CELIAC DISEASE: CLINICAL SPECTRUM AND MANAGEMENT

Advances in Diagnosis and Management of Celiac Disease

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Celiac disease is an autoimmune disorder that is induced by dietary gluten in genetically predisposed individuals. It has a prevalence of approximately 1% in many populations worldwide. New diagnoses have increased substantially, owing to increased awareness, better diagnostic tools, and probable real increases in incidence. The breadth of recognized clinical presentations continues to expand, making the disorder highly relevant to all physicians. Newer diagnostic tools, including serologic tests for antibodies against tissue transglutaminase and deamidated gliadin peptide, greatly facilitate diagnosis. Tests for celiac-permissive HLA-DQ2 and HLA-DQ8 molecules are useful in defined clinical situations. Celiac disease is diagnosed by histopathologic examination of duodenal biopsy specimens. However, according to recent controversial guidelines, a diagnosis can be made without a biopsy in certain circumstances, especially in children. Symptoms, mortality, and risk for malignancy each can be reduced by adherence to a gluten-free diet. This treatment is a challenge, however, because the diet is expensive, socially isolating, and not always effective in controlling symptoms or intestinal damage. Hence, there is increasing interest in developing nondietary therapies.

Celiac disease is defined as a chronic small-intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.[1] It is a common autoimmune disorder, affecting approximately 1% of the population in many parts of the world.[2,3] The only treatment is a strict, lifelong, gluten-free diet (GFD). Although some symptoms are overt and easy to recognize, others may be subtle or only become manifest as long-term complications of untreated disease. Many new diagnoses now are made through screening individuals considered to be at risk because of a family history of celiac disease, type 1 diabetes mellitus, autoimmune thyroid or liver disease, or Down syndrome. Many of these people are asymptomatic (or have subclinical symptoms). The common feature among these at-risk groups is that they carry the alleles encoding HLA-DQ2 or HLA-DQ8. Risk for childhood celiac disease does not appear to be influenced by breast-feeding or the timing of dietary gluten introduction.[4,5]

We review the clinical features of celiac disease, which patients to test, and how to establish a diagnosis. We also discuss treatment and monitoring of patients who have been diagnosed with celiac disease, the challenges of a GFD, and the management of nonresponsive or refractory celiac disease.

Clinical Features

The clinical manifestations of celiac disease are classic (signs and symptoms of malabsorption including diarrhea, steatorrhea, weight loss, or growth failure), nonclassic and symptomatic (with evident gastrointestinal and/or extra-intestinal symptoms), or asymptomatic.[1] Celiac disease has diverse manifestations and associations, so it is important for all physicians to be aware of its many potential clinical presentations. With greater awareness more patients are being diagnosed—particularly with nonclassic or asymptomatic disease.[6,7] As is the case for many other autoimmune disorders, the true population incidence also appears to have increased (in one study up from 0.2% at 50 years ago to 0.9% currently).[6–8] Table 1 presents information about individuals who may be at increased risk for celiac disease and for whom the threshold for testing is, accordingly, lower.

Table 1. Patients Who Might Require Testing for Celiac Disease

Symptoms and signs		Associated conditions
Gastrointestinal	Extraintestinal	
Chronic diarrhea	Iron-deficiency anemia	Family history of celiac disease
Chronic abdominal pain	Other deficiency states (vitamin B12, vitamin D, folate, zinc, vitamin B6)	Type 1 diabetes
Malabsorption		Autoimmune thyroid disease
Bloating	Fatigue	Autoimmune liver disease
Erratic bowel habit (similar to IBS)	Recurrent aphthous stomatitis	Selective IgA deficiency
Constipation (more commonly in children)	Increased hepatic transaminase levels	Sjögren syndrome
Failure to thrive/weight loss	Short stature	Down syndrome
Anorexia	Delayed puberty/menarche	Turner syndrome
Vomiting	Amenorrhea	Williams syndrome
GERD	Early menopause	
	Dermatitis herpetiformis	
	Osteopenia/osteoporosis	
	Dental enamel hypoplasia	
	Peripheral neuropathy	
	Hyposplenism	

GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome.

Gastrointestinal Features

The classic presentation of celiac disease is more common in young children, consisting primarily of gastrointestinal symptoms with malabsorption (chronic diarrhea, abdominal pain, distension, and failure to thrive or weight loss). Some patients also present with constipation. In older teenagers and adults, the presentation of celiac disease often is more subtle and can be mistaken for irritable bowel syndrome. Some patients lack any evident gastrointestinal symptoms and instead present with nutritional deficiencies (most commonly iron deficiency) or extraintestinal symptoms, or are asymptomatic.

Extraintestinal Features

Celiac disease has many extraintestinal manifestations, including delayed puberty and short stature. Fatigue and iron-deficiency anemia are common. Dermatitis herpetiformis, characterized by an often symmetric, intensely itchy, blistering rash, likely is under-recognized. Frequent oral aphthous ulcers and dental enamel hypoplasia can occur, as well as low bone mineral density and osteoporosis. Celiac hepatitis develops in as many as 9% of patients evaluated for cryptogenic increased transaminase levels, and can take 6–12 months to resolve when patients are placed on a GFD. Celiac hepatitis usually follows a benign course, but there have been reports that liver failure was reversed with a GFD. Patients may report fibromyalgia or arthralgia, which might not always respond to a GFD.[9] Young adults with celiac disease also might be at increased risk of early atherosclerosis.[10] In addition, microvascular complications can accelerate in patients who also have type 1 diabetes.[11] There have been reports of cardiomyopathy and carditis in patients with celiac disease, but the evidence for this association is weak.

Infertility and miscarriages have been reported to be a complication of untreated celiac disease; a recent meta-analyses of observational studies supported this association.[12,13] However, another report found that women with celiac disease did not have an overall higher risk of fertility problems than the general population.[14]

Peripheral neuropathy, seizure disorders, ataxia, and impaired cognitive function most often have been described in adults with celiac disease, at a lower incidence than in children.[15,16] Peripheral neuropathy may precede the diagnosis of celiac disease and was reported by 39% of patients, based on responses to a validated questionnaire.[17] Seizures (sometimes associated with bilateral occipital calcifications), headaches, learning disorders, developmental delays, hypotonia, and attention deficit hyperactivity disorder also are observed more frequently in children with celiac disease, compared with controls.[18] Up to one third of adult patients were found to have a history of psychiatric disorders such as depression or personality changes, and, less commonly, psychosis.[19]

Little is understood about the mechanisms by which celiac disease might lead to neurologic disorders. Chronic neurologic changes do not seem to disappear on a GFD. However, a patient's response to a GFD could be more substantial if they are diagnosed early—especially patients with gluten-associated ataxia or those who test positive for antigliadin antibodies with neurologic symptoms or abnormal findings from brain imaging analyses.[20] It is important to note that many of these patients with neurologic symptoms have not met the diagnostic criteria for celiac disease.

Nutritional Deficiencies

Patients with celiac disease frequently have nutritional deficiencies—most commonly in iron, vitamin D folate, vitamin B12, vitamin B6, and zinc.[21] Iron deficiency has been reported in up to half of newly diagnosed adults, and in itself is an indication for screening.[22] A GFD usually leads to

recovery from iron-deficiency anemia within 6–12 months, whereas zinc deficiency improves within weeks.[23,24] Some patients with folate or vitamin B12 deficiency develop macrocytic anemia, which can be hard to detect in patients who also have an iron deficiency. Neurologic disorders have been reported in association with malabsorption of vitamin B12, folate, copper, and vitamin D.[25]

Associated Autoimmune and Other Conditions

Autoimmune thyroid disease and type 1 diabetes mellitus are the most common autoimmune diseases that occur with celiac disease. Celiac disease is observed in approximately 10% of patients with type 1 diabetes. On the other hand, people with celiac disease have a 2.4-fold increase in the risk for type 1 diabetes before they are 20 years old.[26] Celiac disease is observed in approximately 7% of patients with autoimmune thyroid disorders. Autoimmune hypothyroidism, the thyroid disorder associated most frequently with celiac disease, is more than 4-fold more common in people with celiac disease than without.[27]

Celiac disease, type 1 diabetes mellitus, and autoimmune thyroid disease all are associated with HLA risk alleles (namely *HLA*-DQ2 and/or HLA-DQ8). Associations with Sjögren syndrome, Addison's disease, parathyroid disorders, and growth hormone deficiency also have been reported. Celiac disease also has a higher prevalence among patients with autoimmune hepatitis or primary biliary cirrhosis, with weaker data for primary sclerosing cholangitis.[28] There is only weak evidence that a GFD affects the risk for other autoimmune conditions in patients with celiac disease.

Screening for Silent Disease

A substantial proportion of patients with autoimmunity and enteropathy are asymptomatic, identified only because of genetic risk or a celiac-associated disease. There is controversy regarding whether patients without symptoms or signs should be screened and treated. The rationale for proactive testing and treatment is to prevent long-term complications of untreated celiac disease. Conversely, diagnosis and subsequent adherence to a GFD carry substantial economic and psychosocial costs. We need more comprehensive and reliable data on the feasibility and cost:benefit ratio of screening at-risk, symptomless populations for celiac disease, to guide rational development of screening programs.[29]

Diagnosis

The rate of diagnosis of celiac disease is increasing worldwide, in part owing to a greater appreciation of the variability in clinical presentation. Until the 1950s, celiac disease was diagnosed based on clinical observations focused on malabsorptive features. The development of the peroral intestinal biopsy (1955−1956) produced a substantial change in the diagnostic paradigm. Since that time, gluten-dependent enteropathy, based on histologic assessment of intestinal mucosa, has been the standard for diagnosis.[30] In the 1980s, sensitive and specific serologic tests were developed for celiac disease. These now are used as the first step when there is a suspicion of celiac disease to identify patients who should undergo intestinal biopsy analysis (Figure 1).

Histologic Features

Endoscopy allows identification of gross mucosal changes that are markers of enteropathy, sometimes even in patients evaluated for reasons other than suspicion of celiac disease. Although cohort studies have suggested that observation of endoscopic markers such as scalloping is a reliable predictor of enteropathy, other studies have shown less satisfactory results.[31] Chromoendoscopy using indigo carmine or methylene blue and water immersion have been shown to enhance endoscopic markers, allowing for visualization of villi and identification of patchy atrophic areas.[32]

Diagnostic intestinal biopsies should be performed in patients who consume gluten. Mucosal injury generally is more pronounced in the proximal intestine, and mild or absent distally. It is important to note that the location, number, and quality (size and orientation) of biopsy specimens can affect diagnostic yield. As many as 70% of cases have patchy mucosal damage—this should be considered by endoscopists and pathologists.[33] Biopsy samples taken from the duodenum proximal to the ampulla of Vater can have artifacts that can be interpreted falsely as flat mucosa. However, recent studies have estimated that as many as 13% of patients have the characteristic enteropathy, only localized to the duodenal bulb.[34] To maximize diagnostic accuracy, 5 or more duodenal biopsy specimens should be collected, with duodenal bulb samples labeled and submitted separately.[35]

Under light microscopy, the most characteristic histology findings are blunted or atrophic villi, crypt hyperplasia, an increase in the number of intraepithelial lymphocytes (IELs), especially at the villus tip, infiltration of the lamina propria by mononuclear cells, and structural abnormalities in epithelial cells. Since 2000, studies from Europe and North and South America have reported that 13%–46% of cases are misdiagnosed by histology analysis (overdiagnosis and under-diagnosis). For this reason, in equivocal cases, especially when there is a discrepancy between histology and serology results, re-evaluation by a gastrointestinal pathologist with expertise in celiac disease is recommended.

Histologic changes, including increased numbers of IELs and villous atrophy, are not specific for celiac disease; they also are associated with disorders such as giardia infection, common variable immune deficiency, Crohn's disease, and *Helicobacter pylori* infection. Patients with increases in only IELs and positive results from serologic tests are considered potential candidates for celiac disease. However, most patients with only increases in intraepithelial lymphocytes do not have celiac disease.[36,37]

Serologic Features

In the 1980s, a new era in celiac disease research began with the identification of specific antibodies circulating in plasma of untreated patients. IgA and IgG against gliadin,
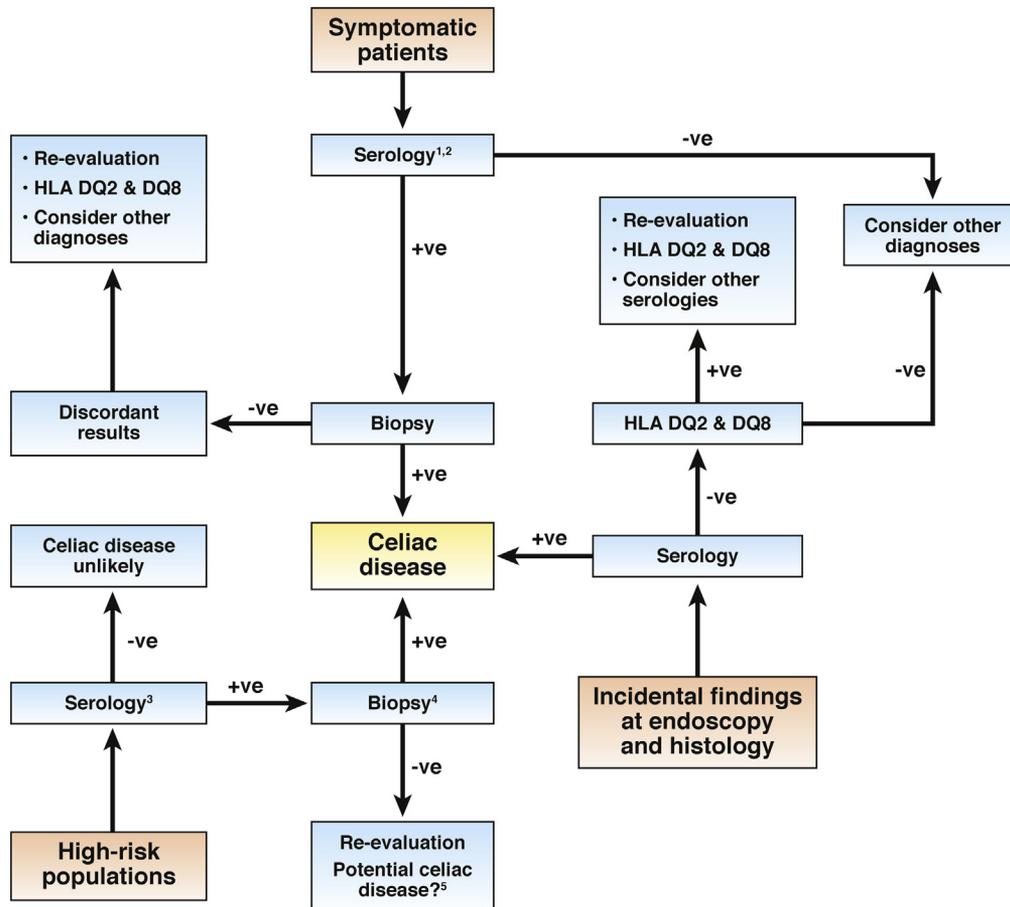
Figure 1. Approach to celiac disease diagnosis. Serology is usually the first step in the diagnosis or exclusion of celiac disease for symptomatic patients or for screening. Biopsy is important for definitive diagnosis. HLA testing is valuable in selected patients. (1) Serologic markers of celiac disease: IgA against tTG, endomysial antibody (IgA), IgA or IgG against deamidated gliadin peptide (DGP), IgG against tTG. (2) A small number of patients with celiac disease have negative results from serologic tests. Biopsies therefore should be performed if the clinical suspicion for celiac disease is high, regardless of these results. (3) Tests for HLA-DQ2 and HLA-DQ8 can be performed. Negative results mean that celiac disease can be excluded permanently. However, many individuals without celiac disease are carriers of these alleles—especially those with a family history of celiac disease or related autoimmune disorder. (4) For symptomless patients, especially children, with mild increases in serologic markers of disease, biopsy analysis can be delayed, pending results from serologic tests performed at intervals of 3–6 months. (5) Potential celiac disease has been defined as a normal small-intestinal mucosa with an increased risk for celiac disease based on results from serologic analysis.[1]

which bind native gliadin, were associated with the disease but identified patients with celiac disease with low levels of sensitivity and specificity, making them obsolete.[3] Subsequently, IgA against the endomysium (EmA) of monkey esophagus was found to be a highly sensitive and specific marker of celiac disease.[38] Although a test for anti-EmA detects celiac disease with lower levels of sensitivity than other modern serologic assays, the antibody is an extremely specific marker of mucosal damage in untreated patients. Further research identified the ubiquitous enzyme tissue transglutaminase (tTG) as the autoantigen that reacts with EmA, leading to the development of enzyme-linked immunosorbent assays that detect antibodies against tTG.[39]

A new generation of IgA- and/or IgG-based antigliadin antibody assays, which use synthetic deamidated gliadin peptides (DGP) as substrates, perform almost as well as the anti-tTG test.[40] Specifically, IgG–DGP tests are the most accurate available assays for patients with selective IgA

deficiency. A study in infants showed that high concentrations of DGP antibodies correlated with the severity of intestinal damage. Tests for DGP antibodies more accurately detect celiac disease in children than tests for anti-tTG, and might be used to evaluate dietary adherence.[41]

Recently, easy-to-use, on-site tests for anti-tTG were introduced for rapid identification of disease candidates, using blood samples collected from a fingertip.[42] These tests appear to be reasonably reliable and well accepted by patients. However, results do not obviate the need for subsequent testing by conventional serology and duodenal biopsy.

Thus, a number of valuable serologic markers now are available, and used routinely for diagnosis and monitoring. However, it is important to note that 2%–3% of people with celiac disease have negative results in serologic tests, have low antibody titers, or titers that fluctuate between positive and negative levels with time. Serologic tests also vary in

quality and some have not been well standardized, which are obstacles in clinical practice. A recent multinational study evaluated the diagnostic performance of IgA–tTG tests in 150 serum samples, blindly assessed in 15 different clinical laboratories, and found a disappointing range of sensitivities (from 62% to 92%).[43] Notwithstanding these limitations, the simultaneous or consecutive determination of IgA–tTG and/or IgG–DGP may be used as strong predictors of celiac disease in most settings.

Capsule Endoscopy

Capsule endoscopy is an alternative method for the evaluation of celiac disease and identification of complications. Markers of celiac disease seem to be identified more accurately by capsule compared with conventional endoscopy.[44] Capsule endoscopy also is able to recognize the patchy distribution of damage and the longitudinal extension of the mucosal compromise. The main limitation of the test is the lack of ability to perform a biopsy. Currently, use of capsule endoscopy for the diagnosis of celiac disease is limited to patients who refuse upper endoscopy, to equivocal cases, and to evaluate patients with nonresponsive disease (to investigate complications such as ulcerative jejunitis or neoplasia).

Genetic Testing

The class II HLA types DQ2 and/or DQ8 are found in almost all patients with celiac disease, but also in 30%–40% of the Western Caucasian population; only 3% of individuals with these haplotypes develop celiac disease.[45] HLA-type analysis has a high negative predictive value (>99%). This is valuable for analysis of subjects with an equivocal diagnosis (eg, seronegative for anti-tTG with enteropathy) or those already on GFDs. Genetic analysis also can be used to rule out celiac disease, and the need for further testing, in individuals at high risk because of family history. Although only one third of family members will be spared repeated testing, particular combinations (eg, homozygosity for DQ2) increase the risk for celiac disease (by up to 40%).[46]

Patients Already on a GFD Without Testing

Frequently in clinical practice, patients present for evaluation of possible celiac disease after a variable time on a GFD. The most practical approach to diagnosis begins with serologic tests (for anti-tTG and/or DGP) and HLA typing. Positive results from serologic tests support a diagnosis of celiac disease and indicate the need for duodenal biopsy analysis. However, negative results from serologic tests are of limited value. Conversely, celiac disease is excluded for patients who are negative for HLA-DQ2 or HLA-DQ8. If serologic (and biopsy) analyses produce negative results but individuals are carriers of HLA-DQ2 or HLA-DQ8, then gluten challenge is appropriate. Recent studies have helped to re-define the timing, doses, and duration of the gluten challenge.[47,48] Interestingly, these studies have shown that mucosal damage can be detected in most patients after as few as 2 weeks of challenge and before seroconversion. Furthermore, a lower level of gliadin (2–3 g/day, equivalent to 1–2 slices of bread) is better tolerated yet still effective for diagnosis.

Is Diagnosis Possible Without Intestinal Biopsy?

Small intestinal biopsy histology has long been considered an essential step for the diagnosis of celiac disease. New assays for anti-tTG and DGP substantially have improved the diagnostic accuracy of serologic analysis. Researchers therefore have explored the possibility of celiac disease diagnosis without endoscopy or biopsy analyses. Most of these studies, based on a retrospective analysis of case–control cohorts, found this strategy to be acceptable for symptomatic patients. More recently, at least 2 prospective studies explored the value of specific serologic analyses of populations with high and low pretest probability, in which diagnosis of the disorder was based on histologic findings. The studies concluded that the concomitant positive results of 2 or 3 specific immunoassay tests are highly predictive of celiac atrophy (Marsh III damage).[49,50]

A consensus guideline produced by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition recently proposed a triple test strategy to avoid intestinal biopsies for children.[51] Candidates for diagnosis without biopsy should be symptomatic, have an IgA tTG level greater than 10-fold above the upper limit of normal, test positive for anti-EmA in a separate blood sample, and have the HLA-DQ2 haplotype.

Since 2012, 4 guidelines for celiac disease diagnosis have been proposed and published under the sponsorship of relevant institutions.[45,51–53] Table 2 summarizes some of the relevant comparative characteristics of these guidelines. All guidelines emphasize the combined use of biopsy and serologic analyses for diagnosis. However, there are some discrepancies in the serologic tests recommended and the use of HLA type analyses. Furthermore, a recent World Gastroenterological Association guideline recommended a no-biopsy algorithm for countries with limited health care resources.[52]

Treatment

The only available therapy for celiac disease is the GFD, which usually reduces clinical symptoms and morbidity and increases nutritional parameters including body weight and bone density.[54–57] However, studies have reported low patient satisfaction, high costs, and continued symptoms and histologic signs of intestinal damage, indicating that the GFD is not always optimal.[58–63] Nonetheless, the concept that the GFD is an ideal therapy has contributed to the lack of effective alternative and adjunct treatments.

For the GFD to be effective, all wheat (gluten), rye (secalin), and barley (hoerdin) products must be strictly avoided. As little as 50 mg of gluten, an amount present in a few crumbs of bread or a small piece of pasta, can increase enteropathy.[64] In addition to obvious sources of gluten such as bread and pasta, many products are contaminated with gluten during harvesting, processing, and packaging.[65,66] A good example is oats, which do not contain gluten, but often

Table 2. Guidelines for Diagnosis of Celiac Disease

Guideline	Guideline design (population)	Intestinal biopsy	Recommended blood tests	Comments and remarks	References
ESPGHAN	Expert consensus (children)	Not mandatory	Anti-tTG, anti-EmA, total IgA, and tests for HLA-DQ2 and HLA-DQ8	Allows for diagnosis without biopsy under certain conditions (see text)	51
WGO	Expert consensus (adults)	Not mandatory	Anti-tTG, anti-EmA, and anti-DGP	Uses a diagnostic cascade based on available local resources. Allows for diagnosis without biopsy under certain conditions	52
ACG	Expert consensus evidence-based (children and adults)	Mandatory	Anti-tTG and anti-DGP	Recommends IgG DGP antibodies in children <2 y	53
BSG	Expert consensus evidence-based (adults)	Mandatory	Anti-tTG, anti-EmA, and anti-DGP	Holds to the position that serology cannot replace biopsy	54

ACG, American College of Gastroenterology; BSG, British Society of Gastroenterology; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition; WGO, World Gastroenterological Organization.

are contaminated heavily with wheat or barley.[67] Certified gluten-free oats are well tolerated by most people with celiac disease and are now an accepted part of the GFD.[68] Because of the combination of contamination of gluten-free foods and accidental and intentional gluten exposures, it is not possible for most people to remain totally gluten free.[69,70] The best that can be accomplished is a diet that is highly gluten-restricted. Although mucosal healing occurs routinely in pediatric patients, it is much less common in adults with celiac disease, for unknown reasons.[71] Most individuals still have intermittent symptoms related to intermittent or ongoing gluten exposure.[60,72] The negative social effects of a highly restricted diet, the constant vigilance required to avoid gluten, and the high frequency of inadvertent exposure are major determinants of the low patient satisfaction and large burden of the GFD.

In addition to the extra costs and difficulties of the GFD, it also can lead to nutritional deficiencies that cause new or continued symptoms.[73] The most common of these is constipation as a result of the lack of fiber in many gluten-free foods. Other common nutritional consequences include a lack of fortification with B vitamins and a high content of fat and simple carbohydrates, compared with non–gluten-free foods, often leading to unwanted weight gain.[74] At the time of diagnosis, patients should receive dietary counseling, ideally by a dietician with expertise in celiac disease; they can significantly improve the nutritional quality of a patient's GFD, and guide their use of gluten-free whole grains.

Nondietary Therapy

Nondietary therapy, with local or systemic corticosteroids or immune modulators, largely is confined to the treatment of refractory celiac disease. However, the limitations of the GFD and the realization that celiac disease is common in many parts of the world have prompted a search for therapies to augment the GFD.[58–63,75] Our understanding of the pathogenesis of celiac disease is far more detailed than for most other autoimmune disorders, so a multitude of therapeutic targets are available.

Strategies include developing reagents to degrade or alter dietary gluten, prevent gluten peptides from crossing the epithelial barrier, inhibit tTG-induced potentiation of gliadin peptides, or block gliadin binding to HLA-DQ2. Immune-based strategies involve preventing T-cell activation or innate and adaptive immune responses (such as by inducing tolerance to gluten).[75] However, only 2 agents are in late phase 2 clinical trials. ALV003 (2 recombinant, orally administered, gluten-specific proteases) reduced the small intestinal mucosal injury caused by 6 weeks of gluten challenge.[76] Larazotide acetate, an oral peptide that modulates intestinal tight junctions, reduced symptoms in patients in response to gluten challenge.[77] Additional studies are underway to determine if these agents are safe and effective for patients with persistent symptoms and mucosal injury despite a continued GFD. These or other effective therapies could reduce the burden of GFD by decreasing the effects of inadvertent gluten exposure.

Monitoring

Celiac disease is a lifelong inflammatory condition that affects multiple organ systems, so patients should be followed up routinely. There are no differences in recommendations for monitoring symptomatic vs asymptomatic patients. Based on expert consensus, at the time of diagnosis, patients should be evaluated for common coexisting autoimmune conditions, such as thyroid and liver diseases, as well as deficiencies in iron, vitamin D, and vitamin B12. It also is important to consider zinc, folate, and other deficiencies, based on regional trends and patient symptoms. There should be a low threshold to test patients for other autoimmune disorders based on their symptoms or signs.

There is general agreement among guidelines (Tables 2 and 3) that patients should be examined at least twice in

Table 3. Monitoring in Celiac Disease

Test	Interval	Comments
Clinical evaluation	Annually or if recurrent symptoms	
Serology	Every 3–6 months until normal, then every 1–2 years	Normal titers are insensitive for ongoing gluten exposure or enteropathy
		Persistently increased or increasing titers indicate significant gluten exposure
Nutritional evaluation	Every 3–6 months until normal, then every 1–2 years	Common deficiencies in iron, 25-OH vitamin D, vitamin B12, folate, and zinc
		Monitor for weight gain, low fiber intake, and constipation
Bone density	Once within first 2 years	Significant increases in bone density often are observed in the first year after diagnosis, many experts therefore advocate testing for the first time after 1 year on the GFD
Liver transaminase levels	At diagnosis, then every 1–2 years	Increased levels of AST and ALT are a common manifestation of celiac disease
		Persistent increases or increasing levels indicate a comorbid liver disorder
Thyroid function tests	At diagnosis, then every 1–2 years	Autoimmune thyroid disease is the most common comorbid autoimmune disorder, found in approximately 15%–20% of adults with celiac disease
Duodenal biopsy	Consider 1–2 years after diagnosis	Repeated biopsies, to evaluate healing, frequently are performed; however, it is not clear if this is necessary for patients with well-treated, clinically responsive celiac disease
Cancer screening	As for general population	Although rates of certain cancers are increased, these are not sufficiently common to warrant disease-specific screening

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

their first year after diagnosis to monitor symptoms, dietary adherence, nutrition, body mass index, and serologic features.[52,53,78] Although it takes varying amounts of time for serologic features of celiac disease to normalize, a significant decrease over the first year is a sign of GFD adherence; patients whose serologic features do not improve should be re-evaluated for continued gluten exposure. Low bone mineral density is one of the more common extraintestinal manifestations of celiac disease, so dual-energy x-ray absorptiometry (DXA) evaluation generally is recommended in the first year after diagnosis.[53]

One of the more controversial aspects of celiac disease monitoring is the role and timing of repeated endoscopic biopsy analyses. Repeating biopsy analysis 6 months to 2 years after diagnosis allows physicians to assess a patient's response to therapy, and GFD adherence for patients with little mucosal healing. However, intestinal healing often is slow, incomplete, and age dependent.[71] Furthermore, persistent enteropathy does not always predict long-term outcome, and histologic abnormalities can have other causes.[59,79] However, there is no doubt that an intestinal biopsy is an important component in the evaluation of patients with persistent symptoms (Figure 2).

Nonresponsive Celiac Disease

Nonresponsive celiac disease (NRCD) can be defined as persistent or recurrent symptoms, signs, or laboratory findings consistent with active celiac disease, despite at least 12 months of treatment with the GFD.[1,60,72,80] A substantial proportion of patients with celiac disease develop NRCD (7%–30% in different series of studies). NRCD has multiple and diverse etiologies; a thorough and systematic evaluation is needed to determine the correct diagnosis and management plan for each patient (Figure 2). The first and essential step is to review the initial diagnosis of celiac disease carefully because patients with other disorders will not respond to GFDs. HLA typing may be required, especially for patients with consistently negative serologic test results for celiac disease.

The most common causes of NRCD are related to diet—the most common of all is continued or intermittent, purposeful or inadvertent, gluten ingestion.[80] Patients' diets therefore should be reviewed carefully, ideally with a specialized celiac dietician. Persistent increases in serum levels of IgA–tTG, or other markers, is often an indicator of gluten exposure. Conversely, normal results from serologic tests do not exclude continued gluten exposure because the tests are not sensitive enough to detect low levels of gluten ingestion. Other dietary factors also can contribute to NRCD, including fermentable, oligosaccharides, disaccharides, monosaccharides, and plyols, so avoidance might be tested. Small intestinal bacterial overgrowth can complicate celiac disease and should be considered, especially for patients with bloating, excess gas, or diarrhea.

Once dietary causes of NRCD have been excluded, a small-bowel biopsy should be performed. For patients with diarrhea, colonic biopsy specimens should be evaluated for microscopic colitis, which develops in 4% of patients with celiac disease.[81] Improvements in histologic features from

baseline indicate that patients' persistent symptoms and signs could have alternative causes. Possibilities in patients with normal (Marsh 0) or near-normal (Marsh I) histology findings include irritable bowel syndrome, microscopic colitis, small intestinal bacterial overgrowth, pancreatic

exocrine insufficiency, and food allergies or intolerances.[1,60,72,80] Persisting duodenal villous atrophy and other histologic features of active celiac disease raise the possibility of refractory celiac disease. However, before this diagnosis is made, it is important to again consider other causes for small-intestinal villous atrophy, especially if patients have had negative results from serologic tests for celiac disease (Figure 2).[36] The possibility of continued gluten ingestion should be re-visited and a period of extremely strict gluten avoidance advocated.[82]

Refractory Celiac Disease

Refractory celiac disease (RCD) can be defined as persistent or recurrent small-intestinal villous atrophy with symptoms of malabsorption, despite 12 months or more of a strict GFD, in the absence of an overt lymphoma or another condition that causes villous atrophy.[1] RCD makes up a small subset (approximately 10%) of NRCDs and occurs in 1% to 2% of patients with celiac disease.[60,72,83] Severe diarrhea and weight loss in patients with NRCD increase the risk for RCD.

RCD is characterized by the absence (type I) or presence (type II) of an aberrant population of IELs that lack lineage differentiation surface markers (eg, CD4, CD8, or the interleukin-2 receptor) but are positive for cytoplasmic CD3, indicating a T-cell phenotype.[84–86] This abnormal population of T cells can be identified by immunohistochemistry, flow cytometry, or T-cell–receptor analysis of small-bowel biopsy tissue. RCD I is diagnosed more commonly in the United States, whereas RCD II predominates in Europe.

The prognoses for patients with RCD I and for RCD II differ markedly.[83–87] RCD I is associated with severe symptoms and malabsorption, but life expectancy is not
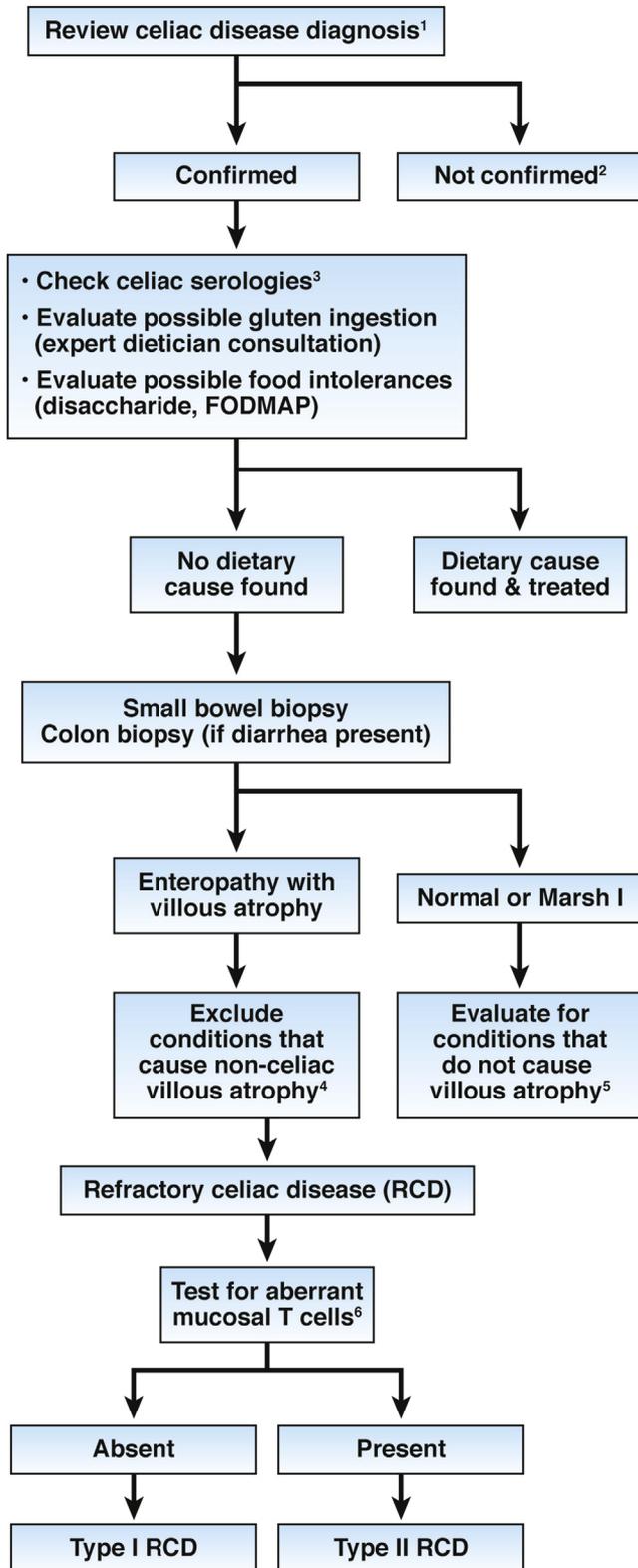

Figure 2. Evaluation of NRCD. (1) Confirm the diagnosis of celiac disease by reviewing findings from serologic tests (not antigliadin antibody tests) and small-bowel histology findings. If patients tested negative for tTG and EMA antibodies, perform HLA-DQ2 and HLA-DQ8 typing. (2) Investigate other possible etiologies for clinical presentation and/or abnormal histology findings. (3) Increased serum levels of IgA against tTG indicate continued gluten ingestion as a cause. (4) Non-celiac villous atrophy can be caused by intestinal infections (eg, giardiasis, small-intestinal bacterial overgrowth, and viral enteritis, including human immunodeficiency virus enteropathy), autoimmune enteropathy, hypogammaglobulinemia, as well as combined variable immunodeficiency, tropical sprue, Crohn's disease, peptic duodenitis, or collagenous sprue. (5) Conditions that present as NRCD without villous atrophy include irritable bowel syndrome, microscopic colitis, food intolerances, small-intestinal bacterial overgrowth, Crohn's disease, and microscopic colitis. (6) Aberrant small-intestinal mucosal and intraepithelial lymphocytes in patients with RCD type II can be identified by immunohistochemistry or flow cytometry (an excess of CD3+ cells without CD4 or CD8 surface proteins) or by T-cell–receptor gene rearrangement analysis showing clonal expansion. FODMAP, fermentable, oligosaccharides, disaccharides, monosaccharides, and plyols. Adapted from Leffler et al,[60] Rubio-Tapia and Murray,[80] and Abdallah et al.[102]

greatly reduced; the disease often responds to treatment with topical steroids and enteric delivery of budesonide.[88] Less commonly, treatment with a systemic steroid, immunosuppressant, or a biologic agent (eg, prednisone, azathioprine, or inflixamab) is required. A strict GFD should be maintained and nutritional supplementation should be given when needed.[82]

The 5-year mortality rate for patients with RCD II is approximately 50%.[83,85,86] The disease often is complicated by transition to enteropathy-associated T-cell lymphoma, ulcerative jejunoileitis, and severe malabsorption with intestinal failure necessitating total parenteral nutrition.[83–87] The initial treatment approaches are the same as for RCD I, but fewer patients with RCD II respond, and responses often are short-lived.[89] Because of the poor response to therapy and the high mortality rate, it has been advocated that RCD II should be treated with a cytotoxic chemotherapeutic agent such as cladribine (2-chlorodeoxyadenosine). However, there have been no controlled trials of treatments for RCD II.[89]

Malignancy

The mortality risk is increased in adult celiac patients (hazard ratio, 1.31; 95% confidence interval, 1.13–1.51 in one study) as a result of an increased risk for fatal malignancy.[90,91] Mortality risk was highest shortly after diagnosis and in those with active malabsorption and enteropathy, suggesting a beneficial effect of the GFD.[79,90–92] Celiac disease was first associated with small-intestinal adenocarcinoma, and then with non-Hodgkin's lymphoma, and, more specifically, small-intestinal T-cell lymphomas, now known as enteropathy-associated T-cell lymphoma (EATL). Risks for other gastrointestinal cancers, including gastric and colon cancer, are not increased substantially, and the risk for a few cancers, including breast cancer, may be lower.[93–95]

Non-Hodgkin's lymphoma is the most common celiac-associated malignancy. Early studies suggesting a high risk of non-Hodgkin's lymphoma were based on relatively small case series. Recent larger and well-designed case series have estimated a 2- to 3-fold increase in the risk for non-Hodgkin's lymphoma in patients with celiac disease.[94,95] The risk of malignancy is highest in the first years after diagnosis and, similar to overall mortality, decreases to normal or near-normal levels by 5 years after diagnosis. The post-diagnosis decrease in lymphoma risk distinguishes celiac disease from many other autoimmune disorders, including rheumatoid arthritis, Sjögrens syndrome, and Crohn's disease, for which the risk of lymphoma remains high or increases with time.[96]

Small intestinal adenocarcinomas are rare in the general population (estimated incidence, 1/100,000); but the risk is increased more than 10-fold in patients with celiac disease.[94,97,98] Unlike EATL, small-intestinal adenocarcinoma is not associated with refractory celiac disease. Patients with celiac disease and obscure gastrointestinal bleeding, new or persistent anemia, or obstructive symptoms should have a careful small-bowel examination, by computed tomography,

magnetic resonance enterography, or capsule endoscopy, depending on local resources and expertise.

As suggested by its name, EATL initially was described based on its strong association with celiac disease. More than half of the cases of EATL are diagnosed simultaneously with celiac disease. Type I EATL is associated with celiac disease and accounts for 80% of cases in Western countries. Its major risk factor is type 2 refractory celiac disease.[99] Type II EATL is less well characterized and is not associated with celiac disease or the associated HLA haplotypes -DQ2 or -DQ8. Fewer than 25% of patients with EATL survive for 5 years, although surgical debulking, combined with chemotherapy or bone marrow transplant, occasionally can produce prolonged remission.[100,101]

Although the risk of certain malignancies is increased in patients with celiac disease, their most frequent causes of morbidity and mortality are the same as those of the general population: cardiovascular disease, breast cancer (in women), prostate cancer (in men), and colon cancers in both sexes. Therefore, there are no celiac-specific cancer screening recommendations.

Future Directions

The past decade has deepened our appreciation of the protean manifestations of celiac disease, which presents at all stages of life, has a diverse geographic distribution, and is a common autoimmune disease. Advances in our understanding of pathogenesis and genetic factors that affect risk have led to the development of and refinements to diagnostic tools. Challenges for the next decade include reducing the burden of treatment by providing easier access to inexpensive gluten-free foods and developing nondietary approaches to increase the efficacy of treatment. Disease prevention, through modification of childhood risk factors, and cure, through induction of immune tolerance to gluten, are important long-term goals.

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1. Extraintestinal features of celiac sprue include:
    a. blistering rash that is most often non-pruritic and asymmetric
    b. elevated liver enzymes
    c. premature osteoporosis
    d. aphthous ulcers in the oral cavity and genital area
    e. peripheral neuropathy

2. Which of the following features are typical of refractory celiac disease with no evidence of aberrant lymphocytes by flow cytometry
    a. severe clinical course with decreased survival
    b. more common in Europe compared to the US
    c. more likely to respond to therapy with topical steroids, such as budesonide
    d. often transitions to T-cell lymphoma

True or False

3. The presence of intraepithelial lymphocytes in duodenal villi even in the absence of other histologic abnormalities is diagnostic for celiac disease

4. The presence of HLA DQ2 or DQ8 in patients who are following a gluten free diet confirms the diagnosis of celiac disease

5. Patients with proven refractory celiac disease should undergo small bowel biopsies for flow cytometry , in the US, most patients will not have an aberrant population of intraepithelial lymphocytes

6. In patients with IgA deficiency, the deaminated gliadin peptide IgG (IgG-DGP) is the most accurate serologic assay for diagnosis of celiac disease

7. The two most common autoimmune diseases associated with celiac sprue are thyroid disease and type 2 diabetes

8. Ulcerative jejunoileitis is more common in refractory celiac sprue associated with aberrant populations of intraepithelial lymphocytes

9. After initiation of a gluten free diet, repeat intestinal biopsies should be considered at 6 months and 2 years to assess compliance and mucosal healing

10. Non-Hodgkin's lymphoma is the most common celiac-associated malignancy, risk decreases after diagnosis

11. Duodenal bulb biopsies may yield false positive findings suggestive of celiac sprue, but in up to 13% of patient with celiac sprue, have typical findings only in the duodenal bulb

12. When celiac is suspected, a minimum of 5 biopsies should be done, including the bulb. Biopsies from the bulb should be labeled separate from the others