What’s New in Celiac Disease

Brooks D. Cash, MD, FACG
Professor of Medicine
Division of Gastroenterology
University of South Alabama

Disclosures

• No relevant disclosures
Objectives

- Review the pathophysiology and epidemiology of celiac disease
- Review the current ACG Guidelines on celiac disease
- Delineate principles of treatment and monitoring
- Become familiar with emerging therapeutic options for celiac disease

Celiac Disease
Intestinal Permeability – Inflammation Loop

Adapted from van Heel, DA et al, Gut 2006;55:1037-1046
Celiac Disease: Simplified Explanation

- Principal toxic components of gluten are proline and glutamine rich peptides
  - Resistant to gastric, pancreatic, and brush border degradation
  - Humans do not have enzyme to break proline-glutamine bond
- Partial digestion of gluten leads to creation of multiple peptides
  - Induce inflammatory cascade in susceptible individuals

Celiac Disease Epidemiology

- Females >> males, adults >> children
  - Any age (median age at presentation = 45)
- 1% of Caucasian population worldwide
- Associated Disorders
  - Autoimmune thyroid disease
  - Type I Diabetics
  - Lupus, Addison's Disease
  - Sjogren's Disease, Microscopic colitis
  - Down's syndrome
  - Dermatitis herpetiformis
- Family members
Who Should get Tested for Celiac Disease?

- Pts with symptoms, signs, lab evidence of malabsorption (Iron deficiency, B12, Vitamin D)-Strong rec
- Pts with symptoms, signs, lab evidence for which CD is a treatable cause-Strong rec
- Pts with 1st degree family member who has confirmed diagnosis of CD with possible signs/symptoms-Strong rec
- Consider testing asymptomatic relatives with 1st degree relative with confirmed diagnosis of CD-Conditional rec
- CD should be sought as a cause for transaminase elevations in the absence of other etiologies-Strong rec
- Pts with Type I DM if there are any symptoms, signs, lab evidence for of CD-Strong rec

Presentations of Celiac Disease

- **Classic Malabsorption (25%)**
  Diarrhea, steatorrhea, weight loss, multiple deficiencies

- **Monosymptomatic (50%)**
  Anemia, diarrhea, constipation, lactose intolerance, recurrent idiopathic pancreatitis

- **Non-GI presentation (25%)**
  Diabetes, infertility, short stature, neuropathy, ataxia, bone disease, abnormal transaminases, chronic fatigue

- **Acute Abdomen (Rare)**
  Perforation, abdominal pain, lymphoma, vomiting, intussusception, obstruction

Diagnosis of Celiac Disease

- IgA anti-TTG is the preferred single test for detection of CD in individuals over the age of 2 years-**Strong rec**
  - Anti-gliadin antibodies are not recommended for primary dx of CD-**Strong rec**
  - Should also test total IgA (to exclude IgA deficiency)
  - If IgA deficiency present, test for IgG TTG or IgG deamidated gliadin peptides (DGP)-**Strong rec**

- If suspicion of CD is strong, pursue intestinal bx even in the absence of + serologies-**Strong rec**

- CD antibody panels marginally increase sensitivity but reduce specificity over TTG IgA alone and are not recommended-**Conditional rec**

- Children < 2 years of age should have TTG IgA and DGP (IgA and IgG) tested-**Strong rec**

Serologic Testing

- TTG is THE primary CD antibody: Targeted epitope
  - IgA and IgG forms
- IgA deficiency present in 2-3% of CD patients (1:131 patients tested for CD)
- “Serologic cascade”: 1) IgA total then either IgA TTG OR if IgA (-) then IgG deamidated gliadin peptide (DGP) or TTG
  - IgG TTG sensitivity 30-70% in IgA sufficiency; 95% in IgA deficiency
- DGP: Specificity similar to TTG; lower sensitivity; IgA/IgG combo similar performance as IgA TTG

Confirming Celiac Disease

- Confirmation should be based on hx, PEX, serology, EGD with several biopsies of the small bowel-Strong rec
- EGD with small bowel biopsies is recommended to confirm the diagnosis-Strong rec
  - Multiple biopsies of the duodenum includes 1-2 bulbar and at least 4 of the distal duodenum-Strong rec
  - Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for CD and other causes should be considered-Strong rec

Endoscopic Appearance of CD

- 10-70% non-oriented bxs adequate for evaluation
- Bulbar biopsies increase yield by 9-13%
- Near 100% sensitivity with 4 post-bulbar bxs and 2 bulbar bxs (9 and 12 o’clock)
- 100-200 ml into deflated duodenum increases sens/spec for villous atrophy; targeted biopsies

Other Causes of Villous Atrophy in the Duodenum

<table>
<thead>
<tr>
<th>Cause</th>
<th>Other Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIBO</td>
<td>Tropical sprue</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
<td>Eosinophilic enteritis</td>
</tr>
<tr>
<td>Hypogammaglobulinemic sprue</td>
<td>Intestinal lymphoma</td>
</tr>
<tr>
<td>Drug associated enteropathy</td>
<td>Intestinal Tb or Infectious enteritis</td>
</tr>
<tr>
<td>Whipple disease</td>
<td>GVHD</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>AIDS enteropathy</td>
</tr>
</tbody>
</table>
Role of Ancillary Testing in Celiac Disease

- HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD - **Strong rec**
- HLA-DQ2/DQ8 testing should be used to effectively rule out CD in selected clinical situations - **Strong rec**
  - Equivocal small bowel biopsies in seronegative pts
  - Evaluation of pts on a GFD in whom no testing was done prior to GFD
  - Pts with discrepant celiac-specific serology and histology
  - Pts with suspicion of refractory CD where original diagnosis is in question
  - Pts with Down's syndrome


---

Role of Ancillary Testing in Celiac Disease

- Capsule endoscopy should not be used for initial diagnosis except for pts with celiac-specific serology who are unwilling to undergo EGD with biopsy - **Strong rec**
- Capsule endoscopy should be considered for the evaluation of pts with complicated CD - **Strong rec**
- Intestinal permeability, D-xylose, and SBFT are neither specific nor sensitive and are not recommended for CD diagnosis - **Strong rec**
- Stool studies or salivary tests are neither validated not recommended for use in the diagnosis of CD - **Strong rec**

Differentiation of CD from Non-celiac Gluten Sensitivity

- Symptoms or symptom response to a GFD alone should not be used to diagnose CD - Strong rec
- Diagnosis of NCGS should only be considered after CD has been excluded with appropriate testing - Strong rec
- Standard dx tests should not be relied upon to exclude CD in pts adhering to a GFD - Strong rec
- DQ2/DQ8 testing should be done prior to embarking on gluten challenge - Strong rec
- Pts who will not undergo gluten challenge with DQ2/DQ8 should be managed in a similar fashion to those with known CD - Conditional rec


Gluten Challenge

1) 3 gm gluten daily for 2 weeks
   a) Do duodenal bx if unable to go further
2) 3 gm of gluten for up to 6 additional weeks
   a) serology at end of challenge if + likely CD (confirm with biopsy)
   b) if serology negative then repeat serology in 2-6 weeks after challenge

Management of CD

- Pts with CD should be on a GFD for life; strict avoidance of wheat, barley, rye-Strong rec
- Oats appear safe in CD but should be introduced into the diet with caution and pts should be monitored for adverse reactions-Strong rec
- Pts with CD should be referred to a registered dietitian knowledgeable about CD-Strong rec
- Pts with newly diagnosed CD should undergo testing and treatment for micronutrient deficiencies (Fe, folate, vitamin D and B12)-Conditional rec

How Much Gluten is Too Much?

- Western diet average gluten intake 10-20 g/day.
  - As little as 50mg of gluten/day for 3 months sufficient to cause significant decrease in intestinal mucosal villous height/crypt depth
  - Daily intake <10 mg is unlikely to produce significant histological abnormalities
  - GFD with threshold at <20 ppm of gluten ensures an intake of <50 mg/D and provides sufficient safety margin


CD Management Quality Measures

- Advocate gluten free diet
- Refer to dietitian who is well-versed in celiac disease
- Check bone density
- Check for Vitamin D, iron and B-vitamin deficiencies
- Lactose free diet initially
- Calcium and Vitamin D replacement
- Strep pneumonia vaccine
- Parental meds if severe disease
- Support group
Other Dietary Guidelines for GFD

- Read all labels (especially processed foods)
- Check medications, food additives, emulsifiers, stabilizers, lip sticks ([www.glutenfreedrugs.com](http://www.glutenfreedrugs.com))
- AVOID beer, ale, lager or stouts (unless gluten free)
- Wine, liquors, spirits generally OK
- Gluten free home to avoid cross contamination

What about Oats?

- Controversial
  - Possible cross-contamination in production
- Studies with conflicting results* - no diff in bxs/sxs to increased sxs/increased IELs
- Best to avoid in severe disease and initially with gradual re-introduction after 12 mos
  - Celiac in remission – 40-60 g/day

Monitoring of CD

- Pts with CD should be monitored regularly for GFD response, adherence, assessment of complications—Strong rec
- Monitoring should be based on combination of history and serology—Strong rec
  - Monitoring should also consist of verification of normalization of laboratory abnormalities detected initially
- EGD with biopsies is recommended for lack of response or relapse of symptoms despite GFD—Strong rec


Monitoring of CD

- Follow-up 3-6 mos after diagnosis to assess adherence/response to treatment
  - Symptoms: typically better in 1-3 mos
  - Serology titers (improves over 6 mos)
  - Monitor: Bone-mineral density, vitamin D, calcium, folate, Cu, zinc, ferritin

- Annual visits thereafter
  - Periodic structured interviews with registered dietitian

- Assess histology after 2 years of GFD
  - 50% of patients have only partial resolution on biopsy (can take 5-7 years to normalize)
Complications Associated with Untreated Disease

- Mortality rate in patients with untreated celiac disease is two fold greater at every age
  - Gastrointestinal malignancies (lymphoma, adenoCA, esophageal cancer, head & neck tumors)
  - Osteoporosis
  - Stunted growth
  - Infertility
  - Gluten ataxia and other neurological disturbances
  - Recurrent stomatitis/dental hypoplasia
  - Refractory disease

Non-responsive or Refractory CD

- Pts with NRCD should be evaluated to identify and treat the specific etiology in each patient-Strong rec
  - Early steps include measurement of celiac serologies and a thorough review of diet by a dietitian experienced in CD management-Strong rec
- Differentiation should be made between Type I and II refractory CD due to different management and prognosis-Strong rec
  - Treatment with medication should be considered as an adjunct to refractory CD-Conditional rec
- Pts with refractory CD should be monitored closely and receive aggressive nutritional support including parenteral nutrition whenever indicated-Strong rec

Corrao et al., Lancet 2001

If patient non-responsive to GFD

- Consider diet, diet and diet
- Consider lactose intolerance
- When appropriate advise flex sig/colon & biopsies to r/o microscopic colitis
- Consider pancreatic insufficiency, SIBO, malignancy, RCD, ulcerative jejunitis

Refractory Sprue

- Two types (based on duodenal bx and immunophenotyping)
  - Type 1 – polyclonal IELs bearing CD3/8 surface markers
  - Type 2 (15%) – IELs with clonal T-cell receptors without surface CD3 markers but preserved intracellular CD3 expression
- 50% 5-year survival
- High rate of lymphoma (EATL)
- Treatment: Corticosteroids, azathioprine, cyclosporine, cladribine (synthetic purine nucleoside), TPN
Celiac Disease – What does the Future hold?

Alternative/Investigational Management Approaches

1. Ancient wheat
2. Assisted digestion of gluten
3. Prevent immunogenic peptide passage
4. Block HLA-DQ2 binding
5. Inhibit TTG
6. Tolerance induction
7. Gluten sequestering polymer
8. Anti-inflammatory therapy
Ancient Wheat

- Ancient wheat had diploid genome (AA, BB, DD)
- Natural hybridization led to development of tetraploid and then hexaploid species
  - DD genome donor (Asian Spring wheat) contains all T cell epitopes identified as immunogenic in CD patients
  - Some durum wheat (AABB) do not have these epitopes
- Current efforts include gene deletion, RNA interference
- Challenges: decrease in baking properties, unknown epitopes may still be present, cross contamination during growing

Assisted Digestion of Gluten
Have to survive gastric degradation

- ALV003: Oral mixture of 2 gluten specific proteases (1 from germinated barley seeds and another from S. capsulatum) active in low pH
  - Phase 2a showed preservation of villous height and less IELs vs placebo; 2b (dose ranging efficacy and safety) trial underway
- Apergillus niger prolyl endoprotease; degrade gluten in vivo
  - Conflicting results thus far
- Pretreatment before ingestion
  - Fermentation with lactobacilli lyses proline/glutamine bonds
  - Probiotic formulations rich in lactobacillus and bifidobacteria (may also stabilize tight junctions)
Prevent Passage of Immunogenic Peptides
Tighten the Junctions

- Larazotide: octapeptide zonulin receptor antagonist (derived from cholera toxin) administered (at least) TID before meals
- 6 clinical trials to date: 3 phase 1, 3 phase 2
  - Safety comparable to placebo; intestinal permeability endpoints not met, but symptomatic improvement was noted
  - Phase 2b in GFD non-responders underway
- Rho kinase (ROCK) also mediates intestinal permeability
  - Current antagonists (fasudil) not appropriate for chronic use but alternative ROCK inhibitors in development

Block HLA-DQ2
Prevent Peptide Binding

- Deamidated gluten (by TTG) are negatively charged and bind to HLA-DQ2/8 on Ag presenting cells
  - Ag presenting cells activate T lymphs (adaptive immunity)
- Substitution of alanine at key positions in immunodominant peptides led to abolition of immunogenicity for T cells
- Challenges include practical aspects (access and delivery) and unknown effects of altering immunosurveillance function in other tissues
Inhibition of TTG

- T cells are biased towards deamidated gluten peptides
  - TTG catalyzes formation of isopeptide bonds between glutamine and lysine, deamidates glutamine residues of gluten, and induces crosslinking of gluten to matrix proteins
- In vitro studies of TTG inhibitor (L682777) have shown promise


Immune Modulation and Gluten Tolerance Induction

- NexVax2 uses 3 gluten peptides to induce tolerance
  - Phase 1 study demonstrated ability to produce anti-gluten T cells
  - Some gluten sensitivity symptoms observed
- Efficacy and safety remain to be established; need to identify most useful immunogenic gluten peptides
Gluten Sequestering Polymer

- Polymeric binder to complex with α-gliadin
  - Poly(hydroxyethyl methacrylate-co-styrene sulfonate) [P(HEMA-co-SS)]
  - Experiment in rats shows decrease in formation of immunogenic peptides
- Primary role if proven effective and safe may be supportive; inadvertent gluten ingestion

Anti-inflammatory Drugs

- Glucocorticoids
  - Celiac crisis, gliadin shock, refractory CD
  - Small reports of adjunctive use with GFD
- Cytokines and Chemokines
  - Anti-interferon-γ and anti TNF-α
  - Anti-interleukin 15
  - Interleukin 10
  - Lymphocyte recruitment blockade/anti-integrins
Summary

**Optimal evaluation/management**

1) Diagnose with TG, IgA level (IgG assays available)
2) EGD with bx if + serology or symptoms suggestive of CD  (10% pts with negative serology may have + bx)
3) HLA typing for confirmation/exclusion
4) Lifelong GFD/monitoring is critical
5) Emerging therapies in development; market drivers