allergy Treatment Center

- Established in 2010 as a dedicated research and treatment facility for providing OIT
- Initial process based upon the published data from Duke (Burks et al.) and University of Arkansas (Jones et al.)
- Initiated PN OIT to study effects of treatment on QOL
- IRB approved protocol

Quality of Life Study

- 100 patients 5-18 years of age enrolled in open trial of PN OIT
- Measures of food-allergy specific quality of life using surveys pre- and post-treatment (maintenance)
- Domains included emotional impact, food-related anxiety, social and dietary limitations and risk of accidental exposure
  

QOL Study Results

- First published study showing significant benefit of PN OIT on food allergy specific quality of life
- Improvement seen in all domains where parents assessed children 5-12 years old
- Teenager self-assessment included and their health relates quality of life greatly improved as well
- 90% patients achieved maintenance dose of 450 mg of peanut protein
Peanut Protocol: Escalation, Build-up and Maintenance

- Initial escalation day – Beginning with 0.1 mg of PN protein consumed
- Patients takes top tolerated dose at home once daily
- Build-up phase-return every 2 weeks for updosing
- Current maintenance dose 10 peanuts (2000 mg of PN protein) or 12 peanut M and M’s
- Maintain top dose for 6 months and return for retesting and, if indicated, a peanut challenge

Patient Commitment

- Duration of visits (initial day 6 hours, subsequent 1 hour visits)
- Daily diaries to be completed by parent/patient
- Each visit: baseline vital signs, patients are examined, interval history obtained, diary information reviewed
- Doses prepared and sent home in parfait cups and storage containers
- Duration of desensitizing process 10-12 months
Adverse Reactions

- Side effects not uncommon, GI in 62%, cutaneous in 22% and respiratory in 10%
- Most common symptoms- itchy mouth and throat, abdominal pain/nausea/reflux
- Similar findings during build-up and maintenance phases
- 1% of patients developed eosinophilic esophagitis as diagnosed by endoscopy
**Systemic Reactions and Epinephrine**

- Systemic reaction observed in 10.6% of patients
- Epinephrine (single dose) required in small percentage of patients
- No life-threatening reactions
- Systemic reactions associated with exercise in 44%, febrile/viral illness 18%, other/no-cofactor 38%

**Reducing Risk of Reactions**

- Dosing should be administered with food
- Hold dose during concurrent illness, especially with fever
- A quiet period with no vigorous exercise for 2 hours post-dose advised
- Maintain control of asthma, avoid hot showers and NSAIDs, caution dosing during menses

**PN OIT: Experience to date**

- Treatment period 2010-2016, ongoing
- >700 peanut allergic patients treated
- Patients from all New England states, NY, NJ, Maryland, Ohio, Canada
- Safety issues addressed and acceptable adverse affect profile
- 92% successfully desensitized – consuming 3-10 peanuts daily
OIT With Other Foods

- Milk - Depending on severity of allergy - milk drops or baked milk desensitization (with milk-containing muffins)
- Egg Protocols - Similar as for milk-egg protein drops, baked egg
- Tree nuts - Cashew ~ 30 patients treated successfully to date, Walnut – just started
- In the future - other tree nuts, sesame

Baked Milk and Egg Containing Diet in Managing Milk and Egg Allergy

- Cooking/heating can change the protein structure of food altering recognition by immune system
- Studies report 70% of milk and egg allergic children can tolerate baked milk or egg
- By eating regularly baked milk/egg, can help desensitize to straight milk/egg
- Should be performed in controlled clinical setting
SLIT

- Sublingual immunotherapy (SLIT) for foods
- SLIT studies have shown some efficacy for hazelnut, peanut, cow’s milk and other foods
- SLIT appears to be associated with fewer systemic side effects than OIT
- However, OIT is more effective for desensitization as shown in studies using milk and peanut

Other treatments

1) Peanut Patch-EPIT (Epicutaneous immunotherapy)
   - Success in phase 2 trials (50% of patients could tolerate 10 x dose with treatment)
   - Phase 3 trials underway-Company: DBV Technologies
2) Peanut protein in capsules-Using standardized pharmaceutical grade food allergens
   - CODIT ™ “characterized oral desensitization immunotherapy” Company: Aimmune
Provider concerns

• “My patient has too severe of a peanut allergy to be treated”
• “PN Specific IgE or PN component levels are too high or skin tests are too large”
• “Side effects are frequent and severe”
• “The cost of treatment must be prohibitive”
• “I’ve heard the risk of EoE is high with treatment”
• “Patients have to take daily food indefinitely”

What the experts think…

• “When performed by experienced investigators in an appropriate setting, peanut OIT is a safe, allergen-specific therapy effective in inducing desensitization and providing protection against accidental ingestion with ongoing therapy”

Summary

• Understand different food allergy conditions
• Risk Factors: possibly low vitamin D, delayed introduction of allergenic foods, hygiene hypothesis
• Primary prevention: LEAP study, hypoallergenic formula
• Oral immunotherapy gaining more acceptance and can be performed safely and effectively in private practice/treatment center