Celiac Disease and Non-celiac Wheat Intolerance

William D. Chey, MD
Professor of Medicine
University of Michigan

Proposed New Criteria for CD Diagnosis

“Four out of five” sufficient to diagnose CD?

- Typical symptoms of CD
- High titer of serum CD IgA class autoantibodies
- HLA-DQ2 and/or HLA-DQ8 genotypes
- Celiac enteropathy by small bowel biopsy
- Response to a GFD

IMPORTANT:
- This proposal remains controversial among other experts in the field
- ESPGHAN has developed similar criteria to diagnose children with CD without biopsies

ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
What is Gluten Sensitivity?

Oslo Definitions

<table>
<thead>
<tr>
<th>Gluten Sensitivity Due to Celiac Disease (CD)</th>
<th>A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Celiac Gluten Sensitivity (NCGS)</td>
<td>One or more immunological, morphological and/or symptomatic alterations triggered by gluten ingestion in individuals in whom celiac disease has been excluded</td>
</tr>
</tbody>
</table>


GFD = gluten-free diet

Changing Prevalence of Celiac Disease (CD)

- Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study
- **Less than 10-15% of current cases of CD have been diagnosed in the US**
- **CD is 4 to 4.5 times more prevalent than 50 yrs ago**
- Cause of "CD epidemic" unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental factors
  - Microbiota

Vita et al, Scand J Gastroenterol, 44:933, 2009
Rubio-Tapia, Am J Gastroenterol, 2012
Celiac Disease
Changes to Intestinal Mucosa

- Inflammation reaction targets mucosa of small intestine, leading to crypt hyperplasia and villous atrophy
- Net results are impaired nutrient absorption and increased water and solute secretion

Other disorders that can cause villous atrophy

- Bacterial overgrowth
- Tropical Sprue
- Peptic duodenitis
- Autoimmune enteropathy
- Lymphocytic enterocolitis
- Crohn’s disease
- Lymphoma

Celiac Disease Pathogenesis

Genetics → Gluten

NECESSARY CAUSES

Gender?
Infant feeding
Infections
Others

RISK FACTORS

Pathogenesis

Celiac Disease

Good and Bad (for CD) Grains – Increasing Consumption of Wheat Worldwide

Bad
Wheat
Barley
Spelt
Bulgur

Rye
Triticale
Kamut
Couscous

Good
Rice
Corn
Tapioca
Arrowroot
Buckwheat
Oats
Potato
Soybean
Sorghum

ACG Regional Postgraduate Course - St. Louis, MO
Copyright 2013 American College of Gastroenterology
Changing Picture of Celiac Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many patients are overweight
- Seroprevalence Male=Female; Diagnosis M<F
- Other presentations are being increasingly recognized:
  - Obstetrical problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?

The Celiac Iceberg

“Atypical is typical:” 50% of newly diagnosed celiac patients present with atypical symptoms
Common Symptoms in Celiac Disease

- Altered bowel habits
  - Diarrhea, constipation and mixed pattern
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
  - However patients with CD can be overweight and even obese
- Abdominal distention or bloating
- Note that there are many other presentations of celiac disease including an asymptomatic state


Symptoms and Conditions That Should Prompt Consideration of Celiac Disease

- GI symptoms
- First and second degree relatives
- Autoimmune connective tissue disorders
- Autoimmune endocrine disorders
- Extraintestinal presentations
- Miscellaneous conditions
- Hepatobiliary conditions

Crowe, SE. In The Clinic: Celiac Disease, Ann Int Med. 154:ITC5-14, 2011
Celiac Disease: Asymptomatic and Potential Forms

These forms are often found in first- or second-degree relatives of patients with biopsy proven celiac disease or in those with CD-associated diseases (DH, autoimmune conditions) and all have HLA DQ susceptibility genes

- **Asymptomatic, Subclinical or Silent CD**
  - No or imperceptible symptoms
- **Potential or Latent CD**
  - Have positive serology but negative small bowel biopsies who are at increased risk of developing CD
- **Genetically at risk of CD**
  - Family members of patients with CD

HLA DQ = DQ locus of the human leukocyte antigen; DH = dermatitis herpetiformis

What are the Best Serologic Tests for Screening for CD?

- Depends on prevalence and age of population
- Overall, TTG IgA is the recommended test to screen for disease but sensitivity varies with lower levels (≤90%) reported in routine practice
- **1 in 10 false negative rate for TTG IgA (not all attributable to IgA deficiency)**
- Check total IgA for assays with narrow range of normal
- EMA IgA is helpful when positive
- TTG, EMA less sensitive for milder histologic stages
- Antibodies to GDP are less sensitive than to TTG
- **Intestinal biopsies remain the gold standard**

TTG IgA = tissue transglutaminase antibody; EMA = anti-endomysial antibodies
Role of HLA DQ Testing in Determining Likelihood of CD Now or in the Future

- DR3-DQ2 or DR5/7-DQ2 – 90-95% of those with CD
- DR4-DQ8 – 5-10% form the rest
- Only HLA DQ2 or DQ8 positive subjects are at risk for getting CD
- Necessary but not sufficient

HLA DQ = DQ locus of the human leukocyte antigen
NPV = negative predictive value

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; absence excludes celiac disease but not NCGS

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

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

- Depends of duration and stringency of GFD
  - If truly on a GFD for years, it is difficult to prove CD
  - Most patients on a self-taught GFD are not highly gluten-free
- Serology can take over a year to normalize
- Histology can take years to become normal
- If an undiagnosed patient wants assessment for CD recommend assessing with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD
- Absence of HLA DQ2, 2.5 or 8 effectively excludes CD now or in the future

EGD = esophagogastroduodenoscopy

Sugal, E, et al, Digestive & Liver Disease, 42:352, 2010
Crowe, SE. In The Clinic : Celiac Disease, Ann Int Med,2011
154(1T):6-14

Effects of a 14 day gluten challenge in patients with Celiac Disease in remission


N = 20
Causes of diarrhea in Celiacs on a Gluten-free diet

- 62/78 (79%) with celiac disease had diarrhea before a gluten-free diet
- 13 (17%) had diarrhea after treatment
- Causes of diarrhea included:
  - microscopic colitis,
  - pancreatic insufficiency,
  - lactose/fructose malabsorption,
  - anal sphincter dysfunction,
  - IBS
  - bacterial overgrowth

Fine Gastroenterol 1997;112:1830
IBS and Celiac Disease (Biopsy Proven): Results from a Meta-analysis

Prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS was more than 4-fold that in controls without IBS


IBS and Celiac Disease: US Data

Case-control study
- IBS patients (physician diagnosis)
- Positive for both tTGA and EMA
- Celiac disease not biopsy-proven

Prospective study
- Non-constipated IBS patients (Rome II)
- Biopsy-proven celiac disease

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. Gastroenterol, 2011;141:1187
Is it Cost-effective to Screen for Celiac Disease 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 greater than $50,000 when the prevalence of CD<1%
  - Testing for CD became the dominant strategy when the prevalence of CD>8%
- Factors affecting the decision to test:
  - Prevalence of CD, test accuracy, cost of IBS therapy, likelihood that symptoms improve on a gluten-free diet.

ICER = incremental cost-effectiveness ratio

Speigel, et al. Gastroenterol 2004;126:1721
Ladabaum et al, Aliment Pharmacol Ther 2004; 19:1199

Between Celiac Disease & IBS: The “No Man’s Land” of Gluten Sensitivity

Is it IBS, Celiac Disease or Something in Between?

Non-celiac Gluten Sensitivity

Non-celiac Gluten Sensitivity

Spectrum of CD

Mobility / visceral sensation
Brain - gut interactions
Immune activation
Altered gut microbiome

Potential / asymptomatic CD
Symptomatic CD

Adapted from Verde SF, et al. Am J Gastroenterol 2009; 104:794
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

Non-Celiac Gluten Sensitivity (NCGS) or Wheat Intolerance?

- Not a new entity, reported in 1980
- Prevalence unknown, probably greater than celiac disease, but no data
- Varies from 0.548% (NHANES) to 30% of US!!
- Studies reporting prevalence reflect referral bias
- Currently no specific criteria or validated tests for diagnosing NCGS!!
- Cannot differentiate between intolerance of gluten, wheat starch or other causes of wheat intolerance/sensitivity
- Reported in association with allergic diseases

Casper, BT, et al., Gastroenterol, 79; 801, 1980
Proposed mechanisms of Non-celiac Wheat Sensitivity

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

GI Symptoms

Adapted from Eswaran S, et al. Gastroenterol Hepatol 2013;9:85
Vazquez-Roque MI, et al. Gastroenterology 2013;144:903

Mean BMs per day in IBS-D patients on Gluten Free and Gluten Containing Diets

N=45 pts with IBS-D

Effect of a Gluten-free Diet on Small Intestinal & Colonic Permeability in IBS-D

Cumulative Mannitol Excretion


In Vitro Cytokine Production by PBMCs in Response to Rice or Gluten in IBS-D

Are *Wheat Intolerance* symptoms from Gluten or FODMAPs?

- 37 pts with NCWS and IBS
- **Interventions:**
  - All pts received a low FODMAP diet for 2 weeks
  - Then assigned to high gluten (16 g/d), low gluten (2 g/d), or control (16 g whey/d) x 1 week
  - Serum and fecal biomarkers for intestinal inflammation/injury and immune activation
- No significant changes in biomarkers with diets
- FODMAP restriction led to symptom improvement
- No specific or dose dependent effects of gluten in patients on a low FODMAP diet were observed

*Biesiekierski JA et al Gastroenterol 2013;online early 6/19/13*

**IBS Patients: 4 Weeks of an Elimination Diet and 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

Patient characteristics according to the dietary treatment group

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Gluten</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Median age (range) in years</td>
<td>40 (29-55)</td>
<td>49 (33-51)</td>
</tr>
<tr>
<td>Men</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Median body mass index range (range)</td>
<td>23 (18-41)</td>
<td>22 (18-33)</td>
</tr>
<tr>
<td>Number with predominant bowel habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation in percentage</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea in percentage</td>
<td>58</td>
<td>33</td>
</tr>
<tr>
<td>Alternating percentage</td>
<td>26</td>
<td>47</td>
</tr>
</tbody>
</table>

**HLA Type**

- DQ2 or DQ8 positive in percentage | 53 | 60 |
- DQ negative in percentage | 47 | 40 |

HLA, human leukocyte antigen.
There were no significant differences between dietary groups for any index (independent samples t-test and \( \chi^2 \) test).

---

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
- Pain: P = 0.02

Proposed Management of Patients with IBS Symptoms and Possible Celiac Sprue

<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>Trials 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.

Summary of CD, NCGS and Other Intolerances to Wheat

- Celiac disease is not rare (1 in 100-300)
- CD can coexist with or mimic IBS and other FGID
- Increased reporting of NCGS
- True prevalence of NCGS is unknown
- Cannot clinically differentiate NCGS and CD
- Gluten-free diet remains the mainstay of therapy for both conditions
- How wheat intolerance contributes to functional GI disorders remains unclear but multiple mechanisms implicated
Proposed Approach to Patients Reporting Adverse GI Reactions to Eating Wheat

Boettcher, E, & Crowe, SE. Am J Gastroenterol. 2013