



World Gastroenterology Organisation Practice Guidelines:

## Celiac Disease

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## 1 Definitions

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*Celiac disease* is a form of enteropathy affecting the (small) intestine in genetically predisposed children and adults, precipitated by the ingestion of gluten-containing foods. It is also referred to as celiac sprue, gluten-sensitive enteropathy, and nontropical sprue.

*Gluten* is the storage protein in wheat, rye, and barley that gives the dough its desired baking properties.

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## 2 Key points

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- The prevalence of celiac disease in a healthy adult population varies between roughly one in 100 and one in 300 in most parts of the world.
- Many patients with celiac disease have minimal symptoms, or present atypically.
- For a diagnosis of celiac disease to be made, the patient should have:
  - Characteristic histopathologic changes in an intestinal biopsy; and
  - Clinical improvement in response to a gluten-free diet
- Serological tests have a role in:
  - Confirming celiac disease
  - Screening for individuals who are at risk or not at risk
  - Identifying patients in whom biopsy might be warranted
  - Investigating patients with an increased risk of the disease
- Patients with celiac disease should not eat wheat, rye, or barley.
- Patients usually need to follow a strictly gluten-free diet for the rest of their lives.
- Patients with active (clinically manifest) celiac disease have an increased risk of death in comparison with the general population. However, this excess death rate returns to normal after 3–5 years on a strictly gluten-free diet.
- In adults, celiac disease (CD) is diagnosed on average over 10 years after the first symptoms.
- It is not true that only Caucasians are affected.
- Oats may be eaten, but must be pure; a small subgroup (less than 5%) of patients with celiac diseases should not eat oats.
- Corn and rice-based diets are also acceptable.
- First-degree and (to a lesser extent) second-degree relatives have an increased risk for CD.

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## 3 Epidemiology

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### 3.1 Introduction

Not so long ago, it was thought that CD was a rare condition and that it occurred only in Caucasians, mostly in children, with a typical presentation of weight loss and diarrhea. We know now that this is not true.

- CD is common throughout the world and affects around one in 100 to one in 300 of the population.
- The female-to-male ratio is 2 : 1.
- CD occurs frequently without gastrointestinal symptoms.
- There are no substantial differences between symptomatic patients and “not-at-risk” patients in all the countries or geographic areas in which epidemiological studies have been carried out.
- CD epidemiology has iceberg characteristics — there are far more undiagnosed cases (below the waterline) than diagnosed cases (above the waterline) (Fig. 1).
- The risks are much greater in first-degree relatives (up to 10%) and less so in second-degree relatives, as well in people with diabetes and other autoimmune

diseases, Down's syndrome, and a number of other associated diseases (see section 5.7 below).

- Fertility is affected in a subset of celiac disease patients.
- Pregnancy may present with an unfavorable course in undiagnosed CD patients, especially in those who have had symptoms earlier.
- A clinically severe picture can develop during pregnancy or during the puerperium in up to 17% of women patients.

### 3.2 Prevalence and incidence

The prevalence of CD — that is, the number of cases that are present in a population at a given time — is similar in different regions of the world. It is uncertain whether the number of new cases of CD found in a specific period in a given population (the incidence) is increasing locally or globally.

All experts agree on the iceberg image (Fig. 1): the prevalence here refers to the total size of the iceberg, while the area below the waterline represents the total number of undiagnosed cases in a given population at a particular point in time. The area above the waterline — the tip of the iceberg — represents the number of clinically diagnosed cases.

Fig. 1 The celiac iceberg



Richard Logan first published the concept of the celiac iceberg in 1991. In Europe, for every case of celiac disease diagnosed on clinical suspicion, there would be many that remained undiagnosed — either because they were latent, silent, misdiagnosed, or asymptomatic. The ratio of diagnosed to undiagnosed CD in Europe is around 5 : 1 to 13 : 1.

A key study by Fasano et al. in 2003 found that the prevalence of CD was as follows:

- At risk — first-degree relatives: one in 10
- At risk — second-degree relatives: one in 39
- At risk — symptomatic patients: one in 56
- Groups not at risk: one in 133

It is now accepted that the total size of the iceberg is more or less the same throughout the world, although the level of the “waterline” may differ from continent to continent. In Europe and the USA, for example, the prevalence is similar in a healthy population and in “at-risk” groups, but the iceberg appears to be more submerged in the USA — fewer cases are diagnosed there than in Europe.

Celiac disease goes is associated with the prevalence of HLA-DQ2, and also to a minor degree with that of DQ8. It is also associated with an extended ancestral haplotype including class I and class II HLA (A, B, DR, DQ). This is a necessary but not a sufficient condition for the development of CD. Gluten load is a key factor — there is no CD without gluten. Populations that do not have DQ2 — e.g., the Chinese and Japanese — are not expected to develop celiac disease, with the exception of individuals with DQ8.

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## 4 Pathogenesis, natural history, and associated conditions

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### 4.1 Pathogenesis and genetic predisposition

CD — also known as celiac sprue, gluten-sensitive enteropathy, and nontropical sprue — is thought to result from the activation of both a cell-mediated (T-cell) and humoral (B-cell) immune response on exposure to the glutes (prolamines and glutenins) of wheat, barley, rye, and (rarely) oats, in a genetically susceptible person. Genetic susceptibility is suggested by a high concordance among monozygotic twins of close to 70%, and an association with certain type II human leukocyte antigens (HLA). HLA-DQ2 is found in up to 95% of CD patients, while most of the remaining patients have HLA-DQ8.

The expression of these HLA-DQ2 or HLA-DQ8 molecules is necessary, but not sufficient, for the disease to develop.

The results of studies in siblings (the sib recurrence risk for celiac disease is 10%) and identical twins suggest that HLA genes are essential, but are not the only genes required for the disease to become manifest. HLA genes are estimated to contribute to about one-third of the genetic variance of the disease.

Genetic predisposition risk (unconfirmed):

- General population: 1%
- Individual DQ2 or DQ8<sup>+</sup>: 2–3%
- First-degree relatives, unknown HLA: 10–15%
- First-degree relatives, DQ2 or DQ8<sup>+</sup>: 20–30%

The presence of autoantibodies to the connective-tissue element surrounding smooth muscle known as endomysium is highly specific for CD. The target of these autoantibodies is now known to be the enzyme tissue transglutaminase (tTG). This enzyme may play a prominent role in the pathogenesis of CD by deamidating gliadin, resulting in a greater proliferative response of gliadin-specific T-cells, which contributes to mucosal inflammation and further B-cell activation in patients with HLA-DQ2 or -DQ8.

## 4.2 Natural history

The natural history of clinically silent CD remains unclear; further research is needed to improve our understanding of the natural history in asymptomatic CD patients. Most of current knowledge about the condition is related to the natural history and clinical course of clinically manifest CD in diagnosed patients (most of them at the severe end of the clinical spectrum). If CD remains unrecognized, it can increase the risk of life-threatening complications that are difficult to manage – for example, intestinal lymphoma (Table 1).

**Table 1** Complications if Celiac Disease remains undiagnosed.

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- Cancer (overall 1.3 : 1.0) (excluding colorectal cancer)
  - Malignant lymphomas
  - Small-bowel neoplasia
  - Oropharyngeal tumors
  - Large-intestine adenocarcinomas
  - Unexplained infertility (12%)
  - Osteoporosis (increased risk for classically symptomatic patients)
  - Stunted growth
  - Autoimmune diseases
- 

## 4.3 Associated conditions

### 4.3.1 Malignant disease

Malignant diseases are more frequent in patients with long-term untreated classical CD. Small-bowel adenocarcinoma, esophageal and oropharyngeal squamous-cell carcinoma, and non-Hodgkin's lymphoma occur more often in CD patients than in healthy control individuals. A gluten-free diet is thought to be protective against the development of malignant disease, although this may not be the case for the development of enteropathy-associated T-cell lymphomas in celiac patients diagnosed over the age of 50.

### 4.3.2 Osteoporosis

Measurement of bone mineral density is recommended when CD has been diagnosed, as reduced bone density is common in both adults and children with CD. The reduction in bone density is more severe in symptomatic CD than in the silent form and is associated with an increased risk of fracture. Bone mineral density improves after a gluten-free diet, but may not return to the normal range.

### 4.3.3 Fertility

CD may be associated with delayed menarche, premature menopause, amenorrhea, recurrent abortions, and fewer children. Studies have reported infertility in subsets of patients, but also a normal number of pregnancies and children in other patients. Further research is needed.

Patients with CD are also reported to have babies with low birthweight, increased perinatal mortality, and a shorter duration of breast feeding. Adherence to a gluten-free diet is associated with a return to normal outcomes.

CD may manifest clinically for the first time during pregnancy or in the puerperium. Undiagnosed CD has been detected in infertile women who were screened for the disease, but not in all studies.

Infertility in men is also associated with CD. In addition, men with the disease also tend to have children with a shorter gestation and lower birthweight than those without the disease.

#### 4.3.4 *Autoimmune disorders*

Whether CD is an inflammatory disorder with secondary autoimmune reactions or whether it is a primary autoimmune disease induced by a known exogenous factor remains unclear. Autoimmune disorders occur ten times more frequently in adult patients with celiac disease than in the general population.

Such disorders include:

- Insulin-dependent type 1 diabetes
- Thyroid disease
- Sjögren's syndrome
- Addison's disease
- Autoimmune liver disease
- Cardiomyopathy
- Neurological disorders

When both autoimmune disease and CD occur in a patient, CD is frequently silent, and as a result the autoimmune disorder is usually diagnosed first.

#### 4.3.5 *Dermatitis herpetiformis*

Dermatitis herpetiformis is considered to be a cutaneous manifestation of gluten sensitivity in patients with CD. Dermatitis herpetiformis (DH) is a severe, itchy, blistering skin disease. The rash usually occurs on the elbows, knees, and buttocks. Although people with DH do not usually have digestive-tract symptoms, they usually have the intestinal damage characteristic of CD. DH is diagnosed by skin biopsy. It is treated with a gluten-free diet and medication to control the rash — for example, with dapsone or sulfapyridine. This treatment may last for several years.

Both the skin disease and the small-bowel diseases are gluten-dependent and are strongly associated with HLA-DQ, with no genetic differences to explain the two phenotypes.

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## 5 Diagnosis of celiac disease

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### 5.1 Introduction

The clinical classification of CD has undergone a change; today, most experts agree with the following classification:

- Classical: mostly gastrointestinal symptoms
- Atypical: mostly nongastrointestinal symptoms — usually monosymptomatic or oligosymptomatic
- Silent: no symptoms, despite the presence of a characteristic intestinal lesion

### 5.2 Differential diagnosis

CD presents a very complex and protean clinical picture, and there are many diseases with mucosal changes similar to those of CD (Table 2).

**Table 2** Conditions with mucosal changes similar to those in Crohn's disease

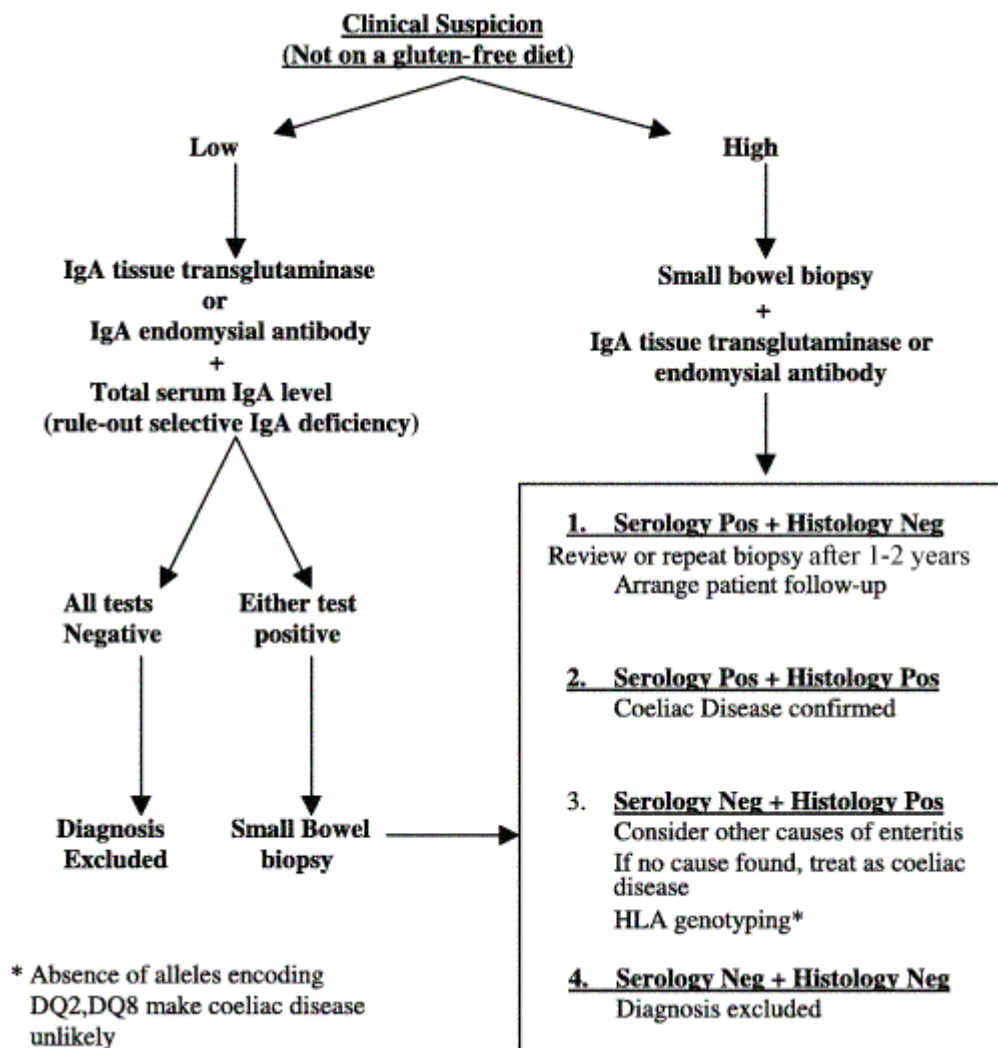
- 
- Tropical sprue
  - HIV enteropathy
  - Combined immunodeficiency states
  - Radiation damage
  - Recent chemotherapy
  - Graft-versus-host disease
  - Chronic ischemia
  - Giardiasis
  - Crohn's disease
  - Eosinophilic gastroenteritis
  - Zollinger–Ellison syndrome
  - Autoimmune enteropathy
  - Enteropathy-associated T-cell lymphoma
  - Refractory sprue
  - Collagenous sprue
- 

N.B.: the last four are probably related to CD.

### 5.3 Diagnostic tests

Only endoscopy with biopsy of the small intestine plus positive CD serology provide a definitive diagnosis. This is the gold standard.

Fig. 1 Diagnosis of celiac disease



*Role of endoscopy in patients with a suspicion of celiac disease.* Although endoscopy may provide an indication for intestinal biopsy, it may not be sufficiently sensitive to detect all manifestations of CD in a population. The characteristic findings on endoscopy include:

- Scalloped folds, fissures and a mosaic pattern
- Flattened folds
- Smaller size and or disappearing of folds with maximum insufflation

*Intestinal biopsy.* Intestinal biopsies together with a positive serology represent the gold standard for diagnosing celiac disease. Multiple biopsies are taken from the second or third part of the duodenum. Endoscopy has become the most convenient method of obtaining biopsies of the small-intestinal mucosa. Suction biopsy (with a Crosby capsule) provides the best samples.

*Histological characteristics of celiac enteropathy.* CD affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine, although in severe cases the lesions can extend to the ileum. The degree of proximal damage varies greatly depending on the severity of the disease. The proximal damage may be very mild in “silent” cases, with little or no abnormality

detectable histologically in the mid-jejunum. Abnormalities in the gastric and rectal mucosa may be observed in some cases.

Occasionally, the lesion in the duodenum/upper jejunum can be patchy, which may justify a second biopsy immediately in selected patients with positive endomysial antibody (EMA). However, this is only warranted if all three samples of the first biopsy show a normal histology.

**Table 3** Marsh's classification of small-intestinal lesions

Stage	Findings
Stage 0	Preinfiltrative mucosa; 5% of patients with DH have small- intestinal biopsy specimens that appear normal
Stage I	Increase in the number of intraepithelial lymphocytes (IELs) to more than 30 per 100 enterocytes
Stage II	Crypt hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height. Gluten challenge can induce these changes, which are seen in 20% of untreated DH and CD patients
Stage III	Villous atrophy — A, partial; B, subtotal; C, total. This is the classical celiac lesion. It is found in 40% of DH patients and 10–20% of first-degree relatives of celiac patients. Despite marked mucosal changes, many individuals are asymptomatic and therefore classified as having subclinical or silent cases. This lesion is characteristic of, but not diagnostic for, CD and can also be seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection.
Stage IV	Total villous atrophy. This can be considered the end-stage lesion in a very small group of patients who are unresponsive to gluten withdrawal and may develop malignant complications. There can be deposition of collagen in the mucosa and submucosa (collagenous sprue, a disorder that may be related to CD). Patients with type IV lesions are usually unresponsive to treatment with steroids, immunosuppressive agents, or chemotherapy.

#### 5.4 Use of serum antibodies to diagnose celiac disease

- IgA endomysial antibody (IgA EMA; highest diagnostic accuracy)
- IgA tissue transglutaminase antibody (IgA tTG)
- IgA antigliadin antibody (IgA AGA)
- IgG antigliadin antibody (IgG AGA)

Serologic studies for celiac disease can be divided into two groups, based on the target antigens:

- Anti-tTG antibody tests
- Antigliadin antibody tests

*IgA EMA.* IgA endomysial antibodies bind to endomysium, the connective tissue around smooth muscle, producing a characteristic staining pattern that is visualized by indirect immunofluorescence. The test result is reported simply as positive or negative, since even low titers of serum IgA endomysial antibodies are specific for CD. The target antigen has been identified as tissue transglutaminase (tTG or

transglutaminase 2). IgA endomysial antibody testing is moderately sensitive and highly specific for untreated (active) CD

*Anti-tissue transglutaminase antibodies (IgA tTG).* The antigen against which antiendomysial antibodies are directed is tTG. Anti-tTG antibodies are highly sensitive and specific for the diagnosis of CD. Enzyme-linked immunosorbent assay (ELISA) tests for IgA anti-tTG antibodies are now widely available and are easier to perform, less observer-dependent, and less costly than the immunofluorescence assay used to detect IgA endomysial antibodies. The diagnostic accuracy of IgA anti-tTG immunoassays has been improved further by the use of human tTG in place of the nonhuman tTG preparations used in earlier immunoassay kits.

*Antigliadin antibody assays (IgA AGA and IgG AGA).* Gliadins are the major proteins of the wheat storage proteins collectively termed gluten. Purified gliadin is readily available and is used as the antigen for ELISA tests to detect serum antigliadin antibodies. Serum antigliadin antibody levels are frequently elevated in untreated CD, and antigliadin assays have been used for some years as a diagnostic aid. Although these tests demonstrate moderate sensitivity and specificity, with the IgA tests being superior, their positive predictive value in the general population is relatively poor. AGA tests are no longer routinely recommended, because of their lower sensitivity and specificity.

## 5.5 Key symptoms

Adults — gastrointestinal symptoms:

- Chronic diarrhea (most common symptom)
- Weight loss
- Anemia
- Abdominal distension
- Lassitude and malaise

Children: gastrointestinal symptoms:

- Failure to thrive, weight loss, down-shift of weight or height centile, short stature
- Vomiting
- Diarrhea
- Recurrent abdominal pain
- Muscle wasting
- Irritable bowel
- Hypoproteinemia
- Irritability and unhappiness

Adults and children: nongastrointestinal symptoms:

- Iron-deficiency anemia
- Dermatitis herpetiformis
- Peripheral neuropathy
- Folic acid deficiency
- Reduced bone density
- Unexplained infertility

CD should be considered in cases of:

- Unexplained folic acid, iron, or vitamin B<sub>12</sub> deficiency
- Reduced serum albumin
- Unexplained hypertransaminasemia
- Osteoporosis and osteomalacia
- Recurrent abdominal pain or bloating
- Skin rashes

Why is celiac disease difficult to diagnose?

- Alternative diagnoses (often irritable bowel syndrome)
- The condition may be oligosymptomatic or asymptomatic
- The condition may have latent periods
- Clinicians are “unaware,” and there are several “myths”:
  - CD is rare
  - CD occurs in Caucasians only
  - CD occurs mostly in Europe and the USA
  - CD occurs only in childhood
  - CD can be cured after (a period of) treatment

## 5.6 Risks

There is an elevated risk for CD in:

- First-degree and second-degree relatives (5–15% basic, 10–30% if DQ2 or DQ8<sup>+</sup>; see section 3.2)
- Down’s syndrome (12%)
- Autoimmune thyroid disease (5%)
- Chronic active hepatitis
- Type 1 diabetes mellitus (5–6%)
- Lymphocytic colitis (15–27%)
- Chronic fatigue syndrome (2%)
- Irritable bowel syndrome

Those with (long-term untreated) CD have an elevated risk for:

- Cancer (overall 1.3 : 1.0)
- Malignant lymphomas
- Small-bowel neoplasia
- Oropharyngeal tumors
- Unexplained infertility (12%)
- Osteoporosis (increased risk for classically symptomatic CD patients).

## 5.7 The global aspect

*Global epidemiology.* CD is common throughout the world and affects between approximately one in 100 and one in 300 individuals. The prevalence of CD is likely to be similar in different regions of the world — so that while the size of the iceberg probably remains the same, the waterline is very different. The waterline determines the ratio of diagnosed to undiagnosed cases. It depends on: 1, awareness of CD; 2, the availability of diagnostic resources; and 3, variations in clinical manifestation (for

example, as a result of local diet). In developing countries, the area above the waterline — the tip of the iceberg (i.e., the number of clinically diagnosed cases) — is probably much smaller. Here almost the entire iceberg is submerged (Fig. 1).

The diagnosis of CD can be made with different diagnostic technologies in different parts of the world, depending on the available resources, but the specificity and validity of the results may vary when tools poorer than those of the “gold standard” are used. Depending on available resources, diagnostic options can be cascaded from a highly resourced setting in which the gold standard described above can be used — endoscopy followed by small-bowel biopsy and specific serology for confirmation or case finding — to a situation in which very few resources are available and only the minimum can be done. If biopsy is not available, “serology only” remains a feasible method of diagnosing CD, also because serological tests are cheaper than endoscopy and biopsy and their statistical value is very similar.

In the absence of a biopsy, the criteria are:

- The presence of auto-antibodies
- Gluten dependency of the auto-antibody titer
- Clinical symptoms, when present
- Improvements in symptoms and reduction in the anti-tTG antibody titer on a gluten-free diet
- In children, catch-up growth, when applicable

The easiest and cheapest serological test would be the dot ELISA. Once a bedside IgA anti-tTG test becomes available and is sufficiently sensitive and specific, it would be ideal for low-income regions.

If a geographic area has very limited resources, clinical aspects become the most important diagnostic tool. A rice-based or corn-based gluten-free diet is the final and vital step in confirming a diagnosis of CD.

**Table 4** Cascade for diagnosing CD

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○ Autoantibodies and endoscopy with intestinal biopsy (gold standard)
○ Endoscopy with intestinal biopsy
○ Autoantibodies
— EMA or anti-tTG, or both (depending on availability and experience)
— Dot ELISA
○ Diagnosis based on “clinical aspects,” with clinical improvement after a corn-based or rice-based gluten-free diet

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Although endoscopy is a very useful tool for detecting CD, it cannot be relied on as a single diagnostic procedure. The presence of markers of mucosal atrophy may be highly suggestive of CD in places where the disease is common, but in other areas of the world there may several differential diagnoses — for example, tropical sprue, malnutrition, heavy-chain disease, etc.).

Nevertheless, the procedure is very helpful when markers are elevated in the course of endoscopies ordered for other reasons. Then the endoscopist must be alert and proceed to intestinal biopsy.

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## 6 Management of celiac disease

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### 6.1 Management

The current treatment for CD is a strictly gluten-free diet for life. In the gluten-free diet, wheat, barley, and rye are avoided. Oats are not toxic in over 95% of patients with CD or dermatitis herpetiformis, but there is a small subgroup (< 5%) for whom oats are not safe.

Additionally, there is a reluctance in some countries to advise liberal use of oats because of the difficulty in guaranteeing that commercially available oats will be free of contamination with other grains. Rice and corn can be part of a gluten-free diet.

Initial approach:

- Prescribe a “natural” gluten-free diet
- Refer to a dietitian and/or support group (see web sites listed below)
- Screen for iron and folate deficiency
- Advise bone-density tests (in some cases)
- Advise vitamin D and calcium supplementation if the patient is osteoporotic
- Advise serological screening for first-degree and second-degree relatives

Most patients have a rapid clinical response to a gluten-free diet (within 2 weeks), although the rate of response varies. Patients who are extremely ill may require hospital admission, repletion of fluids and electrolytes, intravenous alimentation, and, occasionally, steroids. Patients should be encouraged to eat natural high-iron and high-folate foods, especially if a deficiency in these minerals is documented.

Patients should also have a consultation with a dietitian who is knowledgeable about gluten-free diets. However, not all dietitians are familiar with the intricacies of a gluten-free diet, and for this reason local or national support groups provide most of the required information.

For adults, quality of life is improved on a gluten-free diet, even in those whose disease was detected by screening. Children on a gluten-free diet reported a quality of life comparable to that of a reference population. Adolescents have difficulty with dietary compliance.

## 6.2 The gluten-free diet

**Table 5** Foods allowed in a gluten-free diet

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- Rice
  - Corn
  - Sorghum
  - Millet
  - Buckwheat (kasha)
  - Beans, peas
  - Quinoa
  - Potato
  - Soybean
  - Tapioca
  - Amaranth
  - Teff
  - Nuts
  - Fruits
  - Milk and cheeses
  - Meat
  - Fish
  - Egg
  - Oats
- 

The most effective treatment is a rigorous gluten-free-diet for life. This means no wheat, rye, or barley. Oats — provided they are pure and not contaminated with other grains (even minimal amounts of wheat, rye or barley) — are safe to eat in over 95% of cases. Plain meat, fish, rice, corn, fruits, and vegetables do not contain gluten. Examples of foods that are safe to eat and those that are not can be found online. Useful online CD information sites are listed in sections 8 and 9 below.

A gluten-free diet is low in fiber. Patients should be advised to eat a high-fiber diet supplemented with whole-grain rice, maize, potatoes, and ample vegetables. Any dietary deficiencies such as iron, folic acid, calcium and (very rarely) vitamin B<sub>12</sub> deficiency should be corrected.

## 6.3 Persistence of symptoms

A common difficulty with the gluten-free diet is the presence of occult gluten in processed foods and/or medicines (although this is rare). The persistence of symptoms is almost always caused by continued ingestion of gluten.

Reasons for persistence of symptoms:

- (Inadvertent) gluten ingestion (this is the most common reason)
- Wrong diagnosis
- Lactose or fructose intolerance
- Other food intolerances
- Pancreatic insufficiency
- Microscopic colitis
- Bacterial overgrowth

- Collagenous colitis or collagenous sprue
- Irritable bowel syndrome
- Ulcerative jejunitis
- Enteropathy-associated T-cell lymphoma
- Refractory CD

The last three can be regarded as complications of long-lasting CD.

#### **6.4 Refractory celiac disease**

The diagnosis of refractory CD is considered in patients with features of CD who have persistent symptoms, villous atrophy, and failure to respond to a gluten-free diet. This may occur at presentation, or after an initial response to a gluten-free diet. Refractory CD is considered to be a form of low-grade intraepithelial lymphoma, revealed by severe malabsorption that is not responsive to a gluten-free diet. This diagnosis must be considered particularly in celiac disease patients who are diagnosed over the age of 50.

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## **7 Screening for celiac disease**

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### **7.1 Screening for celiac disease**

Good health and growth, as well as quality of life, are key reasons for screening. CD also reduces life expectancy because of a higher risk of malignancies such as:

- Small-bowel lymphoma
- Small-bowel adenocarcinoma
- Esophageal carcinoma
- Ulcerative jejunitis
- Refractory CD
- Enteropathy-associated T-cell lymphoma

Screening is therefore attractive and meets the five World Health Organization criteria for justifying general screening in the population:

- Early detection could be difficult on a clinical basis
- Must be a common disorder causing significant morbidity in the general population
- Tests must be highly sensitive and specific
- Treatment must be available
- If not recognized, the disease could result in severe complications difficult to manage

However, there are resource implications — is this the best use of available limited resources? There are also ethical implications. The current view is that there is not enough evidence to support a decision to carry out mass screening of the general population, nor is there enough evidence to assess the risks of undetected CD.

## 7.2 The future

With the identification of the critically important epitopes within gliadin and gluten and related proteins, and with plans to develop a mouse model of CD, research is focusing on either modifying these proteins or improving tolerance of these proteins in CD patients or in those with a susceptibility to CD. In the meantime, oats (in over 95% of cases), corn, and rice, and possibly industrially purified wheat/starch protein, can be used to expand the relatively limited range of a GFD.

The celiac genetics research community has established sound foundations for the identification of additional disease genes. In addition, alternative, nondietary treatments may soon become available following the identification of the relevant gluten epitopes, with destruction of these epitopes with specific proteases and blockade of HLA-DQ2 and HLA-DQ8.

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## 8 Useful web sites

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- University of Maryland Center for Celiac Research: [www.celiaccenter.org](http://www.celiaccenter.org)
- The Beth Israel Deaconess Medical Center (BIDMC) Celiac Center at Harvard Medical School: [http://bidmc.harvard.edu/display.asp?node\\_id=5449](http://bidmc.harvard.edu/display.asp?node_id=5449)
- The Celiac Disease Foundation: [www.celiac.org](http://www.celiac.org)
- The Celiac Sprue Association: [www.csaceliacs.org](http://www.csaceliacs.org)
- Celiac.com (celiac disease and gluten-free diet information): [www.celiac.com](http://www.celiac.com)
- Gluten-Free.com: [www.glutenfree.com](http://www.glutenfree.com)
- World Gastroenterology Association: [www.omge.org](http://www.omge.org)
- U.S. National Institutes of Diabetes, Digestive, and Kidney Disorders: <http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/>
- The Gluten Intolerance Group: <http://www.gluten.net/>
- Celiac helpline: [www.celiac.co.uk](http://www.celiac.co.uk)
- The Wheat-Free Zone: [www.nowheat.com/grfx/nowheat/index.htm](http://www.nowheat.com/grfx/nowheat/index.htm)
- US National Digestive Diseases Information Clearinghouse (NDDIC): <http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/index.htm>
- WGO “Ask a Librarian” for celiac disease research support: <http://www.omge.org/?askalibrarian>

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## 9 Guidelines, list server and further reading

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### 9.1 Celiac disease guidelines

- National Institutes of Health Consensus Development Conference on Celiac Disease: final statement. June 28–30, 2004 (<http://consensus.nih.gov/2004/2004CeliacDisease118html.htm>).
- Agency for Healthcare Research and Quality. Celiac disease: summary. Evidence report/technology assessment no. 104. AHRQ Publication Number 04-E029-1, June 2004-09-14 (<http://www.ahrq.gov/clinic/epcsums/celiacsum.htm>).
- American Gastroenterological Association medical position statement: Celiac sprue. *Gastroenterology* 2001;120:1522–5 (PMID: 11313323).

- Ciclitira PJ, King AL, Fraser JS. AGA technical review on celiac sprue. *American Gastroenterological Association. Gastroenterology* 2001;120:1526–40 (PMID: 11313324).
- British Society of Gastroenterology. Interim guidelines for the management of patients with coeliac disease (revised by Professor P Ciclitira, April 2002): <http://www.bsg.org.uk/bsgdisp1.php?id=c9c5177d2b91e3228066&h=1&sh=1&i=1&b=1&m=00023>.
- Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:1–19 ([http://www.naspghan.org/user-assets/Documents/pdf/PositionPapers/ceeliac\\_guideline\\_2004\\_jpgn.pdf](http://www.naspghan.org/user-assets/Documents/pdf/PositionPapers/ceeliac_guideline_2004_jpgn.pdf)).
- Celiac disease list server. St. Johns Celiac Listserv Newsgroup. To subscribe, send an e-mail to the following address: [listserv@maelstrom.stjohns.edu](mailto:listserv@maelstrom.stjohns.edu). In the body of the letter, put the following: SUB CELIAC, followed by your first and last name — for example, SUB CELIAC Bob Jones.

## 9.2 Further reading

- Abdulkarim AS, Murray JA. Review article: the diagnosis of coeliac disease. *Aliment Pharmacol Ther* 2003;17:987–95 (PMID: 12694080).
- Arentz-Hansen H, Fleckenstein B, Molberg O, Scott H, Koning F, Jung G, et al. The molecular basis for oat intolerance in patients with celiac disease. *PLoS Med* 2004;1(1):e1 (PMID: 15526039).
- Bolognesi E, Karell K, Percopo S, Coto I, Greco L, Mantovani V, et al. Additional factor in some HLA DR3/DQ2 haplotypes confers a fourfold increased genetic risk of celiac disease. *Tissue Antigens* 2003;61:308–16 (PMID: 12753669).
- Catassi C, Ratsch IM, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, et al. Why is coeliac disease endemic in the people of the Sahara? *Lancet* 1999;354:647–8 (PMID: 10466670).
- Catassi C, Fanciulli G, D'Appello AR, El Asmar R, Rondina C, Fabiani E, et al. Antiendomysium versus antigliadin antibodies in screening the general population for coeliac disease. *Scand J Gastroenterol* 2000;35:732–6 (PMID: 10972177).
- Dieterich W, Esslinger B, Schuppan D. Pathomechanisms in celiac disease. *Int Arch Allergy Immunol* 2003;132:98–108 (PMID: 14600421).
- Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180–8 (PMID: 11796853).
- Fasano A. Celiac disease: how to handle a clinical chameleon. *N Engl J Med* 2003;348:2568–70 (PMID: 12815143).
- Fasano A. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:168–9 (PMID: 12524393).
- Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120:636–51 (PMID: 11179241).
- Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286–92 (PMID: 12578508).
- Gandolfi L, Pratesi R, Cordoba JC, Tauil PL, Gasparin M, Catassi C. Prevalence of celiac disease among blood donors in Brazil. *Am J Gastroenterol* 2000;95:689–92 (PMID: 10710058).
- Green PH, Jabri B. Coeliac disease. *Lancet* 2003;362:383–91 (PMID: 12907013).
- Karpati S. Dermatitis herpetiformis: close to unravelling a disease. *J Dermatol Sci* 2004;34:83–90 (PMID: 15033190).
- Kumar PJ. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:170–1 (PMID: 12524394).
- Louka AS, Sollid LM. HLA in coeliac disease: unravelling the complex genetics of a complex disorder. *Tissue Antigens* 2003;61:105–17 (PMID: 12694579).

- Margaritte-Jeannin P, Babron MC, Bourgey M, Louka AS, Clot F, Percopo S, et al. HLA-DQ relative risks for coeliac disease in European populations: a study of the European Genetics Cluster on Coeliac Disease. *Tissue Antigens* 2004;63:562–7 (PMID: 15140032).
- Moreno ML, Vazquez H, Mazure R, Smecuol E, Niveloni S, Pedreira S, et al. Stratification of bone fracture risk in patients with celiac disease. *Clin Gastroenterol Hepatol* 2004;2:127–34 (PMID: 15017617).
- Mulder CJJ, Bartelsman JFWM. Case finding in coeliac disease seems beneficial, mass screening is still controversial. *Scand J Gastroenterol* [in press].
- Percopo S, Babron MC, Whalen M, De Virgiliis S, Coto I, Clerget-Darpoux F, et al. Saturation of the 5q31-q33 candidate region for coeliac disease. *Ann Hum Genet* 2003;67:265–8 (PMID: 12914578).
- Robins G, Howdle PD. Advances in celiac disease. *Curr Opin Gastroenterol* 2004;20:95–103 (PMID: 15703628).
- Schuppan D, Hahn EG. Gluten and the gut-lessons for immune regulation. *Science* 2002;297:2218–20 (PMID: 12351776).
- Tesei N, Sugai E, Vazquez H, Smecuol E, Niveloni S, Mazure R, et al. Antibodies to human recombinant tissue transglutaminase may detect coeliac disease patients undiagnosed by endomysial antibodies. *Aliment Pharmacol Ther* 2003;17:1415–23 (PMID: 12786636).
- Thompson T. Oats and the gluten-free diet. *J Am Diet Assoc* 2003;103:376–9 (PMID: 12616264).
- United European Gastroenterology Week Working Group. When is a coeliac a coeliac? Report of a working group of the United European Gastroenterology Week in Amsterdam, 2001. *Eur J Gastroenterol Hepatol* 2001;13:1123–8 (PMID: 11564968).
- Vader LW, Stepniak DT, Bunnik EM, Kooy YM, de Haan W, Drijfhout JW, et al. Characterization of cereal toxicity for celiac disease patients based on protein homology in grains. *Gastroenterology* 2003;125:1105–13 (PMID: 14517794).
- Vjero K, Martucci S, Alvisi C, Broglia F, Viera FT, Perego M, et al. Defining a proper setting for endoscopy in coeliac disease. *Eur J Gastroenterol Hepatol* 2003;15:675–8 (PMID: 12840680).
- Wahab PJ, Meijer JW, Dumitra D, Goerres MS, Mulder CJ. Coeliac disease: more than villous atrophy. *Rom J Gastroenterol* 2002;11:121–7 (PMID: 12145668).

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## 10 Queries and feedback

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The Practice Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some procedures are associated with extra risk? Tell us about your own experience. You are welcome to click on the link below and let us know your views.

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