Celiac Disease, Gluten Sensitivity or IBS?

William D. Chey, MD
University of Michigan
Ann Arbor, MI
Rome III Criteria for IBS

Recurrent abdominal pain or discomfort at least 3 days / month in the last 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Longstreth et al, *Gastroenterology* 2006; 130: 1480–91
IBS Subtypes Are Based on Stool Consistency

- IBS-C*: Percentage of loose or watery stools is 0-25, and percentage of hard or lumpy stools is 75-100.
- IBS-M: Percentage of loose or watery stools is 25-50, and percentage of hard or lumpy stools is 50-75.
- IBS-U: Percentage of loose or watery stools is 75-100, and percentage of hard or lumpy stools is 0-25.
- IBS-D†: Percentage of loose or watery stools is 25-50, and percentage of hard or lumpy stools is 50-75.

* Bristol Stool Form Scale 1-2
† Bristol Stool Form Scale 6-7

IBS-M = IBS-mixed
IBS-U = unclassified IBS

Adapted from Longstreth GF, et al. *Gastroenterology.* 2006;130:1480-1491
Celiac Disease (CD): Definition

- Chronic immune-mediated disease in genetically susceptible individuals
- Environmental precipitant—gliadin (toxic fraction of gluten protein)
  - Found in wheat, rye, barley
- Improvement with gluten withdrawal
- Clinical manifestations are variable
Definitions of Celiac Disease

• **Classic:** features of malabsorption, fully developed villous atrophy, GI symptoms

• **Atypical:** no GI symptoms but evaluated for Fe def anemia, short stature, osteoporosis, etc.

• **Silent:** no symptoms, no features or complications; found incidentally

• **Latent:** CD pts who responded to a GFD and have normal histology, OR pts with normal histology now on a gluten diet but who will go on to develop CD

### Which Test for Celiac Disease?

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigliadin IgG</td>
<td>69–85</td>
<td>73–90</td>
</tr>
<tr>
<td>Antigliadin IgA</td>
<td>75–90</td>
<td>82–90</td>
</tr>
<tr>
<td>EMA</td>
<td>85–98</td>
<td>97–100</td>
</tr>
<tr>
<td>IgA tTG - Human</td>
<td>93–96</td>
<td>99–100</td>
</tr>
<tr>
<td></td>
<td>95–98</td>
<td>94–97</td>
</tr>
</tbody>
</table>

Abdulkarim and Murray. Aliment Pharm Ther. 2003;17:987-95
Marsh Lesions

I  II  IIIa  IIIb  IIIc

Symptoms

- Few or no symptoms
- Little malabsorption
- No villous atrophy
- Little crypt hyperplasia
- Increased IELs
- Minimal malabsorption
- Partial villous atrophy
- Some crypt hyperplasia
- Increased IELs
- Extensive malabsorption
- Complete villous atrophy
- Marked crypt hyperplasia
- Increased IELs
IgA tTG testing to Diagnose Celiac Disease in Clinical Practice

- 122 pts from Columbia with suspected CD who had tTG and EGD with biopsies
  - 102 pts diagnosed with CD
  - CD pts divided as classic or silent by symptoms and by degree of villous atrophy

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>70.6%</td>
<td>65%</td>
<td>91.1%</td>
<td>30.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Villous atrophy</strong></td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Partial VA</strong></td>
<td>42.3%</td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Lab 1</strong></td>
<td>40%</td>
<td>100%</td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Lab 2</strong></td>
<td>86.4%</td>
<td>41.7%</td>
<td></td>
<td></td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Abrams, et al. CGH 2006;4:726-30
Genetic Testing for Celiac Sprue

- Human leukocyte antigen (HLA) alleles associated with celiac disease
  - DQ2 found in 95% of celiac patients
  - DQ8 found in remaining patients
  - 30% of the Caucasians carry DQ2 or DQ8
- Genetic testing is sensitive but not specific
- High negative predictive value to rule out celiac disease
  - Negative DQ2/DQ8 excludes celiac disease with 99% confidence

What Role Does Celiac Sprue Play in IBS?
Pretest Probability of Organic Disease

<table>
<thead>
<tr>
<th>Organic GI Disease</th>
<th>IBS Patients (Pretest Probability %)</th>
<th>General Population (Prevalence %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis / IBD</td>
<td>0.51-0.98</td>
<td>0.3-1.2</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0-0.51</td>
<td>0-6</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>0-1.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>4.2</td>
<td>5-9</td>
</tr>
<tr>
<td>Lactose malabsorption</td>
<td>38</td>
<td>26</td>
</tr>
</tbody>
</table>
Biopsy Proven Celiac Disease in IBS vs. Controls: Results from a Meta-analysis

Odds ratio meta-analysis plot [random effects]

- Sanders 2001: 7.29 (1.65, 66.52)
- Sanders 2003: 4.49 (0.97, 17.03)
- Shahbazkhani 2003: 28.23 (1.90, 578.67)
- Chey 2007: 1.52 (0.22, 16.93)
- Ozdil 2008: 0.67 (0.00, 26.11)
- Combined [random]: 4.34 (1.78, 10.58)

Odds ratio (95% confidence interval)
• Celiac disease prevalence roughly 1% among IBS patients in 2 U.S. studies
• Screening is cost-effective if prevalence is greater than 1%

Cash BD and Chey WD, unpublished data.
Is it Cost-effective to Screen for Celiac Sprue in IBS?

- Decision analytic model assessed the cost-effectiveness of celiac testing vs. empiric IBS therapy in pts with suspected IBS
- Testing cost an incremental $11K for one additional symptomatic improvement
  - ICER >$50K when prevalence of CS<1%
  - Testing dominant when prevalence of CS>8%
- Factors affecting the decision to test:
  - Prevalence of CS, test accuracy, cost of IBS therapy, likelihood that symptoms improve on a gluten-free diet

Speigel, et al. Gastroenterol 2004;126:1721
Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B recommendation)
Is it IBS, Celiac Sprue or Gluten Sensitivity or Something Else?
Is it IBS, Celiac Disease or Something in Between?

Gluten Sensitivity

IBS-like Symptoms
- IBS
- Lactose Intolerance
- Food Intolerance
- Altered Gut Microbiome

Spectrum of CD
- Potential CD
- Latent CD
- CD and Complications

Gluten Sensitivity

• Encompasses a collection of medical conditions in which gluten has an adverse effect
  – Gluten sensitive diarrhea
  – Positive celiac serology with normal genetic testing and normal small bowel histology
  – Subtle histological abnormalities after gluten exposure with normal serology and genetics
• Can be clinically indistinguishable from celiac sprue but testing is often negative or inconclusive
• Improves with a gluten free diet
8/10 patients with GI symptoms and minimal mucosal lesions (Marsh I or II) had improved symptoms and histology on a gluten-free diet

12/28 patients with IELs had a symptomatic response to a gluten-free diet

Pts with negative TTG antibodies were shown to have a mucosal lymphocytic infiltrate after a gluten challenge
### Diagnostic Testing in Suspected IBS: A US Multi-center Trial

- 492 IBS by Rome II vs. 458 controls
- 6.3% diagnosed with organic disease

<table>
<thead>
<tr>
<th></th>
<th>IBS</th>
<th>Controls</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD-Antibodies</td>
<td>7.3%</td>
<td>4.8%</td>
<td>0.11</td>
</tr>
<tr>
<td>CD-Biopsy proven</td>
<td>1.2%</td>
<td>0.4%</td>
<td>0.28</td>
</tr>
<tr>
<td>IBD serologies</td>
<td>25%</td>
<td>31%</td>
<td>0.05</td>
</tr>
<tr>
<td>Lactase non-persistence</td>
<td>23.2%</td>
<td>25.8%</td>
<td>0.35</td>
</tr>
</tbody>
</table>

IgG Celiac Abs & HLA DQ2 in Celiac Disease, d-IBS, & IBD

IBS-D by Rome II (IELs allowed on bx)
Wanschaffe et al. CGH 2007;5:844

* p=0.05 vs. IBD
Symptom Normalization in D-IBS after a Gluten Free Diet

Wanschaffe et al. CGH 2007;5:844
• 70 pts with +EMA Abs (referred for “any suspicion of CD”)
• 23/70 had Marsh I/II lesions randomized to regular or gluten free diet
• Patient with Marsh III/IV treated with a GFD
• Patients reevaluated at 1 year

Conclusion:

• **Patients with EMA antibodies benefit from a GFD regardless of degree of enteropathy.** The diagnostic criteria for CD need re-evaluation: EMA+ without atrophy belongs to the spectrum of genetic gluten intolerance and warrants dietary treatment.
Food Hypersensitivity in IBS

- Blood from 120 IBS pts (Rome II) analyzed for:
  - Activation of basophils by food allergens (flow cytometry)
  - Total & food specific IgE

- Pts completed a FH questionnaire and underwent open elimination diet x 4 wks
  - Milk, wheat, egg, tomato, chocolate

- Responders went on to DBPC food challenges
  - Milk/placebo (2 wks) followed by wheat/placebo proteins (2 wks)
• 36% improved with the open elimination diet

• 20% of IBS pts had FH to milk and/or wheat proteins by DBPC food challenges
  – 16% both, 3% milk, 2% wheat
  – Problems appeared after median 3 days
  – 50% had to discontinue food challenge related to symptoms

• Pts overestimated and underestimated FH
  – 12/32 (38%) reporting FH improved with DBPC food challenge
  – Some pts who did not report FH improved with food challenges
  – Basophil activation by FC was >85% accurate for FH
What are FODMAPs?

• Fermentable oligo-, di-, monosaccharides and polyols
• Fruits with fructose exceeding glucose
  – Apples, pears, watermelon
• Fructan containing vegetables
  – Onions, leeks, asparagus, artichokes
• Wheat based products
  – Bread, pasta, cereal, cake, biscuits
• Sorbitol and lactose containing foods
• Raffinose containing foods
  – Legumes, lentils, cabbage, brussels sprouts

Gibson & Shepherd. J Gastro Hepatol 2010;25:252
Fructose and Fructans As Dietary Triggers for IBS symptoms

25 IBS pts with fructose malabsorption who improved with a FODMAP diet

- Glucose
- Fructose
- Fructans
- Both

p<0.002 vs glucose
4 way randomly assigned X-over
2 weeks of each diet with 10d washout

Effect of Gluten on Symptoms in IBS Patients

Overall Symptoms

* * P = 0.001

Gluten
N = 19

Placebo
N = 15

VAS Score: 0 = None
100 = Worst

IBS by Rome III
Improved on GFD
Negative for Celiac Dz
No Δ celiac serologies, permeability, CRP

Effect of Gluten on Fatigue in IBS Patients


Tiredness

VAS (0-100 mm)

-10 0 10 20 30 40 50

* P = 0.001

Gluten Placebo
N = 19 N = 15

VAS Score: 0 = None
100 = Worst

IBS by Rome III
Improved on GFD
Negative for Celiac Dz
Patients with IBS-like Symptoms

Celiac Ab positive
Marsh I/II

Gluten Free Diet

Celiac Ab (-) & Marsh I/II
Or
Celiac Ab (+) & Normal Histology

Genotype Analysis

Positive
Negative

GFD trial

Consider Rebiopsy In 3-6 months
Investigate other causes


<table>
<thead>
<tr>
<th>Symptom</th>
<th>LD</th>
<th>HLA type</th>
<th>Serology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Trial of GFD</td>
</tr>
<tr>
<td>IBS</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Consider other cause</td>
</tr>
<tr>
<td>IBS</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Consider GFD</td>
</tr>
<tr>
<td>IBS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treat IBS</td>
</tr>
</tbody>
</table>

GFD, gluten-free diet; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; LD, lymphocytic duodenosis.
Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B recommendation)
- Role in IBS-C?
- TtG and EMA are very specific
- Sensitivity reduced in pts with Marsh I/II lesions

Gluten sensitivity remains controversial but is likely more common than Celiac Sprue
- Many pts with (+) serology (TtG or gliadin Ab) but (-) small bowel bxs will improve with a gluten free diet
- A subset of IBS sufferers with no evidence of celiac disease will improve on a gluten free diet