An Everyday Case in My Clinic

- A 28 yr old woman comes to see me for food intolerances and gluten sensitivity. She reports abdominal bloating and discomfort after eating various foods, abdominal cramping and loose stools ranging from 2 to 3 per day without blood for the past year. Symptoms are relieved by passage of stool. She also complains of fatigue.
- She went on a gluten free diet two months ago. She feels better but now finds that other foods are also leading to bloating, pain and loose stools. She is concerned about food allergies and asks if she has celiac disease. The patient also asks if her increasingly restrictive diet will cause nutritional problems. She wants to know what type of diet she should eat.

What do you think is the clinical problem and how do you address the patient’s concerns?
What to Eat and What Not to Eat?

- Nearly every patient who sees a GI practitioner wants to know is it something that they eat and/or is there something missing from their diet that is the cause of their GI and other health problems
- The popularity of many types of diets underscore the notion that what we eat is the key to health and well-being
- Marketing of food promoting potential health benefits is becoming more common

Good Grains and Bad Grains?

HIS AND HER’S “SEX” CEREAL

THE DAILY CONSTITUTIONAL AID
Food and the Digestive Tract: Friend or Foe?

- The average human ingests a large amount of food in their lifetime
  - ~ 60,000 pounds - 27,273 kilograms - 30 tons
- The vast majority benefit from this ingestion but a small percentage develop complications:
  - Food poisoning
  - Food allergies
  - Food sensitivities
- However, there is a reported increase in food allergies, celiac disease and seemingly of food sensitivities

Biological Variables that Influence the Developing Immunophenotype of an Infant

Brandtzaeg, Nat Rev Gastroenterol Hepatol, 7: 380-400, 2010
Classification of Adverse Reactions to Food

Adverse food reaction

- Immune
  - IgE (OAS, Hives, Anaphylaxis)
  - Non-IgE (FPIES, Celiac)
  - Mixed (EoE)

- Non-immune
  - Metabolic (Lactose intolerance)
  - Pharmacological (Tyramine)
  - Toxic (Scombroid)
  - Other (Mechanical, physiological)

GI Disorders and ARF

- GI food allergy
- Food protein enteropathies (milk, soy)
- Celiac disease
- Eosinophilic gastroenteritis, esophagitis
- Lactose and other carbohydrate intolerance
- Irritable bowel syndrome and other lower FGIDs
- Inflammatory bowel disease
- Dyspepsia, GERD, peptic ulcer

Adapted from Boyce JA et al. JACI.2010;126(6):1105
Physiological Food Reactions

- Large volume meals (overeating) cause distension, promote regurgitation
- Fatty foods delay gastric emptying, alter motility
- Legumes, cruciferous vegetables, garlic, onions, etc, may lead to flatus (farts)
- Non-absorbable or poorly absorbed sugars and carbohydrates (FODMAPs) can cause diarrhea, bloating, flatulence, etc
- However, intestinal gas is NORMAL (up to 20 farts/day)


Mechanical Problems with Food

- Medical conditions in which foods can be problematic:
  - Strictures
  - Gastric outlet problems
  - Gastroparesis
  - Diverticulitis (NOT diverticulosis!)

- Foods that can cause problems:
  - Insoluble fibers – skins or peel, seeds, nuts, many vegetables
Pharmacological Food Reactions

Reactions to food due to chemical components in foods and food additives such as:

- Histamine
  - Swiss cheese
  - Tuna and other scombroid fish
- Sulfites
- Tartrazine
- MSG
- Caffeine
- Amines

This form of ARF does not tend to result in GI problems but asthma, headaches, and skin manifestations.

Psychological Adverse Reactions to Food

Snow White was poisoned by an apple, Jack found a giant in his beanstalk, and look what happened to Alice when she ate the mushroom! And you wonder why I won’t eat fruits and vegetables?!
Immunological Reactions to Food

• Food hypersensitivity (IgE-mediated)
• Celiac disease (T-cell mediated)
• Eosinophilic GI disorders (eosinophils)
• Food protein enteropathies (mixed)
  • Hypersensitivity
  • Immune complexes
  • T-cells
Sheila E. Crowe, MD, FACG

Food Allergy: Epidemiology

- 4-5% of the population have food allergy
- 20-30% of the population *think* they have food allergy
- 30-40% of patients with FA have asthma/atopic dermatitis
- 50% of anaphylaxis treated in ED are due to FA
- 70% of patients with FA have + FHx of atopic diseases

*Branum AM et al. Pediatrics, 124(6): 1549, 2009*  
*Sicherer SH, Sampson HA, JACI, 125:S116-25, 2010*
Food Allergy – Key Information

**Definition**
- Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food

**Outgrowing phenomena**
- Egg: >50% by age 5
- Milk: >80% by age 5
- Peanut: ~20%

**Big 8**
- Milk, soy, eggs, wheat, peanuts, tree nuts, fish and shellfish

Manifestations of Food Allergy

- GI symptoms (in 30-70%):
  - edema of oropharyngeal mucosa
  - nausea/vomiting, diarrhea, abdominal pain, bloating
- Other manifestations:
  - urticaria, eczema
  - asthma, rhinitis, otitis
  - anaphylaxis
Risk of Anaphylaxis

Food allergy is now the major cause of anaphylaxis in western countries.

Those with increased risk include those:

- with past history of anaphylaxis
- with reactions with respiratory tract symptoms
- with reactions to peanuts, tree nuts, fish, seafood
- taking B-blockers or ACE inhibitors

Peanut Allergy

- Increasing prevalence
- Occurs in 1 in 150-200 individuals
- Varying presentations
- Major cause of anaphylaxis
- Varying dose sensitivity
- Most react on first recognized exposure
- Up to 20% may lose sensitivity
- Associated with other food allergy, atopy
Wheat Allergy and Anaphylaxis

- 4-8% of children, 2-4% adults have food allergies
- 65% of children lose reactivity to wheat by age 12
- GI symptoms in food allergy (in 30-70%):
  - Edema of oropharyngeal mucosa
  - Nausea/vomiting, diarrhea, abdominal pain, bloating
- Dermatological: Urticaria, eczema
- Respiratory Tract: Asthma, rhinitis, otitis
- Systemic: Anaphylaxis
  - Wheat-dependent exercise-induced anaphylaxis (WDEIA)
  - IgE to omega-5-gliadin

Keet, CA et al, Ann Allergy Asthma Immunol, 102:410; 2009
Inomata N, Curr Opin Allergy Clin Immunol, 9:238; 2009

Oral Allergy Syndrome

- Localized IgE - Initial sensitization to pollens results in IgE that cross reacts with fruit and vegetables
- Raw fruit and vegetables
  - Birch pollen – apple, peach, pear, almond, hazelnut, potato, carrot
  - Ragweed pollen – melons, banana, gourd family
  - Mugwort pollen – celery, carrot, spices
  - Grass pollen - tomato
- Itching, ± swelling and/or tingling
- Confined to lips, tongue, roof of mouth and throat
- Affects patients with pollen allergy

Latex – Food Allergy Syndrome

- Sensitization to latex results in IgE that cross reacts with fruit and vegetables
- Exposure to foods give same symptoms as latex
- Natural Rubber Latex contains over 200 proteins, 10 bind IgE (HEV b 1-10)
- Food associations:
  - Kiwi (5)
  - Potato, tomato (7)
  - Avocado, chestnut, banana (6)

Other Immune-Mediated Food Allergy
Food Protein Induced Enterocolitis Syndrome (FPIES)

- Incidence = 0.34%
- Formula-fed young infants
- Provoked by cow’s milk or soy protein-based formula
- Protracted vomiting, diarrhea and GI bleeding
- Mimics IBD or gastroenteritis
- Treatment - extensive hydrolyzed casein formula

Katz Y et al. JACI, 127(3):647, 2011

GI Disorders Associated with Eosinophilia

- Primary:
  - Eosinophilic esophagitis
  - Eosinophilic gastritis
  - Eosinophilic enteritis
  - Eosinophilic gastroenteritis
  - Eosinophilic colitis

- Secondary:
  - Infection-associated eosinophilia
  - Drug-induced eosinophilia
  - IBD and pouchitis
  - Celiac disease
  - Microscopic colitis
  - Connective tissue disease-associated
  - Neoplasia associated
  - Graft versus host disease
  - Autoimmune

Powell, N, Walker, MJ, Talley, NJ, Nat Rev Gastroenterol Hepatol. 7:146; 2010
Eosinophilic Esophagitis (EoE)

- A chronic, immune/antigen-mediated esophageal disease characterized by esophageal dysfunction and eosinophil-predominant inflammation
- Prevalence = 0.03%
- Male (>2/3), mean age 34
- Reflux, chest pain, dysphagia & food impaction

Liacouras CA et al. JACI, 128(1):3-20, 2011

Endoscopic and Histologic Findings

Bischoff & Crowe, Gastroenterology, 128: 1089, 2005
**EoE: Management**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic steroid</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Topical steroid</td>
<td>50-100%</td>
</tr>
<tr>
<td>Restrictive diet</td>
<td>57-77%</td>
</tr>
<tr>
<td>6 food elimination</td>
<td>70-74%</td>
</tr>
<tr>
<td>Elemental diet</td>
<td>88-97%</td>
</tr>
</tbody>
</table>

Aceves, SS, Clin Gastroenterol & Hepatol, 12:1216, 2014

**Eosinophilic Gastroenteritis**

– Affects adults and children
– Not increasing in prevalence in contrast to EoE, food allergy, and celiac disease
– Can involve all layers of gut wall
– Various GI manifestations
– May have food allergies, specific IgE
– Increased peripheral eosinophils
– Varying response to elimination diets, anti-allergic therapies
EGE – Diagnosis and Treatment

– Increased peripheral eosinophils (2/3)
– Food allergy evaluation
– Varying response to elimination diets, anti-allergic therapies
– Exclude other causes of eosinophils
– Steroids are effective

Back to the Case……

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Does she have food allergy? Could she have EGE??
How about celiac disease?
Dietary Response to a Gluten-Free Diet: Is this Diagnostic of Celiac Disease?

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten-free diet often eliminates other dietary factors (additives, preservatives)
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study
- What else is improved by a gluten free-diet?


Patients Already on a Gluten Free Diet: How to Test for Celiac Disease?

- Depends of duration and stringency of the GFD
  - if truly on a GFD for years it is difficult to prove CD
  - many patients on a self-taught GFD are not truly gluten-free
- Serology can take over a year to normalize
  - Check TTG IgA +/- DGP IgA, IgG
- Histology can take several years plus to become normal
- Thus, if an undiagnosed patient wants an assessment for possible CD assess with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD
- Absence of HLA DQ2.2, 2.5 or 8 effectively excludes CD now or in the future

Sugal, E, et al, Digestive & Liver Disease, 42:352, 2010
Crowe, SE. In The Clinic : Celiac Disease, Ann Int Med,2011 154:ITC5-14,
HLA DQ Screening Tests

Risk of celiac disease and HLA status

- General population ≤ 1.0%
- DQ2 homozygous – 31X
- DQ2/DQ8 positive – 14X
- DQ8 homozygous – 10X
- DQ2 heterozygous – 10X
- DQ8 heterozygous – 2X
- DQ2 and DQ8 negative - ≤ 0.1X

Helpful test for its NPV


When to Use Genetic Testing

- **How to test:**
  - PCR of RNA extracted from cells in a cheek swab or blood sample
- **Who to test:**
  - Close relatives of patients with confirmed CD wishing to know if they are at risk of developing CD
  - Patients on a gluten free diet who are candidates to undergo a gluten challenge to confirm possible CD
  - Equivocal histology and serology findings in which a negative test result would make CD highly unlikely
- **How often to test:** Once in a lifetime

Screening Family Members: Who Is at Risk of Celiac Disease?

Gluten Challenge

- Gradual increase of gluten up to target (traditionally 10g - equivalent of 4 slices bread/day) but varies by patient
- Check TTG IgA q2-6 weeks until positive
- EGD/biopsy if diarrhea develops and/or seropositive
- Management if still seronegative at 3 to 6 months needs to be individualized but typically involves EGD/biopsy now or after longer gluten challenge
- One study showed that a 14-day 3 g challenge was sufficient to induce serologic and histologic changes

1Leffler, D, et al, Gut, 2012
How to Evaluate for Causes of Adverse Reactions to Food

- History - ? co-factors (exercise, drugs)
- Assess for lactose intolerance
- Assess for SIBO
- Skin testing for food allergens
- Diet diary
- Hypoallergenic diet trial
- Endoscopy and biopsy

• CBC, eosinophil count
• Quantitative immunoglobulins
• Specific IgE levels (RAST, ELISA)
• Serum IgG to foods – No longer accepted but**
• Celiac serology and/or HLA DQ assay
• Other tests for non-IgE mediated reactions

Food Antigen Challenges

- Skin prick testing
  – Excellent negative predictive value
  – Poor positive predictive value
- Skin patch testing for food allergens
- Double blinded food challenge (NG tube, capsule)
- GI tract by endoscopic mucosal testing
  – Limited studies but appears useful
- Other sites unproven or not accepted
  – Sublingual
  – Neuromuscular
  – Iridology

**Clayton, F. et al, Gastroenterology, 147: 602; 2014
Bischoff & Crowe, Gastroenterology, 128: 1089, 2005
DeGaetani & Crowe, CGH, 8: 755, 2010
Treatment – the 4E’s

- Expert
- Elimination
- Epinephrine
- Education


Management of Food Allergy

- Avoidance of food allergens
- Patient education
  - Understand food allergen groups
  - Since Jan 2006 USA labeling for 8 major food allergens
  - Recognize warning symptoms
- Information networks, newsletters
  - Food Allergy Research and Education (FARE) (www.foodallergy.org)
- Treatments
  - Antihistamines, mast cell inhibitors, cromolyn sodium, corticosteroids
  - Injectable epinephrine
  - No proven role for oral desensitization
Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean change in symptoms over 6 weeks

Overall symptoms

P = 0.047

Bloating

P = 0.031

VAS (0-100 mm)

Week

Gluten (n=19)

Placebo (n=15)

* P-value for analyses at Week 1 and entire study period

Adapted from Biesiekierski JR, et al. Am J Gastroenterol, Jan. 11, 2011 (Epub ahead of print)
Lactose Intolerance

- Symptoms due to lactose malabsorption resulting from lactose deficiency
  - Congenital deficiencies - rare
  - Constitutional lactase insufficiency
    - Genetically programmed decreased in lactase synthesis after weaning
    - Common in native NA, Asians, Africans, those from Mediterranean areas
  - Secondary lactase insufficiency
    - Gastroenteritis, Crohn’s disease, celiac disease
- Most common ARF worldwide

Management of Lactose Intolerance

- Most individuals with lactose intolerance can tolerate 12-15 g lactose (8-10 oz of milk)
- Yoghurt, hard cheeses are naturally lactose-free
- Lactose better tolerated when taken in small, more frequent amounts and with other foods
- Lactase supplements helpful
- No proven benefit for probiotics, adaptation programs
- Triacylglycerol content of many milk products can cause GI symptoms unrelated to lactase insufficiency or cows milk protein (CMP) allergy

Adverse Reactions to FODMAPs

**Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols**

- Fructose and fructans
- Sorbitol
- Sucrose
- Lactose

Many foods (grains including wheat starch, fruits, vegetables) contain FODMAPs

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No Effect of Gluten after Reduced FODMAP Diet in IBS Patients

- 37 subjects with IBS (Rome III) reporting NCGS (celiac disease meticulously excluded) underwent double-blind cross-over study
- 2 wks low FODMAP diet resulted in significant improvement of GI symptoms and fatigue
- Challenge with gluten (high, low or control) did not result in symptomatic or biological changes
- Suggests sensitivity may not be due to gluten

No Effect of Gluten after Reduced FODMAP Diet in IBS Patients

Gluten Coexists with Nonabsorbed Fructans and Other Saccharides

Proposed Mechanisms of Non-Celiac Gluten or Wheat Sensitivity

- Wheat ingestion
- Poorly Absorbed Carbohydrates
- Gluten-mediated
- Excess Fructans
- Fermentation
- Gas production & SCFA formation
- Microbiome changes
- Nociebo Effect
- Immune Activation/Low grade inflammation
- Altered Permeability
- GI Symptoms

SCFA = short chain fatty acids


Back to the Patient

Lab test results
- Normal CBC & diff, CMP
- Stool studies negative for pathogens
- Celiac serology not elevated
- No HLA DQ susceptibility genes
- Specific IgE to wheat negative
- Glucose breath test – no rise in hydrogen or methane

What to do next?
- Consider endoscopy/biopsy
- Check nutritional parameters
- Diet diary
- Referral to a knowledgeable RD
- Trial of low FODMAP diet
- Other dietary trials within reason
- Consider treating SIBO
Take Home Points

Food allergies are not fiction and are not that rare ....Food sensitivities or intolerances are far more common however

• Food allergy can be identified with subsequent dietary elimination providing benefit
• Celiac disease is common and easily screened for
• Lactose intolerance is common and easily treated
• The role of gluten, FODMAPs, and other foods in IBS/FGIDs remains unclear. However, identifying specific food intolerances can be beneficial for IBS patients
• The microbiome/SIBO also contribute to food intolerances
• Patients appreciate the assessment even if it turns out to be negative and they have the non-specific food sensitivity common to most IBS/FGID patients

DeGaetani & Crowe, CGH, 8: 755, 2010