

ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease

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This guideline presents recommendations for the diagnosis and management of patients with celiac disease. Celiac disease is an immune-based reaction to dietary gluten (storage protein for wheat, barley, and rye) that primarily affects the small intestine in those with a genetic predisposition and resolves with exclusion of gluten from the diet. There has been a substantial increase in the prevalence of celiac disease over the last 50 years and an increase in the rate of diagnosis in the last 10 years. Celiac disease can present with many symptoms, including typical gastrointestinal symptoms (e.g., diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) and also non-gastrointestinal abnormalities (e.g., abnormal liver function tests, iron deficiency anemia, bone disease, skin disorders, and many other protean manifestations). Indeed, many individuals with celiac disease may have no symptoms at all. Celiac disease is usually detected by serologic testing of celiac-specific antibodies. The diagnosis is confirmed by duodenal mucosal biopsies. Both serology and biopsy should be performed on a gluten-containing diet. The treatment for celiac disease is primarily a gluten-free diet (GFD), which requires significant patient education, motivation, and follow-up. Non-responsive celiac disease occurs frequently, particularly in those diagnosed in adulthood. Persistent or recurring symptoms should lead to a review of the patient's original diagnosis to exclude alternative diagnoses, a review of the GFD to ensure there is no obvious gluten contamination, and serologic testing to confirm adherence with the GFD. In addition, evaluation for disorders associated with celiac disease that could cause persistent symptoms, such as microscopic colitis, pancreatic exocrine dysfunction, and complications of celiac disease, such as enteropathy-associated lymphoma or refractory celiac disease, should be entertained. Newer therapeutic modalities are being studied in clinical trials, but are not yet approved for use in practice. Given the incomplete response of many patients to a GFD-free diet as well as the difficulty of adherence to the GFD over the long term, development of new effective therapies for symptom control and reversal of inflammation and organ damage are needed. The prevalence of celiac disease is increasing worldwide and many patients with celiac disease remain undiagnosed, highlighting the need for improved strategies in the future for the optimal detection of patients.

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INTRODUCTION

This clinical guideline addresses the diagnosis, treatment, and overall management of patients with celiac disease (CD), including an approach to the evaluation of non-responsive CD. While it is primarily directed at the care of adult patients, variations pertinent to the pediatric population have been included.

Each section will provide specific recommendations based on the current literature and a summary of the evidence supporting those recommendations. The GRADE system was used to evaluate the quality of supporting evidence (1) (Table 1). A "strong" recommendation is made when the benefits clearly outweigh

the negatives and the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefit/potential harm. The quality of the evidence is graded from high to low. "High"-quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect. "Moderate"-quality evidence indicates that further research would be likely to have an impact on the confidence of the estimate, whereas "Low"-quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate.

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Table 1. Criteria for assigning grade of evidence

| | |
|---|--|
| <i>Type of evidence</i> | |
| Randomized trial=high | |
| Observational study=low | |
| Any other evidence=very low | |
| <i>Decrease grade if</i> | |
| • Serious (−1) or very serious (−2) limitation to study quality | |
| • Important inconsistency (−1) | |
| • Some (−1) or major (−2) uncertainty about directness | |
| • Imprecise or sparse data (−1) | |
| • High probability of reporting bias (−1) | |
| <i>Increase grade if</i> | |
| • Strong evidence of association—significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) | |
| • Very strong evidence of association—significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2) | |
| • Evidence of a dose–response gradient (+1) | |
| • All plausible confounders would have reduced the effect (+1) | |
| <i>Definition of grades of evidence</i> | |
| • High=Further research is unlikely to change our confidence in the estimate of effect | |
| • Moderate=Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate | |
| • Low=Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate | |
| • Very low=Any estimate of effect is very uncertain | |
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WHEN TO TEST FOR CD

Recommendations

- (1) Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating, should be tested for CD. (Strong recommendation, high level of evidence)
- (2) Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD. (Strong recommendation, moderate level of evidence)
- (3) Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD. (Strong recommendation, high level of evidence)
- (4) Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD. (Conditional recommendation, high level of evidence)

- (5) CD should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found. (Strong recommendation, high level of evidence)
- (6) Patients with Type I diabetes mellitus (DM) should be tested for CD if there are any digestive symptoms, or signs, or laboratory evidence suggestive of CD. (Strong recommendation, high level of evidence)

Summary of the evidence. CD is one of the most common causes of chronic malabsorption (2). This results from injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and consequential impaired absorption of micronutrients such as fat-soluble vitamins, iron, and potentially B₁₂ and folic acid (3). In addition, the inflammation exacerbates symptoms of malabsorption by causing net secretion of fluid that can result in diarrhea. The failure of absorption of adequate calories leads to weight loss, and the malabsorption results in abdominal pain and bloating (3). These are common symptoms associated with CD (4,5).

CD remains underdiagnosed in the United States (6). CD may present in many ways (7). Currently, active case-finding (serologic testing for CD in patients with symptoms or conditions closely associated with CD) is the favored strategy to increase detection of CD (8). Active case-finding may increase detection of CD among patients with symptoms attending a primary-care office, although this strategy is insufficient to detect most patients with CD (7). There is no consensus regarding which symptoms, laboratory abnormalities, and/or associated diseases require evaluation for CD. The frequency of CD in common clinical scenarios varies from modestly elevated, such as irritable bowel syndrome, to substantially elevated, such as unexplained iron-deficiency anemia (Table 2) (9–11).

The complexity of deciding who to test is exemplified by patients with dyspepsia. The prevalence of biopsy-proven CD in patients with dyspepsia is 1%, similar to that of the general population (12), and therefore systematic screening for CD is not recommended based on disease prevalence alone. However, treatment for dyspepsia can be a clinical challenge (13) and dyspepsia as a symptom of CD will readily respond to the gluten-free diet (GFD) (4,14). Thus, mucosal biopsies of the duodenum should be considered in patients with dyspepsia who undergo investigation with upper endoscopy because of persistent symptoms despite initial therapy, are aged >55 years old, and/or present alarm symptoms (e.g., weight loss or clinical evidence of anemia) (15).

The frequency of CD is substantially increased in patients who have a first-degree family member affected with CD (16,17). The precise risk is highest in monozygous twins, next in human leukocyte antigen (HLA)-matched siblings, siblings, and finally parents and children of patients with CD (16). A lower rate probably applies to second-degree relatives (18). Members of families who have more than one individual already identified with CD are at higher risk of CD and recommendations for screening should extend to all other family members, including second-degree relatives (19). The estimates of prevalence of CD in family members

Table 2. Conditions in which CD occurs more frequently than in the general population and/or for whom a GFD may be beneficial

| CD common (>2 times prevalence of general population) | CD less common but treatable |
|--|--|
| Symptomatic malabsorption | Pulmonary hemosiderosis |
| Diarrhea with weight loss | Unexplained male or female infertility |
| Chronic diarrhea with or without abdominal pain | Dyspepsia |
| Chronic iron deficiency and anemia | Amenorrhea |
| Metabolic bone disease and premature osteoporosis | Chronic fatigue |
| Postprandial bloating and gaseousness | Apparent malabsorption of thyroid replacement medication |
| Unexplained weight loss | Epilepsy or ataxia |
| Abnormal elevated liver enzymes | Constipation |
| Incidental discovery of villous atrophy endoscopically or histologically | Recurrent abdominal pain |
| Dermatitis herpetiformis | |
| Peripheral neuropathy | |
| Oral aphthous ulcers | |
| Growth failure | |
| Discolored teeth or developmentally synchronous enamel loss | |
| Thyroid disease | |
| Irritable bowel syndrome | |
| Down's and Turner's syndromes | |

vary substantially, with one large multicenter study in the United States showing a rate as low as 5% in both first- and second-degree relatives (18). Other studies, especially those that are community-based, show a rate that is substantially higher, affecting up to 20% in siblings and 10% in other first-degree relatives (16). The clinical implications are that newly diagnosed patients with CD should inform their first-degree family members of the potential increased risk for CD and the recommendation for testing. In addition, health-care providers should determine whether there is a family history of CD in patients with symptoms or signs suggestive of CD and if so consider screening the patient.

Testing of truly symptomless first-degree relatives is reasonable but controversial. Even those patients who initially thought themselves to be without symptoms on direct questioning at the time of detection often report improved health after adapting to the GFD because of disappearance of symptoms that may not have been previously explained (20). Others may have symptoms that they did not consider abnormal until after they initiated a GFD and these symptoms resolve (21). Asymptomatic patients detected by screening do not experience new symptoms after onset of a GFD (22). The majority of patients with CD identified on the basis of screening reported dietary adherence and improvements in quality

of life on the GFD (20). A small proportion of patients, however, reported increased health-related anxiety after diagnosis (23). Overall satisfaction with the diagnosis was high (93%) (20).

Abnormal liver blood tests, in particular elevations of alanine aminotransferase and aspartate aminotransferase, are commonly seen in clinical care, although the prevalence of clinically significant liver disease is low (24). In CD, hypertransaminasemia is often a subclinical finding that is gluten dependent (25). Patients with unexplained elevation of liver enzymes should be assessed for CD (26). There are reasonable data to show that gluten-dependent hypertransaminasemia will normalize in most patients (>95%) on a GFD (27). Rarely, CD can be associated with severe liver disease (28,29).

There is evidence that CD is substantially more common in patients with Type I DM than in the general Caucasian population. The estimates vary between 3 and 10% (30–32). In children, it has been suggested that yearly or every-other-year screening for CD be undertaken utilizing serology. Patients with Type I DM who are undergoing upper endoscopy should undergo duodenal biopsies to rule out CD if they have never been tested previously.

After gastrointestinal symptoms, the second most common manifestation of CD in patients with Type I DM is diminished or impaired bone mineralization. There is some evidence suggesting that there is added disease burden to patients already struggling with the management of Type I DM. In addition, there is good evidence that gastrointestinal symptoms present at diagnosis will respond to a GFD with overall improvement in quality of life related to GI symptoms. The impact of the treatment of CD on the management of Type I DM is mixed (33). Some data suggest an increase in absorption, leading to the need for increased insulin doses. Other data suggest improvement of DM controlled by reduction of hypoglycemic events, especially postprandial.

Testing for CD in asymptomatic patients with Type I DM is controversial. No significant adverse outcomes were identified in children with Type 1 DM identified by screening who delay therapy with a GFD for up to 2 years (34). However, it is necessary to look at the potential long-term impact of CD in Type I DM as well (35). A large study from Sweden showed an increased risk of diabetic retinopathy in patients with coexistent Type I DM and CD (36). Patients with undiagnosed CD and Type 1 DM had a higher prevalence of retinopathy (58% vs. 25%) and nephropathy (42% vs. 4%) (37). Treatment with a GFD for 1 year was safe in patients with coexistent Type I DM and CD (37). The effect (if any) of a GFD on DM-related complications requires further investigation.

Parents of children with Type 1 DM or the children of parents with Type 1 DM are at increased risk of CD, estimated to be ~4% (38–40). Because many patients with unrecognized CD may actually have symptoms that improve on a GFD, informing such parents of the risk of CD is suggested. Also, a family history of either CD or Type 1 DM indicates an increased risk of CD in the patient and CD should be considered. There are no data to support a recommendation about when to stop screening for CD in children with Type 1 DM, but screening is not necessary in the absence of HLA-DQ2 and -DQ8.

DIAGNOSIS OF CD

Recommendations

- (1) Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody is the preferred single test for detection of CD in individuals over the age of 2 years. (Strong recommendation, high level of evidence)
- (2) When there exists a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured. An alternative approach is to include both IgA and IgG-based testing, such as IgG-deamidated gliadin peptides (DGPs), in these high-probability patients. (Strong recommendation, moderate level of evidence)
- (3) In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed. (Strong recommendation, moderate level of evidence)
- (4) If the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative. (Strong recommendation, moderate level of evidence)
- (5) All diagnostic serologic testing should be done with patients on a gluten-containing diet. (Strong recommendation, high level of evidence)
- (6) Antibodies directed against native gliadin are not recommended for the primary detection of CD. (Strong recommendation, high level of evidence)
- (7) Combining several tests for CD in lieu of TTG IgA alone may marginally increase the sensitivity for CD but reduces specificity and therefore are not recommended in low-risk populations. (Conditional recommendation, moderate level of evidence)
- (8) When screening children younger than 2 years of age for CD, the IgA TTG test should be combined with DGP (IgA and IgG). (Strong recommendation, moderate level of evidence)

Summary of the evidence. The use of TTG-IgA testing and its accuracy in the primary-care setting and referral cohorts has been extensively studied (9). The sensitivity of the TTG-IgA for untreated CD is about 95% (41). The specificity is also 95% or greater. The higher the titer of the test, the greater the likelihood of a true positive result (9). The test is most commonly based on an enzyme-linked immunosorbent assay test and less commonly on radioimmunoassay (42). There are recognized differences in test performance between the various commercially available test kits, but overall there is consistency in the sensitivity and specificity of the test (42–44).

In the past, several antibody tests have been developed to detect CD (45). Antibodies may be directed against native or altered cereal derived peptides. Anti-gliadin antibodies (AGA) have been used for decades and are reasonably accurate when there is a high pretest prevalence of CD (46). However, it was with the advent of auto-antibodies, first directed against reticulín, then endomysium antibodies (EMA), and finally TTG antibodies, that the truly celiac-specific testing was developed (47). The identification of

TTG IgA antibody as the target antigen for IgA EMA antibodies was a major advance (48). This antigen was initially produced by extraction from the liver or purification from human red cells and, most recently, by recombinant protein production. TTG-based assays have brought accurate serology for CD into the reach of most doctors and hospitals. The College of American Pathology laboratory proficiency survey has included TTG antibody testing for several years and most laboratories in the United States that provide TTG testing participate. Other similar systems are in place outside the United States.

IgA deficiency is more common in CD than in the general population. It affects anywhere between 1 in 400 to 1 in 800 members of the general population, but occurs in 2–3% of patients with CD and 1% of those getting tested for CD (49,50). In patients in whom there is a high pre-test prevalence of CD, the measurement of IgA levels should be considered, especially if IgA-based celiac serology test is negative. One approach is to measure total IgA at the beginning of testing to determine whether IgA levels are sufficient and, if not, to incorporate IgG-based testing into the serology testing cascade. DGPs IgG and/or TTG IgG would then be the preferred test in this circumstance (51,52). EMA IgG is not widely available. It has been suggested that IgA deficiency should be considered if the TTG-IgA levels are undetectable (53,54). However, not all assays can detect this with any accuracy or the result is merely reported as negative. While there are limited data on the sensitivity of each of these tests for CD in an IgA-deficient person, this may be about 80–90% individually and higher if the tests are combined. If the suspicion for CD is high, intestinal biopsy should be pursued even when serologies are negative. Finding IgA deficiency should prompt evaluation for other diseases that may cause villous atrophy, such as giardiasis, small-bowel bacterial overgrowth, or common variable immunodeficiency (55).

The antibodies directed against gliadin or its deamidated products as well as the self-antigen TTG are dependent on the ingestion of gluten. The reduction or cessation of dietary gluten leads to a decrease in the levels of all these celiac-associated antibodies to normal concentrations. While little is known about the precise dynamics of the reduction, a weakly positive individual may become negative within weeks of strict adherence to GFD (56). After 6–12 months of adhering to a GFD, 80% of subjects will test negative by serology (57). By 5 years, more than 90% of those adhering to the GFD will have negative serologies (58).

While antibodies directed against native gliadin (AGA) have been in use for several decades, there is a wide variability in their diagnostic accuracy (43). Both IgA and IgG AGA have sensitivities and specificities inferior to those of the TTG-IgA and DGP-IgA assays (57) and should no longer be included in the routine testing strategy for CD.

No one test for CD has a perfect sensitivity or specificity. Thus, individual tests may be combined in commercially available panels. This strategy may increase the sensitivity if any positive test is regarded as an overall positive result; however, the increased sensitivity comes at the expense of a reduction of specificity (59). Unless all patients who test positive in the panel undergo histological confirmation of CD, this practice may lead to incorrect

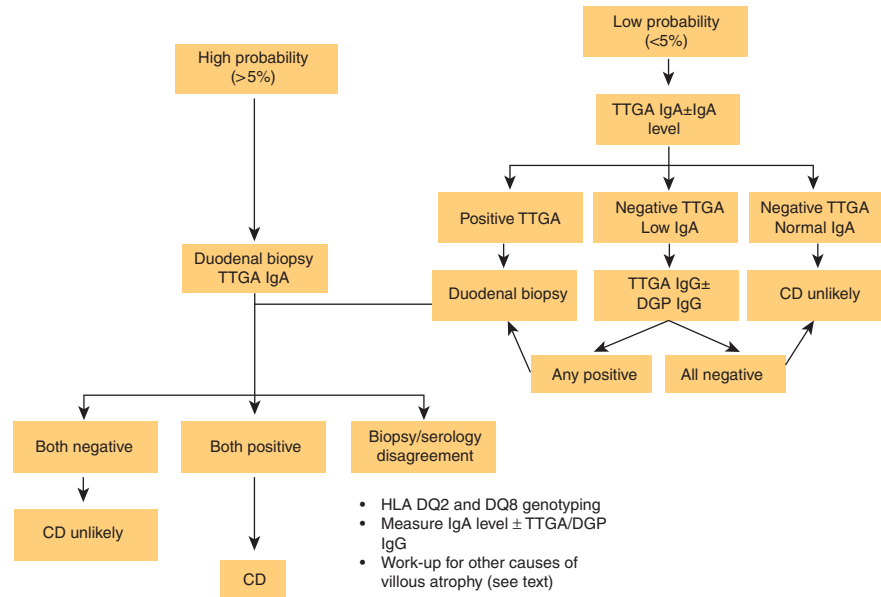


Figure 1. Celiac disease (CD) diagnostic testing algorithm. DGP, deamidated gliadin peptide; HLA, human leukocyte antigen; Ig, immunoglobulin; TTGA, tissue transglutaminase antibody.

and over diagnosis followed by unnecessary treatment with GFD. Conversely, if the threshold is set that all tests within the panel must be positive for a “positive” panel test, then the specificity and hence positive predictive value (PPV) for CD will be increased, but at the expense of sensitivity (9). One diagnostic approach is shown in **Figure 1**.

There is some evidence that both TTG and EMA are less sensitive in young children (less than 2 years of age) (60,61). In this age group the sensitivity of AGA and DGP antibodies is higher than both the TTG and EMA (61–63). In general, AGA have a low sensitivity and specificity and are not recommended as a screening test for CD (64,65). Although DGP tests perform less well than TTG and EMA tests, they are superior to the AGA (66). For this reason it is preferable to combine the TTG with DGP tests when screening young children.

CONFIRMATORY TESTING IN CD

Recommendations

- (1) The confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum. (Strong recommendation, high level of evidence)
- (2) Upper endoscopy with small-bowel biopsy is a critical component of the diagnostic evaluation for persons with suspected CD and is recommended to confirm the diagnosis. (Strong recommendation, high level of evidence)
- (3) Multiple biopsies of the duodenum (one or two biopsies of the bulb and at least four biopsies of the distal duodenum) are recommended to confirm the diagnosis of CD. (Strong recommendation, high level of evidence)

(4) Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for CD and other causes should also be considered. (Strong recommendation, high level of evidence)

Summary of the evidence. Gastrointestinal symptoms alone cannot accurately differentiate CD from other common gastrointestinal disorders (e.g., 20–50% of patients with CD fulfilled the Rome criteria for irritable bowel syndrome) (4,67). A meta-analysis showed a pooled prevalence of irritable bowel syndrome-type symptoms of 38% (95% confidence interval (CI), 27–50%) in patients with CD (68). Improvement of gastrointestinal symptoms or clinical exacerbation after re-introduction of gluten has a very low PPV for CD (36% and 28%, respectively) and should not be used for diagnosis in the absence of other supportive evidence (69). Moreover, ingestion of gluten can cause gastrointestinal symptoms including abdominal pain and bloating in the absence of CD (70). A GFD improved gastrointestinal symptoms in about 60% of patients with diarrhea-predominant irritable bowel syndrome, especially those with HLA-DQ2 (71).

A positive CD-specific serology (TTG, DGP, and EMA) in patients with villous atrophy confirms the diagnosis of CD (43). TTG-IgA may be negative in 5–16% of patients with biopsy-confirmed CD tested when following a gluten-containing diet (41,57). IgA EMA-negative CD has been described in patients with normal IgA (72). Thus, a negative CD-specific serology in patients with villous atrophy does not completely exclude the diagnosis of CD though it does make it much less likely. Other causes of villous atrophy are summarized in **Table 3**.

Histological response to GFD in patients with villous atrophy strongly supports a diagnosis of CD. HLA typing and histological response may help to rule out or confirm the diagnosis of CD in patients with sero-negative CD (73,74).

Small-intestinal biopsy has been central to the confirmation of the diagnosis of CD since the late 50s (75). Traditionally, the diagnosis of CD required three intestinal biopsies: a biopsy on a gluten-containing diet (diagnosis), a biopsy after a period on GFD, and a biopsy after a gluten challenge (76). Subsequent studies demonstrated that a biopsy at the time of diagnosis in children without subsequent intestinal biopsies was able to correctly diagnose 95% of cases (77). The availability of CD-specific serological tests facilitated the recognition of many CD patients and the wide spectrum of clinical manifestations (6,18). A positive serological test is supportive of the diagnosis but no single test is 100% specific for CD and the diagnostic accuracy varies dramatically between laboratories (43). Indeed, a large international study found that laboratory sensitivity ranged from 63 to 93% and specificity ranged from 96 to 100% when comparing TTG assays among various research and clinical laboratories (42). Serological tests may perform less well in the clinical setting than research (a positive result of both TTG and EMA had a sensitivity of 81%) (78).

Table 3. Other causes of villous atrophy in duodenum

| |
|---|
| Tropical sprue |
| Small-bowel bacterial overgrowth |
| Autoimmune enteropathy |
| Hypogammaglobulinemic sprue |
| Drug-associated enteropathy (e.g., olmesartan) |
| Whipple disease |
| Collagenous sprue |
| Crohn's disease |
| Eosinophilic enteritis |
| Intestinal lymphoma |
| Intestinal tuberculosis |
| Infectious enteritis (e.g., giardiasis) |
| Graft versus host disease |
| Malnutrition |
| Acquired immune deficiency syndrome enteropathy |

A diagnosis of CD requires the demonstration of histological changes associated with the disease, which can be classified according to Marsh, Marsh modified (Oberhuber), or the more recent, simplified Corazza classification (79–81) (Table 4). Small-bowel biopsy is also useful for the differential diagnosis of malabsorptive disorders (82,83).

A recent guideline promulgated by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) proposed that it may be possible to avoid any intestinal biopsy in children who meet the following criteria: characteristic symptoms of CD, TTG IgA levels >10× upper limit of normal (confirmed with a positive EMA in a different blood sample), and positive HLA-DQ2 (84). A TTG antibody IgA >5× upper limit of normal was observed in 9% of 236 adult patients with suspected CD and had a PPV for CD of 86.4% (85). PPV was 97.4% among 150 symptomatic children who met the “triple test” ESPGHAN criteria (86). Among 3,031 family members (25% younger than 18 years old) of patients with CD, TTG antibody IgA was abnormal in 336 (11%); of these, 88 (26%) had TTG antibody IgA ≥100 U (87). Population-based data are not available to know how frequent the “triple test” criteria are met by unselected populations. In the absence of standardization of TTG assays, use of a predefined threshold to select a population to avoid intestinal biopsy may not be the optimal strategy (88). Prospective data to validate ESPGHAN recommendation in children or adults are lacking.

Histological abnormalities associated with CD can be patchy (89–93). Multiple biopsies of duodenum should be performed if the diagnosis of CD is considered. Among 132,352 patients without known CD who underwent duodenal biopsy in the United States, the probability of a new diagnosis of CD was significantly increased when ≥4 specimens were submitted (1.8% vs. 0.7%, $P < 0.0001$) (94). Unfortunately, four or more biopsies were taken in only 39% of patients undergoing biopsy for evaluation of malabsorption/suspicion of CD (94). The rate of duodenal biopsy was significantly lower among black, older (70 years and older), and male patients (95). In children and adults with positive CD-specific serologies, adding biopsies of the duodenal bulb increases the diagnostic yield because 9–13% had villous atrophy exclusively in the bulb (96–98). A targeted duodenal bulb biopsy from either the 9- or the 12-o'clock position in addition to biopsies of

Table 4. Summary of histologic classifications frequently used for celiac disease

| Marsh modified (Oberhuber) | Histologic criterion | | | Corazza |
|----------------------------|--|-------------------|-----------------|----------|
| | Increased intraepithelial lymphocytes ^a | Crypt hyperplasia | Villous atrophy | |
| Type 0 | No | No | No | None |
| Type 1 | Yes | No | No | Grade A |
| Type 2 | Yes | Yes | No | |
| Type 3a | Yes | Yes | Yes (partial) | Grade B1 |
| Type 3b | Yes | Yes | Yes (subtotal) | |
| Type 3c | Yes | Yes | Yes (total) | Grade B2 |

^a>40 intraepithelial lymphocytes per 100 enterocytes for Marsh modified (Oberhuber); >25 intraepithelial lymphocytes per 100 enterocytes for Corazza.

the distal duodenum has a sensitivity of 96% for the diagnosis of CD (99). Care must be taken when interpreting duodenal bulb biopsies to allow for the normal surface architectural changes that overlie Brunner's glands and the acute inflammatory changes of peptic duodenitis. Expert opinion suggests that only a single biopsy specimen should be obtained with each pass of the biopsy forceps (5); however, there is no evidence that supports that recommendation. We recommend multiple biopsies of the duodenum including one or two biopsies of the bulb (either 9- or 12-o'clock position) and at least four biopsies of post-bulbar duodenum. There are insufficient data to guide practice in patients who have not yet been tested serologically or in whom the pre-test prevalence is much lower. The added yield of duodenal bulb biopsies is likely to be small in such circumstances.

Lymphocytic infiltration (≥ 25 intraepithelial lymphocytes per 100 epithelial cells), also known as lymphocytic duodenosis, is common in the general population (prevalence of 5.4%) (100). Most patients with lymphocytic duodenosis do not belong to the spectrum of CD and other causes should be sought, including work-up to rule out CD (101,102). The frequency of diarrhea and weight loss was similar among patients with lymphocytic duodenosis and those with CD (102). Anemia, skin disorders, positive TTG, and HLA-DQ2 were more frequent among patients with CD (102). Other disorders have been associated with lymphocytic duodenosis, including *Helicobacter pylori* (*H. pylori*) infection, medications (e.g., non-steroidal anti-inflammatory drugs), small-bowel bacterial overgrowth, and systemic autoimmune disorders (103). Persistent intraepithelial lymphocytosis was observed in 56% of patients with treated CD despite evidence of normal villous architecture; the only factor associated with this finding was oat consumption (104).

Among 56 children without a prior diagnosis of CD and lymphocytic duodenosis evaluated at a referral center, CD was diagnosed in only 9% of these cases (105). GFD may be beneficial in children and adults with either lymphocytic duodenosis or Marsh II lesions and positive EMA (106,107).

ROLE OF ANCILLARY TESTING IN CD

Recommendations

- (1) HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD. (Strong recommendation, moderate level of evidence)
 - (2) HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations. (Strong recommendation, moderate level of evidence)
- Examples of such clinical situations include but are not limited to:
- (3)
 - (a) Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
 - (b) Evaluation of patients on a GFD in whom no testing for CD was done before GFD
 - (c) Patients with discrepant celiac-specific serology and histology

- (d) Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question
- (e) Patients with Down's syndrome
- (4) Capsule endoscopy should not be used for initial diagnosis except for patients with positive-celiac specific serology who are unwilling or unable to undergo upper endoscopy with biopsy. (Strong recommendation, moderate level of evidence)
- (5) Capsule endoscopy should be considered for the evaluation of small-bowel mucosa in patients with complicated CD. (Strong recommendation, moderate level of evidence)
- (6) Intestinal permeability tests, D-xylose, and small-bowel follow-through are neither specific nor sensitive and are not recommended for CD diagnosis. (Strong recommendation, moderate level of evidence)
- (7) Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD. (Strong recommendation, weak level of evidence)

Summary of the evidence. The most important genetic risk factor for CD is the presence of HLA-DQ heterodimers DQ2 (encoded by alleles A1*05 and B1*02) and DQ8 (encoded by alleles A1*03 and B1*0302) (108–110). In a prospective study that included 463 symptomatic patients referred for small-bowel biopsy due to suspicion of CD, the addition of HLA-DQ typing to serological tests (TTG and EMA) did not improve the accuracy of serological tests alone for diagnosis of CD (78).

HLA-DQ2 (~95%) or HLA-DQ8 (~5%) are present in almost all patients with CD (111,112). Testing negative for both HLA-DQ types makes CD diagnosis very unlikely (NPV > 99%) (78). Among rare patients not carrying these heterodimers, the majority encoded half of the HLA-DQ2 heterodimer (113). Because HLA-DQ2 is present in approximately 25–30% of the white population (111,114), testing for CD with either HLA-DQ type is not useful because the PPV is only about 12% (78).

HLA-DQ2 and -DQ8 testing has been useful for exclusion of CD in patients with either equivocal small-bowel histological finding or those following a GFD (74). HLA-DQ2 and -DQ8 testing has been used to exclude a diagnosis of CD in patients with unexplained sprue (115,116). The prevalence of CD among persons affected by Down's syndrome was 10% in the United States (117). HLA-DQ2 was present in 88% of persons with both Down's syndrome and positive EMA, but only 16% of those with Down's and negative EMA (117). In a prospective study including 155 children with Down's syndrome, all children with CD tested positive for either HLA-DQ2 or -DQ8 (118). Testing negative for both HLA-DQ2 and -DQ8 can reassure most parents of children with Down's syndrome about the absence of genetic risk for CD development. The utility of HLA testing in other at-risk groups (such as Type I diabetics or family members) is more limited because a high proportion of these subjects carry the CD susceptibility alleles (e.g., 73% of first-degree family members carry HLA-DQ2) (16).

Capsule endoscopy allows non-invasive visualization of the whole small-bowel mucosa (119). Capsule endoscopy can be

performed in patients who are unable or unwilling to undergo upper endoscopy (120,121). A meta-analysis showed that capsule endoscopy had a pooled sensitivity of 89% and specificity of 95% for diagnosis of CD (122). Capsule endoscopy had better overall sensitivity for detection of macroscopic features of atrophy compared with regular upper endoscopy (92% vs. 55%) (123). The sensitivity of capsule endoscopy is less when there is partial villous atrophy and all non-atrophic lesions (Marsh I–II) may elude visual detection (123). In addition, markers of villous atrophy were not observed by capsule endoscopy among eight patients with positive TTG or EMA and normal duodenal biopsy (124).

Capsule endoscopy can detect severe complications associated with CD (87,125–127). Extensive mucosal damage detected by capsule endoscopy was associated with low albumin and refractory CD Type II (125). Macroscopic features of atrophy found in 31% of the cases was the most frequent finding by capsule endoscopy in patients with non-responsive CD (NRCD) (127). Other capsule findings among patients with NRCD include stenosis, erosions, ulcers, and lymphoma (125,127). Erosions or ulcerations are frequent findings among NRCD patients often associated with the use of non-steroidal anti-inflammatory drugs (127). Capsule findings in complicated CD may be used to assess the need for further evaluation with deep enteroscopy, especially among patients with clinical suspicion of lymphoma, adenocarcinoma, or ulcerative jejunitis (128). Other diagnostic modalities that may be of value in complicated CD include computed tomography enterography and magnetic resonance imaging enterography or enteroclysis (115,129,130).

D-xylose is a pentose absorbed unchanged from the small bowel (131). The D-xylose test involves measurement of serum xylose or measurement of excreted xylose in urine after ingestion of D-xylose (132). The test is abnormal in patients with malabsorption due to mucosal disorders but remains normal in those with maldigestion of pancreatic origin (132). Sensitivity (<65%) and specificity (<74%) for either 1-h plasma test or 4-h urine excretion test are both lower than those obtained with IgA-TTG or IgA-EMA and the accuracy of the test is suboptimal for diagnosis of CD (133,134).

Intestinal permeability is altered in CD (135). Although permeability tests (e.g., sucrose, lactulose-mannitol ratio) can detect the gross changes on intestinal permeability associated with CD, their sensitivity and specificity are quite variable and these tests are not recommended for diagnosis of CD (136–138). Small-bowel follow-through does not have a role in the initial evaluation of patients with suspicion of CD and may have a limited role for evaluation of chronic diarrhea (e.g., suspicion of small-bowel diverticulosis) (139). Jejunoileal fold pattern reversal had a sensitivity of 86% for CD in a retrospective study (140). Other radiological signs of malabsorption (e.g., dilation, flocculation and segmentation of barium) are nonspecific (rarely seen with modern barium preparations) and can be seen in subjects with normal fecal fat analysis (141). Salivary tests for detection of TTG antibodies are under active investigation but there is not enough evidence to make a recommendation for their use (142,143).

The sensitivity of fecal IgA antibodies against TTG was as low as 10%, which is not suitable for accurate screening for CD (144).

DIFFERENTIATION OF CD FROM NON-CELIAC GLUTEN SENSITIVITY

Recommendations

- (1) Symptoms or symptom response to a GFD alone should not be used to diagnose CD, as these do not differentiate CD from non-celiac gluten sensitivity. (Strong recommendation, moderate level of evidence)
- (2) A diagnosis of non-celiac gluten sensitivity should be considered only after CD has been excluded with appropriate testing. (Strong recommendation, moderate level of evidence)

Summary of the evidence. Non-celiac gluten sensitivity, a condition in which individuals do not have the diagnostic features of CD but nonetheless develop celiac-like symptoms upon exposure to dietary gluten, is important to consider in the differential diagnosis of CD (70,145,146). Symptoms alone cannot reliably differentiate CD from non-celiac gluten sensitivity as there is often substantial overlap in symptoms between the two conditions (70,146). Objective tests including celiac serology and small-intestinal histology (both obtained while the patient is consuming a gluten-rich diet) and HLA-DQ typing (to rule out CD if negative) are needed to differentiate between the two disorders (70,146).

Knowledge of the pathogenesis, epidemiology, and natural history of non-celiac gluten sensitivity is quite rudimentary (142,146–148). However, at this time, it appears that non-celiac gluten sensitivity does not have a strong hereditary basis, is not associated with malabsorption or nutritional deficiencies, and is not associated with any increased risk for auto-immune disorders or intestinal malignancy. Given these major differences in natural history and outcomes, the differentiation of CD and non-celiac gluten sensitivity is important for advising patients regarding the importance of ongoing disease monitoring, the required duration and strictness of adherence to the GFD, and for counseling and testing of family members.

DIAGNOSIS AMONG PATIENTS ON A GFD

Recommendations

- (1) While standard diagnostic tests (specific serology and intestinal biopsy) have a high PPV for CD, they should not be relied upon to exclude CD in patients already adhering to a GFD. (Strong recommendation, high level of evidence)
- (2) HLA-DQ2/DQ8 genotyping should be used to try to exclude CD prior to embarking on a formal gluten challenge. (Strong recommendation, high level of evidence)
- (3) CD should be differentiated from non-celiac gluten sensitivity in order to identify the risk for nutritional deficiency

states, complications of CD, risk for CD and associated disorders in family members, and to influence the degree and duration of adherence to the GFD. (Conditional recommendation, moderate level of evidence)

(4) Formal gluten challenge should be considered, where necessary, to diagnose or exclude CD in patients already adhering to a GFD. (Strong recommendation, high level of evidence)

(5) Despite the disadvantages of neither confirming nor excluding a diagnosis of CD, some patients will opt to continue on a strictly GFD without undergoing formal gluten challenge; such patients should be managed in a similar fashion to those with known CD. (Conditional recommendation, low level of evidence)

Summary of the evidence. The specific serologic and histologic features of CD do not normalize immediately upon the initiation of a GFD (8,43,149,150). If the duration of GFD has been brief (less than 1 month), serology and histology are often still abnormal and can be used to diagnose CD in patients already on GFD. Conversely, given that the degree of serologic and histologic abnormality varies substantially in untreated CD, some patients will quickly revert to normal on a GFD. Hence, normal serologic and histologic findings on a GFD cannot be used to exclude CD definitively (8,43,149,150).

As discussed above, the required genotypes, encoding HLA-DQ2 or -DQ8, are not influenced by diet and can be used to evaluate the likelihood of CD in patients either on a normal or on a GFD (8,151). HLA-DQ2/DQ8 testing should be performed prior to embarking on a formal gluten challenge as a negative result will obviate the need for further workup.

Patients with CD treated by a strict GFD may yield negative results on celiac serology testing and small-intestinal histology (8,43,149,151). HLA-DQ2 or -DQ8 positivity will persist but is not sufficiently specific to be useful for positive diagnosis (8). Gluten challenge is the process whereby a patient with suspected but unproven CD and already treated with a GFD reverts to a normal, gluten-rich diet, under medical supervision, to enable diagnostic testing (152,153). Gluten challenge was routine for CD diagnosis in the past, but is now less frequently used because of the high PPV of specific celiac serology testing.

Gluten challenge remains the gold standard for CD diagnosis in HLA-DQ2 or -DQ8-positive patients who have normal serologic and histologic findings when tested on a GFD. It must be noted that patients who develop severe symptoms following gluten ingestion are not suitable candidates for gluten challenge. Although gluten challenge with a diet containing at least 10 g of gluten per day for 6–8 weeks has long been the norm, there are few data to indicate the diagnostic efficacy of this approach or the optimum dose or duration of challenge (154,155). A recent study found that even if a patient can only tolerate lower doses of gluten (3 g per day), diagnostic changes are seen in most CD patients after as little as 2 weeks of gluten ingestion (152). An approach to gluten challenge is presented in **Figure 2** (152).

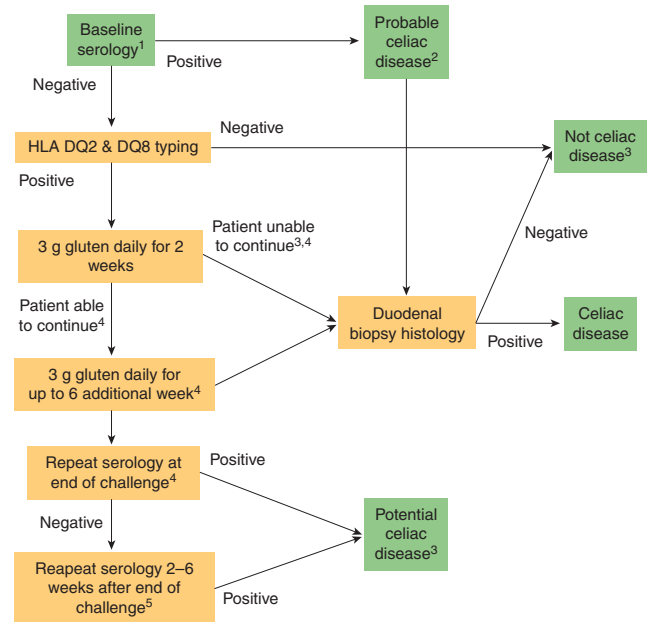


Figure 2. An approach to gluten challenge for the diagnosis or exclusion of celiac disease (CD) in patients maintained on a gluten-free diet without prior definitive diagnostic testing (adapted from Leffler (152)). (1) Tissue transglutaminase, endomysium, and/or deamidated gliadin peptide antibody serology. (2) Normal or non-diagnostic histology in a patient with positive serology while maintaining a gluten-free diet (GFD) requires gluten challenge and repeat biopsy for definitive diagnosis or exclusion of CD. (3) Those with positive celiac serology but a normal biopsy have potential CD and should be evaluated and monitored further depending upon their clinical circumstances. (4) In one study of subjects receiving a gluten challenge for 14 days, Marsh III histology was seen in 68%, positive celiac serology in 75%, and either Marsh III histology or positive serology in 90%. Thus, a 2-week gluten challenge may yield false-negative results in 10% of patients. The added diagnostic sensitivity of extending the challenge to 8 weeks is unknown. (5) Celiac serology antibody concentrations may continue to rise after a gluten challenge ends. In one study positive tissue transglutaminase serology was seen in 25% of subjects and positive deamidated gliadin peptide serology in 30% at the end of a 14-day gluten challenge; 50% had at least one positive serology on day 14. Positivity rates rose to 55% and 45%, respectively, 14 days later, despite the fact that subjects had resumed a GFD; 75% had at least one positive serology on day 28, 14 days after the gluten challenge ended. HLA, human leukocyte antigen.

The importance of differentiating CD from non-celiac gluten sensitivity is outlined above. If a patient is unwilling or unable to undergo testing to make this distinction, then their further management becomes less well-defined. The management of non-celiac gluten sensitivity is symptom-based, without data to elicit major concerns for a long-term sequel of inadequate therapy (146,147). The ongoing management of CD is more complex, as described elsewhere in this document. It is reasonable to manage patients with a moderate to high suspicion for (unproven) CD in a similar fashion to those with known CD. However, this approach will of necessity include unnecessary monitoring, therapy, and expense. Therefore the patient should be aware of the ongoing availability of definitive testing should they so desire.

MANAGEMENT OF CD

Recommendations

- (1) People with CD should adhere to a GFD for life. A GFD entails strict avoidance of all products containing the proteins from wheat, barley, and rye. (Strong recommendation, high level of evidence)
- (2) While pure oats appear to be safely tolerated by the majority of people with CD, oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction. (Strong recommendation, moderate level of evidence)
- (3) People with CD should be referred to a registered dietitian who is knowledgeable about CD in order to receive a thorough nutritional assessment and education on the GFD. (Strong recommendation, moderate level of evidence)
- (4) People with newly diagnosed CD should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12. (Conditional recommendation, low level of evidence)

Summary of the evidence. A GFD is the only effective treatment for CD as there are currently no medications that can reliably and safely prevent the mucosal damage caused by exposure to gluten. The principal sources of dietary gluten are wheat, barley, and rye. While the term “gluten free” implies complete elimination of all sources of gluten, in reality this is not possible due to contamination of foods with trace amounts of gluten. Hence the term “gluten free” indicates a diet that contains gluten at such a low level as to be considered harmless. The exact level below which gluten is harmless is not known, but a recent review suggests less than 10 mg per day is unlikely to cause damage in most patients (156). The current international Codex Alimentarius defines gluten-free foods as having less than 20 p.p.m. of gluten.

A GFD will result in resolution of symptoms and repair of the intestinal damage over time in most people with CD. Failure to adhere to the GFD carries risk for adverse health consequences and increased mortality. There is an increased risk for malignancies (e.g., small-bowel adenocarcinoma, cancer of esophagus, B-cell and T-cell non-Hodgkin lymphomas), and in particular intestinal T-cell lymphomas, in people with CD (157). Evidence suggests the risk for increased mortality and malignancies is reduced in those who adhere to the diet (158–160). There is evidence that a GFD improves nutritional parameters in symptomatic adults and children with CD. This includes increases in body weight, body mass index, and bone mineralization (161–163).

Untreated CD is associated with an increased prevalence of low bone mineral density and risk for fractures. Treatment of CD with a GFD improves bone mineral density in both adults and children (45,164–176). Women with CD have an increased risk of infertility, spontaneous abortions, preterm deliveries, and

delivery of low birth weight infants. Treatment of women with CD with GFD reduces these risks to that of the general population (177–181).

Consumption of oats improves the nutrient content of the diets of people on a GFD by increasing the intake of fiber, vitamin B, magnesium, and iron (182). While in the past there has been concern that oats can cause intestinal mucosal damage in people with CD, recent evidence suggests oats that are pure and uncontaminated by other gluten-containing grains can be safely ingested by most people with CD provided they are taken in limited quantities (183–190). However, there is still need for caution when introducing oats into the diet of people with CD as there is a high likelihood that commercial oats may be contaminated with gluten from other grains (191,192). There is also evidence that a small number of people with CD may be intolerant to pure oats and can develop an immunological response to oat avenins. Based on *in vitro* studies, this may in part be related to a variation in toxicity of oat cultivars (193,194). Commercial oats should only be introduced into the diet of people with CD provided the oats are guaranteed to be pure and uncontaminated by other gluten-containing grains. Even if confirmed to be pure, if oats are introduced into the diet of people with CD there should be careful follow-up to monitor for signs of both clinical and serological relapse.

Following a GFD can be cumbersome and strict avoidance of gluten is difficult because there are many hidden sources of gluten in commercial food products. There is evidence that compliance with the GFD is improved in those who are more knowledgeable about CD and the diet (195–197). Most physicians do not have the knowledge about the diet to adequately counsel patients. Registered dietitians are trained to evaluate patients for potential current and future dietary nutrient deficiencies and advise and educate them on how to maintain a strict GFD with provision of healthy alternatives to gluten. The Academy of Nutrition and Dietetics has published evidence-based guidelines for treatment of CD and it is recommended these are followed (available at <http://www.adaevidencelibrary.com/topic.cfm?cat=3677>). In addition to providing initial counseling and education, once the relationship with a dietitian is established the patient can be monitored for compliance with the diet and undergo repeated assessments for potential dietary nutrient deficiencies, inadequate fiber intake, and excess weight gain, each of which may be associated with adherence to the GFD.

There is some evidence that people with untreated CD are more frequently deficient in a number of micronutrients compared to those without CD. Micronutrient deficiencies identified include iron (198–203), folic acid (198,204), and vitamin B12 and B6 (205–207). Low bone mineral density in people with untreated CD is believed to be partly due to vitamin D deficiency. Other deficiencies described in CD include copper, zinc, and carnitine (199,208,209). Some deficiencies may persist even after a prolonged period on a GFD (210,211). In addition to testing for micronutrient deficiencies, dietary review by a registered dietitian, both at the time of initial diagnosis and after starting a GFD, is helpful for identifying potential nutrient deficiencies.

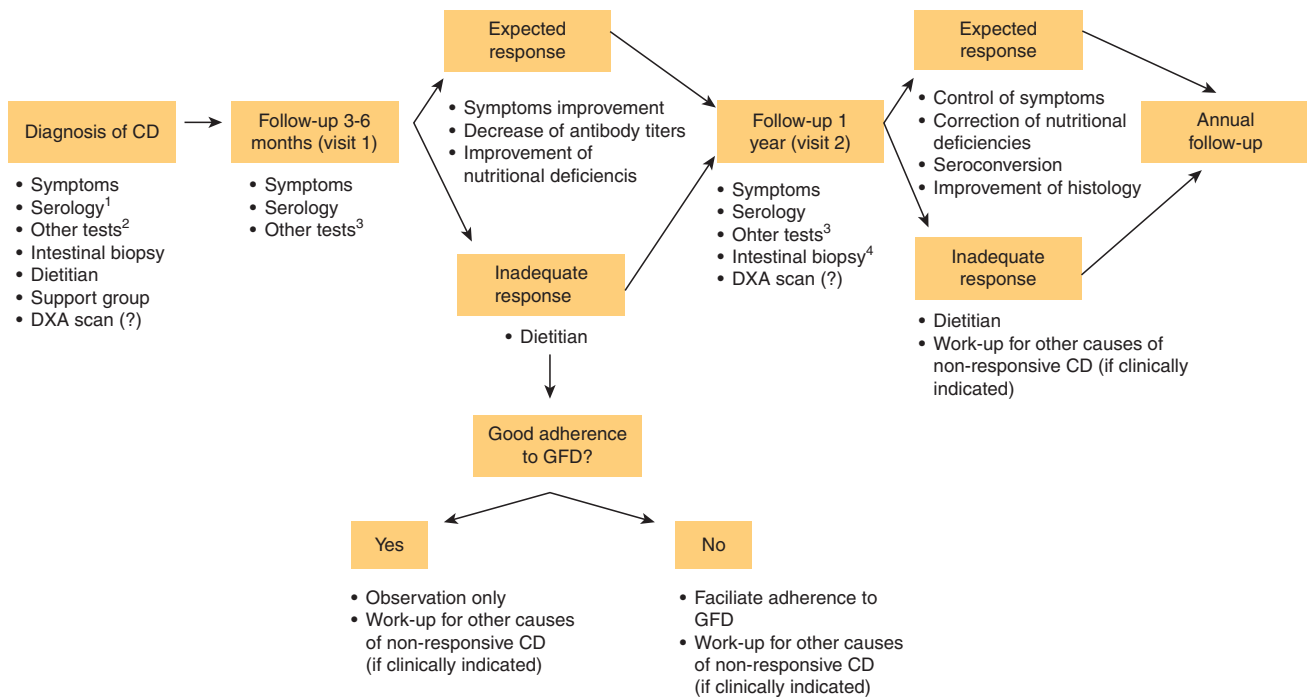


Figure 3. An approach to monitoring celiac disease (CD) (adapted from Rubio-Tapia A. Seguimiento Médico del Paciente Celiaco. En Rodrigo L (ed.) Enfermedad Celiaca. Barcelona, España. *OmniaScience*, 2013, in press). (1) Tissue transglutaminase and deamidated gliadin peptide can be used for monitoring CD. (2) Other tests may include complete blood count, alanine aminotransferase, vitamins (A, D, E, B12), copper, zinc, carotene, folic acid, ferritin, and iron. (3) Blood tests at follow-up should be individualized to verify correction of laboratory tests that were abnormal at baseline. (4) The role of biopsy for monitoring CD is discussed in detail in the text. DXA, dual-energy X-ray absorptiometry; GFD, gluten-free diet.

MONITORING OF CD

Recommendations

- (1) People with CD should be monitored regularly for residual or new symptoms, adherence to GFD, and assessment for complications. In children, special attention to assure normal growth and development is recommended. (Strong recommendation, moderate level of evidence)
- (2) Periodic medical follow-up should be performed by a health-care practitioner with knowledge of CD. Consultation with a dietitian should be offered if gluten contamination is suspected. (Strong recommendation, moderate level of evidence)
- (3) Monitoring of adherence to GFD should be based on a combination of history and serology (IgA TTG or IgA (or IgG) DGP antibodies). (Strong recommendation, moderate level of evidence)
- (4) Upper endoscopy with intestinal biopsies is recommended for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD. (Strong recommendation, moderate level of evidence)
- (5) Monitoring of people with CD should include verification of normalization of laboratory abnormalities detected during initial laboratory investigation. (Strong recommendation, moderate level of evidence)

Summary of the evidence. There is universal agreement on the necessity of long-term monitoring of patients with CD (212). The number of patients with CD who receive follow-up is unknown. In the United States, follow-up appears to be suboptimal in practice (213). A systematic review supports the role of strict adherence to the GFD to control symptoms, improve quality of life, and decrease the risk of complications (214). Normal growth and development are achievable on a GFD and should be goals for monitoring children with CD (215). Control of symptoms (if present), facilitation of adherence to GFD, and avoidance or early detection of complications should be the general goals of monitoring after diagnosis of CD (**Figure 3**).

It is not clear who should perform follow-up of patients with CD and at what frequency. In a survey of patients in the United Kingdom, the health-care practitioner preferred by patients for follow-up was a dietitian with a doctor available if needed (216). In a population-based cohort of 122 patients from the Midwest in the United States, there were 314 follow-up visits over a period of 5 years. Of these visits, 175 (56%) were conducted with primary-care providers and 122 (39%) with gastroenterologists (213). A nationwide study from Finland showed that medical follow-up by primary-care providers was effective (average adherence rate was 88%) (217). Annual follow-up with serology (TTG IgA) was associated with increasing rate of seroconversion of the TTG antibody (99%) among 2,245 patients who underwent systematic follow-up (58). Until more evidence is available, annual follow-up seems reasonable.

There is extensive evidence to support the central role of consultation with a dietitian in patients with NRCd or if gluten contamination is suspected (218,219). There is no evidence to suggest that medical follow-up by a dietitian and a doctor together is better (or worse) in terms of outcome than follow-up done by either provider alone.

There are several methods to assess adherence to GFD: visits with the doctor and/or dietitian, serology, biopsy of intestine, and structured surveys. The gold standard for monitoring adherence to GFD is consultation with a skilled dietitian (220). All serologic markers associated with celiac autoimmunity are gluten-dependent. A decrease from baseline values is expected within months of strict adherence to the GFD (221,222). A gluten challenge produces increasing values of antibodies (222). Lack of declining values and/or persistently positive serology 1 year after starting a GFD strongly suggest gluten contamination (219). Persistently positive serology was seen in only 1% of patients who underwent annual follow-up during a 5-year period (58). Serology is not accurate to detect lesser degrees of gluten contamination. Seroconversion after GFD does not necessarily imply healing of the intestine (73,223,224). The only accurate method available to verify intestinal healing is biopsy. Structured short surveys have been explored as an alternative to dietitian consultation for quick assessment of adherence to the diet (225–227). More studies are needed to examine the role of survey instruments for assessment of adherence in practice.

Patients with persistent or recurrent symptoms despite GFD require additional work-up to investigate the presence of disorders commonly associated with NRCd (see “Evaluation of nonresponsive CD” for details) (228). Observational experience from referral centers supports the role of upper endoscopy with intestinal biopsies for evaluation of NRCd (218,219,229). Intestinal biopsies are the only way to document healing of the intestine. In adults, the intestine will often fail to heal despite negative serology and absence of symptoms (73,224,230). This lack of healing may increase the risk of lymphoma, bone disease, and ultimately the development of refractory CD (73,231). A large Swedish study demonstrated no risk of lymphoma (hazard ratio (HR)=0.97; 95% CI=0.44–2.14) among patients with normal histology, suggesting that mucosal healing could be the goal to consider during follow-up (232). Among a group of 381 patients with baseline and follow-up biopsy after GFD, mucosal healing was associated with a borderline lower risk of death (HR=0.13; 95% CI: 0.02–1.06; $P=0.06$) adjusted for age and sex (73). A much larger study from Sweden failed to confirm a protective role of mucosal healing on mortality risk, yet mortality risk was significantly lower among patients who underwent follow-up biopsy (233). Follow-up biopsy could be considered for assessment of mucosal healing in adults with negative serology and absence of symptoms. In a US study, the median time from onset of GFD to achieve mucosal healing was 3 years (73). It is reasonable to do a follow-up biopsy in adults after 2 years of starting a GFD to assess for mucosal healing. Mucosal healing was observed in 95% of children within 2 years of starting a GFD (230). Follow-up biopsy is not recommended as a routine in children,

although the evidence for mucosal healing after GFD in children is limited.

A significant decrease (or normalization) of markers of malabsorption, such as fat content of the stools, should be expected after GFD (215). Verification of either declining antibody levels or seroconversion of CD-specific antibodies is critical during monitoring follow-up (221). A persistently positive TTG antibody after GFD was significantly associated with abnormal duodenal histology, low ferritin, and poor adherence to GFD (234). Among a heterogeneous group of patients with refractory iron-deficiency anemia, anemia improved in 92% of patients with CD after treatment with a GFD (235). Copper deficiency has been described in association with CD (208,236). Copper levels normalize within a month of adequate supplementation and a GFD, although reversibility of established neurological manifestations is unclear (208). Copper deficiency appears to be a very rare cause of peripheral neuropathy (237). Long-term adherence to GFD leads to significant improvement in bone density, especially among patients with strict adherence to the diet (238). Although it is well accepted that CD is associated with an increased risk of bone fractures (239–241), the protective role of GFD on subsequent fracture risk may not be universal. Low serum vitamin B12 was present in about 12% of patients with CD; correction should be expected with adequate replacement and GFD (205).

NON-RESPONSIVE OR REFRACTORY CD

Recommendations

- (1) Patients with NRCd should be evaluated carefully to identify and treat the specific etiology in each patient. (Strong recommendation, high level of evidence)
- (2) Early steps in the evaluation should include measurement of celiac serologies and a thorough review of the patient’s diet by a dietitian who is experienced in CD management. (Strong recommendation, high level of evidence)
- (3) Differentiation should be made between Type I and Type II refractory CD as this is important for management and prognosis. (Strong recommendation, moderate level of evidence)
- (4) Treatment with medication, as an adjunct to the GFD, should be considered in refractory CD. (Conditional recommendation, moderate level of evidence)
- (5) Patients with RCD should be monitored closely and receive aggressive nutritional support including parenteral nutrition whenever indicated. (Strong recommendation, high level of evidence)

Summary of the evidence. NRCd may be defined as persistent symptoms, signs or laboratory abnormalities typical of CD despite 6–12 months of dietary gluten avoidance (218,219,242,243). NRCd is common, affecting from 7 to 30% of patients treated with a GFD for CD (218,219,242). There are many distinct etiologies, including inadvertent gluten ingestion (the most common cause), other food intolerances (including lactose and fructose

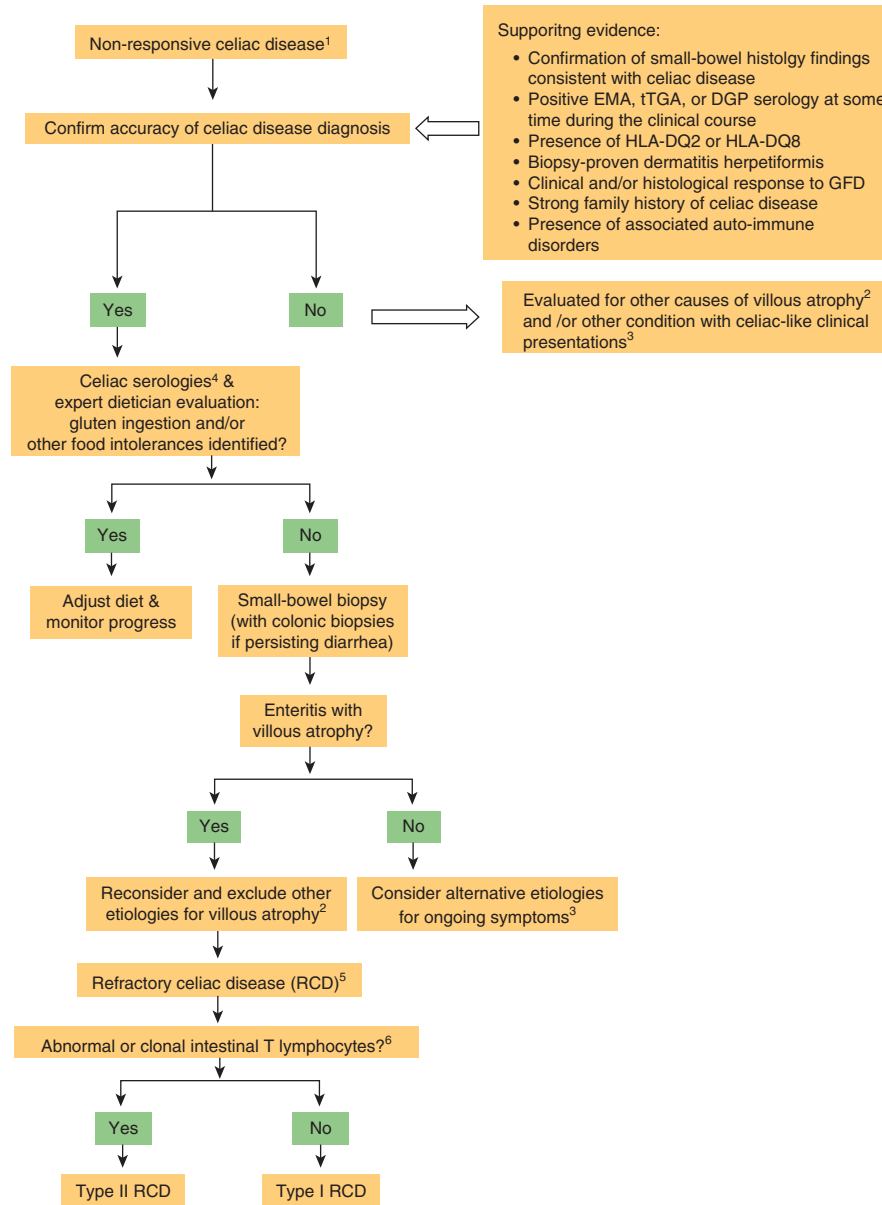


Figure 4. An approach to the investigation of non-responsive celiac disease (NRCD) and refractory celiac disease (RCD) (adapted from references Rubio-Tapia (6) and Abdallah (261)). (1) NRCD may be defined as persistent symptoms, signs, or laboratory abnormalities typical of celiac disease (CD) despite 6–12 months of dietary gluten avoidance. (2) Causes of non-celiac, small-intestinal villous atrophy that may be misdiagnosed as CD include autoimmune enteropathy, tropical sprue, small-intestinal bacterial overgrowth, hypogammaglobulinemia and combined variable immunodeficiency, collagenous sprue, eosinophilic enteritis, Crohn's disease, and peptic duodenitis. (3) Conditions that present clinically in a similar fashion to CD but where villous atrophy is not evident include irritable bowel syndrome, food intolerances, small-intestinal bacterial overgrowth, eosinophilic enteritis, Crohn's disease, and microscopic colitis. (4) Positive celiac serologies despite 12 months of treatment with a gluten-free diet (GFD) suggest that there may be ongoing gluten ingestion. (5) RCD may be defined as persistent or recurrent malabsorptive symptoms and signs with small-intestinal villous atrophy despite a strict GFD for more than 12 months and in the absence of other disorders, including overt lymphoma. (6) Abnormal intestinal lymphocytes may be identified by immunohistochemistry of IELs or by flow cytometry showing an increased number of CD3-positive cells lacking CD8, or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis. DGP, deamidated gliadin peptide; EMA, endomysium antibodies; HLA, human leukocyte antigen; IELs, intraepithelial lymphocytes; TTGA, tissue transglutaminase antibody.

intolerance), small-intestinal bacterial overgrowth, microscopic colitis, pancreatic insufficiency, irritable bowel syndrome and refractory CD (218,219,242–247). Thus, careful evaluation is needed to identify and treat the specific source in any given patient (218,219,242,243). The first step in evaluation is to re-confirm

the initial diagnosis of CD by review of small-intestinal histology and serology obtained at the time of diagnosis (Figure 4). If the diagnosis of CD is not correct then response to a GFD is not to be expected and alternative diagnoses and treatments must be considered (248). In those with confirmed CD the ingestion of

gluten, either purposeful or inadvertent, is the most common cause of NRCD, being identified in 35–50% of cases (218,219). Thus, a careful evaluation of the patient's diet by a dietitian who is experienced in CD management is the next important assessment. This evaluation should also seek other food intolerances, for example, to lactose or fructose. Celiac serologies are helpful if positive, as this points to probable gluten exposure as the cause for NRCD (218). However, normal serologies do not exclude intermittent or low-level gluten ingestion sufficient to cause persistent CD activity. Once dietary causes of NRCD have been excluded, small-intestinal biopsy should be repeated and the findings compared to the diagnostic biopsy. Ongoing inflammatory enteropathy with villous atrophy is consistent with refractory CD, gluten exposure, or possibly small-intestinal bacterial overgrowth and other causes of villous atrophy (115,219,242,245). Normal or near-normal small-intestinal histology suggests other etiologies such as irritable bowel syndrome, microscopic colitis, food intolerances, or pancreatic insufficiency (218,219,242). CD and microscopic colitis do overlap (249,250). There are no sufficient data to make a recommendation for routine testing of CD in patients with microscopic colitis. However, CD should be considered in patients with unresponsive microscopic colitis or those with microscopic colitis and other symptoms or signs suggestive of CD (251).

Refractory CD (RCD) may be defined as persistent or recurrent symptoms and signs of malabsorption with small-intestinal villous atrophy despite a strict GFD for more than 12 months and in the absence of other disorders including overt lymphoma (145,218,252). RCD is uncommon, affecting 1–2% of patients with CD (115,244,245). In Type I RCD, lymphocyte infiltration of the small-intestinal mucosa is similar to that seen in untreated CD (244,246,253,254). In Type II RCD, CD3-positive intraepithelial T cells exhibit an abnormal immunophenotype with lack of expression of normal cell surface differentiation markers such as CD8 (246,253,254). Furthermore, T-cell receptor analyses may reveal oligoclonal T-cell expansion within the small-bowel mucosa (244,246,253,254). These T-cell abnormalities in Type II RCD are associated with a significantly less favorable prognosis as compared to Type I RCD (244,246). In the United States, Type I RCD appears to be more common than Type II RCD (245).

Management of Type I RCD includes excluding inadvertent gluten exposure as a cause of ongoing disease activity and evaluation for and treatment of nutritional deficiencies that may result from enteropathy with malabsorption (115,218,245). Symptomatic treatment to reduce diarrhea is often required. There are no published randomized, controlled trials of therapy for Type I RCD. Traditional medical treatment in severe cases consists of systemic steroid therapy with prednisone or a similar agent. In patients with an incomplete response to steroid treatment or who recur when the steroid dose is reduced, immunosuppressive agents such as azathioprine can be used. Recent reports indicate that budesonide or small-intestinal release mesalamine may be effective and carry the potential advantage of causing fewer side effects (255–257).

The general approach to management of Type II RCD is the same as for Type I RCD (115,244–246). However, symptoms

and signs of disease are more severe in Type II RCD and are less likely to respond to therapy. Malnutrition in Type II RCD may be profound and require parenteral nutritional support. In one study, the 5-year survival of patients with Type II RCD was 44% compared to 93% for Type I RCD (244). Causes of death included lymphoma, malnutrition, and sepsis.

There are no published randomized, controlled trials of therapy for Type II RCD and there are no treatments of proven efficacy. Agents that are used for treatment include systemic corticosteroids, enteric-coated budesonide, azathioprine or 6-mercaptopurine, methotrexate, cyclosporine, anti-TNF antibodies, or cladribine (6,115,116,244,252,255,258–261). Transformation to enteropathy-associated T-cell lymphoma (EATCL) is a prominent risk and may require treatment by surgery, chemotherapy, or bone marrow transplantation (262,263). In some patients EATCL may run a prolonged, non-aggressive course but the overall prognosis remains poor.

SUMMARY OF RECOMMENDATIONS

- (1) Patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating, should be tested for CD. (Strong recommendation, high level of evidence)
- (2) Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD. (Strong recommendation, moderate level of evidence)
- (3) Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD.
- (4) Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD. (Conditional recommendation, high level of evidence)
- (5) CD should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found. (Strong recommendation, high level of evidence)
- (6) Patients with Type I DM should be tested for CD if there are any digestive symptoms, or signs, or laboratory evidence suggestive of CD. (Strong recommendation, high level of evidence)
- (7) IgA anti-TTG antibody is the preferred single test for detection of CD in individuals over the age of 2 years. (Strong recommendation, high level of evidence)
- (8) When there exists a high probability of CD wherein the possibility of IgA deficiency is considered, total IgA should be measured. An alternative approach is to include both IgA and IgG-based testing, such as IgG DGPs, in these high-probability patients. (Strong recommendation, moderate level of evidence)

- (9) In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed. (Strong recommendation, moderate level of evidence)
- (10) If the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative. (Strong recommendation, moderate level of evidence)
- (11) All diagnostic serologic testing should be done with patients on a gluten-containing diet. (Strong recommendation, high level of evidence)
- (12) Antibodies directed against native gliadin are not recommended for the primary detection of CD. (Strong recommendation, high level of evidence)
- (13) Combining several tests for CD in lieu of TTG IgA alone may marginally increase the sensitivity for CD but reduces specificity and therefore are not recommended in low-risk populations. (Conditional recommendation, moderate level of evidence)
- (14) When screening children younger than 2 years of age for CD, the IgA TTG test should be combined with DGPs (IgA and IgG). (Strong recommendation, moderate level of evidence)
- (15) The confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum. (Strong recommendation, high level of evidence)
- (16) Upper endoscopy with small-bowel biopsy is a critical component of the diagnostic evaluation for persons with suspected CD and is recommended to confirm the diagnosis. (Strong recommendation, high level of evidence)
- (17) Multiple biopsies of the duodenum (one or two biopsies of the bulb and at least four biopsies of the distal duodenum) are recommended to confirm the diagnosis of CD. (Strong recommendation, high level of evidence)
- (18) Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for CD and other causes should also be considered. (Strong recommendation, high level of evidence)
- (19) HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD. (Strong recommendation, moderate level of evidence)
- (20) HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations. (Strong recommendation, moderate level of evidence)

Examples of such clinical situations include but are not limited to:

- (a) Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
- (b) Evaluation of patients on a GFD in whom no testing for CD was done before GFD

- (c) Patients with discrepant celiac-specific serology and histology
- (d) Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question
- (e) Patients with Down's syndrome
- (21) Capsule endoscopy should not be used for initial diagnosis except for patients with positive celiac-specific serology who are unwilling or unable to undergo upper endoscopy with biopsy. (Strong recommendation, moderate level of evidence)
- (22) Capsule endoscopy should be considered for the evaluation of small-bowel mucosa in patients with complicated CD. (Strong recommendation, moderate level of evidence)
- (23) Intestinal permeability tests, D-xylose, and small-bowel follow-through are neither specific nor sensitive and are not recommended for CD diagnosis. (Strong recommendation, moderate level of evidence)
- (24) Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD. (Strong recommendation, weak level of evidence)
- (25) Symptoms or symptom response to a GFD alone should not be used to diagnose CD, as these do not differentiate CD from non-celiac gluten sensitivity. (Strong recommendation, moderate level of evidence)
- (26) A diagnosis of non-celiac gluten sensitivity should be considered only after CD has been excluded with appropriate testing. (Strong recommendation, moderate level of evidence)
- (27) While standard diagnostic tests (specific serology and intestinal biopsy) have a high PPV for CD, they should not be relied upon to exclude CD in patients already adhering to a GFD. (Strong recommendation, high level of evidence)
- (28) HLA-DQ2/DQ8 genotyping should be used to try to exclude CD prior to embarking on a formal gluten challenge. (Strong recommendation, high level of evidence)
- (29) CD should be differentiated from non-celiac gluten sensitivity in order to identify the risk for nutritional deficiency states, complications of CD, risk for CD and associated disorders in family members, and to influence the degree and duration of adherence to the GFD. (Conditional recommendation, moderate level of evidence)
- (30) Formal gluten challenge should be considered, where necessary, to diagnose or exclude CD in patients already adhering to a GFD. (Strong recommendation, high level of evidence)
- (31) Despite the disadvantages of neither confirming nor excluding a diagnosis of CD, some patients will opt to continue on a strict GFD without undergoing formal gluten challenge; such patients should be managed in a similar fashion to those with known CD. (Conditional recommendation, low level of evidence)

- (32) People with CD should adhere to a GFD for life. A GFD entails strict avoidance of all products containing the proteins from wheat, barley, and rye. (Strong recommendation, high level of evidence)
- (33) While pure oats appear to be safely tolerated by the majority of people with CD, oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction. (Strong recommendation, moderate level of evidence)
- (34) People with CD should be referred to a registered dietitian who is knowledgeable about CD in order to receive a thorough nutritional assessment and education on the GFD. (Strong recommendation, moderate level of evidence)
- (35) People with newly diagnosed CD should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12. (Conditional recommendation, low level of evidence)
- (36) People with CD should be monitored regularly for residual or new symptoms, adherence to GFD, and assessment for complications. In children, special attention to assure normal growth and development is recommended. (Strong recommendation, moderate level of evidence)
- (37) Periodic medical follow-up should be performed by a health-care practitioner with knowledge of CD. Consultation with a dietitian should be offered if gluten contamination is suspected. (Strong recommendation, moderate level of evidence)
- (38) Monitoring of adherence to GFD should be based on a combination of history and serology (IgA TTG or IgA (or IgG) DGP antibodies). (Strong recommendation, moderate level of evidence)
- (39) Upper endoscopy with intestinal biopsies is recommended for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD. (Strong recommendation, moderate level of evidence)
- (40) Monitoring of people with CD should include verification of normalization of laboratory abnormalities detected during initial laboratory investigation. (Strong recommendation, moderate level of evidence)
- (41) Patients with NRCd should be evaluated carefully to identify and treat the specific etiology in each patient. (Strong recommendation, high level of evidence)
- (42) Early steps in the evaluation should include measurement of celiac serologies and a thorough review of the patient's diet by a dietitian who is experienced in CD management. (Strong recommendation, high level of evidence)
- (43) Differentiation should be made between Type I and Type II refractory CD as this is important for management and prognosis. (Strong recommendation, moderate level of evidence)

- (44) Treatment with medication, as an adjunct to the GFD, should be considered in refractory CD. (Conditional recommendation, moderate level of evidence)
- (45) Patients with RCD should be monitored closely and receive aggressive nutritional support, including parenteral nutrition whenever indicated. (Strong recommendation, high level of evidence)

CONFLICT OF INTEREST

Guarantor of the article: Joseph A. Murray, MD.

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