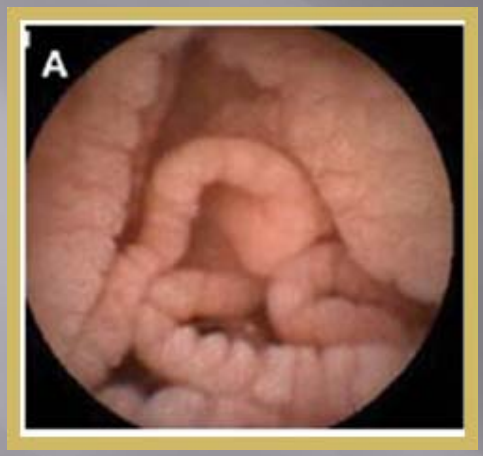
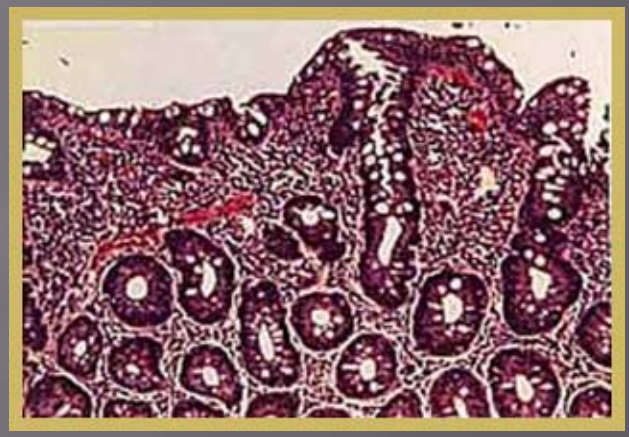




CELIAC DISEASE

Matt McCollough, MD
Fellow, GI/Hep
University of Louisville
March 19, 2009

Objectives

- Define Celiac Disease
- Recognize the epidemiology
- Understand basic pathophysiology
- Be able to employ a diagnostic approach
- Review treatment options including future advances

Definition

- "Celiac Disease (CD) is a permanent intolerance to gluten, a term that is broadly used to describe the storage proteins in wheat, rye, and barley."

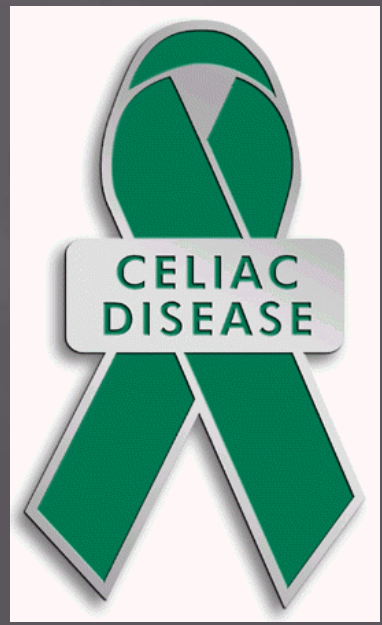
- Synonyms: Celiac sprue, Gluten-sensitive enteropathy, Nontropical sprue, Summer diarrhea

GASTROENTEROLOGY 2006;131:1977–1980

Why is gluten intolerance important?

- Chronic inflammation from gluten intolerance leads to:
  - Decreased absorption of macro- and micro-nutrients
  - Increased net secretion of water and solute
  - The formation of ulcers and strictures
  - Involvement of multiple organ systems
  - Increased risk of certain malignancies

Epidemiology



Prevalence

- Prevalence of CD is 1% in the United States (0.71%-1.25%)
- The United Kingdom, Sweden and Germany have reported the highest adult CD prevalence (> 1.5%)

Rostom, A, et al GASTROENTEROLOGY 2006;131:1981–2002

Prevalence of Celiac Disease in Selected Populations

Population	Prevalence of CD (%)
First Degree Relative	10
Second Degree Relative	2.6 – 5.5
Iron Deficiency Anemia (Unexplained)	3 – 15
Osteoporosis	1.5 – 3
Type 1 Diabetes Mellitus	2 – 5
Liver Disease	1.5 – 9

Rostom, A, et al GASTROENTEROLOGY 2006;131:1981–2002

Diseases Associated With Celiac Sprue

- Iron deficiency anemia
- Osteoporosis
- Type I Diabetes Mellitus
- Autoimmune thyroid disease
- Secondary hyperparathyroidism
- Dermatitis herpetiformis
- Addison's disease
- Acute and chronic pancreatitis
- Crohns disease
- Ulcerative colitis
- IgA nephropathy
- Primary biliary cirrhosis
- Autoimmune Hepatitis
- Primary sclerosing cholangitis
- Cryptogenic liver disease
- Non-Hodgkin's lymphoma
- Hyposplenism
- Idiopathic pulmonary hemosiderosis
- Down syndrome
- Turner's syndrome
- Reproductive complications
- Autoimmune myocarditis
- Idiopathic dilated cardiomyopathy
- Idiopathic epilepsy
- Occipital calcifications
- Ataxia

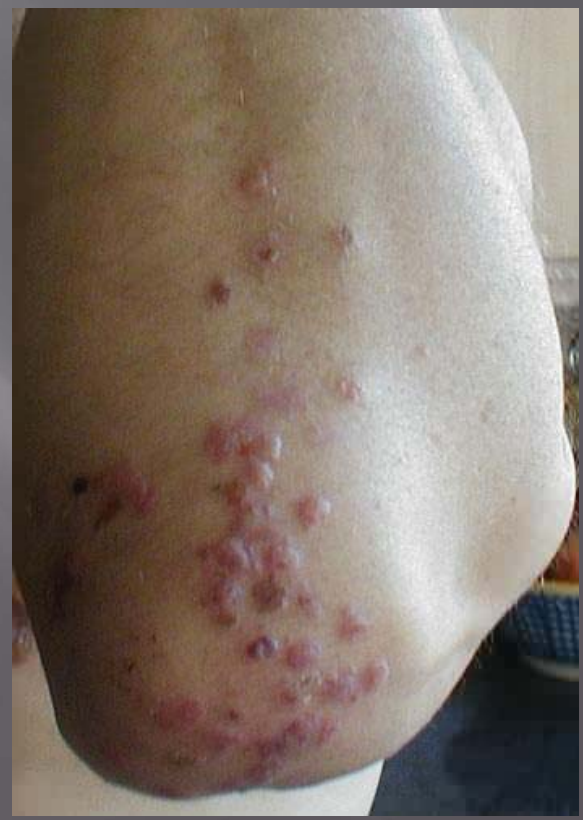
Liver Disease and CD

- CD is associated with mild elevations in liver enzymes (4% of patients with unexplained abnormal LFT's)
- Abnormal liver enzymes may be the only manifestation of CD
- Adherence to a gluten-free diet (GFD) may normalize transaminase levels
- Endomysial antibody (EMA) may be more specific for CD than tTG antibody (tTGA) in this particular population

Farre C, et al. Am J Gastroenterol 2002;97:3176–3181.

Dermatitis Herpetiformis (DH)

- Pruritic papulo-vesicles over the external surface of the extremities trunk
- Histology shows granular IgA deposits along the sub-epidermal basement membrane
- Serology is positive
- 24% of patients with CD have DH
- 85% of patients with DH have CD
- Treated with GFD and dapsone



Collin, P, et al. Arch Dis Child 1997;32:1129
Reunala, T et al. Arch Dis Child 1984;59:517

Cancer Risks

- In celiac patients, two-thirds of cancer related death are due to non-Hodgkin's lymphoma (NHL), both intestinal and extra-intestinal forms
- The prevalence of NHL in CD patients is 120 cases per 100,000 patient-years
- Other cancer related deaths reported in CD patients include esophageal, stomach, pancreatic, liver, biliary, small bowel, pleural, melanoma, and leukemia
- Decreased risk of breast cancer

Rostom, A, et al Gastroenterology 2006;131:1981–2002
Askling, J, et al. Gastroenterology 2002;123:1428

Enteropathy-associated T-cell lymphoma

- Uncommon lymphoma usually associated with CD
- Presents with anorexia, weight loss, abdominal pain, diarrhea, fever, hepatosplenomegaly, duodenal mass, and ascites
- Full thickness intestinal biopsy may be required to make the diagnosis
- Typically high grade with a 10% 5-year survival

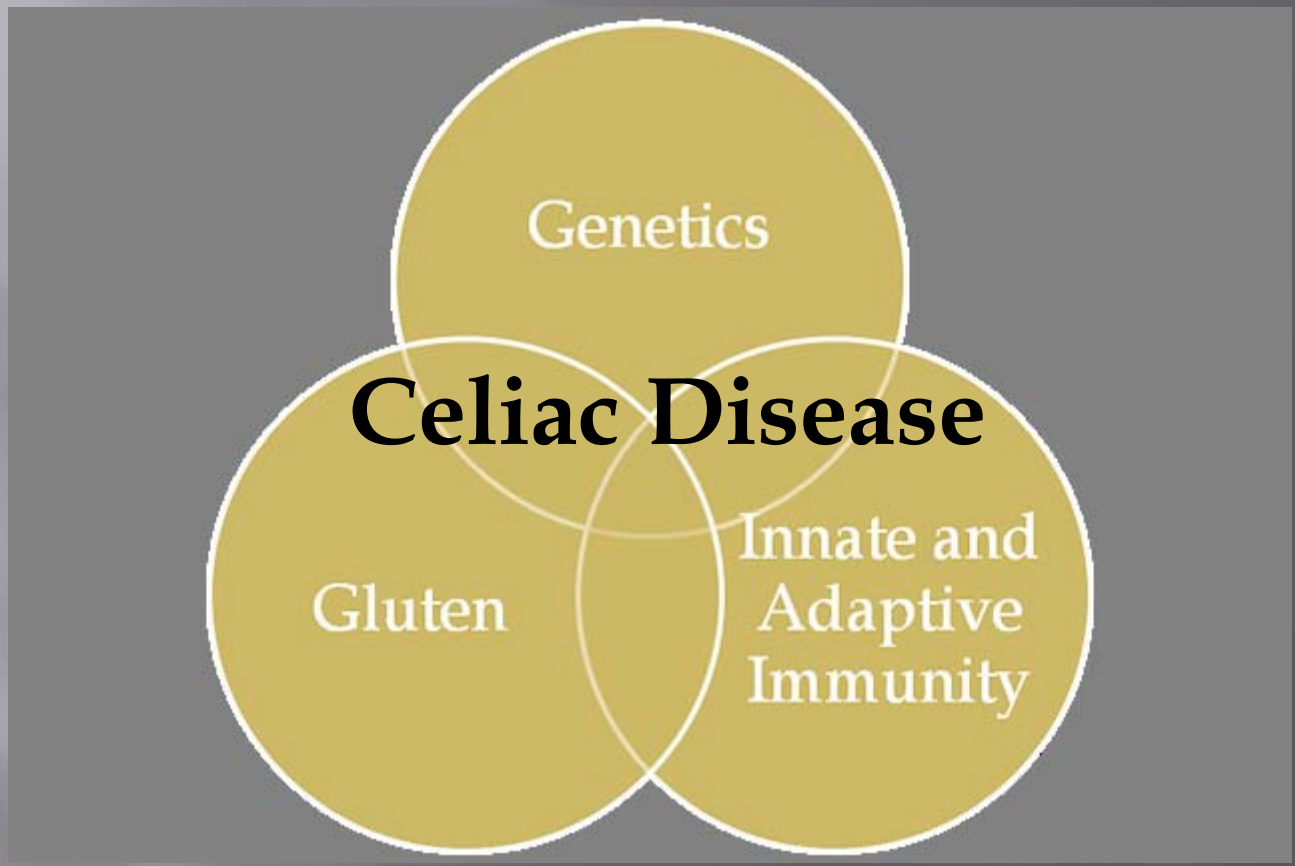
Egan, LJ, et al. J Clin Gastroenterology 1995;21:123

Standardized Mortality Rate (SMR)

- Risk of death in celiac disease patients is higher among:
  - Patients presenting with malabsorption (2.5)
  - Patients with poor adherence to the GFD (6.1-10.7)
  - Delayed diagnosis 1-10 years (2.6), > 10 years (3.8)
- Mild and asymptomatic celiac sprue do not appear to increase mortality

Corrao G, et al. Lancet 2001;358:356–361.

Pathophysiology



Celiac disease is an **immune** disorder triggered by the **environment** (gluten) in **genetically** susceptible individuals

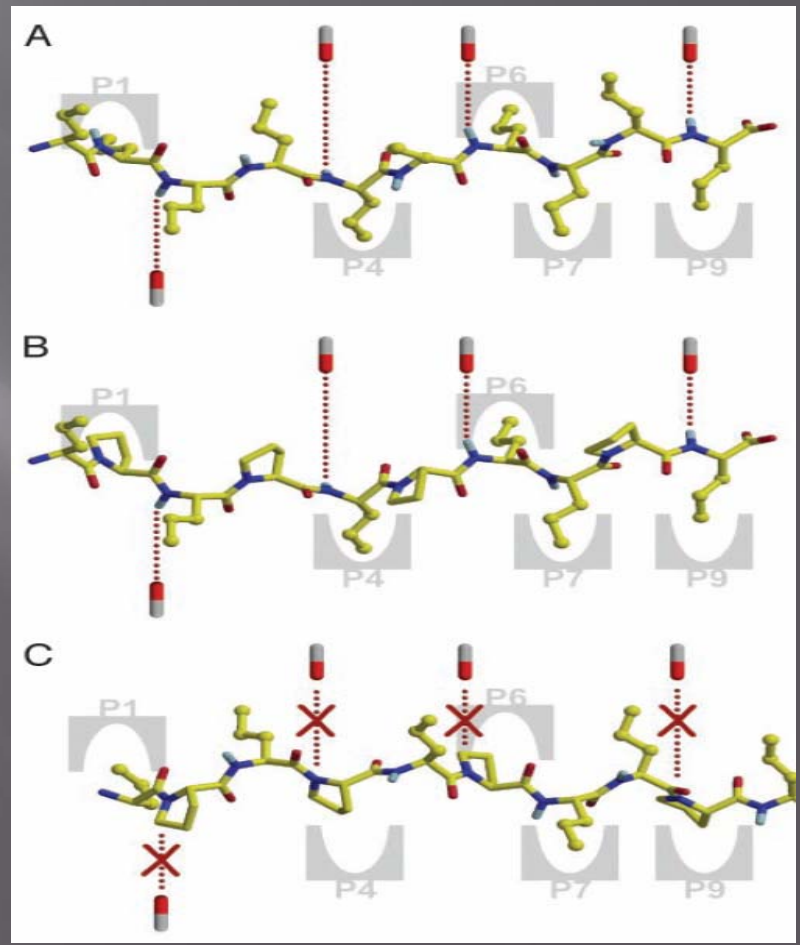
What IS Gluten?

- Storage protein in cultivated grasses: wheat, barley, and rye
  - Mixture of two protein families
    - Gliadins
    - Glutenins
  - Bulky hydrophobic group followed by proline
  - Poor digestion of α-gliadin is due to high prolamine content
  - Exhibits resistance to all gastric, pancreatic and brush border peptidases
- 33-mer digestate major source of toxic fragments

Shewry J Exp Bot 2002:53;947-58
Hausch Am J Physiol Gastro Liver Physiol 2002:283;G996-1003

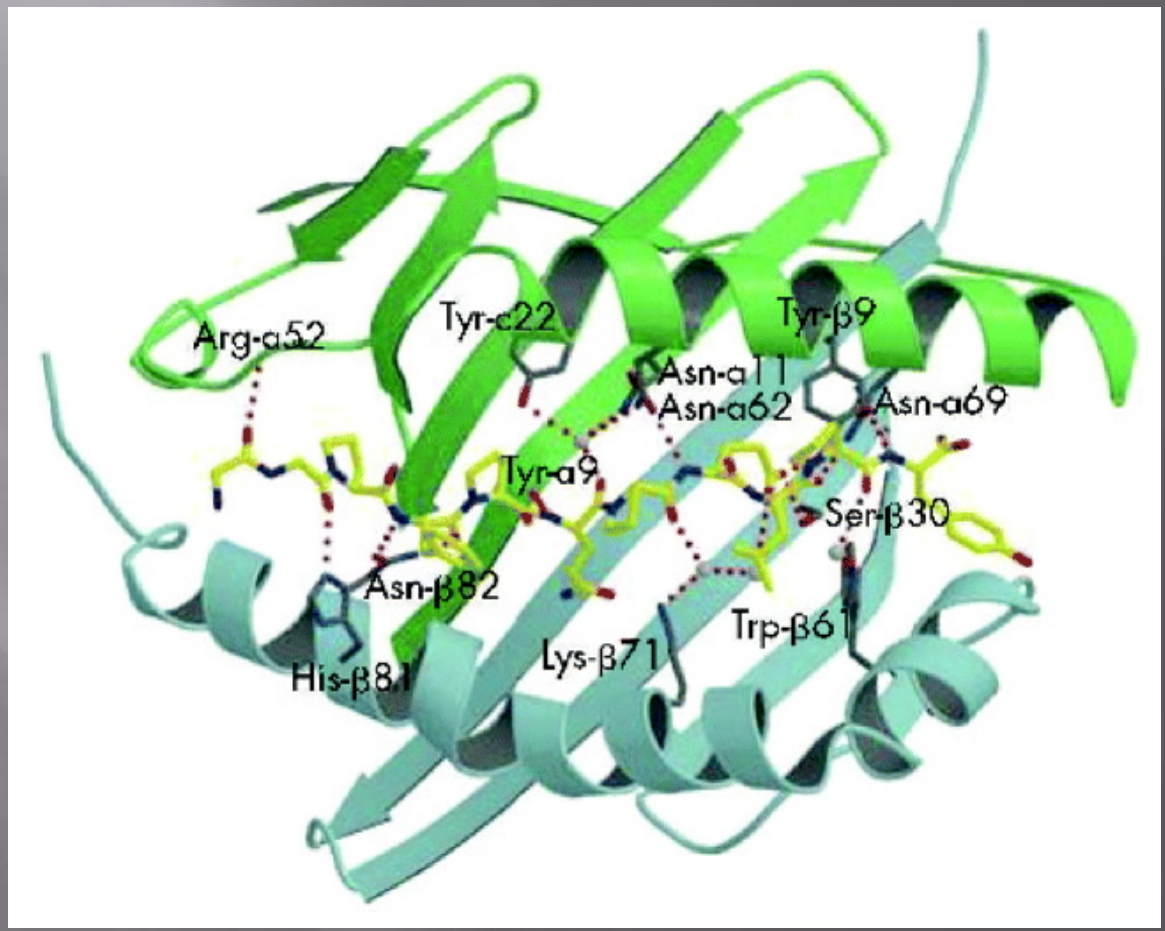
Prolamine and MHC Class II

- Prolamine-rich immunogens from gluten digestion inherently assume left-handed polyproline II helical arrangement
  - Preferred configuration for MHC II ligands
- MHC II ligands bind P1, form hydrogen bond network along backbone
  - Gliadin mimics other MHC II ligands



Kim, Proc Natl Acad Sci 2004:101;4175

Gliadin Fragment Bound to MHC II



Kim *PNAS* 2004:101;4175-79

HLA Expression (MICA/MICB)

- Intestinal epithelial cells (IELs) in CD patients over-express MICA/MICB
  - Non-conventional HLA Class I molecules
  - Usually restricted to intestinal and thymic epithelium
  - Function as signal of cellular distress
  - Trigger cytokine secretion, cellular cytotoxicity
- Immunodominant gliadin fragment p31-49 stimulates MICA expression in IELs from celiacs

Hue ***Immunity*** 2004:21;367-77
Bahram ***Proc Natl Acad Sci USA*** 1994:91;6259-63

Intestinal Epithelial Cell Death

- $CD8^{+}\alpha\beta$ T cells express NKG2D receptor
- NKG2D binding by MIC delivers co-stimulatory signal that recognizes and kills distressed enterocytes
- The gliadin fragment p31-49 also stimulates the antigen presenting cells in the lamina propria to produce IL-15
- IL-15 in turn up-regulates MICA expression[2]
  - Neutralization by anti-IL-15 abrogates expression of MICA

Bahram Proc Natl Acad Sci USA 1994:91;6259-63
Hue Immunity 2004:21;367-77

Genetics

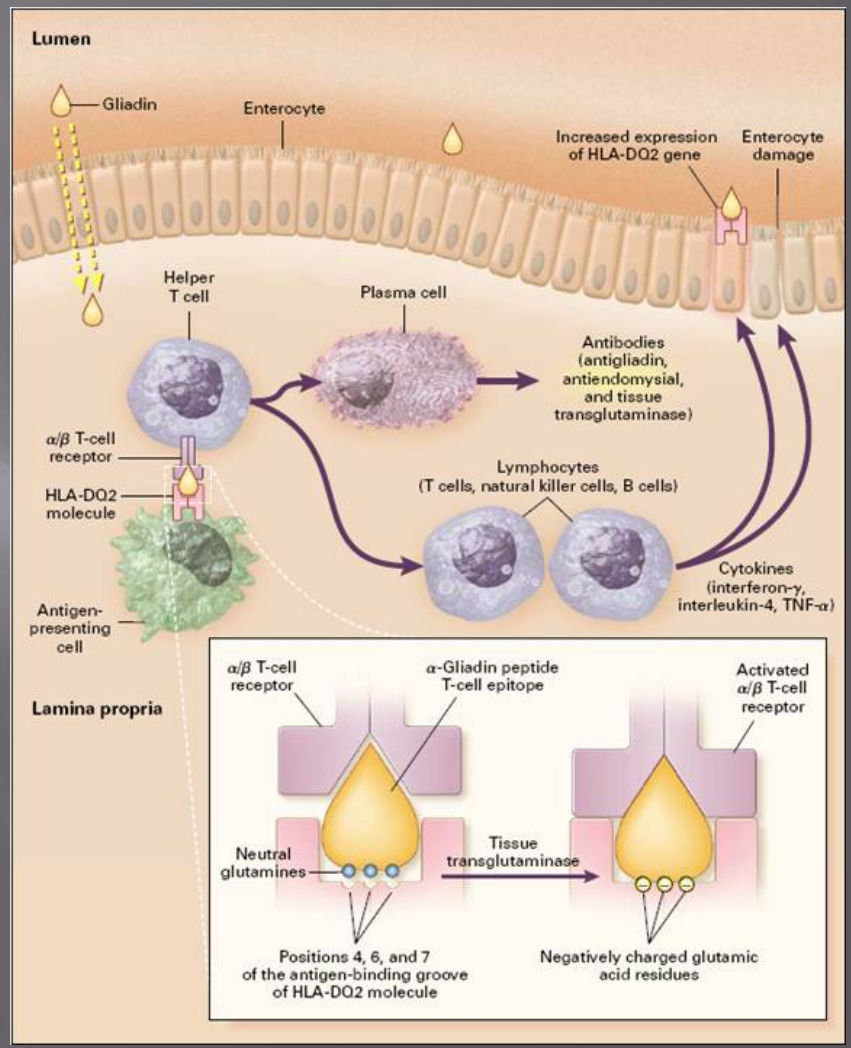
- Nearly 100% of CD patients express either HLA-DQ2 or DQ8 MHC class II molecules
  - DQ2 (DQA1*0501:DQB1*0201)
  - DQ8 (DQA1*0301:DQB1*0302)

- Homozygosity for HLA-DQ2 is associated with refractory celiac disease and enteropathy associated T-cell lymphoma

Maiuri L, et al. Gastroenterology 2005;129:1400–1413.
Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

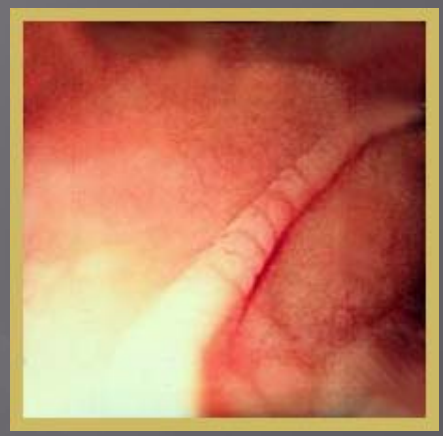
Pathogenesis of CD

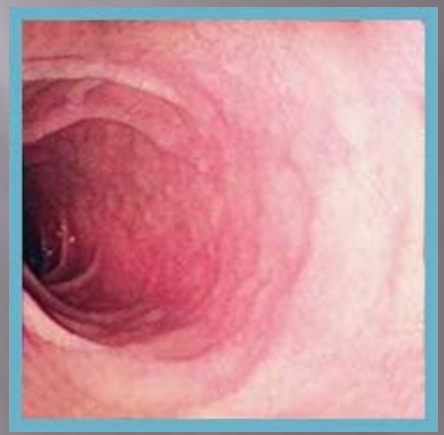
"tTG makes gliadin tastier for the T cells"

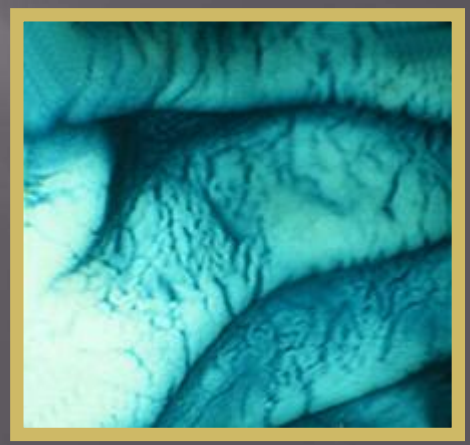


Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

Diagnosis







"Classic" Clinical Manifestations

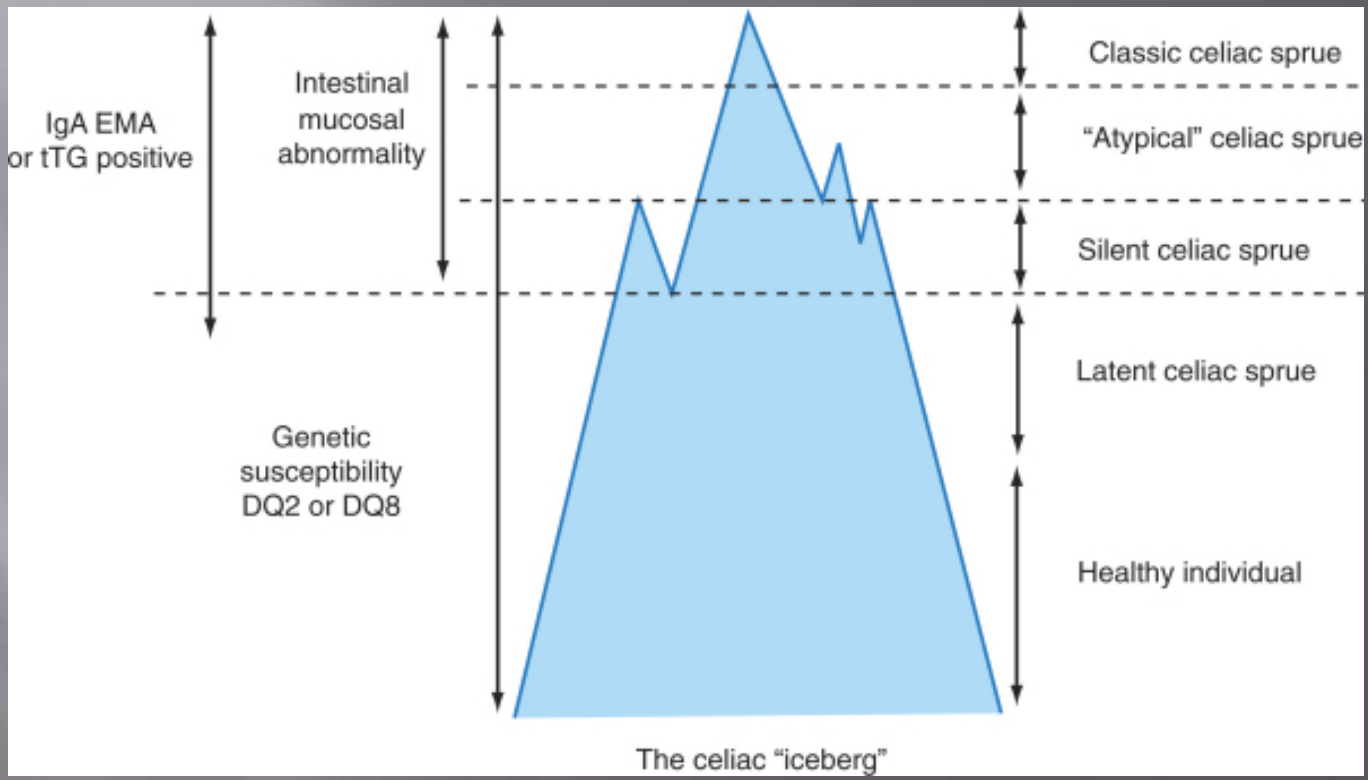
- Usually presents between ages 10 and 40
- Diarrhea is bulky, foul-smelling, and floating
- Meteorism - Gk, *meteorizein,* to hold up;
  - drum-like distention of the abdomen caused by the presence of gas in the intestines

- Consequences of malabsorption include growth failure, weight loss, anemia, neurologic disorders from B12 deficiency, and osteopenia from calcium and vitamin D deficiency

Celiac Disease Classifications

- **Classic** — Symptoms and sequelae of gastro-intestinal malabsorption with total villous atrophy
- **Atypical** — Predominantly extra-intestinal mani-festations with few or no gastrointestinal symptoms
- **Silent** — Asymptomatic villous atrophy +/- sero-logic test results
- **Latent** — Genetic susceptibility without clinical or histologic manifestations
- **Refractory** — Patients with true celiac disease who no longer respond to a GFD

The Celiac "Iceberg"



Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

Diagnosis

- Serologic testing:
  - IgA/IgG tTGA
  - IgA/IgG EMA
  - IgA/IgG antigliadin antibodies (AGA)
- Genetic testing
- Intestinal biopsy – the Gold Standard

Ideally, diagnostic testing should be performed prior to initiation of gluten restriction

Serologic Testing

- IgA tTGA is the best single test for the detection of celiac disease (excellent sensitivity and specificity)
- tTGA uses a quantitative enzyme-linked immunosorbent assay with guinea pig liver or more commonly human recombinant or red cell-derived tTG
- First generation assays had false-positive results in patients with liver disease, congestive heart failure, arthritis, and chronic inflammation. This is now less common.

Rostom A, et al. Evid Rep Technol Assess (Summ) 2004;(104):1–6.

Serologic Testing

- EMA antibodies are directed against connective tissue
- IgA EMA recognizes the tTG auto-antigen
- IgA EMA uses an indirect immunofluorescence assay (monkey esophagus or human umbilical cord substrate) which is more time consuming and operator dependent than IgA tTGA.
- Good sensitivity and excellent specificity

Rostom A, et al. Evid Rep Technol Assess (Summ) 2004;(104):1–6.

Serologic Testing

- IgA AGA uses enzyme-linked immunosorbent assays
- Has a very low positive predictive value

Rostom A, et al. Evid Rep Technol Assess (Summ) 2004;(104):1–6.

Sensitivity and Specificity of Serologic Tests in Celiac Disease

Test	Sensitivity (%)	Specificity (%)
IgA tTGA	95.1	98.3
IgG tTGA	< 70	Up to 100
IgA EMA	90.2	99.6
IgG tTGA	< 70	Up to 100
IgA AGA	85-90	90
IgG AGA	80-90	80-90

Adult patients with normal IgA levels

Rostom, A, et al. GASTROENTEROLOGY 2006;131:1981–2002

What about IgA Deficiency?

- IgA deficiency is the most common human immunodeficiency
- The risk for IgA deficiency is 10-15 times greater in CD patients (1.7-3% prevalence in celiac disease patients)
- Eight percent of patients with IgA deficiency have CD
- If selective IgA deficiency is present, IgG EMA and/or IgG tTG have excellent sensitivity and specificity (each approach 100%)
- In patients with a negative tTGA, but a strong suspicion of CD, measurement of serum IgA levels is appropriate

Trusting Serology

- Efficacy of serologic testing is related to histologic grade of disease and pre-test probability
- Sensitivity of EMA and tTGA in patients with partial villous atrophy can be as low as 30%.
- Since the prevalence of CD in the general population is low (1%) the PPV of serologic testing is low (tTGA PPV = 32.2%)
- Therefore, small bowel biopsies are recommended prior to establishing the diagnosis of CD

Rostom A, et al. Evid Rep Technol Assess (Summ) 2004;(104):1–6.

HLA Molecules and CD

- Nearly 100% of CD patients express either HLA-DQ2 or DQ8 MHC class II molecules
  - DQ2 (DQA1*0501:DQB1*0201)
  - DQ8 (DQA1*0301:DQB1*0302)
- 25% to 40% of the general population in the United States possesses a heterodimer of these alleles (poor positive predictive value)

Rostom A, et al. Evid Rep Technol Assess (Summ) 2004;(104):1–6.

HLA Class II Molecules

- Since virtually all CD patients express HLA-DQ2 or DQ8 alleles, their absence has a negative predictive value of nearly 100%

Intestinal biopsy

- Intestinal biopsy is currently the Gold Standard for diagnosis
- Ideally, 4-6 biopsies from the second portion of the duodenum or beyond are recommended (the proximal duodenum may have more patchy disease obscured by Brunner's glands and peptic changes)
- Histologic findings include crypt lengthening with increased lamina propria and intraepithelial lymphocytes
- Intraepithelial lymphocytes in the absence of mucosal changes may represent latent CD but should not be considered diagnostic

Intestinal biopsy

- Instruct patients to consume a normal diet and to not avoid gluten prior to biopsies
- Four week gluten challenge with repeat biopsies may help in selected patients with negative serologies who started a gluten free diet prior to initial biopsy
- Absence of macroscopic features (mucosal fold scalloping) is NOT sufficient to rule out the diagnosis

Ansaldi N, et al. Pediatr Med Chir 1988;10:3–6

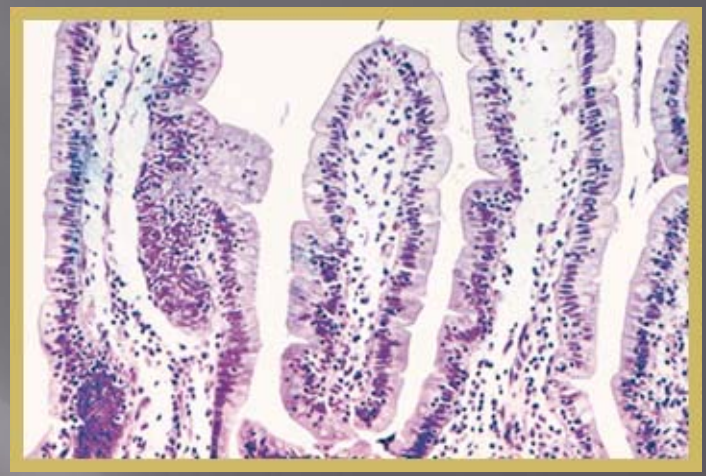
Marsh Histologic Grading

Marsh Grade	Histologic features
0	Normal mucosal and villous architecture
I	Infiltrative (increased numbers of intraepithelial lymphocytes)
II	Hyperplastic (enlarged crypts with increased crypt cell division)
IIIa	Partial villous atrophy (shortened blunted villi, mild lymphocyte infiltration, enlarged hyperplastic crypts)
IIIb	Subtotal villous atrophy (clearly atrophic villi, enlarged crypts with immature epithelial cells, influx of inflammatory cells)
IIIc	Total villous atrophy (complete loss of villi, severe crypt hyperplasia, infiltrative inflammatory lesion)
IV	Hypoplastic (total villous atrophy, normal crypt depth with hypoplasia, normal intraepithelial lymphocyte count)

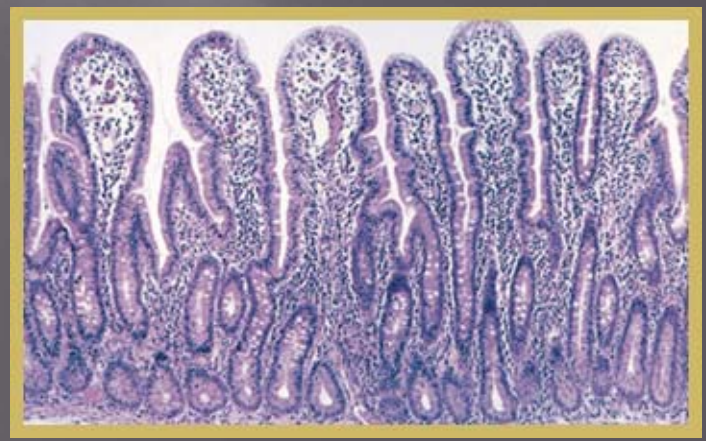
Rostami K, et al. Am J Gastroenterol 1999;94:888–894.

Marsh Grading

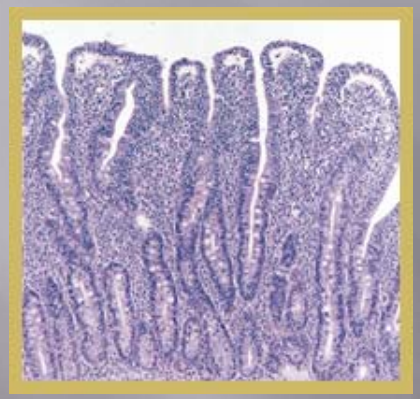
- **Marsh I –** intraepithelial lymphocytes



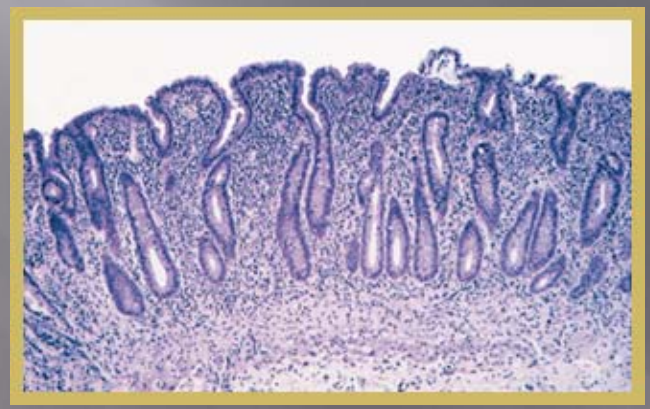
- **Marsh II -** lymphocytic enteritis with crypthyperplasia



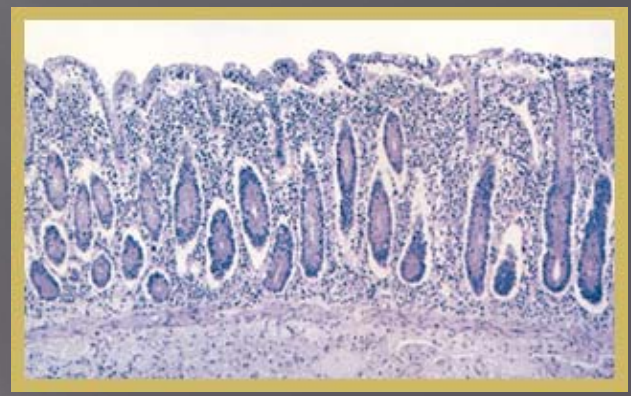
Marsh Grading



Marsh IIIA - partial villous atrophy



Marsh IIIB - subtotal villous atrophy



Marsh IIIC - total villous atrophy

Gluten (Re)Challenge

- Traditional approach to confirm diagnosis
- Administer 10 grams of gluten daily (about 4 slices of regular bread) and perform small bowel biopsy when symptoms occur
- No longer recommended unless the diagnosis is unclear
- Rare risk of fulminant diarrhea (a.k.a. "gliadin shock") characterized by dehydration, acidosis, electrolyte abnormalities

Krainick, HG, et al. Helv Paediatr Acta 1958;13:432

Treatment


CSR
AUSTRALIA'S FAVOURITE
Delicious Gluten Free Delights
CSR
Pure Icing Sugar
CSR
Rich Chocolate Icing Mixture
CSR
Soft Icing Mixture
6
tempting recipes inside

Treatment Objectives

- **C**onsultation with a skilled dietitian
- **E**ducation about the disease
- **L**ifelong adherence to a gluten-free diet
- **I**dentification and treatment of nutritional deficiencies
- **A**ccess to an advocacy group
- **C**ontinuous long-term follow-up by a multidisciplinary team

NIH Consensus Development Conference Statement. Celiac Disease 2004: consensus.nih.gov

The Gluten Free Diet

- Avoid foods containing wheat, barley, and rye
- Accepted substitutes include soybean or tapioca flours, rice, corn, buckwheat, and potatoes
- Patients must be aware of food additives like gluten containing stabilizers or emulsifiers
- Secondary lactose intolerance is common and patients should initially avoid dairy products if symptoms seem to worsen
- In mild disease, moderate consumption of oats is well tolerated (50 to 60 g/day)
- About 70% of patients have clinical improvement within 2 weeks

Pink, IJ, et al. Lancet 1967;1:300

Gluten Free Diet

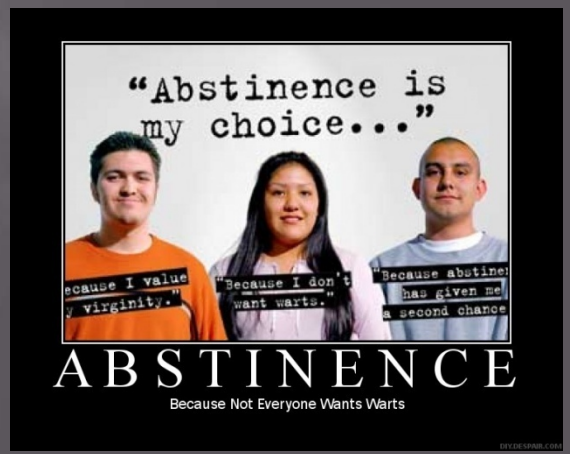
- Total exclusion of gluten, related proteins from the diet
  - Difficult to comply with (<25% after 5 years)
  - Gluten is extremely common in the Western diet
- Hidden gluten is also a problem
  - Likely adds up to 5-50 mg per day
  - Threshold should not exceed 50 mg/day
  - This threshold varies with patients: one patient was reportedly harmed by 1-2 mg gluten/day

Fabiani J. Pediatrics 2000:136;841-3
Catassi Am J Clin Nutr 2007:85;160-66

Do I have to eat like this the rest of my life?

- Answer: YES… for now.
- Once in remission, *some* patients can tolerate small amounts of gluten without noticing symptoms, while other patients are exquisitely sensitive.

- However, there are several reasons to "practice abstinence"



Practicing Abstinence:
The Case For Strict Gluten Avoidance

- Asymptomatic micronutrient deficiencies may improve (i.e. vitamin D deficiency and bone loss)
- Decreases mortality, especially from malignancies like NHL
- Pregnant women with untreated celiac disease are at increased risk for preterm births and low birth weight babies
- Autoimmune disorders related to celiac disease may be related to duration of gluten exposure

Shaker, JL, et al, Arch Intern Med. 1997;157:1013
Holmes, GK, et al. Gut 1989;30:333
Ventura, A, et al. Gastroenterology 1999;117:297
Ludvigsson JF, et al. Am J Gastroenterology 2005;129:454

Perks of Being Gluten Free

- Cohort with 383 patients
- Strict adherence to GFD
- No significant increase in NHL over the general population

Collin P, et al Gut 1996;38:528–530.

General Work-up and Management

- Fe, ferritin, total iron binding capacity
- RBC folate
- Vitamin B12
- 25-OH Vitamin D
- Calcium, ionized calcium
- DEXA scan
- Pneumococcal vaccine (hyposplenism)

Bone Loss

- Mostly due to secondary hyperparathyroidism from vitamin D deficiency
- Laboratory abnormalities include elevated alkaline phosphatase and hypocalcemia

Monitoring Compliance

- NO guidelines exist to direct monitoring of diet adherence
- Sensitivity of serologic tests decrease as histologic grade improves and may be negative prior to full epithelial healing
- In other words, monitoring with serologic tests should be taken "with a grain of salt"
- Some experts suggest repeating small bowel biopsies 3 – 4 months into treatment

Wahab PJ, et al. Am J Clin Pathol 2002;118:459–463.

Refractory Sprue

- Definition: "…continued or recurrent malabsorption and diarrhea with persisting moderate to severe villous atrophy despite adherence to a strict GFD"
- Persistent or intermittent symptoms may be due to inadvertent ingestion of gluten
- Evaluate for coexistent T-cell lymphomas
- Optimal therapy is unknown but often requires immunosuppression

GASTROENTEROLOGY 2006;131:1977–1980

Non-responders to GFD

Microscopic colitis

Lactose intolerance

Pancreatic exocrine insufficiency

Eosinophilic gastroenteritis

Autoimmune enteropathy

Small intestinal bacterial overgrowth

Intestinal lymphoma

Tropical sprue

Common variable immunodeficiency syndrome

True refractory sprue

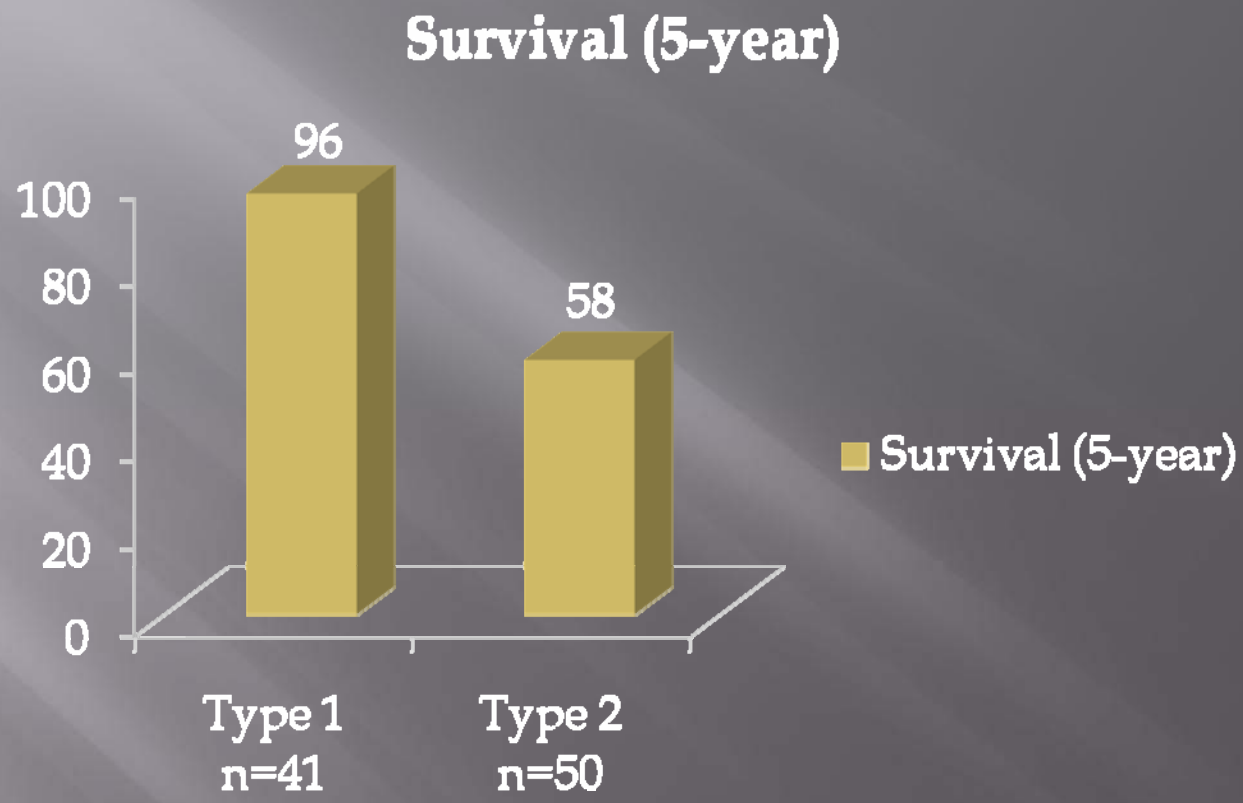
Small bowel stricture

True Refractory Sprue

- Type 1
  - Expansion of phenotypically normal intraepithelial lymphocytes
  - Responds to corticosteroids and/or immunosuppression
- Type 2
  - Clonal expansion of intraepithelial T-cell lymphocytes that express CD3ε, but lack CD4, CD8 and the T-cell receptor β-chain
  - These cells can be driven by interleukin-15 and proliferate independently of gluten stimulation raising the risk of enteropathy associated T-cell lymphoma

Cellier C, et al. Gastroenterology 1998;114:471–481.
Patey-Mariaud DS, et al. Histopathology 2000;37:70–77.

Refractory Sprue 5-Year Survival



Most deaths were due to T-cell lymphoma
No patients with Type 1 disease developed Type 2 disease

Al-Toma, A, et al. Gut 2007;56:1373

Treatment Strategies in Refractory Sprue

- Evidence is limited to clinical experience and case reports
- Aggressively treat nutritional deficiencies, TPN, elemental diets, intravenous steroids, etc.
- Other modalities that have shown success include IV cyclosporine, oral budesonide, azathioprine
- Anti-interleukin-15 antibodies

Areas of Future of CD Treatment

- Adhesion molecule or anti-cytokine therapy
- T-cell immunosuppressive therapy
- Enzymatic therapy to complete gluten digestion
- Tissue transglutaminase inhibitors
- HLA-DQ blockers
- Tight junction enhancement
- Genetic engineering of cereal crops

AT1001-011: Alba's Active Celiac Phase IIb Study

- Larazotide Acetate (AT-1001)
  - Synthetic 8-amino acid peptide intestinal permeability inhibitor
  - Enteric coated multi-particulate bead formulation delivered in gelatin capsules for oral delivery
  - Released 50% into the duodenum and 50% in the jejunum
- Proposal - consumption of AT-1001 15 min. prior to a meal will:
  - temporarily prevent tight junction disassembly caused by gliadin *(via cell cytoskeleton rearrangement)*
  - reduce paracellular leakiness during meal intake and presentation of antigens present within the lumen
  - result in normalization of small bowel pathology and antibody levels

Compliments of G. Dryden, M.D.

CLIN-011
Primary Objective

- To assess the efficacy of larazotide acetate (AT-1001) versus placebo in inducing remission in subjects with active Celiac Disease

- Outcome measurement:
  - histological remission measured by the change of Villous Height to Crypt Depth (Vh:Cd) ratio from Baseline to Day 56
  - Vh:Cd ratio will be determined by duodeno-jejunal biopsy

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Treatment Summary

- This will be an outpatient, randomized, parallel-group, double-blind, multicenter, 8-week study with the following treatment arms:
  - 4 mg, TID (4 mg + placebo)
  - 8 mg, TID (4 mg + 4 mg)
  - Drug Placebo, TID (placebo + placebo)
- Subjects will be divided into 2 groups according to disease presentation:
  - **Intestinal**
    - Subjects experiencing predominantly gastrointestinal symptoms and/or signs.
  - **Extra-intestinal**
    - Subjects experiencing predominantly symptoms and signs other than gastrointestinal, including asymptomatic subjects, but who were diagnosed of Celiac disease based on a positive serology and biopsy/endoscopy.

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Summary

- Celiac Disease is common
- Our understanding of pathophysiology is improving
- IgA tTG auto-antibodies and small intestinal biopsies are the most reliable diagnostic tests
- Alternatives to the gluten free diet are under investigation

THANKS!