

## Food Allergies and FDA Activities

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### Goals

- Define food allergies
  - Celiac disease = "gluten-sensitive enteropathy"
  - ❖ IgE-mediated food allergy
- Discuss pathogenesis and clinical presentations
- Discuss management and prevention (Labeling and other FDA regulatory activities)

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**Case 1**

- 21 yo female asthmatic
- Food allergy to tree nuts
- Develops frequent wheezing episodes when she drinks wine (red) and dried fruits
- Symptoms resolve promptly after she stops drinking/ eating
- Is this a food allergy?

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**Case 1 (cont)**

- No, this is likely Sulfite sensitivity
  - Mechanism may be related to inhaled sulfur gas
  - Up to 5% of asthmatics may be sensitive; some cases of anaphylaxis have been reported
- No treatment - avoidance of products with sulfites
- FDA has established 10 ppm as mandatory level for declaration of sulfites on label
- ❖ Other colors/additives for mandatory declaration: yellow 5 (tartrazine)/yellow 6; cochineal/carmine red

*Cochineal/carmine from insect.*

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**Case 2**

- 16 yo male
- Longstanding h/o springtime allergies, mild asthma, peanut allergy
- Eating left-over tuna steak from last night's dinner
- Develops immediate flushing, headache, diarrhea, shortness of breath and high blood pressure
- Is this a food allergy?

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### Case 2 (cont)

- No, this case is likely Scambroid food poisoning
  - Due to spoiled fish from *Scambroides* family
  - Histidine converted to histamine –toxic reaction
- Treatment is antihistamines and supportive care
- ❖ Contact FDA/ local authorities! Could be seafood food safety problem

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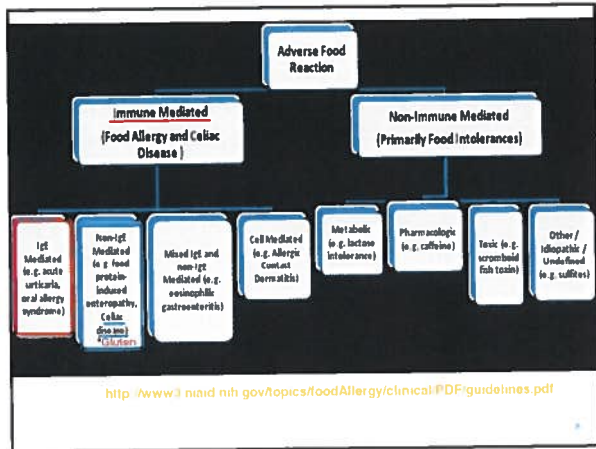
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### Case 3

- 30 yo female
- H/o irritable bowel syndrome and recent diagnosis of iron-deficiency anemia
- Reports feeling bloated when she eats bread products
- Recent complaints of very itchy rash -vesicular, extensor elbow surfaces→
- Family h/o short stature, diabetes
- Is this a food allergy?



**Dermatitis herpetiformis**

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**Wheat**

**Glutens**

- Gluten is the main proteic fraction in wheat (8-14%)
  - ~ 50% gliadin and ~ 50% glutenin
- The toxicity is mainly due to the gliadins; however glutenins also contribute to toxicity

FDA

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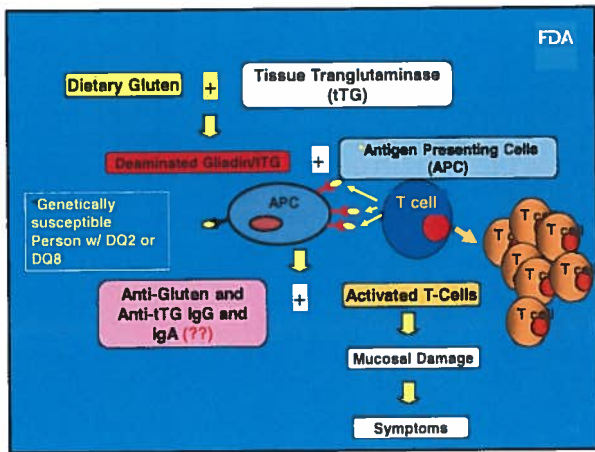
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**Histological Features**

Normal 0    Infiltrative 1    Hyperplastic 2

Partial atrophy 3a    Subtotal atrophy 3b    Total atrophy 3c

*Horvath K. Recent Advances in Pediatrics. 2002*

- ❖ Small intestine is approx. 20 ft long
- Function may still be preserved if not all intestine is involved

FDA

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**Symptoms/manifestations** FDA

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- ❖ **“Classic” GI Manifestations – “sprue”**
  - Usually presents at **6-24 months**; < 10% of individuals
    - Chronic or recurrent diarrhea, vomiting, abdominal distension/pain, anorexia/ failure to thrive, irritability
- ❖ **Atypical Manifestations**
  - Most common age of presentation: **older child to adult**
  - **Majority of individuals**
    - DH, iron-deficiency anemia, hepatitis, arthritis, seizures
- ❖ **Long term complications**
  - **Nutrient deficiencies**
    - Osteoporosis, short stature, delayed puberty
  - **Autoimmune diseases (3-8% of individuals)**
    - Diabetes, Autoimmune thyroid disease
  - **Malignancies (highly fatal)**
    - Enteropathy-associated T cell lymphoma

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**Gluten-free diet (GFD)** FDA

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- Gluten elimination leads to complete resolution of intestinal disease/ mortality risk in most
  - Check adherence, nutritional status
  - Negative serology in weeks; Intestinal mucosal healing 6-12 months
  - Non-responsive or non refractory celiac disease (NRCD) in 7-30%
- Codex Alimentarius: 20 ppm gluten (≈ 20 yrs); considering variable contamination, most diets < 10 mg gluten/day
- Pure oats: increases nutritional value (fiber) of GFD
  - Caution in some highly sensitive individuals
- Difficult; hidden sources in foods, drugs, ?cosmetics

Can recovery vita function

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**Gluten-free (GF) labeling** FDA

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- Codex alimentarius defined 20 ppm in 1990s; no US standard
- Proposed rule -2007, 2011
- Final rule- Aug 2013
  - 20 ppm gluten - based on analytical threshold (10 ppm gliadin) from validated sandwich ELISA methods (R5-Mendez or Morinaga)
  - Problematic area- foods using fermented or hydrolyzed gluten (e.g. beer) as no validated analytical test available; Proposed rule for Gluten-Free Labeling of Fermented or Hydrolyzed Foods
- Guide for small food businesses – June 2014
- Compliance date - Aug 2014

<http://www.fda.gov/food/guidances/ucm103439n/guidanceforindustryinformationforallergensucm362510.htm>

International body

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### Definition of "Gluten-free"



Gluten-containing grain = wheat (spelt, kamut, triticale, etc.), rye and barley; NOT oats

Food\* bearing this claim may:

- ✓ **not** contain a gluten-containing grain or ingredient from a gluten-containing grain not processed to remove gluten (e.g. flour) - cannot intentionally add gluten < 20 ppm
- ✓ have a gluten-containing grain processed to remove gluten (e.g., wheat starch) if < 20 ppm gluten in final product
- ✓ have unavoidable presence of < 20 ppm gluten
- ✓ be inherently gluten-free

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### Products covered by GF rule

- ❖ All FDA-regulated packaged food products, including dietary supplements
  - Includes beers not made from malted barley (e.g., sorghum) and distilled foods (e.g., vinegars) – proposed rule pending to address fermented/ hydrolyzed products

**Not covered:**

- TTB : distilled spirits, wine and beers with malted barley
- USDA: meat, poultry and some egg products
- CDER: medications

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### GF labeling in other countries

- ❖ **Europe:** gluten does not include oats  
 <20 ppm (GF) and <100 ppm (low gluten)  
 ["Parnuts": foods formulated to substitute gluten grains]
- ❖ **Canada:** gluten includes oats; no gluten ingredient allowed, but allows up to 20 ppm contamination
- ❖ **Australia:** gluten includes oats; no detectable gluten; analytical methods below 2.5 ppm gliadin

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**GF labeling issues**

- Voluntary, no testing/record keeping required
- Misbranding/recall if not in compliance w/ GF standard
- Other statements/symbols:
  - Allows use of specific terms such as "no gluten", "free of gluten" and "without gluten" as long as those terms meet GF definition
  - Allows symbols of gluten certification (e.g., < 5 ppm) as long as those terms are truthful and not misleading
  - Allows advisory statements for presence of wheat gluten if truthful and not misleading

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**Case 4**

- 13 yo middle school student
  - H/o moderate eczema and asthma since childhood
  - Develops flushed skin, nasal itchiness, facial swelling and wheezing while eating fish tacos at school cafeteria
  - Exam: skin rash on back ⇒  
 Feels faints; low blood pressure
- What is diagnosis/ treatment for this student?




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**"Food allergy"**

- ❖ "Adverse reaction to food that is IgE Ab-mediated"
- ❖ Typical symptoms - immediate and life-threatening!
- ❖ Involves foods/proteins commonly consumed in diet
  - ❖ US: peanut, soy, egg, milk, wheat, tree nuts, fish, shellfish
  - ❖ Europe: ... sesame, mustard, celery
  - ❖ Japan: ... buckwheat
- ❖ Affects 3-4% of Americans
- ❖ Genetic AND environmental
- ❖ No effective treatment – Labeling/ avoidance is key!
- ❖ Lifetime risk for many

Lupion - Bean

No good food allergy studies

Only 3-4% has

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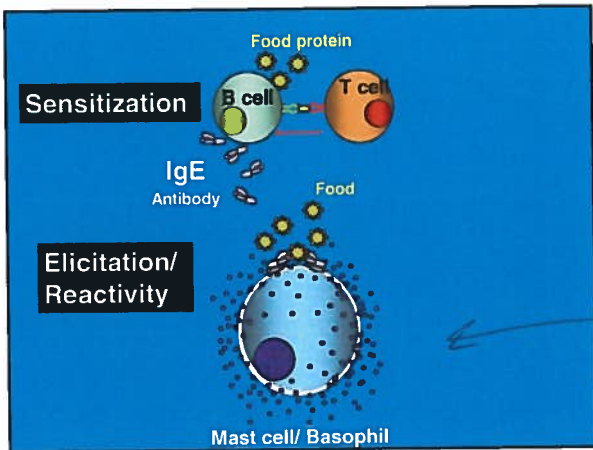
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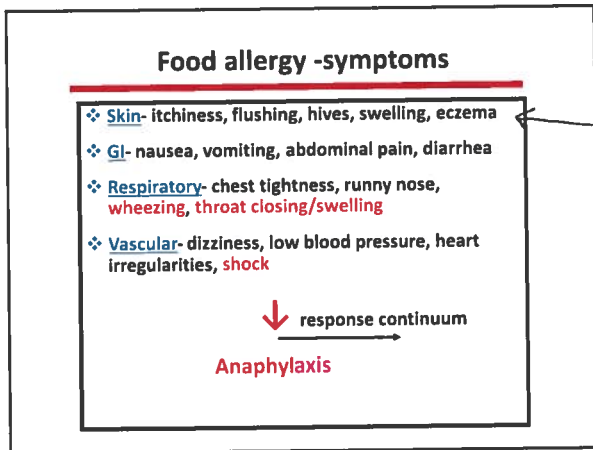
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Mast cell



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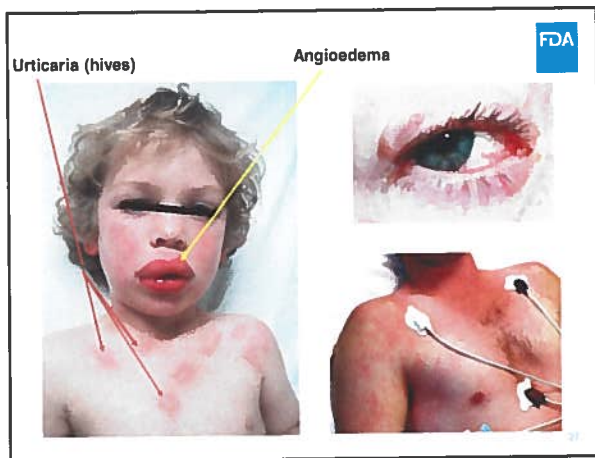
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50% on skin



Giving peanut early in life  
 may help.

Egg did not show  
 same affect.

20-25 deaths a year  
 less than lightning

Once in shock, 50%  
 chance of dying.

### Acute allergic attack FDA

- ❖ Severity on a response continuum (may be very rapid!)
- ❖ Skin rash/ GI + any uneasiness (wheezing/ faintness, etc.):
  - Call 911 or go to ER!
  - Epinephrine (Epi-pen) – 2 may be needed!
    - Epi-pen Jr (0.15mg): 33-66 lbs
    - Epi-pen (0.3mg): > 66 lbs
  - Antihistamines (Benadryl/ Claritin, etc.)
  - Treat asthma/wheezing with inhaler
  - Have patient lie down with legs raised and give fluids
- ❑ Possibility of delayed (> 4 hrs) or protracted reactions
  - Monitor; may give steroids (e.g. prednisone, etc.)

2 pens, because 1  
 none not be enough

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### Serious sequelae

- ❖ Most reactions are mild and self-limited; however, ~ 20% lead to anaphylaxis
  - ❑ 30,000 cases, 2500 hospitalizations and 150 deaths/ yr
  - ❑ Most common cause of anaphylaxis in ERs
  - ❑ Tree nuts and peanuts most commonly involved
- ❖ Food allergies early in life ⇒ asthma and/or other serious allergic disorders later on
- ❖ Difficult to predict who is at risk for severe reaction
  - Risk + consumer fears = ↑ psychosocial impact and ↓ quality of life

Higher risk to pass  
 on in genetics.

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### Prevalence

Food	*Children	*Adults	^Objective	*Outgrown?
Milk	2.5%	0.3%	0.6-0.9%	80%
Egg	1.3%	0.2%	0.3-0.9%	60-80%
Peanut	0.8%	0.6%	0.4-0.8%	20%
Tree nut	0.2%	0.5%	0.4%	9%
Fish	0.1%	0.4%	0.2-0.3%	No ?
Shellfish	0.1%	2.0%	0.6%	No ?
Other	-	-	Soy - 0.03-0.7% Wheat - 0.2-1.2%	Wheat 30-65%
Total	6%	3.7%	3.0%	

\*Sampson, JACI, May 2004; ^NIH clinical guidelines, 2010

➢ 3% (12% self) of US population: Infants (5-6%) >> adults (2-3%)

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### Management/ key FDA activities



- No effective treatment/ prevention – Avoidance !!!
- ❖ Allergen Labeling
- ❖ Premarket evaluation of novel food ingredients
- ❖ Compliance, enforcement and surveillance
- ❖ Education (<http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAllergens/default.htm>)
- Other - Review of food allergen desensitization trials and drug treatments (e.g., patches) done in other centers

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### Allergen Labeling



- ❖ Food Allergen Labeling & Consumer Protection Act (FALCPA)
- ❖ In effect since 1/1/06
- ❖ Food ingredients that contain protein from "major food allergens" (8):

- |           |  |
|-----------|--|
| - Peanut  | - Tree nuts (list of 17 nuts; incl. coconuts)  |
| - Milk    | - Wheat (any species in <i>Triticum</i> genus) |
| - Egg     | - Fish (list species)                          |
| - Soybean | - Crustacean shellfish (list species)          |

Only country which include coconuts

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### Allergen Labeling



- FALCPA does not address labeling for unintentional introduction of allergens into products by way of cross-contact:
  - **Advisory or precautionary allergen labeling (PAL) voluntary statements:**
    - "May contain..."
    - "Produced in a factory ..."
    - "Produced on the same line as..."
  - FDA public hearing (09/2008)
- ❖ FDA Food Safety Modernization Act (FSMA) - Final Rule for Preventive Controls for Human Food (2015)
  - Defines "cross contact"
  - Requires preventive controls for food allergens

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**Premarket allergenicity safety assessment**

Is or will the novel protein be an allergen?

- ✓ **Source of protein**
- ✓ **Amino acid sequence homology**
- ✓ **Pepsin resistance**
- ✓ **Specific serum screening**

*Codex Alimentarius, 2003*

- ❖ **Ex:** Brazil-nut 2S albumin in transgenic soybeans (*Nordlee et al. NEJM 334:688-92*)
- ❖ **Optional:** Targeted serum screening, animal models, whole food allergen compositional analysis

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**Compliance, enforcement and surveillance**

- ❖ **Inspections and enforcing good manufacturing practices**
  - FSMA allergen preventative controls**
- ❖ **Review and validation of analytical methods for allergens**
  - **Gluten, hydrolyzed proteins**
- ❖ **Recalls** – about one third of all total recalls, **milk** is predominant allergen
- ❖ **Postmarket**– CAERS (CFSAN Adverse Event Reporting System) – report to **FDA district offices** or **Medwatch** (<https://www.accessdata.fda.gov/scripts/medwatch/>)

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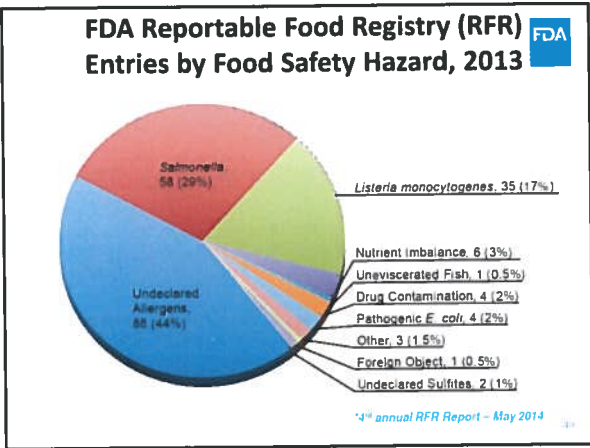
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FDA U.S. FOOD & DRUG ADMINISTRATION

**Thank you for your attention**

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