Annals of Internal Medicine®

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Celiac Disease

Gluten-related disorders, including celiac disease, wheat allergy, and nonceliac gluten sensitivity (NCGS), are increasingly reported worldwide. Celiac disease is caused by an immune-mediated reaction to ingested gluten in genetically susceptible persons. NCGS is largely a diagnosis of exclusion when other causes of symptoms have been ruled out. All patients with celiac disease should be referred to a registered dietitian nutritionist with expertise in celiac disease and a gastroenterologist who specializes in celiac disease and malabsorptive disorders, and they should remain on a strict gluten-free diet indefinitely. This article provides an overview of gluten- and wheat-related disorders.

Prevention

Screening

Diagnosis

Treatment

Patient Education

CME/MOC activity available at Annals.org.

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doi:10.7326/AITC202001070

CME Objective: To review current evidence for prevention, screening, diagnosis, treatment, and patient education of celiac disease.

Funding Source: American College of Physicians.

Disclosures: Dr. Rubin, ACP Contributing Author, reports personal fees from RMEI Medical Education outside the submitted work. Dr. Crowe, ACP Contributing Author, reports grants from the National Institutes of Health and the University of California, San Diego, during the conduct of the study; personal fees from Takeda and Calypso Biotech during the conduct of the study; grants and other support from the University of California, San Diego, outside the submitted work; and a pending patent for biomarkers to stratify different clinical presentations of celiac disease. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-2234.

With the assistance of additional physician writers, the editors of ***Annals of Internal Medicine*** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians.

The Patient Information page was written by Monica Lizarraga from the Patient and Interprofessional Education Program at the American College of Physicians.

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Celiac disease is a multisystem disorder affecting approximately 0.7% of Americans and 1% of non-Hispanic white persons; however, many cases are not diagnosed (1, 2). It results from an inappropriate T-cell–mediated immune response to ingested gluten that causes immune-mediated injury to the small intestine in genetically predisposed persons (3). Damage to proximal mucosa of the small intestine leads to malabsorption of nutrients. The average age at diagnosis of celiac disease in the United States is in the fifth decade of life (3), and prevalence has increased 4- to 5-fold over the past 3 to 4 decades (4). Almost every body system can be affected, but the dermatologic, hematologic, neurologic, musculoskeletal, endocrine, reproductive, and digestive systems are most commonly involved. Celiac disease is associated with various autoimmune conditions whose clinical course may be affected by the diagnosis and treatment of celiac disease. Although most patients respond well to treatment with a gluten-free diet (GFD), unrecognized or untreated disease is associated with increased mortality (4, 5) and risk for intestinal lymphoma (6).

Nonceliac gluten sensitivity (NCGS), or nonceliac wheat sensitivity, seems to have increased, but the absence of diagnostic biomarkers and an incomplete understanding of the disease have made accurate diagnoses difficult. Many patients with NCGS start a GFD without consulting a physician. NCGS is characterized by irritable bowel syndrome (IBS)–like symptoms and/or extraintestinal symptoms several hours to days after eating foods containing wheat, and it improves after removal of wheat and gluten from the diet. Patients without autoantibodies associated with celiac disease or enteropathy fall into the NCGS group. Controversy persists about NCGS because symptom overlap with IBS complicates the diagnosis. Such patients do well with a GFD or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), with specific avoidance of fructose and fructans. However, indefinite adherence to a strict GFD is not necessarily warranted as it is in the setting of diagnosed celiac disease. Double-blind studies on NCGS have been done in Europe, but a recent meta-analysis showed poor correlation between symptoms and gluten ingestion (7). Another double-blind crossover challenge in Oslo, Norway, evaluated 3 bars (gluten, fructan, or commercial) and found that the fructan bar caused the most bloating (8). Greater understanding of NCGS is needed (9). The absence of HLA-DQ2 or HLA-DQ8 alleles rules out celiac disease among patients on a self-prescribed GFD and can guide providers and patients in managing NCGS.

Prevention

Risk for celiac disease is 10% to 15% in persons who have a first-degree relative with celiac disease. It was previously believed that breastfeeding and delaying the introduction of gluten into the diet of the immunologically immature infant gut may prevent or delay gluten sensitization (10, 11), but more recent randomized studies revealed that delaying the introduction of gluten and breastfeeding did not modify risk for celiac disease in high-risk infants (12, 13). Current recommendations are to introduce gluten into an infant's diet between ages 4 and 12 months (14). The optimum amount of gluten to be introduced at the time of wean-

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ing has not been established; however, higher gluten intake in the first 5 years of life in high-risk children has been associated with increased risk for celiac disease and celiac disease autoimmunity (15). A report suggests that rotavirus vaccine early in the life of genetically susceptible infants may decrease development of celiac autoantibodies (16).

Screening

Who should be screened?

Screening for celiac disease is controversial. In Finland, widespread screening has revealed a prevalence of 2.4% compared with 0.7% to 0.8% in the United States, and prevalence of 1% is generally considered a reasonable estimate in most Western countries (17).

The American College of Gastroenterology (ACG) clinical guidelines on celiac disease state that testing should be considered when a first-degree family member has biopsy-confirmed disease (18). A recent retrospective study from the Mayo Clinic showed a high prevalence of celiac disease (44%) in screened first-degree relatives, with more than 90% of persons with positive results having nonclassic symptoms or no symptoms (19). Inherited HLA-DQ2 and/or HLA-DQ8 genes are necessary but not sufficient for celiac disease to develop. The absence of both genes has a high negative predictive value and rules out disease (20), which is useful in selecting family members who require additional screening and prevention strategies. Persons with autoimmune diseases that share these HLA susceptibility genes with celiac disease (for example, type 1 diabetes and autoimmune endocrine, connective tissue, and hepatobiliary disorders) and conditions known to be associated with celiac disease (for example, Down [21] and Turner [22] syndromes) are also candidates for screening (see the **Box**: Symptoms and Conditions That Should Prompt Consideration of Celiac Disease). Individual patients should be tested if they are willing to undergo endoscopy with intestinal biopsies if necessary for disease confirmation and to begin a GFD.

The U.S. Preventive Services Task Force and the American Academy of Family Physicians found insufficient evidence to recommend universal or targeted screening in persons with a first-degree relative with biopsy-confirmed celiac disease (23). There was inadequate evidence on the accuracy of screening, potential benefits and harms of screening, and potential benefits and harms of treatment in persons who tested positive. Current practice in the United States is largely case-finding to detect celiac disease (23), but in general, screening should be decided by the patient and practitioner.

How should people be screened?

Serum IgA antibodies to tissue transglutaminase (tTG), a ubiquitous enzyme also called transglutaminase 2, are increased in most cases of active celiac disease, and testing for these antibodies is the recommended screening procedure in older children and adults (24). One exception is patients with IgA deficiency, who should be tested with an IgG assay if one is available (see the Diagnosis section).

A large systematic review that included 60 individual studies and 13 systematic reviews reported that the anti-tTG IgA serum antibody marker had high sensitivity (92.5%) and spec-

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Symptoms and Conditions That Should Prompt Consideration of Celiac Disease

First- and second-degree relatives with celiac disease

Gastrointestinal symptoms
- Irritable bowel syndrome–like symptoms
- Heartburn
- Dyspepsia
- Diarrhea
- Altered bowel habits
- Bloating
- Lactose intolerance

Extraintestinal presentations
- Dermatitis herpetiformis*
- Iron deficiency*
- Folate deficiency*
- Osteopenic bone disease
- Chronic fatigue
- Neuropsychiatric manifestations
- Short stature*
- Infertility*
- Recurrent fetal loss*
- Low birthweight*

Autoimmune endocrine disorders
- Type 1 diabetes
- Autoimmune thyroid disease
- Autoimmune adrenal disease

Autoimmune connective tissue disorders
- Sjögren syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus

Hepatobiliary conditions
- Primary sclerosing cholangitis
- Primary biliary cirrhosis
- Autoimmune cholangitis
- Elevated aminotransferase levels

Other inflammatory luminal gastrointestinal disorders
- Lymphocytic gastritis*
- Microscopic colitis*
- Inflammatory bowel disease*

Miscellaneous conditions
- IgA deficiency
- IgA nephropathy*
- Down syndrome
- Turner syndrome

*Unlikely to be associated with nonceliac gluten sensitivity.

ificity (97.9%) (25). A related antibody, anti-endomysial IgA antibody, which detects a structurally homologous protein as tTG antibodies (26), was reported to have lower sensitivity (79%) but high specificity (99%) (24, 25). Antibodies to gliadin were previously used to screen for celiac disease but are no longer recommended because of the low sensitivities and specificities of IgA and IgG antigliadin antibodies (24). IgG and IgA antibodies to deamidated gliadin peptide have shown promise, with high sensitivity (87.8%) and specificity (94.1%) (25).

The first screening test for relatives of patients with celiac disease is polymerase chain reaction testing of a blood sample or cheek swab for HLA-DQ2 or HLA-DQ8 (see the **Box**: HLA-DQ2 and HLA-DQ8 Testing). Persons who are positive for either allele should then be tested for serum anti-tTG IgA. Such testing in genetically at-risk children should begin after age 2 years and after at least 1 year on a wheat-containing diet or with suggestive signs or symptoms. Previous guidelines recommended tTG IgA testing every 3 years in children with a family history, but this is now considered unnecessary unless they have the HLA-DQ2 or HLA-DQ8 gene. Because celiac disease can develop at virtually any time, with an average age at diagnosis in the fifth decade of life, identifying family members

HLA–DQ2 and HLA–DQ8 Testing

How to test:
- Polymerase chain reaction of RNA extracted from cells in a cheek swab or blood sample

Whom to test:
- Close relatives of patients with confirmed celiac disease who want to know whether they are at risk
- Patients on a gluten-free diet who are candidates for a gluten challenge to confirm possible celiac disease; only genetically susceptible patients at risk for celiac disease should be challenged
- Patients with equivocal histologic and serologic findings in whom a negative test result would make celiac disease highly unlikely

How often to test:
- Once in a lifetime

who are at risk by using HLA-DQ testing can prevent unnecessary tTG IgA testing in those who are not at risk. Duodenal biopsies should be considered for screening in patients with an autoimmune disorder associated with increased risk (see the **Box**: Symptoms and Conditions That Should Prompt Consideration of Celiac Disease) when endoscopy is being done for another reason.

Screening... Screening of asymptomatic adults at high risk for celiac disease is controversial. First-degree relatives of patients with confirmed celiac disease and those with such conditions as type 1 diabetes, autoimmune thyroid disease, autoimmune hepatobiliary diseases, and Down or Turner syndrome should be considered for HLA-DQ2 or HLA-DQ8 testing to identify those who are at risk for celiac disease and need serum testing. In patients who test positive for HLA-DQ2 or HLA-DQ8, tTG IgA should be used to test adults and older children unless they have IgA deficiency, in which case IgG testing should be used if available. All persons with a positive result on a tTG antibody test should undergo esophagogastroduodenoscopy with duodenal biopsy to confirm the diagnosis.

CLINICAL BOTTOM LINE

Diagnosis

What signs and symptoms should prompt clinicians to consider a diagnosis of celiac disease?

Celiac disease may affect multiple organ systems and may have protean manifestations. Commonly recognized gastrointestinal symptoms include diarrhea (occurring in approximately 50% of patients), altered bowel habits, flatus, dyspepsia, heartburn, and weight loss. Less readily recognized manifestations may include headaches, depression, paresthesia, joint symptoms, rashes, and fatigue, among many others. Celiac disease is usually not associated with specific physical signs other than dermatitis herpetiformis (DH), and physical examination may not yield specific findings. Patients with severe disease may have nonspecific findings, but a small subset may have severe manifestations at the time of diagnosis (see the **Box**: Physical Findings in Patients With Severe Celiac Disease).

Physical Findings in Patients With Severe Celiac Disease*

- Muscle wasting
- Loss of adipose tissue
- Pallor (due to anemia)
- Bruising
- Edema (due to hypoproteinemia)
- Stomatitis
- Aphthoid ulceration of the oral mucosa
- Cheilosis
- Vertebral fractures and limb girdle weakness and pain (osteoporosis or osteomalacia)
- Postural hypotension from dehydration
- Tetany (Trousseau or Chvostek signs)
- Finger clubbing
- Protuberant abdomen (more common in children; rare in adults)
- Short stature
- Dental enamel defects

*All are unlikely to be associated with nonceliac gluten sensitivity.

Diarrhea is a common presenting sign of the classic form of celiac disease, although nonclassic forms are now more commonly encountered (27). Steatorrhea is

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relatively uncommon, but approximately half of patients have lactose intolerance at the time of presentation. Maldigestion of sugars may cause postprandial bloating, flatulence, and diarrhea. Serologic testing for celiac disease is not advised for patients with typical IBS but is recommended for those with diarrhea-predominant or mixed-type IBS (28).

A systematic review and meta-analysis of 14 studies found that the likelihood of biopsy-confirmed celiac disease in patients meeting criteria for IBS was increased more than 4-fold compared with non-IBS controls (29). However, whether such findings truly reflect an increased association between the diseases remains a matter of debate.

Iron deficiency is common in celiac disease and is often seen in newly diagnosed patients. When patients referred for upper endoscopy as part of the investigation of iron deficiency anemia are examined for celiac disease via duodenal biopsy, 6% to 10% will have celiac disease even in the absence of other signs and symptoms (30). Celiac disease should be considered in menstruating women and in persons younger than 50 years with unexplained iron deficiency, especially if they are resistant to oral iron supplementation. Patients older than 50 years with unexplained iron deficiency anemia should be referred for gastrointestinal testing, including upper endoscopy with duodenal biopsy and colonoscopy.

Celiac disease can result in vitamin D and calcium malabsorption, and patients with unexplained metabolic bone disease or severe osteoporosis should be assessed for celiac disease, even in the absence of gastrointestinal symptoms. This applies especially to patients with osteomalacia or reduced bone density at a young age or males who develop osteoporosis. A GFD corrects bone loss in patients with mild disease and provides significant amelioration in patients with severe malabsorption. Diminished bone density is associated with increased risk for fractures in patients with celiac disease, and a GFD reduces this risk (31).

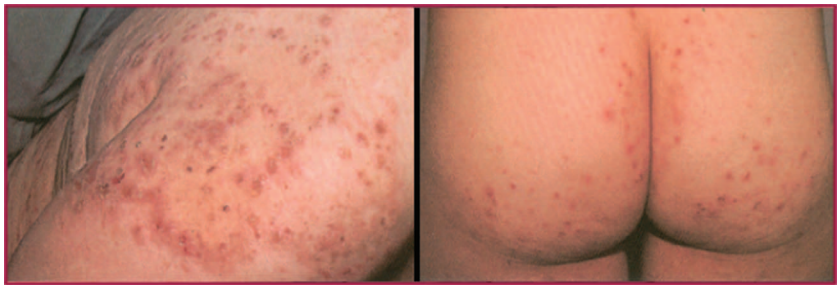
An evaluation for celiac disease, starting with serologic tests, should be considered in women and men with unexplained infertility and women with recurrent spontaneous abortion. The mechanism of these problems may be abnormal hormone levels, general malnutrition, or other autoimmune disorders (32, 33). Pregnancy in women with untreated celiac disease may result in babies who are small for their gestational age and intrauterine growth restriction (32–34). Treating celiac disease seems to improve fertility and pregnancy outcomes (32, 35), although systematic follow-up studies have not been done.

Axonal neuropathy and cerebellar ataxia are among the more common extraintestinal symptoms associated with celiac disease (36) and have been associated with elevated levels of antigliadin antibodies, even when duodenal pathologic characteristics are lacking. Migraines, depression, behavioral disorders, autism, and other neurologic or psychiatric conditions have been reported, but there is no proof that celiac disease is causal in most of these conditions (37). Because some patients have been reported to respond to a GFD, serologic assessment for celiac disease should be considered in idiopathic peripheral neuropathy or cerebellar ataxia.

What is the significance of DH in patients with suspected celiac disease?

DH is an uncommon but characteristic papulovesicular rash that affects the extensor surfaces of the elbows, knees, and trunk and

Figure 1. **Dermatitis herpetiformis.**



This disorder is an intensely pruritic papulovesicular rash affecting extensor surfaces, such as the shoulders (*top*), elbows, knees, back, and buttocks (*bottom*). Although all patients with dermatitis herpetiformis have the intestinal lesions associated with celiac disease, few have gastrointestinal symptoms. Immunofluorescent detection of IgA deposits at the dermal–epidermal junction in a perilesional biopsy sample from a fresh skin lesion is sufficient for diagnosis and precludes the need for intestinal biopsy.

is intensely pruritic (**Figure 1**). Although intestinal biopsy specimens from patients with this disorder are indistinguishable from those with celiac disease (38), typical symptoms of malabsorption are often absent when DH is present. DH is an immunologic response to intestinal gluten sensitivity, but the relationship is frequently not recognized, and treatment of the dermatologic problem alone is often pursued with suppressive therapy, such as dapsone. DH should prompt a dermatologic consultation to obtain skin biopsy specimens of perilesional areas for histologic and immunofluorescence staining. When skin biopsy confirms the diagnosis, intestinal biopsies are not needed. A lifelong GFD is recommended, even in patients whose dermatologic disease has responded to dapsone or sulfapyridine (39).

Which patients are at risk for lymphoma?

Patients with refractory celiac disease are at greatest risk for T-cell lymphoma, and such patients, as well as those who develop new or recurrent malabsorption, abdominal pain, fever, and weight loss despite adherence to a GFD, require evaluation for potential cancer of the small intestine. The evaluation should include imaging with contrast-enhanced computed tomography as well as video capsule endoscopy. An endoscopic examination is also required to assess for cancer, and multiple biopsy specimens should be obtained from the duodenum and more distal small intestine, depending on the findings of radiologic and endoscopic studies. In addition to histologic appraisal, evaluation of the biopsy samples should include immunohistochemistry and molecular diagnostic studies to assess for abnormal lymphoid cells. Flow cytometry and molecular genetic studies for rearrangement of T-cell genes are used to categorize refractory celiac disease into type I (without monoclonal gene rearrangement) and type II (with gene rearrangement). Several retrospective studies indicate that 5-year mortality among patients with type II refractory celiac disease is approximately 50% (40, 41), but no prospective studies have documented the natural history of persons identified to have this presumed prelymphoma state. Causes of death in patients with refractory celiac disease include malnutrition; lymphoma; and infection, including sepsis.

When lymphoma or prelymphoma is suspected, bone marrow biopsy and consultation with a hematologist/oncologist are

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indicated. Full-thickness surgical biopsies of the small intestine to evaluate for lymphoma may be needed. Management is complex, and only small case series are available for guidance in this rare cancer; parenteral nutrition is typically needed. Given the complexity of care, patients with refractory celiac disease are often referred to tertiary centers specializing in celiac disease (42).

What other diagnoses should clinicians consider?

Many conditions can be mistaken for celiac disease. These include such common disorders as intolerance to lactose and other carbohydrates, functional gastrointestinal disorders, idiopathic inflammatory disorders of the intestine (inflammatory bowel diseases), other food protein–mediated conditions (hypersensitivity, protein enteropathies), drug-induced enteropathy, and malabsorptive disorders (see the **Box**: Conditions or Disorders to Consider in the Diagnosis of Celiac Disease).

What is the role of endoscopy in the evaluation of a patient with possible celiac disease?

Endoscopy is used primarily to confirm the diagnosis by obtaining biopsy samples of the proximal small intestine in patients with positive serologic test results or if there is high clinical suspicion of celiac disease in the absence of positive serologic test results. A pattern visible on endoscopic examination, including scalloping or notching of mucosal folds, can be seen (**Figure 2**). This suggests to the trained endoscopist the diagnosis of celiac disease or other conditions that cause villous atrophy (43). However, endoscopic changes have low sensitivity, and biopsies should be done if they are absent (44). Taking at least 1 or 2 biopsy specimens from the duodenal bulb and at least 4 from the postbulbar duodenum is recommended (18).

Small-intestine biopsies show varying degrees of villous blunting and lymphocytic and plasma cell infiltrates (**Figure 3**). Although not pathognomonic for celiac disease, these findings are highly predictive of response to a GFD. Biopsy specimens must be carefully evaluated to differentiate celiac disease from other conditions, such as peptic duodenitis; effects of nonsteroidal anti-inflammatory drugs, olmesartan, or recent chemotherapy; tropical sprue; radiation damage; graft-versus-host disease; chronic ischemia; severe giardiasis; Crohn disease; common variable immunodeficiency; and autoimmune and other enteropathies (45). Ideally, a pathologist with expertise in gastrointestinal diseases should examine the biopsy slides, especially if the diagnosis is uncertain.

Can endoscopy be avoided?

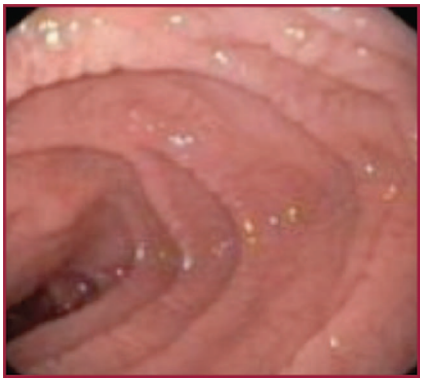
Controversy persists about whether all patients need a confirmatory endoscopic biopsy, and studies have evaluated whether some adult patients can avoid endoscopy to confirm the diag-

Conditions or Disorders to Consider in the Diagnosis of Celiac Disease*

- Irritable bowel syndrome
- Nonceliac gluten sensitivity
- Inflammatory bowel diseases
- Microscopic colitis
- Lactose intolerance
- Other carbohydrate intolerances
- Eosinophilic gastroenteritis
- Food protein–induced enteropathies
- Small intestinal bacterial overgrowth
- *Giardia* infection
- Pancreatic insufficiency
- Intestinal lymphoma
- IgA deficiency
- Common variable immunodeficiency
- Autoimmune enteropathy

*Some can coexist with or complicate celiac disease.

Figure 2. **Endoscopic appearance of celiac disease.**



Such features include scalloping or notching of the folds, as shown. Fissuring or cracking of the flat intervening mucosa between the folds can also be seen. These endoscopic features are helpful for targeting biopsy sites, but their absence does not rule out the diagnosis. Therefore, intestinal biopsy specimens should be obtained during upper endoscopy to evaluate for celiac disease.

nosis. In a recent Finnish study, the investigators found that 33% of all patients newly diagnosed with celiac disease could avoid biopsy on the basis of 3 criteria: a tTG antibody level greater than 10 times the upper limit of normal, a positive result for endomysial antibodies, and appropriate genetics without requirement of symptoms (46). A recent clinical practice update from the American Gastroenterological Association recognizes that a tTG antibody level greater than 10 times the upper limit of normal and a positive result for endomysial antibodies have a positive predictive value of nearly 100% (47). However, cutoff values of the common tTG assays are not standardized. More studies are needed before this approach can be recommended, and North American guidelines still recommend a confirmatory biopsy (48).

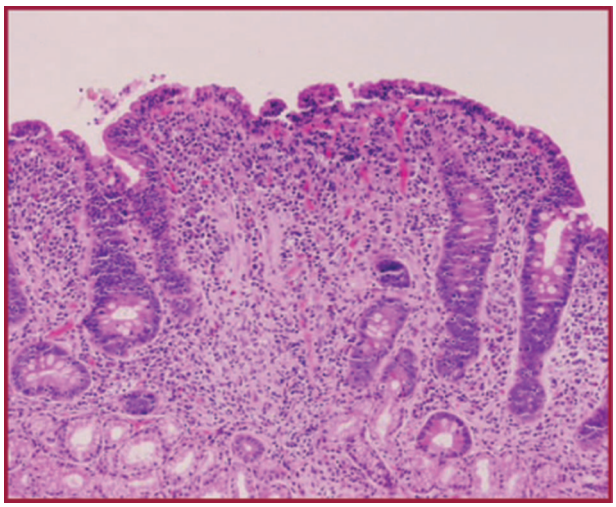
How can a patient who is already on a GFD be diagnosed?

An empirical trial of a GFD without a biopsy-confirmed diagnosis of celiac disease is not recommended because a beneficial response may be seen in other disorders. Many dietary components besides gluten are typically eliminated in a GFD, and symptom relief may result in such functional gastrointestinal disorders as IBS, gastroesophageal reflux disease, and functional dyspepsia. In one study, the positive predictive value of a beneficial response in celiac disease was only 36% (49). Differentiating between celiac disease and other disorders that may respond to a GFD is important to help determine whether lifelong dietary changes are required and because of the implications for long-term management and risk assessment of relatives if celiac disease is present.

Many patients initiate a GFD before appropriate diagnostic testing. In such cases, the effect of gluten withdrawal on the accuracy of diagnostic serologic testing or biopsies depends on the duration of the GFD, the degree to which gluten has been avoided, and the severity of the underlying disease. Because histologic abnormalities often take months or even years to return to normal on a GFD, it is reasonable to perform serologic studies for celiac disease at the first visit, even if the patient reports following a GFD. If tTG IgA levels are elevated, an intestinal biopsy should be done; if they are not, and if a lack of elevation is not attributable to IgA deficiency, further diagnostic testing may be deferred until gluten has been reintroduced into the diet for a sufficient duration to reproduce the serologic abnormality and the characteristic intestinal damage.

Initial HLA-DQ2 or HLA-DQ8 testing is now recommended, and a gluten challenge should be done only in persons who are genetically susceptible to celiac disease. Because some patients may have a severe reaction to a gluten challenge, a gradual increase in gluten may be advised. Patients should be challenged for 3 to 4 weeks with enough gluten to produce symptoms (an average of 3 to 4 slices of whole

Figure 3. **Histologic appearance of celiac disease.**



Characteristic features of the intestinal mucosa include inflammation and varying degrees of villous atrophy. Inflammation comprises lymphocytes, plasma cells, macrophages, and other chronic inflammatory cells in the lamina propria. It also includes intraepithelial lymphocytes, which are more prominent toward the tips of the villi. This biopsy specimen shows partial villous atrophy with characteristic inflammatory changes.

wheat bread per day). If symptoms do not recur, development of antibodies may be used to guide the timing of intestinal biopsy, although data are insufficient and there are no specific guidelines for the use of antibody testing in such cases. If there are no clinical symptoms or characteristic serologic features (anti-tTG or antiendomysial antibody) with the initial gluten challenge, it should be continued for at least 3 to 6 months and intestinal biopsies should be done.

Diagnosis... Celiac disease should be considered in a wide variety of clinical presentations that may manifest from malabsorption, including gastrointestinal and nongastrointestinal syndromes, such as endocrine and bone diseases. Celiac disease may mimic common conditions, such as IBS and dyspepsia. DH is characteristic but rare. Celiac disease is diagnosed by the presence of tTG antibodies in the serum; characteristic histologic findings on intestinal biopsies; and expected clinical, serologic, and, in some cases, histologic response to a GFD.

CLINICAL BOTTOM LINE

Treatment

When should patients be hospitalized?

Hospitalization is rarely required for celiac disease but may be necessary when severe malabsorption results in fluid or electrolyte abnormalities in need of short-term treatment, such as in severe refractory celiac disease. Closer monitoring may also be required in some patients with severe disease when enteral feeding is resumed (see the **Box**: Indications for Hospitalization).

What is the importance of diet?

A GFD is the cornerstone of therapy for celiac disease. Removal of the antigenic substance responsible for the abnormal immune response and enteropathy nearly always reverses disease manifestations, including DH. However, the diet is complex and has many potential pitfalls. Patient motivation and education are crucial, particularly because there is no alternative treatment. Nonadherence is common, especially in adolescents. Ingestion of even small amounts of gluten—as little as 50 mg/d—may cause a return of symptoms in previously well-controlled cases (50) and may be associated with histologic changes of the small bowel, even in the absence of overt clinical symptoms.

A systematic review provides evidence that adherence to a GFD and mucosal healing prevent or ameliorate the complications of celiac disease (51). The authors suggest that long-term follow-up is essential but acknowledge that the evidence is limited. In general, outcome studies of celiac disease are limited by their retrospective nature and the inherent difficulty of assessing adherence.

Although symptoms often resolve within days or weeks of the onset of treatment, damage will recur if gluten is reintroduced into the diet because immunologic intolerance to gluten does not go away. Patients may incorrectly believe that the absence of symptoms when eating gluten-containing food indicates that it can be consumed without harm. Accordingly, they should be encouraged to strictly adhere to the diet to avoid such complications as bone loss and increased risk for cancer. The most recent clinical guideline on diagnosis and management of celiac disease published by the ACG recommends lifelong adherence to a GFD as the treatment of choice (18). Although dapsone may manage DH, it does not ameliorate intestinal mucosal injury; a GFD is required.

What specific dietary recommendations should be made?

Previously, gluten-free flours were not nutrient-enriched, which led to nutritional deficiencies (for example, in iron or B vitamins) in patients with celiac disease following a GFD. Current recommendations focus on what can be eaten and on choosing naturally gluten-free products with high nutritional value, including fiber (see the **Box**: Nutritional Advice for Patients With Celiac Disease). Patients should also avoid processed foods that are high in sugar and fat for better nutrition.

Indications for Hospitalization

- Acutely ill patients needing rehydration and/or parenteral nutritional support
- Presence of tetany, frank dehydration, severe electrolyte disorders, or severe malnutrition
- Weight loss of more than 10% in a short period
- Patients with refractory celiac disease being transitioned from parenteral nutrition to enteral tube-feeding with concerns about relapse and severe diarrhea and malabsorption

Are vitamin supplements required?

Vitamin D production through sun exposure has a role in maintaining vitamin D levels, but living in northern latitudes and concerns about skin damage can lead to lower levels. Many people have low vitamin levels, in which case oral supplements are necessary. Lactose intolerance is common in celiac disease, especially in the early stage, with damage to the microvilli resulting in avoidance of milk and other dairy products, which can contribute to osteopenic diseases. If vitamin D levels are low, supplemental vitamin D and monitoring to ensure normal blood levels are necessary. Bone density should also be assessed in newly diagnosed patients, especially those with low vitamin D levels. Dietary sources are excellent sources of bioavailable calcium, and consumption of these in addition to calcium supplementation should be encouraged. Lactose intolerance should resolve with intestinal recovery resulting from the GFD. However, lactase insufficiency is common in many races worldwide, and in such cases, low-lactose dairy products and lactase supplements are required for the long term. Patients must be instructed not to avoid all dairy products—hard cheeses, yogurt, and other fermented milk products are naturally low in lactose.

Celiac disease can lead to malabsorption of fat-soluble vitamins (D, E, A, and K) as well as folic acid and iron, which are preferentially absorbed through the proximal small intestine. Deficiencies in thiamin, vitamin B_6, and vitamin B_{12} may occur but are less common. Levels of certain minerals, including magnesium, copper, zinc, and selenium, can be low depending on disease severity and dietary intake. Vitamin and mineral replacement is recommended in addition to a GFD until the intestine heals and previously low levels are replete.

How should patients be monitored?

Although evidence-based guidelines for follow-up and lifelong management are lacking, follow-up within a few weeks of diagnosis to discuss the results of the intestinal biopsy and other tests is recommended. At that time, the diagnosis of celiac disease should be discussed; questions should be answered; and disorders that may complicate the disease, such as nutritional deficiencies and osteoporosis, should be evaluated. Ideally, a visit with an expert registered dietitian nutritionist (RDN) should be scheduled for the same day or soon thereafter. As recommended by the ACG (18), follow-up is necessary to confirm the diagnosis via an objective response to a GFD and to assess dietary adherence. Clinical, laboratory, and serologic responses to dietary therapy are typically sufficient to gauge the response. Patients should be evaluated at regular intervals by a health care team that includes a physician and an RDN. The frequency of the visits should be individualized to the needs of the patient and the family and should take into account the complexity of the medical condition. In general, lifelong follow-up is recommended, although health care visits may be as infrequent as those in a normal population for persons whose health has improved on a GFD.

Are repeated endoscopies and biopsies required for follow-up?

Most patients can be followed on the basis of symptom resolution, improved laboratory abnormalities, and decreasing levels of serologic markers. Antibodies that are initially elevated are typically measured every 3 to 6 months until they are within the normal range, but this practice is not based on scientific studies. Initially high antibody titers generally take longer to return to normal than lower levels. If antibodies remain elevated or become positive after 6 to 12 months of treatment, repeated endoscopy with biopsy should be considered. Despite normal antibody levels, intestinal healing lags behind serologic response, and histologic features may remain abnormal for years with persistent inflammation, even if the diet seems to be gluten-free (52). This may be due to low levels of gluten contamination, a persistent immune response independent of gluten, or other unknown mechanisms. The clinical consequences of such low-grade inflammation in apparently

Nutritional Advice for Patients With Celiac Disease

- Maintain a lifelong gluten-free diet*
- Choose naturally gluten-free foods*
- Optimize the nutritional content of meals and snacks
- Minimize consumption of processed or packaged foods
- Focus on what can be eaten rather than what cannot
- Avoid lactose-containing dairy products (milk, cream, ice cream, fresh cheeses) for the first few weeks after starting a gluten-free diet until intestinal lactase levels are restored (unless the patient is lactose-intolerant as well, in which case lactose should be avoided indefinitely)*
- Continue to consume dairy products that are naturally low in lactose, such as yogurt, older cheeses, or kefir
- Choose foods that are rich in bioavailable iron, especially dark meat, poultry, and fish (plant sources or oral supplements are less bioavailable)

*Not necessary for those with nonceliac gluten sensitivity, but all other recommendations are helpful for most persons.

healthy, asymptomatic persons are not known, so the rationale for repeated biopsies in such cases is unclear.

Why might preclude patients from responding to a GFD?

Although most patients respond rapidly to a GFD, approximately 5% do not. The primary cause is continued ingestion of gluten, whether unintentional or intentional. The first step in evaluating a patient with nonresponsive celiac disease is to carefully review the dietary history, usually in conjunction with an expert RDN.

Other reasons for a lack of response are conditions that complicate or coexist with celiac disease, such as intolerance of lactose and other carbohydrates, pancreatic insufficiency, microscopic colitis, and small intestinal bacterial overgrowth with or without IgA deficiency. Gastroparesis, IBS, and other functional gastrointestinal disorders are common and may be postinflammatory in nature. Rarely, patients may have both celiac disease and IBS. These possibilities should be evaluated and addressed by a specialist.

A tertiary referral center reported a 70-fold increased risk for microscopic colitis in persons with celiac disease compared with the general population (53), underscoring the importance of obtaining biopsy specimens from the colon in patients with persistent diarrhea despite adherence to a GFD. In most cases, microscopic colitis was detected after diagnosis of celiac disease and often required therapy beyond a GFD.

Under certain circumstances, it may also be important to reconsider the diagnosis of celiac disease. Misdiagnosis may result from incorrect interpretation of intestinal specimens. Consultation with a gastroenterologist who has expertise in celiac disease should be considered, and consultation with an expert pathologist is often helpful.

The most serious cause of nonresponsiveness is refractory celiac disease, defined as persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a GFD for 6 to 12 months in the absence of other causes of nonresponsiveness or overt cancer (54). Complications of refractory celiac disease include ulcerative jejunitis, collagenous sprue, and low-grade and ultimately high-grade T-cell lymphoma arising from intraepithelial lymphocytes (55).

In a series of 55 patients being investigated for nonresponsive celiac disease, almost 50% had inadvertent gluten contamination. Six of these patients were found not to have celiac disease after biopsy review. Other causes of nonresponsiveness were microscopic colitis, IBS, pancreatic exocrine insufficiency, and bacterial overgrowth. Eighteen percent of patients in this group had true refractory celiac disease (56).

In a larger series of patients investigated for nonresponsive celiac disease at another tertiary center, more than one third had inadvertent gluten contamination. Other common causes of failure to respond were IBS (22%), lactose intolerance (8%), and microscopic colitis (6%). Only 10% had true refractory celiac disease (57).

When is immunosuppressive therapy required?

Most patients with refractory celiac disease require treatment beyond or other than a GFD. Such patients should be referred to a gastroenterologist for evaluation and treatment. Various drugs have been used, usually beginning with corticosteroids (typically budesonide) and then immunomodulators, including thiopurines, cyclosporin, and other immunosuppressive agents (40, 41). Steroids are very effective in alleviating symptoms but should be avoided because many patients already have poor bone density. Biologic treatments used in inflammatory bowel disease are often used in refractory celiac disease. No randomized trials have evaluated immunosuppressive agents for treatment of refractory disease, and the few observational studies that have been done have not shown a consistent benefit (42).

Are novel nondietary therapies available?

As discussed, a strict GFD is the mainstay of treatment for celiac disease, but adherence is difficult and patients often remain symptomatic despite the diet. There is an unmet need for novel nondietary therapeutic options as adjuncts to a GFD. No U.S. Food and Drug Administration–approved nondietary medications are available, but many novel targets are in clinical trials at this time. Various pathways are being addressed, including enzymatic degradation of dietary gluten, sequestration of dietary gliadin, protection of epithelial cells from gliadin with a probiotic, prevention of gliadin-induced permeability via tight junction modulation, direct inhibition of transglutaminase 2 to prevent the transformation of native gliadin into the more potent deamidated gliadin peptide, gluten tolerization with a vaccine, and immune cell–targeted therapy (58). Although some of these therapies are further along than others, a new nondietary option may become available in the future.

Is it ever safe to discontinue a GFD?

Although a lifelong GFD is currently recommended, GFDs are often not completely gluten-free, and the effect of this on long-term health is unknown. One study (59) suggests that some patients start to tolerate gluten in their diet over time, but this is not endorsed by other studies or experts in the field. For example, a retrospective U.S. study found that mortality from untreated celiac disease was increased 4- to 5-fold over control populations (4). It has been proposed that mortality from celiac disease

is increased if gluten intake is high both before and after diagnosis (60).

When should a nutritionist be consulted?

Patients with celiac disease should be referred to an RDN who has expertise in celiac disease and the GFD; not all RDNs have such expertise. The GFD is challenging to learn and teach, and few physicians, including gastroenterologists, have the detailed knowledge of food ingredients, the training, or the time to effectively instruct patients. Important topics for dietary counseling include identifying hidden sources of gluten, ensuring adequate nutrition while eliminating gluten, focusing on what can be eaten rather than what cannot, the increased costs of prepared gluten-free foods, and the importance of lifelong adherence to a GFD. Additional counseling may be required for concomitant issues, such as diabetes, obesity, hyperlipidemia, vegetarianism, and food allergies. RDNs can also help identify gluten in medications.

When should a gastroenterologist be consulted?

Patients with serologic features indicative of celiac disease should be referred to a gastroenterologist for esophagogastroduodenoscopy with intestinal biopsy to confirm the diagnosis. A gastroenterologist should also be consulted for evaluation of unexplained iron deficiency anemia, chronic diarrhea, malabsorption, weight loss, and other problems suggesting celiac disease despite negative results on serologic tests; these might include unexplained osteoporosis or infertility. In addition, a gastroenterologist should evaluate patients with biopsy-confirmed celiac disease who have not responded to a GFD or have experienced relapse despite continuation of a GFD.

Treatment... A lifelong GFD is the cornerstone of treatment for celiac disease. An expert RDN should be involved to teach the patient and family members about the intricacies of the GFD and to follow progress. Initially, other dietary modifications may be necessary, including a low-lactose diet and nutritional supplements, such as iron, vitamin D, and other vitamins and minerals. Lack of response to a GFD should signal the physician and RDN to look for intentional or inadvertent gluten ingestion. If not present, many additional factors can cause nonresponsiveness, including comorbid conditions, an incorrect initial diagnosis, and complications of celiac disease. True refractory celiac disease or lymphoma should also be considered. In many of these situations, treatments other than a GFD are necessary and usually require involvement of a gastroenterologist who specializes in management of nonresponsive celiac disease.

CLINICAL BOTTOM LINE

Patient Education

What is the role of patient education?

Education of patients and their families is central to the management of celiac disease. Patients should understand the causes of celiac disease, the medical complications of insufficiently controlled disease, the risk for family members to develop it, and the importance of maintaining a strict lifelong GFD. Specific challenges of a GFD include meal planning, eating out, traveling, consuming adequate calories, and meeting the needs of growth and development in children and teenagers. Many foods contain derivatives of wheat, rye, or barley that may damage the intestine. Other dietary restrictions due to religious or personal beliefs may also need to be factored into the GFD. An RDN with expertise in celiac disease management should help provide patient education. Nonadherence to the GFD is common, and patients should be informed that it may be associated with increased risk for certain types of cancer and death. Patients should also be told that the absence of symptoms or the ability to tolerate certain symptoms resulting from nonadherence to a GFD does not reduce the health risks of gluten exposure.

What resources are available?

Research on and awareness of celiac disease have increased dramatically among health care providers and the general public in the past 20 years. Unfortunately, not all information is evidence-based, and misinformation is included in some otherwise helpful Web sites and books. Physicians with expertise in celiac disease can help patients and other professional colleagues with less expertise by recommending appropriate local or national support. The National Institutes of Health has a celiac disease awareness campaign that can be accessed online (http://celiac.nih.gov). This Web site includes helpful educational materials and resources, lists professional and voluntary organizations that are devoted to celiac disease awareness, and provides examples of a GFD.

In the Clinic
Tool Kit

Celiac Disease

Patient Information

www.niddk.nih.gov/health-information/digestive-diseases/celiac-disease
Information for patients in English and Spanish from the National Institute of Diabetes and Digestive and Kidney Diseases.

https://medlineplus.gov/celiacdisease.html
Patient information and handouts in English and Spanish from the National Institutes of Health's MedlinePlus.

https://celiac.org/gluten-free-living/gluten-free-foods
Gluten-free food recommendations from the Celiac Disease Foundation.

Information for Health Professionals

www.niddk.nih.gov/health-information/diagnostic-tests/celiac-disease-health-care-professionals
Information on testing for health care professionals from the National Institute of Diabetes and Digestive and Kidney Diseases.

https://journals.lww.com/ajg/Fulltext/2013/05000/ACG_Clinical_Guidelines__Diagnosis_and_Management.7.aspx
Clinical guidelines on diagnosis and management from the American College of Gastroenterology.

www.aafp.org/afp/2017/0915/od1.html
Recommendation statement on screening from the American Academy of Family Physicians.

https://celiac.org/about-celiac-disease/resources-for-professionals
Resources for health professionals from the Celiac Disease Foundation.

WHAT YOU SHOULD KNOW ABOUT CELIAC DISEASE

What Is Celiac Disease?

Celiac disease happens when your body's immune system reacts to ingestion of gluten. Gluten is a protein in wheat, rye, and barley and is present in foods like bread and pasta. This immune response damages the small intestine and affects your body's ability to absorb nutrients. Some people are sensitive to gluten but do not have celiac disease.

What Are the Symptoms?

Digestive symptoms of celiac disease include:

- Diarrhea (this is most common)
- Bloating or excess gas
- Changes in bowel movements
- Indigestion or heartburn
- Weight loss

Other symptoms may include headaches, depression, rash, numbness, tingling, joint pain, and tiredness. However, some people have no symptoms. Celiac disease can also cause iron deficiency, bone disease, infertility, or recurrent miscarriages. In rare cases, it may be associated with lymphoma and intestinal cancer.

Because many other conditions can be confused with celiac disease, it is important to be tested by your doctor if you have symptoms.

Am I at Risk?

If you have a parent, sibling, or child with celiac disease or if you have certain autoimmune diseases, you have a higher risk for celiac disease. Talk to your doctor about your chances of having the disease and whether testing makes sense for you.

How Is It Diagnosed?

- Your doctor will ask you questions about your medical and family history and your symptoms and will do a physical examination.
- If your doctor suspects you have celiac disease, he or she will do a blood test to look for certain markers, called antibodies. If you stop eating foods with gluten before this test, the results may be negative even if you have the disease. Wait until your diagnosis has been confirmed to start a gluten-free diet.
- If the blood test suggests you have celiac disease, your doctor will perform a biopsy of your small intestine to be sure. For this test, a long, thin tube called an endoscope is passed through your mouth and stomach into the small intestine.
- Your doctor may do a skin biopsy if you have a rash. Dermatitis herpetiformis, an itchy, blistering rash usually found on the elbows, knees, and torso, occurs in some people with celiac disease.

How Is It Treated?

There are currently no medications to treat celiac disease. The only treatment is a lifelong gluten-free diet. Following a gluten-free diet stops symptoms in most people; heals intestinal damage; and prevents further complications, such as bone loss. However, it can be hard to stick with. Often, people who do not improve on a gluten-free diet may be consuming small amounts of gluten without knowing it. Gluten can be in products like vitamins, toothpaste, and lip balm.

Fortunately, there are plenty of gluten-free options available. Choosing naturally gluten-free foods will ensure you maximize your nutrient intake. Avoid processed foods and focus on naturally gluten-free foods like fruit, vegetables, meat, fish, dairy products, beans, and grains like rice and corn.

If your symptoms improve on a gluten-free diet, even small amounts of gluten can make your symptoms return. Working with a registered dietitian who has expertise in celiac disease and gluten-free diets can help you develop an eating plan you can maintain in the long term. They can also help with meal planning, eating out, traveling, and getting enough calories and nutrients.

Questions for My Doctor

- What foods should I eat, and what should I avoid?
- What other lifestyle changes do I need to make?
- Will you help me find a nutritionist who knows about celiac disease?
- What should I do if my symptoms do not improve with a gluten-free diet?
- How often do I need to follow up?
- Do I need to see other medical specialists?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Celiac Disease Foundation
https://celiac.org

National Institutes of Health Celiac Disease Awareness Campaign
http://celiac.nih.gov

Patient Information