I have NO disclosures!
HAZARDOUS BRIDGE AHEAD
Opinions are like toothbrushes
Everybody has one, so there’s no need to share
Goals

- Define food allergy
- Recognize food intolerance mimics allergy
- Review Eosinophilic GI disease
- Interpret common tests of food allergy
- Recommend approach

- Lots of conflicting information – known knowns, known unknowns
NO, I'M NOT A DOCTOR
but I'll take a look
Prevalence of IgE Food Allergy

**Adult**

20% of adult patients perceive food intolerance

Confirmed DBFC 1.4%

**Pediatric** (Bock)

480 infants and children < 3yrs

28% perceived food intolerance, 80% in 1st year

8% (37) confirmed by challenge

2/3 cow’s milk

Severe and multiple food allergies increasing
Definitions
Adverse reaction to food

• Exposure leads to symptoms/signs
• Reproducible

• Non-immune vs Immune
Food Allergy or Intolerance

- Definitions

- IgE + non-IgE mediated disease

- Non-Immune
  - Chemical sensitivity
  - Lactose intolerance

- Many modifying factors and confounders
Confounders - examples

- Lactose hidden or with heavy meal
- Formula vs raw milk
- Organic vs non-organic
- Ice cream carageenan allergy
- Timing Type I vs FPIES
- Disorders where eating triggers symptoms
  - GB
  - IBS  gastro-colic reflex
- Diaries  !! ??  Majority do not have food induced ds
Food Induced Symptoms

- Allergy + Celiac
- GI
  - Peptic disease
  - Hepatobiliary disease
  - Anatomic abnormalities
  - Motility disorders
  - IBS- gastro colic reflex
  - IBD
- Lactose intolerance, other disacch def
- Non-GI - eating disorders
Food Reactivity

Non-Immune Intolerance

Food Allergy: Immune Type 1, Type 4, FPIES, Celiac

Food Unrelated
Prevalence of Food Allergy

- **Pediatric** 5-8% plus celiac 1%
- Atopy: Increasing
- Food allergy increasing:
  - e.g. doubling of peanut allergy
- Severe, multiple food allergic children are increasing
- Madness is also increasing
IgE Mediated Food Allergy

symptom onset < 2 hrs

• Skin
  urticaria, flushing flaring atopic derm
• Airway
  – laryngeal
• Lung
  – bronchospasm
• Circulation
  – Hypotension/shock

• GI
  Oral allergy syndrome
  Vomiting
  Pain
  Diarrhea
  3\textsuperscript{rd} space fluid loss
  Bleeding
# IgE Cross-Reactivity of Foods

<table>
<thead>
<tr>
<th>If Allergic to:</th>
<th>Risk of Reaction to at Least One:</th>
<th>Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A legume*</td>
<td>Other legumes</td>
<td>5%</td>
</tr>
<tr>
<td>peanut</td>
<td>peas, lentils, beans</td>
<td></td>
</tr>
<tr>
<td>A tree nut</td>
<td>Other tree nuts</td>
<td>37%</td>
</tr>
<tr>
<td>walnut</td>
<td>cashew, brazil, hazelnut</td>
<td></td>
</tr>
<tr>
<td>A fish*</td>
<td>Other fish</td>
<td>50%</td>
</tr>
<tr>
<td>salmon</td>
<td>swordfish, sole</td>
<td></td>
</tr>
<tr>
<td>A shellfish</td>
<td>Other shellfish</td>
<td>75%</td>
</tr>
<tr>
<td>shrimp</td>
<td>crab, lobster</td>
<td></td>
</tr>
<tr>
<td>A grain*</td>
<td>Other grains</td>
<td>20%</td>
</tr>
<tr>
<td>wheat</td>
<td>barley, rye</td>
<td></td>
</tr>
<tr>
<td>Cow’s milk*</td>
<td>Beef</td>
<td>10%</td>
</tr>
</tbody>
</table>

## IgE Cross-Reactivity of Foods

<table>
<thead>
<tr>
<th>Cow's milk*</th>
<th>Goat's milk</th>
<th>92%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow's milk*</td>
<td>Mare's milk</td>
<td>4%</td>
</tr>
<tr>
<td>Pollen</td>
<td>Fruits/vegetables</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Fruits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vegetables</td>
<td></td>
</tr>
<tr>
<td>Pollen</td>
<td>Other Rosaceae</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Other fruits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fruits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>latex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Latex</td>
<td>11%</td>
</tr>
</tbody>
</table>


- Cow's milk and Goat's milk share 92% cross-reactivity.
- Cow's milk and Mare's milk share 4% cross-reactivity.
- Pollen and Fruits share 55% cross-reactivity.
- Other Rosaceae and Other fruits share 55% cross-reactivity.
Evaluation of IgE

• History of acute reaction (<2 hrs)

• Confirm with test for IgE
  – Skin prick test
  – IgE CAPRAST

• Skin test useful in mixed foods, multiple foods
IgE CAP RAST

<table>
<thead>
<tr>
<th>Food</th>
<th>&gt;95% PPV</th>
<th>&gt;90% PPV</th>
<th>&gt;95% NPV</th>
<th>&gt;90% NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>6</td>
<td>2</td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>Milk</td>
<td>32</td>
<td>23</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Peanut</td>
<td>15</td>
<td>9</td>
<td>Best NPV = 85% at &lt;0.35 kU/L</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>9.5</td>
<td>0.9</td>
<td>5</td>
</tr>
<tr>
<td>Soy</td>
<td>Best PPV = 50% at 65 kU/L</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>Best PPV = 75% at 100 kU/L</td>
<td>5</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Predicts risk of acute reaction to food from DBPCFC

Treatment of IgE Food Allergy:

• Avoid!!!
• Dietician
• Support Allergy/Asthma Information Assoc Food Allergy Anaphylaxis Network
• Epi Pen
• ER/ambulance if reaction occurs

Keep in ER 4-6 hours
Non-IgE Food Allergy

• More commonly seen by GI - diverse presentations mimic other conditions

• Nutritional problems associated with avoidance of food

• Immunologic Abnormality : Th1-Th2, Treg

• Not IgE or IgG mediated
Gastrointestinal Hypersensitivity Disorders

IgE
Immediate Hypersensitivity

Non-IgE
Dietary Protein Enterocolitis
Dietary Protein Proctitis
Celiac
Allergic eosinophilic Esophagitis
Allergic eosinophilic Gastroenteritis

IgE-Mast cell mediated Response
preformed mediators (leukotrienes, histamines, prostaglandins)
Clinical Symptoms

Eosinophil ± IgE mediated Response
preformed mediators (eosinophil granular proteins MBP, ECP, chemokines, cytokines)
Clinical Symptoms
Clinical Spectrum
Non-IgE Food Allergy

- Celiac Disease-Gluten Induced Enteropathy
- Failure to thrive / Protein-losing enteropathy
- Gastroesophageal Reflux Symptoms
- Eosinophilic Colitis
- Enterocolitis Syndrome
- Atopic Dermatitis
- ‘Infantile Colic’
- Preterm infant feeding intolerance
Celiac Disease

- Patients do NOT present with symptoms from ingesting gluten
- After gluten free frequently get sick with gluten
- Patients should NOT be prescribed gluten free diets for diagnosis
- Non celiac gluten sensitivity is a FAD but….
  - We eat too much starch
  - Obesity, Type 2 diabetes, hyperlipidemia
  - Most feel better with less starch
Histology in Celiac Disease
Changing Face of Celiac

• Decreasing incidence with classic features

• Increasing in non-caucasian population

• Environmental factors may influence the way celiac manifests itself clinically
  – Need gluten
  – Need class II (HLA DQ 2 or 8)
Diagnosis of celiac disease

• Screen IgA TTG Ab  sens/spec  90+%
  (IgA deficient: IgG antigliadin, TTG)

• Small bowel biopsy to confirm ‘STANDARD’

• Follow decline of Ab on gluten free diet
Who should be Screened??

- Symptoms/signs of malabsorption
- First degree relatives
- Type 1 Diabetes
- Trisomy 21, Turner, Williams
- unexplained Fe deficiency
- osteopenia
- short stature
- constipation with FTT, anemia etc
Wheat Belly Fad

- Is there a non-IgE, non-celiac gluten sensitivity?
- Some individuals improved symptoms and QOL on gluten-free
- ?Mechanism  ? Placebo – difficult to blind
- Difficult in children
- Removing whole grain affects AP, flora
Why do you drink my milk ???
Common Presentations of Non-IgE Milk Allergy

• Allergic colitis in early infancy
  – Loose stool with blood, well infant
• GERD symptoms in infants
• Cow’s Milk Protein Enteropathy (hypoalbumumemia, anemia and FTT)

• If scoped: eosinophilia in tissue
‘Distressed Infant’ + Allergy

• 19/19 ‘distressed’ infants with GER symptoms benefit from AA based formula
• Unresponsive to H2 blocker

• 12/19 relapse on DBPC formula challenge

• subgroup of irritable infants are allergic

Take Home

• Milk allergy 5+% infants

• Trial of removing milk from breastfeeding mom or changing infant formula for 1-2 weeks often warranted

• If no change switch back

• Late introduction of milk may delay dx
Atopic dermatitis and food allergy

- Allergists + Dermatologists often disagree

- 50-60% food allergy with severe AD
  - Especially young age
  - Often have GI symptoms

- Take Home: test for food allergy in severe atopic dermatitis in young children
Unusual Case

• 10 month old child presents with vomiting (5X), severe lethargy
• ER-neg labs except WBC 20, left shift
• plain films negative
• Contrast enema - negative
• PICU, IVF, antibiotics
Case

- Next day- appears well
- Passes small amount of blood per rectum with a loose stool
Case

• Feeding history
  – GERD as an infant, cow milk formula
  – Tried cereal multiple times to thicken bottle
  – Cereal made reflux worse
  – Acute flu-like illness after cereal at 5 months
  – Day of admission had stage 3 infant food (turkey dinner with rice, soy, milk) at lunch, 4pm started vomiting, rapid deterioration

• Challenge!
Food Protein-Induced Enterocolitis Syndrome

- Lethargy, vomit, diarrhea + blood
- Acidosis, leukocytosis

- 4-6 hrs post ingestion (up to 12 hrs)

- Recovery with IVF, time
- No demonstrable IgE mechanism
- Dx: Careful history
- Natural history: Outgrow in 2-3 yrs
EGE

• Idiopathic eosinophilic disease with no food allergy  RARE ! Except EoE
• Symptoms follow site of involvement

• Eosinophils in tissue “allergic” enteropathy is NOT synonymous with food allergy
• If elemental diet works that is NOT synonymous with food allergy
EGE

- **Mucosal** (Most common)
  - Diarrhea, PLE

- **Muscular**
  - vomiting

- **Serosal**
  - Eosinophilic ascites
Treatment

- Elemental diet
- Corticosteroids
  - Short course vs Crohn
  - ?self limited or chronic?
- Ketotifen (mast cell stabilizer)
Elemental Diet Tx EE
Review of literature:

Limited data, few controlled data, much expert opinion
A clinicopathological disease characterized by:

• Symptoms including food impaction and dysphagia in teens/adults, and feeding intolerance and GERD symptoms in children

• $\geq 15$ eos/max HPF: distal and mid esophagus

• Exclusion of other disorders with similar clinical, histological, or endoscopic features, especially GERD

• Normal pH monitoring

• Failure of high dose PPI

Furuta et al. Gastroenterology 2007
ENDOSCOPIC, X-Ray FEATURES
HISTOLOGIC FEATURES

>15 Eos/HPF

Basal zone hyperplasia

Normal

Courtesy: Fred Weinstein, Chris Liacouras
CLINICAL PRESENTATION:
SYMPTOMS/SIGNS SUGGESTIVE OF EoE

Age-related

Young Children
• Feeding aversion/intolerance
• Vomiting/regurgitation
• Failure to thrive
• GERD refractory to medical management
• GERD refractory to surgical management

Teens/Adults
• Dysphagia
• Food impaction
• Slow eating
• GERD

Furuta et al. Gastroenterology 2007
<table>
<thead>
<tr>
<th><strong>GERD</strong></th>
<th><strong>EoE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily a distal disease</td>
<td>Usually panesophageal</td>
</tr>
<tr>
<td>Causes erosions/ulcers</td>
<td>Not an ulcerating disease</td>
</tr>
<tr>
<td>Barrett’s</td>
<td>No Barrett’s</td>
</tr>
<tr>
<td>Strictures</td>
<td>Strictures</td>
</tr>
<tr>
<td>Few Eos on biopsy</td>
<td>Eosinophilia impressive-distal and mid</td>
</tr>
<tr>
<td>Distal ds</td>
<td>May be patchy</td>
</tr>
<tr>
<td>Responds to acid suppression</td>
<td>Typically no response/may respond</td>
</tr>
<tr>
<td>No response to steroids or hypoallergenic diet</td>
<td>Responds to steroids or hypoallergenic diet</td>
</tr>
<tr>
<td>An old disease</td>
<td>A new disease</td>
</tr>
</tbody>
</table>
Evaluation

• Empiric milk free diet trial
• Skin prick/patch tests
  – May not correlate with disease
  – Proof is difficult

Empiric steroid or other diet elimination
**DIETARY RESTRICTION OR ELIMINATION**

<table>
<thead>
<tr>
<th>Description</th>
<th>% Obtaining Dietary Success</th>
<th>Reduction of Eos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Restriction - Kagalwalla</td>
<td>74</td>
<td>13.6</td>
</tr>
<tr>
<td>Dietary Restriction - Spergel</td>
<td>77</td>
<td>12.8</td>
</tr>
<tr>
<td>Dietary Elimination - Liacouras</td>
<td>95</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*References:
- Spergel et al. Asthma Immunol 2005
<table>
<thead>
<tr>
<th>TABLE III. Recommended doses of corticosteroids for EoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical swallowed corticosteroids</strong></td>
</tr>
<tr>
<td>Initial doses (see references for preparation and administration information)</td>
</tr>
<tr>
<td>Fluticasone (puffed and swallowed through a metered-dose inhaler)</td>
</tr>
<tr>
<td>Adults: 440-880 μg twice daily</td>
</tr>
<tr>
<td>Children: 88-440 μg twice to 4 times daily (to a maximal adult dose)</td>
</tr>
<tr>
<td>Budesonide (as a viscous suspension)</td>
</tr>
<tr>
<td>Children (&lt;10 y): 1 mg daily</td>
</tr>
<tr>
<td>Older children and adults: 2 mg daily</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
</tr>
<tr>
<td>For severe cases (eg, small-caliber esophagus, weight loss, and hospitalization)</td>
</tr>
<tr>
<td>Prednisone: 1-2 mg/kg</td>
</tr>
</tbody>
</table>

2011 JACI Consensus Statement
EFFECT OF PHARMACOLOGIC THERAPY
ESOPHAGEAL EOSINOPHILIA

Average number of esophageal eosinophils per hpf

Figure 2. Change in Mayo dysphagia questionnaire (MDQ) score following...
Change in peak eosinophil counts with therapy

- Fluticasone (n=21):
  - 19% < 7
  - P = 0.102

- Esomeprazole (n=21):
  - 33% < 7
  - P = 0.174
  - NS
Investigation Non-IgE /EGE

- ? Delayed reaction
- Chronic GI symptoms
- Rule out other GI disease
Investigation Non-IgE / EGE

- Endoscopic biopsies
- Eosinophilic inflammation
- CBC, IgA, E, albumin
- IgE RAST/skin prick
- ? Patch test
Manage Non-IgE or EGE

- Eosinophils in Tissue
- Avoid skin positive food
- Avoid milk protein
- ? Response / Rechallenge

- Consider elimination / elemental diets
- Consider corticosteroids
“Oh boy! . . . It’s dog food AGAIN!”
Conclusion

• Increasing incidence + severity of food allergy

• Non- IgE is under-recognized-delayed rx

• EoE is much more common than EGE

• Most ‘intolerance’ to food is still not allergic (immune mediated)