Celiac Disease, Non-celiac Gluten Sensitivity, Wheat Intolerance: What’s a Clinician to do?

William D. Chey, MD
Professor of Medicine
University of Michigan
Ann Arbor, MI
Objectives

• Describe the similarities and differences between celiac disease and IBS, including the role of celiac testing in patients with IBS-like symptoms

• Identify the potential causes of non-celiac gluten sensitivity

• Describe the role of dietary modification in managing IBS symptoms
How often does Celiac Disease Overlap with IBS?
<table>
<thead>
<tr>
<th>Event</th>
<th>IBS Patients, %</th>
<th>General Population, %</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 (varies with age)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>4.2</td>
<td>5-9</td>
</tr>
<tr>
<td>GI infection</td>
<td>0-1.5</td>
<td>NA</td>
</tr>
<tr>
<td>Celiac sprue</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>38</td>
<td>26</td>
</tr>
</tbody>
</table>

IBS and Celiac Disease (bx proven): 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)

IBS and Celiac Disease: US Data

- Celiac disease prevalence roughly ≤1% among IBS patients in 2 U.S. studies
- Screening is cost-effective if prevalence is greater than 1%

EMA=anti-endomysium
Cash BD and Chey WD. Gastroenterology, 2011;141:1187-1193.
Is it cost-effective to screen for Celiac Sprue (CS) in IBS?

• Decision analytic model assessed the cost-effectiveness of celiac testing vs empiric IBS therapy in patients with suspected IBS

• Testing cost an incremental $11K for one additional symptomatic improvement
  – ICER $\geq 50K$ 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

ICER=incremental cost-effectiveness ratio
What about “Non-Celiac Gluten Sensitivity”?
Is it IBS, Celiac Disease (CD), or Something in-between?

Non-Celiac Gluten Sensitivity

IBS symptoms
- Motility/visceral Sensation
- Brain-gut Interactions
- Immune activation
- Altered gut microbiome

Spectrum of CD
- Latent/asymptomatic CD
- Symptomatic CD
- Refractory CD (types I&II)

Non-Celiac Gluten Sensitivity

- Gluten sensitivity
- Gluten hypersensitivity
- Gluten intolerance

Non-Celiac Gluten Sensitivity

- Gluten sensitivity
- Gluten hypersensitivity
- Gluten intolerance
- Non-Celiac gluten intolerance
- Wheat intolerance??

Non-Celiac Gluten Sensitivity (NCGS)

- Up to 10% of the general population reports symptoms when ingesting gluten
- NCGS vs. wheat intolerance
- Encompasses a collection of medical conditions in which gluten leads to an adverse effect
  - Not associated with increased intestinal permeability
  - Innate immunity markers TLR2 & FOXP3 altered in gluten sensitivity but not celiac disease
- Improves with a gluten free diet

Possible Causes of NCGS

- Nocebo effect
- Opioid-like activity
- IgE mediated wheat allergy
- Innate immune reaction to gluten
- Starch/CHO Malabsorption
- Low grade inflammation

NCGS=non-celiac gluten sensitivity
### Celiac Testing in Suspected IBS: A US Multi-center Trial


<table>
<thead>
<tr>
<th>Test</th>
<th>Suspected IBS (n=492), n(%)</th>
<th>Healthy controls (n=458), n(%)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bx proven celiac disease</td>
<td>2 (0.04)</td>
<td>2 (0.04)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Any abnormal celiac disease test</td>
<td>36 (7.32)</td>
<td>22 (4.8)</td>
<td>0.25</td>
<td>1.49 (0.76, 2.90)</td>
</tr>
<tr>
<td>AGA IgG</td>
<td>24 (4.88)</td>
<td>14 (3.06)</td>
<td>0.70</td>
<td>1.19 (0.5, 2.79)</td>
</tr>
<tr>
<td>AGA IgA</td>
<td>8 (1.63)</td>
<td>8 (1.75)</td>
<td>0.54</td>
<td>1.41 (0.47, 4.22)</td>
</tr>
<tr>
<td>EMA</td>
<td>3 (0.61)</td>
<td>2 (0.44)</td>
<td>0.66</td>
<td>1.65 (0.17, 15.42)</td>
</tr>
<tr>
<td>TTG IgA</td>
<td>6 (1.22)</td>
<td>2 (0.44)</td>
<td>0.15</td>
<td>2.79 (0.61, 24.7)</td>
</tr>
<tr>
<td>DQ2</td>
<td>164 (33.33)</td>
<td>180 (39.30)</td>
<td>0.004</td>
<td>0.61 (0.44, 0.86)</td>
</tr>
<tr>
<td>DQ8</td>
<td>81 (16.46)</td>
<td>83 (18.12)</td>
<td>0.54</td>
<td>1.14 (0.76, 1.70)</td>
</tr>
</tbody>
</table>
IgG Celiac Antibodies & HLA DQ2 in Celiac Disease, IBS-D, & IBD

IBS-D by Rome II

*P = .05 vs. IBD
Symptom Normalization in IBS-D after a Gluten Free Diet

IBS-D by Rome II
Blood from 120 IBS patients (Rome II) analyzed for:

- Activation of basophils by food allergens (flow cytometry)
- Total and food-specific IgE

Patients completed a food hypersensitivity questionnaire and underwent open elimination diet x 4 weeks

- Milk, wheat, egg, tomato, chocolate

Responders went on to double-blind placebo controlled food challenges

- Milk/placebo (2 wks) followed by wheat/placebo proteins (2 wks)

Food Hypersensitivity in IBS

- 36% improved with the open-elimination diet
- 20% of IBS patients had food hypersensitivity to milk and/or wheat proteins by double-blind, placebo controlled food challenges
  - 16% both, 3% milk, 2% wheat
  - Problems appeared after median 3 days
  - 50% had to discontinue food challenge related to symptoms
- Patients overestimated and underestimated food hypersensitivity
  - 12/32 (38%) reporting food hypersensitivity improved with double-blind, placebo controlled food challenge
  - Some patients who did not report food hypersensitivity improved with food challenges
  - Basophil activation by flow cytometry (FC) was >85% accurate for food hypersensitivity

FC = Flow cytometry
Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B recommendation).

- TtG and EMA are very specific.
- Sensitivity reduced in pts with partial villous atrophy or intraepithelial lymphocytosis.
- Many patients with a positive celiac serology (TtG or anti-gliadin antibodies) but normal small bowel biopsies will still improve on a gluten free diet.
- Role of anti-gliadin antibodies to identify nonceliac gluten sensitivity?
### Proposed Management of Patients with IBS Symptoms and Possible Celiac Sprue

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Serology</th>
<th>LD</th>
<th>HLA</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>GFD or follow</td>
</tr>
<tr>
<td>IBS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treat IBS Trial of GFD?</td>
</tr>
</tbody>
</table>

GFD, gluten-free diet; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; LD, lymphocytic duodenosis
Does a Gluten-free Diet Improve IBS Symptoms?
Gluten Free: More than a fad?

• Euromonitor International forecasts:
  – Sales have more than doubled since 2005
  – 2011 = $1.31 billion US, $2.67 billion worldwide
  – 2015 = $1.68 billion US, $3.38 billion worldwide

  – Big Industry is buying in:
    • General Mills: Chex cereal
    • Betty Crocker: Cake & brownie mixes, Bisquick
    • Anheuser Busch: Gluten free REDBRIDGE beer
    • PF Changs & Subway
Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean Change in Symptoms Over 6 Weeks

*P-value for analyses at Week 1 and entire study period.
Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean Change in Symptoms Over 6 Weeks

*P-value for analyses at Week 1 and entire study period.
Outcomes of IBS Patients after 4 Weeks of an Elimination Diet and Double Blind Food Challenge

160 IBS patients (Rome II)

90 patients with unchanged or worsened symptoms on elimination diet (IBS unrelated to FH)

70 patients with improved symptoms on elimination diet

40 patients with positive DBPC (FH patients)

30 patients with negative DBPC (IBS unrelated to FH)

30 DBPC positive for both cow’s milk and wheat proteins

6 DBPC positive for cow’s milk proteins

4 DBPC positive for wheat proteins

4 week Elimination Diet: cow’s milk, wheat, egg, tomato, and chocolate

DBPC challenge: 2 wks of cow’s milk or wheat proteins

DBPC=double-blind, placebo-controlled; FH=food hypersensitivity

Outcomes of IBS Patients After 4 Weeks of an Open Elimination Diet

Open elimination diet: cow’s milk, wheat, egg, tomato, and chocolate

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

Low FODMAP vs. Standard Diet for IBS

FODMAP n=43 (after 6/09)
Standard diet n=39 (before 6/09)
Consecutive IBS pts (NICE) from London

Patients with IBS-D/M should be screened for celiac disease

- Expected US prevalence in IBS patients is ≤1% but likely varies based upon population genetics

Non-celiac gluten sensitivity is a symptom-based disorder of heterogeneous pathogenesis

NCGS is likely to be much more common than celiac disease

Nomenclature, diagnostic criteria and biomarkers are needed

Mounting evidence suggests that a gluten-free diet may offer benefits to patients with IBS symptoms

Summary
877.462.6935
Functional Bowel Disorders Clinic
888-229-7408