Abstract and Introduction

Abstract

There are 10 things that all gastroenterologists should know about celiac disease (CD). (1) The immunoglobulin A tissue transglutaminase is the single best serologic test to use for the detection of CD. (2) CD can be recognized endoscopically, and water immersion enhances villi detection, although a normal endoscopic appearance does not preclude the diagnosis. (3) It is recommended that 4 biopsies be taken from the second part of the duodenum and 2 bulb biopsies be taken at the 9 o’clock and 12 o’clock positions to maximize the sensitivity for histologic confirmation of CD. (4) Consider serologic testing of first-degree relatives, patients with type 1 diabetes mellitus, Down’s, Turner's, and Williams’ syndromes, as well as those with premature osteoporosis, iron deficiency, abnormal liver biochemistries, and other manifestations of CD. (5) Patients already on a prolonged gluten-free diet (GFD) should be tested for the presence of HLA DQ2 or DQ8, thereby avoiding the need for further evaluation of CD in non-allelic carriers. (6) The basic treatment of CD is a strict, lifelong GFD, enabled by an expert dietitian. (7) Newly diagnosed adults with CD should be assessed for micronutrient deficiencies (iron, B₁₂, folate, zinc, copper), fat soluble vitamin deficiencies (vitamin D), and bone densitometry. (8) All patients diagnosed with CD should have clinical follow-up to ensure response and adherence to a GFD. (9) In those with persistent or relapsing symptoms, the robustness of the original diagnosis should be reviewed, gluten exposure sought, and a systematic evaluation for alternative and associated diseases performed. (10) Evaluate those with refractory disease for malignant transformation.

Introduction

Celiac disease (CD) is increasingly common and topical for both the general and medical communities; therefore, gastroenterologists will be called on for expertise in this area. How CD is diagnosed has changed over time, and confusion abounds regarding the use and interpretation of diagnostic tests, which are often confounded by adoption of the gluten-free diet (GFD). Herein, we address 10 important things that gastroenterologists need to know about CD, which are based on current evidence and our experience in Mayo Clinic’s Celiac Disease Clinic.

1. How to Use Serology to Diagnose Celiac Disease

Serologic testing for CD has significantly advanced during the past 2 decades. The long-used anti-gliadin antibodies have been supplanted by serology with better test characteristics. For example, endomysial antibody (EMA), used for more than 20 years, has specificity of 99%, although the sensitivity varies because of the technical issues inherent in direct immunofluorescence. This high specificity keeps EMA in use despite tissue transglutaminase (TTG) being identified as the targeted epitope. EMA is used primarily when discordance exists between other markers and histologic findings or when TTG immunoglobulin (Ig) A antibodies are equivocal.

TTG antibodies come in both IgA-based and IgG-based assays, which are performed with enzyme-linked immunosorbent assay by using human recombinant/derived proteins. IgA TTG has high sensitivity and specificity of ~98% and is the endorsed serologic marker for evaluating CD. It is well-known that IgA deficiency affects 2%–3% of CD patients and occurs in 1:131 patients tested for CD; thus, IgA-based assays alone are not always reliable. To avoid missing IgA-deficient CD, a serologic cascade testing starting with serum IgA level can be performed, and if normal, an IgA TTG is adequate; however, if the IgA level is low or absent, IgG-based testing with deamidated gliadin peptide (DGP) and/or TTG could be added/substituted (Figure 1). The accuracy of IgG TTG is poor (30%–70%) in IgA sufficiency, so this test in isolation should not be used for routine CD screening. However, IgG TTG performs well with known IgA deficiency, with sensitivity and specificity approaching 95%.
Figure 1.

Schematic approach to serologic diagnosis of CD.

Point-of-care finger stick TTG antibody testing has been developed as a rapid screen for CD, and although the specificity was reportedly 100%, the sensitivity was only 82%. It cannot be recommended until sensitivity improves.\[7\]

The newest serologic marker is the DGP antibody, which comes in both IgA-based and IgG-based assays and is significantly better than anti-gliadin antibody testing.\[6\] Despite specificity that is close to TTG assays, the sensitivity of either the IgA-based or IgG-based DGP in isolation is lower;\[8\] however, a combined IgA/IgG DGP panel has accuracy equivalent to IgA-based TTG.\[2\]

In children older than 2 years, IgA TTG is the preferred test. Serologic markers may have decreased sensitivity in children younger than 2 years. The combination of DGP IgA/IgG with IgA TTG is the recommended strategy.\[3\]
Should panels of serologic studies for CD be more widely used? The answer is no. The widespread use of panels would not be cost-effective as first-line testing; although it may slightly improve overall sensitivity, it reduces specificity, leading to unnecessary endoscopy.\[3\]

Practical Suggestion

IgA-based TTG is the serologic test of choice for evaluating CD in patients consuming a gluten-containing diet. IgG-based tests are needed in IgA deficiency. The use of celiac cascade testing starting with serum IgA level could direct downstream serology. Equivocal or discrepant serologic tests should be interpreted with caution.

2. Can Celiac Disease Be Recognized Endoscopically?

Gross Endoscopic Views

There are several well-described endoscopic features of CD, including mucosal fold loss, mosaic pattern, scalloping, nodularity, fissuring, and prominent submucosal vascularity (Figure 2A and B). The sensitivity of endoscopic markers varies (59%–94%), yet the specificity is high (92%–100%)\[9,10\]. The pattern of endoscopic markers may differ between adults and children. A mosaic pattern is found commonly in children, and although the frequency of other endoscopic markers of CD increases with age, the mosaic pattern does not.

![Images of the duodenum in CD. (A) Typical changes of villous atrophy characterized by scalloping of the folds, mosaic pattern, and nodularity. (B) Loss of the folds in patient with treated CD.](source: Clin Gastroenterol Hepatol © 2015 AGA Institute)

Water Immersion

Water immersion involves instilling 100–200 mL water into the duodenum after deflation, takes only 30 seconds to perform, has high sensitivity and specificity for detecting total villous atrophy\[11\] and may help target duodenal biopsies because of the patchy nature of CD\[12\]. Combining water immersion with intravenous hyoscine butylbromide may increase the positive predictive value and specificity for CD compared with air insufflation alone (84% vs 99% and 87% vs 99%, respectively).\[13\]

Other Endoscopic Techniques

Video capsule endoscopy (VCE) may be indicated in patients with CD who are unable to undergo upper endoscopy, have alarm features, or have normal histology but positive celiac serologies\[14\]. VCE can examine the entire small bowel but lacks sensitivity for partial villous atrophy, is subject to interpretation, and lacks a standardized grading system for CD. The sensitivity of VCE in CD is 89% with specificity of 95%.\[15\]
Although VCE adds little to the work-up of uncomplicated CD, it is useful when evaluating refractory or atypical features.

Double-balloon endoscopy (DBE) or push enteroscopy may be useful in patients with CD who have patchy small bowel involvement, disease limited to the jejunum, or in those undergoing an evaluation for complications of the disease. Antegrade DBE may uncover ulcerative jejunitis or enteropathy-associated T-cell lymphoma (EATL) and could be considered in CD patients with refractory celiac disease (RCD) type II, ongoing weight loss, continued intussusception despite a sustained GFD, suspicious lesions in the small intestine, or other alarm features.

Chromoendoscopy enhances mucosal features of CD but alone adds little to a skilled endoscopist. However, high-magnification endoscopy with chromoendoscopy may improve accuracy for detecting partial villous atrophy compared with conventional endoscopy. Optical band imaging may also enhance mucosal detail without dye to detect total and partial villous atrophy patterns.

Practical Suggestion

Biopsy for CD is suggested, even in the absence of endoscopic markers. Although novel techniques may enhance visualization of the mucosa, biopsies are still needed. Water immersion is simple and may be useful to target biopsies or evaluate patients without a prior indication for biopsy.

3. What Biopsies Should Be Taken to Evaluate for Celiac Disease?

Endoscopically obtained, non-jumbo duodenal biopsies are standard for the evaluation of CD. Studies report that 10%–70% of non-oriented duodenal biopsies were adequate for evaluation. Duodenal bulb biopsies increase the diagnostic yield for newly diagnosed CD by 9%–13% and uncover villous atrophy not seen on post-bulbar biopsies in 14% with established CD. High sensitivity (100%) was achieved when 4 post-bulbar biopsies were combined with bulb biopsies from both the 9 o'clock and 12 o'clock positions. Whether the post-bulbar and bulbar biopsies must be submitted separately versus combined in 1 jar is unclear.

Practical Suggestion

Take 4 biopsies from the post-bulbar duodenum and 1–2 biopsies from the 9 o'clock and/or 12 o'clock position of the bulb (Figure 3).
4. Which At-risk Patients Should Be Tested for Celiac Disease?

First-degree relatives, especially siblings, of those with CD are at increased risk of CD. When sibling pairs have CD, the familial risk is further elevated. It is controversial whether asymptomatic family members should be tested. However,
CD is more common in type 1 diabetes mellitus (T1DM), with higher prevalence in children (3%–8%) compared with adults (2%–5%). Both conditions share the same HLA DQ2/8 alleles. Although some suggest that all patients with T1DM be screened for CD, most recommend testing only symptomatic patients. However, patients with T1DM and features of CD or repeated hypoglycemia should be evaluated. In any patient with T1DM presenting for upper endoscopy, duodenal biopsies could be considered. Because of the shared HLA alleles between CD and T1DM, screening should be done with serology. Duodenal biopsies should be performed if there is high concern of CD despite negative serologies. Screening for CD is not routinely recommended in those with thyroid and other autoimmune conditions unless there are features of disease.

Patients with Down's syndrome are 5 times more likely to develop CD compared with the general population, although prevalence rates vary. Although there is not uniform consensus regarding screening for CD in those with Down's syndrome, there is agreement that patients with CD features be evaluated. One approach in Down's syndrome is to first test for permissive haplotypes (HLA DQ2 and DQ8), and if absent, future testing is unnecessary. In those with permissive haplotypes, serologic surveillance is suggested. It is not known whether repeat future testing is needed. Patients with Turner's and Williams' syndromes are also at increased risk of CD.

Practical Suggestion
Consider serologic testing for all first-degree relatives of a patient with CD, even those apparently asymptomatic. Test relatives of affected sib pairs. Test symptomatic (and consider screening asymptomatic) patients with T1DM and Down's, Turner's, and Williams' syndromes by using serology in diabetic patients and HLA haplotyping in those with chromosomal abnormalities. In these patients, diagnostic testing should be the terminology used rather than screening to ensure insurance coverage.

5. How Does One Evaluate for Celiac Disease in a Patient on a Gluten-free Diet?

With increasing frequency, patients start a GFD before testing for CD. With data showing that patients with diarrhea-predominant irritable bowel syndrome may benefit from a GFD, and because of the media focus on a GFD, the trend will continue. Although there is little harm beyond cost to a patient on a balanced GFD, CD may be overlooked and complications ignored.

Ideally, patients who self-initiated a GFD should be evaluated for CD. First, determine the patient's willingness to resume gluten intake for testing. In the patient who refuses to resume eating gluten, this poses a challenge. The sensitivity of serology and histology diminishes with longer duration on a GFD. Although serology could be checked first, a positive result is the only helpful result and indicates duodenal biopsies are needed. However, if the patient has been on a GFD for less than 1 month, begin with serology because the yield may be reasonable in this period. In the patient on a prolonged GFD, HLA haplotyping can be done first. Although 30%–40% of the normal population will be positive for HLA DQ2 or DQ8, the absence of permissive genes will allow 60%–70% of patients to be reassured that CD is ruled out. A gluten challenge should be discussed for those carrying HLA DQ2 or DQ8 before further testing.

In the past, a gluten challenge entailed consumption of 8–10 g gluten daily for 4 weeks. However, as little as 3 g gluten daily for 2 weeks will allow 75% of patients to meet diagnostic criteria for CD. For those intolerant to the gluten challenge after 2 weeks, serology and duodenal biopsies should be performed. In patients tolerating gluten ingestion after the 2-week period, the challenge should continue 6 additional weeks, with serology performed after the 8-week challenge. If serology is positive, then duodenal biopsies are done. If seronegative, repeat serology after 2–6 additional weeks because a delayed rise in serologic titers may occur.

Practical Suggestion
In patients requiring an evaluation for CD while on a GFD, testing for the presence of HLA DQ2 or DQ8 identifies those requiring further testing. In patients positive for HLA DQ2 or DQ8 and not highly sensitive to gluten ingestion, testing after a low-dose (3 g daily) gluten challenge for 6 weeks may suffice to diagnose CD.

6. How Is Celiac Disease Managed?

A strict, lifelong GFD, avoiding wheat, rye, and barley, remains the treatment of CD. How much is too much? Although the
maximum safe amount of gluten for patients with CD is unknown. <10 mg daily of gluten is probably safe in preventing ongoing
intestinal injury. For foods to be labeled as gluten-free, the Food and Drug Administration requires there be <20 parts per million
of gluten in the product;[44] however, restaurants and foods with meat, poultry, and eggs are not covered by these regulations.

Previously, patients with CD were advised to avoid oats because of cross-contact or cross-sensitivity. Oat avoidance limits food
choices.[45] Oats belong to the same subfamily as wheat, rye, and barley but to a different tribe and contain very few
deleterious peptides. Cross-sensitivity to oats may occur in highly sensitive patients, but it is rare. Initial avoidance of oats
should be considered in newly diagnosed CD with severe malabsorption, with reintroduction after 1 year when symptom-free.
Cross-contact of oats with gluten-containing grains occurs. For patients doing well on a GFD, pure oats can be consumed in
moderation, but if symptoms recur or serologic titers rise, then withhold oats.[3]

All patients with CD should be referred to a dietitian well-versed in a GFD. Guidelines are now available for dietitians to follow in
regard to assessing patients with CD.[46] If left to research a GFD on their own, patients encounter misinformation[47] and may
unnecessarily restrict intake. Other practical topics addressed by dietitians include how to avoid cross-contact at home (eg,
separate toasters or jars of spread), travel and restaurant tips, and reliable information on the Internet. In addition, it is
necessary to review the overall health of a patient's GFD, because obesity, diabetes, and other comorbidities are increasingly
common.[48]

Patients with CD should have all medications and supplements reviewed by a pharmacist to ensure that they are gluten-free,
[49] recognizing this may be manufacturer-dependent. Food and Drug Administration food labeling rules do not apply to
medications.

Practical Suggestion
All patients should follow a strict, lifelong GFD avoiding wheat, rye, and barley. All patients should be counseled on a GFD by
an expert dietitian, and a pharmacist should review all medications and supplements. Oats should be eliminated for the first
year in patients with significant features of disease and only gluten-free oats reintroduced later if well controlled.

7. What Should Be Assessed in the Patient With Newly Diagnosed Celiac Disease?
Vitamin and mineral deficiencies should be sought, and bone health should be assessed. Patients with overt malabsorption
may have multiple deficiencies of fat soluble vitamins, minerals, and micronutrients.

Iron deficiency anemia (IDA) is a very common manifestation of CD, affecting up to 32% of adults; CD is frequent in patients
undergoing endoscopy for IDA.[50] A complete blood count and ferritin should be assessed in newly diagnosed CD, and CD
should be considered in all patients with IDA without documented bleeding.

Vitamin B\(_{12}\) deficiency occurs in CD because of (1) terminal ileal involvement, (2) pancreatic insufficiency, or (3) concomitant
autoimmune gastritis, which causes B\(_{12}\) deficiency in 10.5% of CD patients.[51] Vitamin B\(_{12}\) deficiency occurs in 12%–41% of
patients with CD,[51] yet the true prevalence may be higher because most studies use serum B\(_{12}\) levels without methylmalonic
acid (MMA) levels. Because of the potential irreversible neurologic sequelae from untreated deficiency, all patients with CD
should have vitamin B\(_{12}\) levels checked, with follow-up MMA levels when B\(_{12}\) is low normal.

Folate is also absorbed in the proximal intestine, and although low levels of folate have been found in 35%–49% of CD patients,
resultant anemia is less common. Serum folate levels may be normal to elevated in CD with concomitant bacterial overgrowth.
Folate levels should be measured in CD, and emphasis should be placed on folate supplementation in women of childbearing
age.

Copper deficiency occurs in 6.8%–33% with CD[52] and can cause microcytic anemia, neutropenia, and thrombocytopenia and
rarely myeloneuropathy.[53] Because copper deficiency may occur without anemia, levels should be checked in newly
diagnosed patients to prevent neurologic sequelae. Zinc deficiency affects 20%–31% of patients with CD and can cause poor
tissue healing, dermatitis, or dysgeusia.[52]

Bone disease is frequent in CD, resulting from malabsorption of calcium and/or vitamin D, with subsequent osteopenia,
osteoporosis, or osteomalacia. In newly diagnosed patients, the prevalence of osteoporosis is approximately 28% in the spine
and 15% in the hip. Bone mineral density improves on a GFD, especially in the first year,[54,55] however, fracture risk is
increased both before and after diagnosis.[56] Although vitamin D deficiency is common in CD, the prevalence of osteomalacia
is unknown.[54] All patients with CD should have calcium and 25-hydroxyvitamin D levels at baseline, and many recommend
bone densitometry for adults at diagnosis[3] or after 1 year to allow stabilization.[54]
Patients with newly diagnosed CD should have a complete blood count, ferritin, vitamin B\textsubscript{12}, folate, copper, zinc, calcium, and 25-hydroxy vitamin D checked. Parenteral vitamin B\textsubscript{12} should be given with severe deficiency, neurologic features, or ongoing malabsorption. Bone densitometry should be performed in adults with CD.

8. How Are Adherence and Response to a Gluten-free Diet Measured?

Adherence to a GFD can be measured by self-report, dietitian inquiry, structured surveys, serologic titers, and assessment of mucosal healing. Most patients with CD will claim to be gluten-free; however, true adherence ranges from 42% to 91%\cite{57}.

Multiple factors affect compliance, including the ability to follow the GFD in relation to changes (travel, dining out, social events, stress, mood), being involved in CD support groups, and comprehension of the GFD. Although self-reporting may be useful early in GFD, its reliability declines over time.

All CD patients should have a follow-up consultation with a dietitian well-versed in the GFD if adherence is questionable or additional resources are needed. Brief adherence surveys have been developed that are as good, if not better, than following serologic titers. The Celiac Dietary Adherence Test is a 7-item validated questionnaire that correlates with results of a structured dietitian assessment and serologic concentrations\cite{58}. Similarly, a 1-minute, 4-question survey with a 5-level scoring system correlates well with serologic positivity, villous atrophy, and celiac-related complications, with lower scores predicting adverse outcomes\cite{59}.

Once on a GFD, there is improvement of clinical, serologic, and histologic features, albeit at differing rates. In adults, diarrhea improves within days, with mean time to symptom improvement of 4 weeks, and two-thirds of patients have complete resolution by 6 months. Abdominal pain, fecal incontinence, and bloating all improve similarly\cite{60}. Failure of symptoms to improve should prompt evaluation for associated disorders or celiac-related complications\cite{61}.

Serologic titers fall soon after initiating a GFD, with substantially lower antibody levels at 1 year with ongoing decline to negative/normal by 2 years. Although antibody levels will decline in incompletely compliant patients, the rate of decline will be less than with strict compliance\cite{62}. Normal serology does not guarantee strict GFD adherence; in addition, many patients have ongoing mucosal atrophy despite normal serology\cite{63}.

Histologic improvement is slow in adults and delayed compared with symptomatic or serologic improvement\cite{64}. Mucosal recovery, defined by a villous:crypt ratio of 3:1, was present in 34% at 2 years and in 66% at 5 years\cite{63} with healing complete in 90% by 9 years. Persistent injury is more likely in those who are noncompliant or who had severe symptoms or total villous atrophy at baseline\cite{63}. Therefore, repeat biopsies after 1 year on a GFD may still show mucosal injury, and providers could consider waiting 2 years before assessing healing. Mucosal recovery is faster and more complete in children, with 95% recovery in 2 years and 100% recovery long-term in children following a GFD.

Physicians should provide consistency in the follow-up care of patients with CD\cite{3}. Currently, there is significant variability in the care provided\cite{65}, with suboptimal follow-up of CD at 1 and 5 years of 41.0% and 88.7%, respectively\cite{66}.

Practical Suggestion

A follow-up visit should be scheduled 3–6 months after CD is diagnosed, with serologic titer considered then, and annual visits and serology thereafter. Assess for adherence to a GFD with structured interview with an expert dietitian. Patients can be assessed for histologic improvement after 2 years on a GFD.

9. What Is the Approach to the Nonresponsive Celiac Patient?

Nonresponsive celiac disease (NRCD) is defined as a lack of response to 6 months on a GFD or recurrence of celiac-related features despite compliance\cite{30,67}. NRCD is common and has been reported in 10%–19% with CD\cite{68,69}. Applying a stepwise approach to NRCD is imperative\cite{3}.

The first step in those with NRCD is to verify the diagnosis of CD, reviewing baseline serologic titer(s) and intestinal biopsies. In the patient with enteropathy but negative serology on a gluten-containing diet, other causes of villous atrophy need to be considered, including, but not limited to, small intestinal bacterial overgrowth, autoimmune enteropathy, tropical sprue, drug-associated enteropathy (eg, olmesartan), Crohn’s disease, combined variable immunodeficiency, collagenous sprue, and eosinophilic gastroenteritis\cite{70,71}. CD can be excluded by the absence of HLA DQ2 and DQ8\cite{70}.

If the initial diagnosis of CD is robust, the next step is to evaluate whether gluten exposure (blatant, surreptitious, or
A persistent or recurrent elevation of serologic titer suggests gluten ingestion, although a normal value does not ensure compliance. There may be gluten exposure in non-food items such as medications, supplements, cosmetics, and glues.

If gluten ingestion is unlikely, then duodenal biopsies should be performed. Biopsy the duodenum for RCD and the colon for microscopic colitis, which is 50-fold to 72-fold more common in CD.

If duodenal and colonic biopsies are normal, then other causes of diarrhea need to be considered, such as disaccharidase deficiency, small intestinal bacterial overgrowth, pancreatic insufficiency, or irritable bowel syndrome; the latter is most common among these associated conditions and reported in 22% of NRCD.

**Practical Suggestion**

In NRCD, verify the original CD diagnosis, and seek gluten ingestion. If gluten exposure is not present, then duodenal and colonic biopsies can be helpful. If these tests are negative, then systematic evaluation is needed.

### 10. What Do We Do With Refractory Celiac Disease?

RCD is defined as recurrent or persistent villous atrophy associated with malabsorption despite 12 months or more on a verified GFD in patients with CD, without other diagnoses or gluten contamination. RCD affects only 1.5% of CD patients. RCD is divided into 2 types. RCD type I is defined as those who meet the definition of RCD, with polyclonal intraepithelial lymphocytes bearing typical CD3 and CD8 surface markers, whereas RCD type II has clonal T-cell receptors, without the typical CD3–T-cell receptor surface markers, but preserved intracellular CD3 expression. Of those with RCD, approximately 15% are RCD type II. Prognosis in RCD II is poor, with 5-year survival at 44%–58% and a high risk of lymphoma. To evaluate for RCD, duodenal biopsies should undergo immunophenotyping and T-cell rearrangement studies. RCD, ulcerative jejunitis, and EATL are complications of CD that need to be considered carefully in NRCD.

**Practical Suggestion**

Ongoing villous atrophy should prompt immunophenotyping and T-cell rearrangement studies to look for RCD II and lymphoma. RCD prompts further highly specialized investigations, including determination of type and ongoing close surveillance for EATL.

### References


30. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the


**Abbreviations used in this paper**

CD, celiac disease; DBE, double-balloon endoscopy; DGP, deamidated gliadin peptide; EATL, enteropathy-associated T-cell lymphoma; EMA, endomysial antibody; GFD, gluten-free diet; IDA, iron deficiency anemia; Ig, immunoglobulin; MMA, methylmalonic acid; NRCD, nonresponsive celiac disease; RCD, refractory celiac disease; TTG, tissue transglutaminase; T1DM, type 1 diabetes mellitus; VCE, video capsule endoscopy.