Diagnosis of celiac disease in adults

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INTRODUCTION

Celiac disease is a small bowel disorder characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and demonstrate improvement after withdrawal of gluten from the diet. Celiac disease should be differentiated from nonceliac gluten sensitivity in order to identify the risk for nutritional deficiency and complications of celiac disease and to determine the necessary degree and duration of adherence to a gluten-free diet. The diagnosis of celiac disease also has important implications for family members who may be at risk for celiac disease and associated disorders.

This topic will review the diagnosis of celiac disease. Our recommendations are largely consistent with a consensus statement from the National Institutes of Health, the American College of Gastroenterology and American Gastroenterological Association guidelines [1-3]. The clinical manifestations and management of celiac disease in children and adults is discussed in detail separately. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults" and "Management of celiac disease in adults" and "Diagnosis of celiac disease in children" and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children" and "Management of celiac disease in children".)

WHO SHOULD BE TESTED

The benefit of population screening for asymptomatic celiac disease has not been demonstrated [4-9]. However, guidelines suggest screening for celiac disease be considered in asymptomatic first-degree relatives of patients with a confirmed diagnosis of celiac disease [3,9]. Serologic testing for celiac disease is recommended in adults with any of the following:

Suggestive gastrointestinal symptoms — Gastrointestinal symptoms include chronic or recurrent diarrhea or constipation, malabsorption, unexpected weight loss, abdominal pain, distension, or bloating. Testing should therefore be performed in patients with symptoms suggestive of irritable bowel syndrome or refractory lactose intolerance. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults", section on 'Laboratory testing' and "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management".)

Extraintestinal signs/symptoms suggestive of celiac disease — Patients with extraintestinal symptoms, signs, or laboratory evidence for which celiac disease is a treatable cause. This includes patients without other explanations for iron deficiency anemia, folate or vitamin B12 deficiency, persistent elevation in serum aminotransferases, dermatitis herpetiformis, fatigue, recurrent headaches, recurrent fetal loss, low birthweight offspring, reduced fertility, persistent aphthous stomatitis, dental enamel hypoplasia, metabolic bone disease and premature osteoporosis, idiopathic peripheral neuropathy, or nonhereditary cerebellar ataxia.

DIAGNOSTIC APPROACH

Overview — The diagnostic approach is based on the risk for celiac disease and whether the patient is on a gluten-containing diet. All testing for celiac disease should ideally be performed while patients are on a gluten-containing diet. An approach to diagnosis of celiac disease is summarized in the following algorithm (algorithm 1). (See 'Patients on a gluten-free diet' below.)

Individuals with low celiac disease probability — The probability of celiac disease is low in individuals with one or more of the following clinical scenarios:

- Absence of suggestive signs or symptoms of malabsorption such as significant chronic diarrhea/steatorrhea or weight loss
- Absence of family history of celiac disease
- Chinese, Japanese, or Sub-Saharan African descent

Individuals at low risk for celiac disease should undergo serologic testing. Patients with positive serologic testing, should undergo an upper endoscopy with small bowel biopsy to diagnose

celiac disease. The serum tissue transglutaminase (tTG)-immunoglobulin A (IgA) and endomysial (EMA)-IgA antibody tests have similar sensitivities. A negative result for either test in individuals at low risk for celiac disease has a high negative predictive value and obviates the need for small bowel biopsy. The specificities of the EMA IgA and tTG-IgA are high. Thus, their positive predictive values are high even in low-risk populations [4,5,10]. The EMA-IgA test has the highest diagnostic accuracy but is more costly and less widely available than the tTG-IgA test (algorithm 1) [10,11]. Combining several tests for celiac disease is not recommended in low-risk populations in lieu of performing tTG-IgA alone as this may marginally increase the sensitivity but substantially reduces specificity. (See 'Serologic evaluation' below.)

Individuals with high celiac disease probability — Both serologic testing and small bowel biopsy (regardless of celiac specific serology results) should be performed in individuals with a high probability of celiac disease (algorithm 1). (See 'Serologic evaluation' below and 'Endoscopy with small bowel biopsy' below.)

Individuals with a high celiac disease probability include:

- Individuals whose clinical presentation is highly suggestive for celiac disease such as chronic diarrhea/steatorrhea with weight loss.

- Individuals with both risk factors that place them at moderate to high risk of celiac disease and consistent gastrointestinal or extraintestinal symptoms/signs of celiac disease. (See 'Suggestive gastrointestinal symptoms' above and 'Extraintestinal signs/symptoms suggestive of celiac disease' above.)

  Risk factors that place an individual at moderate to high risk for celiac disease include:

  - First- and second-degree relative with confirmed celiac disease
  - Type 1 diabetes
  - Autoimmune thyroiditis
  - Down and Turner syndromes
  - Pulmonary hemosiderosis (moderate risk)

Serologic evaluation — Tissue transglutaminase (tTG)-IgA antibody is the single preferred test for detection of celiac disease in adults. In addition, we concurrently measure total IgA levels. In patients with IgA deficiency, we perform IgG-based testing with deamidated gliadin peptide (DGP)-IgG. An alternative approach is to perform both IgA- and IgG-based testing, in particular, tTG-IgA and DGP-IgG, in patients with a high probability of celiac disease. (See 'IgA deficiency' below.)

Serum antibody assays — Serologic studies for celiac disease can be divided into two groups based upon their target antigens [11]:

- **Autoantibodies**:
  - Anti-endomysial antibody (EMA-IgA)
  - Anti-tissue transglutaminase antibodies (tTG) (tTG-IgA, tTG-IgG)
- **Antibodies targeting gliadin**:
  - Antibody to native gliadin: Antigliadin antibody (AGA-IgA, AGA-IgG)
  - Antibodies against synthetic deamidated gliadin peptides: Deamidated gliadin peptide (DGP)-IgA, DGP-IgG
- **Anti-endomysial antibody** – Endomysial antibodies bind to connective tissue surrounding smooth muscle cells and produce a characteristic staining pattern, which is visualized by indirect immunofluorescence [4,5,10-17]. The target antigen has been identified as a tissue transglutaminase. EMA-IgA is moderately sensitive and highly specific for untreated celiac disease (sensitivity 85 to 98 percent; specificity 97 to 100 percent, respectively) [18-22]

  The test result is often reported simply as positive or negative since even low titers of EMA-IgA are specific for celiac disease. Serum levels of EMA-IgA fall on a gluten-free diet [14]. Limitations of this test include its cost, complexity, and operator dependency that may result in interobserver variation.
- **Anti-tissue transglutaminase antibodies** – The antigen against which antiendomysial antibodies are directed is tTG-2 [23]. Anti-tTG antibodies are highly sensitive and specific for the diagnosis of celiac disease (sensitivity 90 to 98 percent; specificity 95 to 97 percent) [24-28]. The positive predictive value of a strongly positive TG2-IgA (>10 upper normal limit) combined with a positive endomysial antibody is approximately 100 percent [2].

  Enzyme-linked immunosorbent assay tests for tTG-IgA antibodies are now widely available and are easier to perform and less costly than the immunofluorescence assay used to detect IgA endomysial antibodies. The diagnostic accuracy of anti-tTG immunoassays has been improved further by the use of human tTG in place of the nonhuman tTG preparations used in earlier immunoassay kits [29].
- **Antigliadin antibody assays** – Gliadin is a component of the wheat storage protein, gluten.

- **Anti-deamidated gliadin peptide** – The DGP uses synthetic gliadin peptides that mimic tTG-modified gliadin sequences to capture serum IgA or IgG against DGP [19,20]. DGP-IgA has a sensitivity and specificity of 94 percent and 99 percent, respectively. The DGP-IgG has a sensitivity and specificity of 92 percent and 100 percent, respectively [18-22]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

- **Antigliadin antibody** – The traditional antigliadin antibody tests (AGA-IgA and AGA-IgG) have lower diagnostic accuracy as compared with other serologic tests for celiac disease and are no longer recommended because they yield false-positive results in 15 to 20 percent of subjects tested [11,12].

The diagnostic performance of serologic tests for celiac disease are influenced by the following factors:

- **Variation among testing methods** – Technical and methodologic factors might affect the reported accuracies of diagnostic tests. However, the literature reports wide variations in test sensitivity and specificity among different laboratories [11,30]. It is therefore important to know the sensitivity and specificity of the assay as performed by the testing laboratory before determining the clinical significance of a particular test result [31].

- **Severity of celiac disease** – In addition to laboratory variation, the sensitivity of these tests may depend upon the severity of celiac disease. In one report, as an example, serum antibodies were determined in 101 patients with biopsy-proven celiac disease [32]. The sensitivity of EMA-IgA varied from 100 percent in patients with total villous atrophy to only 31 percent in those with partial villous atrophy.

- **Dietary factors** – A weakly positive serologic test for celiac disease may become negative within weeks of adherence to a gluten-free diet. (See 'Patients on a gluten-free diet' below.)

- **Patient age** – tTG-IgA and EMA-IgA may be falsely negative in children under two years. (See "Diagnosis of celiac disease in children", section on 'Children younger than two years'.)

- **IgA deficiency** – Undetectable IgA levels but not partial immunoglobulin A deficiency (low but detectable serum IgA) decreases the sensitivity of TTG-IgA [33]. (See 'IgA deficiency' below.).

Test interpretation

Positive serology — Individuals with positive serology require a small bowel biopsy to confirm the diagnosis. Exceptions are patients with positive serology and biopsy-proven dermatitis herpetiformis in whom the diagnosis can be established without a small bowel biopsy. (See 'Endoscopy with small bowel biopsy' below and 'Dermatitis herpetiformis' below.)

Negative serology — Serologic studies are useful in excluding the diagnosis of celiac disease but cannot exclude celiac disease with 100 percent accuracy. Negative celiac serologies in patients with celiac disease may be due to any one of the following:

- **IgA deficiency** – tTG-IgA serology will be falsely negative in untreated celiac disease in patients with IgA deficiency, common variable immunodeficiency, or the use of an immunosuppressant. (See 'IgA deficiency' below.)

- **Low gluten/gluten-free diet** – The individual may already be on a low gluten diet. An approach to diagnosis of celiac disease in patients on a gluten-free diet is summarized in the following algorithm (algorithm 2). (See 'Patients on a gluten-free diet' below.)

- **False negative** – The serologic test (tTG-IgA) could be falsely negative. tTG-IgA antibodies have a very high sensitivity (90 to 98 percent), but a false-negative serologic test is possible. False-negative serology is more common in patients with mild disease on histology. In such cases, DGP (IgA or IgG) antibody testing may be useful. However, a small bowel biopsy is needed to make a diagnosis. (See 'Endoscopy with small bowel biopsy' below.)

Endoscopy with small bowel biopsy — Upper endoscopy with small bowel biopsy serves to establish the diagnosis in patients with suspected celiac disease (algorithm 1).

Endoscopic features and biopsy technique — Endoscopic features of celiac disease include atrophic appearing mucosa with loss of folds, visible fissures, nodularity, scalloping, and prominent submucosal vascularity (picture 1). However, endoscopic features suggestive of celiac disease have low sensitivity (59 to 94 percent). The reported specificity ranges from 92 to 100 percent and these findings may be seen with other disorders such as giardiasis, autoimmune enteropathy, and HIV infection [34]. Histology remains important in making a diagnosis of celiac disease, regardless of the endoscopic appearance.

Multiple biopsies of the duodenum (one or two from bulb and four from distal duodenum) are necessary for diagnosis of celiac disease [3]. Bulb biopsies, if taken, should be clearly labeled as such to help ensure that the pathologist takes into account the different mucosal architecture of the bulb to avoid false-positive reports of villous atrophy. The accuracy of biopsies can be improved with staining techniques and magnification endoscopy; however, these approaches

are not routinely used [35-37]. (See "Magnification endoscopy" and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Gastrointestinal manifestations'.)

Histologic features — Histologic features of celiac disease in the small intestine range from a mild alteration characterized only by increased intraepithelial lymphocytes, to a severely atrophic mucosa with complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia [38-43]. The histologic severity of intestinal lesions in celiac disease is graded using the Marsh-Oberhuber classification (figure 1) or the Corazza classification [3,44]. Marsh type 2 and 3 lesions (Corazza B1 or B2), while not pathognomonic for celiac disease, are supportive of the diagnosis (figure 1 and table 1). Causes of small intestinal villous atrophy other than celiac disease are shown in a table (table 2 and algorithm 3). (See 'Positive serology and diagnostic small bowel biopsy' below.)

Intestinal biopsies should be interpreted by an expert pathologist. A gradient of decreasing histologic severity from the proximal to the distal small intestine is often observed, correlating with the higher proximal concentration of dietary gluten. The degree of the villous atrophy does not necessarily correlate with the severity of clinical symptoms, and sampling error can occur due to some inhomogeneity of mucosal inflammation and injury.

Interpretation and additional evaluation

Positive serology and diagnostic small bowel biopsy — The diagnosis of celiac disease is established when duodenal biopsy samples showing increased intraepithelial lymphocytes with crypt hyperplasia (Marsh type 2), or, more commonly, also with villous atrophy (Marsh type 3) in a patient with positive celiac serology (algorithm 1).

Discordant serology and small bowel biopsy

- **Positive serology and nondiagnostic small bowel biopsies** – tTG-IgA serology may occasionally be positive but the small intestinal biopsy may be normal or equivocal (Marsh 0 or 1, respectively) (figure 1). Discordant serology and biopsy results may be due to the following:

  - **False-positive tTG** – False-positive tTG results are rare but do occur and are usually low titer (typically less than twice the upper limit of normal). Case reports suggest that tTG-IgA antibodies may be falsely elevated during or after a febrile illness [45]. There are also concerns about the quantitative variability and lack of standardization between commercially available serologic tests for celiac disease. (See 'Serum antibody assays' above.)

- **False-negative biopsy results** – Celiac disease may have a patchy distribution or initially be confined to the duodenal bulb. (See 'Endoscopic features and biopsy technique' above.)

The intestinal biopsy should be reviewed by a pathologist familiar with celiac disease to look for subtle abnormalities of celiac disease. In addition, we perform an alternate antibody test (EMA-IgA or DGP-IgA). If serology and histology remain discordant, we perform HLA-DQ2/DQ8 typing (algorithm 1).

- If HLADQ2/DQ8 is negative, celiac disease is excluded. Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for celiac disease and other causes should be considered. Other conditions associated with lymphocytic duodenosis, including *Helicobacter pylori* infection, medications (eg, nonsteroidal anti-inflammatory drugs), small intestinal bacterial overgrowth, and systemic autoimmune disorders [46]. (See 'HLA testing in selected patients' below.)

- If HLADQ2/DQ8 is positive, the patient can be placed on a high-gluten diet (>10 grams per day, equivalent of at least four slices of gluten containing bread per day) and, after 6 to 12 weeks, additional biopsies obtained from multiple sites in the mid and distal duodenum since celiac disease enteropathy can be patchy and missed due to sampling error. Staining techniques and high resolution magnification endoscopy can help identify areas of villous atrophy for biopsy. (See 'Serum antibody assays' above.)

  The finding of Marsh type 2 or 3 lesions on histology in a patient with positive celiac serology is diagnostic of celiac disease (figure 1). (See 'Positive serology and diagnostic small bowel biopsy' above.)

  Patients with positive celiac-specific serologies in the absence of crypt hyperplasia or villous atrophy (Marsh 0 or Marsh 1) are considered to have potential celiac disease (figure 1) [3,47]. This is most frequently encountered in patients screened for celiac disease due to a positive family history or a diagnosis of type 1 diabetes mellitus. Symptomatic patients with potential celiac disease are likely to benefit from treatment with a gluten-free diet. Asymptomatic patients can remain on a normal diet unless clinical features of celiac disease develop [48]. (See 'Suggestive gastrointestinal symptoms' above and 'Extraintestinal signs/symptoms suggestive of celiac disease' above and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults", section on 'Clinical manifestations'.)

- **Negative serology and abnormal small bowel biopsy** – For patients with histologic findings suggestive of celiac disease (eg, villous atrophy) but negative serologies, we

perform HLA-DQ2/DQ8 genotyping. If haplotypes HLA-DQ2 or DQ8 are present, we recommend a gluten-free diet for 12 to 24 months and monitor the clinical response. We also perform a repeat upper endoscopy with biopsies after 12 to 24 months of a gluten-free diet to confirm mucosal healing. Patients with a histologic response are likely to have sero-negative celiac disease. Individuals without a histologic response likely have non-celiac villous atrophy (table 2 and algorithm 3).

HLA testing in selected patients — The haplotypes HLA-DQ2 or DQ8 are present in almost all patients with celiac disease. Testing for these haplotypes has a negative predictive value of greater than 99 percent, but positive predictive value is only around 12 percent because these haplotypes are common in the general population [49]. Hence, HLA testing is useful only in ruling out celiac disease:

- Patients with discordant celiac-specific serology and histology (see 'Discordant serology and small bowel biopsy' above).
- Patients who refuse upper endoscopy (see 'Patients unable/unwilling to undergo upper endoscopy' below).
- Evaluation of patients on a gluten-free diet with negative baseline serologies (see 'Patients on a gluten-free diet' below).
- Patients with suspicion of refractory celiac disease where the original diagnosis of celiac disease remains in question (see "Management of celiac disease in adults", section on 'Non-responders').
- HLA typing is sometimes performed in patients at high risk for celiac disease (eg, family history of celiac disease). A negative result will exclude celiac disease risk. This approach is most commonly used in at-risk children to obviate the need for periodic serology testing. (See "Diagnosis of celiac disease in children", section on 'Members of high-risk groups'.)

Diagnosis — The diagnosis of celiac disease is established by the presence of increased intraepithelial lymphocytes with crypt hyperplasia (Marsh type 2) alone, or in conjunction with villous atrophy (Marsh type 3) on small bowel biopsy in a patient with positive celiac serology (figure 1 and algorithm 1). Demonstration of histologic normalization on a gluten-free diet is not required to establish the diagnosis of celiac disease in adults.

In patients with biopsy-proven dermatitis herpetiformis, the diagnosis can be established by serology without a small bowel biopsy. (See 'Dermatitis herpetiformis' below.)

Symptomatic adults who are unwilling or unable to undergo upper GI endoscopy but have a high-level tTG IgA (>10-fold elevation above the upper limit of normal) with a positive endomysial antibody (EMA) in a second blood sample can be diagnosed as likely celiac disease [3]. (See 'Patients unable/unwilling to undergo upper endoscopy' below.)

EVALUATION IN SPECIAL SITUATIONS

Patients on a gluten-free diet — While there are limited data with regard to the decrease in antibody titers in individuals on a gluten-free diet, a weakly positive test may become negative within weeks of strict adherence to a gluten-free diet [50]. After 6 to 12 months on a gluten-free diet, approximately 80 percent of individuals with celiac disease will test negative by serology. By five years, more than 90 percent of patients on a gluten-free diet will have negative serologies [51,52]. An approach to diagnosis of celiac disease in patients on a gluten-free diet is summarized in the following algorithm (algorithm 2) [3,53].

- **Baseline evaluation and gluten challenge** – Baseline antibody testing should be performed. Patients with positive serology should undergo a small bowel biopsy (algorithm 2). (See 'Endoscopy with small bowel biopsy' above.)

  Patients with negative serologies should undergo HLA-DQ2/DQ8 testing to determine if the patient is genetically susceptible to celiac disease.

  - If HLA-DQ2/DQ8 testing is negative, celiac disease is excluded.
  - If HLA-DQ2/DQ8 testing is positive, patients should undergo a gluten challenge with 3 g gluten per day (equivalent to 1 slice of gluten-containing bread) for two weeks. If tolerated, the gluten challenge should be extended for an additional six weeks). Duodenal biopsies are performed at the end of the gluten challenge (ie, after two weeks or, ideally, eight weeks of challenge). Serology should be checked at the end of the gluten challenge and, if negative, serology should be repeated two to four weeks later.

  Patients who opt to continue on a strictly gluten-free diet without undergoing formal gluten challenge may be managed in a similar fashion to those with known celiac disease (algorithm 2). (See "Management of celiac disease in adults".)

- **HLA-DQ-gluten tetramer** – A novel HLA-DQ-gluten tetramer-based assay that detects gluten-specific T cells in blood may be able to identify patients with celiac disease, regardless of whether testing is performed on a gluten-free diet [54]. While the assay has

demonstrated a high degree of accuracy in an early study, the results require validation before it can be used clinically.

IgA deficiency — IgA deficiency is more common in celiac disease (2 to 5 percent) than in the general population (<0.5 percent). IgA EMA and IgA tTG are falsely negative in patients with IgA deficiency. In patients in whom very low IgA or selective IgA deficiency is identified, IgG-based testing should be performed. We perform IgG DGP due to its higher sensitivity and specificity as compared with IgG anti-tissue transglutaminase antibodies. IgG antigliadin is also usually positive in the 1 to 2 percent of celiac patients who have IgA deficiency [55,56].

Dermatitis herpetiformis — The diagnosis of celiac disease in patients with biopsy-proven dermatitis herpetiformis can be established by serology alone without a small bowel biopsy. (See 'Serologic evaluation' above and "Dermatitis herpetiformis".)

Patients unable/unwilling to undergo upper endoscopy — Symptomatic adults who are unwilling or unable to undergo upper GI endoscopy but have a high-level TTG IgA (>10-fold elevation above the upper limit of normal) with a positive endomysial antibody (EMA) in a second blood sample can be diagnosed as likely celiac disease [3].

In patients without a high-level tTG IgA, we perform HLA testing. Absence of alleles encoding DQ2 or DQ8 excludes celiac disease. In patients who are DQ2- or DQ8-positive and have positive celiac serologies, a video capsule endoscopy (VCE) may reveal visible features of celiac disease in the small intestine. However, as endoscopic features are not specific for celiac disease, VCE 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 [57]. (See "Wireless video capsule endoscopy", section on 'Small bowel tumors, polyps, and other pathology'.)

DIFFERENTIAL DIAGNOSIS

The most common disorders in the differential diagnosis of celiac disease include irritable bowel syndrome, small intestinal bacterial overgrowth, lactose intolerance, chronic pancreatitis, microscopic colitis, and inflammatory bowel disease. Celiac disease can be differentiated from these by serologic evaluation and small bowel biopsy. Approach to the evaluation of patients with diarrhea is discussed in detail separately. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults", section on 'Diagnosis' and "Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis", section on 'Diagnosis' and "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management" and "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management",

section on 'Diagnostic evaluation' and "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'Initial evaluation'.)

Non-celiac gluten sensitivity (NCGS) describes a syndrome of symptomatic response to gluten ingestion in patients with **no** serologic or histologic evidence of celiac disease. The clinical response to a gluten-free diet may be caused by a variety of mechanisms, including placebo effect and fermentable oligo-, di-, and monosaccharides and polyols reduction, as well as by true gluten sensitivity in some of patients. For individuals with symptoms that they attribute to gluten, it is important to test for both celiac disease and IgE-mediated wheat allergy. NCGS is discussed in detail separately. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children", section on 'Nonceliac gluten sensitivity'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Celiac disease" and "Society guideline links: Dermatitis herpetiformis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Celiac disease (The Basics)")
- Beyond the Basics topics (see "Patient education: Celiac disease in children (Beyond the Basics)" and "Patient education: Celiac disease in adults (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: Celiac disease".)

SUMMARY AND RECOMMENDATIONS

- **When to suspect celiac disease** – Testing for celiac disease should be performed in adults with suggestive gastrointestinal or extraintestinal signs/symptoms of celiac disease. Extraintestinal signs/symptoms of celiac disease include unexplained iron deficiency anemia, folate or vitamin B12 deficiency, persistent elevation in serum aminotransferases, dermatitis herpetiformis, fatigue, recurrent headaches, recurrent fetal loss, low birthweight offspring, reduced fertility, persistent aphthous stomatitis, dental enamel hypoplasia, metabolic bone disease and premature osteoporosis, idiopathic peripheral neuropathy, or nonhereditary cerebellar ataxia. (See 'Who should be tested' above.)

- **Diagnostic approach** – Testing for celiac disease should ideally be performed while patients are on a gluten-containing diet. The testing approach varies based on the probability of celiac disease.

  - **Individuals with a low probability of celiac disease** – Evaluation begins with serologic testing. Patients with positive serologic testing should undergo an upper endoscopy with small bowel biopsy to diagnose celiac disease. (See 'Individuals with low celiac disease probability' above.)

  - **Individuals with a high probability of celiac disease** – Both serologic testing and small bowel biopsy (regardless of celiac-specific serology results) should be performed (algorithm 1). (See 'Individuals with high celiac disease probability' above.)

  - **Patients on a gluten-free diet** – For patients who are already on a gluten-free diet, an approach to diagnosis of celiac disease is summarized in the following algorithm (algorithm 2). (See 'Patients on a gluten-free diet' above.)

- **Serologic evaluation** – Immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody is the single preferred test for detection of celiac disease in adults. In addition, we concurrently measure total IgA levels. In patients with IgA deficiency we perform IgG-

based testing with deamidated gliadin peptide (DGP) IgG. (See 'Serologic evaluation' above and 'Evaluation in special situations' above.)

- **Diagnostic histologic features on small bowel biopsy** – The diagnosis of celiac disease is established by the presence of increased intraepithelial lymphocytes with crypt hyperplasia (Marsh type 2) alone, or in conjunction with villous atrophy (Marsh type 3) on small bowel biopsy in a patient with positive celiac serology (figure 1). However, villous atrophy can be patchy and may also be present in a variety of other disorders that should be considered in appropriate clinical settings (table 2). (See 'Dermatitis herpetiformis' above.)

- **Additional evaluation in patients with equivocal or discordant results**

  - **Positive serology and nondiagnostic small bowel biopsies** – Discordant serology and biopsy results may be due to a false-positive tTG serology or a false-negative biopsy result as celiac disease may have a patchy distribution. The intestinal biopsy should be reviewed by a pathologist familiar with celiac disease to look for subtle abnormalities of celiac disease. In addition, we perform an alternate antibody test (EMA-IgA or DGP-IgA). If serology and histology remain discordant, we perform HLA-DQ2/DQ8 typing (algorithm 1).

  - **Negative serology and abnormal small bowel biopsy** – For patients with histologic findings suggestive of celiac disease (eg, villous atrophy) but negative serologies, we perform HLA-DQ2/DQ8 genotyping. If haplotypes HLA-DQ2 or DQ8 are present, we recommend a gluten-free diet for 12 to 24 months and monitor the clinical response. We also perform a repeat upper endoscopy with biopsies after 12 to 24 months of a gluten-free diet to confirm mucosal healing. Patients with a histologic response are likely to have celiac disease. Individuals without a histologic response likely have non-celiac villous atrophy (table 2 and algorithm 3).

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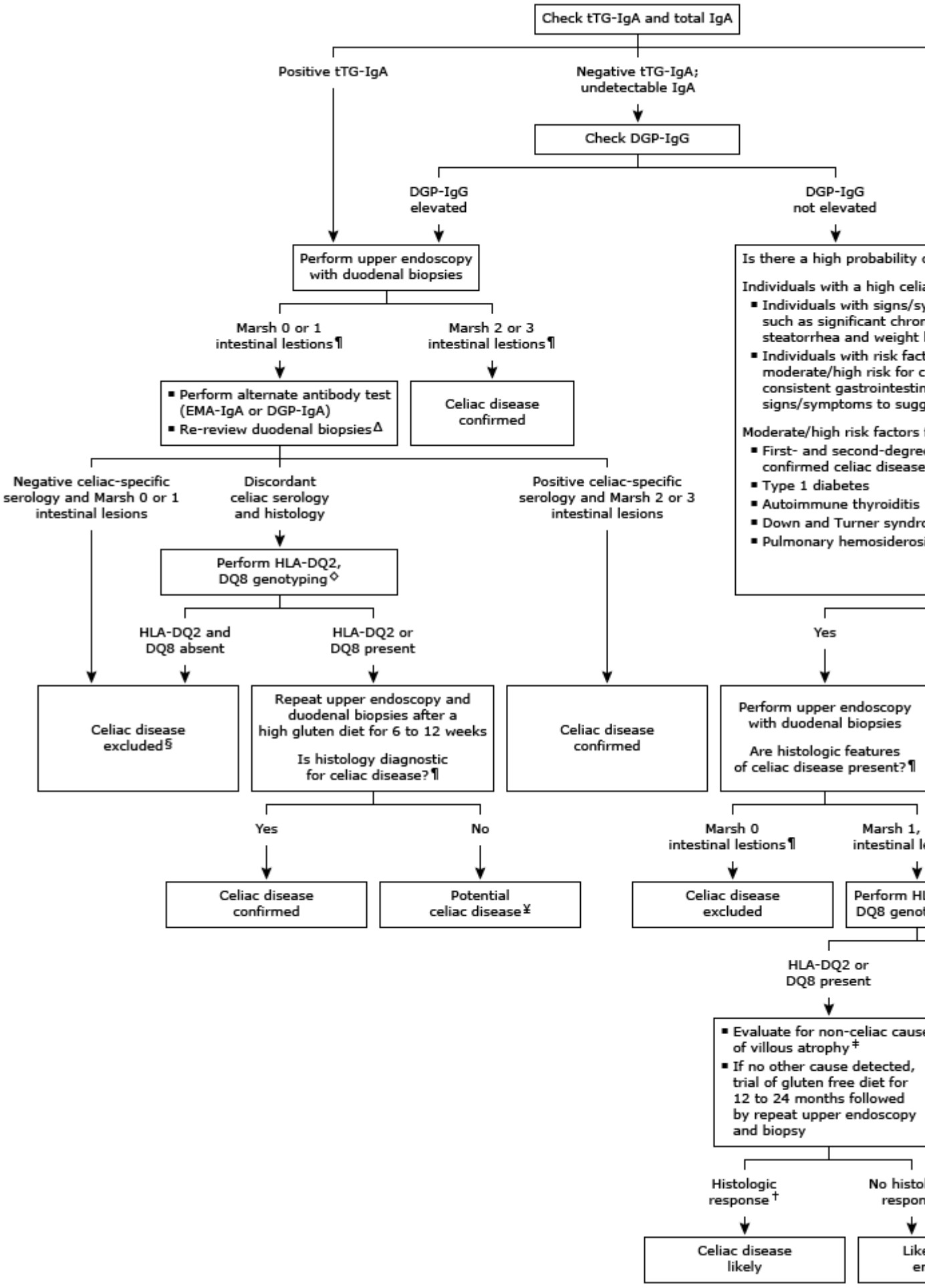
Topic 4771 Version 38.0

GRAPHICS

Diagnostic approach for suspected celiac disease in an adult patient on gluten


Check tTG-IgA and total IgA
Positive tTG-IgA
Negative tTG-IgA; undetectable IgA
Check DGP-IgG
DGP-IgG elevated
DGP-IgG not elevated
Perform upper endoscopy with duodenal biopsies
Marsh 0 or 1 intestinal lestions¶
Marsh 2 or 3 intestinal lestions¶
Perform alternate antibody test (EMA-IgA or DGP-IgA)
Re-review duodenal biopsies△
Celiac disease confirmed
Negative celiac-specific serology and Marsh 0 or 1 intestinal lesions
Discordant celiac serology and histology
Positive celiac-specific serology and Marsh 2 or 3 intestinal lesions
Perform HLA-DQ2, DQ8 genotyping◇
HLA-DQ2 and DQ8 absent
HLA-DQ2 or DQ8 present
Celiac disease excluded§
Repeat upper endoscopy and duodenal biopsies after a high gluten diet for 6 to 12 weeks
Is histology diagnostic for celiac disease?¶
Celiac disease confirmed
Yes
No
Celiac disease confirmed
Potential celiac disease¥
Is there a high probability
Individuals with a high celi
Individuals with signs/sy
such as significant chron
steatorrhea and weight
Individuals with risk fact
moderate/high risk for c
consistent gastrointestin
signs/symptoms to sugg
Moderate/high risk factors
First- and second-degre
confirmed celiac disease
Type 1 diabetes
Autoimmune thyroiditis
Down and Turner syndr
Pulmonary hemosiderosi
Yes
Perform upper endoscopy with duodenal biopsies
Are histologic features of celiac disease present?¶
Marsh 0 intestinal lestions¶
Marsh 1, intestinal l
Celiac disease excluded
Perform HL
DQ8 genot
HLA-DQ2 or DQ8 present
Evaluate for non-celiac caus
of villous atrophy‡
If no other cause detected, trial of gluten free diet for 12 to 24 months followed by repeat upper endoscopy and biopsy
Histologic response†
No histo
respon
Celiac disease likely
Like
er

This algorithm is intended for use in conjunction with additional UpToDate content on celiac disease. Refer t
on diagnosis of celiac disease in adults for additional details of diagnostic testing.

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tTG: tissue transglutaminase; IgA: immunoglobulin A; DGP: deamidated gliadin peptide; IgG: immunoglobul
antibody; HLA: human leukocyte antigen.

* Testing for celiac disease should be performed in adults with suggestive gastrointestinal or extraintestinal
celiac disease. Testing for celiac disease should ideally be performed while patients are on a gluten containi

¶ The histologic severity of intestinal lesions in celiac disease are graded using the Marsh-Oberhuber classif
are consistent with a diagnosis of celiac disease in individuals with positive celiac-specific serology. Marsh 1
0 is normal. Refer to UpToDate content on the diagnosis of celiac disease.

Δ The intestinal biopsy should be reviewed by a pathologist familiar with celiac disease to look for subtle abr
disease.

◇ Absence of alleles encoding DQ2 or DQ8 excludes celiac disease.

§ Other conditions associated with lymphocytic duodenosis include *Helicobacter pylori* infection, medications
antiinflammatory drugs), small bowel bacterial overgrowth, and systemic autoimmune disorders.

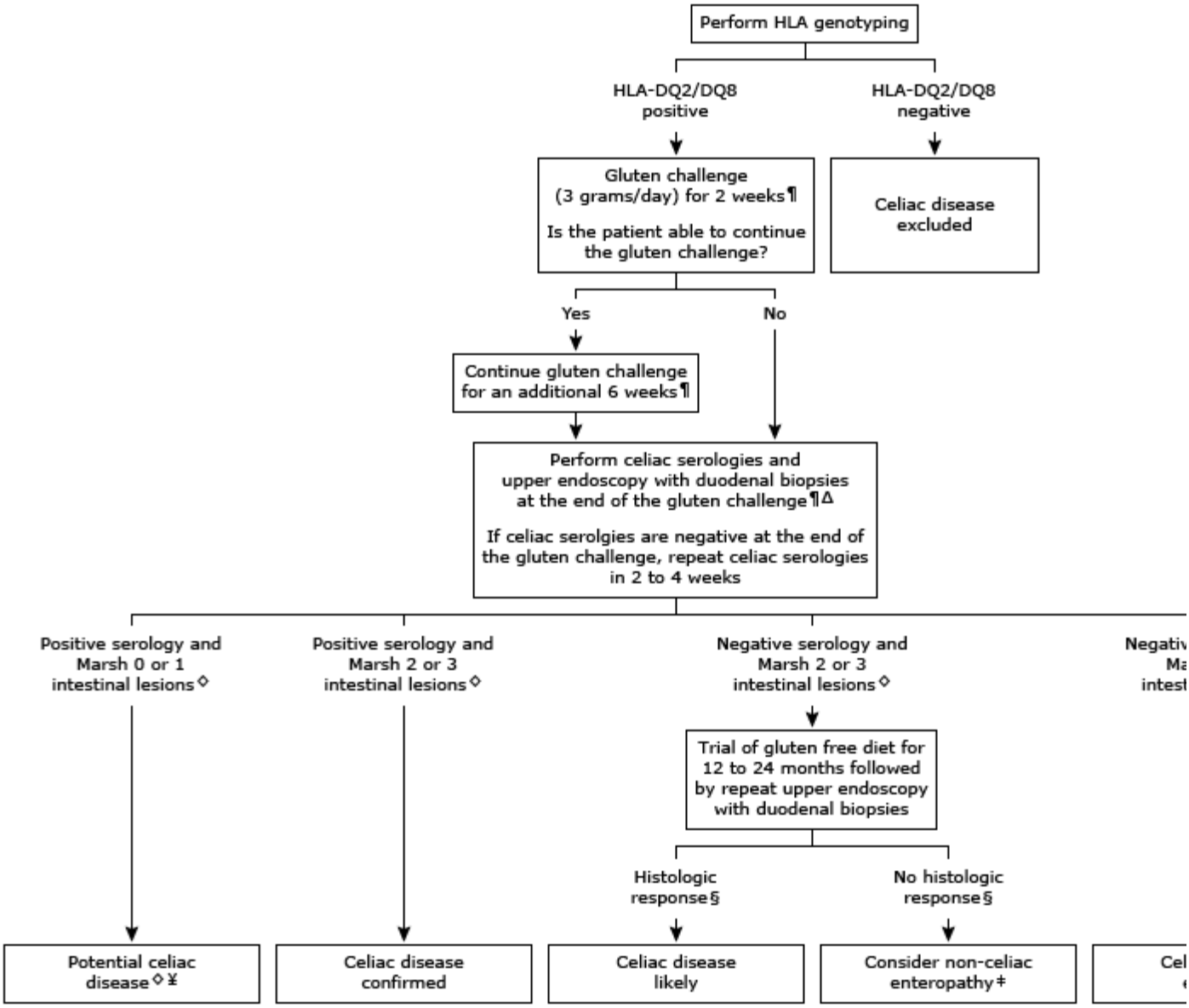
¥ Individuals with positive celiac-specific serology but Marsh 0 or 1 intestinal lesions on duodenal biopsy hav
disease. Individuals with potential celiac disease should be evaluated and monitored further depending upo
circumstances. Symptomatic patients with potential celiac disease are likely to benefit from treatment with a
Asymptomatic patients can remain on a normal diet unless clinical features of celiac disease develop.

‡ There are several causes of non-celiac enteropathy (villous atrophy in duodenum). Potential causes include
bacterial overgrowth, and common variable immunodeficiency. For a more comprehensive list of causes, ref
on diagnosis of celiac disease.

† An improvement in histology (with or without complete resolution) on a gluten free diet in patients with vi
supports a diagnosis of celiac disease.

Graphic 119163 Version 1.0

Diagnostic approach for suspected celiac disease in an adult patient on gluten negative baseline serologies*



This algorithm is intended for use in conjunction with additional UpToDate content on celiac disease. Refer t UpToDate topic on diagnosis of celiac disease in adults for additional details of diagnostic testing.

HLA: human leukocyte antigen; tTG: tissue transglutaminase; IgA: immunoglobulin A; IgG: immunoglobulin deamidated gliadin peptide.

* Testing for celiac disease should be performed in adults with suggestive gastrointestinal or extraintestinal signs/symptoms of celiac disease.

¶ A two-week gluten challenge may yield false-negative results in 10% of patients. The added diagnostic ser extending the challenge to a total of eight weeks is unknown.

Δ tTG-IgA antibody is the single preferred test for detection of celiac disease in adults. In addition, we concu measure total IgA levels. In patients with IgA deficiency, we perform IgG based testing with DGP-IgG.

◇ The histologic severity of intestinal lesions in celiac disease are graded using the Marsh-Oberhuber classif Marsh 2 and 3 are consistent with a diagnosis of celiac disease in individuals with positive celiac-specific ser 1 is equivocal and Marsh 0 is normal. Refer to UpToDate content on diagnosis of celiac disease.

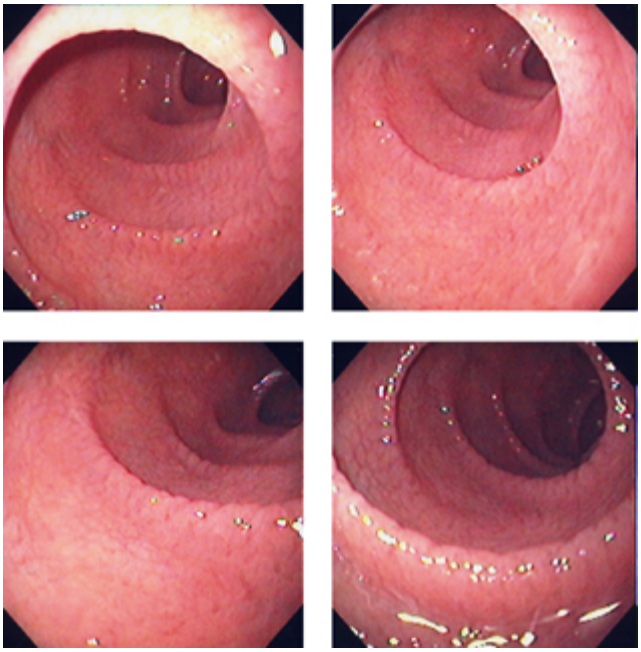
§ An improvement in histology, even in the absence of complete histologic resolution, is supportive of the di celiac disease.

¥ Individuals with positive celiac-specific serology but Marsh 0 or 1 intestinal lesions on duodenal biopsy hav celiac disease. Individuals with potential celiac disease should be evaluated and monitored further dependir clinical circumstances. Symptomatic patients with potential celiac disease are likely to benefit from treatmer gluten free diet.

‡ There are several causes of non-celiac enteropathy (villous atrophy in duodenum). Potential causes include small intestinal bacterial overgrowth, and common variable immunodeficiency. For a more comprehensive l refer to UpToDate content on diagnosis of celiac disease.

Graphic 119164 Version 1.0

Celiac disease

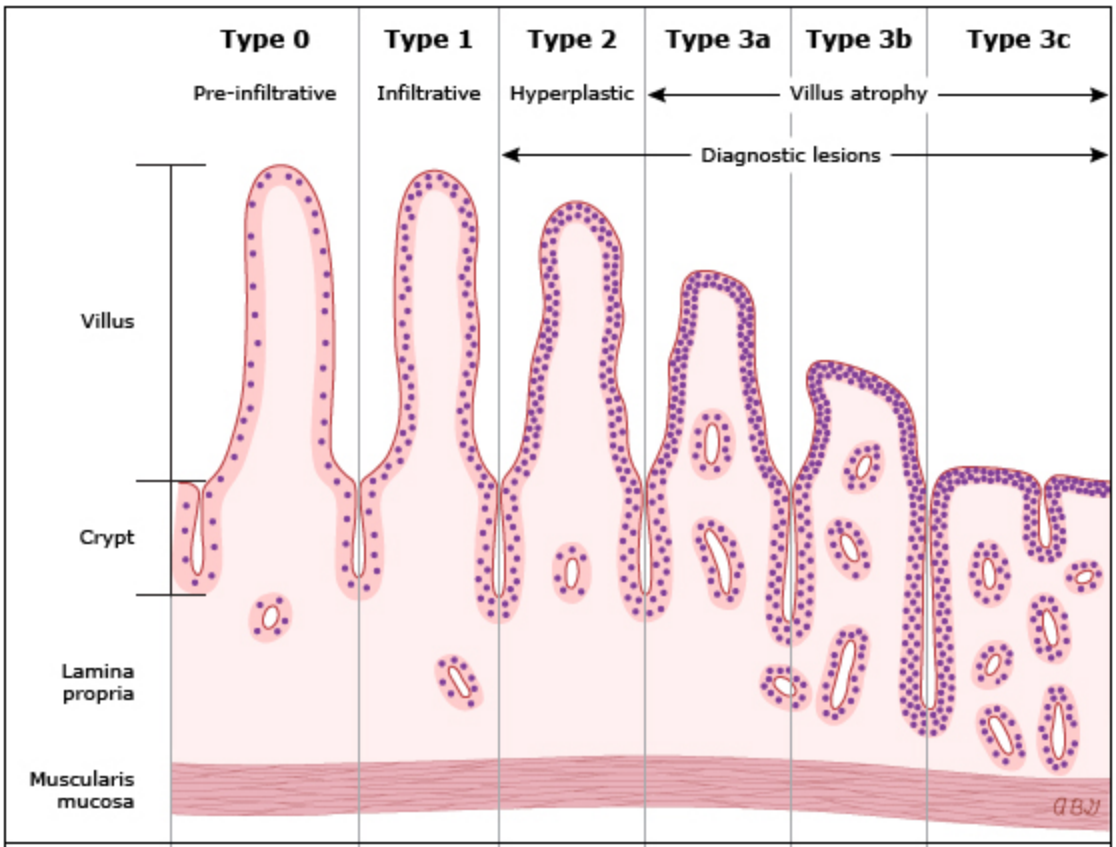


Scalloped duodenal folds seen on endoscopy in a patient with celiac disease.

Courtesy of Eric D Libby, MD.

Graphic 65969 Version 1.0

Intestinal lesions in celiac disease



	Type 0	Type 1	Type 2	Type 3a	Type 3b	Type 3c
Villus	Normal	Normal	Normal	Mild atrophy	Moderate atrophy	Severe atrophy
Crypt	Normal	Normal	Hyperplasia	Hyperplasia	Hyperplasia	Hyperplasia
Ratio, villus height: crypt depth	3:1	3:1	<3:1	<2:1	1:1	<1:1
IEL/ 100 EC	<40	>40	>40	>40	>40	>40

Schematic drawing of the characteristic histologic changes seen in celiac disease as described by Marsh. The lesions range in severity from only increased numbers of intraepithelial lymphocytes in the early stages (Type I) to elongation of the crypts (Type II) and progressive villus atrophy (Type 3a to 3c).

IEL: intraepithelial lymphocytes; EC: epithelial cells (in villus).

Modified from: Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102:330.

Graphic 60343 Version 6.0

Histologic criteria used in celiac disease

Marsh	IELs Marsh/Corazza	Crypts	Villi	Corazza
Type 0	<40	Normal	Normal	
Type 1	>40/>25	Normal	Normal	Grade A
Type 2	>40/>25	Hypertrophic	Normal	
Type 3	>40/>25	Hypertrophic	Partial to subtotal	Grade B1
	>40/>25	Hypertrophic	Total	Grade B2
Type 4	<40	Normal	Total	

IELs: intraepithelial lymphocytes (per 100 enterocytes).

References:

1. *Corazza GR, Villanacci V, Zambelli C, et al. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol 2007; 5:838.*
2. *Marsh MN. Gluten, major histocompatibility complex, and the small intestine: A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102:330.*

Graphic 140661 Version 1.0

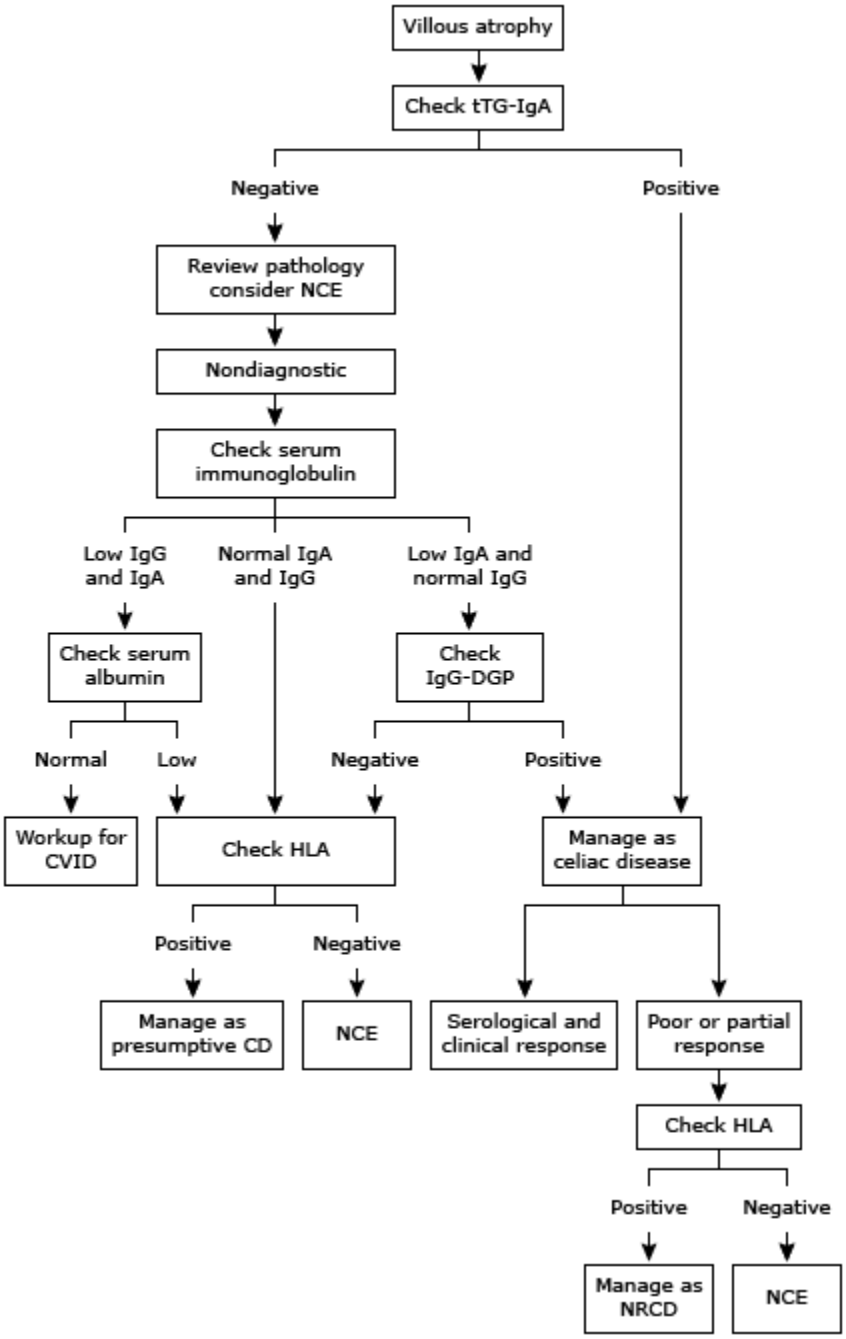
Causes of small intestinal villous atrophy other than celiac disease

Small intestinal bacterial overgrowth
Crohn disease
Cow's milk or soy protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Intestinal lymphoma
Peptic duodenitis
Post-gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)
Medications (eg, olmesartan, NSAIDs)
Whipple disease
Malnutrition
Intestinal tuberculosis
Graft-versus-host disease

AIDS: acquired immunodeficiency syndrome; NSAIDs: nonsteroidal anti-inflammatory drugs.

Graphic 60030 Version 9.0

Diagnostic algorithm for small intestinal villous atrophy



NCE: non-celiac enteropathy; tTG: tissue transglutaminase antibody; IgA: immunoglobulin A; IgG: immunoglobulin G; DGP: deamidated gliadin peptide; HLA: human leukocyte antigen; NRCD: nonresponsive celiac disease; CVID: common variable immunodeficiency; CD: celiac disease.

From: Pallav K, Leffler DA, Tariq S, et al. Noncoeliac enteropathy: the differential diagnosis of villous atrophy in contemporary clinical practice. Aliment Pharmacol

Ther 2012; 35:380. Copyright © 2012. Reproduced with permission of John Wiley & Sons, Inc.

Graphic 61019 Version 2.0

Contributor Disclosures

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