BMJ Best Practice

Celiac disease

The right clinical information, right where it's needed

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Summary

- Systemic autoimmune disease triggered by dietary gluten peptides found in wheat, rye, barley, and related grains.
- Common, affecting up to 1% of the general population, and may present at any age.
- Presentation is varied and ranges from diarrhea and failure to thrive, to iron-deficiency anemia or osteoporosis.
- Diagnosis is suggested by positive immunoglobulin A tissue transglutaminase serology, but must be confirmed by duodenal biopsy and histology.
- The only current therapy is a strict, lifelong gluten-free diet.
- Complications of untreated celiac disease include gastrointestinal symptoms, malabsorption, increased risk of malignancy, and higher overall mortality than in the general population.

Definition

Celiac disease is a systemic autoimmune disease triggered by dietary gluten peptides found in wheat, rye, barley, and related grains. Immune activation in the small intestine leads to villous atrophy, hypertrophy of the intestinal crypts, and increased numbers of lymphocytes in the epithelium and lamina propria. Locally these changes lead to gastrointestinal symptoms and malabsorption. Systemic manifestations are diverse, potentially affecting almost every organ system.

Epidemiology

Celiac disease is a common disorder in the US and in Europe. A relatively uniform prevalence has been found in many countries, ranging between 1 in 67 and 1 in 250 with an approximate average of 1% in well-designed studies from diverse areas including North and South America, eastern and western Europe, Turkey, the Middle East, and North Africa.[1] [2] [3] [4] [5] [6] [7] [8] [9] It is far less common in people from southeast Asia and sub-Saharan Africa.

In population studies, men and women are roughly equally affected. In clinical practice, however, women tend to make up almost two-thirds of patients. The first peak period of presentation is in childhood around age 6 to 7 years, but celiac disease can arise as soon as gluten is introduced. A second, larger peak occurs in the fourth and fifth decades. Although the most common age at diagnosis in the US is about 40 years, celiac disease may be diagnosed at any age.[10] [11]

Silent celiac disease is serologic and histologic evidence of celiac disease, but without any evident symptoms, signs, or deficiency states. The proportion of celiac disease that is truly silent is not well known, but it is thought to account for at least 20% of cases.

Refractory celiac disease is a specific diagnosis within the category of nonresponsive celiac disease, defined as the persistence of clinical symptoms and histologic abnormalities after at least 6 months on a strict gluten-free diet and in the absence of other evident causes or of overt lymphoma. The incidence of refractory celiac disease in patients with celiac disease is not well known but is felt to be approximately 1%.

Etiology

Celiac disease is a systemic autoimmune disorder triggered by gluten peptides from grains including wheat, rye, and barley. Almost all people with celiac disease carry one of 2 major histocompatibility complex class-II molecules (HLA-DQ2 or -DQ8) that are required to present gluten peptides in a manner that activates an antigen-specific T cell response. The requirement for DQ2 or DQ8 is a major factor in the genetic predisposition to celiac disease. However, most DQ2- or DQ8-positive people never develop celiac disease despite daily exposure to dietary gluten. The additional environmental or genetic factors that are required for loss of immune tolerance to dietary gluten are unknown. Factors that have been hypothesized to play a role include: the timing of initial gluten exposure; gastrointestinal infection leading to gluten antigen mimicry; or direct damage to the intestinal-epithelial barrier leading to abnormal exposure of the mucosa to gluten peptides.

Pathophysiology

Loss of immune tolerance to gliadin peptide antigens derived from wheat, rye, barley, and related grains is the central abnormality of celiac disease. These peptides are resistant to human proteases, allowing them to persist intact in the small intestinal lumen.[12] It is unknown how these peptides gain access to the lamina propria, but leading hypotheses include faulty tight junctions, endothelial cell transcytosis, sampling of the intestinal lumen by dendritic cells, and passage during resorption of apoptotic villous enterocytes.

In the intestinal submucosa these peptides trigger both innate and adaptive immune activation. The mechanism of innate immune activation is not fully known. Gluten peptides are clearly able to stimulate interleukin-15 production by dendritic cells and macrophages, which then stimulate intraepithelial lymphocytes, leading to epithelial damage.[13] [14] In the submucosa, gluten peptides are deamidated by tissue transglutaminase (tTG), an enzyme normally involved in collagen cross-linking and tissue remodeling. Deamidation of the gliadin peptide allows for, first, high-affinity binding to the celiac-associated HLA peptides (DQ2 or DQ8) found on antigen-presenting cells, and second, activation of helper T (Th) cells.[15] For this reason people must carry either HLA-DQ2 (95% of patients with celiac disease) or -DQ8 (5% of patients with celiac disease) to develop celiac disease. Stimulation of Th cells has 2 consequences. Cell death and tissue remodeling with villous atrophy and crypt hyperplasia are induced by Th1-derived cytotoxic T lymphocytes. Th2 triggers plasma cell maturation and subsequent antigliadin and anti-tTG antibody production.[16]

Classification

Subgroups of celiac disease

There is no formal classification of celiac disease; however, it can be divided into common subgroups.

1. Classic celiac disease: typical symptoms including diarrhea, weight loss, abdominal pain and discomfort, and fatigue. Classic symptoms are found in <50% of patients.
2. Atypical celiac disease: lacks the typical gastrointestinal symptoms of malabsorption; presents with deficiency states (e.g., iron deficiency) or extraintestinal manifestations (e.g., fatigue, elevated liver enzymes, or infertility). However, atypical disease likely accounts for the largest proportion of patients with a diagnosis of celiac disease.
3. Silent celiac disease: serologic and histologic evidence of celiac disease, but without any evident symptoms, signs, or deficiency states. The proportion of celiac disease that is truly silent is not well known, but it is thought to account for at least 20% of cases.
4. Nonresponsive celiac disease: clinical symptoms or laboratory abnormalities typical of celiac disease fail to improve within 6 months of gluten withdrawal, or typical symptoms or laboratory abnormalities recur while the patient is on a gluten-free diet.
5. Refractory celiac disease: specific diagnosis within the category of nonresponsive celiac disease, defined as the persistence of clinical symptoms and histologic abnormalities after at least 6 months on a strict gluten-free diet and in the absence of other evident causes or of overt lymphoma. The incidence of refractory celiac disease in patients with celiac disease is not well known but is felt to be approximately 1%.

Secondary prevention

The current accepted approach is aggressive case finding with vigilance for the many potential manifestations of celiac disease and a low threshold for serologic testing. Perhaps the group of most concern is young children with a first-degree relative with celiac disease, as the approximate 7% risk of celiac disease is considerable and delayed diagnosis has the potential to lead to a permanent loss in growth potential. For this reason serologic testing may be considered before the onset of symptoms in at-risk children. Well-designed, randomized clinical trials do not suggest that either breastfeeding or timing of gluten introduction into the diet alter the risk of celiac disease in children with a family history of celiac disease.[78] [79] [80]

Case history

Case history #1

A 46-year-old woman presents with fatigue and is found to have iron deficiency with anemia. She has experienced intermittent episodes of mild diarrhea for many years, previously diagnosed as irritable bowel syndrome and lactose intolerance. She has no current significant gastrointestinal symptoms. Examination reveals 2 oral aphthous ulcers and pallor. Abdominal examination is normal and results of fecal testing for occult blood are negative.

Other presentations

Atypical presentations include an asymptomatic patient, elevated liver enzymes, vitamin D deficiency, osteopenia or osteoporosis, constipation, aphthous stomatitis, nausea or vomiting, heartburn or gastroesophageal reflux disease, hyposplenia or asplenia, myalgias, arthralgias, peripheral neuropathy, alopecia, headaches, infertility, and adverse pregnancy outcomes.

Step-by-step diagnostic approach

Celiac disease can present in many varied ways and requires a high degree of clinical suspicion.

Presenting features

Patients with unexplained gastrointestinal symptoms (including those diagnosed with irritable bowel syndrome and/or dyspepsia), chronic diarrhea, unexplained iron deficiency anemia, or a skin rash consistent with dermatitis herpetiformis should be tested for celiac disease.[27] [28] Other situations that may prompt testing include failure to thrive, short stature, vitamin deficiency (B12, D, or folate), recurrent severe aphthous stomatitis, recurrent spontaneous abortion, and infertility.[29]

Investigations

Before testing, it is crucial to ensure that the patient is ingesting gluten, because all diagnostic tests will normalize on a gluten-free diet.

1. Serology

- Immunoglobulin A-tissue transglutaminase (IgA-tTG) titer should be evaluated.[30] [31] Although not supported by evidence, quantitative IgA is often routinely requested to assess for IgA deficiency.
- Endomysial antibody (EMA) is a more expensive alternative to IgA-tTG, with greater specificity but lower sensitivity, which may be used if IgA-tTG is unavailable.[32] Unlike tTG, which is an ELISA, EMA is based on immunofluorescence and thus is operator dependent.
- In cases of IgA deficiency, request IgG-deamidated gliadin peptide (DGP) serology, although the diagnostic accuracy of this test is somewhat less than that of IgA-tTG.[31] [33] Patients with an elevated IgA-tTG level should be advised to remain on a gluten-containing diet and referred for duodenal biopsy. It is also reasonable to proceed to duodenal biopsy in patients with IgA deficiency. IgG-tTG was previously one of the common serologic tests for celiac disease in individuals with

known or suspected IgA deficiency. However, this test has been largely replaced by the newer and more accurate IgG DGP or IgA/IgG DGP.
- A normal IgA-tTG and total IgA test result are adequate to exclude a diagnosis in patients with a low clinical index of suspicion for celiac disease.

2. Histology

- Patients with an elevated IgA-tTG level should be advised to remain on a gluten-containing diet and referred for duodenal biopsy.
- Small intestinal biopsies should be obtained regardless of the IgA-tTG result in patients with a high clinical index of suspicion. However, pediatric patients with symptoms consistent with celiac disease and a high IgA-tTG titer (above normal range for laboratory) may go on to have confirmatory EMA and HLA-DQ2/-DQ8 testing. If both of these are positive, celiac disease may be considered confirmed without a small intestinal biopsy. However, the accuracy and cost-effectiveness of this strategy has not been rigorously evaluated in adults or outside of European populations.[34]
- Duodenal biopsy changes in celiac disease are typically graded by the Marsh classification, from 0 to 4.[35] To diagnose celiac disease, intraepithelial lymphocytes should be increased and the villous-to-crypt ratio decreased. The presence of only one of these changes raises the possibility of a different diagnosis.
[Fig-1]
- The presence of typical celiac changes on duodenal histology with clinical improvement on a gluten-free diet confirms the diagnosis. A repeat duodenal biopsy after gluten withdrawal is no longer routinely necessary for verification.
[Fig-2]

[Fig-3]

[Fig-4]

3. HLA testing

- May be used to rule out celiac disease in patients already on a gluten-free diet or in patients with an idiopathic celiac-like enteropathy, but is not helpful for diagnosis.

4. Endoscopy

- Atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa may be seen, but the endoscopic appearance of the small bowel is generally not helpful in diagnosis.
[Fig-5]

[Fig-6]

Gluten challenge

People with celiac disease on a gluten-free diet prior to evaluation cannot be differentiated from healthy controls. In these cases, gluten challenge is necessary. In a gluten challenge, the person is placed back on a gluten-containing diet, with serologic tests and small bowel histology assessed after 2 to 8 weeks on the gluten-containing diet.[36]

Home-performed quick tests

Rapid finger-stick tTG tests are available that can give a positive or negative results either at home or at the bedside. Results are available within 30 minutes. Accuracy appears similar to that of standard tTG testing, but the lack of a titer that can be followed over time is a disadvantage. The clinical role for this is still being evaluated, but clearly in areas where a lab for running standard tests is not available, point-of-care testing should be considered.

Saliva celiac genetic tests can show the presence of the HLA-DQ2 or HLA-DQ8 genes. It is important to counsel that having these genes is not equivalent to having celiac disease, and having these genes alone does not have any known prognostic value. If the test is negative, a person's risk for celiac disease is extremely low.

Risk factors

Strong

FHx of celiac disease

- Multiple studies have shown an increased risk in family members, likely secondary to genetic factors.[17]

IgA deficiency

- Multiple studies have shown an association between IgA deficiency and celiac disease. Although the pathogenesis is unclear, it has been proposed that a lack of secretory IgA and Peyer patch malfunction allow for increased free gluten peptides in the submucosa.[18]

type 1 diabetes

- Multiple studies have shown an association between type 1 diabetes mellitus and celiac disease. This is probably due to genetic factors favoring autoimmunity. Leaky gut, with tight junction defects leading to increased passage of luminal peptides into the submucosa, resulting in immune activation, is also hypothesized.[19] [20]

autoimmune thyroid disease

- Multiple studies have shown an association between thyroid disease and celiac disease. Pathogenesis is similar to that of type 1 diabetes mellitus.[21]

Weak

Down syndrome

- Many studies show an association between Down syndrome and celiac disease, although one study refutes this. The mechanism is unclear because celiac disease does not appear to be linked to genes found on chromosome 21.[22] [23]

Sjogren syndrome

- Some studies have shown an increased prevalence of celiac disease in patients with Sjogren syndrome.[24]

inflammatory bowel disease

- A few studies have shown an increased prevalence of celiac disease in patients with Crohn disease and, to a lesser extent, ulcerative colitis.[25]

primary biliary cirrhosis

- Studies have shown an increased prevalence of celiac auto-antibodies in patients with primary biliary cirrhosis and other liver diseases, but false positives appear higher in these populations.[26]

History & examination factors

Key diagnostic factors

IgA deficiency (common)

- Multiple studies have shown an association between IgA deficiency and celiac disease. Although the pathogenesis is unclear, it has been proposed that a lack of secretory IgA and Peyer patch malfunction allow for increased free gluten peptides in the submucosa.[18]

diarrhea (common)

- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[30] Patients may present with chronic or intermittent diarrhea.

bloating (common)

- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[30]

abdominal pain/discomfort (common)

- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[30] Patients may present with recurrent abdominal pain, cramping, or distension.[38]

anemia (common)

- Iron deficiency anemia is the most common clinical presentation in adults. Folate (and rarely vitamin B12) deficiency may lead to a macrocytic anemia.[39]

dermatitis herpetiformis (uncommon)

- Characterized by intensely pruritic papulovesicular lesions that occur symmetrically over the extensor surfaces of the arms and legs, as well as on the buttocks, trunk, neck, and scalp.[39] Biopsy-proven dermatitis herpetiformis almost universally occurs in association with celiac disease.

Other diagnostic factors

FHx (common)

- FHx of celiac disease or other autoimmune disorders.

osteopenia/osteoporosis (common)

- History of bone pain or previous fracture, due to vitamin D deficiency and hypocalcemia.

fatigue (common)

- Associated with iron deficiency anemia.[39]

weight loss (common)

- Likely multifactorial, primarily due to malabsorption but also to changes in motility, metabolism, and appetite.[39]

failure to thrive (common)

- In children, faltering growth and delayed puberty are indications for testing for celiac disease.[40]

type 1 diabetes (uncommon)

- Clinicians caring for patients with type 1 diabetes mellitus should be aware of the association with celiac disease and consider testing if symptoms occur.[37]

autoimmune thyroid disease (uncommon)

- Clinicians caring for patients with autoimmune thyroid disease should be aware of the association with celiac disease and consider testing if symptoms occur.[37]

aphthous stomatitis (uncommon)

- Caused by various nutritional deficiencies, although the particular deficiency is not always evident.[41] May be recurrent.

dental enamel hypoplasia (uncommon)

- The exact etiology is unclear but is felt to be due to nutritionally derived abnormalities in mineralization.

alopecia (uncommon)

- Alopecia areata is an autoimmune disease associated with celiac disease that may be reversed with a gluten-free diet.

easy bruising (uncommon)

- Vitamin K deficiency may lead to a coagulopathy.

peripheral neuropathy (uncommon)

- The etiology of neurologic dysfunction may be the result of either vitamin deficiencies (B12, E, or D; folate or pyridoxine) or autoimmune activity against neural antigens.[41]

ataxia (uncommon)

- Cerebellar ataxia is one of the more common neurologic symptoms.[41]

Diagnostic tests

1st test to order

Test	Result
CBC and blood smear • Iron deficiency anemia is the most common clinical presentation in adults. • Folate (and rarely vitamin B12) deficiency may lead to a macrocytic anemia.[39]	**low Hb and microcytic red cells**
IgA-tTG • Order an immunoglobulin A-tissue transglutaminase (IgA-tTG) test in any case of suspected celiac disease.[30] • Higher titers have increased positive predictive value.	**titer above normal range for laboratory**
EMA • Endomysial antibody (EMA) is a more expensive alternative to IgA-tTG with greater specificity but lower sensitivity. • Perform initially if IgA-tTG is unavailable.[32]	**elevated titer**
skin bx • Order this test initially in any cases of skin lesions suggestive of dermatitis herpetiformis. • Both sensitivity and specificity are high.	**granular deposits of IgA at the dermal papillae of lesional and perilesional skin by direct immunofluorescence**
IgG DGP or IgA/IgG DGP (deamidated gliadin peptide) • Test of choice for individuals with IgA deficiency.	**elevated titer**
IgG-tTG • IgG-tTG was previously one of the common serologic tests for celiac disease in individuals with known or suspected IgA deficiency. However, this test has been largely replaced by the newer and more accurate IgG DGP or IgA/IgG DGP (deamidated gliadin peptide).	**elevated titer**

Other tests to consider

Test	Result
HLA typing • This genetic test is useful to rule out celiac disease in patients already on a gluten-free diet or in patients with an idiopathic celiac-like enteropathy.	**positive HLA-DQ2 or -DQ8**
small bowel - macroscopic • The endoscopic appearance is generally not helpful in diagnosis. [Fig-5] [Fig-6]	**atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa**

Test	Result
small bowel - histology • Small-bowel histology is the most specific and sensitive test. • If possible, grade the results according to the Marsh criteria. • Perform small-bowel histology in cases of positive serology or IgA deficiency or in cases of high clinical suspicion despite negative serology. • Pediatric patients with symptoms consistent with celiac disease and a high IgA-tTG titer (above normal range for laboratory) may go on to have confirmatory EMA and HLA-DQ2/-DQ8 testing. If both of these are positive, celiac disease may be considered confirmed without a small intestinal biopsy.[34] • Both sensitivity and specificity are high. [Fig-1] [Fig-2]	**presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia**
gluten challenge • People with celiac disease on a gluten-free diet prior to evaluation cannot be differentiated from healthy controls. In these cases, gluten challenge is necessary. In a gluten challenge, the person is placed back on a gluten-containing diet, with serologic tests and small bowel histology assessed after 2 to 8 weeks on the gluten-containing diet.[36]	**increase in celiac serologic tests and presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia on small intestinal biopsy**

Emerging tests

Test	Result
point-of-care tTG testing • Rapid finger-stick tTG tests are now available that can give a positive or negative result either at home or at the bedside. Results are available within 30 minutes. Accuracy appears similar to standard tTG testing, but the lack of a titer that can be followed over time is a disadvantage. The clinical role for this is still being evaluated, but clearly in areas where a lab for running standard tests is not available, point-of-care testing should be considered.	**positive or negative**
saliva celiac genetic test • It is important to counsel that having HLA-DQ2 or HLA-DQ8 is not equivalent to having celiac disease, and having these genes alone does not have any known prognostic value. If this test is negative, a person's risk for celiac disease is extremely low.	**positive or negative for either HLA-DQ2 or HLA-DQ8**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Peptic duodenitis	• Patients present with chronic or recurrent abdominal pain or discomfort centered in the upper abdomen that is commonly related to eating. There may be a history of nonsteroidal anti-inflammatory drug (NSAID) use and use of antacid medications to relieve the discomfort.	• Peptic duodenitis is associated with acid injury and leads to a spectrum of histologic mucosal changes that may be difficult to distinguish from that seen in celiac disease.[42] For this reason it is recommended that biopsies are not taken in the duodenal bulb, but rather in the second or third portion of the duodenum, which are relatively protected from peptic injury.
Crohn disease	• Crohn disease can affect any part of the gastrointestinal tract, and symptoms may be extremely variable.	• The classic findings on histologic examination include granulomas, ulcerations, and acute and chronic inflammation often extending throughout all layers of bowel wall. • Tissue transglutaminase (tTG) serology is usually negative and there should be no response to gluten withdrawal.
Giardiasis	• Giardiasis is a diarrheal illness caused by infection with a waterborne parasite, *Giardia lamblia* . A history of exposure to contaminated water may suggest the diagnosis.[43]	• Multiple stool specimens usually reveal the parasite. Alternative methods for detection are antigen detection tests by enzyme immunoassays and detection of parasites by immunofluorescence.[43]
Small-intestinal bacterial overgrowth	• History may show conditions that alter intestinal anatomy, motility, and gastric acid secretion (such as use of proton pump inhibitors or anatomic disturbances in the bowel, including fistulae, diverticula, and blind loops created after surgery).[44]	• The definitive investigation requires culture of jejunal fluid that grows in excess of 10^5 bacteria/mL. Hydrogen breath testing may show malabsorption but is not very sensitive or specific for bacterial overgrowth. A trial of treatment with antibiotics for 1 week may give the diagnosis.[45]

Condition	Differentiating signs / symptoms	Differentiating tests
Postgastroenteritis	• In some children a clinical episode indistinguishable from acute gastroenteritis is followed by protracted diarrhea. This may be related to prolonged rotavirus infection[46] or transient lactose intolerance.	• Usually no investigations are required.
Eosinophilic enteritis	• Eosinophilic enteritis may affect any part of the alimentary canal and can present with anemia, diarrhea, abdominal pain, and weight loss. Often no cause is identified, although nematode infections are often isolated.[47]	• Diagnosis follows endoscopic or laparoscopic biopsy of the affected bowel with histology showing eosinophilic infiltrates.[47]
Tropical sprue	• Tropical sprue is a disease that causes progressive villous atrophy in the small intestine that is similar to celiac sprue. It is believed to be initiated or sustained by a still-undefined infection. The relapse rate is substantial in treated patients who remain in, or return to, endemic areas in the tropics.[48]	• Antibiotic therapy with tetracyclines for 6 months normalizes mucosal structure in the small intestine.[48]
CVID and other immunodeficiency states	• Common variable immune deficiency (CVID) and related disorders have a history of recurrent infections.	• Negative tTG serology and decreased immunoglobulin levels suggest immunodeficiency.
GVHD	• Graft-versus-host disease (GVHD) can occur with any organ transplantation but is most common after bone marrow transplantation. Patients have high-volume watery diarrhea about 3 weeks after transplantation if GVHD is present.[49]	• Endoscopic biopsy showing the presence of increased numbers of apoptotic epithelial cells in the intestinal crypts is diagnostic.[49]
Autoimmune enteropathy	• This condition is characterized by villous atrophy that is unresponsive to any dietary restrictions.[50]	• Negative for immunoglobulin A antigliadin and antiendomysial antibodies. • Immunofluorescence staining may show enterocyte antibodies.[50]

Condition	Differentiating signs / symptoms	Differentiating tests
Drug-induced enteropathy	• May be clinically and pathologically indistinguishable from celiac disease. • Olmesartan, an angiotensin-II receptor antagonist, has been associated with enteropathy.[51] • There have also been case reports with other angiotensin-II receptor antagonists and mycophenolate.[52]	• tTG serology is normal. • Symptoms remit once causative drug is stopped.

Diagnostic criteria

Marsh criteria[35]

Histologic changes on small intestinal biopsy

- 0: normal villous architecture with no increase in intraepithelial lymphocytes
- I: normal villous architecture with increased intraepithelial lymphocytes
- II: increased intraepithelial lymphocytes and crypt hyperplasia with normal villi
- IIIa: increased intraepithelial lymphocytes and crypt hyperplasia with partial villous atrophy
- IIIb: increased intraepithelial lymphocytes and crypt hyperplasia with subtotal villous atrophy
- IIIc: increased intraepithelial lymphocytes and crypt hyperplasia with total villous atrophy.

Step-by-step treatment approach

The only accepted treatment of celiac disease is a strict lifelong gluten-free diet.

Dietary advice

The diet should not be started until definitive diagnosis has been made by small intestinal histology. After diagnosis the patient should be referred to a nutritionist with specific training in celiac disease and the gluten-free diet. Gluten-free diet adherence has been shown to be difficult, with dietary lapses in the majority of patients.[58] For this reason the importance of the diet should be stressed, and social support evaluated and encouraged within the family and by membership in celiac disease advocacy groups.

Supplementation

After diagnosis, patients should be checked for common deficiencies including iron and vitamin D. All patients with celiac disease should be recommended to take calcium and vitamin D supplements. Iron should only be given to individuals with iron deficiency. Bone mineral density should be evaluated after approximately 1 year on a gluten-free diet to assess for osteopenia or osteoporosis.

Failure to respond to treatment

For individuals who do not respond to a gluten-free diet, the most common problem is continued gluten exposure. The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase (IgA-tTG) titer and referral to a nutritionist with expertise in celiac disease. If there is no evidence of continuing gluten intake, referral to a gastroenterologist with experience in the evaluation of nonresponsive celiac disease is recommended.

Refractory celiac disease is defined as the persistence of villous atrophy despite strict gluten withdrawal and no evidence of another abnormality including overt lymphoma. It is present in <1% of patients with celiac disease and is felt to be a spectrum determined by T-cell clonality and loss of normal intraepithelial cell markers.[59] Common associations with refractory celiac disease include ulcerative jejunitis and enteropathy-associated T-cell lymphoma. The outlook for patients is generally poor. They should be cared for at a center experienced in celiac disease.

Celiac crisis

Celiac crisis is rare and presents with hypovolemia, severe watery diarrhea, acidosis, hypocalcemia, and hypoalbuminemia. Patients are often emaciated and have nutritional deficiencies caused by longstanding, untreated celiac disease. In addition to rehydration and correction of electrolyte abnormalities, these few patients may benefit from a short course of systemic glucocorticoid therapy until the gluten-free diet takes effect.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Ongoing		(summary)
Patient group	**Tx line**	**Treatment**

Ongoing (summary)

celiac disease	1st	gluten-free diet
	plus	calcium and vitamin D supplementation ± iron
▪ refractory celiac disease	plus	referral to nutritionist or gastroenterologist
▪ celiac crisis	plus	rehydration + correction of electrolyte abnormalities
▪ celiac crisis	adjunct	corticosteroid

Treatment options

Ongoing

Patient group	Tx line	Treatment
celiac disease	**1st**	**gluten-free diet**

» The gluten-free diet is the only accepted treatment of celiac disease. Adherence is difficult, and dietary changes may lead to deficiencies in fiber and other nutrients, so consultation with a nutritionist should be sought.[58] Although the safety of oats in celiac disease has been controversial, there is substantial evidence that oats that are not contaminated by wheat or barley are safe for the vast majority of patients with celiac disease.[60] [61] [62] In practice, oats should be avoided until the patient is in clinical remission, and then wheat-free oats may be gradually added to the diet.

» A number of agents are under investigation, but these treatments appear unlikely to replace the gluten-free diet. Rather, they may be used to allow for laxity in situations of low-level gluten exposure: for example, in food additives.

plus **calcium and vitamin D supplementation ± iron**

» After diagnosis, patients should be checked for common deficiencies including iron and vitamin D.

» All patients with celiac disease should take calcium and vitamin D supplements. Iron should only be given to individuals with iron deficiency.

» Bone mineral density should be evaluated after approximately 1 year on gluten-free diet to assess for osteopenia or osteoporosis.

» Doses are individualized according to age and presence of deficiencies or decreased bone density.

Primary options

» ergocalciferol (vitamin D2): 1000-2000 units orally once daily
-and-
» calcium carbonate: 1000-1500 mg/day orally given in 3-4 divided doses
Dose refers to elemental calcium.

Ongoing

Patient group	Tx line	Treatment
		OR **Primary options** » ergocalciferol (vitamin D2): 1000-2000 units orally once daily **-and-** » calcium carbonate: 1000-1500 mg/day orally given in 3-4 divided doses Dose refers to elemental calcium. **-and-** » ferrous sulfate: 300 mg orally (immediate-release) two to four times daily Dose refers to ferrous sulfate salt.
refractory celiac disease	**plus**	**referral to nutritionist or gastroenterologist** » For individuals who do not respond to a gluten-free diet, the most common problem is continued gluten exposure. The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase (IgA-tTG) titer and referral to a nutritionist with expertise in celiac disease. If there is no evidence of continuing gluten intake, referral to a gastroenterologist with experience in the evaluation of nonresponsive celiac disease is recommended. » The outlook for patients can be poor. They should be cared for at a center experienced in celiac disease.
celiac crisis	**plus**	**rehydration + correction of electrolyte abnormalities** » Celiac crisis is rare and presents with hypovolemia, severe watery diarrhea, acidosis, hypocalcemia, and hypoalbuminemia. Patients are often emaciated and have nutritional deficiencies caused by longstanding, untreated celiac disease.
celiac crisis	**adjunct**	**corticosteroid** » In addition to rehydration and correction of electrolyte abnormalities, patients with celiac crisis may benefit from a short course of glucocorticoid therapy until the gluten-free diet takes effect. » If patients are able to take oral medications, budesonide may be used initially. If this is not effective, prednisone or an equivalent systemic corticosteroid can be started, and should be tapered slowly after the patient is able to

Ongoing

Patient group	Tx line	Treatment
		maintain hydration and nutritional status without intravenous supplementation. **Primary options** » budesonide: 9 mg orally (enteric-coated) once daily **OR** **Primary options** » prednisone: 40-60 mg orally once daily initially then taper dose slowly **OR** **Secondary options** » methylprednisolone sodium succinate: consult specialist for guidance on dose

Emerging

Endopeptidases

Glutenase ALV003 may digest gluten within the intestinal lumen into nonantigenic peptides. Based on a phase II trial, it appears to attenuate gluten-induced mucosal injury in the small intestine in patients with celiac disease.[63]

Zonulin antagonists

These antagonists may strengthen tight junctions and prevent gluten from infiltrating the mucosa.[64]

tTG inhibitors

Tissue transglutaminase (tTG) inhibitors may prevent the deamidation and resultant potentiation of gliadin peptides.[16]

Blockers of the interaction of gliadin peptides with HLA-DQ2 or -DQ8

These agents may prevent T cell activation.

Immune modulation

Immune modulation may restore gluten tolerance.[65]

Probiotics

Early evidence suggests some strains of probiotics may assist with intestinal healing.[66]

Recommendations

Monitoring

Although not supported by data, many clinicians will check immunoglobulin A-tissue transglutaminase (IgA-tTG) titers every 3 months until normalized and then yearly as a rough test of diet adherence. In most cases, IgA-tTG titer should normalize within 6 to 9 months.[77]

Refer to a nutritionist at diagnosis and yearly to instruct and monitor gluten-free diet adherence.

Treat deficiency states present at diagnosis with oral supplementation and monitor until resolved.

Repeat endoscopy is not routinely necessary in patients responding well clinically and in whom IgA-tTG has normalized.

Patient instructions

Immediately upon diagnosis the patient should be recommended to avoid all products containing wheat, rye, barley, and spelt. [National Digestive Diseases Information Clearinghouse: celiac disease] [Gluten-free drugs] [New England Celiac Organization] Although not technically a trigger for celiac disease, oats should be avoided at the outset as many products are contaminated with wheat and a minority of celiac patients may be oat-intolerant. The gluten-free diet is demanding, especially at the outset, and referral to both a nutritionist skilled in celiac disease and a local support/advocacy group is strongly recommended. Patients should be reassured that adopting the diet is a challenge and mistakes and difficulties adjusting early on are common.

Complications

Complications	Timeframe	Likelihood
osteoporosis/osteopenia	**variable**	**medium**
Reduced bone mineral density is common in celiac disease and often improves significantly within 1 year of gluten withdrawal. Although no evidence supports this, bone mineral density may be checked in patients after they have been on a gluten-free diet for 1 year.[74] [75] [76]		
dermatitis herpetiformis	**variable**	**medium**
Dermatitis herpetiformis is the skin manifestation of active celiac disease. Episodes can recur even on a strict gluten-free diet. In these cases, treatment with dapsone in conjunction with the gluten-free diet may be helpful.		
malignancy	**variable**	**low**
Some malignancies are more common in patients with celiac disease, including intestinal and extraintestinal lymphoma and carcinomas of the upper digestive tract. The magnitude of increased risk is moderate (standardized incidence ratio of 1.3, 95% CI 1.2 to 1.5 in one study[71]) and appears to normalize within a few years of gluten withdrawal. No additional screening is recommended.[72] [73]		

FOLLOW UP

Complications	Timeframe	Likelihood
idiopathic recurrent acute pancreatitis/chronic pancreatitis	**variable**	**low**
Celiac disease may present as recurrent acute pancreatitis or be complicated by chronic pancreatitis. Both conditions are unusual and do not warrant screening. In patients with treated celiac disease and persistent diarrhea, pancreatic exocrine insufficiency can be considered.		

Prognosis

The prognosis for patients with celiac disease is good.[69] Most, up to 90% in some studies, will have complete and lasting resolution of symptoms on a gluten-free diet alone. For the 10% with persistent symptoms, most of these will be attributed to ongoing gluten exposure, lactose intolerance, and irritable bowel syndrome. Less than 1% can be expected to develop refractory celiac disease.[70]

Diagnostic guidelines

International

Celiac disease: screening US Preventive Services Task Force. Celiac disease: screening. March 2017. https://www.uspreventiveservicestaskforce.org (last accessed 5 June 2017). https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/celiac-disease-screening

Published by: US Preventive Services Task Force **Last published:** 2017

Summary: Concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for celiac disease in asymptomatic adults, adolescents, and children.

Diagnosis and management of celiac disease 23609613 Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108:656-676. http://gi.org/guideline/diagnosis-and-management-of-celiac-disease/

Published by: American College of Gastroenterology **Last published:** 2013

Summary: Recommendations for the diagnosis and management of patients with celiac disease.

Guideline for the diagnosis and treatment of celiac disease in children 15625418 Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40:1-19. http://journals.lww.com/jpgn/Fulltext/2005/01000/Guideline_for_the_Diagnosis_and_Treatment_of.1.aspx

Published by: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition **Last published:** 2005

Summary: Diagnosis guidelines pertaining specifically to the pediatric population.

WGO practice guideline: celiac disease World Gastroenterology Organisation. WGO practice guideline: celiac disease. July 2016. http://www.worldgastroenterology.org/ (last accessed 5 June 2017). http://www.worldgastroenterology.org/guidelines/global-guidelines/celiac-disease/celiac-disease-english

Published by: World Gastroenterology Organisation **Last published:** 2016

Summary: Recommends diagnostic tests for celiac disease, including intestinal biopsy and specific serum antibodies (IgA EMA, IgA tTg, IgA AGA, IgG AGA). Details the clinical presentation, epidemiology, and differential diagnosis for celiac disease.

International

Coeliac disease: recognition, assessment and management National Institute for Health and Care Excellence. Coeliac disease: recognition, assessment and management. September 2015. https://www.nice.org.uk (last accessed 5 June 2017). https://www.nice.org.uk/guidance/ng20

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2015

Summary: Covers assessment of celiac disease in children, young people, and adults.

Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders 25826168 Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2015;47:352-376. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1391855

Published by: European Society of Gastrointestinal Endoscopy **Last published:** 2015

Summary: Recommends against the use of small-bowel capsule endoscopy for suspected celiac disease but suggests that capsule endoscopy could be used in patients unwilling or unable to undergo conventional endoscopy.

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease 22197856 Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-160. http://journals.lww.com/jpgn/Fulltext/2012/01000/European_Society_for_Pediatric_Gastroenterology,.28.aspx

Published by: European Society for Paediatric Gastroenterology, Hepatology, and Nutrition **Last published:** 2012

Summary: Guidelines for the diagnosis of celiac disease, based on scientific and technical developments using an evidence-based approach.

International

Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease 18664878 Fasano A, Araya M, Bhatnagar S, et al; Celiac Disease Working Group, FISPGHAN. Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease. J Pediatr Gastroenterol Nutr. 2008;47:214-219. http://journals.lww.com/jpgn/Fulltext/2008/08000/Federation_of_International_Societies_of_Pediatric.19.aspx

Published by: Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition **Last published:** 2008

Summary: Reviews current knowledge, controversies, and emerging research in celiac disease including issues related to diagnosis.

Treatment guidelines

International

Celiac disease evidence-based nutrition practice guideline Academy of Nutrition and Dietetics (American Dietetic Association). Celiac disease evidence-based nutrition practice guideline. May 2009. http://www.andevidencelibrary.com (last accessed 5 June 2017). http://andevidencelibrary.com/topic.cfm?cat=3677&auth=1

Published by: Academy of Nutrition and Dietetics (American Dietetic Association) **Last published:** 2009

Summary: Covers medical nutrition therapy for people with celiac disease, with the primary goals to promote optimal health, prevent and treat malabsorption/malnutrition and other comorbidities, and improve quality of life.

Guideline for the diagnosis and treatment of celiac disease in children 15625418 Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40:1-19. http://journals.lww.com/jpgn/Fulltext/2005/01000/Guideline_for_the_Diagnosis_and_Treatment_of.1.aspx

Published by: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition **Last published:** 2005

Summary: Treatment guidelines pertaining specifically to the pediatric population.

International

Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease

18664878 Fasano A, Araya M, Bhatnagar S, et al; Celiac Disease Working Group, FISPGHAN. Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition consensus report on celiac disease. J Pediatr Gastroenterol Nutr. 2008;47:214-219. http://journals.lww.com/jpgn/Fulltext/2008/08000/Federation_of_International_Societies_of_Pediatric.19.aspx

Published by: Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition **Last published:** 2008

Summary: Reviews current knowledge, controversies, and emerging research in celiac disease including issues related to treatment.

Transition from childhood to adulthood in coeliac disease: the Prague consensus report

27196596 Ludvigsson JF, Agreus L, Ciacci C, et al. Transition from childhood to adulthood in coeliac disease: the Prague consensus report. Gut. 2016;65:1242-1251. http://gut.bmj.com/content/65/8/1242

Published by: Association of European Coeliac Societies **Last published:** 2016

Summary: Outlines recommendations for the management of celiac disease in adolescents and young adults, and how to facilitate the transition to adult healthcare for patients with celiac disease.

Online resources

1. National Digestive Diseases Information Clearinghouse: celiac disease *(external link)*
2. Gluten-free drugs *(external link)*
3. New England Celiac Organization *(external link)*

Key articles

- Hogberg L, Falth-Magnusson K, Grodzinsky E, et al. Familial prevalence of coeliac disease: a twenty-year follow-up study. Scand J Gastroenterol. 2003;38:61-65. Abstract
- van der Windt DA, Jellema P, Mulder CJ, et al. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. JAMA. 2010;303:1738-1746. Full text Abstract
- Husby S, Koletzko S, Korponay-Szabó IR, et al; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-160. Full text Abstract
- AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology. 2006;131:1977-1980. Full text Abstract
- National Institute for Health and Care Excellence. Coeliac disease: recognition, assessment and management. September 2015. https://www.nice.org.uk (last accessed 5 June 2017). Full text
- Hogberg L, Laurin P, Falth-Magnusson K, et al. Oats to children with newly diagnosed coeliac disease: a randomised double blind study. Gut. 2004;53:649-654. Abstract
- Academy of Nutrition and Dietetics (American Dietetic Association). Celiac disease evidence-based nutrition practice guideline. May 2009. http://www.andevidencelibrary.com (last accessed 5 June 2017). Full text
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Images

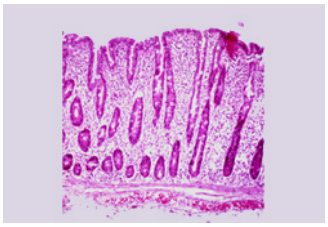

Figure 1: Histologic image of small intestinal villous atrophy and crypt hyperplasia

From the personal collection of D.A. Leffler; used with permission

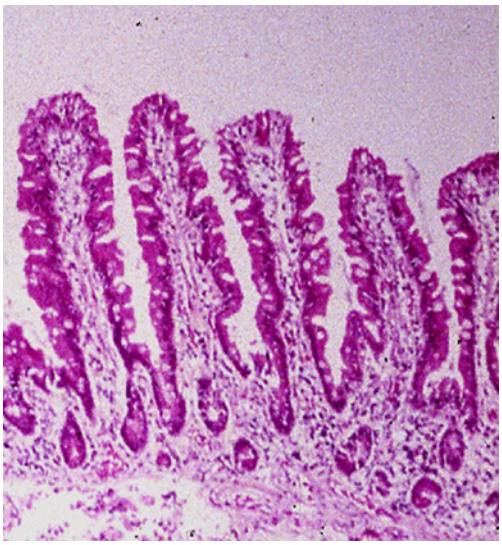

Figure 2: Histologic image of small intestinal villi showing resolution of intestinal injury on gluten-free diet

From the personal collection of D.A. Leffler; used with permission

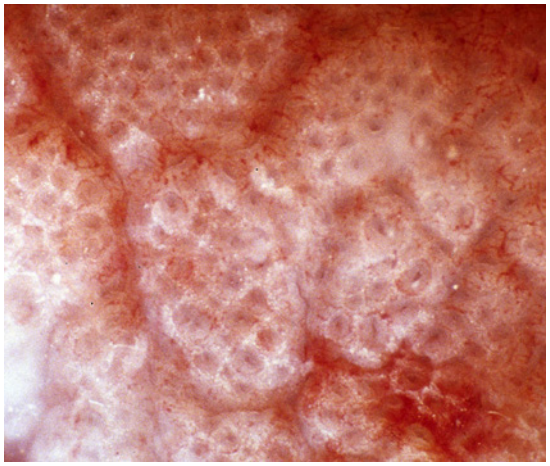

Figure 3: Photograph of small intestinal villi affected by celiac disease

From the personal collection of D.A. Leffler; used with permission

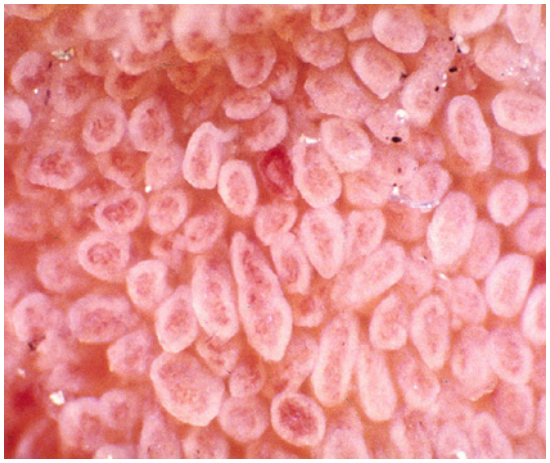

Figure 4: Photograph of normal small intestinal villi

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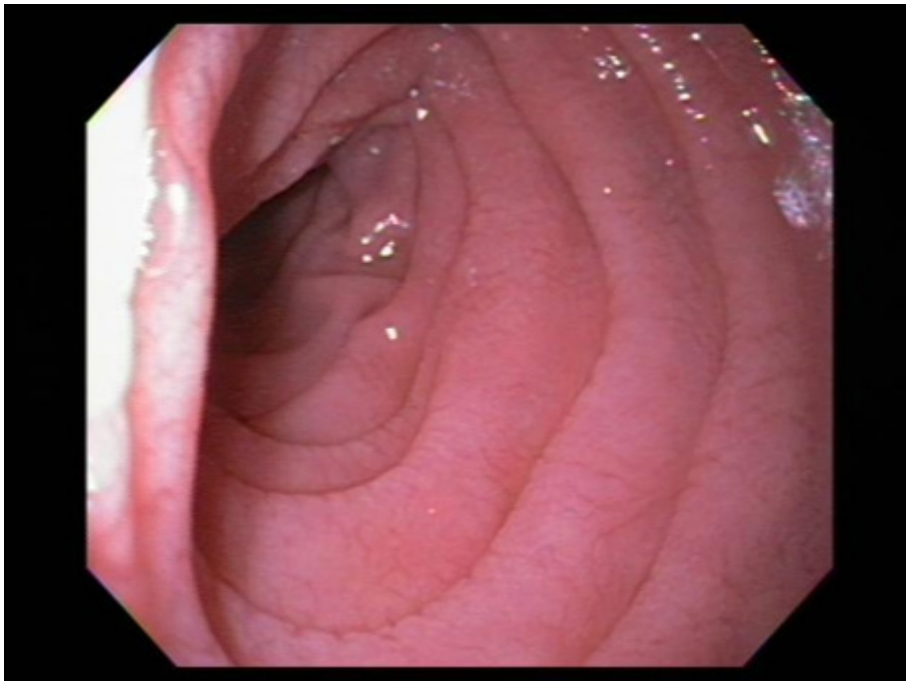

Figure 5: Scalloping of the duodenal mucosa in a patient with celiac disease

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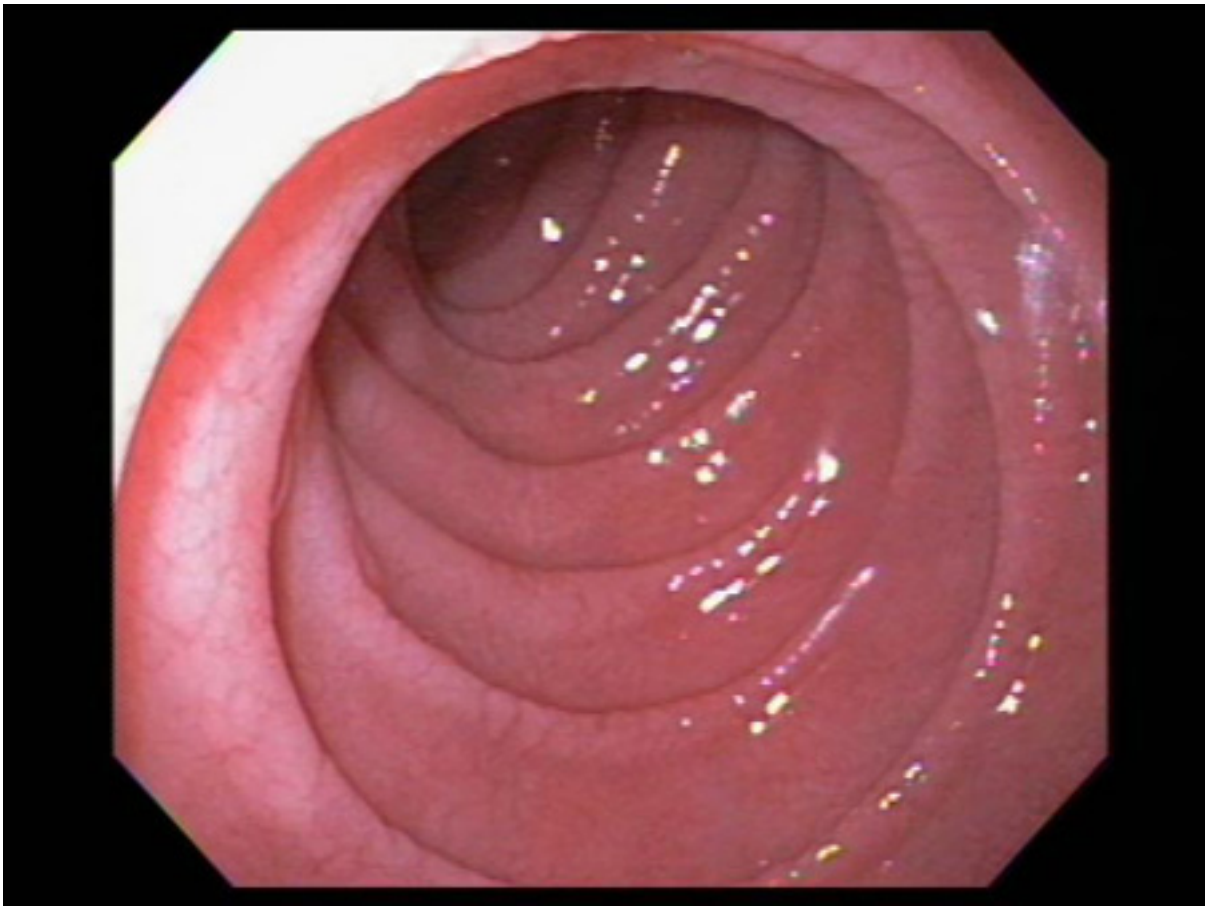

Figure 6: Scalloping of the duodenal mucosa in a patient with celiac disease

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