Celiac disease (CD) affects approximately 1% of the general population, although most cases remain unrecognized. Because CD is a multisystem disorder with protean clinical manifestations, a high index of suspicion is needed to make an appropriate diagnosis. A diagnosis of CD is made in a patient who is genetically predisposed based on the presence of compatible clinical features, positive highly specific celiac serologic findings, duodenal biopsies that document enteropathy, and improvement with a gluten-free diet. The differential diagnoses for the clinical features and the histologic findings seen in patients with CD are numerous and need to be considered; because the management of celiac disease consists of a lifelong gluten-free diet, ensuring that the diagnosis is correctly established is of utmost importance. The aim of this review is to provide practicing clinicians with the most current information on the diagnosis and management of CD, including new developments and the approach to controversial issues.
CELIAC DISEASE

and routine medical follow-up for life. A gluten-free diet is very effective in most patients; however, recurrent or persistent symptoms are common in clinical practice. Nonresponsive CD is an umbrella term for persistent or recurrent symptoms despite attempted adherence to a gluten-free diet, with the most common cause being inadvertent gluten contamination. Refractory CD (RCD) is a severe complication defined by persistent or recurrent symptoms and villous atrophy despite proven strict adherence to a gluten-free diet and exclusion of malignancy or other causes of nonresponsiveness.

PATHOGENESIS OF CD
A detailed discussion of CD pathogenesis is beyond the scope of this article but is reviewed elsewhere.1-3 In susceptible persons, exposure to immunogenic gliadin peptides originating from gluten in the diet leads to a cascade of changes in both the surface epithelium and the lamina propria through immune-mediated mechanisms involving both the innate and adaptive immune systems.4 Intestinal microbiota is recognized as an emerging new player in modulating immune responses in patients with CD after ingestion of gluten.5,6 Gliadin can be injurious to the surface epithelium, which results in an increase in cytotoxic intraepithelial lymphocytes in response to overexpression of interleukin 15.7 Once gliadin reaches the lamina propria, it becomes more immunogenic after being deamidated by TTG, with facilitation of interaction between deamidated peptides and the permissive celiac haplotypes on antigen-presenting cells. Immune cell activation and cytokine release cause the histologic changes that are a hallmark of CD.8 Additionally, B lymphocytes produce CD-specific autoantibodies, which allows for serologic detection of CD.

EPIDEMIOLOGY OF CD
Celiac disease is a global disease of both children and adults, and although the mean age at diagnosis is 38 years in the United States, approximately 20% of patients are diagnosed after age 60 years.8 The diagnosis is more common in women (ratio 1.3-3:1), a pattern typically seen with autoimmune disorders. The availability of highly specific celiac serology has been crucial to understanding the epidemiology of CD. It is widely accepted that CD is a common problem based on prevalence studies, but most cases remain undiagnosed (“iceberg phenomenon”). Celiac disease has a wide geographic distribution and affects persons from multiple ethnic and racial backgrounds.9 The overall prevalence of CD in Europe has been reported at 1%, but the prevalence varies widely among countries (eg, 0.3% in Germany and 2.4% in Finland).10 One of the higher prevalence rates reported to date is 5.6% among the Saharawi people of northwest Africa.11 The prevalence of CD in the general population of the United States is 0.8%12,13 and has increased 4-fold in the past 40 years.14 A larger proportion of persons living at latitudes of 35° north or higher have CD compared with persons living in the south.15

Although less is known about the incidence of CD globally, an increasing incidence in both men and women has been clearly documented in Olmsted County, Minnesota, over the past 30 years (Figure 1). In fact, the adjusted incidence of CD between 2000 and 2010 was 17.4 per 100,000 person-years.8 Hypotheses to explain this trend include increased awareness of CD, changes in wheat processing and intake, route of delivery, timing of introduction of gluten into the diet during infancy, case finding, availability of serologic tests, a true increase in people affected, and innate changes to the microbiome. Elucidation of the underlying reason(s) remains a relevant challenge with the potential goal to implement effective preventive measures. However, modification of timing of introduction into or amount of gluten in the diet and breastfeeding failed to reduce the overall risk of CD compared with placebo.16,17

Interestingly, the frequency of classic CD among incident cases has decreased over time, while those presenting with nonclassic features has increased.18 Similar trends in the presentation of CD have been reported in...
referral populations. Based on National Health and Nutrition Examination Survey data, less than 20% of patients with CD have been officially diagnosed, whereas greater than 80% of patients with CD remain undiagnosed and untreated. However, the proportion of people with undiagnosed CD may be decreasing in a more recent National Health and Nutrition Examination Survey (2013-2014) despite stable overall prevalence.

CD-RELATED DEFINITIONS

Celiac disease is a multisystem disease and may present a diagnostic challenge given the numerous associated ways that a patient may seek medical attention and the varying terms used to label individuals with gluten-related disorders. The 2011 Oslo definitions consensus, although not without controversy, summarizes currently accepted terminology for common terms related to CD. Understanding the terminology helps the clinician to fully appreciate the wide spectrum of the clinical manifestations of CD. Asymptomatic CD is used to define patients who do not have symptoms at the time of the initial diagnosis of CD, even in response to direct questioning. Symptomatic CD is used to characterize those who have clinically evident gastrointestinal and/or extraintestinal features attributable to gluten intake. Classic CD is the term used to describe patients with CD who present with features of a malabsorption syndrome; a combination of diarrhea, steatorrhea, weight loss, or growth failure is usually required. This clinical presentation predominated before the 2000 but may explain only about 30% of diagnosed cases in the past decade. Nonclassic CD is the term used to describe the most common clinical manifestations of CD at the present time, characterized by a predominance of extraintestinal features, often monosymptomatic (eg, iron deficiency anemia, premature metabolic bone disease, infertility, elevated transaminase levels) in the absence of clinical malabsorption. Potential CD is used to describe patients with normal small intestinal mucosa who are at increased risk for development of CD as indicated by positive CD serologic findings. Celiac disease autoimmunity is characterized by increased TTG antibody or endomysial antibody (EMA) on at least 2 occasions when the status of the duodenal histology is unknown. This feature could be the clinical presentation of potential CD (if the biopsy result is negative), vs actual CD (if the biopsy result is positive). Finally, the use of latent CD has been discouraged because of the multiple definitions in the literature.

DIAGNOSIS OF CD

A diagnosis of CD is based on the presence of compatible clinical features, positivity of CD-specific serology, small bowel biopsy specimens with characteristic histologic features, and response to a gluten-free diet (Figure 2). Clinical suspicion of CD is based on symptoms, associated conditions, or the presence of at-risk conditions. For persons with a low pretest probability of CD, serology followed by biopsy, if serologic result is positive, is the most reasonable and cost-effective approach. The preferred initial serology is TTG IgA with measurement of total IgA to rule out IgA deficiency. Persons with a high pretest
probability of CD require both serologic testing (including total IgA level) and intestinal biopsy to substantiate the presence or absence of the diagnosis. The diagnostic accuracy of serologic testing and small intestinal histology for CD is severely affected by elimination of gluten from the diet (e.g., sensitivity of 16% for IgA TTG after a median of 11 months on a gluten-free diet). Therefore, testing for CD should be done when patients are consuming a gluten-containing diet.

**Clinical Features**

Patients with CD may present with classic features such as short stature, failure to thrive in childhood, delayed puberty, lethargy, and weight loss. However, more than 10% of patients with CD are obese, so this population of patients should not be overlooked. In terms of gastrointestinal symptoms, diarrhea, flatulence, bloating, abdominal discomfort, and nausea may be seen. It should be noted that approximately 20% of patients with CD may actually report constipation. Rarely, CD may present as a life-threatening diarrheal illness or “celiac crisis” with multiple electrolyte disturbances.

Although previously termed *atypical CD*, the term *nonclassic CD* is more appropriate, given that these manifestations are currently the typical presenting features. Patients with CD may be anemic and due to iron, folate, or vitamin B₁₂ deficiency; therefore, patients may present with microcytic, macrocytic, or normocytic anemia based on a combination of one or more deficiencies. Iron deficiency anemia is the most common extraintestinal feature of CD. In a patient with iron deficiency anemia without any gastrointestinal symptoms, the prevalence of CD ranges from 3% to 9%, whereas those with gastrointestinal symptoms may have

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**FIGURE 2.** Clinical algorithm to assess for celiac disease. EMA = endomysial antibody; GFD = gluten-free diet; HLA = human leukocyte antigen; NEG = negative; POS = positive; TTG = tissue transglutaminase antibody.
prevalence rates as high as 10% to 15%. Celiac disease may be most overlooked in the population of menstruating women, which is the demographic more likely to get CD. Therefore, CD should be considered in all patients undergoing a work-up for iron deficiency anemia, and small bowel histology should be obtained in any patient being evaluated for iron deficiency anemia who is undergoing upper endoscopy.

Metabolic bone disease is a leading cause of morbidity in patients with CD, with a fracture risk that may be 2 to 3 times higher than in the general population. Chronic inflammation and malabsorption of calcium and/or vitamin D can lead to osteopenia, osteoporosis, or osteomalacia. Therefore, CD should be considered in any patient with premature metabolic bone disease, and conversely, all patients with newly diagnosed CD should undergo an assessment of bone health.

Patients with untreated CD commonly have abnormal liver biochemistry results. Elevation of alanine aminotransferase and/or aspartate aminotransferase may be seen because of a reactive hepatitis (“celiac liver”), autoimmune hepatitis, or nonalcoholic fatty liver disease. Alkaline phosphatase elevation may be seen because of vitamin D deficiency, but levels may also be elevated in the setting of concomitant primary sclerosing cholangitis or primary biliary cholangitis. Liver biopsy is rarely necessary in patients with CD. However, in a subgroup of patients with CD who underwent liver biopsy, more than half were found to have an autoimmune cause of liver disease, with autoimmune hepatitis being the most common. Interestingly, those with autoimmune disease were less likely to have gastrointestinal symptoms related to their underlying CD. All patients with elevated liver biochemistry results of unknown etiology should undergo assessment for CD. Conversely, all patients with known CD who have persistent elevation of serum transaminases should be assessed for autoimmune liver disease.

Dermatitis herpetiformis is the cutaneous manifestation of CD. Interestingly, dermatitis herpetiformis is more common in men. The primary skin lesion includes pruritic papulovesicular lesions most often located in the extensor surfaces of elbows, knees, and buttocks (Figure 3 A and B). The secondary skin lesion consists of scratched papules and macules with superficial bleeding due to intense itching. A definitive diagnosis requires a biopsy of healthy-looking skin adjacent to the affected area. Direct immunofluorescence reveals granular deposits of IgA at the level of the basal membrane between the dermis and epidermis junction.

![Figure 3](image1.png)

**FIGURE 3.** Dermatitis herpetiformis. A, Typical distribution of the skin lesion with scratched macules and papules on the elbows. B, Direct immunofluorescence showing granular IgA deposits at the basal membrane zone. Images courtesy of T. T. Salmi, MD, and K. Kaukinen, MD, University of Tampere, Tampere, Finland.
Antibodies against epidermal transglutaminase (transglutaminase type 3) are present in 80% of the cases but are not necessary to confirm the diagnosis. A rapid clinical response to dapsone (25-50 mg daily) strongly supports the diagnosis. Long-term prognosis is excellent with consumption of a gluten-free diet, although clinical response is slow and most patients require dapsone initially to control rash-related symptoms. Iodine ingestion may cause flares of the disease and should be discouraged.

Other associated features of CD include functional asplenia, enteropathy-associated arthropathy, seizures, peripheral neuropathy, ataxia, infertility, recurrent aphthous stomatitis, dental enamel defects, headaches, and “brain fog.”

Serology
The presence of antibodies directed against gluten and connective tissue proteins is a hallmark of CD. Several antibodies have clinical relevance because of good sensitivity and/or specificity among patients presenting with abdominal symptoms or clinical suspicion of CD (Table). IgA TTG, along with measurement of total IgA, is the serology of choice for screening patients for CD. A result that is 3 times the upper limit of normal is strong evidence for a diagnosis of CD. False-positive results are more likely when lower titers are found, especially in the presence of other conditions such as cirrhosis, heart failure, or concurrent autoimmune disease. Sensitivity may vary among clinical laboratories. A negative TTG result is not sufficient to rule out CD in patients when there is a high suspicion for the disease. False-negative results are usually explained by initiation of a gluten-restricted diet before testing, coexistent IgA deficiency, or mild enteropathy. Seronegative CD should be considered in patients with a high pretest probability of CD, enteropathy on small bowel biopsies, serologic tests that are negative (in the absence of IgA deficiency), and permissive celiac haplotyping, as long as other mimickers of CD have been ruled out (eg, medication effect).

The use of celiac serologic panels is discouraged; although such panels may increase the sensitivity of case finding, it comes at the expense of decreased specificity, leading to unnecessary testing. All of the celiac serologies come in both an IgA- and IgG-based assay, with the exception of the EMA, which is an IgA-based test. Although IgA deficiency may be seen in approximately 2% to 3% of patients with CD, it is inappropriate to solely use IgG-based serology for testing for all patients. Although IgG-based serology has excellent sensitivity and specificity for patients with CD and known IgA deficiency, such serology has very low sensitivity in patients with CD who are not IgA deficient. In a patient with suspected IgA deficiency, clinicians could either measure the IgA level or use a combination IgA and IgG serology.

Histology
Histopathologic documentation of small intestine enteropathy is considered the criterion standard method to confirm the diagnosis of CD in adult patients. Endoscopic findings such as loss of folds, scalloping, fissuring, or cobblestone mucosa lack sensitivity but when present are strongly suggestive of enteropathy, although not specific for CD.

### TABLE. Summary of Diagnostic Accuracy of Available Serologic Tests for Celiac Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue transglutaminase</td>
<td>89 (82-94)</td>
<td>98 (95-99)</td>
<td>Test of choice</td>
</tr>
<tr>
<td>Endomysial antibody</td>
<td>90 (80-95)</td>
<td>99 (98-100)</td>
<td>Operator dependent, requires immunofluorescence</td>
</tr>
<tr>
<td>Deamidated gliadin peptides</td>
<td>88 (85-90)</td>
<td>94 (92-95)</td>
<td>Comparable to tissue transglutaminase</td>
</tr>
<tr>
<td>Gliadin</td>
<td>80 (57-100)</td>
<td>90 (47-94)</td>
<td>No longer recommended</td>
</tr>
</tbody>
</table>

Data from JAMA and Aliment Pharmacol Ther, and adapted from Am J Gastroenterol, with permission.
(Figure 4 A, B, and C). Therefore, in patients with a clinical suspicion of CD, biopsies are recommended regardless of the presence or absence of endoscopic findings. Multiple duodenal biopsies are suggested for assessment of CD because of the patchy nature of the disease. Ideally, 4 biopsy specimens should be obtained from the distal (postbulbar) duodenum and 2 specimens from the duodenal bulb, ideally at the 9- and 12-o'clock positions.

There is incremental evidence to support making a diagnosis of CD without the need for biopsies in both children and adults. Currently, a nonbiopsy approach to the diagnosis is recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition for selected pediatric cases with classic symptoms, presence of TTG antibody (>10 times the upper normal limit), presence of HLA-DQ2 or HLA-DQ8, and a separate blood sample with a positive EMA result, although HLA-DQ2/HLA-DQ8 testing may not be necessary for all.

Characteristic histologic features include a combination of increased tip-predominant intraepithelial lymphocytes (>25 per 100 enterocytes), partial or total villous atrophy, crypt hyperplasia, and chronic inflammatory infiltrate in the lamina propria. Multiple CD histologic classification systems are available (Marsh, Oberhuber-Marsh, Corazza, and Ensari) to improve communication between pathologists and clinicians. Although the utility of grading of villous atrophy has been challenged recently, a complete histopathologic report is mandatory in everyday clinical practice.

There are a number of conditions that may histologically mimic CD. There has been an increase in the number of duodenal

**FIGURE 4.** Endoscopic and pathologic findings in celiac disease. Endoscopy shows loss of mucosal folds (A) and scalloping, nodularity, and mosaic pattern (B). C, Duodenal biopsy specimen showing increased intraepithelial lymphocytosis, villous atrophy, crypt hyperplasia, and a chronic inflammatory infiltrate in the lamina propria (hematoxylin-eosin, original magnification \( \times 200 \)). Pathologic image courtesy of T. T. Wu, MD, Mayo Clinic, Rochester, Minnesota.
biopsies reported to have elevated intraepithelial lymphocyte levels with normal villous architecture, ranging from 3.0% of all duodenal biopsies in 2000 to 10.9% in 2010. Although known or newly diagnosed CD may account for some cases, others were thought to be related to nonsteroidal anti-inflammatory drug use, small intestinal bacterial overgrowth, *Helicobacter pylori* infection, and known or newly diagnosed inflammatory bowel disease, but many cases remained unexplained. Similarly, there are entities known to cause villous atrophy besides CD, such as medications (eg, olmesartan, mycophenolate mofetil), autoimmune enteropathy, combined variable immunodeficiency, tropical sprue, and collagenous sprue.

Endoscopic and/or histologic findings that should make one question the diagnosis of CD include mucosal erosions/ulcerations, neutrophilic-predominant infiltrate, loss of goblet or plasma cells, crypt abscesses, or a thickened collagen band.

**Haplotyping**

Celiac disease is strongly associated with HLA-DQ2 (DQA1*05/DQB1*02) and HLA-DQ8 (DQA1*03/DQB1*03). The permissive genes are present in approximately 30% of the general white population, so a test revealing permissive celiac genes has limited diagnostic value. The absence of both of these permissive genes is helpful to rule out CD in clinical practice and therefore has strong negative predictive value. Genetic testing is not affected by a gluten-free diet, so this test can be considered in patients who are consuming a gluten-free diet with no prior work-up for CD before embarking on a gluten challenge. Haplotyping may also be considered in selected clinical scenarios, such as patients with discordance between serologic and pathologic results, as well as those with certain at-risk conditions (eg, Down or Turner syndrome).

**SCREENING FOR CD**

Active screening in persons with conditions at risk for CD (case finding) is a proposed strategy to increase clinical detection (Figure 5). However, recent evidence strongly suggests that case finding may not be effective to distinguish between persons with undiagnosed CD and referent individuals at a population level. Therefore,
more evidence is needed related to screening for CD in asymptomatic individuals. Moreover, the strength of evidence supporting the recommendation for testing is variable among the accepted indications for clinical testing. Currently, case finding is recommended for the following: first-degree family members of an index case or both first- and second-degree relatives of sibling pairs with CD, autoimmune thyroid disease, Down or Turner syndrome, unexplained elevation of serum transaminases, type 1 diabetes mellitus, diarrhea-predominant irritable bowel syndrome, IgA deficiency, growth stunting in children, unexplained iron deficiency anemia, unexplained ataxia or neuropathy, premature metabolic bone disease, and infertility.

MANAGEMENT OF CD
Strict, lifelong adherence to a gluten-free diet, avoiding wheat, barley, and rye, is the most effective treatment for CD (Figure 7). A baseline visit and subsequent follow-up with an experienced dietitian is essential and cost-effective in order for patients to obtain accurate information about the gluten-free diet. Moreover, patients may prefer to see a dietitian for long-term follow-up. Although pure oats are typically safe for patients with CD to consume, there is the concern for potential cross-contamination, and it may be reasonable to recommend that oats be withheld for the first year after CD is diagnosed in patients with features of severe malabsorption. Active membership in a CD support group is recommended because it may be beneficial to improve adherence to a gluten-free diet.

Adult patients with newly diagnosed CD should undergo bone densitometry either at the time of diagnosis or 1 year after starting treatment because the frequency of osteoporosis may be as high as 34% in patients with malabsorption; if normal at baseline, bone densitometry would not need to be repeated until other risk factors for metabolic bone disease are present (eg, menopause, corticosteroid exposure). Those with osteopenia or osteoporosis at baseline should be advised about the recommended replacement of calcium and vitamin D according to age, with consideration of rechecking bone densitometry after 2 years of initiation of a gluten-free diet. Although there is no universal agreement on the type of laboratory workup that should ensue in patients with newly diagnosed CD, it is reasonable to do some basic blood work, including a complete blood cell count (to assess for anemia) and measurement of ferritin, vitamin B12, folate, 25-hydroxyvitamin D, both alkaline phosphatase and alanine aminotransferase (to containing product when amount of gluten is known) for 2 weeks, assess tolerability, and, if able, continue the daily gluten consumption for 6 additional weeks before testing is performed.

GLUTEN CHALLENGE FOR PATIENTS CONSUMING A GLUTEN-FREE DIET
A gluten challenge consists of a medically supervised exposure to gluten (usually 3-10 g/d) with close monitoring for symptoms and subsequent serologic and/or histologic testing for CD. A gluten challenge is more helpful to make or exclude the diagnosis of CD in patients with permissive genes for CD who have been consuming a gluten-free diet without a prior definitive diagnostic evaluation. It is unnecessary for the patient who does not have either permissive gene because the diagnosis will already have been excluded.

There is no consensus about the best way to conduct a gluten challenge. A kinetic study suggests that serologic and histologic changes of clinical significance are present as early as day 14 of a gluten challenge with more than 3 g/d in the majority of patients with CD. Better tolerance and an ability to endure a longer challenge may be additional advantages of a lower-dose gluten challenge. The duration of a gluten challenge may vary from 2 to 8 weeks, depending on clinical circumstances (Figure 6). Given that a slice of wheat bread typically contains 2 g of gluten (range of 2-5 g based on product), a reasonable approach would be to have the patient consume the equivalent of 2 slices of wheat bread daily (or other gluten-containing product when amount of gluten is known) for 2 weeks, assess tolerability, and, if able, continue the daily gluten consumption for 6 additional weeks before testing is performed.
assess for cholestatic or hepatitis conditions associated with CD), and thyrotropin levels. If the patient has features of malabsorption, additional testing should include serum albumin, vitamins A and E, international normalized ratio, copper, and zinc measurements. Other laboratory studies should be individualized based on the patient’s presentation. Some patients with CD may be functionally asplenic (as evidenced by

![Diagram](Proposed modified gluten challenge. From Gut, with permission. HLA = human leukocyte antigen.)


![Benefits and Challenges](Benefits and challenges of the gluten-free diet for treatment of celiac disease.)

FIGURE 7. Benefits and challenges of the gluten-free diet for treatment of celiac disease.
Howell-Jolly bodies on a peripheral smear), and consideration should be given to vaccinating against encapsulated organisms in that situation. Patients should be instructed to have first-degree family members undergo testing for CD, which can be done with an IgA TTG antibody test.\textsuperscript{24,87}

There are a number of conditions that are seen with increased frequency in those with CD, so clinicians should have a high index of suspicion for these associated disorders during follow-up visits. These conditions include autoimmune thyroid disease, type 1 diabetes mellitus, adrenal insufficiency, various connective tissue disorders such as rheumatoid arthritis, lupus, and Sjögren syndrome, selective IgA deficiency, inflammatory bowel disease, microscopic colitis, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, and IgA nephropathy.

**FOLLOW-UP**

Symptom relief is typically quite fast in patients with CD once a gluten-free diet has been commenced.\textsuperscript{26} The mean time to symptom improvement is 4 weeks, with two-thirds of patients noting complete relief at 6 months. Celiac serologic titers also decline quickly after a gluten-free diet is started, with a notable decrease by 6 months.\textsuperscript{88} Historically, clinical follow-up after diagnosis has been inadequate.\textsuperscript{89} We recommend follow-up 3 to 6 months after the initial diagnosis of CD to assess the clinical response to the gluten-free diet and to recheck serologic titers at that time. If the patient is struggling to follow a gluten-free diet, they should be offered another visit with the dietitian for further review. At the initial follow-up visit, any vitamin or mineral levels that were abnormal at the time of diagnosis should be rechecked to see if replacement has been adequate. After clinical improvement, routine follow-up every year with serology may be sufficient for most patients. Small bowel histology is slower to improve after initiation of a gluten-free diet, and time to healing increases with patient age.\textsuperscript{80}

Although not without controversy, given the absence of accurate noninvasive methods, we recommend that adult patients undergo upper endoscopy with small bowel biopsies in follow-up to prove there has been histologic healing in view of the excess comorbidity in patients without healing.\textsuperscript{91,92} If follow-up biopsy is considered, it should be done no sooner than 1 year after the gluten-free diet has been started and most ideally at 2 years to ensure the possibility for full healing before reassessment.\textsuperscript{80}

**NONRESPONSIVE CD**

Nonresponsive CD is a common clinical problem characterized by persistent or recurrent symptoms after starting a gluten-free diet.\textsuperscript{93} The most common symptoms are diarrhea, abdominal pain, weight loss, fatigue, and bloating.\textsuperscript{94} The first step in the work-up of patients with persistent or recurrent symptoms is a meticulous review of the evidence that supported the initial diagnosis of CD, including reviewing the initial serology and having the pathologic material reexamined if necessary to make sure that the diagnosis of CD is solid. The most common etiology for nonresponsive CD is gluten contamination, either blatant or inadvertent.\textsuperscript{94}

Deliberate ingestion of gluten is an obvious reason for persistent or recurrent symptoms but is infrequent. Those who may be less compliant with the gluten-free diet include those who were asymptomatic or had nonclassic features at presentation, teenagers, those who are diagnosed later in life, frequent travelers or socialites, and those with any change in social situation (eg, starting college).\textsuperscript{76,83} A dietitian consultation may be useful for the patient to obtain additional education about the gluten-free diet and to investigate sources of accidental contamination. The most frequent reason for inadvertent gluten consumption is cross-contamination in packaged foods, at restaurants, or during social events or with medications or supplements.\textsuperscript{94} Overlooked sources of gluten include beer and other alcohol, sauces, lip stick or lip balm, medications, and over-the-counter supplements.

Persistently positive serologic results after 12 months of consuming a gluten-free
diet is unexpected and strongly supports gluten contamination. Conversely, negative serologic findings do not exclude gluten contamination as the cause of persistent symptoms. Upper endoscopy with duodenal biopsies is often recommended to clarify the etiology of persistent symptoms, and in the presence of ongoing diarrhea and negative serologic results, colonoscopy (or flexible sigmoidoscopy) with random biopsies should also be considered to rule out microscopic colitis given the strong association between microscopic colitis and CD. Other diagnoses commonly found in patients with persistent symptoms include irritable bowel syndrome, small intestinal bacterial overgrowth, pancreatic insufficiency, lactose or fructose intolerance, inflammatory bowel disease, gastroesophageal reflux disease, and peptic ulcer disease (Figure 8).

**REFRACTORY CD**

Refractory CD is an uncommon cause of persistent or recurrent symptoms, but it is a relevant diagnosis due to the clinical severity and mortality risk. Patients with RCD should be treated in a dedicated celiac center with expertise. Refractory CD is characterized by persistent or recurrent symptoms and enteropathy despite strict adherence to a gluten-free diet for at least 12 months after exclusion of other causes of nonresponsive CD and malignancy. There are 2 recognized types of RCD: type 1, with normal intraepithelial lymphocyte morphology, and type 2, with aberrant intraepithelial lymphocytes and T-cell receptor clonality. Survival is reduced in patients with both types but worse in patients with type 2 (5-year survival, 80% vs 50%, respectively). Low serum albumin concentration is an independent risk factor for mortality. Refractory CD type 1 responds well to therapy with corticosteroids (including open-capsule budesonide) alone or in combination with azathioprine. Some treatments proposed for RCD type 2 include corticosteroids, immunosuppressants, cyclosporine, alemtuzumab, cladribine, or autologous stem cell transplant. Aggressive
nutritional support, together with open-
capsule budesonide, is a common preferred
initial therapy for RCD type 2.\textsuperscript{105} Other ther-
apies should be discussed in a case-by-case
manner in patients without response to
nutritional support and budesonide.

FUTURE POSSIBILITIES IN CD
Celiac disease awareness has improved over
the past decade. There is emerging evidence
to support a nonbiopsy diagnosis of CD in
children (and possibly for adults) that may
facilitate detection of new cases in the appro-
priate clinical scenario. Currently, there is
limited access to specialty CD care centers
across the world, and this problem needs
to be improved in the coming years. There
is also an unmet need for nondietary thera-
pies in CD.

There are several nondietary therapies
under different stages of development and/
or clinical trials. The best outcome measures
for CD trials are evolving.\textsuperscript{107} More nondiet-
ary options are likely to become available
as our understanding of the pathophysiology
of CD increases.\textsuperscript{108} Different targets in the
pathophysiology of CD have been identified
in clinical and preclinical trials as potential
nondietary therapies (reviewed else-
where\textsuperscript{109-111}). The potential to induce toler-
ance to gluten in patients with CD with
epitope-specific immunotherapy targeting T
cells is exciting and a potentially remarkable
discovery.\textsuperscript{112} Other potential targets for non-
dietary therapies include oral proteases for
gluten detoxification, zonulin antagonist to
modulate tight junctions, gluten-
sequestering polymers, transglutaminase
type 2 inhibitors, and HLA-DQ2 blockers.
These novel strategies provide promise of
alternative or adjunctive treatment options
beyond the gluten-free diet.

There are evolving tools to allow patients
to assess their food for gluten contamination
including portable handheld gluten detec-
tion devices,\textsuperscript{113} and both urine and stool
tests are under development to detect gluten
immunogenic peptides that may help to
gauge gluten ingestion.\textsuperscript{114,115} The specific
role of these tools in clinical practice will
require further study.

There is an increased interest in other
wheat/gluten-related disorders, but valida-
tion of diagnostic criteria and mechanistic
insight are urgently needed. New therapies
for RCD type 2 are also needed. Interleukin
15 inhibitors are under active investigation
to avoid expansion and activation of aberrant
intraepithelial lymphocytes.

CONCLUSION
Celiac disease has a wide geographic distri-
bution across the world and affects 1% of
non-Hispanic whites in the United States. A
high index of clinical suspicion is needed
for early diagnosis. The diagnosis is strongly
supported on the basis of serologic testing,
and duodenal histology is recommended to
confirm the diagnosis in most clinical situa-
tions. Lifelong adherence to a gluten-free
diet remains the only effective therapy for
CD. Persistent or recurrent symptoms of
CD are not uncommon after starting a
 gluten-free diet, and this situation requires
a systematic evaluation to rule out gluten
contamination and other associated condi-
tions, including RCD.

Abbreviations and Acronyms: CD = celiac disease; EMA =
endomysial antibody; RCD = refractory CD; TTG = tissue
transglutaminase

Potential Competing Interests: The authors report no
competing interests.

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The Thematic Review Series on Gastroenterologic
Diseases will continue in an upcoming issue.

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