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Guest Editors: Robert Cassidy, Crystal Kidd, and Samantha Wright, Pharm.D. Candidates 2013

Key Inforbits

- Introduction to Celiac Disease
- Presentation of Celiac Disease
- Diagnosis of Celiac Disease
- Nonpharmacological Therapy
- Other Treatment Options

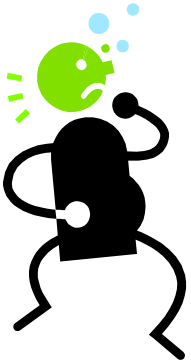
October is…
Celiac Disease Awareness Month

Introduction to Celiac Disease

Celiac disease (CD), also known as celiac sprue, is a common genetic inflammatory disorder with an autoimmune component. It is characterized by the malabsorption of nutrients in the small intestines following the ingestion of wheat gluten or related proteins from rye or barley.[1] This is largely due to the presence of flat lesions affecting the mucosa of the small intestines which result in the absence of normal intestinal villi. Intestinal villi are hair like projections in the intestines which aid in nutrient digestion and increase the surface area. In celiac disease villi are often shortened and/or fused thus reducing the overall surface area and the ability to absorb nutrients. The severity of clinical symptoms is related to the length of the lesion and is significantly improved with a gluten-free diet. It may take months or even years for the mucosa to revert back to normal.[2]

The exact pathogenesis of CD is not completely understood. CD is distinguished from other inflammatory bowel diseases by the presence of the following: class II human leukocyte antigens (HLA)-DQ2 or DQ8, auto-antibodies to the enzyme tissue transglutaminase (tTG), and an environmental trigger (typically gluten).[3] The majority (95%) of the cases of CD are associated with human leukocyte antigen HLA-DQ2 whereas the remaining cases of CD are associated with HLA-DQ8.[4] The introduction of dietary gluten is responsible for initiating the intestinal inflammatory response and the subsequent mucosal injury and destruction.[3] With strict adherence to a gluten free diet these antibodies begin to disappear.[4]

It is estimated that CD affects 1:200 to 1:300 people (~3 million Americans) in Western countries with the majority (95-97%) of patients being undiagnosed. It is estimated that CD affects women more than men (3:1) and is most often found in people of European descent.[5,6,7] The onset of CD often presents in early childhood as failure to thrive due to the malabsorption of nutrients; 25% of new cases of CD are now being diagnosed after the age of 45.[6]



Compared to the general population, people with CD have an increased risk of mortality. Patients with CD appear to have a 3-fold increased risk of non-Hodgkin lymphoma which is substantially less than 40-70-fold increased risk that as was previously thought to exist.[2,3] People with CD are also at an increased risk for other gastrointestinal cancers, anemia, vitamin and mineral deficiencies, depression, neuropathies, and elevated liver enzymes. With strict maintenance of a gluten free diet these risks are decreased to that of the general population.[3]

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Presentation of Celiac Disease

Symptoms of celiac disease will vary depending on the patient's age when the disease begins to appear.

Table 1: Symptoms of Celiac Disease[1]

Infants and young children	Adolescents	Adults
• Diarrhea • Abdominal distention • Failure to thrive **Additional Symptoms:** • Vomiting • Irritability • Anorexia • Constipation	• Poor food absorption • Short stature • Neurologic symptoms • Anemia	• ~50% have diarrhea with or without abdominal discomfort (often misdiagnosed as IBS) **Less Common Symptoms:** • Abdominal pain • Constipation • Weight loss • Neurologic symptoms • Skin rash • Low protein in the blood • Low calcium • Iron-deficiency anemia • Osteoporosis • Elevated liver enzyme levels

Diagnosis of Celiac Disease[1]

- Most people with celiac disease remain undiagnosed; however the rate of diagnosis is rising due to a greater understanding of the disease.
- When a patient presents with the typical symptoms (Table 1), a simple blood test for endomysial IgA antibodies may be ordered to assess if celiac disease could be the underlying cause.
- Two steps are then used to confirm a diagnosis of celiac disease:
    1. An endoscopic exam to take biopsy samples of intestines is the preferred way to document signs of celiac disease.
    2. Celiac disease is finally confirmed when initiating a gluten-free diet resolves all symptoms.

References
1. Green PHR, Cellier C. Celiac disease. N Engl J Med. 2007;357:1731-43.

Management of Celiac Disease

Currently, the only approved treatment for managing celiac disease is establishing a lifelong diet that excludes barley, rye, and wheat.[1,2,3,4] The proteins found in these products have been associated with the autoimmune response seen in celiac disease. Patients must be cautious about the amount of gluten they consume each day. To avoid mucosal damage, celiac patients can safely consume 10 mg of gluten, but no more than 100 mg per day.[1] Table 2 provides examples of foods that contain these causative proteins that are collectively referred to as "gluten"; these examples should be excluded from the diet of celiac patients.

Table 2: Common Sources of Wheat, Rye, and Barley[1,2,3,4]

Causative Proteins	Source	Examples	Substitutions
Gluten	**Wheat**	○ Pasta ○ Bread ○ Cereal ○ Crackers ○ Malt beer	○ Rice/Corn pasta ○ Bread made from tapioca, potato starch, and rice ○ Corn/Puffed rice cereal ○ Sorghum beer
Hordeins	**Barley**	○ Cereal ○ Beer	
Secals	**Rye**	○ Bread ○ Beer	

According to a proposal made by the FDA, manufacturers can state that their food is free of gluten if the following ingredients are not contained in the product:[3]

- Any type of barley, rye, or wheat- including all crossbreeds of these grains
- Unprocessed derivatives of the grains
- Processed ingredients derived from the grains that contain ≥20 parts per million (ppm) of gluten
- Any ingredient that makes the food product contain ≥20 ppm of gluten

Patients with celiac disease need to avoid all sources of gluten, including the gluten that may be in over-the-counter (OTC) and prescription medications.[6] Gluten that is consumed while taking medications can be enough to elicit an unwanted immune response. In fact, consuming just 50 mg of gluten can result in damage to the intestinal mucosa.[6] Patients are advised to ask their pharmacist for help when evaluating which of their prescription medications and OTC products contain gluten. The following list provides various gluten-associated drug excipients:

Drug Excipients That May Contain Gluten[4]

- Dextrins
- Dextrates(unspecified source)
- Dextri-maltose (barley)
- Maltodextrin
- Modified Starch (unspecified source)
- Pregelantinized Starch
- Sodium starch glycolate

Resources for Gluten Status of Medications:[6,7]

- Drug manufactures may be able to provide information about the inactive ingredients that may be sources of gluten.
- The following website provides prescription and OTC medication lists of gluten free drugs:
  www.glutenfreedrugs.com
  www.theceliacsite.com

Patients with celiac disease may still encounter various complications, even if they abide by the lifelong gluten free diet. Most patients will need nutritional supplements due to decreased absorption of nutrients. Various deficiencies are

common to celiac patients, including: vitamin B_{12}, calcium, iron, folate and fat soluble vitamins.[6] Patients may even need additional therapy if they still experience gastrointestinal symptoms while following a gluten free diet. When gluten free dieting isn't enough, patients may need to include immunosuppressive agents such as systemic corticosteroids and the purine analog, azathioprine.

Drug Therapies To Consider[1,6]

- **Systemic corticosteroids**: These agents are considered for immunosuppression in patients who fail to have symptom relief after strictly adhering to a gluten free diet.
- **Azathioprine**: This immunosuppressive agent has been useful when administered after clinical remission has been established with corticosteroid therapy.
- **Infliximab:** This agent is typically considered after patients fail to have improvement following systemic corticosteroid therapy.
- **Dapsone:** This agent may be used when patients initiate their gluten free diet. It helps control itching and rash by suppressing inflammation.
- **Nutritional supplements:** Supplementation of vitamins and minerals is recommended for most celiac patients, especially if they are suffering from deficiencies due to absorption issues.
- **Bisphosphonates:** Are recommended in patients that are diagnosed with osteoporosis

Additional Recommendations[2]

- Regular visits with a dietitian
- Regular laboratory exams to evaluate nutritional status
- Continuous monitoring of gastrointestinal symptoms
- Annual assessment of gluten-free diet adherence
- Monitoring of tTG (tissue transglutaminase)
- Adults with celiac disease should have their bone density evaluated within 1 year of treatment

Recent Developments

- **Reduced-gluten grains**: Genetic modification of wheat by selective breeding
- **Oral enzyme therapeutics**: Clinical studies of endoproteases (ALV003, FM-PEP, and AN-PEP) may help reduce immunogenic response to gluten when administered with gluten-containing meals.
- **Reduced intestinal permeability**: AT-1001 binds to zonulin protein that is up-regulated in the intestinal tissues of celiac patients. Reducing the permeability helps decrease IFN-γ production and decreases intestinal symptoms.
- **Reduced absorption of gluten**: Agents to bind gluten peptides and prevent gut absorption such as Poly (HEMA-co-SS). This monomeric agent interacts with gluten and prevents it from being broken down and stops absorption.
- **Drugs that prevent T cell activation by gluten**: tTG inhibitors (Cystamine) decrease the affinity for gluten-derived peptides, thereby reducing the immune response to gluten.

- **Probiotics**: *Lactobacillus casei* and *Bifidobacteriumlactis* are currently being studied in vitro and in vivo for the restoration of intestinal homeostasis
- **Helminth infections**: *Necatoramericanus* is being studied in clinical phase 2 trials; gluten tolerance has not improved with this therapy
- **Vaccinations to re-establish tolerance to gluten**: Nexvax2 is a vaccination that may induce tolerance to gluten; it is currently in phase 2 clinical trials.

Additional Resources

Organizations

- Celiac Disease Foundation: www.celiac.org
- Gluten Intolerance Group of North America: www.gluten.net
- American Celiac Disease Alliance: www.americanceliac.org

Gluten free diet information

- Gluten free diet guides: www.glutenfreediet.ca
- Restaurant guides: www.triumphdining.com

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The last "dose" …

"If the patient can be cured at all, it must be by means of diet."

~Dr. Samuel Jones Gee [1839 – 1911; English physician and pediatrician]

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