Objectives:

- Identify the foods most commonly associated with food allergy in pediatric and adult populations.
- Recognize the differences between food allergy and food intolerance, including the limitations of currently available testing modalities.
- Describe the atypical presentations of certain, clinically relevant food allergies

Disclosures:

- No disclosures

Question #1: Best Answer

7 year old boy presents to clinic with mom to discuss gradual failure to thrive, abdominal bloating, diarrhea and fatigue. What is the most like diagnosis?

- A. Colon cancer
- B. Gluten intolerance
- C. Irritable bowel syndrome
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40 yo man with seasonal allergies, complains of oral itching and tingling sensation when he eats fresh apples, cherries, kiwi and honeydew melon. What is the treatment of choice?

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- C. Tissue transglutaminase (anti-TTG) IgA and total serum IgA blood test
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Question #4:
16 yo male patient presents to ER with profound anaphylaxis after ingestion of shrimp cocktail. His blood pressure is not detectable. The best route of administration for epinephrine is:
- A. Intravenous
- B. Subcutaneous
- C. Intratracheal, following intubation
- D. Intramuscular

Question #5:
70 yo woman with repeated episodes of moderate-severe anaphylaxis to almonds, needs a refill on her injectable epinephrine device. The next best step is:
- A. Refill the device and ask the pharmacy staff to educate her on the proper use
- B. Personally instruct her on proper device usage, make sure she has a trainer device for practice and discuss purchase of a identification jewelry piece
- C. Give her a coupon for her co-pay
- D. Tell her to stop eating peanut butter sandwiches (she just had one for lunch today, no problems)

Frequently Asked Questions!
- “Why are food allergies increasing?”
- “Will I (or my child) outgrow the food allergy?”
- “Will the food allergy get worse?”
- “What about yeast allergy?”
- “Can’t I just be tested for all the foods?”
- “Can you test me for dairy?”
- “I have eaten _____ all my life, why am I allergic now?”

Overview
- Adverse Food Reactions (AFRs): Definitions and Overview
- Examples of atypical food anaphylaxis
- Treatment of food anaphylaxis
- Current injectable epinephrine options
- A cautionary word on diagnostics

Food allergy: A practice parameter update—2014
Hugh A. Sampson, MD, Seema Aziz, MD, PhD, S. Alian Bock, MD, John James, MD, Stacie Jones, MD, David Lang, MD, Karl Nadeau, PhD, RD, Anna Flahak-Witgorski, PhD, John Oppenheimer, MD, Jamaica T. Perry, MD, Christopher Randolph, MD, Scott H. Sicherer, MD, Ronald A. Simon, MD, Bruce P. Valvéry, MD, and Robert Wood, MD

Chief Editors: Hugh A. Sampson, MD, and Christopher Randolph, MD
Adverse Food Reactions (AFRs): Rules of Engagement

- **Food allergy**: “an adverse health effect arising from a specific immune response, occurring reproducibly on exposure to a given food”
- **Food intolerance**: “Non-immunologic reaction (metabolic, pharmacologic, toxic and/or undefined/unknown mechanism) on exposure to a given food”

IgE Mediated AFRs

- IgE – “the allergic antibody”
  - Evolutionary purpose = protection against parasites
  - Developed countries – atopic (allergic) conditions
  - “Sensitive” or “Sensitized” – antibody present (by skin or blood test), but no clinical reaction
  - “Allergic” – antibody present and a potentially life-threatening clinical reaction with each subsequent ingestion

IgE Mediation of AFRs

http://www.kyowa-kirin.co.jp/antibody/english/basics/isotypes.html

http://paleolifestyledoctor.com/common-food-allergies-may-causing-symptoms/

http://www.gordonmedical.com
Anaphylaxis: A Multi-Organ Concern

- Skin: hives, swelling, redness, itching, urticaria
- Respiratory: wheezing, shortness of breath, hoarseness, chest pain or tightness, throat tightness, trouble breathing, cyanosis, swelling of face, ears, lips, tongue, throat
- Gastrointestinal: nausea, vomiting, diarrhea, cramps, abdominal pain, abdominal distension, tongue swelling, belching
- Cardiovascular: palpitations, arrhythmias, hypotension, hypovolemia, hypertension, shock, lightheadedness, fainting
- Neurological: anxiety, dizziness, sweating, numbness, tingling, headache, altered level of consciousness

Alpha Gal Allergy

- IgE-mediated allergic reaction to galactose-alpha-1,3-galactose – a sugar
- Alpha-gal is found on cells and tissues of non-primate mammals
- History of tick bites (usually multiple)
- Mammalian red meats (e.g., beef, pork, lamb, and venison) have a similar alpha-gal to that found in tick saliva
- Delayed anaphylaxis (3-6 hours) following ingestion of red meat, pork, lamb especially
- Can have negative, initial allergy testing to the meats!

Food Dependent, Exercise Induced Anaphylaxis

- Anaphylaxis which occurs during significant physical exertion, hours following ingestion of particular foods
- Digestive mechanism, prognosis unclear
- Culprit foods (depends on part of the world) in U.S. include:
  - Wheat, shellfish, celery, lentils, peaches, apples, grapes, hazelnuts, cheeses, beef, pork, corn and many others!
- Skin testing for foods can be very helpful !!!
- Exercising first thing in the morning is encouraged – injectable epinephrine is mandatory

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Shattuck et al., 2009

Cruzanborders.blogspot.com
Food Allergy: Management

- Injectable epinephrine (administered into the middle, upper/outer thigh muscle) is the ONLY life-saving treatment for an allergic reaction!
- Avoidance!
- Education, including a clear anaphylaxis action plan
- Identifying high-risk settings (buffets, bakeries, etc)
- Transition to self-care in adolescence
- Identification jewelry strongly encouraged
- Support at school (e.g., zero tolerance for bullying)
- Identifying anaphylaxis, and not denying that symptoms are anaphylaxis!

FPIES: Food Protein-Induced Enterocolitis Syndrome

- ~1/300 in first year of life
- Recurrent vomiting, poor weight gain, bloody stools (possibly diarrhea, lethargy) up to 4 hours following ingestion, can present with sepsis-like picture
- Mean age at presentation about 6 months, presents with increased white blood count, dehydration, hypothermia
- Common foods in the order of occurrence: Cow milk, soy, rice, other (i.e., sweet potato is most common vegetable)
- Mediated by non-IgE mechanism (Ag-specific T cells, pro-inflammatory cytokines)

Gluten Intolerance: Celiac Disease

- 1% of U.S. population
- Abnormal immune response to gluten (storage protein) in wheat, barley and rye
- Chronic inflammation of the proximal small intestine resulting in malabsorption
- Children: diarrhea, failure to thrive, abdominal pain, distention
- Adults: diarrhea, anemia, bone pain, severe skin rash called dermatitis herpetiformis
- Most specific blood test is tissue transglutaminase (tTG-IgA)
- HLA typing may be useful to exclude CD or assess genetic susceptibility (DQ2, DQ8)
- Treatment = gluten free diet

Gluten Intolerance: Non-celiac gluten sensitivity

- Symptoms: abdominal pain, bloating, diarrhea/constipation, “foggy mind”, headache, fatigue, joint and muscle pain, leg or arm numbness, dermatitis, depression, anemia (others?)
- Mechanism unknown
- No standardized diagnostic testing available – skin testing to multiple foods often returns negative
- Can be difficult to assess strict gluten-free diet adherence (i.e., ‘allergen’ exposure)
- No major complication of untreated NCGS has so far been described
Atopic Dermatitis

- Most common chronic inflammatory skin disease
- Of moderate-severe AD patients, about 1/3 have related food allergies
  - Milk, hen’s egg, wheat, soy, peanut, fish, tree nuts account for >90%
- Abnormal skin barrier, dry skin, itch-scratch cycle
- Predisposed to colonization or infection by pathogenic microbes, most notably *Staphylococcus aureus* and herpes simplex virus
- Basic, initial therapy includes skin hydration measures, topical steroids, topical calcineurin inhibitors etc.
- Refractory cases treated with cyclosporine, methotrexate, azathioprine, IL-6 blockade, dust mite immunotherapy (when indicated), wet wrap therapy, and UV light

J Allergy Clin Immunol 2014;134:769-79

Eosinophilic Esophagitis

- Increasingly recognized cause of vomiting, dysphagia and food impaction over the last 20-30 years, especially in younger male patients
- Normal esophageal mucosa does not contain eosinophils
- Definitive method of skin or serum testing for food allergies has not been defined
- Empiric avoidance of egg, milk, wheat, soy, peanut, tree nut, fish and shellfish has led to symptomatic improvement in 53-82% of patients.

Endoscopic features of eosinophilic esophagitis
Scombroid Fish Poisoning

- Illness caused by eating spoiled fish
- Especially with mackerel, tuna, bluefish, mahi-mahi, bonito, sardines, anchovies, others
- At temperatures above 60F, histidine enzymatically converted to histamine (not deactivated by cooking)
- Pseudo-allergic reaction can result:
  - Symptoms consist of skin flushing, throbbing headache, oral burning, abdominal cramps, nausea, diarrhea, palpitations, a sense of unease

Sulfite Use in Foods

<table>
<thead>
<tr>
<th>Technical Attribute</th>
<th>Specific Food Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of enzymatic browning</td>
<td>Fried, frozen, and preserved fish, eggs, potatoes, salads, black-spot formation, pickled vegetables, dried fruits, citrus, kiwi, blackstrap molasses, starch, corn syrup, wine, beer, mead</td>
</tr>
<tr>
<td>Inhibition of non-enzymatic browning</td>
<td>Frozen and canned vegetables, canned meats, sauces, syrups, milk, chocolate milk, ice cream, some confectionery, starch, corn syrup, wine, beer, mead</td>
</tr>
<tr>
<td>Aminonitrate action</td>
<td>Frozen, pickled, marinated meats, semi- and dry-cured meats, cheese, sauces</td>
</tr>
<tr>
<td>Bleaching effect</td>
<td>Humidity, shelf-life, coloration of cereals</td>
</tr>
</tbody>
</table>

This diagram allowed by US FDA.

Sulfites and Asthma Attacks

- Adverse reactions with sulfites have been best established in asthma
- Sulfur dioxide, sodium metabisulfite, potassium metabisulfite etc...
- Less than 5% of all asthmatics
- Oral, IV, ocular drops, inhalation routes all may apply
- Severe, steroid-dependent asthmatics seem to be at highest risk of fatal reactions from sulfites

Food Allergy vs. Food Intolerance

- Food Allergy:
  - Usually comes on suddenly
  - Small amount of food can trigger
  - Happens every time you eat the food
  - Can be life-threatening
- Food Intolerance:
  - Usually comes on gradually
  - May only happen when you eat a lot of the food
  - May only happen if you eat the food often
  - Is not life-threatening

http://www.webmd.com/allergies/foods-allergy-intolerance
Limitations of Modern Food “Allergy” Testing

- "IgG" or "IgG4" – suggests past exposure, only – NOT an Adverse Food Reaction
- “Shotgun” food allergy testing carries a false positive rate approaching 50% (coin flip)
- Currently-available testing modalities cannot accurately predict or diagnose food intolerance
- Hydrogen breath test can suggest lactose intolerance in high pre-test probability patients – need a trial of lactose free diet to confirm

So... How IS a Food Allergy Diagnosed?

Clinical history is the most important tool!!!

........

Diagnostic testing is not a crystal ball – it should ONLY be used to confirm clinical suspicion !!!

Treatments of Life-Threatening Food Allergy

- Avoidance of offending food!
- Know how to use injectable epinephrine device
- Keep injectable epinephrine immediately available always
- Recognize early signs/symptoms of anaphylaxis
- Administer injectable epinephrine early, without delay!

Options for Injectable Epinephrine: 2016

- AdrenaClick
- EpiPen
- Auvi-Q

Fatal Anaphylaxis in the United States

- National Mortality Database in the United States between 1999 and 2010 (Anaphylaxis ICD-10 Coding)
- 2458 fatal anaphylaxis cases in U.S.
- 4 categories:
  - Drug or serum = 58.8%
  - Unspecified = 19.3%
  - Venom = 15.2%
  - Food = 6.7%


New Advances in Peanut Allergy Diagnostics

- Peanut (Arachis hypogaea)
  - Most common food associated with fatal anaphylaxis in westernized countries
  - Numerous allergens identified, but 6 allergens stand out:
    - Ara h 1, 2, 3, 6, 8 and 9
    - Ara h 1, 2 and 3 (especially Ara h 2) associated with severe peanut allergy
  - Commercially available testing and even skin testing can be falsely positive up to 77% of the time!!!
  - Clinical correlation is essential before settling on the diagnosis of peanut allergy, proper
New Advances in Peanut Allergy Diagnostics

- Swedish study: component-resolved diagnostics
- 144 children with peanut sensitization from two databases (Ara h 8, but NOT Ara h 1, 2 or 3)
- 82 tolerated peanut already, so were excluded
- 62 were invited for observed food challenge
  - 47 passed challenge – no symptoms
  - 14 had localized oral cavity symptoms, only
  - 1 reacted (found to have Ara h 6)
- Isolated Ara h 8 sensitization seems to indicate peanut tolerance. Peanuts can be carefully introduced at home in children with such sensitization.

A Word On The Title

- Much is unknown regarding adverse food reactions
- Clinical history is important, as is patient recall and provider interpretation
- Genetics plays a role in both food intolerance and food allergy
- Diagnostic testing in 2015 is quite limited and is by no means a “crystal ball”
- Not all unusual symptoms (real and perceived) can be explained by adverse food reactions!

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Thank You For Your Attention!

Call or email me with questions!
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