

World Gastroenterology Organisation Global Guidelines on Celiac Disease



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DEFINITIONS

Celiac disease (CD) is a chronic, immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults. It is precipitated by the ingestion of gluten-containing foods.^{1,2} It is also referred to as celiac sprue, gluten-sensitive enteropathy, or nontropical sprue.

Gluten can be defined as the rubbery protein mass that remains when wheat dough is washed to remove starch.³ The major protein fractions of gluten, gliadin and glutenin are storage proteins in wheat. They are present in wheat, rye, and barley and gives the dough its desired baking properties. Gluten is widely used as an ingredient in food processing.

KEY POINTS

- Gluten and gluten-related proteins present in wheat, rye, and barley are the causative external antigens of CD.
- The prevalence of CD in an adult population varies between roughly 1 in 100 and 1 in 300 in most parts of the world.
- First-degree and (to a lesser extent) second-degree relatives have an increased risk for CD. Its clinical presentation varies widely, and the onset of the disease or symptoms may occur at any time in life.

- Many patients with CD have few symptoms or present atypically, whereas a minority of patients have malabsorption (classical CD).
- Patients with active CD have an increased risk of complications, including death, in comparison with the general population. However, this excess rate of major complications seems to return to normal after 3 to 5 years on a strictly gluten-free diet.

Key Diagnostic Findings Include:

- Histopathologic changes in an intestinal biopsy, characterized by crypt hyperplasia, intraepithelial lymphocytosis, and destruction of the surface epithelial lining
- Evidence that the small bowel enteropathy is dependent on gluten shown by positive CD-specific antibodies and/or clinical and/or histologic improvement in response to a gluten-free diet

Serological Tests Can:

- Confirm CD in patients with a demonstrated characteristic enteropathy
- Screen for individuals at risk
- Identify patients in whom biopsy may be warranted.
- Be used to identify gluten consumption during follow-up in diagnosed patients

The presence of autoantibodies directed against transglutaminase-2 suggests that CD has an autoimmune component.⁴ In adults, CD is diagnosed on average > 10 years after the first symptoms appear.⁵

Patients with CD should not eat products containing wheat, rye, or barley. Patients usually need to follow a strictly gluten-free diet for the rest of their lives.⁶ Oats may be consumed, but they are very often contaminated by wheat, and pure oats are often not available. A small subgroup of patients with CD (< 5%) may also be intolerant to pure oats.⁷

EPIDEMIOLOGY

Introduction

CD is common throughout the world and affects around 1 in 100 to 1 in 300 of the population.^{8,9} This

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The authors declare that they have nothing to disclose.

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prevalence is significantly higher than that recognized 20 years ago.^{10,11} The epidemiology of CD has iceberg characteristics that there are far more undiagnosed cases (below the waterline) than diagnosed cases (above the waterline).

A key study by Fasano et al¹² in 2003 found that the prevalence of CD was as follows:

- At risk, first-degree relatives: 1 in 10
- At risk, second-degree relatives: 1 in 39
- At risk, symptomatic patients: 1 in 56
- Groups not at risk: 1 in 100

Ethnicity

Early epidemiology studies regarded CD as a disease of individuals with white ancestry, mainly located in Europe and North America.^{13,14} However, although there is a lack of worldwide epidemiological information, further studies in other areas of the world have shown a similar prevalence.^{15,16} Some of these studies detected CD among people with Amerindian or African American ancestry.¹⁷⁻¹⁹ Recent reports have shown that CD is a common disorder in North Africa, the Middle East, India, and Pakistan.²⁰⁻²² Very recent reports from China have shown that both, the CD-predisposing HLA-DQ alleles and the disorder itself are not rare in the provinces of Jiangsu and Zhejiang, at least.²³ In summary, worldwide distribution of gluten-containing foods, predisposing genotypes, and factors involved in the pathogenesis of CD, are likely to be responsible to the widespread and almost universal emergence of the disorder.

At-risk Populations

CD should be considered in the following cases (estimated prevalence are given in brackets, if available)^{6,24}:

- First-degree and second-degree relatives of celiac patients (10% and 5%, respectively)
- Unexplained iron-deficiency anemia (3% to 15%)
- Unexplained folic acid, iron, or vitamin B₁₂ deficiency
- Reduced serum albumin
- Unexplained hypertransaminasemia (2% to 9%)
- Osteoporosis and osteomalacia of premature onset (2% to 4%)
- Recurrent abdominal pain or bloating
- Other autoimmune disorders: type 1 diabetes mellitus (2% to 15%), thyroid dysfunction (2% to 7%), Addison disease, and autoimmune hepatitis (3% to 6%)
- Ataxia and idiopathic neuropathy
- Down syndrome and Turner syndrome (6% each)
- Irritable bowel syndrome (3%)

DIAGNOSIS OF CD

Introduction

The considerable increase in the number of patients being diagnosed with CD correlates with the recognition of a remarkably wide variety of clinical manifestations of the disorder, the development of accurate screening tests, and also a true increase in the incidence.

Current Diagnosis

In current practice, the diagnosis of CD hinges on a diagnostic intestinal biopsy and the concomitant presence of a positive CD-specific serology.^{6,14,24-28} A second (posttreatment) biopsy is not necessary for most patients if they respond satisfactorily to the specific treatment and should be reserved for patients in whom the first biopsy and

serological test are inconclusive (eg, seronegative enteropathy) or for patients on a strict gluten-free diet but fail to respond.^{26,27} A gluten challenge, in which the offending agent is reintroduced while the patient is on a restrictive diet, should be reserved for patients who are receiving treatment but have a doubtful diagnosis.²⁴⁻²⁸

Diagnostic Tests

Intestinal Biopsy

An intestinal biopsy together with positive serology represents the gold standard in diagnosing CD. In 1992, Marsh¹⁴ reviewed the intensity of mucosal damage observed in treated CD patients who were confronted with increased amounts of gluten (Fig. 1).

Histologic Characteristics of Celiac Enteropathy

Histologic damage is considered characteristic, but not pathognomonic, of CD, as similar lesions are seen in several other disorders.²⁹ CD affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity toward the distal small intestine, although in severe cases the lesions can extend to more distal areas.^{14,26}

The severity and extent of the histologic damage seem to correlate with the intensity of the clinical symptoms.^{26,28} The proximal damage may be very mild in atypical or silent cases, with little or no abnormality histologically detectable in the intestine. Abnormalities in the gastric and rectal mucosa may be observed in some cases.¹⁴

The lesion in the duodenum/upper jejunum may be patchy, as a result of which it may be missed if there is insufficient mucosal sampling.²⁴ Four to 6 biopsy samples must be taken: 3 or 4 from the second part of the duodenum distal to the papilla and at least 1 from the duodenal bulb.³⁰ A negative histologic diagnosis may justify a second biopsy in selected patients who have positive autoantibodies such as endomysial antibodies (EMA).^{26,31}

Biopsy samples taken from the proximal duodenum above the papilla of Vater may have artifacts (eg, stretching of villi) produced by submucosal Brunner glands, which may be falsely interpreted as flat mucosa.³⁰

Under light microscopy, the most characteristic histologic findings in patients who are taking a gluten-containing diet are^{14,29}:

- Blunted or atrophic villi
- Crypt hyperplasia
- Mononuclear cell infiltration in the lamina propria
- Epithelial changes, including structural abnormalities in epithelial cells
- Intraepithelial lymphocyte infiltration

A series of well-designed studies by Marsh made it possible to interpret the wide range of mucosal damage induced by gluten, with the celiac histologic modifications being categorized as ranging from normal mucosa to complete flat villi. The modified Marsh classification is widely used in clinical practice to characterize the histologic damage.^{32,33}

Key factors to be considered for making histologic diagnosis reliable include:

- Number of biopsies procured
- Quality of biopsy samples
- Handling of samples
- Patchiness of mucosal damage
- Different grades of lesion
- Subjective histologic interpretation

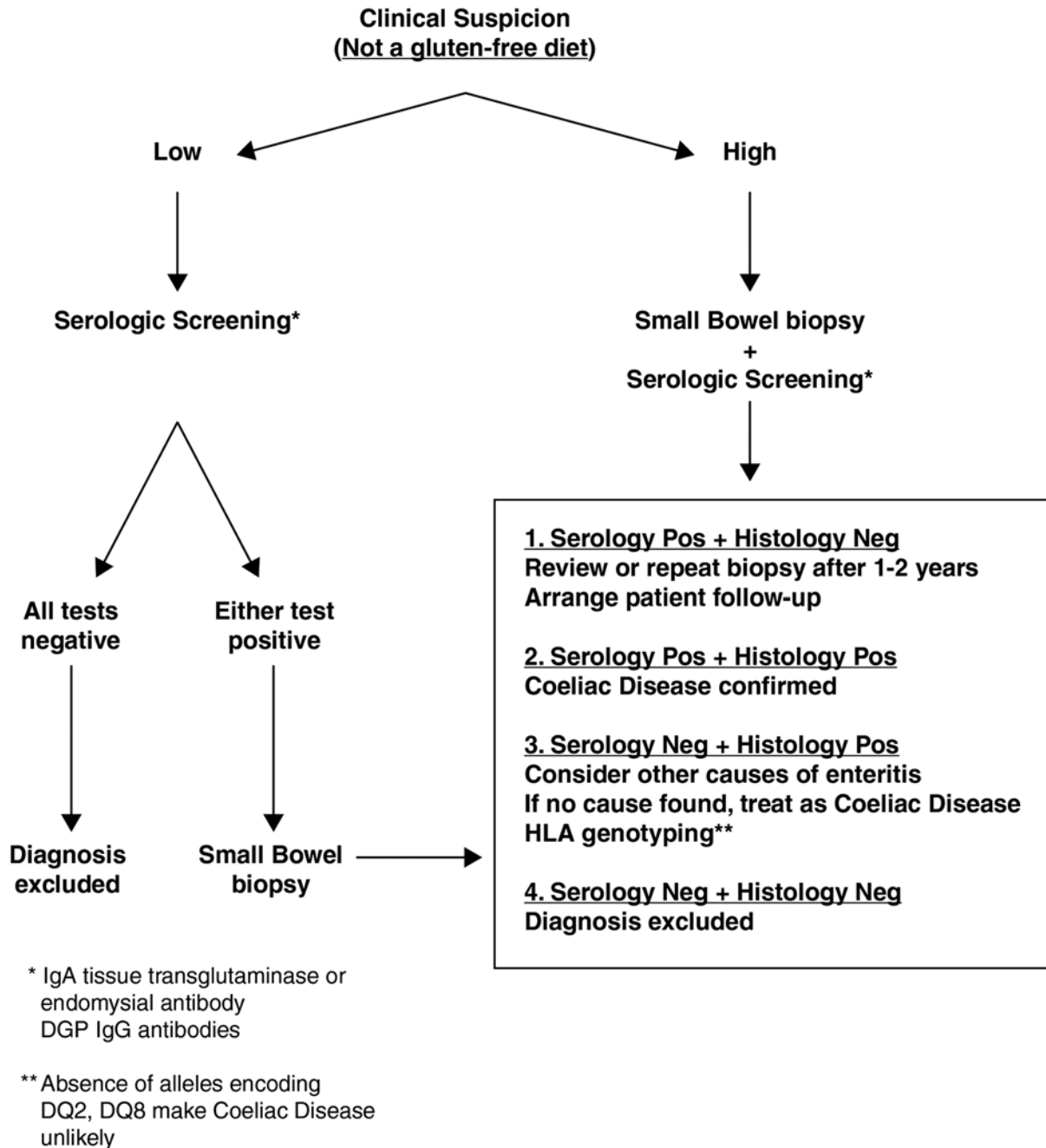


FIGURE 1. Diagnosis of celiac disease.

Serum Antibodies for Suspicion and Diagnosis of CD

CD-specific serological tests, which have been in use for >20 years now, are important for 2 purposes: to select patients in whom biopsies are appropriate and to confirm the diagnosis in cases in which an enteropathy has been detected.³⁴⁻³⁷ A number of serological markers have been shown repeatedly in many studies to be highly sensitive and specific for untreated CD. On the basis of the target antigens, serological tests for CD can be divided into 2 groups:

- *Autoantibodies*: antiendomysial (EMA) and antitissue transglutaminase (tTG) antibody tests^{4,34}

- *Antibodies targeting the offending agent (gliadin)*: conventional antigliadin antibodies (nowadays considered obsolete for diagnostic purposes).³⁵ Antibodies against synthetic deamidated gliadin peptides (DGPs)³⁷⁻⁴⁰

All of these antibodies are based on immunoglobulin A (IgA) or immunoglobulin G (IgG). Specifically, IgG-based tests are useful for detecting CD in selected IgA-deficient patients.⁴⁰

Choosing the Most Appropriate Serological Test in Different Clinical Scenarios

1. To confirm gluten dependence in patients with a demonstrated enteropathy while consuming a gluten-containing

diet. Both IgG DGP seems to be very helpful in IgA-deficient patients and for some EMA-negative and tTG-negative patients.

2. To select patients for duodenal biopsy: to reduce the need for duodenal biopsies, and on the basis of the different accuracy of serological tests, a series of serological algorithms are used to select patients for biopsy in different clinical scenarios:

- From the general population (screening). tTG and DGPs show similar performance and have a high sensitivity. These tests have low positive predictive values in the general (low risk) population (with a prevalence of 1%). A serological algorithm, with serial use of more specific screening assays (eg, EMA) has therefore been widely used to improve the diagnostic accuracy in the general population. A recent study has suggested that the single assay detecting IgA and IgG subtypes of tTG and DGP is the most sensitive test. Simultaneous or serial use of 2 tests (eg, IgA and IgG DGP/tTG plus either IgA tTG or IgA DGP or IgG DGP) provides the highest positive and negative predictive values. A combination of tests therefore improves suspicion of cases.³⁷⁻⁴⁴
- Case finding in high-risk populations. Any of the given tests can be used as a single assay, as they all show similar performance as a single test, or in combination. A combination of tests does not improve case finding.

The EMA test requires expert observers, and ELISA tests for detecting tTG antibodies should therefore be recommended in settings with low expertise.^{35,36}

Genetic Testing for Diagnosis

Human leukocyte antigen (HLA) class II haplotypes DQ2 and DQ8 are found in virtually all patients (almost 100% sensitivity) and also in 30% to 40% of the population in Europe, where the great majority will never develop CD. These haplotypes are essential for the recognition of gliadin epitopes by antigen-presenting cells and are therefore a key factor in the development of adaptive immunity. On the basis of its extremely high-negative predictive value, HLA typing can help support exclusion of a diagnosis of CD in equivocal cases in which the patient lacks HLA-DQ2 and DQ8.^{14,45,46}

Role of Endoscopy

Endoscopy is a valuable tool for obtaining duodenal biopsy samples. Endoscopy may show typical duodenoscopic features that are highly predictive of mucosal damage.⁴⁷⁻⁴⁹ Characteristic findings on endoscopy include: scalloped folds, fissures, and a mosaic pattern; flattened folds; and smaller size and/or disappearance of folds with maximum insufflation. Although endoscopic signs of mucosal atrophy have a low sensitivity for diagnosing CD in the general population,⁵⁰ the procedure is very helpful when these signs are detected during endoscopies that are being conducted for other reasons. In such cases, the endoscopist can follow-up with an intestinal biopsy due to a strong suspicion of mucosal atrophy (Table 1).

TABLE 1. Cascade for Diagnosing Celiac Disease

Gold Standard: Intestinal Biopsy and Celiac Disease-specific Antibodies

↓
Medium resources

Antibody assessment as a single tool, as the only diagnostic measure when trained pathologists are not available
Anti-tTG or EMA, or both (depending on availability and experience). IgA assays are the most commonly used test with anti-tTG more sensitive but less specific than IgA EMA
IgG and/or IgA DGP antibodies: These have a similar performance to IgA anti-tTG, and both DGPs are very useful for children under the age of 3 years (in whom anti-tTG has poorer performance) and in IgA-deficient patients (use the IgG DGP test)

Intestinal biopsy: in settings in which pathology is available, perhaps remotely, but clinical laboratories cannot reach standards
Pitfalls in histologic diagnosis are common and should be considered when biopsies are assessed by nonexpert pathologists. Findings are characteristic but not specific. The strategy can be combined with the demonstration of clinical and/or histologic improvement after introduction of a gluten-free diet

↓
Low resources

A simple anti-tTG IgA test may be considered in low-resource settings
Anti-tTG IgA can be assessed in the physician's office by using the self antibody-based rapid test, carried out on a fingertip blood sample. The test is simple, takes only a few minutes, and has shown high sensitivity and specificity
Endoscopic identification of duodenal markers indicative of mucosal atrophy is not diagnostic of celiac disease, but strongly increases the suspicion of the disorder

A diagnosis only based on "clinical assessment" and improvement after a gluten-free diet should be strongly discouraged. This has been a source of misdiagnosis and can only be helpful in a minority of patients from the overall population (those with overt celiac disease) and in areas with extremely limited resources. It could cause confusion making a nonspecific diagnosis of celiac disease in patients with nonceliac disease gluten sensitivity. The gluten-free diet can produce a nonspecific effect due to nongluten-dependent dietary modifications or because of a "placebo effect" that may be falsely attributable to a celiac disease diagnosis.

MANAGEMENT OF CD

Introduction

The only treatment for CD is a strictly gluten-free diet for life. No foods or medications containing gluten from wheat, rye, and barley, or their derivatives can be taken, as even small quantities of gluten may be harmful.^{6,14,24,27,31}

Oats are not toxic in over 95% of patients with CD, but there is a small subgroup (< 5%) in whom oats are not safe. In addition, there is reluctance in some countries to advise liberal use of oats, because of difficulties in guaranteeing that commercially available oats are free of contamination with other grains.^{7,51}

Complete removal of gluten from the diet will result in symptomatic, serological, and histologic remission in most patients.⁵² Growth and development in children returns to normal with adherence to the gluten-free diet and many disease complications in adults are avoided, with an improvement in the quality of life.⁵³⁻⁵⁵

Approximately 70% of patients reported an improvement in symptoms within 2 weeks after starting the gluten-free diet.⁵² With strict dietary control, antibody levels may

decrease very soon after the diet has been instituted. In contrast, complete histologic resolution is not always achieved, or may take years.

Monitoring

Compliance is difficult, and patients should therefore be advised of the importance of strict adherence to a gluten-free diet.^{55–57} A multidisciplinary approach can produce more meaningful outcome information. The following is a summary of recommendations for follow-up after diagnosis and tools for monitoring adherence to a gluten-free diet, during the first year after diagnosis (with follow-up appointments every 3 to 6 mo):

- Clinical visits: check symptoms and laboratory tests. CD serology tests (best predictors: quantitative determination of DGP IgA and tTG IgA)
- Visit to an expert nutritionist: assessment of nutritional status and adherence to a gluten-free diet based on an interview, a food diary, and the frequency of consumption (coinciding with the clinical visit)

After the first year and once the patient is stable, visits for consultation can be reduced to 1 per year. Follow-up intestinal biopsy is not required.

Laboratory Assessment

Specific serological tests should be less frequent, depending on the degree of compliance and the length of time spent on a gluten-free diet. Recent studies suggest that periodical testing for IgA DGP and/or IgA tTG is the preferred method for monitoring compliance.^{36,52} Although these tests do not identify minor dietary indiscretions, a continued reduction in serum concentrations helps to assess compliance with the diet.⁵²

Nutritionist Consultation^{58–64}

An expert dietitian should be consulted in order to:

- Assess the patient's current nutritional status
- Identify macronutrient and/or micronutrient intake and detect deficiencies and/or excesses
- Analyze eating habits and potential factors affecting access to the diet
- Provide information and initiate the gluten-free diet
- Provide dietary education
- Monitor and evaluate dietary compliance and reinforce alimentary counseling

Patients who are unable to adhere to the diet may require support with psychological counseling.

Persistence of Symptoms

The persistence of symptoms is almost always caused by continued ingestion of gluten.⁵⁵ A common difficulty with the gluten-free diet is cross-contamination and the presence of unsuspected gluten in processed foods and/or medicines (although the latter is rare). Gluten may be a hidden ingredient, so it is prudent for patients to routinely check the ingredient list before purchasing any product; available lists should be checked for allowable food-stuffs.^{60,62,64} Serology can detect major and continued lapses in dietary adherence.^{52,55,56}

Note

Further details and evidence are available in the full text of this guideline on the World Gastroenterology Organization web site, at: <http://www.worldgastroenterology.org/ceeliac-disease.html>.

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