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# Celiac disease: Managing a multisystem disorder

## ABSTRACT

Celiac disease is a multisystem autoimmune disorder that can cause symptoms involving the gastrointestinal tract and other organ systems such as the skin and bones. This paper reviews the pathogenesis, diagnosis, and management of celiac disease and associated diseases.

## KEY POINTS

Besides gastrointestinal symptoms, celiac disease is associated with a variety of diseases, including dermatitis herpetiformis, malabsorption of several nutrients (potentially leading to osteoporosis, iron deficiency anemia, and other disorders), and intestinal malignancies.

While serologic testing for immunoglobulin A antibodies to tissue transglutaminase can be used as an initial screening test for this condition, the confirmatory tests are invasive, involving upper endoscopy for duodenal biopsy in celiac disease and skin biopsy in dermatitis herpetiformis.

The only effective treatment is lifelong adherence to a gluten-free diet, and nonadherence is a common cause of refractory disease.

Concomitant conditions such as anemia and vitamin deficiency often require nutritional supplements. In addition, patients with dermatitis herpetiformis often require treatment with dapsone.

**C**ELIAC DISEASE is an autoimmune disorder that occurs in genetically predisposed individuals in response to ingestion of gluten. Its prevalence is about 0.7% of the US population.<sup>1</sup>

*See related editorial, page 228*

The gold standard for diagnosis is duodenal biopsy, in which the histologic features may include varying gradations of flattening of intestinal villi, crypt hyperplasia, and infiltration of the lamina propria by lymphocytes. Many patients have no symptoms at the time of diagnosis, but presenting symptoms can include diarrhea along with features of malabsorption,<sup>2</sup> and, in about 25% of patients (mainly adults), a bullous cutaneous disorder called dermatitis herpetiformis.<sup>3,4</sup> The pathogenesis of celiac disease and that of dermatitis herpetiformis are similar in that in both, ingestion of gluten induces an inflammatory reaction leading to the clinical manifestations.

The mainstay of treatment of celiac disease remains avoidance of gluten in the diet.

## ■ GENETIC PREDISPOSITION AND DIETARY TRIGGER

The pathogenesis of celiac disease has been well studied in both humans and animals. The disease is thought to develop by an interplay of genetic and autoimmune factors and the ingestion of gluten (ie, an environmental factor).

Celiac disease occurs in genetically predisposed individuals, ie, those who carry the HLA alleles *DQ2* (*DQA1\*05*, *DQB1\*02*), *DQ8* (*DQA1\*03*, *DQB1\*0302*), or both.<sup>5</sup>

Ingestion of gluten is necessary for the disease to develop. Gluten, the protein component of

TABLE 1

**Diseases associated with celiac disease**

**Endocrine**

Hashimoto thyroiditis  
Type 1 diabetes mellitus  
Addison disease  
Osteoporosis  
Osteopenia

**Dermatologic**

Dermatitis herpetiformis  
Alopecia areata

**Hepatic**

Autoimmune hepatitis  
Primary biliary cirrhosis  
Primary sclerosing cholangitis  
Nonalcoholic fatty liver disease

**Obstetric and gynecologic**

Amenorrhea  
Delayed menarche  
Early menopause  
Recurrent spontaneous abortion  
Infertility  
Loss of libido

**Neurologic**

Cerebellar ataxia  
Peripheral neuropathy  
Epilepsy  
Dementia

**Psychiatric**

Depression  
Schizophrenia

**Oncologic**

Intestinal T-cell lymphoma  
Adenocarcinoma of small intestine

**Cardiac**

Autoimmune myocarditis

Celiac disease occurs in carriers of HLA-DQ2, HLA-DQ8, or both

wheat, barley, and rye, contains proteins called prolamins, which vary among the different types of grain. In wheat, the prolamins are gliadin, which is alcohol-soluble. In barley the prolamins are hordein, and in rye it is secalin.<sup>4</sup> The prolamins content in gluten makes it resistant to degradation by gastric, pancreatic, and intestinal brush border proteases.<sup>6</sup> Gluten crosses the epithelial barrier and promotes an inflammatory reaction

by both the innate and adaptive immune systems that can ultimately result in flattening of villi and crypt hyperplasia (Figure 1).<sup>7</sup>

Tissue transglutaminase also plays a central role in the pathogenesis, as it further deaminates gliadin and increases its immunogenicity by causing it to bind to receptors on antigen-presenting cells with stronger affinity. Furthermore, gliadin-tissue transglutaminase complexes formed by protein cross-linkages generate an autoantibody response (predominantly immunoglobulin A [IgA] type) that can exacerbate the inflammatory process.<sup>8,9</sup>

Certain viral infections during childhood, such as rotavirus and adenovirus infection, can increase the risk of celiac disease.<sup>10-13</sup> Although earlier studies reported that breastfeeding seemed to have a protective effect,<sup>14</sup> as did introducing grains in the diet in the 4th to 6th months of life as opposed to earlier or later,<sup>15</sup> more recent studies have not confirmed these benefits.<sup>16,17</sup>

**CLINICAL FEATURES**

Most adults diagnosed with celiac disease are in their 30s, 40s, or 50s, and most are women.

**Diarrhea** remains a common presenting symptom, although the percentage of patients with celiac disease who present with diarrhea has decreased over time.<sup>18,19</sup>

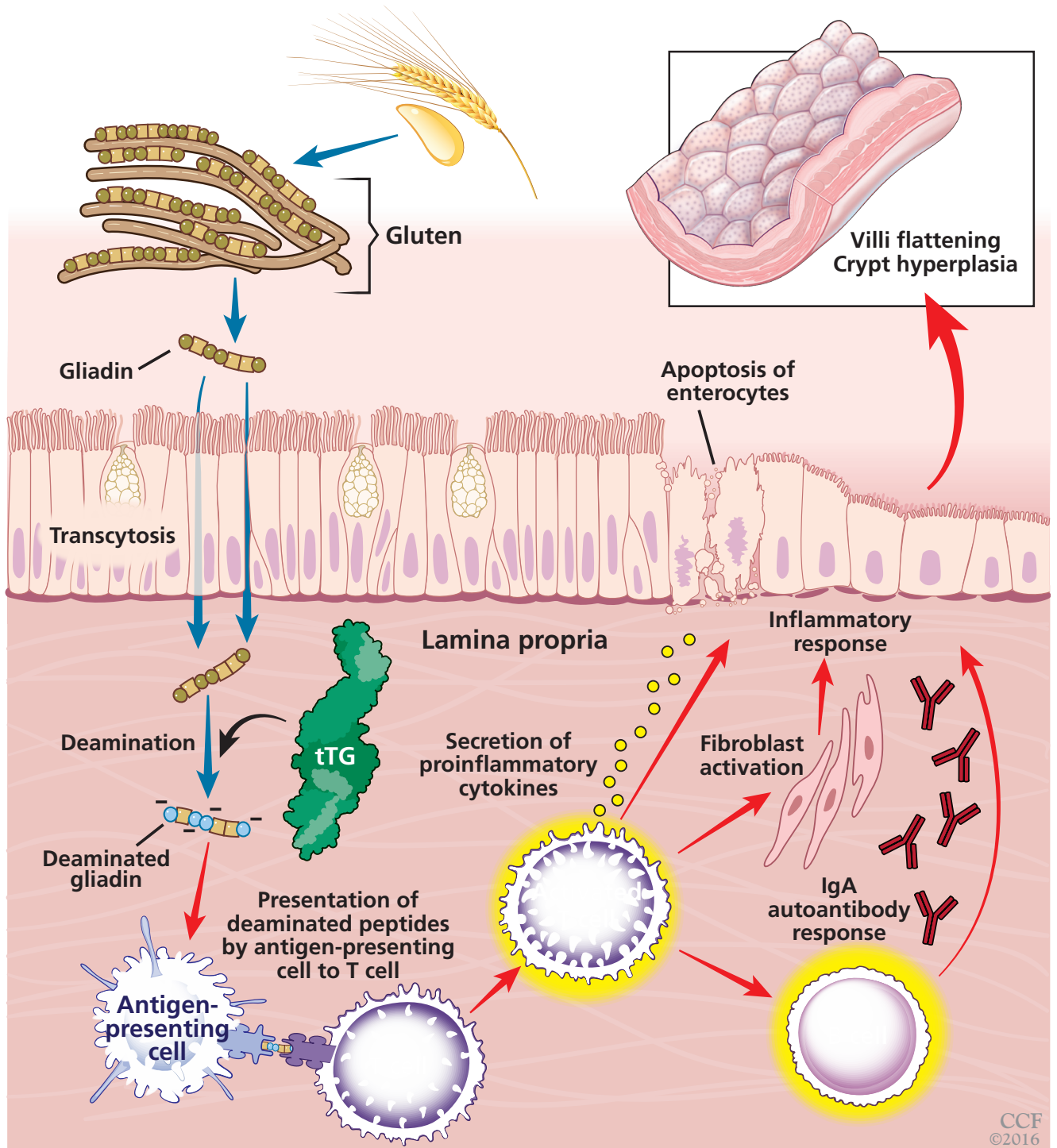
**Abdominal pain and weight loss** are also common.<sup>20</sup>

**Pallor or decreased exercise tolerance** can develop due to anemia from iron malabsorption, and some patients have **easy bruising** due to vitamin K malabsorption.

**Gynecologic and obstetric complications** associated with celiac disease include delayed menarche, amenorrhea, spontaneous abortion, intrauterine growth retardation, preterm delivery, and low-birth-weight babies.<sup>21,22</sup> Patients who follow a gluten-free diet tend to have a lower incidence of intrauterine growth retardation, preterm delivery, and low-birth-weight babies compared with untreated patients.<sup>21,22</sup>

**Osteoporosis and osteopenia** due to malabsorption of vitamin D are common and are seen in two-thirds of patients presenting with celiac disease.<sup>23</sup> A meta-analysis and position

# Pathogenesis of celiac disease



Medical Illustrator: David Schumick

**FIGURE 1.** Celiac disease is an autoimmune disorder that, in genetically susceptible individuals, is triggered by ingestion of foods containing gluten. IgA = immunoglobulin A; tTG = tissue transglutaminase.



**FIGURE 2.** Eroded and crusted erythematous plaques with scalloped borders on the elbow of a patient with dermatitis herpetiformis.

Photo courtesy of Alok Vij, Department of Dermatology, Cleveland Clinic.

statement from Canada concluded that dual-energy x-ray absorptiometry should be done at the time of diagnosis of celiac disease if the patient is at risk of osteoporosis.<sup>24</sup> If the scan is abnormal, it should be repeated 1 to 2 years after initiation of a gluten-free diet and vitamin D supplementation to ensure that the osteopenia has improved.<sup>24</sup>

### ■ OTHER DISEASE ASSOCIATIONS

Celiac disease is associated with various other autoimmune diseases (Table 1), including Hashimoto thyroiditis,<sup>25</sup> type 1 diabetes mellitus,<sup>26</sup> primary biliary cirrhosis,<sup>27</sup> primary sclerosing cholangitis,<sup>28</sup> and Addison disease.<sup>29</sup>

### Dermatitis herpetiformis

Dermatitis herpetiformis is one of the most common cutaneous manifestations of celiac disease. It presents between ages 10 and 50, and unlike celiac disease, it is more common in males.<sup>30</sup>

The characteristic lesions are pruritic, grouped erythematous papules surmounted by vesicles distributed symmetrically over the extensor surfaces of the upper and lower extremities, elbows, knees, scalp, nuchal area, and buttocks<sup>31</sup> (Figures 2 and 3). In addition, some patients also present with vesicles, erythematous macules, and erosions in the oral mucosa<sup>32</sup> or purpura on the palms and soles.<sup>33–35</sup>

The pathogenesis of dermatitis herpetiformis in the skin is related to the pathogenesis of celiac disease in the gut. Like celiac disease, dermatitis herpetiformis is more common in genetically predisposed individuals carrying either the *HLA-DQ2* or the *HLA-DQ8* haplotype. In the skin, there is an analogue of tissue transglutaminase called epidermal transglutaminase, which helps in maintaining the integrity of cornified epithelium.<sup>36</sup> In patients with celiac disease, along with formation of IgA antibodies to tissue transglutaminase, there is also formation of IgA antibodies to epidermal transglutaminase. IgA antibodies are deposited in the tips of dermal papillae and along the basement membrane.<sup>37–39</sup> These deposits then initiate an inflammatory response that is predominantly neutrophilic and results in formation of vesicles and bullae in the skin.<sup>40</sup> Also supporting the linkage between celiac disease and dermatitis herpetiformis, if patients adhere to a gluten-free diet, the deposits of immune complexes in the skin disappear.<sup>41</sup>

### ■ CELIAC DISEASE-ASSOCIATED MALIGNANCY

Patients with celiac disease have a higher risk of developing enteric malignancies, particularly intestinal T-cell lymphoma, and they have smaller increased risk of colon, oropharyngeal, esophageal, pancreatic, and hepatobiliary cancer.<sup>42–45</sup> For all of these cancers, the risk is higher than in the general public in the first year after celiac disease is diagnosed, but after the first year, the risk is increased only for small-bowel and hepatobiliary malignancies.<sup>46</sup>



### T-cell lymphoma

T-cell lymphoma is a rare but serious complication that has a poor prognosis.<sup>47</sup> Its prevalence has been increasing with time and is currently estimated to be around 0.01 to 0.02 per 100,000 people in the population as a whole.<sup>48,49</sup> The risk of developing lymphoma is 2.5 times higher in people with celiac disease than in the general population.<sup>50</sup> T-cell lymphoma is seen more commonly in patients with refractory celiac disease and *DQ2* homozygosity.<sup>51</sup>

This disease is difficult to detect clinically, but sometimes it presents as an acute exacerbation of celiac disease symptoms despite strict adherence to a gluten-free diet. Associated alarm symptoms include fever, night sweats, and laboratory abnormalities such as low albumin and high lactate dehydrogenase levels.

Strict adherence to a gluten-free diet remains the only way to prevent intestinal T-cell lymphoma.<sup>52</sup>

### Other malignancies

Some earlier studies reported an increased risk of thyroid cancer and malignant melanoma, but two newer studies have refuted this finding.<sup>53,54</sup> Conversely, celiac disease appears to have a protective effect against breast, ovarian, and endometrial cancers.<sup>55</sup>

## ■ DIAGNOSIS: SEROLOGY, BIOPSY, GENETIC TESTING

### Serologic tests

Patients strongly suspected of having celiac disease should be screened for IgA antibodies to tissue transglutaminase while on a gluten-containing diet, according to recommendations of the American College of Gastroenterology (Figure 4).<sup>56</sup> The sensitivity and specificity of this test are around 95%. If the patient has an IgA deficiency, screening should be done by checking the level of IgG antibodies to tissue transglutaminase.

### Biopsy for confirmation

If testing for IgA to tissue transglutaminase is positive, upper endoscopy with biopsy is needed. Ideally, one to two samples should be taken from the duodenal bulb and at least four samples from the rest of the duodenum, preferably from two different locations.<sup>56</sup>



**FIGURE 3.** Vesicles in a patient with dermatitis herpetiformis.

Photo courtesy of Alok Vij, MD, Department of Dermatology, Cleveland Clinic.

Celiac disease has a broad spectrum of pathologic expressions, from mild distortion of crypt architecture to total villous atrophy and infiltration of lamina propria by lymphocytes<sup>57</sup> (Figures 5 and 6). Because these changes can be seen in a variety of diarrheal diseases, their reversal after adherence to a gluten-free diet is part of the current diagnostic criteria for the diagnosis of celiac disease.<sup>56</sup>

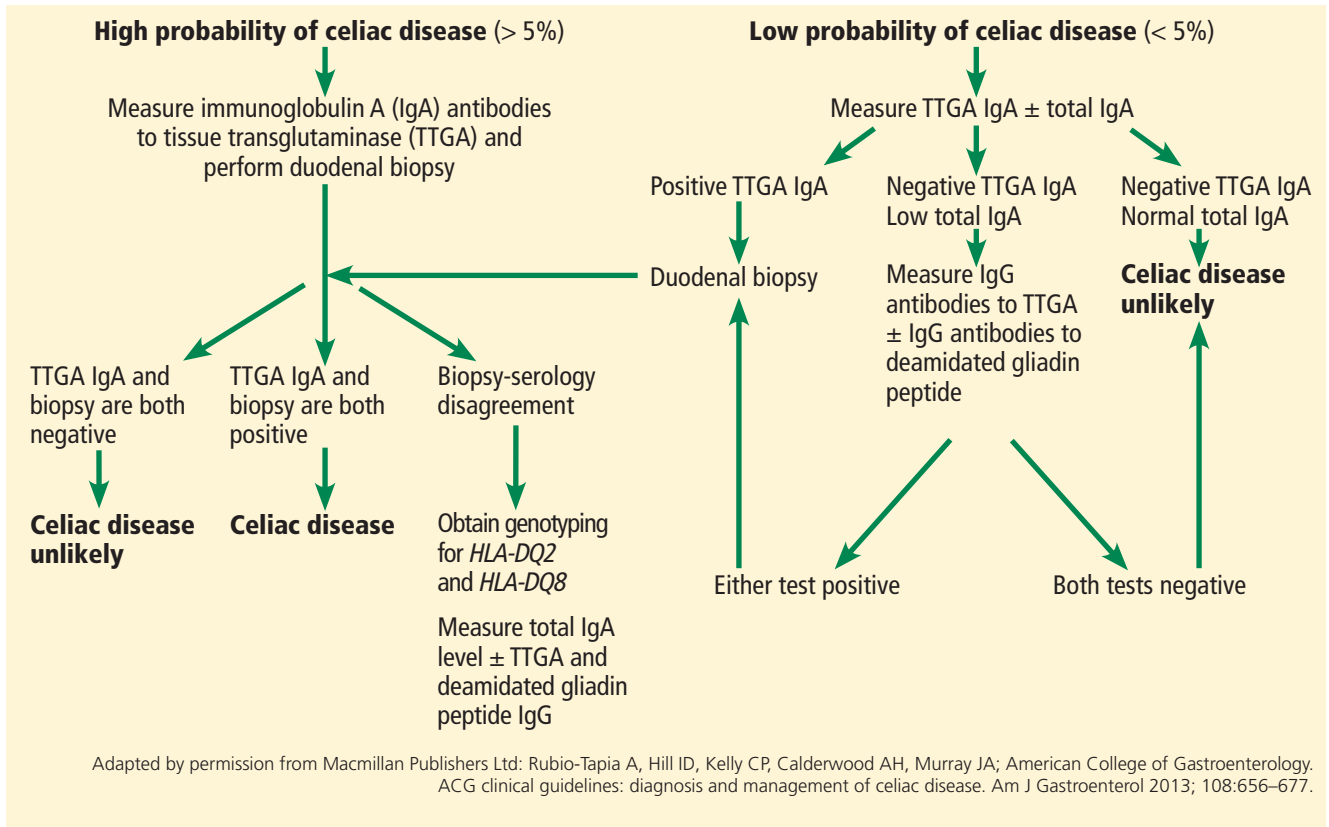
### Genetic testing

Although the combination of positive serologic tests and pathologic changes confirms the diagnosis of celiac disease, in some cases one type of test is positive and the other is negative. In this situation, genetic testing for *HLA-DQ2* and *HLA-DQ8* can help rule out the diagnosis, as a negative genetic test rules out celiac disease in more than 99% of cases.<sup>58</sup>

Genetic testing is also useful in patients who are already adhering to a gluten-free diet at the time of presentation to the clinic and who have had no testing done for celiac disease in the past. Here again, a negative test for both *HLA-DQ2* and *HLA-DQ8* makes a diagnosis of celiac disease highly unlikely.

If the test is positive, further testing needs to be done, as a positive genetic test cannot differentiate celiac disease from nonceliac gluten sensitivity. In this case, a gluten challenge needs to be done, ideally for 8 weeks, but for

**Osteoporosis and osteopenia due to malabsorption of vitamin D are common in celiac disease**



**FIGURE 4.**

**The combination of positive serologic tests and pathologic changes confirms the diagnosis of celiac disease**

at least 2 weeks if the patient cannot tolerate gluten-containing food for a longer period of time. The gluten challenge is to be followed by testing for antibodies to tissue transglutaminase or obtaining duodenal biopsies to confirm the presence or absence of celiac disease.

#### Standard laboratory tests

Standard laboratory tests do not help much in diagnosing celiac disease, but they should include a complete blood chemistry along with a complete metabolic panel. Usually, serum albumin levels are normal.

Due to malabsorption of iron, patients may have iron deficiency anemia,<sup>59</sup> but anemia can also be due to a deficiency of folate or vitamin B<sub>12</sub>. In patients undergoing endoscopic evaluation of iron deficiency anemia of unknown cause, celiac disease was discovered in approximately 15%.<sup>60</sup> Therefore, some experts believe that any patient presenting with unexplained iron deficiency anemia should be screened for celiac disease.

Because of malabsorption of vitamin D, levels of vitamin D can be low.

Elevations in levels of aminotransferases are also fairly common and usually resolve after the start of a gluten-free diet. If they persist despite adherence to a gluten-free diet, then an alternate cause of liver disease should be sought.<sup>61</sup>

#### Diagnosis of dermatitis herpetiformis

When trying to diagnose dermatitis herpetiformis, antibodies against epidermal transglutaminase can also be checked if testing for antibody against tissue transglutaminase is negative. A significant number of patients with biopsy-confirmed dermatitis herpetiformis are positive for epidermal transglutaminase antibodies but not for tissue transglutaminase antibodies.<sup>62</sup>

The confirmatory test for dermatitis herpetiformis remains skin biopsy. Ideally, the sample should be taken while the patient is on a gluten-containing diet and from an area of normal-appearing skin around the lesions.<sup>63</sup> On histopathologic study, neutrophilic infiltrates are seen in dermal papillae and a perivascular lymphocytic infiltrate can also be

seen in the superficial zones.<sup>64</sup> This presentation can also be seen in other bullous disorders, however. To differentiate dermatitis herpetiformis from other disorders, direct immunofluorescence is needed, which will detect granular IgA deposits in the dermal papillae or along the basement membrane, a finding pathognomonic of dermatitis herpetiformis.<sup>63</sup>

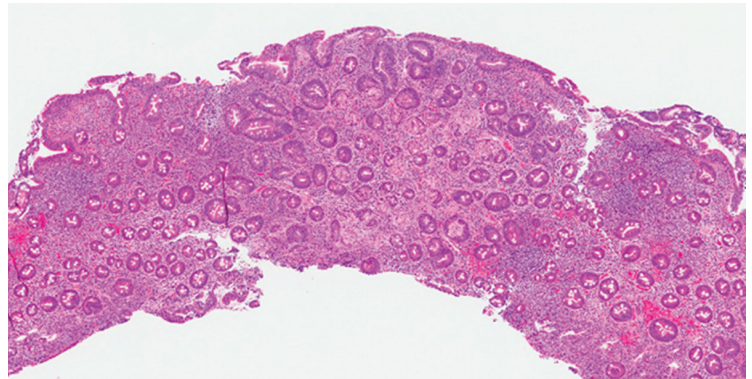
### ■ A GLUTEN-FREE DIET IS THE MAINSTAY OF TREATMENT

The mainstay of treatment is lifelong adherence to a gluten-free diet. Most patients report improvement in abdominal pain within days of starting this diet and improvement of diarrhea within 4 weeks.<sup>65</sup>

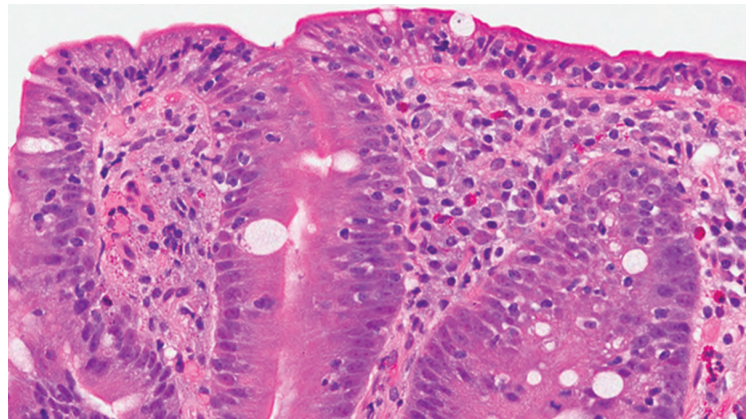
The maximum amount of gluten that can be tolerated is debatable. A study established that intake of less than 10 mg a day is associated with fewer histologic abnormalities,<sup>66</sup> and an earlier study noted that intake of less than 50 mg a day was clinically well tolerated.<sup>67</sup> But patients differ in their tolerance for gluten, and it is hard to predict what the threshold of tolerance for gluten will be for a particular individual. Thus, it is better to avoid gluten completely.

According to the US Food and Drug Administration, a food can be labeled as gluten-free if it is inherently gluten-free. If the food has a gluten-containing grain, then it should be processed to remove the gluten, and the resultant food product should not contain more than 20 parts per million of gluten. Gluten-free products that have gluten-containing grain that has been processed usually have a label indicating the gluten content in the food in parts per million.

Patients who understand the need to adhere to a gluten-free diet and the implications of not adhering to it are generally more compliant. Thus, patients need to be strongly educated that they need to adhere to a gluten-free diet and that nonadherence can cause further damage to the gut and can pose a higher risk of malignancy. Even though patients are usually concerned about the cost of gluten-free food and worry about adherence to the diet, these factors do not generally limit diet adherence.<sup>68</sup> All patients diagnosed with celiac disease should meet with a registered dietitian to



**FIGURE 5.** Low-power view of a duodenal biopsy sample in a patient with celiac disease shows altered duodenal mucosal architecture with villous blunting and crypt hyperplasia (hematoxylin and eosin, original magnification  $\times 20$ ).



**FIGURE 6.** There are increased intraepithelial lymphocytes, including at the tips of villi, as well as an expanded lamina propria lymphoplasmacellular infiltrate (hematoxylin and eosin, original magnification  $\times 20$ ).

Photomicrograph courtesy of Homer Wiland MD, Department of Pathology, Cleveland Clinic.

discuss diet options based on their food preferences and to better address all their concerns.

With increasing awareness of celiac disease and with increasing numbers of patients being diagnosed with it, the food industry has recognized the need to produce gluten-free items. There are now plenty of food products available for these patients, who no longer have to forgo cakes, cookies, and other such items. Table 2 lists some common foods that patients with celiac disease can consume.

### Nutritional supplements for some

If anemia is due purely to iron deficiency, it may resolve after starting a gluten-free diet, and no additional supplementation may be



**TABLE 2**

**Foods that can be eaten on a gluten-free diet**

**Foods allowed**

Beans	Vegetables	Potatoes
Seeds	Dairy products	Vegetable oil
Nuts (unprocessed)	Corn	Olive oil
Fresh eggs	Millet	Rice cakes
Fresh meat	Rice	Homemade popcorn
Fish	Sorghum	Tea
Poultry	Soy	Coffee
Fruits	Oats	Fresh juices

**Foods allowed if they are labeled as gluten-free**

Beer	Cereals	Salad dressings
Bread	Cookies	Milk puddings
Cakes	Crackers	Ice creams
Pies	French fries	
Candies	Pasta	

**A negative test for both HLA-DQ8 and HLA-DQ2 makes celiac disease highly unlikely**

needed. However, if it is due to a combination of iron plus folate or vitamin B<sub>12</sub> deficiency, then folate, vitamin B<sub>12</sub>, or both should be given.

In addition, if the patient is found to have a deficiency of vitamin D, then a vitamin D supplement should be given.<sup>69</sup> At the time of diagnosis, all patients with celiac disease should be screened for deficiencies of vitamins A, B<sub>12</sub>, D, E, and K, as well as copper, zinc, folic acid, and iron.

**Follow-up at 3 to 6 months**

A follow-up visit should be scheduled for 3 to 6 months after the diagnosis and after that on an annual basis, and many of the abnormal laboratory tests will need to be repeated.

If intestinal or extraintestinal symptoms or nutrient deficiencies persist, then the patient's adherence to the gluten-free diet needs to be checked. Adherence to a gluten-free diet can be assessed by checking for serologic markers of celiac disease. A decrease in baseline values can be seen within a few months of starting the diet.<sup>70</sup> Failure of serologic markers to decrease by the end of 1 year of a gluten-free diet usually indicates gluten contamination.<sup>71</sup> If adherence is confirmed (ie, if baseline values fall) but symptoms persist, then further workup needs to be done to find the cause of refractory disease.

**Skin lesions should also respond to a gluten-free diet**

The first and foremost therapy for the skin lesions in dermatitis herpetiformis is the same as that for the intestinal manifestations in celiac disease, ie, adherence to a gluten-free diet. Soon after patients begin a gluten-free diet, the itching around the skin lesions goes away, and over time, most patients have complete resolution of the skin manifestations.

**Dapsone** is also frequently used to treat dermatitis herpetiformis if there is an incomplete response to a gluten-free diet or as an adjunct to diet to treat the pruritus. Patients often have a good response to dapsone.<sup>72</sup>

The recommended starting dosage is 100 to 200 mg a day, and a response is usually seen within a few days. If the symptoms do not improve, the dose can be increased. Once the lesions resolve, the dose can be tapered and patients may not require any further medication. In some cases, patients may need to be chronically maintained on the lowest dose possible, due to the side effects of the drug.<sup>3</sup>

Dapsone is associated with significant adverse effects. Methemoglobinemia is the most common and is seen particularly in dosages exceeding 200 mg a day. Hemolytic anemia, another common adverse effect, is seen with dosages of more than 100 mg a day. Patients with a deficiency of glucose-6-phosphate dehydrogenase (G6PD) are at increased risk of hemolysis, and screening for G6PD deficiency is usually done before starting dapsone. Other rare adverse effects of dapsone include agranulocytosis, peripheral neuropathy, psychosis,<sup>73</sup> pancreatitis, cholestatic jaundice, bullous and exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, nephrotic syndrome, and renal papillary necrosis.

Besides testing for G6PD deficiency, a complete blood cell count, a reticulocyte count, a hepatic function panel, renal function tests, and urinalysis should be done before starting dapsone therapy and repeated while on therapy. The complete blood cell count and reticulocyte count should be checked weekly for the first month, twice a month for the next 2 months, and then once every 3 months. Liver and renal function tests are to be done once every 3 months.<sup>74</sup>



## ■ NOVEL THERAPIES BEING TESTED

Research is under way for other treatments for celiac disease besides a gluten-free diet.

**Larazotide** (Alba Therapeutics, Baltimore, MD) is being tested in a randomized, placebo-controlled trial. Early results indicate that it is effective in controlling both gastrointestinal and nongastrointestinal symptoms of celiac disease, but it still has to undergo phase 3 clinical trials.

**Sorghum** is a grain commonly used in Asia and Africa. The gluten in sorghum is different from that in wheat and is not immunogenic. In a small case series in patients with known celiac disease, sorghum did not induce diarrhea or change in levels of antibodies to tissue transglutaminase.<sup>75</sup>

**Nonimmunogenic wheat** that does not contain the immunogenic gluten is being developed.

**Oral enzyme supplements** called glutenases are being developed. Glutenases can cleave gluten, particularly the proline and glutamine residues that make gluten resistant to degradation by gastric, pancreatic, and intestinal brush border proteases. A phase 2 trial of one of these oral enzyme supplements showed that it appeared to attenuate mucosal injury in patients with biopsy-proven celiac disease.<sup>76</sup>

These novel therapies look promising, but for now the best treatment is lifelong adherence to the gluten-free diet.

## ■ NONRESPONSIVE AND REFRACTORY CELIAC DISEASE

Celiac disease is considered nonresponsive if its symptoms or laboratory abnormalities persist after the patient is on a gluten-free diet for 6 to 12 months. It is considered refractory if symptoms persist or recur along with villous atrophy despite adherence to the diet for more than 12 months in the absence of other causes of the symptoms. Refractory celiac disease can be further classified either as type 1 if there are typical intraepithelial lymphocytes, or as type 2 if there are atypical intraepithelial lymphocytes.

Celiac disease is nonresponsive in about 10% to 19% of cases,<sup>76</sup> and it is refractory in 1% to 2%.<sup>77</sup>

## Managing nonresponsive celiac disease

The first step in managing a patient with nonresponsive celiac disease is to confirm the diagnosis by reviewing the serologic tests and the biopsy samples from the time of diagnosis. If celiac disease is confirmed, then one should re-evaluate for gluten ingestion, the most common cause of nonresponsiveness.<sup>78</sup> If strict adherence is confirmed, then check for other causes of symptoms such as lactose or fructose intolerance. If no other cause is found, then repeat the duodenal biopsies with flow cytometry to look for CD3 and CD8 expression in T cells in the small-bowel mucosa.<sup>79</sup> Presence or absence of villous atrophy can point to possible other causes of malabsorption including pancreatic insufficiency, small intestinal bowel overgrowth, and microscopic colitis.

## Managing refractory celiac disease

Traditionally, corticosteroids have been shown to be beneficial in alleviating symptoms in patients with refractory celiac disease but do not improve the histologic findings.<sup>80</sup> Because of the adverse effects associated with long-term corticosteroid use, azathioprine has been successfully used to maintain remission of the disease after induction with corticosteroids in patients with type 1 refractory celiac disease.<sup>81</sup>

Cladribine, a chemotherapeutic agent used to treat hairy cell leukemia, has shown some benefit in treating type 2 refractory celiac disease.<sup>82</sup>

In type 2 refractory celiac disease, use of an immunomodulator agent carries an increased risk of transformation to lymphoma.

Because of the lack of a satisfactory response to the agents available so far to treat refractory celiac disease, more treatment options acting at the molecular level are being explored.

## ■ NONCELIAC GLUTEN SENSITIVITY DISORDER

Nonceliac gluten sensitivity disorder is an evolving concept. The clinical presentation of this disorder is similar to celiac disease in that patients may have diarrhea or other extra-intestinal symptoms when on a regular diet and have resolution of symptoms on a gluten-free diet. But unlike celiac disease, there is no serologic or histologic evidence of celiac disease even when patients are on a regular diet.

**Screen all patients with celiac disease for deficiencies of vitamins A, B<sub>12</sub>, D, E, and K and copper, zinc, folic acid, and iron**

One of every 17 patients who presents with clinical features suggestive of celiac disease is found to have nonceliac gluten sensitivity disorder, not celiac disease.<sup>83</sup> In contrast to celiac disease, in which the adaptive immune system is thought to contribute to the disease process, in nonceliac gluten sensitivity disorder the innate immune system is believed to play the dominant role,<sup>84</sup> but the exact pathogenesis of the disease is still unclear.

The diagnosis of nonceliac gluten sensitivity disorder is one of exclusion. Celiac disease

needs to be ruled out by serologic testing and by duodenal biopsy while the patient is on a regular diet, and then a trial of a gluten-free diet needs to be done to confirm resolution of symptoms before the diagnosis of nonceliac gluten sensitivity disorder can be established.

As with celiac disease, the treatment involves adhering to a gluten-free diet, but it is still not known if patients need to stay on it for the rest of their life, or if they will be able to tolerate gluten-containing products after a few years.

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