ACG Clinical Guideline: Diagnosis and Management of Celiac Disease

Alberto Rubio-Tapia, MD[1], Ivor D. Hill, MD[2], Ciarán P. Kelly, MD[3], Audrey H. Calderwood, MD[4] and Joseph A. Murray, MD[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; [3]Celiac Center, Division of Gastroenterology, Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, Massachusetts, USA; [4]Gastroenterology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA

Am J Gastroenterol 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013

Abstract

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.

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.

Table 1. Criteria for assigning grade of evidence
Type of evidence
Randomized trial=high
Observational study=low
Any other evidence=very low
Decrease grade if
• 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)
Increase grade if
• 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)
Definition of grades of evidence
• 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
Reprinted with permission from Camilleri *et al.* (264).

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)

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	

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)

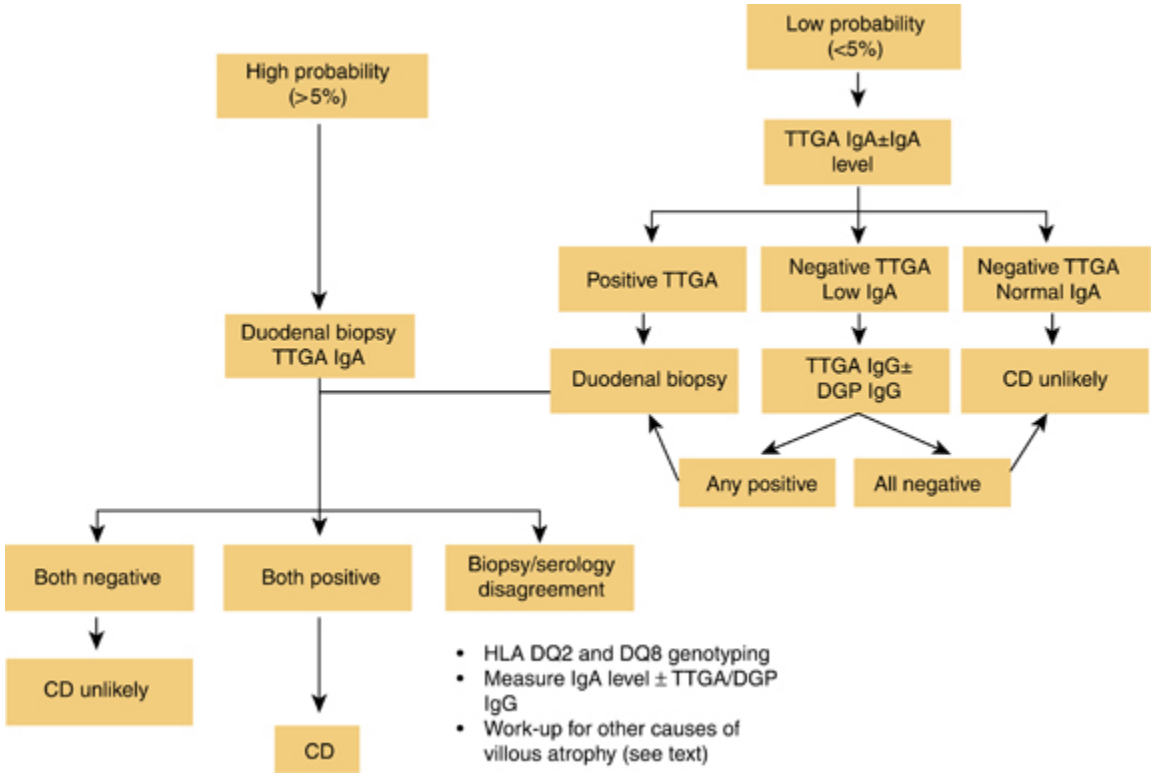

Figure 1. Celiac disease (CD) diagnostic testing algorithm. DGP, deamidated gliadin peptide; HLA, human leukocyte antigen; Ig, immunoglobulin; TTGA,
tissue transglutaminase antibody

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)

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

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:
   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
3. 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)
4. Capsule endoscopy should be considered for the evaluation of small-bowel mucosa in patients with complicated CD. (Strong recommendation, moderate level of evidence)
5. 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)
6. Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD. (Strong recommendation, weak level of evidence)

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)

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)

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.

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)

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)

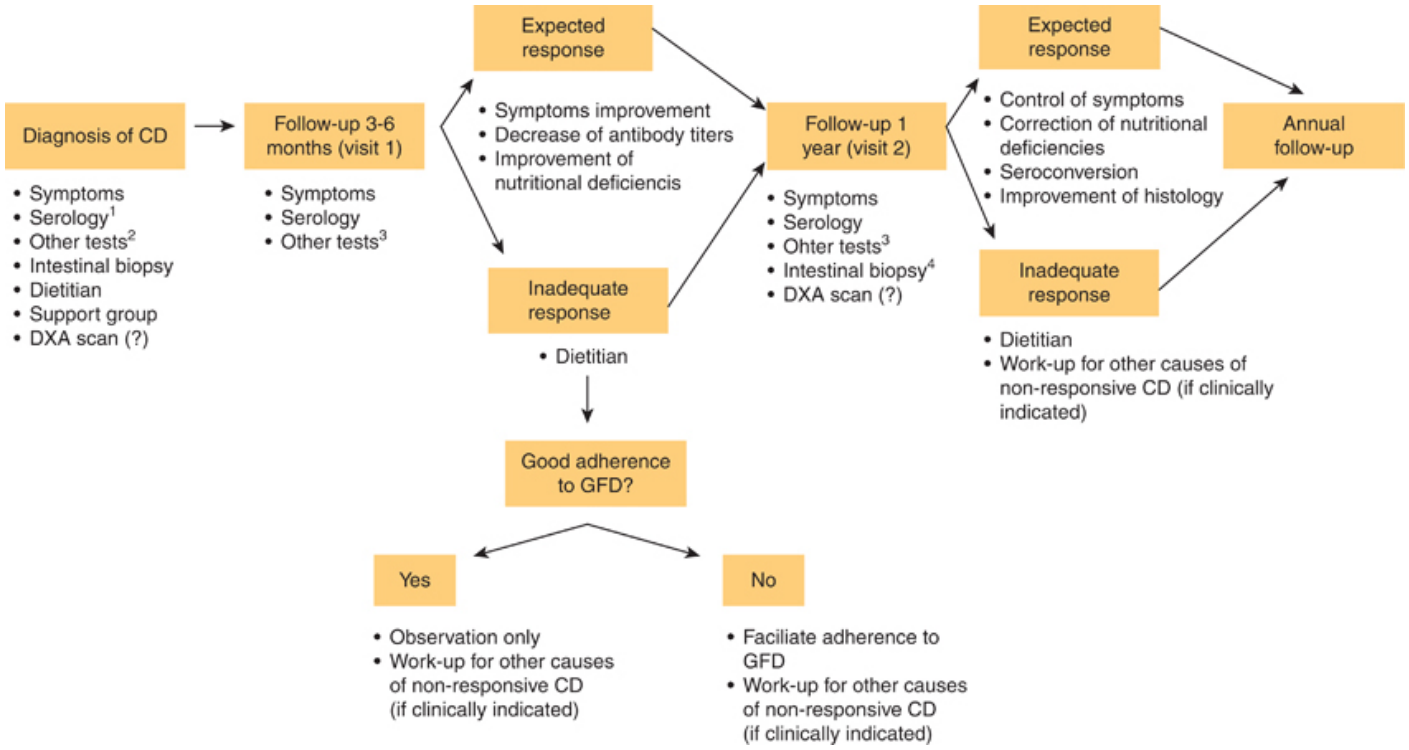

Figure 3. An approach to monitoring celiac disease (CD) (adapted from Rubio-Tapia A. Seguimiento Médico del Paciente Celiaco. En Rodrigo L (ed.) Enfermedad Celiaca. Barcelona, España. *OmniaScience*, 2013, in press). (1) Tissue transglutaminase and deamidated gliadin peptide can be used for monitoring 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.

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)

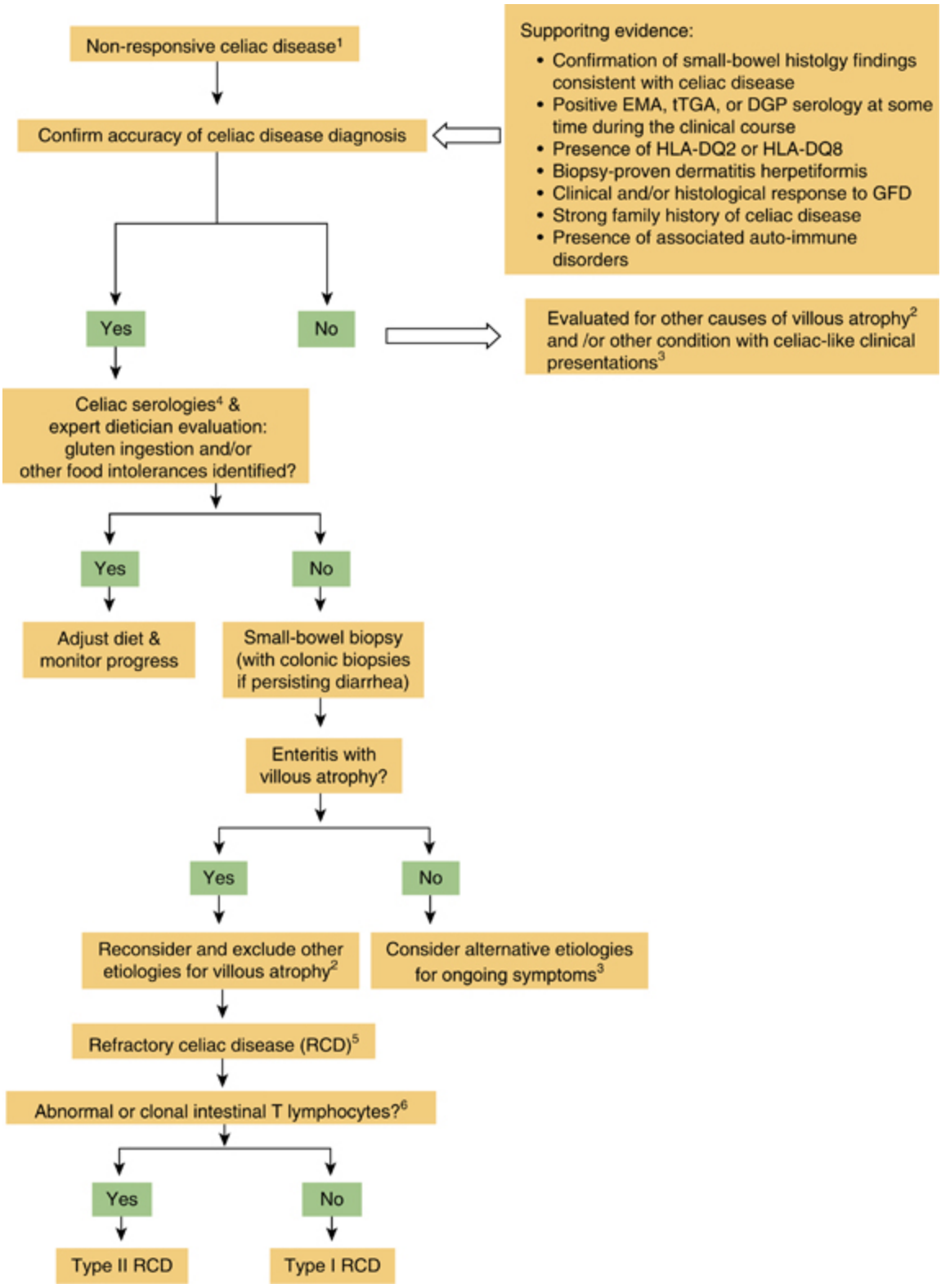

Figure 4. An approach to the investigation of non-responsive celiac disease (NRCD) and refractory celiac disease (RCD) (adapted from references Rubio-Tapia (6) and Abdallah (261). (1) NRCD may be defined as persistent symptoms, signs, or laboratory abnormalities typical of celiac disease (CD) despite 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.