**10:30 – 11:15 am**

**Celiac Disease and Gluten Sensitivity: Similarities, Differences and Uncertainties**

**SPEAKER**
**Daniel Leffler, MD, MS**

## Presenter Disclosure Information

**The following relationships exist related to this presentation:**

- Daniel Leffler, MD, MS: Consultant for Alba Therapeutics; Alvine Pharmaceuticals; and Glenwood Pharmaceuticals. Speaker for Inova Diagnostics.

**Off-Label/Investigational Discussion**

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

# Celiac Disease and Gluten Sensitivity:
## Similarities, Differences and Uncertainties

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## Objectives

- Recognize the diagnostic criteria for celiac disease.
- Assess the prevalence of celiac disease in patients with predisposing conditions.
- Review the long term management of patients with celiac disease.
- Differentiate celiac disease from non-celiac gluten sensitivity.

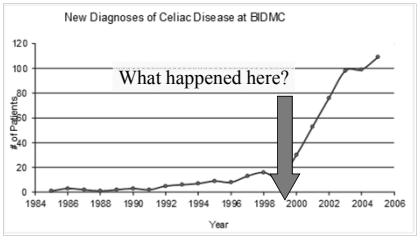
## Case Study

Heather is a 38-year-old woman who presents to her PCP for evaluation of chronic IBS-type symptoms and mild chronic LFT elevations attributed to fatty liver

Her mother has autoimmune thyroid disease but family history is otherwise unremarkable

Heather reports that, on the advice of a friend, she has started a gluten free diet and has noticed significant improvement. She wants to know if you recommend any testing.

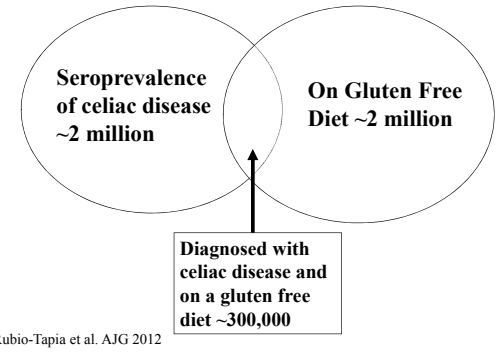
## Changing Prevalence




IgA TTG serology
> 95% accurate

Lohi et al. APT 2007, Rubio-Tapia Gastro 2009

## Current Epidemiology of Celiac Disease in the United States




Rubio-Tapia et al. AJG 2012

## Celiac Disease: A Myopic Impression

- The classic presentation of celiac disease:
  - Rare
  - White, preferably of Irish or Italian decent
  - Early childhood onset
  - Symptoms of diarrhea, abdominal pain, weight loss and failure to thrive

## An Expanded Perspective

- Common in many ethnic backgrounds
- Average age of diagnosis is ~40
- Onset at any age when there is exposure to gluten
- Highly diverse presentation
- Average of 10 years of symptoms prior to diagnosis

*Green AJG 2001, Cranney DDS 2007*

## Pathophysiology

Step 1:
Gluten Entry into the Submucosa

Step 2:
Deamidation of Gluten by Tissue Transglutaminase (tTG)

Step 3: Immune Activation

Only HLA DQ2 and DQ8 are able to bind gluten!

Green, Cellier NEJM 2007

## Celiac Test Performance

| Test | Sensitivity (Range) | Specificity (Range) | PPV* | NPV* |
|---|---|---|---|---|
| IgA AGA | 85 (57-100) | 90 (47-94) | 18 | 99 |
| IgG AGA | 85 (42-100) | 80 (50-94) | 31 | 99 |
| EMA | 95 (86-100) | 99 (97-100) | 83 | 99 |
| IgA anti-tTG | 98 (78-100) | 98 (90-100) | 72 | 99 |
| IgG anti-tTG | 70 (45-95) | 95 (94-100) | 42 | 99 |
| IgA anti-DGP | 88 (74-100) | 95 (90-99) | 44 | 99 |
| IgG anti-DGP | 80 (63-95) | 98 (90-99) | 68 | 99 |
| IgA/IgG anti-DGP | 97 (75-99) | 95 (87-100) | 51 | 99 |

* pretest probability of 5%

*Leffler, Schuppan AJG 2010*

## Celiac Disease Diagnosis

**Necessary:**

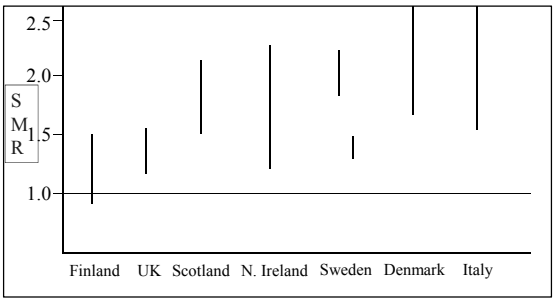
- Duodenal biopsy compatible with celiac AND one or both of the following:
  - Clinical or histological response to gluten-free diet
  - Positive CD-specific serology (tTG, EMA or DGP)

**Supportive**:

- HLA DQ2 or DQ8 (absence excludes CD)
- Biopsy proven dermatitis herpetiformis
- Family history of celiac disease

*Rostom A et al, Gastroenterology 2006;131:1981*
*("Amsterdam criteria"). Eur J Gastroenterol Hepatol 2001;13:1123*

## Mortality Risk in Celiac Disease




Ludvigsson *JAMA*. 2009, Grainge AJG 2011, Logan Gastro 1989, Nielsen Scand J Gastro 1985, Cottone DDS 1999, Corrao Lancet 2001, Peters Arch Int Med 2003, West BMJ 2004, Viljamaa DLD 2006, Anderson WJG 2007, Solaymani AJG 2007

## Case Study

Back to Heather:

38-year-old woman with IBS-type symptoms and mild chronic LFT elevations attributed to fatty liver on a gluten free diet and feeling well.

What is the best next step?

1. No further testing indicated as she is feeling well
2. Proceed with EGD and biopsy for celiac diagnosis
3. Test for IgA-tTG and HLA DQ2/DQ8
4. Advise an eight week gluten challenge followed by serologic testing and duodenal biopsy

## Gluten Elimination May Be Therapeutic but is Not Diagnostic

Wheat Allergy:

- Rare in adults, consider allergy testing

Gluten Intolerance:

- Functional symptoms related to gluten exposure without an immune response
- Up to 70% of patients with IBS will report improvement on a low gluten diet

Non-Responsive Celiac Disease

- 10% of people with celiac will not fully respond to a GFD

All serologic tests will normalize on a gluten free diet, so testing must be done on a normal diet!

*Leffler. CGH 2008, Biesiekierski AJG 2010, Wahnschaffe CGH 2007*

## Current Definitions

- Celiac disease is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.

vs.

- Non-Celiac Gluten Sensitivity (NCGS) relates to one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded.

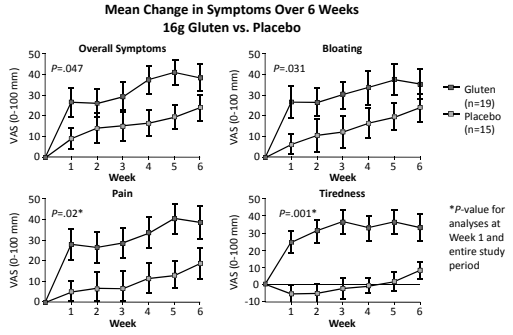
Ludvigsson J. Et al. GUT 2012.

## A Short History of NCGS

- Case reports since the 1970s and the first controlled study published in 1980.
- Interest really begins in last 5 years with increased interest in celiac disease and 'overflow' of the GFD into the general population

Cooper BT et al. *Gastroenterol*. 1980

## Gluten Exposure in Individuals without Celiac Disease reporting Gluten Responsive GI symptoms




VAS, visual analog scale.

Biesiekierski JR, et al. *Am J Gastroenterol*. 2011;106:508.

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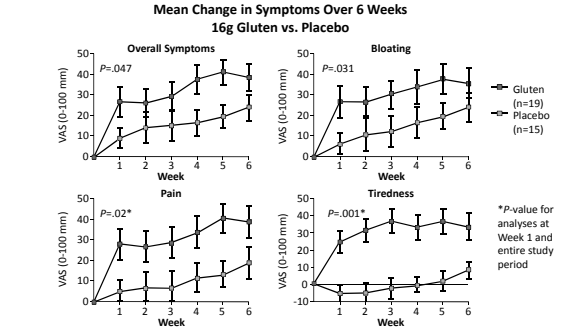


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## What are FODMAPs?

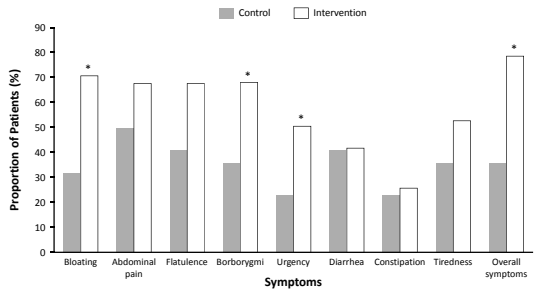
**Fermentable oligo-, di-, monosaccharides and polyols**

| | |
|---|---|
| **Excess Fructose** | Honey, apples, pears, peaches, mangos, fruit juice, dried fruit |
| **Fructans** | Wheat (large amounts), rye (large amounts), onions, leeks, zucchini |
| **Sorbitol** | Apricots, peaches, artificial sweeteners, artificially sweetened gums |
| **Lactose** | Milk, Cheese, Dairy |
| **Alcohols** | Cider, some wines |

Shepherd SJ, et al. *Clin Gastroenterol Hepatol.* 2008;6:765.
Shepherd SJ, Gibson PR. *J Am Diet Assoc.* 2006;106:1631.



## FODMAP Diet Reduces Symptoms: Randomized Trial in IBS

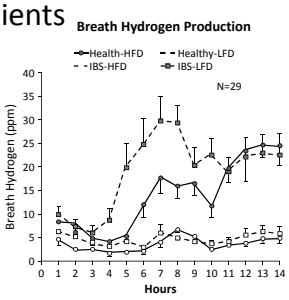



Saudacher HM, et al. *J Nutr*. 2012;142(8):1510.



## High FODMAP Diets Induce Increased Breath Hydrogen and Symptoms in IBS Patients

- Design
  - Single-blind crossover study in 15 healthy and 15 IBS patients
  - 2-day consumption of high-FODMAP diet (50 g/d) or low-FODMAP diet (9 g/d)
- Results
  - Higher levels of $H_2$ produced with high FODMAP diet
  - GI symptoms and lethargy induced by high FODMAP diet in IBS not control patients

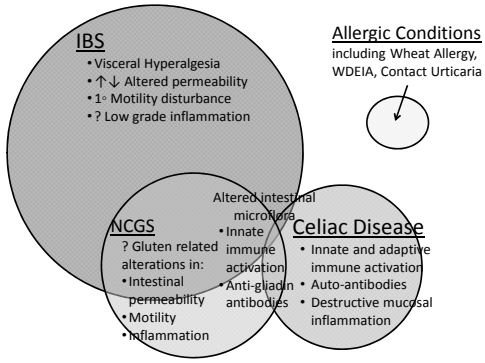



HFD, high-FODMAP diet; LFD, low-FODMAP diet.

Ong DK, et al. *J Gastroenterol Hepatol*. 2010;25:1366.



## Current Paradigm




## Case Study

Back to Heather:

- IgA tTG was 64 (Normal <20)
- Duodenal biopsy reveals patchy villous atrophy and celiac disease is confirmed

How should Heather be followed?

1. She should be recommended to see a celiac RD
2. She should have a DEXA to evaluate for low bone density
3. She should have IgA-tTG followed to ensure normalization
4. She should be assessed for nutritional deficiencies
5. All of the above

## Let Thy Food Be Thy Medicine

Hippocrates, 400 AD

- Strict gluten free diet is the only accepted treatment for celiac disease
- The GFD is one of the more challenging treatments we assign patients
- Involves avoidance of all wheat, rye and barley products
- Less than 50 mg of gluten (1/30th of a slice of bread) can cause significant, sustained mucosal inflammation
- Untreated celiac disease increases risk of malignancy, infection, and results in a 2-3 fold increase in mortality

## Nutritional Assessment in CD/GFD

| Nutrient | Prevalence | Testing | Treatment |
|---|---|---|---|
| Iron | Deficient in up to 50% | At diagnosis<br>Q3-6 months until normal<br>Q 1-2 years | Oral or IV iron depending on tolerance/severity |
| Vitamin D | Deficient in up to 65% | At diagnosis<br>Q3-6 months until normal<br>Q 1-2 years | Oral OTC<br>50,000 IU weekly for levels <20 |
| Zinc | Deficient in up to 50% | At diagnosis<br>Q3-6 months until normal<br>Q 1-2 years | 25-40 mg daily until normal |
| Fiber | Inadequate in up to 50% on GFD | Regular dietary assessment | 25-35 g/day based on age/gender |
| B12 | Deficient in up to 20% | At diagnosis<br>Q 1-2 years | If low consider SIBO<br>Oral sufficient |
| Folate | Rare in North America | Consider at diagnosis<br>Check prior to pregnancy | 1 mg/day |
| Calcium | Inadequate in up to 50% on GFD | Regular dietary assessment | 1500 mg/day |

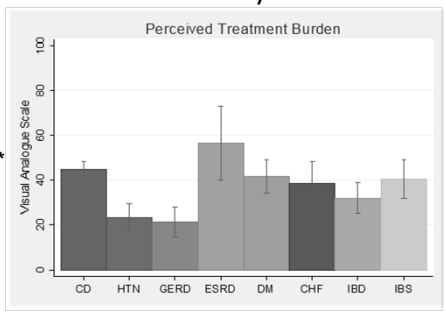
## Patient Satisfaction with the GFD is Low

- Controversial in the past
- Better scientific data and a more diverse celiac population → general acceptance

Sanders JGLD 2011

## Treatment Burden is also Second Only to Hemodialysis

VAS*



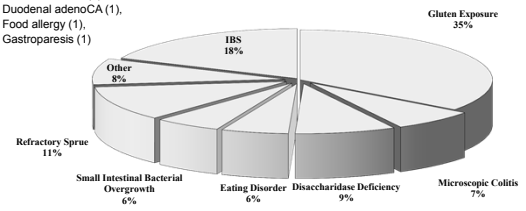

*VAS: 0=Very Easy
100=Very Difficult

Shah S, Leffler DA, AJG 2014

## "Non-Responsive" Celiac Disease

**Persistent or recurrent signs/symptoms occur in ~10-30% of patients**

Other included:
Peptic ulcer disease (2),
Crohn's disease (1),
Duodenal adenoCA (1),
Food allergy (1),
Gastroparesis (1)




Leffler et al. CGH 2006

## Current Recommendations for Celiac Monitoring

- Currently: No standard practice regarding need for and timing of clinical, serologic and histologic follow up
- Commonly recommended:
  - Clinical and serologic follow up Q3-6 months until normal than Q1-2 years
  - Histologic follow up: Consider at 1-2 years
  - DXA at least once

## Gluten Sensitivity Conclusions

- Gluten sensitivity appears to be common but true prevalence is unknown
- A significant but unknown portion of the IBS population without celiac disease responds well to gluten avoidance
- Durability and markers of response are unclear
- Pathogenesis is uncertain
- Lack of accepted diagnostic criteria hinder research and clinical diagnosis

## Celiac Disease Conclusions

- Diagnostic tools are excellent and diagnosis is improving
- IgA-tTG is the test of choice in most settings and should be considered in any patient with chronic unexplained symptoms or nutritional abnormalities
- The GFD is difficult and all patients should be referred to a skilled RD and/or a local/national advocacy organization
- All celiac patients should be followed to ensure normalization of tTG, nutritional levels and symptoms, and assessed for comorbid conditions including bone, thyroid and liver disease