This review will focus on the pathogenesis, clinical manifestations, diagnosis, and management of celiac disease (CD). Given an increasing awareness of gluten-related disorders, medical professionals of all varieties are encountering patients with a diagnosis of CD or who are thought to have food intolerances to gluten. The prevalence of CD among the general population is estimated to be 1% in Western nations, and there is growing evidence for underdiagnosis of the disease, especially in non-Western nations that were traditionally believed to be unaffected. The development of serologic markers specific to CD has revolutionized the ability both to diagnose and monitor patients with the disease. Additionally, understanding of the clinical presentations of CD has undergone a major shift over the past half century. Although it is well understood that CD develops in genetically predisposed subjects exposed to gluten, the extent of other environmental factors in the pathogenesis of the disease is an area of continued research. Currently, the main therapeutic intervention for CD is a gluten-free diet; however, novel nondietary agents are under active investigation. Future areas of research should also help us understand the relationship of CD to other gluten-related disorders. (J Allergy Clin Immunol 2015;135:1099-106.)

Key words: Celiac disease, gluten intolerance, food allergy

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Food sensitivities are increasing in prevalence within the general population, and wheat-related proteins play a prominent contributing role in this trend. Wheat is composed of 4 classes of proteins divided on the basis of their solubility in different solvents: water (albumins), dilute salt solutions (globulins), aqueous alcohol (gliadins), and dilute alkali or acid (glutenins). The role of these various proteins in the development of disease is an expanding area of study. Currently, there are 3 major wheat-related food illnesses: celiac disease (CD), nonceliac gluten sensitivity (NCGS), and wheat allergy. Although there might be an overlap in the symptoms associated with NCGS, wheat allergy, and CD, the conditions have distinct characteristics.

CD is an autoimmune disorder involving both an innate and adaptive immune response that occurs among genetically predisposed subjects who are exposed to gluten-containing foods and other environmental factors. Unlike food allergies, the pathogenesis of CD is not mediated by an immediate hypersensitivity reaction through an IgE-dependent mechanism. Instead, gluten protein is the pathogenic agent activated by the enzyme tissue

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Activity Objectives
1. To describe the epidemiology of celiac disease.
2. To understand the pathophysiology of celiac disease.
3. To use appropriate screening and confirmatory tests for celiac disease.

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transglutaminase (TG), allowing its presentation to CD4+ T cells in the lamina propria of the small intestine. The release of cytokines results in histologic changes in the intestinal mucosa (e.g., intraepithelial lymphocytosis and villous atrophy) and a resulting variety of clinical manifestations (e.g., abdominal pain, diarrhea, anemia, osteoporosis, and failure to thrive).3

At the same time that CD is becoming more common, the entity of NCGS is also gaining recognition.4,7 NCGS is a term that refers to a spectrum of clinical phenotypes in which ingestion of gluten or other wheat-related proteins is thought to produce gastrointestinal and other extraintestinal symptoms that often overlap with symptoms seen in patients with CD (e.g., abdominal pain, diarrhea, fatigue, rash, and depression). However, unlike CD, there are no characteristic histologic or serologic abnormalities identified. Indeed, there is much disagreement as to what extent NCGS is a true clinical entity.5

Wheat allergy is distinct from both CD and NCGS in that it is an IgE-mediated hypersensitivity response that occurs within minutes to hours of wheat ingestion.3 The main routes of sensitization are through oral ingestion of wheat products or inhalation of wheat flour.9 The clinical spectrum of wheat allergy includes gastrointestinal and respiratory symptoms (also referred to as baker’s asthma), exercise-induced anaphylaxis, and contact urticaria. The gastrointestinal symptoms that develop after wheat ingestion can include abdominal pain, bloating, and flatulence, and these occur more often in children than in adults, with a peak at age 1 year. The protein of wheat responsible for allergic reactions resides in the albumin/globulin fraction (nongluten). The amylase trypsin inhibitors present in wheat are considered a true clinical entity.6

Several European countries, the overall prevalence is also near 1%, although exact percentages vary by country (e.g., 0.3% in Germany, 0.7% in Italy, 1.2% in England, and 2.4% in Finland).10-13 The distribution of CD also extends beyond persons primarily of European ancestry, with significant prevalence identified in such disparate populations as the Middle East, Asia, South America, and North Africa.14-17 One proposed reason for this trend is that, with a globalizing world market, developing nations that traditionally relied on gluten-free grains, such as rice and maize, are increasingly incorporating wheat-based foods into their diets.18 As more mass screening studies are performed in different populations, more cases of previously undiagnosed CD are identified. Particularly on a global scale, there is evidence that CD is a missed diagnosis in many children in whom infection and malnutrition are quite common and the presumed cause for diarrheal illness.19-23

Sex differences also exist with respect to the rate of diagnosis of CD. One study found a female/male ratio of 2 to 3:1. The sex difference was true only in diagnoses made in adulthood, in which iron deficiency anemia was a significant presenting manifestation among women.24 However, there is indication that the prevalence among male and female subjects based on serologic screening is comparable at about 1%.26,27 The differential rates of diagnosis among sexes is thought to reflect several factors, including a higher rate of autoimmune disease among women in general, more regular health care interaction in female than male subjects, and a higher likelihood of symptomatic disease among women than men.28

Among the pediatric population, diarrhea and malabsorption syndrome are seen in the very young, whereas growth issues (failure to thrive and short stature) occur in children of all ages. Recurrent abdominal pain and screening of high-risk groups account for the other clinical presentations and are more common in older children.29 The age at diagnosis has also increased over

### Abbreviations used
- AN-PEP: Aspergillus niger prolyl endopeptidase
- CD: Celiac disease
- DH: Dermatitis herpetiformis
- EMA: Endomysial antibody
- GFD: Gluten-free diet
- NCGS: Nonceliac gluten sensitivity
- TTG: Tissue transglutaminase

### PATHOGENESIS OF CELIAC DISEASE

#### GENETIC FACTORS
- HLA DQ2/8

#### EPITHELIUM
- Innate response
- Lamina propria
- Adaptive response

#### ENVIRONMENTAL FACTORS
- Intraepithelial lymphocytosis
- Villous atrophy

#### AUTOANTIBODIES
- (TTG, EMA)

#### GASTROINTESTINAL AND SYSTEMIC MANIFESTATIONS

**FIG 1.** The pathogenesis of CD involves a triad of predisposing genes, gluten, and environmental factors. The main genes in CD are the HLA-DQ2 and/or HLA-DQ8 haplotypes. Dietary gluten is the major exposure among patients with CD. Numerous other environmental factors influence the development of CD but are less well defined than gluten. The reaction to gluten fragments occurs at the small intestinal epithelium, with both an innate and adaptive immune response. The results are characteristic autoantibodies, histologic changes (intraepithelial lymphocytosis and villous atrophy), and clinical symptoms (e.g., diarrhea or iron deficiency anemia).
time in the pediatric population, and there has been an increase in the diagnosis of CD in adulthood. Adults present less with intestinal manifestations and instead with abnormalities, such as iron deficiency anemia or osteoporosis.

Pathogenesis

Genes. The pathogenesis of CD is dependent on the interaction of a triad of genes, gluten, and environmental influences (Fig 1). The underlying predisposing genes among patients with CD primarily consist of 2 HLA class II genes: HLA-DQ2 (DQA1*05-DQB1*02) and HLA-DQ8 (DQA1*03-DQB1*0302). Various other non-HLA genes are thought to contribute to the development of CD in different populations; however, HLA-DQ2 and/or HLA-DQ8 are present in virtually all patients with CD. Although not sufficient for the diagnosis, given that 30% to 40% of the general population are carriers for at least 1 of these alleles, the absence of either HLA-DQ2 or HLA-DQ8 has a negative predictive value of nearly 100% in excluding the diagnosis of CD.

Gluten. In addition to a genetic predisposition, the development of CD relies on exposure to dietary gluten, a ubiquitous feature of Western populations. Gluten proteins actually encompass both gliadins, which contain monomeric proteins, and glutenins, which are polymeric aggregated proteins. These proteins are rich in alcohol-soluble proline and glutamine peptides, which are poorly digested in the human gastrointestinal tract because they resist degradation by luminal and brush border endopeptidases. Once consumed, gluten is partially digested into gliadin fragments that gain entry through the epithelial barrier of the intestinal mucosa in the setting of increased mucosal permeability. It is in the lamina propria that an important step in the immunopathogenesis of CD occurs as a result of the activity of the enzyme TTG. Gliadin is deamidated by the enzyme TTG, rendering it a more immunogenic molecule with effects on the adaptive immune system.

The adaptive immune response to gliadin involves antigen-presenting cells, such as macrophages, dendritic cells, and B cells, which express the HLA class II DQ2 and/or DQ8 molecules on their surfaces and uptake and display gliadin peptides. These antigen-presenting cells interact with gliadin-specific CD4+ T cells, which produce inflammatory cytokines, such as IFN-γ.

The innate immune response to gliadin occurs in the epithelial component of the intestinal mucosa and involves increased production of cytokines, in particular IL-15, which is proliferated by enterocytes, macrophages, and dendritic cells. The result is the differentiation of intraepithelial lymphocytes into cytotoxic CD8+ T cells that express the natural killer cell marker NK-G2D. In addition, production of IL-15 also promotes upregulation of the epithelial ligand for NK-G2D, which is the MHC class I chain–related A molecule. The cumulative resulting damage to the intestinal mucosa from this cascade of inflammatory mediators manifests as villous atrophy and crypt hyperplasia, the characteristic histologic findings of CD.

Environment. Whereas predisposing genes and ingestion of gluten are both pivotal to the development of CD, most HLA-DQ2/DQ8 carriers (about 30% of the population) who are exposed to gluten (>99% of the population) do not have CD. In fact, only 1% of the population has CD, indicating the importance of environmental factors. Various environmental factors other than gluten have been implicated in the pathogenesis of CD, from vitamin D to season of birth. In particular, early-life factors that influence the intestinal environment, such as breast-feeding, infection, and alterations in the intestinal microbiota, have gained much interest. For example, it has been suggested that infections of the gastrointestinal tract in infancy and adulthood are a risk factor for later development of CD. The rationale was that an increased permeability between epithelial enterocytes allows the entry of proteins, such as gliadin, into the lamina propria; infections might activate TTG; and infections lead to increased interferon production. However, some studies showed no significant association between infections during infancy and the subsequent development of CD.

Infant feeding practices have also been implicated in the development of CD, with conflicting conclusions. Some studies show a protective effect of breast-feeding, especially in those infants who are breast-fed during dietary gluten introduction, whereas other studies show no such effect. Until quite recently, the consensus of data suggested that breast-feeding might have a protective effect against the development of CD, especially if continued during a period of gluten introduction at 4 to 6 months of age. Infants at this age were thought to be in a window of developing immune tolerance to intestinal antigens, and therefore gluten exposure during this period could prove protective against the development of CD. However, 2 recently published studies refute the protective effect of either breast-feeding or the administration of gluten at early (at 4-6 months) versus delayed (up to 12 months) time points.

The degree to which the intestinal microbiome is an environmental influence in the development of CD is also an emerging field of investigation. An early association between the altered microbiome in patients with CD was demonstrated in analysis of duodenal biopsy specimens in children with CD who were either treated or untreated on a gluten-free diet (GFD). Those with untreated CD had increased proportions of Bacteroides species along with reductions of Bifidobacterium species compared with both those with CD who were symptom free on a GFD and control subjects who did not have CD. Furthermore, the proportions of Bacteroides versus Bifidobacterium species normalized in patients with untreated CD once controlled with a GFD, suggesting a potential marker or pathogenic role of certain intestinal species. Several of the factors that increase the risk of CD, such as antibiotic and proton pump inhibitor use, support an important role of the microbiome.

To this point, a recent randomized, placebo-controlled trial examined the effect of daily administration of a Bifidobacterium species along with a GFD among patients with CD, looking in particular at the resulting cytokine and secretory IgA profile, as well as intestinal microbiome composition. Results of the study showed a decrease in Bacteroides species, as well as secretory IgA levels in stools, adding more favorable evidence for a pathogenic influence from the proportion of certain bacteria in the development of CD. Although these studies present promising results, further research is necessary before asserting conclusions on the immunopathogenic or therapeutic role of the intestinal microbiome in patients with CD.

Clinical presentation

The clinical presentation of CD is varied, and patients can present with a spectrum of intestinal and extraintestinal
TABLE I. Serologic testing for CD

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTG IgA</td>
<td>Highly sensitive and specific first-line test</td>
</tr>
<tr>
<td>EMA IgA</td>
<td>Highly specific but operator-dependent test</td>
</tr>
<tr>
<td>Deamidated gliadin peptide IgG</td>
<td>Might be increased in IgA-deficient patients with CD</td>
</tr>
<tr>
<td>TTG IgG</td>
<td>Might be increased in IgA-deficient patients with CD</td>
</tr>
<tr>
<td>Antigliadin antibody IgA and IgG</td>
<td>Not as sensitive or specific as TTG</td>
</tr>
<tr>
<td>Total IgA</td>
<td>Screens patient for selective IgA deficiency</td>
</tr>
</tbody>
</table>

Diagnosis and management

Serology. The diagnosis of CD relies on both serologic and histologic studies, as well as a response to a GFD. Along with symptomatic disease, many patients with CD are now given diagnoses through serologic screening of at-risk populations. Groups at increased risk include family members of an affected subject and persons with type 1 diabetes or Down syndrome. Overall, despite increased awareness of the disease and increased awareness of gluten, the rate of diagnosis in the United States remains low, with less than 20% of those with CD receiving a diagnosis. Given that CD overall is underdiagnosed and that the majority of presentations are not overt gastrointestinal symptoms, some argue for routine screening of the general population. However, this strategy is not yet recommended. Instead, targeted screening of symptomatic subjects and those at increased risk is advised.

Currently, various assays for detecting specific antibodies associated with CD are available. These include antibodies against deamidated gliadin peptide, the TTG, and the endomysium (Table I). Endomysial antibodies (EMAs; anti-endomysial IgA) are directed at reticulin-like structures of the gastrointestinal smooth muscle and have been shown to have a specificity for the diagnosis of CD near 100%. However, obtaining a diagnosis with EMA measurement is relatively expensive and performed through immunofluorescence and requires microscopic evaluation with potential interobserver variation. Therefore IgA TTG measurement is the initial test of choice and is highly sensitive and specific for the diagnosis of CD. Conversely, the older antibodies to native gliadin antibodies are not sensitive or specific enough for the diagnosis of CD. Deamidated gliadin peptide antibodies might be more sensitive only in the pediatric population for infants younger than 18 months. Because selective IgA deficiency occurs in up to 1 in 40 patients with CD, total IgA levels should also be determined in addition to specific IgA autoantibody tests. If IgA deficiency is observed, testing for IgG antibodies against TTG or deamidated gliadin peptide is suggested.

Histology. In addition to serologic testing, biopsy of the small intestinal mucosa for evaluation of histologic evidence of CD is part of the diagnostic evaluation. Currently, European guidelines suggest an exception to this rule among the pediatric population in which upper endoscopy for biopsy can be bypassed: symptomatic children considered otherwise to have a strong pretest probability for CD (eg, strongly positive IgA TTG, EMA antibody, and HLA-DQ2/DQ8 results). When performed, the biopsy should occur while a patients is on a gluten-containing diet for at least 2 to 8 weeks, and at least 4 to 6 endoscopic specimens (including from the duodenal bulb) should be retrieved to ensure adequate sampling of the often-patchy disease process.

The most commonly used system for grading the degree of mucosal damage observed in patients with CD is the Marsh classification, which divides histologic findings of CD into 3 main subgroups of increasing severity from intraepithelial lymphocytosis to crypt hyperplasia, partial villous atrophy, and subtotal or total villous atrophy (Fig 2). Rarely, in about 10% of cases, findings on biopsy are inconsistent with serologic data, and there remains uncertainty regarding the diagnosis of CD. For instance, those patients who lack autoantibodies consistent with CD but who have histologic changes characteristic of CD (eg, villous atrophy) can be classified as having seronegative CD. However, once this diagnosis is entertained, it is important to evaluate for other potential causes of intestinal villous atrophy.
GFD. The mainstay of treatment for CD is a GFD, which entails avoidance of the gluten-containing grains wheat, rye, and barley. Acceptable grains include rice, oats, buckwheat, corn, millet, and quinoa. A patient given a diagnosis of CD benefits from a consultation with a nutritionist who can help with appropriate food selection and avoidance. Although the availability of gluten-free foods is still generally limited and there is a higher financial cost associated with following a GFD, recent years have witnessed an increase in the market advertising gluten-free products.\(^8\)\(^1\)\(^8\)\(^2\) In this setting there is also increased regulatory oversight in labeling foods as gluten free and ensuring compliance with a standardized definition (typically <20 parts per million) of such products.\(^8\)\(^3\)\(^8\)\(^4\)

Although the GFD is a therapeutic treatment to which a patient with CD must adhere to avoid active disease, with its attendant symptoms and complications, it has gained popularity among many persons without CD. Indeed, the global market for gluten-free products neared $2.5 billion (US dollars) in international sales in 2010.\(^4\) Part of the use of a GFD stems from patients with the poorly defined clinical entity of NCGS. As mentioned above, there is no general consensus on what constitutes NCGS. The prevalence of this condition is difficult to approximate, with some estimates ranging from 3% to 6%.\(^8\)\(^5\) However, our analysis of recent National Health and Nutrition Examination Survey data revealed that only about 0.5% of the US population are adhering to a GFD in the absence of CD.\(^9\) Typically, NCGS is a self-diagnosis. CD needs to be excluded in these patients, a task made difficult by the fact that they are already on a GFD. However, the diagnosis of NCGS is one of exclusion on the basis of serologic and histologic studies not consistent with CD in a patient who experiences symptoms similar to CD with improvement on a GFD and recurrence of symptoms with reintroduction of gluten.\(^9\)\(^5\)

Whether gluten is the pathogenic agent in NCGS or whether there are yet unidentified wheat proteins involved in its pathogenesis is unclear. One study of patients who avoid wheat, gluten, or both in the absence of CD found alternative diagnoses in 30% of patients (eg, small intestinal bacterial overgrowth and fructose intolerance).\(^9\)\(^6\) Similarly, a recent randomized, double-blind, placebo-controlled crossover rechallenge study found no evidence of specific or dose-dependent effects of gluten in patients with NCGS started on a diet low in fructose, oligosaccharides, disaccharides, and monosaccharides, and poyols, suggesting an alternative food intolerance other than gluten in these patients.\(^5\)

**Novel therapeutics.** Nondietary therapies under investigation for the treatment of CD target various aspects of CD pathogenesis and include intraluminal agents, immunomodulators, and vaccination.\(^8\)\(^9\)\(^10\) The intraluminal agents include larazotide acetate (AT-1001), which is a peptide derived from cholera toxin that regulates intestinal paracellular permeability by inhibiting opening of intestinal epithelial tight junctions. To date, clinical trials have not observed decreased intestinal permeability among patients with CD taking larazotide, although decreased TTG IgA levels and improved clinical symptoms were observed.\(^9\)\(^1\)\(^2\)

Other intraluminal therapies include endopeptidases aimed at degrading toxic gluten peptides (ie, glutenases). ALV003 is a recombinant form of 2 proteases and has been shown in a recent randomized placebo-controlled trial to reduce intestinal villous atrophy and intraepithelial lymphocytosis among patients with CD undergoing a gluten (2 g/d) challenge.\(^9\)\(^3\) A randomized placebo-controlled trial of another enzyme, *Aspergillus niger* prolyl endopeptase (AN-PEP), administered to patients with CD who underwent a gluten challenge (7 g/d) showed no difference in the primary end point of histologic change by Marsh classification between placebo and AN-PEP, although the study did show some evidence of decreased TTG IgA staining in duodenal biopsy specimens in the AN-PEP group.\(^9\)\(^4\)

As for extraluminal therapies, a vaccine (NexVax2) produced to restore immune tolerance to gluten among HLA-DQ2–positive patients with CD is under active investigation.\(^9\)\(^5\) In addition, researchers are exploring the immune regulatory response to parasite administration to test the hypothesis that inducing a TH2 response with the human hookworm *Necator americanus* would inhibit the autoimmune TH1 response to gluten among patients with CD.\(^9\)\(^6\) Inoculation with hookworm larvae or placebo was performed, and established infection was verified before a gluten (16 g/d) challenge was administered to patients with CD. One of the primary end points regarding Marsh classification showed no statistical difference between the 2 groups with substantial increases in Marsh scores in both those infected with *Necator americanus* and those injected with placebo.\(^9\)\(^6\) Finally, a chemokine receptor inhibitor to CCR9 (CCX282B or Traficet-EN) that blocks T-cell migration from the blood into the intestinal mucosa is also under investigation for its application in patients with...
CD. Despite the promise of these various therapies, however, the GFD remains the mainstay of management for CD.

**Disease monitoring and complications**

Monitoring compliance with a GFD is part of the long-term management of CD. Not only are the EMA and TTG antibodies a factor in arriving at the diagnosis, they also correlate with the degree of histologic damage and are used to monitor disease activity. The importance of the following response to a GFD rests in the long-term complications that can arise in the setting of active CD. These include the development of other autoimmune conditions, adenocarcinoma of the small intestine, enteropathy-associated T-cell lymphomas, and extraintestinal lymphoproliferative disorders, such as T- and B-cell non-Hodgkin lymphomas. The overall risk of cancer in patients with CD is approximately twice that of the general population. Although it is not currently the standard of care as a target of treatment for CD, achieving mucosal healing in patients with CD has been shown to have important prognostic implications. For instance, in a population-based cohort study, an increased risk of lymphoproliferative malignancies was associated with persistent villous atrophy on biopsy.

Refractory CD, which affects up to 5% of those with CD, is commonly defined as persistent or recurrent clinical symptoms along with histologic changes despite a strict GFD. Before diagnosing refractory CD, one must first ensure compliance with the GFD because this is the most common reason for persistent findings of disease often in the setting of unintentional microin-gestion of gluten-containing foods. For instance, gluten challenge studies show no histologic changes at a daily intake of less than 10 mg of gluten but increased villous height-to-crypt depth ratio at even 50 mg of gluten daily and more severe abnormalities of increased intraepithelial lymphocytosis and villous atrophy with daily ingestions from 100 to 500 mg/d.

Among those with a true diagnosis of refractory CD, there are 2 types with different prognostic implications. Type 1 exhibits normal intraepithelial lymphocytes as opposed to type 2, in which there is a clonal expansion of aberrant intraepithelial lymphocytes. Type 2 refractory CD is associated with an increased risk for ulcerative jejunitis, as well as enteropathy-associated T-cell lymphoma.

**CONCLUSIONS**

Over the decades since the initial description of CD, there has been a major increase in the awareness of the disease among the general population. Although generally underdiagnosed, CD appears to have an increasing prevalence worldwide. The introduction of wheat-based products into societies throughout the globe might contribute to the trend; however, other environmental factors that allow for patients with a predisposing genetic background to have the disease are only partially understood. Many patients with CD present with nonclassical extraintestinal manifestations, such as anemia and osteoporosis. Various serologic assays are available to help make the diagnosis with a high sensitivity and specificity; however, routine screening of asymptomatic patients is not yet recommended. The GFD is the mainstay of treatment for those given a diagnosis of CD, although there is a significant amount of research into alternative targeted therapies.

**What do we know?**

- CD is increasing in prevalence, although it is generally underdiagnosed.
- The development of CD occurs among subjects with specific HLA genes who are exposed to gluten and other environmental factors.
- CD displays a distinct pathogenic mechanism from both wheat allergy and NCGS.
- CD is diagnosed on the basis of characteristic autoantibodies and small intestinal histologic changes, which can both be used as markers to monitor the level of disease control.
- Health care providers should maintain a high degree of suspicion to CD diagnosis because patients might present with fewer intestinal and more extraintestinal manifestations, such as iron deficiency anemia.
- The main therapeutic intervention for CD is a GFD, although there is research into novel nondiagnostic agents.

**What is still unknown?**

- The reason for an increasing prevalence of CD and gluten-related disorders
- The extent to which environmental factors other than gluten might contribute to the development of CD
- The best screening approach to increase the diagnosis of CD among affected patients
- The degree to which mucosal healing might be a therapeutic target in monitoring patients with CD
- Whether there are therapeutic interventions for CD other than a GFD

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