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**Summary**

Coeliac disease is common, affecting up to 1% of the general population, and may present at any age.

Presentation is varied and ranges from diarrhoea and failure to thrive, to iron-deficiency anaemia 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 coeliac disease include gastrointestinal symptoms, malabsorption, increased risk of malignancy, and higher overall mortality than in the general population.

**Definition**

Coeliac 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**

Coeliac 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 coeliac 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 coeliac 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 coeliac disease appears stable in recent years.[8]

Women are slightly more likely to be affected by coeliac disease.[2] In clinical practice they make up almost two-thirds of diagnosed patients. The incidence of refractory coeliac disease in patients with coeliac disease is not well known but may be approximately 1%. The first peak period of presentation is in infancy soon after the initial exposures to gluten, with a second, larger peak in the fourth and fifth decades. Although the most common age at diagnosis in the US is about 40 years, coeliac disease may be diagnosed at any age.[9] [10]

The prevalence of asymptomatic coeliac disease is thought to account for at least 20% of patients. The incidence of refractory coeliac disease in patients with coeliac disease is approximately 1%.

**Aetiology**

Coeliac disease is a systemic autoimmune disorder triggered by gluten peptides from grains including wheat, rye, and barley. Almost all people with coeliac disease carry one of two 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 coeliac disease. However, most DQ2- or DQ8-positive people never develop coeliac 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 hypothesised 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 coeliac disease. The risk of coeliac 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 coeliac disease, one case-control study reported an association between previous enterovirus infection during early childhood and later development of coeliac disease.[13]

**Pathophysiology**

Loss of immune tolerance to peptide antigens derived from prolamin in wheat (gliadin), rye (secalin), barley (hordein), and related grains is the central abnormality of coeliac disease. These peptides are resistant to human proteases, allowing them to persist intact in the small intestinal lumen.[14] It is unknown how these
Coeliac disease

Theory

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 intra-epithelial lymphocytes, leading to epithelial damage. In the submucosa, gluten peptides are de-amidated by tissue transglutaminase (tTG), an enzyme normally involved in collagen cross-linking and tissue remodelling. De-amidation of the gliadin peptide allows for, first, high-affinity binding to the coeliac-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 coeliac disease) or HLA-DQ8 (5% of patients with coeliac disease) to develop coeliac disease. Stimulation of Th cells has 2 consequences. Cell death and tissue remodelling with villous atrophy and crypt hyperplasia are induced by Th1-derived cytotoxic T lymphocytes. Th2 triggers plasma cell maturation and subsequent anti-gliadin and anti-tTG antibody production.

Classification

Subgroups of coeliac disease

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

1. Classic coeliac disease: clinical symptoms and signs of malabsorption, including diarrhoea, steatorrhoea, weight loss or growth failure, abdominal pain and discomfort, and fatigue. Classic symptoms are found in <50% of patients.

2. Atypical coeliac disease: lacks the typical gastrointestinal symptoms of malabsorption; presents with other gastrointestinal symptoms, deficiency states (e.g., iron deficiency), or extra-intestinal manifestations (e.g., fatigue, elevated liver enzymes, or infertility). Atypical disease likely accounts for the largest proportion of patients with a diagnosis of coeliac disease.

3. Asymptomatic coeliac disease: serological and histological evidence of coeliac disease, but without any evident symptoms, signs, or deficiency states. The proportion of coeliac disease that is truly asymptomatic is not well known, but it is thought to account for at least 20% of patients.

4. Non-responsive coeliac disease: clinical symptoms or laboratory abnormalities typical of coeliac 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 coeliac disease: subtype of non-responsive coeliac disease. Persistence of clinical symptoms and signs with histological 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 coeliac disease in patients with coeliac 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 anaemia. She has experienced intermittent episodes of mild diarrhoea for many years, previously diagnosed as irritable bowel syndrome and lactose intolerance. She has no current significant gastrointestinal symptoms such as diarrhoea, bloating, or abdominal pain. Examination reveals two oral aphthous ulcers and pallor. Abdominal examination is normal and results of faecal testing for occult blood are negative.

Case history #2

A 9-year-old boy presents with vomiting for 5 days. His sister, who has coeliac disease, has had similar symptoms. His growth has been normal and he has not experienced any other possible symptoms of coeliac disease, except for intermittent constipation. Immunoglobulin A-tissue transglutaminase titre 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 gastro-oesophageal reflux disease, hyposplenism or asplenia, myalgia, arthralgia, peripheral neuropathy, alopecia, headaches, infertility, and adverse pregnancy outcomes.
Approach

Coeliac 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 diarrhoea, unexplained iron deficiency anaemia, or a skin rash consistent with dermatitis herpetiformis should be tested for coeliac 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 normalise on a gluten-free diet.

1. Serology
   
   - Immunoglobulin A-tissue transglutaminase (IgA-tTG) titre 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 serological tests for coeliac 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 coeliac 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 coeliac disease may not have circulating tTG at the time of diagnosis (seronegative coeliac disease).[45]
   
   - Paediatric patients with symptoms consistent with coeliac disease and a high IgA-tTG titre (above 10 times normal range for laboratory) may go on to have confirmatory EMA testing. If EMA is positive, coeliac disease may be diagnosed without a small intestinal biopsy.[46]
   
   - Some experts advise that adult patients with very high IgA-tTG titres (above 10 times normal range for laboratory), and positive EMA in a second blood sample, may be diagnosed without duodenal biopsy.[47]
Coeliac disease

Diagnosis

- Duodenal biopsy changes in coeliac disease are typically graded by the Marsh classification, from 0 to 4.\textsuperscript{[48]} To diagnose coeliac disease, intra-epithelial 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.

![Histological image of small intestinal villous atrophy and crypt hyperplasia](From the personal collection of DA Leffler; used with permission)

- The presence of typical coeliac 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.

\[\text{Histological image of small intestinal villous atrophy and crypt hyperplasia}\]

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

From the personal collection of DA Leffler; used with permission
3. Human leukocyte antigen (HLA) typing

- May be used to rule out coeliac disease in patients already on a gluten-free diet or in patients with an idiopathic coeliac-like enteropathy, but is not helpful for diagnosis.
- HLA typing may be used as a first-line screening test to rule out coeliac disease among first-degree relatives.[23] 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 coeliac disease diagnosis.
Scallopining of the duodenal mucosa in a patient with coeliac disease

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

People with coeliac 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 serological 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 counselled to discuss their symptoms with their healthcare professional, irrespective of the test outcome.

Commercially available tests for the assessment of individual risk for coeliac disease detect the presence of HLA-DQ2 and HLA-DQ8 genes in saliva.[50] However, UK guidelines recommend against HLA-DQ2 and HLA-DQ8 testing in the initial diagnosis of coeliac disease in non-specialist settings.[51]

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.[52]

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

Diagnosis

History and exam

Key diagnostic factors

**immunoglobulin (IgA) deficiency (common)**

- Multiple studies have shown an association between IgA deficiency and coeliac disease. Although the pathogenesis is unclear, it has been proposed that a lack of secretory IgA and Peyer’s patch malfunction allow for increased free gluten peptides in the submucosa.[24]

**diarrhoea (common)**

- Patients with long-standing or refractory abdominal symptoms should be screened for coeliac disease.[41] Patients may present with chronic or intermittent diarrhoea.

**bloating (common)**

- Patients with long-standing or refractory abdominal symptoms should be screened for coeliac disease.[41]

**abdominal pain/discomfort (common)**

- Patients with long-standing or refractory abdominal symptoms should be screened for coeliac disease.[41] Patients may present with recurrent abdominal pain, cramping, or distension.[51]

**anaemia (common)**

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

**dermatitis herpetiformis (uncommon)**

- Characterised 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 coeliac disease.
Other diagnostic factors

family history (common)

- Family history of coeliac disease or other autoimmune disorders. Members of families who have more than one individual with coeliac 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 hypocalcaemia.

fatigue (common)

- Frequent at diagnosis, with a prevalence of 37%.[60] May be multi-factorial; screening for depression, sleep disorders, and thyroid disease is advisable, especially in the absence of iron deficiency anaemia.[61] [62]
weight loss (common)
• Likely to be multi-factorial, 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.[63]

failure to thrive (common)
• In children, faltering growth and delayed puberty are indications for testing for coeliac disease.[64]

type 1 diabetes (uncommon)
• The association between type 1 diabetes mellitus and coeliac 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 coeliac disease.[55] European guidelines recommend routine screening for coeliac disease among patients with type 1 diabetes, but optimal screening intervals have not been established.[23][56]

autoimmune thyroid disease (uncommon)
• Clinicians caring for patients with autoimmune thyroid disease should be aware of the association with coeliac disease and consider testing if symptoms occur.[31][55] Unexplained increasing need for levothyroxine or treatment-refractory hypothyroidism should also lead to coeliac disease testing.[57][58] Correspondingly, patients with coeliac disease should be screened for thyroid disease.[59]

aphthous stomatitis (uncommon)
• Association mostly reported in children.[65] Caused by various nutritional deficiencies; may be triggered by gluten exposure and responds to a gluten-free diet.[66] However, differential diagnosis is broad and the process may not be related to coeliac disease.[67]

dental enamel hypoplasia (uncommon)
• The exact aetiology is unclear but may be due to nutritionally derived abnormalities in mineralisation. It is mostly found in children, at the time of the formation of secondary teeth.[65][68]

easy bruising (uncommon)
• Vitamin K deficiency may lead to a coagulopathy.

peripheral neuropathy (uncommon)
• The aetiology of neurological 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.[69][70]

ataxia (uncommon)
• Cerebellar ataxia is one of the most studied neurological symptoms. Although it is triggered by gluten ingestion, most people with gluten ataxia do not have coeliac disease.[71] Rapid introduction of a gluten-free diet helps prevent irreversible cerebellar damage.[70][72]

unexplained elevation of serum aminotransferase levels (uncommon)
• Coeliac disease may be the cause of 2% to 12% of cases of cryptogenic elevation of serum aminotransferases.[73] Elevated serum aminotransferases typically normalise on a gluten-free diet.[74]
Risk factors

Strong

family history of coeliac disease

- Multiple studies have shown an increased risk in family members, probably secondary to genetic factors.\cite{21} \cite{22} Members of families who have more than one individual with coeliac disease are at higher risk of developing the disease.\cite{23}

immunoglobulin A deficiency

- Multiple studies have shown an association between immunoglobulin A (IgA) deficiency and coeliac 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.\cite{24}

type 1 diabetes

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

autoimmune thyroid disease

- Multiple studies have shown an association between thyroid disease and coeliac disease. Pathogenesis is similar to that of type 1 diabetes mellitus.\cite{30} Coeliac disease may be more prevalent in individuals with hyperthyroidism than in those with hypothyroidism.\cite{31}

Weak

Down's syndrome

- Patients with Down's syndrome have a six-fold increased risk of coeliac disease.\cite{32} The mechanism is unclear because coeliac disease does not appear to be linked to genes found on chromosome 21.\cite{33}

Sjogren's syndrome

- Some studies have shown an increased prevalence of coeliac disease in patients with Sjogren's syndrome.\cite{34}

inflammatory bowel disease

- A few studies have shown an increased prevalence of coeliac disease in patients with Crohn's disease and, to a lesser extent, ulcerative colitis.\cite{35}

primary biliary cholangitis

- Studies have shown an increased prevalence of coeliac auto-antibodies in patients with primary biliary cholangitis and other liver diseases, but false positives appear higher in these populations.\cite{36}
## Investigations

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBC and blood smear</strong></td>
<td>low Hb and microcytic hypochromic red cells</td>
</tr>
<tr>
<td>• Iron deficiency anaemia 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 anaemia.</td>
<td></td>
</tr>
<tr>
<td><strong>immunoglobulin A-tissue transglutaminase (IgA-tTG)</strong></td>
<td>titre above normal range for laboratory</td>
</tr>
<tr>
<td>• Order an IgA-tTG test in any patient with suspected coeliac disease.</td>
<td></td>
</tr>
<tr>
<td>• Higher titres have increased positive predictive value. Serological testing should be done on a gluten-containing diet.</td>
<td></td>
</tr>
<tr>
<td><strong>endomysial antibody (EMA)</strong></td>
<td>elevated titre</td>
</tr>
<tr>
<td>• EMA is a more expensive alternative to IgA-tTG with greater specificity but lower sensitivity. Perform initially if IgA-tTG is unavailable.</td>
<td></td>
</tr>
<tr>
<td><strong>skin biopsy</strong></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. Both sensitivity and specificity are high.</td>
<td></td>
</tr>
<tr>
<td><strong>IgG DGP (deamidated gliadin peptide) or IgA/IgG DGP</strong></td>
<td>elevated titre</td>
</tr>
<tr>
<td>• Test of choice for individuals with IgA deficiency.</td>
<td></td>
</tr>
<tr>
<td><strong>IgG-tTG</strong></td>
<td>elevated titre</td>
</tr>
<tr>
<td>• IgG-tTG was previously one of the common serological tests for coeliac 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).</td>
<td></td>
</tr>
<tr>
<td><strong>small bowel endoscopy</strong></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>
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</tbody>
</table>
### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Scallop of the duodenal mucosa in a patient with coeliac disease</td>
<td>Presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia</td>
</tr>
</tbody>
</table>

**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 histological analysis.

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### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>human leukocyte antigen (HLA) typing</strong></td>
<td>- This genetic test is useful to rule out coeliac disease in patients already on a gluten-free diet or in patients with an idiopathic coeliac-like enteropathy.</td>
</tr>
<tr>
<td></td>
<td>- positive HLA-DQ2 or HLA-DQ8</td>
</tr>
<tr>
<td><strong>gluten challenge</strong></td>
<td>- People with coeliac 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 serological tests and small bowel histology assessed after 2 to 8 weeks on the gluten-containing diet.</td>
</tr>
<tr>
<td></td>
<td>- increase in coeliac serological tests and presence of intra-epithelial lymphocytes, villous atrophy, and crypt hyperplasia on small intestinal biopsy</td>
</tr>
<tr>
<td><strong>video capsule endoscopy</strong></td>
<td>- Video capsule endoscopy enables imaging of the entire small intestine and has good sensitivity for the detection of macroscopical features of coeliac disease. In 3% of cases, villous atrophy is only found in the jejunum, reducing the yield of upper endoscopy and duodenal biopsies for diagnosis.</td>
</tr>
<tr>
<td></td>
<td>- Capsule endoscopy is, however, typically used to detect complications of coeliac disease, such as ulcerative jejunitis or lymphoma.</td>
</tr>
<tr>
<td></td>
<td>- Video capsule endoscopy is not recommended when a stricture is suspected.</td>
</tr>
</tbody>
</table>

### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- A single biopsy specimen should be collected with each pass of the forceps, to improve the diagnostic quality of the specimens.</td>
</tr>
<tr>
<td></td>
<td>- Biopsy results are graded using the Marsh criteria.</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 centred in the upper abdomen that is commonly related to eating. There may be a history of non-steroidal 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 histological mucosal changes that may be difficult to distinguish from that seen in coeliac disease. 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’s disease</td>
<td>• Crohn’s disease can affect any part of the gastrointestinal tract, and symptoms may be extremely variable.</td>
<td>• The classical findings on histological 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 diarrhoeal illness caused by infection with a waterborne parasite, <em>Giardia lamblia</em>. A history of exposure to contaminated water may suggest the diagnosis.</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.</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 anatomical disturbances in the bowel, including fistulae, diverticula, and blind loops created after surgery).</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.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
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<td>---------------------------------</td>
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<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Post-gastroenteritis</td>
<td>• In some children a clinical episode indistinguishable from acute gastroenteritis is followed by protracted diarrhoea. This may be related to prolonged rotavirus infection[83] 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 anaemia, diarrhoea, abdominal pain, and weight loss. Often no cause is identified, although nematode infections are often isolated.[84]</td>
<td>• Diagnosis follows endoscopic or laparoscopic biopsy of the affected bowel with histology showing eosinophilic infiltrates.[84]</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td>• Tropical sprue causes progressive villous atrophy in the small intestine that is similar to coeliac sprue. • There are no clinical, endoscopic, or histological features that can differentiate tropical sprue from coeliac disease.[85] Specific serological tests for coeliac disease are required. • Tropical sprue 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.[86]</td>
<td>• Negative for anti-tissue transglutaminase and anti-endomysial antibodies.[87]</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 diarrhoea about 3 weeks after transplantation if GVHD is present.[88]</td>
<td>• Endoscopic biopsy showing the presence of increased numbers of apoptotic epithelial cells in the intestinal crypts is diagnostic.[88]</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 characterised by villous atrophy that is unresponsive to any dietary restrictions.[89]</td>
<td>• Negative for immunoglobulin A anti-gliadin and anti-endomysial antibodies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immuno-fluorescence staining may show enterocyte antibodies.[89]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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 coeliac 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.[90]</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.[91] Use of non-steroidal anti-inflammatory drugs is also associated with lymphoplasmacytic infiltrate and partial villous atrophy.</td>
<td></td>
</tr>
<tr>
<td>Non-coeliac gluten sensitivity</td>
<td>• May share similar symptoms with coeliac disease, with improvement on a gluten-free diet. There should not be any villous atrophy.</td>
<td>• Tissue transglutaminase serology remains normal. FBC, iron, folate, B12, and vitamin D levels are typically within normal ranges, but may be deficient in a minority of patients.[92] 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]**

Histological changes on small intestinal biopsy

- 0: normal villous architecture with no increase in intra-epithelial lymphocytes
- I: normal villous architecture with increased intra-epithelial lymphocytes
Coeliac disease

Diagnosis

- II: increased intra-epithelial lymphocytes and crypt hyperplasia with normal villi
- IIIa: increased intra-epithelial lymphocytes and crypt hyperplasia with partial villous atrophy
- IIIb: increased intra-epithelial lymphocytes and crypt hyperplasia with subtotal villous atrophy
- IIIc: increased intra-epithelial 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 coeliac disease and a low threshold for serological testing. Perhaps the group of most concern is young children with a first-degree relative with coeliac disease, as the approximate 7% risk of coeliac disease is considerable and delayed diagnosis has the potential to lead to a permanent loss in growth potential. For this reason, serological testing may be considered before the onset of symptoms in at-risk children. Well-designed, randomised clinical trials do not suggest that either breastfeeding or timing of gluten introduction into the diet alter the risk of coeliac disease in children with a family history of coeliac disease.[93] [94] [95]
Coeliac disease

Management

Approach

The only accepted treatment of coeliac 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 dietician with specific training in coeliac disease and the gluten-free diet. Dietary counselling is important because the gluten-free diet has been associated with lower intake of fibre, as well as vitamin and micronutrient deficiencies, and a higher intake of calories, simple carbohydrates, and saturated fats.[63] [96] Coeliac disease patients are at risk of becoming overweight/obese.[97]

Quality of life for coeliac patients has been shown to improve with adherence to a gluten-free diet.[98] However, gluten-free diet adherence is difficult, with dietary lapses in the majority of patients.[99] The importance of the diet should be stressed, and social support evaluated and encouraged within the family and by membership in coeliac disease advocacy groups.

Supplementation

Patients should be checked for common deficiencies including iron, vitamin D, vitamin B12, and folate. All patients with coeliac 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.[100] [101]

The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase (IgA-tTG) titre and referral to a dietician with expertise in coeliac disease. If there is no evidence of continuing gluten intake, referral to a gastroenterologist with experience in the evaluation of non-responsive coeliac disease is recommended. While gluten exposure is the most common cause of non-responsive coeliac disease, many other conditions can explain symptoms, such as irritable bowel syndrome, other food intolerances, microscopic colitis, or small intestinal bacterial overgrowth.[102] [103]

Although positive IgA-tTG is indicative of intestinal injury and gluten exposure, a negative value cannot exclude continued intestinal injury.[104] [105] If symptoms persist or relapse without an alternative explanation, repeat oesophagogastroduodenoscopy and duodenal biopsies should be performed regardless of serological titres.[105]

Refractory coeliac disease

Refractory coeliac 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 coeliac disease, and may be a spectrum determined by
T-cell clonality and loss of normal intra-epithelial cell markers.[106] Common associations with refractory coeliac disease include ulcerative jejunitis and enteropathy-associated T-cell lymphoma. The outlook for patients is generally poor. They should be cared for at a centre experienced in coeliac disease.

**Coeliac crisis**

Coeliac crisis is rare and presents with hypovolaemia, severe watery diarrhoea, acidosis, hypocalcaemia, and hypoalbuminaemia. Patients are often emaciated and have nutritional deficiencies caused by long-standing, untreated coeliac 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>
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<tbody>
<tr>
<td>coeliac disease</td>
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<tr>
<td>1st</td>
<td>gluten-free diet</td>
</tr>
<tr>
<td>plus</td>
<td>vitamin and mineral supplementation</td>
</tr>
<tr>
<td>failure to respond to therapy/ refractory coeliac disease</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>referral to dietician or gastroenterologist</td>
</tr>
<tr>
<td>coeliac crisis</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>rehydration + correction of electrolyte abnormalities</td>
</tr>
<tr>
<td>adjunct</td>
<td>corticosteroid</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.
Coeliac disease

Management

Ongoing

coeliac disease

1st gluten-free diet

» The gluten-free diet is the only accepted treatment of coeliac disease. Consultation with a dietitian should be sought because: adherence is difficult; dietary changes may lead to deficiencies in fibre and other nutrients; the gluten-free diet can involve a higher intake of calories, simple carbohydrates, and saturated fats.\[63\] \[96\] Coeliac disease patients are at risk of becoming overweight/obese.\[97\]

» 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 coeliac disease.\[107\] \[108\] \[109\] Some patients may, however, be sensitive.\[110\] 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: 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: 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: 1000-2000 micrograms orally once daily for 1-2 weeks, followed by 500-1000 micrograms once daily; 1000
Coeliac disease

Management

**Ongoing**

- 1000 micrograms intramuscularly/subcutaneously once daily for 1 week, followed by 1000 micrograms once weekly for 1-2 months, then 1000 micrograms once monthly; 500 micrograms into one nostril once weekly

OR

- **folic acid:** 0.4 to 0.6 mg orally once daily

- Patients should be checked for common deficiencies including iron, vitamin D, vitamin B12, and folate.

- All patients with coeliac disease should 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 gluten-free diet to assess for osteopenia or osteoporosis.

- Doses are individualised according to age and presence of deficiencies or decreased bone density.

**failure to respond to therapy/refractory coeliac disease**

1st **referral to dietician or gastroenterologist**

- 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.[100] [101]

- The initial step in the evaluation should be repeating immunoglobulin A-tissue transglutaminase titre and referral to a dietician with expertise in coeliac disease. If there is no evidence of continuing gluten intake, referral to a gastroenterologist with experience in the evaluation of non-responsive coeliac disease is recommended.

- If symptoms persist or relapse without an alternative explanation, repeat oesophagogastroduodenoscopy and duodenal biopsies should be performed regardless of serological titres.[105]
Ongoing

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

celiac crisis

1st rehydration + correction of electrolyte abnormalities

» Coeliac crisis is rare and presents with hypovolaemia, severe watery diarrhoea, acidosis, hypocalcaemia, and hypoalbuminaemia. Patients are often emaciated and have nutritional deficiencies caused by long-standing, untreated coeliac disease.

adjunct corticosteroid

Treatment recommended for SOME patients in selected patient group

Primary options

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

OR

» prednisolone: 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 coeliac 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, prednisolone 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 non-antigenic peptides. One study failed to demonstrate overall histological or symptom improvement in non-responsive coeliac disease.\[111\] A post-hoc subgroup analysis suggested symptom improvement among patients with coeliac disease with positive tissue transglutaminase (tTG) despite a gluten-free diet.\[112\]

Tight junction regulators

Larazotide may strengthen tight junctions and prevent gluten from infiltrating the mucosa.\[113\] Symptomatic improvement among individuals experiencing continued symptoms, despite gluten-free diet adherence, has been noted.\[102\] \[113\]

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 coeliac disease undergoing gluten challenge).\[114\]

Immunomodulation

Immunomodulation may restore gluten tolerance.\[115\] TIMP-GLIA is a nanoparticle-based therapeutic being studied for the treatment of coeliac 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.\[116\]

Interleukin-15 antagonists

Interleukin-15 has been shown to be a key component for intra-epithelial lymphocyte survival and mucosal damage. Agents that act to block this cytokine are under development for non-responsive and refractory coeliac disease. One phase 2a trial of an interleukin-15 inhibitor, AMG 714, in patients with refractory coeliac disease reported no change in the proportion of aberrant intra-epithelial lymphocytes in the treatment group compared with the placebo group. The patients in the treatment group reported a reduction in diarrhoea symptoms.\[117\]

Probiotics

Early evidence suggests that some strains of probiotics may act on gluten immunogenicity, assist with intestinal healing, and improve patients’ symptoms.\[118\] \[119\] 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, hydrolysation with lactobacilli and fungal proteases, or gene sequencing alterations.\[120\] \[121\] \[122\] Treatment of wheat flour with microbial transglutaminases is another option being explored.\[123\]

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 intra-epithelial lymphocytes, and possibly accelerate mucosal healing.\[124\]
Secondary prevention
One study found that infants predisposed to coeliac disease who received the rotavirus vaccine had a lower risk of developing the disease following a gastrointestinal infection than those not vaccinated.[144]

Patient discussions
As soon as the patient is diagnosed with coeliac 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) [National Celiac Association] (https://nationalceliac.org/) Although not technically a trigger for coeliac disease, oats should be avoided at the outset as many products are contaminated with wheat and a minority of coeliac patients may be oat-intolerant.

The gluten-free diet is demanding, especially at the outset, and referral to both a dietician skilled in coeliac 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 dietician 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 normalisation of immunoglobulin A-tissue transglutaminase (IgA-tTG) and mucosal healing.[104] Complete mucosal recovery takes varying amounts of time; less than half of patients with coeliac disease show normalisation of duodenal histology after 1 year on a gluten-free diet, with adults being less likely than children to show mucosal healing.[137] Symptoms are poor predictors of mucosal inflammation or recovery.[138]

If the patient is in clinical and serological 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 titres 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] [105] In most patients, IgA-tTG titre should normalise within 6 to 9 months,[139] but it may take more than 3 years in some patients (e.g., children with severe mucosal atrophy, type 1 diabetes, and very high titres at the time of diagnosis).[140] [141] No immediate action is required if the IgA-tTG titre 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 normalised.

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] [132] [133] [142] [143]
### 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 coeliac 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 coeliac 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 coeliac disease, including intestinal and extra-intestinal lymphoma and carcinomas of the upper digestive tract. The magnitude of increased risk is moderate (standardised incidence ratio of 1.3, 95% confidence interval 1.2 to 1.5 in one study[127]) and appears to normalise within a few years of gluten withdrawal. No additional screening is recommended.[128] [129]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>idiopathic recurrent acute pancreatitis/chronic pancreatitis</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>Coeliac 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 coeliac disease and persistent diarrhoea, pancreatic exocrine insufficiency can be considered.[130]</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 coeliac disease, thus increasing the risk of infections from encapsulated bacteria such as pneumococcus.[131] Some guidelines recommend vaccination against pneumococci, <em>Haemophilus influenzae</em>, and meningococci for coeliac disease patients.[132] [133]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-response 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 coeliac disease.[134] [135] Confirming the response to immunisation is advisable and non-responders should be re-vaccinated once adherence to the gluten-free diet is optimal.[135] [136]</td>
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</table>

### Prognosis

The prognosis for patients with coeliac disease is good.[125] 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 coeliac disease.[126]
## Diagnostic guidelines

### Europe

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

*Published by:* European Society for the Study of Coeliac Disease  
*Last published:* 2019

**Coeliac disease: recognition, assessment and management** ([https://www.nice.org.uk/guidance/ng20](https://www.nice.org.uk/guidance/ng20))  
*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2015

**Diagnosis and management of adult coeliac disease** ([https://www.bsg.org.uk/clinical/bsg-guidelines.html](https://www.bsg.org.uk/clinical/bsg-guidelines.html))  
*Published by:* British Society of Gastroenterology  
*Last published:* 2014

### International

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

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

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<tr>
<th>Title</th>
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<th>Last published</th>
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<tr>
<td>Clinical practice update on diagnosis and monitoring of celiac disease - changing utility of serology and histologic measures: expert review</td>
<td>American Gastroenterology Association</td>
<td>2019</td>
</tr>
<tr>
<td>Clinical practice guidelines for the use of video capsule endoscopy</td>
<td>American Gastroenterology Association</td>
<td>2017</td>
</tr>
<tr>
<td>Celiac disease: screening</td>
<td>US Preventive Services Task Force</td>
<td>2017</td>
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<tr>
<td>Diagnosis and management of celiac disease</td>
<td>American College of Gastroenterology</td>
<td>2013</td>
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### Treatment guidelines

### Europe

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<tr>
<td>Transition from childhood to adulthood in coeliac disease: the Prague consensus report</td>
<td>Association of European Coeliac Societies</td>
<td>2016</td>
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<tr>
<td>Diagnosis and management of adult coeliac disease</td>
<td>British Society of Gastroenterology</td>
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### International

**WGO practice guideline: celiac disease**

*Guidelines*

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

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<td>Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition</td>
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### North America

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

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<th>Last published:</th>
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<tbody>
<tr>
<td>Academy of Nutrition and Dietetics (American Dietetic Association)</td>
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**Guideline for the diagnosis and treatment of celiac disease in children**

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<th>Last published:</th>
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<tbody>
<tr>
<td>North American Society for Pediatric Gastroenterology, Hepatology and Nutrition</td>
<td>2005</td>
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</tbody>
</table>
Online resources


3. National Celiac Association (https://nationalceliac.org/) (external link)
Key articles


References


43. Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther.


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


References


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

From the personal collection of DA Leffler; used with permission
Figure 2: Histological 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 coeliac 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: Scalloping of the duodenal mucosa in a patient with coeliac disease

From the personal collection of DA Leffler; used with permission
Figure 6: Scalloping of the duodenal mucosa in a patient with coeliac disease

From the personal collection of DA Leffler; used with permission
Figure 7: Dermatitis herpetiformis: typical lesions on extensor surface of forearm

From the collection of Adam Reich MD, PhD
Coeliac disease

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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.

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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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