# What Role Does Wheat Play in the Symptoms of Irritable Bowel Syndrome?

Shanti Eswaran, MD, Akash Goel, MD, and William D. Chey, MD

Dr. Eswaran is a Clinical Lecturer at the University of Michigan Health System in Ann Arbor, Michigan. Dr. Goel is a Resident Physician in the Department of Internal Medicine at New York–Presbyterian Hospital, Columbia University in New York, New York. Dr. Chey is a Professor of Medicine, Director of the GI Physiology Laboratory, Co-Director of the Michigan Bowel Control Program, and H. Marvin Pollard Institute Scholar, all at the University of Michigan Health System in Ann Arbor, Michigan.

Address correspondence to:
Dr. William D. Chey
Division of Gastroenterology
University of Michigan Health System
3912 Taubman Center, SPC 5362
Ann Arbor, MI 48109-5362;
Tel: 734-936-4775;
E-mail: wchey@umich.edu

Keywords
Celiac disease, food, gluten sensitivity, irritable bowel syndrome, wheat intolerance

**Abstract:** Recently, increasing attention has been paid to the pathologic role of food in irritable bowel syndrome (IBS). Nevertheless, healthcare providers often avoid addressing diet with their patients because of a lack of training, guideline consensus, and high-quality data. Recent literature supports the existence of a subgroup of IBS patients with undiagnosed nonceliac gluten sensitivity (NCGS), a term that is used to describe individuals who experience gastrointestinal and extraintestinal symptoms as a result of immunologic, morphologic, or symptomatic abnormalities that are precipitated by the ingestion of gluten. NCGS represents an important subgroup of patients with IBS who are highly treatable via dietary modification. Gluten may influence gastrointestinal symptoms through immune activation or alteration of intestinal permeability, but the true role of food in functional gastrointestinal symptomatology remains unclear. For example, gluten is just 1 component of the complex milieu of nutrients found in wheat and related grains, and NCGS likely represents only the tip of the iceberg as it pertains to the role of food in IBS.

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder that affects 7–20% of the adult population in the United States.[1,2] Since there are no reliable biomarkers, IBS is defined by the presence of characteristic symptoms. Rome III diagnostic criteria define IBS as recurrent abdominal pain or discomfort for at least 3 days per month in the past 3 months that is associated with 2 or more of the following: improvement with defecation, onset associated with a change in the frequency of stool, or onset associated with a change in the form (appearance) of stool.[2] In addition to abdominal pain or discomfort, patients with IBS experience disordered defecation with diarrhea, constipation, or a mixture of both.

A number of factors have been suggested to play a role in the pathogenesis of IBS, including disturbed motility, alterations in the brain-gut axis, genetic factors, impaired gut barrier function, immunologic dysregulation, changes in the gut microbiome, and psychosocial factors. Recently, there has been increasing attention

on the role of food in IBS. Patients have long associated IBS symptoms with the ingestion of certain foods.[3] In fact, more than 60% of patients with IBS report the onset or worsening of symptoms after meals (within 15 minutes of eating in 28% of patients and within 3 hours in 93% of patients).[1] Despite this clear message from patients, healthcare providers have often viewed dietary interventions for patients with IBS with skepticism, likely due to a lack of formal training in this area and high-quality data from randomized, controlled trials. In fact, in a 2009 evidence-based review, the American College of Gastroenterology IBS Task Force stated, "Patients often believe that certain foods exacerbate their IBS symptoms. There is, however, insufficient evidence that food allergy testing or exclusion diets are efficacious in IBS."[4] This lack of enthusiasm for dietary counseling has increasingly caused healthcare providers to be misaligned with their patients, who are increasingly seeking more holistic solutions for their IBS symptoms. Out of desperation, many patients attempt dietary manipulations, such as the reduction of fatty foods, carbohydrates, gluten, or milk/dairy products or the modification of dietary fiber content after seeking advice from family, friends, or the Internet.[5] It should come as no surprise that this disorganized and largely nonvalidated approach can result in frustration for both patients and healthcare providers. Furthermore, the adoption of highly restrictive diets for extended periods of time without appropriate supervision or monitoring can lead to the development of malnutrition.[5]

## Overlap Between Celiac Disease and Irritable Bowel Syndrome

Meta-analyses of case-control studies from around the world suggest that patients with IBS symptoms are significantly more likely to have serologic evidence, as well as biopsy confirmation, of celiac disease.[6,7] Although the sum of the world's literature supports an association between celiac disease and IBS, it is important to note that the data currently available from the United States have not identified a significantly increased risk of celiac disease among patients with IBS symptoms.[8,9] Recently, a prospective study from the United States found that the prevalence of biopsy-confirmed celiac disease was 0.4% in 492 patients with IBS symptoms and 0.4% in a convenience sample of 458 asymptomatic individuals who were undergoing colonoscopy for colorectal cancer screening or surveillance.[9] Although this difference was not statistically significant, it is notable that 7.3% of patients with IBS and 4.8% of control patients had at least 1 abnormal celiac serology test result (adjusted odds ratio, 1.49; 95% confidence interval, 0.76–2.90; $P$=.25). Thus, in this study of US populations, the likelihood of identifying evidence of an immunologic response to gluten was far more common than identifying biopsy-confirmed celiac disease in patients with IBS and control patients.

It has been argued that some patients with positive celiac antibody testing and evidence of genetic predisposition (positive human leukocyte antigen [HLA]-DQ2 or DQ8 status) but only subtle abnormalities or entirely normal small bowel histology will eventually develop villous atrophy and, thus, belong to the spectrum of celiac disease.[10,11] Wahnschaffe and associates described a group of patients who had IBS with diarrhea (IBS-D) symptoms, positive HLA-DQ2 status, minimal immunopathologic changes on duodenal biopsies (increased intraepithelial lymphocytes), elevated levels of celiac disease–associated antibodies in duodenal aspirates, and increased immunoglobulin (Ig) A deposition in intestinal villi.[12] In this unblinded study, patients with IBS-D experienced significant reductions in symptoms with a gluten-free diet. Subsequent studies have shown a high likelihood of response to a gluten-free diet in patients with gastrointestinal symptoms, abnormal celiac disease antibody testing, and genetic markers (HLA-DQ2/DQ8) but normal or minimal small intestinal mucosal lesions.[11-14] In a follow-up study, Wahnschaffe and colleagues examined 41 patients who had IBS-D, positive HLA-DQ2/DQ8 status, positive levels of IgA and IgG antibodies to tissue transglutaminase (TTG) and/or gliadin (AGA), and normal or near normal duodenal histopathology (increased intraepithelial lymphocytes). Gastrointestinal symptoms and antibody levels were re-examined after patients were on a gluten-free diet for 6 months.[15] Positive levels of AGA or TTG serum IgG antibodies (37%) and HLA-DQ2 expression (39%) were significantly more common in patients with IBS-D than in a control group of patients with inflammatory bowel disease (18% and 23%, respectively). After 6 months of a gluten-free diet, stool frequency and gastrointestinal symptom scores returned to normal values in 60% of patients with IBS-D who previously had positive HLA-DQ2 status and celiac disease–associated serum IgG levels and in 12% of patients with IBS-D who had been negative for these 2 findings ($P$<.05). The authors concluded that positive levels of AGA or TTG serum IgG and HLA-DQ2 expression may identify a subset of patients with IBS-D who will respond to a gluten-free diet.

## Why Might Patients with Irritable Bowel Syndrome Develop Symptoms After Ingesting Foods with Gluten?

Although the concept of NCGS is not new, a great deal of attention has recently been paid in the lay press and medical literature to patients with IBS who experience symptoms after ingesting foods that contain gluten.[16]

**Table 1.** Terminology of Gluten-Related Disorders

| Term | Symptoms | HLA-DQ2/8 | Duodenal biopsy | Serologic tests | Treatment |
|---|---|---|---|---|---|
| Classic celiac disease | Diarrhea, bloating, weight loss, abdominal pain | + | + | + | Gluten-free diet |
| Nonclassic celiac disease | Ataxia, dermatitis herpetiformis, anemia | + | + | + | Gluten-free diet |
| Asymptomatic celiac disease | None | + | + | + | Debated |
| Potential celiac disease | None | + | – | + | None |
| Nonceliac gluten sensitivity | May be identical to celiac disease | +/– | – | +/– | Trial of gluten-free diet |

HLA=human leukocyte antigen.

Adapted from Sapone A, et al[17] and Ludvigsson JF, et al.[18]

Unlike patients with celiac disease, these patients do not demonstrate signs of significant intestinal mucosal injury in response to gluten ingestion. The term gluten-related disorders is used to describe all conditions that occur as a result of ingesting foods that contain gluten (including disorders such as celiac disease, dermatitis herpetiformis, gluten ataxia, and NCGS), and the medical community has come to recognize that there is likely a spectrum of disorders related to gluten ingestion (Table 1).[17,18] Gluten is becoming increasingly recognized as an important culprit of food intolerance, particularly in patients with IBS. This is evidenced by the fact that the number of individuals embracing a gluten-free diet far exceeds the number of individuals who are diagnosed with celiac disease. Sales in the global market for gluten-free products totaled an estimated $2.5 billion in 2010.[17] Therefore, the remainder of this paper will review literature that supports a causal link between gluten and IBS symptoms as well as evidence that supports the use of a gluten-free diet for treatment of patients with IBS.

## What Is Nonceliac Gluten Sensitivity?

There is no widely accepted definition for NCGS. Broadly speaking, this term relates to 1 or more of a variety of immunologic, morphologic, or symptomatic manifestations that are precipitated by the ingestion of gluten in individuals in whom celiac disease has been excluded. Patients with NCGS demonstrate symptomatic manifestations—both intestinal (eg, diarrhea, abdominal discomfort, bloating, and flatulence) and extraintestinal (eg, headache, lethargy, attention deficit/hyperactivity disorder, depression, and ataxia)—that are precipitated by the ingestion of gluten and improve after gluten withdrawal. As opposed to celiac disease, NCGS may show signs of an activated innate immune response but without significant enteropathy. Patients with NCGS may or may not exhibit elevations in TTG, endomysial, or deamidated gluten peptide antibodies. Such patients often experience gastrointestinal symptoms that can be clinically indistinguishable from those of celiac disease or IBS.[12,19] There is currently no standard diagnostic approach to patients with NCGS, but these patients are an important subgroup to identify, as their condition is eminently treatable via dietary modification.

## Does Nonceliac Gluten Sensitivity Exist in Patients with Irritable Bowel Syndrome?

There is increasing evidence to suggest that gluten induces functional gastrointestinal symptoms in patients who do not meet the diagnostic criteria for celiac disease. Biesiekierski and coworkers confirmed the existence of NCGS in patients with IBS-D in a randomized, double-blind, placebo-controlled, rechallenge trial.[20] This study included 34 patients with IBS (based on Rome III criteria) who had experienced symptomatic relief with a gluten-free diet for at least 6 weeks before study enrollment. Patients with celiac disease or other confounders were excluded from the study. Throughout the 6-week, double-blind, randomization phase of the trial, 19 patients received 16 g of nonfermentable gluten per day via bread and a muffin, whereas the other 15 patients received gluten-free bread and a muffin. The endpoint of the study was adequate symptom relief according to a questionnaire and visual analogue scale. After completion of the study, the researchers found that a significantly greater number of patients in the gluten group did not experience adequate symptom control compared with the gluten-free group (68% vs 40%; $P$=.001). Patients who received a gluten-free diet reported significantly greater improvements in pain ($P$=.016), bloating ($P$=.031), satisfaction with stool consistency ($P$=.024), and tiredness ($P$=.001) than patients who ingested a diet containing gluten. The researchers also evaluated a number of potential biomarkers before and

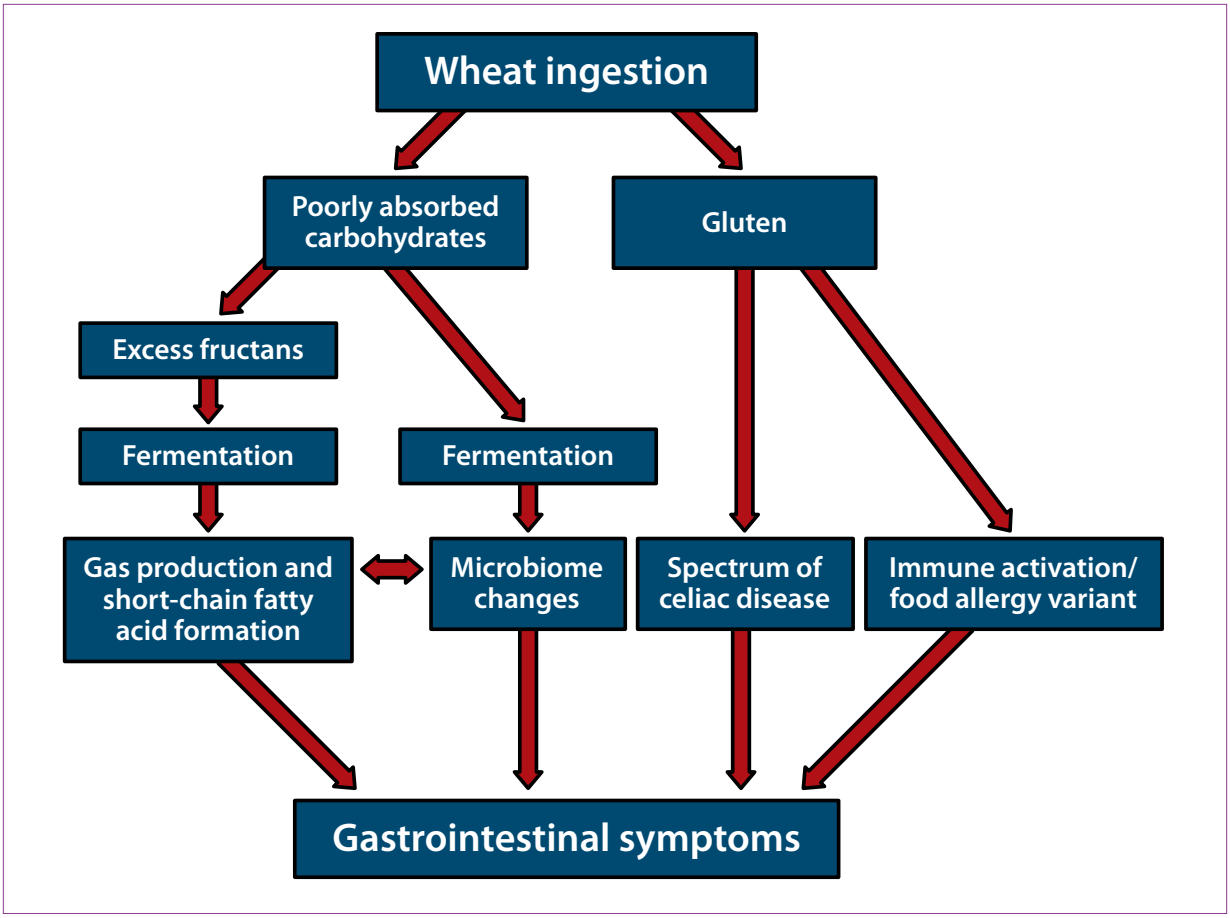


**Figure 1.** Proposed mechanisms of nonceliac wheat sensitivity.

after dietary intervention. There were no significantly different changes in levels of fecal lactoferrin, celiac antibodies, or highly sensitive C-reactive protein before and after dietary intervention. HLA-DQ2/DQ8 status had no bearing on clinical outcomes, which argues against undiagnosed celiac disease as a cause of symptomatic response to a gluten-free diet. Based on these results, the researchers concluded that NCGS may well be a distinct clinical entity and that gluten ingestion is associated with the development of gastrointestinal symptoms in a subset of patients with IBS.

## Proposed Mechanisms of Gluten-Induced Symptoms in Patients with Irritable Bowel Syndrome

It has been suggested that immune activation and perhaps low-grade inflammation are present in a subset of patients with IBS; in addition, abnormalities in intestinal permeability have recently been reported in a subset of patients with IBS.[21-24] This mechanism of action is interesting, given what is known regarding the pathogenesis of celiac disease, in which gliadin induces dysfunction of intercellular tight junctions through increased intestinal expression of zonulin, a modulator of intestinal permeability.[25,26] In the face of increased intestinal permeability, it is reasonable to hypothesize that environmental factors, such as food antigens, could lead to immune activation or could trigger a low-grade inflammatory response, leading to the generation of symptoms in a susceptible individual.[24,27,28] Small preliminary studies suggest that, unlike celiac disease, gluten sensitivity is not associated with increased intestinal permeability.[17,20] As previously discussed, Biesiekierski and colleagues measured levels of fecal lactoferrin (a marker of injury and intestinal permeability) before and after ingestion of a gluten-free or gluten-containing diet.[20] Despite the worsening of symptoms after gluten ingestion, no changes were identified in fecal lactoferrin levels.[20] Similarly, Sapone and associates found that the lactulose/mannitol test, which is a marker of intestinal permeability, was actually significantly lower in gluten-sensitive patients than in control patients

($P$=.0308), signifying a conserved mucosal barrier function in gluten-sensitive patients.[29] The same study reported that the innate immunity markers TLR2 and FOXP3 were altered in gluten-sensitive patients but not patients with celiac disease. Along with a lack of association with HLA-DQ2/DQ8 status, these immunologic differences suggest that gluten sensitivity and celiac disease may, in fact, be distinct conditions.

There is additional evidence supporting an immunologic pathogenesis in a subset of patients with food sensitivity and IBS. Carroccio and coworkers recently performed a double-blind, placebo-controlled study that utilized oral food challenges with cow's milk and wheat proteins in patients who fulfilled Rome II criteria for IBS.[27] Improvement was seen in 20% of patients with IBS during the double-blind, placebo-controlled milk and/or wheat elimination phase, while symptoms associated with both milk and wheat developed in 16% of patients, with milk alone in 3%, and with wheat alone in 2%. Symptoms developed within a mean of 3 days of milk or wheat reintroduction, and half of these patients had to discontinue their food challenge due to recurrent symptoms. Many patients who thought they had food sensitivities did not improve with food elimination. Surprisingly, some patients who did not think that food was related to their symptoms improved with double-blind, placebo-controlled, food elimination. This study also found that basophil activation measured by surface expression of CD63 was 87% accurate for identifying patients with sensitivity to milk and/or wheat. These findings were corroborated by the same researchers in a second study.[28]

It should be remembered that gluten is just 1 component of the complex milieu of nutrients found in wheat and related grains. In fact, the studies by Carroccio and associates did not specify which components of wheat were utilized in their studies.[27,28] Therefore, gluten may not have been the sole agent responsible for the development of symptoms in patients who consumed wheat. In addition to a number of other proteins, wheat contains fructans and galactans, poorly absorbed short-chain carbohydrates that are highly fermentable in the presence of gut bacteria. Fermentation of these substrates results in gas and short-chain fatty acid production. These short-chain fatty acids produce an osmotic load that leads to increased luminal water content, luminal distension, and secondary peristalsis involving the distal small bowel and proximal colon. It is not difficult to imagine how these physiologic events could lead to the development of symptoms such as bloating, distension, abdominal pain/cramping, or diarrhea, particularly in patients with underlying IBS (Figure 1).[30] Recent research suggests that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (which, along with fructans and galactans, are known as FODMAPs) offers clinical benefits for IBS symptoms.[31-33] In addition to simply reducing exposure to fermentable substrates, it is also conceivable that elimination of these dietary fermentable carbohydrates might alter the gut microbiome through prebiotic effects, reduce or change the products of fermentation, improve intestinal barrier function, or affect function of smooth muscle or the enteric nervous system.[34,35]

## Conclusion

It is becoming increasingly clear that there are patients in whom gastrointestinal and nongastrointestinal symptoms develop following the ingestion of wheat. Some of these patients may well represent a variation of celiac disease or food allergy. For such patients, it is quite possible that gluten is the culprit and that its exclusion may be a potentially effective solution. On the other hand, nongluten-related issues may underlie the development of symptoms following the ingestion of wheat in patients with IBS. Immunologic responses to gluten proteins (which differ from those of celiac disease) or fermentation of unabsorbed carbohydrates may also lead to symptoms in patients with IBS, who often have underlying alterations in the gut microbiome as well as exaggerated motor and sensory responses. Further research is clearly warranted to characterize the complex and overlapping pathophysiology of gastrointestinal and nongastrointestinal symptoms following the ingestion of wheat.

In addition, the development of a widely accepted nomenclature for patients who experience symptoms after the ingestion of wheat would be of great benefit. The current label of NCGS may be overly restrictive, as it implies that the gastrointestinal and nongastrointestinal symptoms that these patients experience are exclusively the result of ingesting gluten. As previously discussed, this may or may not be the case. In many ways, the current indiscriminant use of this term is reminiscent of the use of nonerosive reflux disease (NERD) to describe all patients with heartburn and normal endoscopic findings. After NERD became part of the gastroenterology vernacular, it became quite apparent that a substantial proportion of patients with heartburn and normal esophagogastroduodenoscopy findings off of proton pump inhibitor therapy, as well as the majority of such patients on proton pump inhibitor therapy, have no demonstrable evidence of acid or nonacid reflux based on ambulatory impedance–pH monitoring. It is now recognized that many patients with heartburn and normal endoscopic findings (particularly patients who experience symptoms despite receiving proton pump inhibitor therapy) are more appropriately labeled as experiencing functional heartburn. In the hopes of avoiding a similar mistake, the medical community should consider a more inclusive label

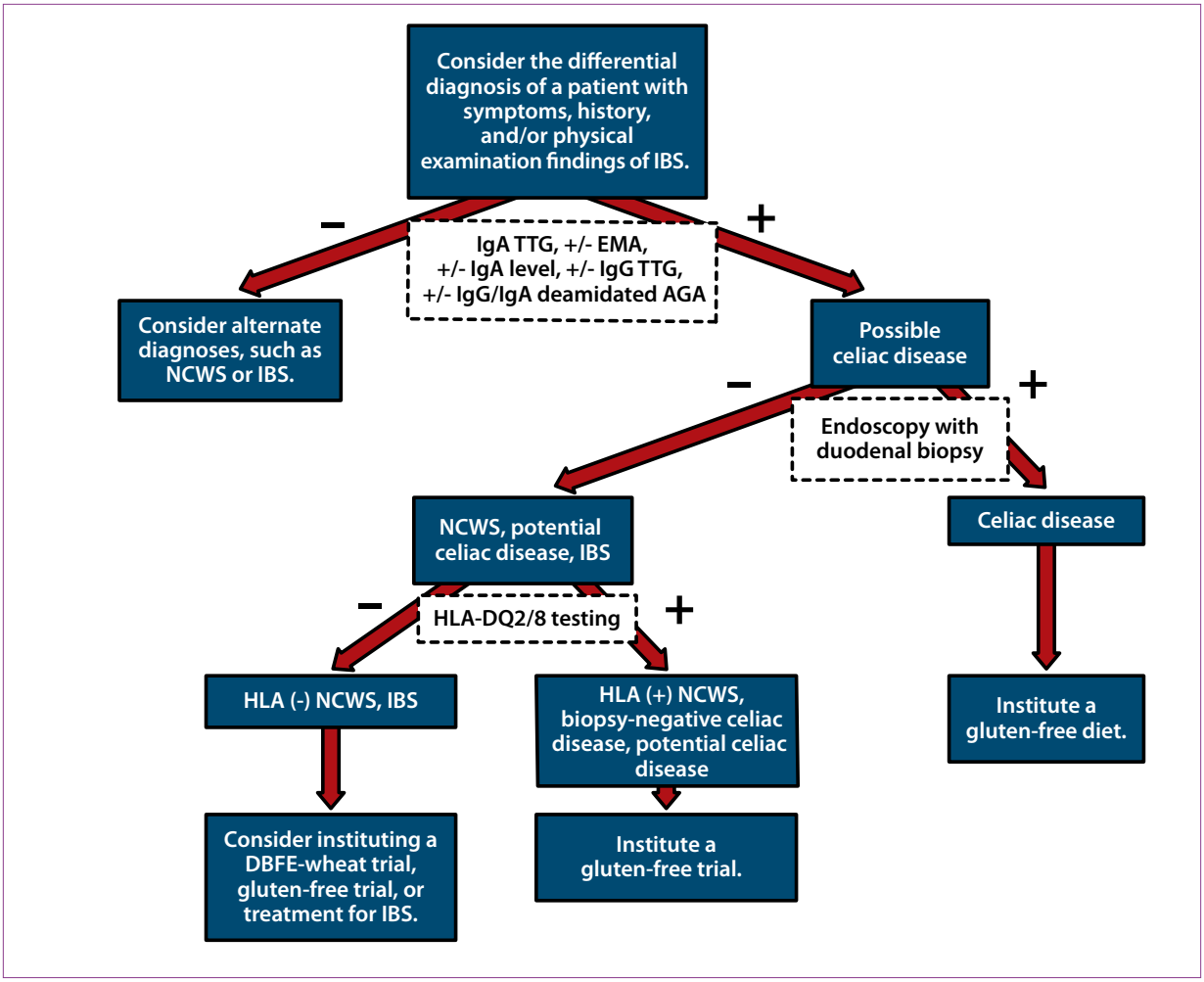


**Figure 2.** A potential algorithm for the diagnosis of celiac disease and other gluten-related disorders. Serologic testing should be obtained in patients on a gluten-containing diet. If there is high suspicion for celiac disease (eg, family history, type 1 diabetes, Down syndrome), confirmatory endoscopy with duodenal biopsy should be considered, even in the setting of normal serologic test results.

AGA=antigliadin antibody; DBFE=double-blind food elimination; EMA=endomysial antibody; HLA=human leukocyte antigen; IBS=irritable bowel syndrome; Ig=immunoglobulin; NCWS=nonceliac wheat sensitivity; TTG=tissue transglutaminase.

for patients with wheat-related symptoms. Terms such as wheat intolerance or nonceliac wheat sensitivity would include patients with NCGS and patients in whom symptoms develop via nongluten-related mechanisms.

As the societal preoccupation with gluten continues to grow, it is becoming increasingly clear that healthcare providers are more likely to encounter patients with NCGS than patients with true celiac disease in day-to-day practice. Despite the frequent rush to treat a wide range of gastrointestinal and nongastrointestinal symptoms with a gluten-free diet, healthcare providers should keep several important practical issues in mind. Due to the relatively low prevalence of celiac disease, it is always advisable to formally test for this condition before instituting a gluten-free diet (Figure 2). Most healthcare providers have encountered patients who started a gluten-free diet after consulting the Internet or speaking to a friend, relative, or another healthcare provider. It is often difficult to convince patients to go back to a gluten-containing diet once their symptoms have improved on a gluten-free diet. Even in situations in which patients agree to include gluten in their diet, it is unclear how much and for how long gluten should be reintroduced before blood or biopsy-based testing for celiac disease becomes reliable. In addition, although a gluten-free diet can be safe even when implemented for long periods of time, it is our opinion that individuals starting a gluten-free diet should see a dietician on at least 1 occasion to ensure that they institute

their diet in a medically responsible manner. Healthcare providers should make sure that patients are not solving one set of problems only to create another set of problems in their haste to find a solution for their IBS symptoms.

## References


1. Chey WD, Olden K, Carter E, Boyle J, Drossman D, Chang L. Utility of the Rome I and Rome II criteria for irritable bowel syndrome in U.S. women. *Am J Gastroenterol*. 2002;97:2803-2811.
2. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130:1480-1491.
3. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am*. 2011;40:141-162.
4. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
5. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome—etiology, prevalence, and consequences. *Eur J Clin Nutr*. 2006;60:667-672.
6. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol*. 2002;97:2812-2819.
7. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med*. 2009;169:651-658.
8. Saito-Loftus Y, Brantner T, Zimmerman J, Talley N, Murray J. The prevalence of positive serologic tests for celiac sprue does not differ between irritable bowel syndrome (IBS) patients compared with controls. *Am J Gastroenterol*. 2008;103:S472.
9. Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with nonconstipated irritable bowel syndrome is similar to controls. *Gastroenterology*. 2011;141:1187-1193.
10. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol*. 2009;104:1587-1594.
11. Kurppa K, Collin P, Viljamaa M, et al. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. *Gastroenterology*. 2009;136:816-823.
12. Wahnschaffe U, Ullrich R, Riecken EO, Schulzke JD. Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. *Gastroenterology*. 2001;121:1329-1338.
13. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med*. 1997;3:797-801.
14. Kaukinen K, Maki M, Partanen J, Sievanen H, Collin P. Celiac disease without villous atrophy: revision of criteria called for. *Dig Dis Sci*. 2001;46:879-887.
15. Wahnschaffe U, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2007;5:844-850.
16. Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology*. 1980;79(5 pt 1):801-806.
17. Sapone A, Bai JC, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med*. 2012;10:13.
18. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013;62:43-52.
19. Loft DE, Nwokolo CU, Ciclitira PJ. The diagnosis of gluten sensitivity and coeliac disease—the two are not mutually inclusive. *Eur J Gastroenterol Hepatol*. 1998;10:911-913.
20. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol*. 2011;106:508-514; quiz 515.
21. Ohman L, Simren M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol*. 2010;7:163-173.
22. Schmulson M, Chey WD. Abnormal immune regulation and low-grade inflammation in IBS: does one size fit all? *Am J Gastroenterol*. 2012;107:273-275.
23. Dunlop SP, Hebden J, Campbell E, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol*. 2006;101:1288-1294.
24. Vivinus-Nebot M, Dainese R, Anty R, et al. Combination of allergic factors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. *Am J Gastroenterol*. 2012;107:75-81.
25. Fasano A, Not T, Wang W, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet*. 2000;355:1518-1519.
26. Lammers KM, Lu R, Brownley J, et al. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology*. 2008;135:194-204.e3.
27. Carroccio A, Brusca I, Mansueto P, et al. A cytologic assay for diagnosis of food hypersensitivity in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2010;8:254-260.
28. Carroccio A, Brusca I, Mansueto P, et al. Fecal assays detect hypersensitivity to cow's milk protein and gluten in adults with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2011;9:965-971.e3.
29. Sapone A, Lammers KM, Casolaro V, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med*. 2011;9:23.
30. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: the FODMAP approach. *J Gastroenterol Hepatol*. 2010;25:252-258.
31. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol*. 2008;6:765-771.
32. Ong DK, Mitchell SB, Barrett JS, et al. Manipulation of dietary short-chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol*. 2010;25:1366-1373.
33. Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet*. 2011;24:487-495.
34. Argenzio RA, Meuten DJ. Short-chain fatty acids induce reversible injury of porcine colon. *Dig Dis Sci*. 1991;36:1459-1468.
35. Soret R, Chevalier J, De Coppet P, et al. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology*. 2010;138:1772-1782.