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## Disclaimer
Celiac disease

Summary
Celiac disease is 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.

Celiac disease

**Epidemiology**

Celiac disease is a common disorder in the US and in Europe. A relatively uniform prevalence has been found in many countries, with pooled global seroprevalence and biopsy-confirmed prevalence of 1.4% and 0.7%, respectively, according to well-designed studies.[2] [3] [4] However, although seroprevalence is similar globally, biopsy-confirmed celiac disease is slightly less common in South America, the Middle East, Turkey, and sub-Saharan Africa.[2] [5] Israel and India show the same seroprevalences and biopsy-confirmed rates of celiac disease as European and North American countries.[5] With the exception of Malaysia and Vietnam, population-based studies from the far East, including China, Japan, and Southeast Asia, are lacking.[6] [7] In North America, after several decades of rising prevalence, the prevalence of celiac disease appears stable in recent years.[8]

Women are slightly more likely to be affected by celiac disease.[2] In clinical practice they make up almost two-thirds of diagnosed 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.[9] [10]

The prevalence of asymptomatic celiac disease is thought to account for at least 20% of patients. The incidence of refractory celiac disease in patients with celiac disease is 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 (human leukocyte antigen [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. One large prospective birth cohort study of children with HLA-DQ2 and -DQ8 genotypes found that a higher gluten intake in the first five years of life was associated with an increased risk of celiac disease. The risk of celiac disease increased with every 1g/day increase in gluten from the reference amount.[11]

Reovirus infection has also been shown to promote inflammatory immunity and a decrease in oral tolerance to gluten.[12] In keeping with the hypothesis of viral infection as an environmental trigger of celiac disease, one case-control study reported an association between previous enterovirus infection during early childhood and later development of celiac disease.[13]

**Pathophysiology**

Loss of immune tolerance to peptide antigens derived from prolamins in wheat (gliadin), rye (secalin), barley (hordein), 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.[14] 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, macrophages, and intestinal epithelial cells, which then stimulate intraepithelial lymphocytes, leading to epithelial damage. 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. For this reason people must carry either HLA-DQ2 (95% of patients with celiac disease) or HLA-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.

### Classification

#### Subgroups of celiac disease

There is no formal classification of celiac disease. Common subgroups include:

1. Classic celiac disease: clinical symptoms and signs of malabsorption, including diarrhea, steatorrhea, weight loss or growth failure, 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 other gastrointestinal symptoms, deficiency states (e.g., iron deficiency), or extraintestinal manifestations (e.g., fatigue, elevated liver enzymes, or infertility). Atypical disease likely accounts for the largest proportion of patients with a diagnosis of celiac disease.
3. Asymptomatic 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 asymptomatic is not well known, but it is thought to account for at least 20% of patients.
4. Nonresponsive celiac disease: clinical symptoms or laboratory abnormalities typical of celiac disease fail to improve within 12 months of gluten withdrawal, or typical symptoms or laboratory abnormalities recur while the patient is on a gluten-free diet.
5. Refractory celiac disease: subtype of nonresponsive celiac disease. Persistence of clinical symptoms and signs with histologic abnormalities (villous atrophy) after at least 12 months on a strict gluten-free diet, and no evidence of another abnormality including overt lymphoma. The incidence of refractory celiac disease in patients with celiac disease is not well known, but may be approximately 1%.

### 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 such as diarrhea, bloating, or abdominal pain. Examination reveals 2 oral aphthous ulcers and pallor. Abdominal examination is normal and results of fecal testing for occult blood are negative.

**Case history #2**

A 9-year-old boy presents with vomiting for 5 days. His sister, who has celiac disease, has had similar symptoms. His growth has been normal and he has not experienced any other possible symptoms of celiac disease, except for intermittent constipation. Immunoglobulin A-tissue transglutaminase titer is 5 times the upper limit of normal.

**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.
**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.[37] [38] [39]

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.[40]

**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.[41] [42] 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.[43] Unlike tTG, which is an enzyme-linked immunosorbent assay, EMA is based on immunofluorescence and thus is operator dependent.
   
   - In patients with IgA deficiency, request IgG-deamidated gliadin peptide (DGP) serology, although the diagnostic accuracy of this test is somewhat less than that of IgA-tTG.[42] [44] 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, since 2% of patients with celiac disease may not have circulating tTG at the time of diagnosis (seronegative celiac disease).[45]
   
   - Pediatric patients with symptoms consistent with celiac disease and a high IgA-tTG titer (above 10 times normal range for laboratory) may go on to have confirmatory EMA testing. If EMA is positive, celiac disease may be diagnosed without a small intestinal biopsy.[46]
   
   - Some experts advise that adult patients with very high IgA-tTG titers (above 10 times normal range for laboratory), and positive EMA in a second blood sample, may be diagnosed without duodenal biopsy.[47]
• Duodenal biopsy changes in celiac disease are typically graded by the Marsh classification, from 0 to 4.\textsuperscript{[48]} 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.

\begin{center}
\includegraphics[width=0.5\textwidth]{histologic-image.png}
\end{center}

*Histologic image of small intestinal villous atrophy and crypt hyperplasia*

\textit{From the personal collection of DA Leffler; used with permission}

• 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.
Histologic image of small intestinal villi showing resolution of intestinal injury on gluten-free diet

From the personal collection of DA Leffler; used with permission
Photograph of small intestinal villi affected by celiac disease

From the personal collection of DA Leffler; used with permission
Celiac disease

Diagnosis

Photograph of normal small intestinal villi
From the personal collection of DA Leffler; used with permission

Capsule endoscopy pictures of ulcerative jejunitis in a patient with celiac disease
From the personal collection of CP Kelly; used with permission

3. Human leukocyte antigen (HLA) typing
- 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.
- HLA typing may be used as a first-line screening test to rule out celiac disease among first-degree relatives. However, the availability and cost of this test may be prohibitive.

4. Endoscopy

- Atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa may be seen, but these findings are not sensitive for celiac disease diagnosis.
Gluten challenge

People with celiac disease on a gluten-free diet prior to evaluation cannot be differentiated from healthy controls. In these patients, gluten challenge is necessary. In a gluten challenge, the person is placed back on a gluten-containing diet, containing 3 to 10 grams of gluten per day (2-5 slices of wheat bread), with serologic tests and small bowel histology assessed after 2 to 8 weeks on the gluten-containing diet.[49]

Commercial kits

Patients who have used a home-testing kit, or are considering using one, should be counseled to discuss their symptoms with their healthcare professional, irrespective of the test outcome.

Commercially available tests for the assessment of individual risk for celiac disease detect the presence of HLA-DQ2 and HLA-DQ8 genes in saliva.[50]

Healthcare professionals should be aware that patients who test positive for tTG antibodies using self-administered blood tests (finger-prick tests) may begin a gluten-free diet before being evaluated by their healthcare professional.[51]

Tests for detection of tTG antibodies in saliva are being investigated, but there is insufficient evidence to recommend their use.[23]
History and exam

Key diagnostic factors

**immunoglobulin (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.[24]

**diarrhea (common)**
- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[41] Patients may present with chronic or intermittent diarrhea.

**bloating (common)**
- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[41]

**abdominal pain/discomfort (common)**
- Patients with longstanding or refractory abdominal symptoms should be screened for celiac disease.[41] Patients may present with recurrent abdominal pain, cramping, or distension.[52]

**anemia (common)**
- Iron deficiency anemia is the most common clinical presentation in adults. One systematic review and meta-analysis showed that 1 in 31 patients with iron deficiency anemia had histologic evidence of celiac disease.[53]
- Folate (and rarely vitamin B12) deficiency may lead to a macrocytic anemia.[54]

**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.[54] Biopsy-proven dermatitis herpetiformis almost universally occurs in association with celiac disease.
Other diagnostic factors

family history (common)
- Family history of celiac disease or other autoimmune disorders. Members of families who have more than one individual with celiac disease are at higher risk of developing the disease. [23]

osteopenia/osteoporosis (common)
- History of bone pain or previous fracture, due to vitamin D deficiency and hypocalcemia.

fatigue (common)
- Frequent at diagnosis, with a prevalence of 37%. [59] May be multifactorial; screening for depression, sleep disorders, and thyroid disease is advisable, especially in the absence of iron deficiency anemia. [60] [61]
weight loss (common)
- Likely multifactorial, primarily due to malabsorption but also to changes in motility, metabolism, and appetite.[54] One study reported that 25% of newly diagnosed patients had weight loss at the time of presentation.[62]

failure to thrive (common)
- In children, faltering growth and delayed puberty are indications for testing for celiac disease.[63]

type 1 diabetes (uncommon)
- The association between type 1 diabetes mellitus and celiac disease is well known.[25] Clinicians caring for patients with type 1 diabetes mellitus should consider testing these patients if there are any digestive symptoms or laboratory changes to suggest celiac disease.[55]

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.[31] Unexplained increasing need for levothyroxine or treatment-refractory hypothyroidism should also lead to celiac disease testing.[56] [57] Correspondingly, patients with celiac disease should be screened for thyroid disease.[58]

aphthous stomatitis (uncommon)
- Association mostly reported in children.[64] Caused by various nutritional deficiencies; may be triggered by gluten exposure and responds to a gluten-free diet.[65] However, differential diagnosis is broad and the process may not be related to celiac disease.[66]

dental enamel hypoplasia (uncommon)
- The exact etiology is unclear but may be due to nutritionally derived abnormalities in mineralization. It is mostly found in children, at the time of the formation of secondary teeth.[64] [67]

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. Peripheral neuropathy may persist despite a gluten-free diet.[68] [69]

ataxia (uncommon)
- Cerebellar ataxia is one of the most studied neurologic symptoms. Although it is triggered by gluten ingestion, most people with gluten ataxia do not have celiac disease.[70] Rapid introduction of a gluten-free diet helps prevent irreversible cerebellar damage.[69] [71]

unexplained elevation of serum aminotransferase levels (uncommon)
- Celiac disease may be the cause of 2% to 12% of cases of cryptogenic elevation of serum aminotransferases.[72] Elevated serum aminotransferases typically normalize on a gluten-free diet.[73]
Celiac disease

### Diagnosis

**Strong**

**family history of celiac disease**
- Multiple studies have shown an increased risk in family members, likely secondary to genetic factors.[21] [22] Members of families who have more than one individual with celiac disease are at higher risk of developing the disease.[23]

**immunoglobulin A deficiency**
- Multiple studies have shown an association between immunoglobulin A (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.[24]

**type 1 diabetes**
- The association between type 1 diabetes mellitus and celiac disease is well known.[25] One meta-analysis found a weighted prevalence of celiac disease of 4.5% among patients with type 1 diabetes.[26] This association is probably based on genetic factors favoring autoimmunity, including the presence of human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 and single nucleotide polymorphisms shared by both diseases.[27] [28] Leaky gut, with tight junction defects leading to increased passage of luminal peptides into the submucosa, resulting in immune activation, is also hypothesized, as well as enhanced basal expression of inflammatory markers.[29]

**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.[30] Celiac disease may be more prevalent in individuals with hyperthyroidism than those with hypothyroidism.[31]

**Weak**

**Down syndrome**
- Patients with Down syndrome have a six-fold increased risk of celiac disease.[32] The mechanism is unclear because celiac disease does not appear to be linked to genes found on chromosome 21.[33]

**Sjogren syndrome**
- Some studies have shown an increased prevalence of celiac disease in patients with Sjogren syndrome.[34]

**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.[35]

**primary biliary cholangitis**
- Studies have shown an increased prevalence of celiac auto-antibodies in patients with primary biliary cholangitis and other liver diseases, but false positives appear higher in these populations.[36]
# Investigations

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC and blood smear</td>
<td>low Hb and microcytic hypochromic red cells</td>
</tr>
<tr>
<td>• Iron deficiency anemia is the most common clinical presentation in adults.</td>
<td></td>
</tr>
<tr>
<td>• Folate (and rarely vitamin B12) deficiency may lead to a macrocytic anemia.</td>
<td></td>
</tr>
<tr>
<td>immunoglobulin A-tissue transglutaminase (IgA-tTG)</td>
<td>titer above normal range for laboratory</td>
</tr>
<tr>
<td>• Order an IgA-tTG test in any patient with suspected celiac disease.</td>
<td></td>
</tr>
<tr>
<td>• Higher titers have increased positive predictive value. Serologic testing should be done on a gluten-containing diet.</td>
<td></td>
</tr>
<tr>
<td>endomysial antibody (EMA)</td>
<td>elevated titer</td>
</tr>
<tr>
<td>• EMA is a more expensive alternative to IgA-tTG with greater specificity but lower sensitivity.</td>
<td></td>
</tr>
<tr>
<td>• Perform initially if IgA-tTG is unavailable.</td>
<td></td>
</tr>
<tr>
<td>skin biopsy</td>
<td>granular deposits of IgA at the dermal papillae of lesional and perilesional skin by direct immunofluorescence</td>
</tr>
<tr>
<td>• Order this test initially in any patient with skin lesions suggestive of dermatitis herpetiformis.</td>
<td></td>
</tr>
<tr>
<td>• Both sensitivity and specificity are high.</td>
<td></td>
</tr>
<tr>
<td>IgG DGP (deamidated gliadin peptide) or IgA/IgG DGP</td>
<td>elevated titer</td>
</tr>
<tr>
<td>• Test of choice for individuals with IgA deficiency.</td>
<td></td>
</tr>
<tr>
<td>IgG-tTG</td>
<td>elevated titer</td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>small bowel endoscopy</td>
<td>atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa</td>
</tr>
<tr>
<td>• The endoscopic appearance is not sensitive for diagnosis, and may be normal in up to one third of cases at diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>Scalloping of the duodenal mucosa in a patient with celiac disease</td>
<td>Small-bowel histology is essential and the gold-standard test to confirm the diagnosis. Biopsies should be performed while on a gluten-containing diet. Patients with an elevated IgA-tTG level should be 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.[45] Two biopsies of the duodenal bulb and at least four biopsies of the distal duodenum should be submitted for histologic analysis.</td>
</tr>
</tbody>
</table>

Scalloping of the duodenal mucosa in a patient with celiac disease

*From the personal collection of DA Leffler; used with permission*

**Small-bowel histology**

- Small-bowel histology is essential and the gold-standard test to confirm the diagnosis.
- Biopsies should be performed while on a gluten-containing diet. Patients with an elevated IgA-tTG level should be 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.[45]
- Two biopsies of the duodenal bulb and at least four biopsies of the distal duodenum should be submitted for histologic analysis.

**Presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia**
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single biopsy specimen should be collected with each pass of the forceps, to improve the diagnostic quality of the specimens. [23]</td>
<td></td>
</tr>
<tr>
<td>Biopsy results are graded using the Marsh criteria.</td>
<td></td>
</tr>
</tbody>
</table>

### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>human leukocyte antigen (HLA) typing</td>
<td>positive HLA-DQ2 or HLA-DQ8</td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>gluten challenge</td>
<td>increase in celiac serologic tests and presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia on small intestinal biopsy</td>
</tr>
<tr>
<td>• People with celiac disease on a gluten-free diet prior to evaluation cannot be differentiated from healthy controls. In these patients, gluten challenge is necessary. In a gluten challenge, the person is placed back on a gluten-containing diet (at least 2 slices of wheat bread daily), and serologic tests and small bowel histology assessed after 2 to 8 weeks on the gluten-containing diet. [49]</td>
<td></td>
</tr>
<tr>
<td>video capsule endoscopy</td>
<td>atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa; sensitive for the detection of villous atrophy</td>
</tr>
<tr>
<td>• Video capsule endoscopy enables imaging of the entire small intestine and has good sensitivity for the detection of macroscopic features of celiac disease. In 3% of cases, villous atrophy is only found in the jejunum, reducing the yield of upper endoscopy and duodenal biopsies for diagnosis. [75]</td>
<td></td>
</tr>
<tr>
<td>• Capsule endoscopy is, however, typically used to detect complications of celiac disease, such as ulcerative jejunitis or lymphoma. [76] [77]</td>
<td></td>
</tr>
<tr>
<td>• Video capsule endoscopy is not recommended when a stricture is suspected.</td>
<td></td>
</tr>
</tbody>
</table>
# Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic duodenitis</td>
<td>• 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 use and use of antacid medications to relieve the discomfort.</td>
<td>• 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.[78] For this reason, biopsies should be taken both in the duodenal bulb and in the second or third portion of the duodenum (relatively protected from peptic injury). Biopsies from the bulb and distal duodenum should be submitted to pathology in separate jars.</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>• Crohn disease can affect any part of the gastrointestinal tract, and symptoms may be extremely variable.</td>
<td>• The classic findings on histologic examination include granulomas, ulcerations, and acute and chronic inflammation often extending throughout all layers of the bowel wall. Tissue transglutaminase serology is usually negative and there should be no response to gluten withdrawal.</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>• Giardiasis is a diarrheal illness caused by infection with a waterborne parasite, <em>Giardia lamblia</em>. A history of exposure to contaminated water may suggest the diagnosis.[79]</td>
<td>• Multiple stool specimens usually reveal the parasite. Alternative methods for detection are antigen detection tests by enzyme immunoassays and detection of parasites by immunofluorescence.[79]</td>
</tr>
<tr>
<td>Small-intestinal bacterial overgrowth</td>
<td>• 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).[80]</td>
<td>• 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.[81]</td>
</tr>
</tbody>
</table>

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[78]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2836938/
[79]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725275/
[80]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4197272/
[81]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3833056/
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postgastroenteritis</td>
<td>• In some children a clinical episode indistinguishable from acute gastroenteritis is followed by protracted diarrhea. This may be related to prolonged rotavirus infection[82] or transient lactose intolerance.</td>
<td>• Usually no investigations are required.</td>
</tr>
<tr>
<td>Eosinophilic enteritis</td>
<td>• 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.[83]</td>
<td>• Diagnosis follows endoscopic or laparoscopic biopsy of the affected bowel with histology showing eosinophilic infiltrates.[83]</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td>• Tropical sprue causes progressive villous atrophy in the small intestine that is similar to celiac sprue.</td>
<td>• Negative for antitissue transglutaminase and antiendomysial antibodies.[86]</td>
</tr>
<tr>
<td>Common variable immune deficiency (CVID) and other immunodeficiency states</td>
<td>• CVID and related disorders have a history of recurrent infections.</td>
<td>• Negative tissue transglutaminase serology and decreased immunoglobulin levels suggest immunodeficiency. Absence of plasmocytes in the lamina propria.</td>
</tr>
<tr>
<td>Graft-versus-host disease (GVHD)</td>
<td>• 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.[87]</td>
<td>• Endoscopic biopsy showing the presence of increased numbers of apoptotic epithelial cells in the intestinal crypts is diagnostic.[87]</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
<td>• This condition is characterized by villous atrophy that is unresponsive to any dietary restrictions.[88]</td>
<td>• Negative for immunoglobulin A antigliadin and antiendomysial antibodies.</td>
</tr>
<tr>
<td></td>
<td>• Negative for immunoglobulin A antigliadin and antiendomysial antibodies.</td>
<td>• Immunofluorescence staining may show enterocyte antibodies.[88] Lymphocytic infiltration in the crypt epithelium, crypt abscesses, and apoptotic bodies.</td>
</tr>
<tr>
<td>Drug-induced enteropathy</td>
<td>• May be clinically and pathologically indistinguishable from celiac disease.</td>
<td>• Tissue transglutaminase serology is normal.</td>
</tr>
<tr>
<td></td>
<td>• Olmesartan, an angiotensin-II receptor antagonist, has been associated with enteropathy.[89]</td>
<td>• Symptoms remit once causative drug is stopped.</td>
</tr>
<tr>
<td></td>
<td>• There have also been case reports with other angiotensin-II receptor antagonists and mycophenolate.[90] Use of nonsteroidal anti-inflammatory drugs is also associated with lymphoplasmacytic infiltrate and partial villous atrophy.</td>
<td></td>
</tr>
<tr>
<td>Nonceliac gluten sensitivity</td>
<td>• May share similar symptoms with celiac disease, with improvement on a gluten-free diet. There should not be any villous atrophy.</td>
<td>• Tissue transglutaminase serology remains normal. CBC, iron, folate, B12, and vitamin D levels are typically within normal ranges, but may be deficient in a minority of patients.[91] Small intestinal histology is normal. There is improvement of symptoms after 6 weeks (or less) on the gluten-free diet and recurrence with reintroduction of gluten.</td>
</tr>
</tbody>
</table>

Criteria

Marsh criteria[48]

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.

Screening

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. [92] [93] [94]
Celiac disease

Management

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 dietitian with specific training in celiac disease and the gluten-free diet. Dietary counseling is important because the gluten-free diet has been associated with lower intake of fiber, as well as vitamin and micronutrient deficiencies, and a higher intake of calories, simple carbohydrates, and saturated fats.[62][99] Celiac disease patients are at risk of becoming overweight/obese.[100]

Quality of life for celiac patients has been shown to improve with adherence to a gluten-free diet.[101] However, gluten-free diet adherence is difficult, with dietary lapses in the majority of patients.[102] 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**

Patients should be checked for common deficiencies including iron, vitamin D, vitamin B12, and folate. 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. Vitamin B12 (cyanocobalamin) and folate deficiencies should be corrected, especially since the gluten-free diet may be low in folate.

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. There is evidence that, on a supposedly adequate gluten-free diet, patients consume enough gluten to trigger symptoms.[103][104]

The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase (IgA-tTG) titer and referral to a dietitian 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. While gluten exposure is the most common cause of nonresponsive celiac disease, many other conditions can explain symptoms, such as irritable bowel syndrome, other food intolerances, microscopic colitis, or small intestinal bacterial overgrowth.[105][106]

Although positive IgA-tTG is indicative of intestinal injury and gluten exposure, a negative value cannot exclude continued intestinal injury.[107][108] If symptoms persist or relapse without an alternative explanation, repeat esophagogastroduodenoscopy and duodenal biopsies should be performed regardless of serologic titers.[108]

**Refractory celiac disease**

Refractory celiac disease is defined as the persistence of malabsorption symptoms and villous atrophy despite strict gluten withdrawal for 12 months and no evidence of another abnormality including overt lymphoma. It is present in <1% of patients with celiac disease, and may be a spectrum determined by T-
Celiac disease

Management

cell clonality and loss of normal intraepithelial cell markers.[109] 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 algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>celiac disease</td>
<td></td>
</tr>
<tr>
<td>1st gluten-free diet</td>
<td></td>
</tr>
<tr>
<td>plus vitamin and mineral supplementation</td>
<td></td>
</tr>
<tr>
<td>failure to respond to therapy/ refractory celiac disease</td>
<td></td>
</tr>
<tr>
<td>1st referral to dietitian or gastroenterologist</td>
<td></td>
</tr>
<tr>
<td>celiac crisis</td>
<td></td>
</tr>
<tr>
<td>1st rehydration + correction of electrolyte abnormalities</td>
<td></td>
</tr>
<tr>
<td>adjunct corticosteroid</td>
<td></td>
</tr>
</tbody>
</table>
Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Celiac disease Management

#### Ongoing celiac disease

**1st gluten-free diet**

» The gluten-free diet is the only accepted treatment of celiac disease. Consultation with a dietitian should be sought because: adherence is difficult; dietary changes may lead to deficiencies in fiber and other nutrients; the gluten-free diet can involve a higher intake of calories, simple carbohydrates, and saturated fats.\[62\] \[99\] Celiac disease patients are at risk of becoming overweight/obese.\[100\]

» Oats should be avoided until the patient is in clinical remission, and then wheat-free oats may be gradually added to the diet. 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.\[110\] \[111\] \[112\] Some patients may, however, be sensitive.\[113\] Oats are not recommended as part of a gluten-free diet in some countries, and local guidance should be consulted before recommending them.

**plus vitamin and mineral supplementation**

Treatment recommended for ALL patients in selected patient group

**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.

**OR**

» **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.

**OR**

» **cyanocobalamin (vitamin B12):** 1000-2000 micrograms orally once daily for 1-2 weeks, followed by 500-1000 micrograms once
### Management

<table>
<thead>
<tr>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>daily; 1000 micrograms intramuscularly/subcutaneously once daily for 1 week, followed by 1000 micrograms once weekly for 1-2 months, then 1000 micrograms once monthly</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>cyanocobalamin (vitamin B12) nasal: 500 micrograms into one nostril once weekly</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>folic acid (vitamin B9): 0.4 to 0.6 mg orally once daily</td>
</tr>
<tr>
<td>Patients should be checked for common deficiencies including iron, vitamin D, vitamin B12, and folate.</td>
</tr>
<tr>
<td>All patients with celiac disease should take calcium and vitamin D supplements. Iron should only be given to individuals with iron deficiency.</td>
</tr>
<tr>
<td>Vitamin B12 (cyanocobalamin) and folate deficiencies should be corrected, especially since the gluten-free diet may be low in folate.</td>
</tr>
<tr>
<td>Bone mineral density should be evaluated after approximately 1 year on gluten-free diet to assess for osteopenia or osteoporosis.</td>
</tr>
<tr>
<td>Doses are individualized according to age and presence of deficiencies or decreased bone density.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>failure to respond to therapy/refractory celiac disease</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1st referral to dietitian or gastroenterologist</td>
</tr>
<tr>
<td>For individuals who do not respond to a gluten-free diet, the most common problem is continued gluten exposure. There is evidence that, on a supposedly adequate gluten-free diet, patients consume enough gluten to trigger symptoms.[103] [104]</td>
</tr>
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<td>The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase titer and referral to a dietitian 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.</td>
</tr>
</tbody>
</table>

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Ongoing

» If symptoms persist or relapse without an alternative explanation, repeat esophagogastroduodenoscopy and duodenal biopsies should be performed regardless of serologic titers.[108]

» The outlook for patients with refractory celiac disease can be poor. They should be cared for at a center experienced in celiac disease.

celiac crisis

1st  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.

adjunct  corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

» budesonide: 9 mg orally (enteric-coated) once daily

OR

» prednisone: 40-60 mg orally once daily initially then taper dose slowly

Secondary options

» methylprednisolone sodium succinate: consult specialist for guidance on dose

» 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 maintain hydration and nutritional status without intravenous supplementation.
Emerging

Endopeptidases

Latiglutenase (formerly ALV003) may digest gluten within the intestinal lumen resulting in nonantigenic peptides. One study failed to demonstrate overall histologic or symptom improvement in nonresponsive celiac disease.[114] A post-hoc subgroup analysis suggested symptom improvement among patients with celiac disease with positive tissue transglutaminase (tTG) despite a gluten-free diet.[115]

Tight junction regulators

Larazotide may strengthen tight junctions and prevent gluten from infiltrating the mucosa.[116] Symptomatic improvement among individuals experiencing continued symptoms, despite gluten-free diet adherence, has been noted.[105][116]

Tissue transglutaminase (tTG) inhibitors

tTG inhibitors may prevent the deamidation and resultant potentiation of gliadin peptides.[20] One phase 2a efficacy/tolerability study of the tTG inhibitor ZED1227 is ongoing (in patients with well-controlled celiac disease undergoing gluten challenge).[117]

Immune modulation

Immune modulation may restore gluten tolerance.[118] TIMP-GLIA is a nanoparticle-based therapeutic being studied for the treatment of celiac disease. It is designed to reverse gluten sensitivity and stimulate immune tolerance by delivering encapsulated gliadin to tolerogenic immune cells. Phase 1 trials are in progress.[119]

Interleukin-15 antagonists

Interleukin-15 has been shown to be a key component for intraepithelial lymphocyte survival and mucosal damage. Agents that act to block this cytokine are under development for nonresponsive and refractory celiac disease. One phase 2a trial of an interleukin-15 inhibitor, AMG 714, in patients with refractory celiac disease reported no change in the proportion of aberrant intraepithelial lymphocytes in the treatment group compared with the placebo group. The patients in the treatment group reported a reduction in diarrhea symptoms.[120]

Probiotics

Early evidence suggests some strains of probiotics may act on gluten immunogenicity, assist with intestinal healing, and improve patients’ symptoms.[121][122] Caution is advised because some probiotics may be contaminated with gluten.

Modified wheat gluten

Various methods are being examined to alter the gluten immunogenic peptides present in wheat flour, thus decreasing their immunogenicity, either by microwaves, gamma irradiation, hydrolyzation with lactobacilli and fungal proteases, or gene sequencing alterations.[123][124][125] Treatment of wheat flour with microbial transglutaminases is another option being explored.[126]

Montelukast

A pilot study has shown that montelukast, a leukotriene receptor antagonist used for the treatment of asthma, could suppress the production of inflammatory mediators by intraepithelial lymphocytes, and possibly accelerate mucosal healing.[127]
Secondary prevention

One study found that infants predisposed to celiac disease who received the rotavirus vaccine had a lower risk of developing the disease following a gastrointestinal infection than those not vaccinated.[149]

Patient discussions

As soon as the patient is diagnosed with celiac disease, they should be advised to avoid all products containing wheat, rye, barley, and spelt. [National Digestive Diseases Information Clearinghouse: celiac disease] (https://www.niddk.nih.gov/health-information/digestive-diseases/celiac-disease)  [Gluten-free drugs] (http://www.glutenfreesdrugs.com)  [National Celiac Association] (https://nationalceliac.org/)

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 dietitian 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.
Monitoring

Patients should be referred to a dietitian at diagnosis, and then have yearly check-ups to instruct and monitor their gluten-free diet adherence. Following the initiation of a gluten-free diet, there may be discordance between normalization of immunoglobulin A-tissue transglutaminase (IgA-tTG) and mucosal healing.[107] Complete mucosal recovery takes varying amounts of time; less than half of patients with celiac disease show normalization of duodenal histology after 1 year on a gluten-free diet, with adults being less likely than children to show mucosal healing.[142] Symptoms are poor predictors of mucosal inflammation or recovery.[143]

If the patient is in clinical and serologic remission after 1 year on a gluten-free diet, annual follow-up interval for the following 2 years may be considered, and then every 2 years thereafter.[23]

Patients should be prescribed oral supplementation to treat any nutritional deficiencies present at diagnosis, and should be monitored until deficiencies are resolved.

IgA-tTG titer are typically checked at least three times in the first year following the diagnosis (3 months, 6 months, and 12 months), and then yearly as an indication of diet adherence.[23] [108] In most patients, IgA-tTG titer should normalize within 6 to 9 months,[144] but it may take more than 3 years in some patients (e.g., children with severe mucosal atrophy, type 1 diabetes, and very high titers at the time of diagnosis).[145] [146] No immediate action is required if the IgA-tTG titer is trending down, the patient is asymptomatic, and nutritional deficiencies are resolved.

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

Bone mineral density may be assessed in adults at the time of diagnosis, or after they have been on a gluten-free diet for 1 year.[23] [55] [137] [138] [147] [148]
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteoporosis/osteopenia</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Reduced bone mineral density is common in celiac disease and often improves significantly within 1 year of gluten withdrawal.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dermatitis herpetiformis</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Dermatitis herpetiformis is the skin manifestation of active celiac disease. Episodes can recur even on a strict gluten-free diet. In these patients, treatment with dapsone in conjunction with the gluten-free diet may be helpful.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malignancy</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>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% confidence interval 1.2 to 1.5 in one study[132]) and appears to normalize within a few years of gluten withdrawal. No additional screening is recommended.[133] [134]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>idiopathic recurrent acute pancreatitis/chronic pancreatitis</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>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.[135]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumococcal infection</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>Hyposplenism has been associated with celiac disease, thus increasing the risk of infections from encapsulated bacteria such as pneumococcus.[136] Some guidelines recommend vaccination against pneumococci, <em>Haemophilus influenzae</em>, and meningococci for celiac disease patients.[137] [138]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonresponse to hepatitis B virus vaccine</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>A predisposition to poor immune response to the hepatitis B virus vaccine has been observed in both adults and children with active celiac disease.[139] [140] Confirming the response to immunization is advisable and nonresponders should be revaccinated once adherence to the gluten-free diet is optimal.[140] [141]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prognosis

The prognosis for patients with celiac disease is good.[130] Most, up to 90% in some studies, will have complete and lasting resolution of symptoms on a gluten-free diet alone. Ongoing gluten exposure, lactose intolerance, and irritable bowel syndrome account for most of the 10% of cases with persistent symptoms. Fewer than 1% of patients can be expected to develop refractory celiac disease.[131]
# Diagnostic guidelines

## International

### Clinical practice update on diagnosis and monitoring of celiac disease - changing utility of serology and histologic measures: expert review

- **Published by:** American Gastroenterology Association
- **Last published:** 2019

### Clinical practice guidelines for the use of video capsule endoscopy

- **Published by:** American Gastroenterology Association
- **Last published:** 2017

### Celiac disease: screening

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

### Diagnosis and management of celiac disease

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

### Guideline for the diagnosis and treatment of celiac disease in children

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

### WGO practice guideline: celiac disease

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

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

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

### Guidelines for the diagnosis of pediatric coeliac disease

- **Published by:** European Society for Paediatric Gastroenterology, Hepatology, and Nutrition
- **Last published:** 2020
## International

**European Society for the Study of Coeliac Disease (ESsCD)**

guideline for coeliac disease and other gluten-related disorders


Published by: European Society for the Study of Coeliac Disease

Coeliac disease: recognition, assessment and management

(https://www.nice.org.uk/guidance/ng20)

Published by: National Institute for Health and Care Excellence (UK)

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## Treatment guidelines

### International

**Celiac disease evidence-based nutrition practice guideline**

(http://www.andeal.org/a_z_index.cfm)

Published by: Academy of Nutrition and Dietetics (American Dietetic Association)

**Guideline for the diagnosis and treatment of celiac disease in children**

(http://www.naspghan.org/content/51/en/Celiac-Disease)

Published by: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

**WGO practice guideline: celiac disease**

(http://www.worldgastroenterology.org/guidelines/global-guidelines)

Published by: World Gastroenterology Organisation

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

(http://journals.lww.com/jpgn/Fulltext/2008/08000/Celiac_Disease_in_Arabs.19.aspx)

Published by: Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition

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

(http://gut.bmj.com/content/65/8/1242)

Published by: Association of European Coeliac Societies
Online resources


3. Gluten-free drugs (http://www.glutenfreedrugs.com) (external link)

Key articles


Celiac disease


42. Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Ther. 2010


117. EU Clinical Trials Register. ZED1227. 30 January 2018 [internet publication]. Full text (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002241-30/LT)


Celiac disease


Images

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

From the personal collection of DA 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 DA Leffler; used with permission
Figure 3: Photograph of small intestinal villi affected by celiac disease

From the personal collection of DA Leffler; used with permission
Figure 4: Photograph of normal small intestinal villi

From the personal collection of DA Leffler; used with permission
Figure 5: Capsule endoscopy pictures of ulcerative jejunitis in a patient with celiac disease

From the personal collection of CP Kelly; used with permission
Figure 6: Scalloping of the duodenal mucosa in a patient with celiac disease

From the personal collection of DA Leffler; used with permission
Figure 7: Scalloping of the duodenal mucosa in a patient with celiac disease

From the personal collection of DA Leffler; used with permission
Figure 8: Dermatitis herpetiformis: typical lesions on extensor surface of forearm

From the collection of Adam Reich MD, PhD


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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

**Interpretation of numbers**

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

**Figure 1 – BMJ Best Practice Numeral Style**
Contributors:

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