Celiac Disease

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Educational Gaps

1. Most celiac disease remains undiagnosed in the United States. Unfamiliarity on the part of health care professionals to recognize the protean manifestations of celiac disease and use appropriate tests to identify affected children is in large part responsible for this deficiency.
2. Many children are advised to start a gluten-free diet before confirming a diagnosis of celiac disease via biopsy of the small intestine. A lifelong gluten-free diet is essential for people with celiac disease but has major quality-of-life implications. Therefore, it is important to confirm a diagnosis of celiac disease beyond doubt before starting treatment.

Objectives

After completing the article the reader should be able to:

1. Recognize the spectrum of clinical presentations of celiac disease in children and adolescents and identify those populations who are at risk for developing celiac disease.
2. Discuss the appropriate choice of diagnostic tests to screen for celiac disease and recognize which patients should be referred to a pediatric gastroenterologist for further testing.
3. List the key foods in which gluten can be found and recognize that there are many hidden sources of gluten.

AUTHOR DISCLOSURE Drs Ediger and Hill disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AGA	antigliadin antibody
EMA	antiendomysium antibody
DGP	deamidated gliadin peptide
tTG	tissue transglutaminase

INTRODUCTION

Celiac disease is an autoimmune small intestinal enteropathy caused by a permanent sensitivity to gluten from wheat, rye, and barley in genetically susceptible individuals. Before the availability of serologic tests for celiac disease, it was thought to have the highest prevalence in Western Europe followed by the United States, with low prevalence throughout the rest of the world. With the advent of reliable serologic tests to screen and identify those with possible celiac disease, the condition has now been identified throughout the world, with the highest prevalence in the Saharawi population of Western Sahara Africa and Spain. (1) Current estimates in the United States suggest a prevalence of 1:100, which is

similar to that now described throughout Europe and elsewhere. (2)(3) Historically, celiac disease was thought to present mainly in early childhood. It is now known that the initial manifestations of celiac disease can occur at any age from childhood to late in adult life. Although celiac disease is increasingly recognized in the past 2 decades, the condition is still undiagnosed in most people, (4) and it is estimated that for every known patient with celiac disease, there are at least 50 with undetected disease.

PATHOGENESIS

There is both a genetic component and an environmental trigger for celiac disease. Evidence for the genetic component includes a higher incidence in first-degree relatives of an index case (approximately 10%), concordance between monozygotic twins of least 70%, and concordance between HLA-identical siblings of 30% to 40%. (5) The strongest evidence for a genetic component comes from the association between celiac disease and HLA-DQ2 and HLA-DQ8. More than 95% of patients with celiac disease express HLA-DQ2 (coded for by the alleles DQA1*0501 and B1*0201), and the remainder express HLA-DQ8 (DQA1*0301 and B1*0302). However, the DQ2 genotype is also found in 30% to 40% of the general population, (6) indicating that although these HLA genes are necessary, they are not sufficient for development of the disease and other non-HLA genes must be involved. To date, at least 39 non-HLA genes have been identified as associated with celiac disease, most of which are involved in immune regulation. (6) Each is believed to play a limited role in the pathogenesis of the condition, and probably multiple genes are needed to cause disease.

The environmental trigger is gluten, a compound protein composed of glutenin, and gliadin, which is found in wheat, with similar prolamines found in barley and rye. As little as 50 mg of gluten (1/100th a slice of bread) can trigger disease in susceptible people. (7) The glutamine-rich proteins cannot be completely digested by the endogenous peptidases found in the intestinal tract of humans, and the residual peptides are responsible for initiating damage within the small intestine (for an elaborated review of pathogenesis, readers are referred to Green et al [8]). In brief, a 33-mer peptide enters the lamina propria primarily via paracellular migration as the tight junctions are disrupted in people with celiac disease due to upregulation of the protein zonulin, which controls the microskeleton of the tight junctions. Within the lamina propria the peptides undergo deamidation by tissue transglutaminase, which changes the glutamine residues into glutamic acid, thereby increasing the negative charge of the molecule. The increase in negative charge, in turn, promotes binding of the peptide in the peptide-binding groove of the HLA-DQ2 and HLA-DQ8 molecules on the surface of the antigen-presenting cells. Other gluten-derived peptides stimulate the innate immune system within the lamina propria. All these events precipitate an inflammatory cascade that involves interleukin 15, $CD4^+$ T cells, and B cells, resulting in the villus atrophy and crypt hyperplasia that are the histologic hallmarks of celiac disease (**Figure**); furthermore, the cascade initiates the production of antigliadin antibody (AGA), tissue transglutaminase (tTG), and antiendomysium antibody (EMA) that are now used to test for the condition. It has also been proposed that infectious agents, such as rotavirus and enterovirus, and various toxins may act as additional trigger factors in some cases, possibly through disruption of the mucosal integrity and mimicry of the gliadin molecule. However, the evidence for these additional triggers is not strong.

CLINICAL MANIFESTATIONS

The clinical manifestations of celiac disease are extremely varied. Symptoms may occur singly or in combination, and the age at onset can be anytime from infancy to late in adult life. Gastrointestinal symptoms (Table 1) are usually predominant in children, whereas in adults nongastrointestinal manifestations are more common as the presenting finding (Table 2). Classic celiac disease presents in the young child between ages 6 months and 2 years with the gastrointestinal manifestations of diarrhea, weight loss, muscle wasting, and abdominal distension. In rare cases, the symptoms are severe, and the child presents with celiac crisis, a potential life-threatening emergency with accompanying electrolyte imbalance, hypoproteinemia, and vascular compromise. Abdominal pain, failure to thrive, and diarrhea should prompt an investigation for celiac disease. In older children, constipation, rather than diarrhea, may be the chief symptom, with greater than 10% of children presenting in this manner. Nongastrointestinal presentations are now known to be more common among adolescent and adult patients and involve multiple systems (Table 2). (8)

Isolated short stature has been identified as the initial presentation for celiac disease in up to 10% of those referred to an endocrine clinic for evaluation, and delayed onset of puberty can affect both sexes. Iron deficiency anemia, often poorly responsive to therapy with iron supplementation, is a well-recognized initial presentation of celiac disease. Dermatitis herpetiformis, characterized by pruritic papular eruption over the extensor surfaces around the elbows, knees, and buttocks, is a well-recognized skin manifestation of

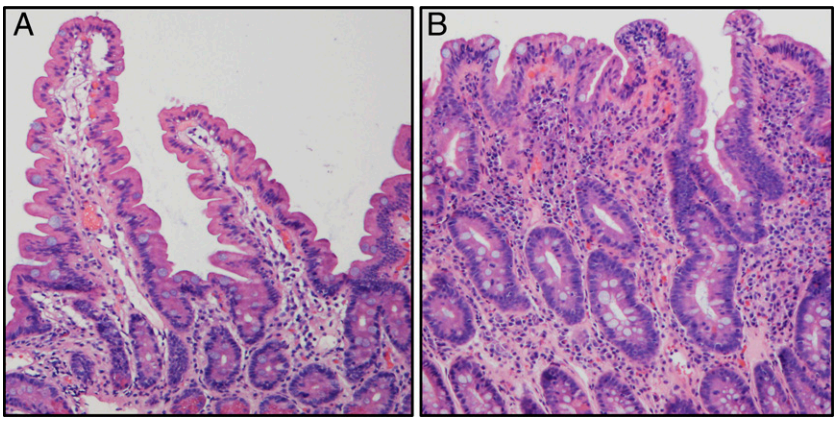

Figure. Representative histologic features of the small intestine. In the normal duodenal biopsy (A), the villi are elongated and the crypts relatively short. This is in contrast to the small intestinal tissue affected by celiac disease (B), which demonstrates marked villus blunting and crypt hyperplasia.

celiac disease; histologically, this rash reveals a characteristic subepithelial deposition of IgA. Orally, aphthous ulcers are a common finding in those with celiac disease, and dental enamel hypoplasia that involves the secondary dentition is also a characteristic feature.

In addition, a number of conditions are now known to be associated with celiac disease, and people with these conditions are at increased risk for developing celiac disease. These conditions include first-degree relatives of a person with a confirmed case of celiac disease and a number of other autoimmune diseases and genetic syndromes (Table 3). (3)(4)

Recommendations on Whom to Test

1. **Children with typical gastrointestinal manifestations of celiac disease (diarrhea, weight loss, and abdominal distension) should undergo testing for celiac disease early in the diagnostic workup.**
2. **Children with less typical gastrointestinal manifestations or nongastrointestinal manifestations should undergo testing for celiac disease if no other cause for the symptoms has been identified.**
3. **Testing for celiac disease should be considered in people belonging to groups at increased risk for celiac disease (first-degree relatives and those with type 1 diabetes) even if they are asymptomatic.**

TABLE 1. **Gastrointestinal Manifestations of Celiac Disease**

Abdominal distension	Diarrhea (chronic or recurrent)
Abdominal pain	Failure to thrive
Anorexia	Vomiting
Constipation	Weight loss

Current evidenced-based guidelines all recommend testing for celiac disease in children and adolescents with the following unexplained symptoms and signs (9): chronic abdominal pain; chronic or intermittent diarrhea; growth failure; iron deficiency anemia; nausea or vomiting; chronic constipation not responding to usual treatment; weight loss; chronic fatigue; short stature; delayed puberty; amenorrhea; recurrent aphthous stomatitis; dermatitis herpetiformis; repetitive fractures, osteopenia, or osteoporosis; and unexplained abnormal liver biochemical test results. In those with typical gastrointestinal manifestations, testing for celiac disease should be one of the first tests considered in the diagnostic workup. For all other less typical gastrointestinal and nongastrointestinal manifestations, testing for celiac disease should be considered if no other obvious cause for the symptoms can be found.

There is lack of consensus among the guidelines on the recommendation to screen asymptomatic people who belong to groups at increased risk for celiac disease. The

TABLE 2. **Nongastrointestinal Manifestations of Celiac Disease**

Anemia or iron deficiency	Headaches
Aphthous stomatitis	Hypotonia
Arthritis	Infertility
Ataxia	Neuropathy
Behavioral problems	Osteopenia
Dental enamel defects	Osteoporosis
Depression	Pubertal delay
Dermatitis herpetiformis	Short stature
Epilepsy with intracranial calcifications	Transaminase elevation

TABLE 3. **Conditions Associated With Celiac Disease**

Autoimmune liver disease	Thyroiditis
Diabetes mellitus (type 1)	Turner syndrome
Down syndrome	Williams syndrome
IgA deficiency	

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines recommend all such children be tested starting after age 3 years provided they are on a gluten-containing diet. (3) The guidelines from the adult gastroenterology societies do not recommend routine screening of such cases but suggest they be followed and that if these people ever develop any symptoms associated with celiac disease they be tested. (10) The reasons for this difference of opinion stem from the fact that on the one hand there is concern for potential adverse long-term health consequences in those who have celiac disease but are not yet symptomatic and remain untreated, whereas on the other hand the natural history of celiac disease is unknown and as of yet there are no good data to demonstrate any benefits of treating someone who is truly asymptomatic.

Recommendations for Serologic Testing

1. **For routine testing, request a tTG IgA and total serum IgA level.**
2. **In those with selective IgA deficiency, request the tTG IgG, EMA IgG, or DGP IgG level.**
3. **In children younger than 2 years, request both the tTG IgA and DGP IgG.**
4. **If the clinical suspicion for celiac disease is strong, consider performing an intestinal biopsy even if all serologic test results are negative.**

Initial laboratory testing for celiac disease is by means of serologic tests. Commercially available tests include AGA, EMA, tTG, and DGP. The AGA and DGP tests are usually available as both IgA and IgG antibodies, whereas the EMA and tTG tests are usually offered as an IgA antibody but can also be requested as an IgG antibody from some companies. The relative sensitivities and specificities of these tests are listed in Table 4. As can be seen, the AGA tests are not sensitive or specific, and these values can vary widely among laboratories. The EMA IgA and tTG IgA tests are both highly sensitive and specific. (11) The DGP antibodies perform better than the AGA, but they are not quite as good as the EMA IgA or tTG IgA antibodies. Where available, the EMA IgG and tTG IgG antibodies are less accurate than the respective IgA antibodies. (11) The advantage of the tTG over the EMA test is that the tTG test is less expensive and also less prone to operator error because it is based on an enzyme-linked immunosorbent assay or radioimmunoassay technique, whereas the EMA test uses an immunofluorescent method.

Current evidenced-based guidelines recommend use of the tTG IgA test alone as the most cost-effective and accurate means of serologic testing for celiac disease. (9) It is strongly recommended that the AGA tests no longer be used because they are considered unreliable. It is also recommended that a serum IgA level be obtained at the time of testing to correctly interpret the test result. In cases of selective IgA deficiency, which occurs more commonly in those with celiac disease, the tTG IgA test would be potentially misleading and could give a false-negative result. In those with selective IgA deficiency, the tTG IgG, EMA IgG, or DGP IgG test is recommended to screen for celiac disease. In the young child (age <2 years), the tTG IgA and EMA IgA tests are less accurate, probably because of relative physiologic IgA insufficiency. For this reason, combining the tTG IgA with DGP IgG is recommended.

Patients suspected of having celiac disease on the basis of positive serologic markers should be referred to a gastroenterologist for confirmatory testing. Because the various sensitivities and specificities of these tests are usually established in a research setting where the pretest probability of celiac disease is much higher than in the general population, the tests may not perform as well in clinical practice. Therefore, if the clinical suspicion for celiac disease is strong, the patient should be considered for a definitive diagnostic intestinal biopsy even if all serologic test results are negative.

Recommendations for the Use of HLA Tests for Celiac Disease

1. **Routine testing for HLA-DQ2 or HLA-DQ8 is not recommended for the diagnosis of celiac disease.**
2. **Testing for HLA-DQ2 or HLA-DQ8 should only be used in special circumstances, such as a diagnostic dilemma or when a patient has instituted a gluten-free diet before the diagnosis of celiac disease was confirmed.**
3. **A negative test result for HLA-DQ2 and HLA-DQ8 virtually excludes celiac disease, and other causes of the patient's symptoms should be sought.**

More than 95% of patients with celiac disease have the HLA-DQ2 genotype, and the remainder are positive for the HLA-DQ8 genotype. However, approximately 40% of the general population is HLA-DQ2 positive, and only approximately 1% to 2% of these will develop celiac disease. (6) Therefore, the presence of HLA-DQ2 or HLA-DQ8 cannot be used to diagnose celiac disease. Conversely, the absence of HLA-DQ2 and HLA-DQ8 virtually excludes the diagnosis

TABLE 4. **Sensitivities and Specificities of the Serologic Tests for Celiac Disease (4)(10)**

SEROLOGIC TEST	SENSITIVITY, % (RANGE)	SPECIFICITY, % (RANGE)
AGA IgA	80 (52-100)	85 (47-100)
AGA IgG	80 (42-100)	80 (47-94)
EMA IgA	90 (86-100)	98 (94-100)
tTG IgA	95 (86-100)	96 (90-98)
DGP IgA	88 (74-100)	90 (80-95)
DGP IgG	80 (70-95)	98 (90-100)

AGA=antigliadin antibody; DGP=deamidated gliadin peptide; EMA=antiendomysium antibody; tTG=tissue transglutaminase.

of celiac disease. Therefore, testing for HLA types should not be used in the routine diagnostic workup for celiac disease but should be reserved for special circumstances, such as diagnostic dilemmas where there is discordance between the serologic test results and the intestinal histologic findings or in cases where the gluten-free diet has been instituted before confirmation of the diagnosis. In those who have neither the HLA-DQ2 nor HLA-DQ8 genotype, the diagnosis of celiac disease can virtually be excluded, and other causes for any symptoms should be sought.

Recommendations for Confirming the Diagnosis of Celiac Disease

1. **Demonstration of the characteristic histologic changes of celiac disease on a small intestinal biopsy specimen is still considered the gold standard for diagnosing the condition.**
2. **All patients with an elevated titer of antibodies for celiac disease should be referred for upper gastrointestinal tract endoscopy and biopsy.**
3. **Patients in whom there is a strong clinical suspicion for celiac disease but who have negative serologic test results should be considered for an intestinal biopsy.**

A confirmed diagnosis of celiac disease mandates that the patient remain on a strict gluten-free diet for life. Because this dietary change is cumbersome and expensive and also has quality-of-life implications, it is extremely important to confirm the diagnosis of celiac disease beyond doubt before starting treatment. Confirmation of the diagnosis in most cases is based on finding the characteristic mucosal changes of celiac disease on a small intestinal biopsy specimen (**Figure**). Patients suspected of having celiac disease on the basis of a positive serologic test result or a strong clinical suspicion should be referred to a gastroenterologist for upper gastrointestinal tract endoscopy and biopsies. Because the mucosal changes can be patchy, it is initially essential that the endoscopist obtain multiple biopsy specimens from the duodenal bulb and distal duodenum. (9) Findings of villous atrophy with crypt hyperplasia and an increase in intraepithelial lymphocytes are diagnostic of celiac disease, and all such cases should be treated. (12) Recent guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition have suggested that in some patients with typical symptoms of celiac disease and a tTG greater than 10 times the upper limit of normal it may be possible to forgo the biopsy and treat the patient. (9) This recommendation has not yet been widely adopted within the United States because there is considerable concern based largely on the fact that there is no laboratory standardization of the serologic tests and hence this level cannot always be reliable. In the future, it is hoped that other means will be found to enable a confident diagnosis of celiac disease to be made without a biopsy.

Recommendations for Treatment of Celiac Disease

1. **All those with a confirmed diagnosis of celiac disease should follow a strict gluten-free diet for life.**
2. **A gluten-free diet involves complete elimination of all foods that contain gluten, including, but not limited to, wheat, barley and rye ingredients (Table 5).**
3. **Oats should not be ingested unless they are guaranteed pure and free of contamination with wheat flour.**
4. **All patients with celiac disease should be referred to a nutritionist with specialized knowledge of celiac disease and the gluten-free diet.**

Currently, the only acceptable treatment for celiac disease is strict adherence to a gluten-free diet for life. (3)(4) This requires complete elimination of all foods that contain wheat, barley, or rye. Table 5 lists some gluten-containing grains. Table 6 lists some potential hidden sources of gluten,

TABLE 5. **Gluten-Containing Grains to Avoid**

Barley	Faro	Spelt
Barley or malt extract	Graham flour	Triticale
Bran	Kamut	Udon
Bulgur	Matzo flour or meal	Wheat
Couscous	Orzo	Wheat bran
Durum	Panko	Wheat germ
Einkorn	Rye	Wheat starch
Emmer	Seitan	
Farina	Semolina	

such as soy sauce, communion wafers, certain lipsticks, and some medications, that may be easily overlooked. Table 7 lists some gluten-free grains and starches. Although the gluten-free diet is essentially a healthy diet that emphasizes ingestion of fresh fruits, vegetables, meat, and dairy products, strict adherence to such a diet is cumbersome and increases the cost of food by approximately one-third of normal. Patients with newly diagnosed celiac disease require intensive education on how to avoid these products, and they have to learn how to read food labels for hidden sources of gluten. For this reason, it is essential that all patients be referred to a knowledgeable health care professional who can educate them on the diet and conduct a nutritional evaluation to look for potential deficiencies of trace elements and minerals. Pure oats are considered safe for most people with celiac disease. However, there is a high likelihood of cross-contamination of oats with wheat flour during the milling process, so unless the oats can be guaranteed pure, they should not be ingested by those with celiac disease. On a strict gluten-free diet, most patients will have complete symptom resolution and recovery from the intestinal mucosal damage. After institution of a gluten-free diet, patients should be seen at regular intervals to ensure adherence to the diet and resolution of symptoms. With a strict gluten-free diet, the serologic tests will reveal a decrease in levels and in most cases will normalize by approximately 1 year after starting treatment. (13) Subsequently performing the serologic testing at approximately 6-month intervals until they have normalized, then annually thereafter, provides a reasonable means of monitoring for dietary adherence. (13) An increase in antibody levels after they have returned to normal suggests the patient may once again be ingesting gluten. Continued ingestion of gluten in people with celiac disease is associated with potential long-term adverse health consequences, including bone demineralization, an increased risk for intestinal malignant tumors, and an increased mortality rate. (8) Because of the increased psychological and social pressures the diagnosis of celiac disease and subsequent dietary restrictions impose on a patient, families may find some relief in joining a local or regional celiac support group.

FUTURE DIRECTIONS IN THE TREATMENT OF CELIAC DISEASE

Because many people with celiac disease find the long-term need for a gluten-free diet to be burdensome, alternative forms of treatment are being sought. Those currently under investigation include the following:

1. Use of digestive enzymes derived from bacterial substrates that will completely digest the gluten peptides and render them nontoxic.
2. Administration of polymers that will bind the gluten peptides within the lumen of the intestinal tract and render them nonabsorbable.
3. Administration of a zonulin receptor antagonist that will transiently inhibit opening of the tight junction between enterocytes and prevent passage of the gluten-derived peptides.
4. Administration of biologic agents that contain monoclonal antibodies against the inflammatory cytokines involved in the inflammatory cascade that results in the tissue damage found in celiac disease.
5. Administration of a vaccine to induce tolerance to the gluten-derived peptides in those at risk for celiac disease.

TABLE 6. **Products Containing Potentially Hidden Sources of Gluten**

Ales	Soup base
Beers and lagers	Stuffing
Breading	Self-basting poultry
Brown rice syrup	Imitation bacon or seafood
Coating mix	Soy sauce
Communion wafers	Marinades
Croutons	Supplements
Candy	Prescription medicines
Luncheon meats	Over-the-counter medicines
Broth	Vitamin and mineral supplements
Pasta	Lipstick
Roux	Gloss and balms
Sauces	

TABLE 7. **Gluten-Free Grains and Starches**

Amaranth	Potato flour
Arrowroot	Quinoa
Buckwheat	Rice
Corn	Rice bran
Flax	Sago
Nuts, bean, and seed flour	Sorghum
Millet	Soy
Potato starch	Tapioca
Teff	

Although these proposed alternative methods of treatment for celiac disease offer some potentially exciting possibilities for the celiac population, any future treatment prescribed will have to be as effective and as safe as the gluten-free diet before it will be acceptable for general use.

Summary

- On the basis of strong evidence, gastrointestinal symptoms and failure to thrive are classic presentations of celiac disease, but atypical, nongastrointestinal symptoms are also extremely common, particularly in the older child and adolescent. (3)(4)(8)
- On the basis of some research evidence and consensus, guidelines recommend celiac testing in symptomatic children with typical and atypical symptoms and consideration of testing in those with associated conditions and first-degree relatives of those with celiac disease. (3)(9)
- On the basis of strong research evidence, measurement of tTG IgA and total serum IgA level has been reported to be the most cost-effective and accurate means of serologic testing for celiac disease and is the test of choice unless the child is younger than 2 years or IgA deficient. (9)
- On the basis of strong research evidence, children with elevated titers of celiac antibodies or strong clinical suspicion for celiac disease should be referred to a gastroenterologist for upper endoscopy and biopsy. Until this procedure is performed, the child should continue on a diet with ingestion of gluten. (3)(9)
- On the basis of strong research evidence, all those with a confirmed diagnosis of celiac disease should follow a strict gluten-free diet for life, with avoidance of all foods that contain wheat, barley, and rye ingredients. (3)(4)
- Referral to a health care professional with specialized knowledge of celiac disease and the gluten-free diet is critical because of the numerous ways, often hidden, in which gluten may be present in the diet and environment.

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PIR Quiz

1. You have recently diagnosed a 5-year-old patient as having celiac disease. Her father recently went to his internist, who performed "celiac genetic testing" that revealed that he has the HLA-DQ2 genotype. Which of the following statements is most accurate to inform the parents regarding the father's test results?
    A. The father should begin a gluten-free diet.
    B. The father should undergo an endoscopy to check for celiac disease.
    C. The HLA-DQ2 allele does not increase the risk of celiac disease.
    D. The HLA-DQ2 allele is present in 30% to 40% of the general population.
    E. The HLA-DQ2 allele is protective against celiac disease.
2. Current evidenced-based guidelines recommend testing for celiac disease in children and adults with which of the following unexplained symptoms and signs?
    A. Acne vulgaris.
    B. Atopic dermatitis.
    C. Dermatitis herpetiformis.
    D. Molluscum contagiosum.
    E. Seborrheic dermatitis.
3. A 14-year-old male patient presents to your office with a history of always being short but having fallen from the 10th to the 3rd percentile in the last 2 years. His only gastrointestinal symptom is periumbilical abdominal pain. His thyroid test results were within normal limits. You decide to evaluate him for celiac disease. Of the following, which is recommended as initial testing?
    A. Antiendomysium antibody IgA antibody and serum IgA level.
    B. Deaminated gliadin peptide.
    C. HLA testing for DQ2 and DQ8.
    D. Tissue transglutaminase IgA antibody and serum IgA level.
    E. Tissue transglutaminase IgA antibody, IgA level, and deaminated gliadin peptide.
4. A patient in your practice has anemia and diarrhea and a recent serologic screening result positive for celiac disease. You refer the patient to a gastroenterologist for endoscopy and duodenal biopsy, but the family questions the need for the procedure. Which of the following is the best explanation for why endoscopy is indicated for this patient?
    A. Endoscopy is necessary to confirm celiac disease and lifelong dietary commitment.
    B. Endoscopy is necessary to confirm Crohn disease and initiate important medicinal interventions.
    C. Endoscopy is necessary to determine whether the patient has irritable bowel syndrome.
    D. Endoscopy is necessary to evaluate for comorbid lactase deficiency and strict dietary regulations.
    E. Endoscopy is necessary to exclude lymphoma and avoid difficult treatment protocols.
5. The parents of a 6-year-old female patient recently diagnosed as having celiac disease are meeting with a nutritionist. The nutritionist discusses gluten-containing grain products to avoid and foods that can be green-lit, meaning these are gluten-free grains and starches their daughter can eat. Which of the following food products should be safe for their child with celiac disease?
    A. Barley.
    B. Bran.
    C. Couscous.
    D. Corn.
    E. Rye.

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Pediatrics in Review 2014;35;409
DOI: 10.1542/pir.35-10-409

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