Celiac Disease

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EDUCATION GAPS

Patients with celiac disease are quite common, yet most remain undiagnosed, in part because practitioners underrecognize the extreme diversity of associated symptoms and fail to include celiac disease in the differential diagnosis. For patients with established celiac disease, pediatricians must have some knowledge regarding the gluten-free diet and recommendations for yearly follow-up care.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize that signs and symptoms suggestive of underlying celiac disease are extremely diverse and frequently overlooked and identify patient populations that are at increased risk for developing celiac disease.
2. Recommend the best laboratory testing to identify possible celiac disease and correctly interpret results for appropriate referral to a gastroenterologist for confirmatory endoscopy.
3. List the key foods to be avoided in a gluten-free diet and identify other sources of hidden gluten, understanding that because of such complexities, guidance from a celiac dietitian/educator is of utmost importance.
4. Recommend appropriate follow-up care for established patients with celiac disease, including monitoring for psychosocial concerns that often accompany this disease.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy triggered by ingestion of gluten in genetically susceptible individuals. Withdrawal of gluten, a compound protein found in wheat, barley, and rye, from the diet reverses the intestinal damage and relieves signs and symptoms. Previously, CD was thought to occur primarily in young children of European ancestry; however, with better serologic testing, recognition of potential manifestations, and more widespread testing, we now know that CD affects all age groups and occurs throughout the world, with an average prevalence of approximately 1 in 100 persons. (1)(2) Variations

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ABBREVIATIONS

CD	celiac disease
GFD	gluten-free diet
Ig	immunoglobulint
TG	tissue transglutaminase

exist with some groups, such as the Saharawi population of Western Sahara Africa and Spain, with estimates of 1 in 18 having CD, (3) whereas in most parts of Asia, excluding India, the incidence of CD is quite low.

This variation is likely due to a combination of dietary, genetic, and other as yet unrecognized factors. We also used to think that CD was only a gastrointestinal (GI) disease. Although many patients do have GI symptoms, non-GI symptoms frequently occur simultaneously, may be extremely diverse, and may be the only initial patient complaint. Recognizing potential signs and symptoms and performing the correct diagnostic testing can be challenging for clinicians, and for patients with CD, learning and implementing the gluten-free diet (GFD) can be even more difficult. Although CD seems to be more "on the radar" for health-care practitioners than in the past, several misconceptions about the disease, testing, and treatment are frequently seen in the reason for patient referral and with instructions given to patients. Herein we aim to clarify some misconceptions with review of the current literature, guidelines, and recommendations.

PATHOGENESIS

In keeping with autoimmune conditions, onset of CD requires a genetic predisposition and an environmental trigger factor. Historically, a genetic component was suspected due to the increased risk in first-degree relatives of an index case and concordance of greater than 70% in monozygotic twins and 30% to 40% in HLA-identical siblings. (4) It is now known that CD is associated with genes coding for the HLA-DQ2 and HLA-DQ8 molecules, with more than 95% of cases being DQ2 positive and the remainder having the DQ8 genotype. Absence of either of these genotypes renders the likelihood of a person developing CD virtually zero. However, approximately 40% of the general population will also have either the DQ2 or DQ8 genotype, and most of these will not ever develop CD. (5) Thus, although having the DQ2 or DQ8 genotype is necessary it is not sufficient, and clearly other non-HLA genes are involved in the pathogenesis of the condition. Currently there are more than 40 non-HLA genes that have been identified as being strongly associated with CD, many of which are associated with autoimmune regulation. (5) Individually, each of these genes is believed to play a small role in the pathogenesis of the condition, and it is likely that several are needed in combination to precipitate CD.

Gluten, which is the term applied loosely to describe the protein components of wheat, barley, and rye, serves as the trigger factor required to precipitate CD in individuals with the genetic predisposition. These proteins are rich in glutamine and proline and cannot be completely digested by the enzymes of the human GI tract. This incomplete digestion results in a variety of peptide molecules containing a varied number of amino acids that are now known to be "toxic" to those at risk for CD, with a 33-mer peptide being most notable in this regard. Transfer of these peptides from the intestinal lumen to the lamina propria is believed to occur by both paracellular and transcellular pathways. In the lamina propria, tissue transglutaminase (tTG) acts on glutamine in the peptide, changing glutamine to glutamic acid through a process of deamidation. In so doing, the negative charge of the peptide greatly increases, which, in turn, promotes binding to the HLA-DQ molecule residing on the surface of antigen-presenting cells. Other peptides are believed to stimulate the innate immune system, and together these events precipitate an inflammatory cascade resulting in the production of interleukin-15 and interferon-γ, with proliferation of CD4+ T cells and B cells (for an elaborated review of the pathogenesis, readers are referred to the article by Tye-Din et al [6]). Combined, these activated cells and cytokines are responsible for the characteristic small intestinal mucosal damage and production of antibodies to gliadin, endomysium, and tTG, which are the hallmarks of CD. Although the role of these antibodies remains unclear, their identification has provided a valuable means of testing for CD.

In some cases, it is believed that an additional trigger factor, such as a preceding infection with rotavirus or a stress-related event such as pregnancy, plays a role in precipitating onset of the condition. Although this might explain some of the variability in age at onset and severity of symptoms in some patients, the evidence for an additional trigger factor other than gluten is still not strong.

The following sections introduce misconceptions frequently seen in the clinical setting, with clarification and education surrounding each topic based on the current literature and guidelines. These sections are broadly broken into the categories of initial suspicion of CD, evaluation for CD, management of CD, and patient follow-up.

INITIAL SUSPICION OF CD

Misconception: CD is unlikely in the absence of GI symptoms, and only those with poor growth can have CD

CD may present with highly variable signs and symptoms, often in combination and often subtle. Classically, CD was thought to present in the young child with GI

manifestations, including diarrhea, bloating, and failure to thrive. We now recognize that CD may develop at any age, with an upward trend in age at presentation. GI symptoms are very common, particularly in younger children, (7) and in addition to those noted previously herein can include abdominal pain, nausea and vomiting, anorexia, and surprisingly, in up to 50%, constipation rather than diarrhea (Table 1). A rare but noteworthy severe and sometimes life-threatening presentation of celiac crisis may occur in very young children with associated electrolyte imbalance, hypoproteinemia, and vascular compromise. There are also numerous non-GI signs and symptoms that may be the earliest and sometimes only manifestations. (7) These signs and symptoms are noted in Table 2 and include a characteristic rash, dermatitis herpetiformis, which is a pruritic bilateral papular eruption around the elbows, knees, and buttocks that has a classic histologic appearance if biopsied and is responsive to gluten withdrawal. (8) Aphthous ulcers and dental enamel hypoplasia are common oral manifestations. Isolated short stature has been identified as the initial presentation for CD in up to 10% of those referred to an endocrine clinic for evaluation, but it is also well-recognized that many patients with CD are within the normal growth parameters for age, and several studies have demonstrated that more than 10% of patients may, in fact, be overweight. (9) Anemia has emerged as one of the most common extraintestinal manifestations of CD. (10)

Misconception: CD causes type 1 diabetes, autoimmune thyroid disease, and other autoimmune diseases

Several autoimmune diseases have an increased prevalence in individuals with CD, including type 1 diabetes and autoimmune thyroid disease, where 5% to 10% will develop both conditions. (11)(12) Autoimmune liver disease and some rheumatologic disorders also have extensive overlap. However, these diseases are neither the cause nor the result of CD. Instead, they co-occur because of the underlying genetic predisposition, for example, the DQ2/DQ8 genes and other overlapping genes involved with immune regulation. CD prevalence is elevated in several syndromic conditions as well, including Down syndrome, Williams syndrome, and Turner syndrome (Table 3), and testing these subpopulations is recommended even if asymptomatic. (2)(13)

TABLE 1. Gastrointestinal Manifestations of Celiac Disease

Abdominal distention	Diarrhea
Abdominal pain	Failure to thrive
Anorexia	Vomiting
Constipation	Weight loss

EVALUATION FOR CD

Misconception: Celiac genetics can diagnose CD

Checking celiac genetics should be performed only in selective cases, probably best orchestrated by a pediatric gastroenterologist. If ordered in general practice, it is important to note whether the specific haplotype alleles are evaluated. DQ2 (DQA*0501; B1*0201) is the most common haplotype conferring increased risk of development of CD. (14) DQ8 (DQA1*0301; B1*0302) also increases risk. Important in the interpretation of the genetics is that although the child has the alleles associated with CD, this cannot be used to make the diagnosis because these are also found in a large percentage of the general population. The test is of benefit only if one is negative for both the DQ2 and DQ8 alleles. If negative for all risk haplotypes, the patient may be reassured that it is nearly impossible to have or ever develop CD. Of note, several of the direct-to-consumer genetic screening services do not search for all relevant haplotypes, so a negative result can give a false sense of security.

Use of the genetic test should be reserved for specific circumstances, such as when there is a diagnostic dilemma due to a discrepancy between the serology and biopsies, or if a patient is already following a GFD without having undergone any previous testing. Under these circumstances, a negative genetic test result would help rule out CD. If appropriate serologic antibody testing for CD is negative, the presence of a risk allele is of no help in the diagnosis, and referral to a gastroenterologist to look for CD is unnecessary. If the clinical concern was the presence of GI symptoms, then the referral would be warranted to search for other causes of GI disease.

Misconception: Serum immunoglobulin (Ig) A levels are indicative of CD

As noted, activated T cells stimulate B cells to secrete antibodies specific to gliadin, endomysium, and tTG. Checking these antibody serum levels has become a powerful screening tool that, if elevated, suggest a patient might have CD. The individual antibody tests vary significantly in sensitivity and specificity as well as cost and technical difficulty (Table 4). (15) With available testing platforms, determination of the IgA antibody against tTG (IgA-tTG) is recommended as the most cost effective, sensitive, and

TABLE 2. Nongastrointestinal Manifestations of Celiac Disease

Alopecia	Chronic fatigue	Hypotonia
Amenorrhea	Dental enamel defects	Infertility
Anemia or iron deficiency	Depression	Neuropathy
Aphthous stomatitis	Dermatitis herpetiformis	Osteopenia/osteoporosis
Arthritis/joint pain	Epilepsy with intracranial calcifications	Pubertal delay
Ataxia	Foggy mind	Short stature
Behavioral problems	Headaches	Transaminase elevation

specific test. (13)(15)(16) Because this is an IgA-based antibody test, a serum IgA level should be checked to ensure that the child does not have IgA insufficiency. Furthermore, with the current sensitivity of IgA-tTG kits, even if an IgA level is less than the laboratory lower level of normal it is likely sufficient for celiac testing purposes. A serum IgA level below 15 mg/dL (<0.15 g/L) should raise concern about the validity of the IgA-tTG result if this is negative for CD, and under such circumstances an alternative IgG-based antibody test is recommended (usually IgG-deamidated gliadin peptide). Selective IgA deficiency is the most common immunodeficiency, with prevalence of approximately 1:500 in the general population. Generally, those with selective IgA deficiency have minimal symptoms, although in some there is an increase in sinopulmonary or GI infections. (17) Those with severe IgA deficiency also have increased risk of blood product transfusion anaphylaxis, (18) and referral to an immunologist might be warranted. IgA deficiency occurs more frequently in those with CD, with rates 10 to 15 times higher than the general population, (19) highlighting the importance of determining a serum IgA level when investigating for CD and the need to use alternative serum tests based on IgG antibodies in these cases. Elevated serum IgA levels, likewise, are not uncommon and are not indicative of CD.

Misconception: A panel of antibody tests is better than a single test for CD

Commercially available panels of antibodies exist that simultaneously measure several different serum markers and often check celiac genetics at the same time. These panels are more expensive and often include older serum tests, such as the antigliadin IgA and IgG antibodies, which are no longer recommended owing to their very low sensitivities and specificities. (13)(15)(16) Although measuring several antibodies simultaneously might increase sensitivity slightly, it does so at the expense of greatly reducing specificity. Furthermore, the IgA-tTG test has sensitivity and specificity in excess of 97% and, therefore, is recommended by guidelines from all GI societies as the single test of choice for use in IgA-sufficient patients. (13)(16) In the past it was believed that the IgA-tTG test performed less well in children younger than 2 years, and recommendations were to include an additional IgG-based test, usually IgG antibodies to deamidated gliadin peptide. More recent data examining this question with current testing platforms have shown that providing the child has a sufficient IgA level, no testing in addition to the IgA-tTG test is necessary. (20) The pitfalls of celiac genetic testing to diagnose CD are discussed in a preceding misconception.

TABLE 3. Conditions Associated with Celiac Disease

Autoimmune liver disease	Lymphocytic/microscopic colitis
Diabetes mellitus (type 1)	Thyroiditis
Down syndrome	Turner syndrome
Immunoglobulin A deficiency	Williams syndrome

Misconception: Once serum testing suggests CD, the child should start a GFD immediately

Guidelines from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition suggest that when serum testing is suggestive of CD, or if there is a strong clinical suspicion even without indicative laboratory data, an upper GI endoscopy with small intestinal biopsies is required to confirm the diagnosis. (16) It is critical that the child remains on a normal, gluten-containing diet until the endoscopy has been completed. Although it does take some time for the tissue to normalize after the start of a GFD, partially or fully healed intestinal mucosa after dietary changes may render interpretation of histologic findings challenging or misleading. The modified Marsh criteria provide a grading schema to look for progressive damage to the duodenal mucosa, progressing from Marsh 0 (normal tissue), with increasing evidence including intraepithelial lymphocytes (Marsh 1), crypt hyperplasia (Marsh 2), and progressive villus blunting (Marsh 3a, b, and c). (21) Typically, Marsh 2 with symptoms or Marsh 3 findings confirm CD. European guidelines differ somewhat from those of the North American Society for

TABLE 4. Sensitivities and Specificities of the Serologic Tests for Celiac Disease (15)

SEROLOGIC TEST	SENSITIVITY, % (RANGE)	SPECIFICITY, % (RANGE)
AGA IgA	85 (57–100)	90 (47–94)
AGA IgG	85 (42–100)	80 (50–94)
EMA IgA	95 (83–100)	99 (94–100)
tTG IgA	**98 (74–100)**	**98 (78–100)**
DGP IgA	88 (74–100)	95 (90–99)
DGP IgG	80 (63–95)	98 (90–99)

AGA=antigliadin antibody; DGP=deamidated gliadin peptide; EMA=antiendomysium antibody; tTG=tissue transglutaminase. Bold indicates the recommended first-line testing modality.

Pediatric Gastroenterology, Hepatology, and Nutrition and suggest that if the IgA-tTG testing is greater than 10 times the upper limit of normal for that laboratory AND the endomysial antibody titer is elevated on a separate blood sample, then a child may be considered to have CD and started on a GFD with close monitoring of tTG titers and symptom resolution to confirm the diagnosis. (13)(22) These guidelines have not been widely adopted in North America, in part because of the wide variance in testing platforms and concern for laboratory variability. If one opts to follow the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines it is critical to ensure that the testing exceeds the 10 times the upper limit of normal threshold and to understand that mild to moderate elevations in serum markers do not automatically confirm disease. Patients with CD diagnosed without a biopsy must still follow all recommendations for dietary adherence, education, and GI follow-up. Confirmation of a diagnosis of CD should always be obtained before instituting treatment with a lifelong GFD.

MANAGEMENT OF CD

Misconception: "The diet is both healthy and easy, just don't eat bread"

The only current treatment for CD is complete avoidance of gluten ingestion, meaning restricting wheat, barley, and rye from the diet in any form. With strict adherence to this diet the tissue most often heals and symptoms resolve. The diet, however, can be difficult to maintain for social, economic, and palatability reasons; this stems, in part, from the fact that gluten recognition can be tricky and gluten is often hidden among the ingredients or additives. The 2004 Food Allergen Labeling and Consumer Protection Act mandates that wheat and 7 other specific food allergens be listed in the ingredient list by either their "common or usual name" or in a "contains" statement immediately after the ingredient list. (23) However, rye and barley do not meet the same requirement, so it is imperative that those with CD or their caretakers learn to thoroughly read ingredient labels. Key words to identify include wheat, barley, rye, malt, brewer's yeast, and oats, but the full list is much more extensive (Table 5). Oats are inherently gluten-free but are frequently contaminated in the harvesting and milling process; thus, only oats labeled gluten-free are considered safe for ingestion by those with CD. Education by a trained celiac dietitian or celiac educator is essential for patient understanding and disseminating accurate information. Nonprocessed meats without spices and fruits and vegetables are inherently gluten-free, and there are many gluten-free grains that can be introduced into the diet to substitute for gluten-containing counterparts (Table 5). Through research, the threshold of gluten found to be safe for ingestion is only 10 mg daily (1/250th a slice of bread), (24) and the Food and Drug Administration's (FDA's) gluten-free labeling rule, enacted

TABLE 5. Gluten-Containing and Gluten-Free Grains

GLUTEN-CONTAINING GRAINS TO AVOID			GLUTEN-FREE GRAINS AND STARCHES	
Barley	Farina	Semolina	Amaranth	Quinoa
Barley or malt extract	Faro (farro)	Spelt	Arrowroot	Rice
Bran	Graham flour	Triticale	Buckwheat	Rice bran
Bulgur	Kamut	Udon	Corn	Sago
Couscous	Matzo flour or meal	Wheat	Flax	Sorghum
Dinkel	Orzo	Wheat bran	Millet	Soy
Durum	Panko	Wheat germ	Nut, bean, and seed flour	Tapioca
Einkorn	Rye	Wheat starch	Potato flour	Teff
Emmer	Seitan		Potato starch	Oats[a]

[a]If labeled "gluten-free."

in 2013, (25) set the standard for what constitutes gluten-free as 20 parts per million or less (2 mg of gluten in 100 g of the food product). Most products labeled gluten-free that have been tested adhere to this standard (although it is always recommended to review the ingredient list), and studies have shown that a person who eats multiple gluten-free foods that are less than the 20 parts per million will remain well below the daily 10-mg threshold. (26) Although a strict GFD is essential for people with CD it should be noted that the gluten-free foods are lower in fiber, protein, iron, folate, and other B vitamins than their gluten-containing counterparts. As such, without appropriate supplements and monitoring by a knowledgeable dietitian, the GFD cannot be considered "healthy" for those who do not have CD. Celiac educators also teach about ways to avoid gluten cross-contact in home, school, and restaurant settings. Nonfood items may also contain gluten and if ingested will trigger celiac-related enteropathy. Some examples include medications, cosmetics, communion wafers, and school supplies such as papier mache or pasta used for artwork or sensory tables. Recent studies suggest that some supplies, such as commercial play dough, might not transfer substantial gluten as previously suspected (27); however, further studies are needed to clarify exactly which supplies might or might not cause damage. These studies emphasize the fact that frequent handwashing with good technique and soap and water is of utmost importance and eliminates the transfer of gluten. (27)

Misconception: Current supplements exist that allow patients with CD to eat a "normal" diet

There are several over-the-counter enzymes available that claim to digest gluten. In likelihood they do decrease the total amount of gluten, but none currently on the market have been shown to decrease the amount of the antigenic peptides sufficiently to protect against the inflammatory effects of gluten in CD. These enzymes should not be recommended because they give patients a false sense of security, even if they are taking them only as "just in case" therapy. Proteolytic digestion of the gluten peptides from nonendogenous sources is one of the mechanisms currently under investigation. (28) In time, possibly with several types of enzymes working in combination, a digestive enzyme may offer a valid therapy, at least in the rescue setting.

For multiple reasons, including palatability, social acceptance, and easier lifestyle, patients with CD would prefer to eat a "normal diet" or at least gluten in moderation. However, most when questioned about alternative therapies to the GFD remained more concerned about the potential for intestinal damage and long-term adverse health consequences from gluten exposure in their diet. (29)

Active research examining potential interventions in nearly every step in the pathogenesis of CD leading to mucosal damage is currently ongoing. In addition to the digestive enzymes being studied, this includes administration of polymers that bind gluten peptides in the intestinal tract, rendering them nonabsorbable as another means of luminal blockade. (30) Zonulin, a peptide upregulated by gliadin, disrupts tight junctions in the small intestinal epithelium. There are ongoing clinical trials examining zonulin antagonists that transiently inhibit opening of the tight junction between enterocytes to prevent passage of gluten-derived peptides into the lamina propria via a more downstream mechanism. (31) Administration of monoclonal antibodies against the inflammatory cytokines in the inflammatory cascade may inhibit subsequent tissue damage. Initial studies examining a vaccine to induce tolerance to the gluten-derived proteins in those at risk for CD showed promise, (32) but further examination failed to demonstrate efficacy. A similar concept, using infused nanoparticle shells surrounding the gluten peptides, may better target the antigens to preferred locations in the body to initiate a more robust and long-lasting immune response. Current clinical studies have shifted in that investigational direction (eg, clinical trial NCT03486990). Whatever the potential novel therapy, weighing the risks and benefits is a must, and finding something as safe, effective, and cost containing as the GFD may prove difficult.

PATIENT FOLLOW-UP

Misconception: Once gluten is eliminated from the diet, screening tests rapidly normalize and symptoms disappear

A follow-up challenge for both the gastroenterologist and the primary care provider alike is nonnormalization of the IgA-tTG in patients with CD once a strict GFD is instituted. It is well-known that this normalization can take several months to 2 years, and although we like to think that normalization of tTG equals a completely healed small intestine mucosa, this is not always the case. Several recent studies in which patients underwent repeated endoscopy have shown cases of normal serum tTG levels but persistent duodenal inflammation, and the converse is true in which those with persistently elevated levels of tTG

demonstrate histologically normal mucosa. (33)(34) These findings emphasize the fact that the tTG is a good screening tool to search for CD but that better markers of mucosal healing are needed, an area of active research. In the future, following the recommendations for other mucosal GI diseases, such as inflammatory bowel disease and eosinophilic esophagitis, repeated endoscopy for patients with CD to look for mucosal healing might become the norm.

If one encounters persistently elevated tTG levels, initial investigation should be an interview of the patient and family by a celiac dietitian/educator to delve deeply into the food preparation and eating practices in the home, school, restaurant, and social settings. If after intense review and modification the tTG level remains elevated, some children may benefit from an even more strict GFD, known as the gluten contamination elimination diet, in which foods that might contain trace levels of gluten, below that required to be considered gluten-free, are removed from the diet for several months. (35)(36) This diet should be implemented by celiac experts, and these patients should be followed closely by a celiac dietitian. In addition, there are home testing kits available that test for dietary gluten exposure in the past 2 to 6 days by monitoring for nondegradable immunogenic gluten peptides in the urine or stool. (37)(38)

Besides dietary changes and laboratory monitoring, assessment for depression and poor quality of life should also become part of routine celiac follow-up. Several studies have demonstrated that patients with CD and their parents assess the affected child as having a lower quality of life, and it is unclear whether this normalizes as their disease improves on a GFD. (39)(40) Even if symptoms resolve, the diet itself can be socially isolating and may serve as a source for bullying as it highlights the child as different from peers, so although physically better, the patient with CD may perceive reduced quality of life. Multiple support groups exist for children with CD and their families, and they should be encouraged to join. Likewise, normalcy of the "alternate/restrictive diets" in school and social settings is encouraged, and several CD centers suggest a more formal Section 504 plan to ensure fair treatment of the child in an academic setting and with all school activities.

Although screening and diagnosis guidelines have been well documented in several forms, (13)(16) ancillary testing at diagnosis and follow-up recommendations have been less protocolized. Recently Snyder and collaborators (41) came together as experts in pediatric CD and reviewed available data to put forth recommendations in 6 identified areas in the management of CD. Their recommendations for the initial diagnosis of CD are in accordance with published guidelines. Other recommended laboratory tests at the time of diagnosis include a complete blood cell count, ferritin, iron, total iron-binding capacity, 25-hydroxyvitamin D, thyrotropin, and alanine aminotransferase/aspartate aminotransferase (Table 6). Hepatitis B vaccine nonresponder status is more frequently associated with specific HLA haplotypes, including HLA-DQ2; therefore, checking immunization status in patients with CD is recommended as a public health initiative. (42)(43) If this testing is not initiated by the gastroenterologist, it may fall to

TABLE 6. Initial and Follow-up Recommendations for Screening

BEST PRACTICES	CHECK AT DIAGNOSIS	CHECK AT FOLLOW-UP
Bone		
25-hydroxyvitamin D level	Yes	If prior abnormal
Hematologic		
Complete blood cell count	Yes	Yes
Iron/ferritin/total iron-binding capacity	Yes	If prior abnormal
Endocrine		
Thyrotropin	Yes	Yes
Liver		
ALT and AST	Yes	If prior abnormal
Screen for hepatitis B immunization status	Yes	If prior abnormal[a]
Nutrition		
Assessment of growth parameters	Yes	Yes
Access to an experienced dietitian	Yes	Yes
Testing		
Serum IgA-tTG level	Yes	Yes
Upper endoscopy with biopsy of duodenum	Yes	Select circumstances[b]

Based on recommendations by Snyder et al. (41) ALT=alanine aminotransferase, AST=aspartate aminotransferase, IgA-tTG=immunoglobulin A–tissue transglutaminase.

[a]Repeat serologies after revaccination series.

[b]Can be used to reassess for mucosal healing; not routinely recommended at this time.

the primary care provider to complete these laboratory tests. In addition, if patients are found to be hepatitis B nonimmune, the revaccination schedule typically falls back to primary care responsibility. Yearly follow-up, ideally with their gastroenterologist, is recommended, but in cases in which the patient is doing extremely well or there is substantial travel distance to specialized care, follow-up responsibility may also fall to the primary care provider. Yearly routine nutritional assessment and anthropometric measures and adherence to the GFD is recommended along with yearly laboratory testing, including IgA-tTG, complete blood cell count, and thyroid studies. Routine screening for 25-hydroxy-vitamin D, transaminases, and hepatitis B immune status need only be repeated if previously abnormal. (41)

Summary

- On the basis of strong evidence, both gastrointestinal and nongastrointestinal manifestations are prevalent in the presentation of celiac disease (CD); thus, CD should be considered frequently in the differential diagnosis, and one should have a low threshold to send screening tests for this disease. (7)(16)
- On the basis of North American and European guidelines, serum immunoglobulin A (IgA)–tissue transglutaminase (tTG) in conjunction with serum IgA level is the test of choice to screen for CD. Genetic testing is recommended only in select circumstances and can be used to eliminate CD from the differential diagnosis but cannot diagnose the disease. (13)(15)(16)
- On the basis of North American guidelines, an upper endoscopy with biopsies from the duodenum should be performed to verify laboratory findings or if strong suspicion exists for the disease even in the absence of serologic evidence. (15)(16) The patient must continue a gluten-containing diet until the procedure has been completed.
- If the endoscopic surveillance is omitted, following European guidelines, the threshold tTG level must be met and confirmatory serum testing performed, as well as close monitoring for normalization of titers and resolution of symptoms on a gluten-free diet (GFD) before a firm diagnosis of CD can be made. (13)(22) Minimal elevation in serum markers must be further evaluated.
- On the basis of strong research evidence, all those with confirmed CD should be referred for education to a celiac dietitian or educator and should follow a strict GFD for life, avoiding ingestion of foods or other substances containing wheat, barely, or rye. (13)(16)(41)
- On the basis of some research evidence and expert consensus, yearly follow-up is recommended for patients with CD to monitor growth parameters, assess adherence to the GFD, and perform laboratory evaluation for tTG levels, thyroid studies, and markers of anemia, as well as for normalization of any laboratory abnormalities identified at diagnosis. (41)

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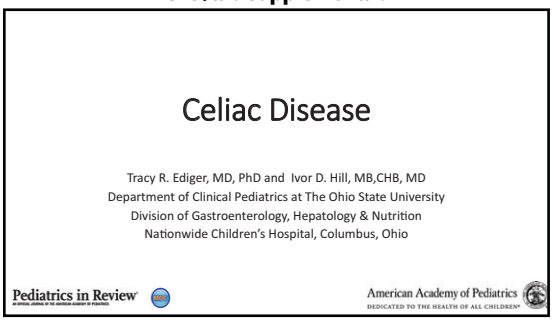

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 10/529.

PIR QUIZ

1. You are seeing a 12-year-old boy for a health supervision visit. He is accompanied by his mother, who recently learned that some members of the extended family have been diagnosed as having celiac disease (CD). Although the child currently has no gastrointestinal symptoms and is growing well, his mother wonders whether her son will ever develop CD. She also asks whether there are any tests that can help estimate her son's risk of developing CD. Which of the following test results would indicate a near-zero likelihood of this patient ever developing CD?

   A. Absence of HLA-DQ2 and HLA-DQ8 genotype.
   B. Absence of hepatitis B surface antibody.
   C. Negative deamidated gliadin immunoglobulin (Ig) G.
   D. Negative IgA–tissue transglutaminase (tTG).
   E. Serum IgA level of 0 mg/dL (0 g/L).

2. A 5-year-old girl is brought to the clinic by her parents due to a 4-month history of weight loss, loose stools, and generalized abdominal pain. Her parents are concerned because she has less energy than normal and seems more gassy to them as well. They deny fever, rash, emesis, bloody stools, or joint complaints. She consumes a regular diet by mouth. On physical examination she is thin and appears mildly unwell. A few shallow aphthous ulcers are noted on her buccal mucosa. Her abdomen is soft but mildly protuberant and without hepatosplenomegaly. The clinician begins an evaluation. Besides ordering a serum IgA antibody level, which of the following is the most appropriate test to order in this patient at this time?

   A. Antigliadin IgA antibody.
   B. C-reactive protein.
   C. HLA-DQ2 and HLA-DQ8 genotyping.
   D. IgA-tTG antibody.
   E. Thyrotropin.

3. A 16-year-old boy presents to your office with abdominal pain and headache for the past 3 months. He describes episodes of generalized abdominal pain that occur 2 to 3 days per week. The pain does not radiate to his back and is not associated with eating, urination, or defecation. Both his weight for age and stature for age are at the 65th percentile. His physical examination findings are normal. You order laboratory studies, and his serum IgA-tTG antibody level is 27 CU/mL (upper limit of normal, 20 CU/mL). Serum IgA level is normal. Which of the following is the most appropriate next step to confirm the diagnosis in this patient?

   A. Fluoroscopic upper gastrointestinal series.
   B. Pediatric immunology referral.
   C. Thyrotropin level.
   D. Trial of a gluten-free diet.
   E. Upper endoscopy with small intestinal biopsies.

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4. A 7-year-old girl has recently developed loose stools, bloating, and belly pain. Her IgA-tTG antibody level was elevated at 107 CU/mL. She was referred by her primary care physician to a pediatric gastroenterologist to confirm her diagnosis of C.D. She has since undergone upper endoscopy and small intestinal biopsies, which revealed villous atrophy in her duodenal biopsy samples, confirming the diagnosis. Which of the following is the most appropriate step in management to treat this patient's condition?

   A. Administration of a CD vaccine.
   B. Continuation of a regular diet along with gluten-digesting enzyme supplements.
   C. Dietary avoidance of gluten.
   D. Oral gluten-peptide binder therapy.
   E. Zonulin antagonist therapy.

5. You are seeing a 9-year-old girl for a health supervision visit. When you saw her 3 years ago you had suspected she had CD based on her complaints of abdominal pain and loose stools. Her IgA-tTG antibody level was elevated at that time. She was subsequently referred to a pediatric gastroenterologist, and upper endoscopy with biopsy confirmed the CD diagnosis. Her family tells you she has consumed a gluten-free diet since her biopsy results came back. She does not purposefully ingest gluten. She is up-to-date on her immunizations. You order blood work and find that her IgA-tTG antibody remains elevated 30 months after diagnosis. Which of the following is the most appropriate next step in management?

   A. Educational session with a celiac dietitian.
   B. Referral to pediatric psychology for adjustment disorder.
   C. Repeated hepatitis B immunization.
   D. Serum thyrotropin level.
   E. Upper endoscopy with biopsy.