Celiac disease: Protean Manifestations

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Celiac Disease: Pop quiz

True or False?

Celiac disease is:

1. An uncommon condition in the US (~1:5000) that is more common in Europe (~1:500)  **False**

2. Usually presents with severe diarrhea and malabsorption **False**

3. Usually a pediatric diagnosis  **False**

4. Diagnosed by clinical improvement following treatment with gluten free diet  **False**
Prevalence of celiac disease by continent

Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis.
Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis.
During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, Annal Med (on line ahead of print)
Celiac Disease: Age of presentation

- Classically after weaning
  - Peak #1: 4 to 7 years
- Symptoms often improve during adolescence
  - Celiac “honeymoon”
- Can present for the first time at any age
  - Most common - Peak #2: 30 to 50 years
  - BIDMC means:
    - 46 years - age at diagnosis
    - 11 years – interval from symptom onset to diagnosis
    - 6 years - interval from presentation to diagnosis
The protean clinical manifestations of celiac disease

Can presenting at any age to any medical specialty

**Table 1. The Spectrum of Clinical Presentations of Celiac Sprue.**

<table>
<thead>
<tr>
<th>COMMON FEATURES</th>
<th>LESS COMMON FEATURES</th>
<th>ASSOCIATED CONDITIONS</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>General features</td>
<td>Definite associations</td>
<td>Refractory sprue</td>
</tr>
<tr>
<td>Iron-deficiency anemia</td>
<td>Short stature</td>
<td>Dermatitis herpetiformis</td>
<td>Enteropathy-associated T-cell</td>
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<tr>
<td>Diarrhea</td>
<td>Delayed puberty</td>
<td>IgA deficiency</td>
<td>lymphoma</td>
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<tr>
<td>Children</td>
<td>Gastrointestinal features</td>
<td>Type 1 diabetes</td>
<td>Carcinoma of the oropharynx, esophagus, and small bowel</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Recurrent aphthous stomatitis</td>
<td>Autoimmune thyroid disease</td>
<td>Ulcerative jejunoileitis</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Recurrent abdominal pain</td>
<td>Sjogren’s syndrome</td>
<td>Collagenous sprue</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>Steatorrhea</td>
<td>Microscopic colitis</td>
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<td></td>
<td>Extraintestinal features</td>
<td>Rheumatoid arthritis</td>
<td></td>
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<td></td>
<td>Folate-deficiency anemia</td>
<td>Down’s syndrome</td>
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<tr>
<td></td>
<td>Osteopenia or osteoporosis</td>
<td>IgA nephropathy</td>
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<td></td>
<td>Dental enamel hypoplasia</td>
<td>Possible associations</td>
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<td>Vitamin K deficiency</td>
<td>Congenital heart disease</td>
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<td>Hypertransamminasemia</td>
<td>Recurrent pericarditis</td>
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<td>Thrombocytosis (hypoplenism)</td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>Arthralgia or arthropathy</td>
<td>Cystic fibrosis</td>
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<td></td>
<td>Polyneuropathy</td>
<td>Fibrosing alveolitis</td>
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<td></td>
<td>Ataxia</td>
<td>Lung cavities</td>
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<td></td>
<td>Epilepsy (with or without cerebral calcification)</td>
<td>Pulmonary hemosiderosis</td>
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<td></td>
<td>Infertility</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td></td>
<td>Recurrent abortions</td>
<td>Autoimmune hepatitis</td>
<td></td>
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<td></td>
<td>Anxiety and depression</td>
<td>Primary biliary cirrhosis</td>
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<td></td>
<td>Follicular keratosis</td>
<td>Addison’s disease</td>
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<td>Vasculitis</td>
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<td></td>
<td>Polymyositis</td>
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<tr>
<td></td>
<td></td>
<td>Myasthenia gravis</td>
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<tr>
<td></td>
<td></td>
<td>Schizophrenia</td>
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</tr>
</tbody>
</table>

The clinical spectrum of Celiac Disease

- Genetic susceptibility (HLA DQ2 or DQ8)
  - Healthy individual
  - ~40%
  - ~0.1%
- Mucosal abnormality
  - IgA TTG positive
  - ~1%
  - ~0.1%
- "Potential CD"
- "Atypical" CD
  - ~0.5%
  - ~0.1%
- Silent CD
  - ~0.4%
- Classical CD

The celiac "iceberg"
Diversity of celiac disease:
Global, multiple symptoms, any age

- **Who?**
  - Common in many ethnic backgrounds

- **When?**
  - Any age after gluten ingestion
  - Average age at diagnosis ~45 yrs

- **How?**
  - Highly diverse presentations.
  - Average 11 years of symptoms prior to diagnosis

Celiac Disease Foundation

Green AJG 2001, Cranney DDS 2007
Who to test for celiac disease

Diarrhea +/- malabsorption
- IBS-like (especially D-IBS)
- Lactose (or fructose) Intolerance-like
  but not responding fully to dietary measures

Nutritional deficiencies
- Iron deficiency anemia (most common)
- B12, Folate (now rare)
- Vit D / osteopenia/osteoporosis

Other
- Dermatitis Herpetiformis
- Impaired fertility
- CNS: Ataxia, peripheral neuropathy
- Severe aphthous stomatitis
- Abnormal LFTs
How to diagnose Celiac disease

1. Specific celiac serology
   - IgA tTG (tissue TransGlutaminase) – the single best test
   - IgG tTG – less sensitive than IgA tTG
   - IgA DGP (Deamidated Gliadin Peptide)
   - IgG DGP – most accurate IgG-based assay
   - Total IgA – optional (IgG DGP more accurate)

2. Characteristic histology (EGD with biopsy)
How NOT to diagnose Celiac disease

Common Pitfalls:

- Clinical response to GFD
- Positive serum IgG or IgA anti-gliadin antibodies
- Positive fecal anti-gliadin antibodies
- HLA DQ2 or DQ8 positivity (required but not sufficient)
- Flawed interpretation of biopsy histology:
  - Villus distortion and inflammation in duodenal bulb
  - Increased IELs [intraepithelial lymphocytes]
  - Villus atrophy from another cause (TTG & DGP negative)
Endoscopic small intestinal biopsy for diagnosis of Celiac Disease

Macroscopic features:

- Loss of folds
- Mosaic pattern
- Nodularity
- Scalloping

Specific (92%) but not Sensitive (59%)

Oxentenko et al. Am J Gastroenterol 2002;97:933-8
Is small intestinal biopsy still needed to diagnose celiac disease?

Yes because:

- Celiac disease is defined by enteropathy
- Biopsy is relatively simple and safe
- False positive serology does occur
- A false positive diagnosis is very costly in terms of the patient’s lifelong treatment burden
- Symptom response to GFD is not reliable for diagnosis
- The diagnosis cannot be confirmed or refuted easily after treatment with a GFD (gluten free diet)
Treatment of Celiac Disease

Gluten free diet

# Lifelong supply
Management of Celiac Disease

NIH Celiac Disease Consensus Conference 2004

- **C**onsultation with a skilled celiac dietician
- **E**ducation about the disease
- **L**ifelong adherence to a gluten-free diet
- **I**dentification & treatment of nutritional deficiencies
- **A**ccess to a support and advocacy group
- **C**ontinuous long-term follow up by a multidisciplinary team
Celiac Disease: Response to GFD

**tTG IgA > 100 units**

- Small intestinal villous atrophy & crypt hyperplasia

**tTG IgA normal [<20 units]**

- Resolution of intestinal injury on gluten free diet

Resolution of intestinal injury on gluten free diet
Most patients with CD respond well to GFD

~10% are non-responsive:

**Primary:** Ongoing symptoms, signs or lab. abnormalities of CD after > six months of gluten withdrawal

**Secondary:** Recurrence of symptoms, signs or lab. abnormalities of CD after an initial response and while still on a strict GFD for > 6 months

**Primary & Secondary:**
Similar frequency
Similar demographics
Etiologies and Predictors of Diagnosis in Nonresponsive Celiac Disease

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

>10 times more likely if TTG elevated after >12 months on GFD

Gluten Exposure 36%

Microscopic Colitis 7%

Disaccharidase Deficiency 9%

Eating Disorder 6%

Small Intestinal Bacterial Overgrowth 6%

Refractory Sprue 11%

Other 8%

IBS 18%

Other included:
Peptic ulcer disease (2),
Crohn’s disease (1),
Duodenal adenoCA (1),
Food allergy (1),
Gastroparesis (1)
Gluten – where will it hide next?

- Toothpaste
- Envelope gum
- Lipstick
- Candy
- Flavorings
- Medications
- Vitamins & supplements
- “Safe” gluten-free grains


<table>
<thead>
<tr>
<th>Product</th>
<th>Allergen advisory statement</th>
<th>Extraction 1a ppmb gluten</th>
<th>Extraction 2 ppm gluten</th>
<th>Mean ppm</th>
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<td>No</td>
<td>&lt;5</td>
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</tbody>
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*aAssay used: Sandwich R5 enzyme-linked immunosorbent assay with cocktail extrac-
Tiny gluten exposures perpetuate active disease

Histology post 90 day, 50 mg gluten/day microchallenge

Villus height: Crypt depth

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Baseline</th>
<th>50 mg challenge</th>
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<tbody>
<tr>
<td>Celiac</td>
<td>2.9</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>P = 0.03</td>
<td></td>
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</tbody>
</table>

Normal diet ~10 g/day
Slice of bread ~2 g
1/40th slice of bread ~50 mg (0.05 g)
How to Evaluate GFD adherence

- **Patient self-report**
  - CDAT: a Validated GFD adherence measure
    - *When did you last eat gluten? &*
    - *How confident are you that you are avoiding gluten when dining outside your own home?*

- **Serology (IgA TTG)**
  - useful if positive after 6 - 12 months
  - negative result less useful (not sensitive)

- **Expert dietician evaluation** = “gold standard”

- **Biopsy histology** – a measure of disease activity, often abnormal despite strict GFD

- **Measure it!** – Gluten EIA in food, feces or urine

Risk of neoplasia in celiac disease

- Sweden in-patient register
- 1964 to 1994
- 11,019 with CD
- 1,580 with DH
- * Standardized incidence ratio (SIR) for neoplasia
- SIR in DH 1.2
- Risks declined with time and duration of follow up

<table>
<thead>
<tr>
<th>Site</th>
<th>SIR Celiac</th>
<th>% of cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>1.3*</td>
<td>2.3%</td>
</tr>
<tr>
<td>Oral</td>
<td>2.3</td>
<td>0.07%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4.2</td>
<td>0.05%</td>
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<tr>
<td>Small intest.</td>
<td>10.0</td>
<td>0.07%</td>
</tr>
<tr>
<td>Colon</td>
<td>1.9</td>
<td>0.2%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5.9</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>4.6</td>
<td>0.05%</td>
</tr>
<tr>
<td>NHL</td>
<td>6.3</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Clinical response to a GFD does not always equate to a diagnosis of celiac disease

A 46 year old woman reports previous abdominal pain and bloating. Diagnosed as IBS.
Now on a self-prescribed gluten-free diet for 9 months with substantial improvement.
Laboratory tests including IgA-TTG (on current GFD) are normal.

Q: She wants to know if she has celiac disease and whether her children should also be tested for celiac disease.

Which of the following tests would you recommend doing first for this patient?

a) Test of symptom response to gluten ingestion
b) IgA EMA (endomysial antibody)
c) Formal gluten challenge
d) HLA DQ-2 and DQ-8.
e) IgA / IgG DGP (Deamidated Gliadin Peptide)
Why test?
- High NPV (~99% of celiac disease patients positive)
- Very low PPV (40% of general population are positive)
- Not altered by GFD

Who to test?
- Prior to considering a gluten challenge in a patient already on a GFD without prior diagnostic testing
- Equivocal histology and serology
  - e.g. villous atrophy but TTG negative
- Determine whether a relative (sibling) is at risk for CD
Small bowel biopsy of patients with diarrhea & bloating

Normal Villous atrophy

Which person can’t eat gluten?

Neither can tolerate it

Slide Atlas of Gastroenterology, Misiewicz et al, 1984
Non-celiac gluten sensitivity

Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

**Similar & significant differences for:** Abdominal pain, bloating, tiredness & satisfaction with stool consistency

1. **NCGS is a real phenomenon**
2. **Celiac disease cannot be diagnosed by a trial of GFD**
Epidemiology of Celiac Disease & Use of the Gluten free Diet in the US


- Celiac disease
  - Seroprevalence 0.71%; >2 million
- On Gluten Free Diet ~2 million

Diagnosed with celiac disease, and on a gluten free diet ~300,000

- Most people in the US with CeD remain undiagnosed
- NCGS may be very common
Do we need non-dietary treatments for Celiac Disease?

The GFD is highly effective in celiac disease BUT:

- > 10% Non-responsive to GFD
- 1 - 2% Refractory to GFD
- ~ 30% of adults on GFD for celiac disease have ongoing partial villous atrophy on biopsy

- Strict GFD difficult to maintain
  - At social events
  - For food prepared outside the home
    - When travelling
    - In restaurants & cafeterias
    - Take-out
  - For the elderly
  - For the illiterate
  - For those with mental or psychological impairment

Sanders JGLD 2011
70% of Celiac Disease Patients Report Gluten Exposures on GFD

- Intentional and known inadvertent lapses: 28%
- Intentional lapses but not known inadvertent lapses: 12%
- No intentional or known inadvertent lapses: 30%

Gluten measured by EIA over 10 days: 66% of celiac patients had gluten in:
- Food and/or
- Feces and/or
- Urine

Reported intentional and inadvertent gluten consumption (n=269)

Low satisfaction with the GFD amongst patients with Celiac disease

Satisfaction with GFD

- Very poor: 42%
- Poor: 35%
- Average: 23%

Sanders JGLD 2011
Perceived treatment burden is very high in Celiac disease

Renal disease on Hemodialysis = 56.4
Celiac disease = 44.9

Higher than:
- Insulin dependant diabetes
- Irritable bowel syndrome
- Congestive heart failure
- Inflammatory bowel disease
- Hypertension
- GERD

\[ \text{VAS}^\dagger \]

\[ \begin{align*}
\text{CD} & = 44.9 \\
\text{HTN} & = 23.5^* \\
\text{GERD} & = 21.3^* \\
\text{ESRD} & = 56.4 \\
\text{DM} & = 41.7 \\
\text{CHF} & = 38.4 \\
\text{IBD} & = 31.9 \\
\text{IBS} & = 40.4
\end{align*} \]

\[ ^\dagger \text{VAS: 0 = Very Easy} \]
\[ 100 = \text{Very Difficult} \]

*Compared with CeD, \( p<0.001 \)

Social isolation is part of the treatment burden of CeD

Patient responses regarding:
Social isolation
Burden of requesting and explaining GFD
Inhibition of social interactions

Homework Question: What having celiac disease means to you?
Many steps in Celiac disease pathogenesis are well elucidated

**Gluten / gliadin**

1. Ingested
2. Survives digestion
3. Crosses gut lining
4. “Made tastier” by TTG
5. Taken up by “antigen presenting cells” (APCs)
6. Genetically encoded DQ2 or DQ8 present
7. Presented on DQ2/8
8. T cells activated
   - Inflammation
   - Antibody production
   - Tissue damage

Figure from Schuppan et al. Gastroenterol 2009;137:1912-33
Experimental non-dietary therapies for celiac disease (2010)

**Alvine:** ALV-003

**Alba:** Larazotide acetate

**Chemocentryx:** Traficet EN

**ImmusanT:** NexVax2

**James Cook Univ:** Necator americanus

*Slide courtesy of Dr F Leon*
**Experimental non-dietary therapies for celiac disease (2018)**

**Universities:** Modified G

**Probiotics** – Ph2

- **ImmunogenX:** Latiglutenase/IMGX-003 (formerly Alvine’s ALV-003) – Ph2b
- **PvP Biologics:** KumaMax – Ph1 (Takeda)
- **Allergan:** Viokase/pancrelipase – Ph2a

**Innovate:** – INN-202 - Ph2b
(formerly Alba’s larazotide)

**Zedira/Falk Pharma:** ZED1227 – Ph2a
**Sitari:** Pre-clinical tTG inhib (GSK)
**UCB:** Pre-clin tTG inhibitor

**IGY Life Sciences:** IgY – Ph1/2

**Provention Bio:** PRV-015 (a.k.a. AMG 714) – Ph2b (Amgen)
**Mayo Clinic/NCI:** HuMikb1 – Ph2a

**Calypo:** CALY 002 – Pre-clinical (Merck KGa)
**Bioniz:** BNZ-2 – Pre-clinical (Takeda)
**TEVA:** 04H04 - Preclinical

**Takeda:** Vedolizumab/ENTYVIO – Ph1b

**Provid:** Pre-clinical

- **ImmusanT:** NexVax2 – Ph2a
- **James Cook Univ:** Hookworm NainCeD-3 – P1b
- **Cour:** NP-GLI -Ph1b –(Takeda)
- **Kanyos Bio:** Pre-clinical (Astellas/Anokion/Celgene)
- **Topas:** Pre-clinical (Lilly)
- **Selecta:** Pre-clinical
The many faces of Celiac Disease

- Common (~1% of population)
- Complex presentations
  - All ages
  - With or without
    - GI symptoms
    - Deficiency states
      - esp. iron deficiency
- Easy to diagnose (or exclude) prior to GFD
  - by IgA-tTG (plus biopsy if positive)
- GFD is the only treatment
  - Usually effective
  - Often considered burdensome
  - Increasingly popular
    - esp for “Non-celiac gluten sensitivity”
  - Non-dietary treatments under investigation
Welcome to CeliacNow

This website focuses on nutrition for celiac disease*. It is designed for people with celiac disease who:

- May not have access to celiac clinicians and specialized nutrition care
- Want to share the site’s information with their own clinician
- Want to read more about nutrition and the gluten-free diet from an introductory to a more advanced level

COPYRIGHT

*Note: Please consult your healthcare provider for personalized advice.