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Gluten-related Disorders From Bench to Bedside

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Celiac disease, non-celiac gluten sensitivity, and wheat allergy comprise 3 of the main conditions with wheat- and gluten-containing foods as the symptom trigger. Distinguishing between these entities can be daunting. In this review, we compare and contrast celiac disease, non-celiac gluten sensitivity, and wheat allergy to allow clinicians to determine which diagnosis fits their patient to facilitate high-quality management and longitudinal care.

Keywords: Enteropathy; Food Intolerance; Gastrointestinal Symptoms; Immunology.

It can be difficult to interpret a patient's food-related symptoms and provide them with a correct diagnosis; this becomes even more challenging when conditions are similar, or symptoms are heterogeneous. Celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy are both. Gluten-containing foods and wheat are the culprit in CD, NCGS, and wheat allergy collectively known as gluten-related disorders, and they exhibit overlap in many signs and symptoms.

Gluten is the term for the water insoluble storage protein in certain grains such as wheat, barley, and rye. The word gluten refers to a mixture of hundreds of distinct yet related proteins, such as gliadins and glutenins in wheat, hordeins in barley, and secalins in rye. These proteins give dough its elastic texture and have use as an additive to improve moisture retention, texture, and flavor.

Gluten is the definitive determinant factor in CD pathogenesis; however, the role of gluten as a trigger for symptoms in the absence of CD remains controversial. Moreover, there is an increasing number of people (likely millions in the United States) avoiding gluten-containing foods without a diagnosis of CD who identify themselves as "gluten sensitive," increasing the complexity of a definitive clinical diagnosis. The goal of this narrative review is to facilitate the diagnosis and management of gluten-related disorders. It will cover definitions and epidemiology, current concepts in pathophysiology, clinical presentations, strategies for diagnosis, treatment plans, and potential complications of CD, NCGS, and wheat allergy, respectively.

Celiac Disease

Definition and Epidemiology

CD is an immune-mediated enteropathy that arises in genetically susceptible people after ingestion of dietary gluten per the Oslo definitions.[1] CD is a common disease recognized in multiple ethnicities and encountered across the globe.[2] Prevalence is estimated at around 1%—rates based on serology only are higher than small intestine biopsy studies.[3,4] Regional and ethnic variability have been described.[5,6] In a nationally representative sample from the United States, the prevalence was 1 in 141 (Supplementary Figure).[7] It is one of the most common lifelong disorders that is food-related.

Pathophysiology

Eating gluten results in the generation of immunogenic gluten peptides, which set off innate and adaptive immune responses in genetically predisposed individuals. Because of the richness of prolamins and glutamines in gluten protein, it resists degradation by gastric, pancreatic, and intestinal brush border peptidases; remaining peptides can be 33 amino acids in length.[8] Gluten peptides remain largely intact as they cross from the lumen into small intestine submucosa. Transglutaminase 2 deamidates these gluten peptides.[9] This enzyme action creates an environment for high-affinity binding of the epitope to human leukocyte antigen (HLA) molecules DQ2 or DQ8.[9] After recognition by T-cells, a pro-inflammatory cascade is triggered in patients with CD resulting in enteropathy. Tissue transglutaminase (TTG) antibodies are formed by abundant plasma cells; they have an uncertain role in modulation of CD but are a marker for diagnosis. Increased intraepithelial lymphocytes signal the role of innate immunity and play a part in enterocyte cytolysis. They are responsible for interferon gamma and granzyme B synthesis in large quantities and natural killer cell receptor upregulation (induced by interleukin [IL]-15) to facilitate cytotoxic effects and apoptosis.[10]

Abbreviations used in this paper: **AGA, anti-gliadin; ATI, amylase-trypsin inhibitor; CD, celiac disease; DGP, deamidated gliadin peptide; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GFD, gluten-free diet; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; IgA, immunoglobulin A; IgE, immunoglobulin E; IL, interleukin; NCGS, non-celiac gluten sensitivity; TCR, T-cell receptor; TTG, tissue transglutaminase; TTG-IgA, tissue transglutaminase antibody immunoglobulin A.**

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Clinical Presentation

The ensuing inflammation "drowns" the villi and apoptosis occurs resulting in a shortened or blunted appearance of the small intestine mucosa.[11] When the villi flatten, this decreases the surface area available for absorption of nutrients and fluids. The associated inflammation in the lamina propria intensifies the condition by resulting in net fluid secretion causing diarrhea. Not all patients present with malabsorption and its accompanying clinical picture of diarrhea, weight loss, steatorrhea, and nutritional deficiencies. Some exhibit abdominal pain or cramping, bloating or distention, or other gastrointestinal ailments. Others have extraintestinal manifestations including anemia, aphthous ulceration, dental enamel defects, short stature, skin rashes, arthralgia, fatigue, elevated liver chemistries, bone disease, neurologic symptoms, infertility, or a multitude of other presentations.[12] It is estimated that >50% of pediatric and adult patients experience at least one extraintestinal indicator of CD.[13] There are even asymptomatic patients who are screened for CD due to related conditions, such as diabetes mellitus type 1 or family history of CD.[14,15] Nonclassical symptoms are more common than classical malabsorptive ones. In population-based studies of patients with CD, around one-third have diarrhea at diagnosis.[16-18] It is a multisystem disorder that can affect essentially any tissue or organ and present at any age.[19] Because loss of tolerance to gluten can occur at any time during a patient's lifespan, other factors beyond genetic predisposition and the immune trigger of gluten are felt to be involved in disease onset. In children, the major clinical phenotypes are growth difficulties, recurrent abdominal pain, and asymptomatic screening of high-risk individuals; diarrhea predominance is found in only 10% of pediatric patients.[20] Diarrhea is one of many phenotypes for CD in adults (Figure 1). This laundry list of potential presentations accounts for CD's reputation as a clinical chameleon.

Diagnosis

A diagnosis of CD is made in the setting of positive serology and villous flattening on duodenal biopsy while on a gluten-containing diet (Figure 2). The screening test of choice for CD is the tissue transglutaminase antibody immunoglobulin A (TTG-IgA).[14,15] It performs well in both primary care and referral settings with a sensitivity approaching 95% and specificity between 96% and 100%.[21,22] It should be obtained with a total IgA level to evaluate for IgA deficiency; if this is uncovered, then the TTG-IgA ceases to be a valid test. IgG-based testing such as the TTG-IgG or deamidated gliadin peptide (DGP-IgG) should be performed instead.[23,24] The step of ordering a total IgA is essential because IgA deficiency affects up to 1 in 28 patients with CD.[25] Anti-gliadin and anti-reticulin antibodies are obsolete because of inferior performance.[14,15]

Current guidelines mandate small intestine biopsy during esophagogastroduodenoscopy for CD diagnosis in adults. Histologic changes in CD are patchy.[26,27] Endoscopic appearance of villous atrophy such as scalloping, fissuring, nodularity, or fold reduction is not sufficiently sensitive to preclude biopsy.[28] Tissue should be sampled even when endoscopic appearance is normal. Guidelines require a minimum of 4 biopsies from the post-bulbar or distal duodenum and 1 to 2 biopsies from the bulb taken from the 9 o'clock or 12 o'clock position.[14,15] Sampling the bulb is important as around 10% of patients with suspected CD have villous atrophy limited to the bulb.[26,29,30] Characteristic features of CD on histopathology include increased intraepithelial lymphocytes, crypt hyperplasia, and villous changes such as flattening, blunting, or atrophy. These histologic findings may be reported using Marsh or Corazza classification.[31,32]

A biopsy-sparing approach is suggested for pediatric populations with a TTG-IgA >10 times laboratory normal.[15,33] A confirmatory endomysial antibody test in a separately drawn blood sample is required.[33] A nonbiopsy diagnosis is suggested by the updated American College of Gastroenterology guidelines but still not part of the most recent North American pediatric guidelines, and thus, a biopsy-proven diagnosis remains standard for children in the United States, Canada, and Mexico.[34]

Assessing a patient's response to a gluten-free diet (GFD) without testing or partial testing is not reliable. Symptoms alone cannot distinguish between CD and other conditions on the differential diagnosis. The positive predictive value of symptom improvement following gluten withdrawal for CD is merely 36%.[35] Even adding back in gluten and following for symptom recurrence has just a 28% positive predictive value.[35] Asking patients to limit gluten in their diet prior to diagnosis could obscure results by decreasing or normalizing celiac-associated antibodies and intestinal villi. Serology and biopsy should be performed in patients eating a standard diet without reducing gluten.

If a patient requires evaluation while already limiting or eliminating gluten, consider genetic testing as a first step. HLA-DQ2 or DQ8 play a key role in the immune system activation in CD; however, around one-third of adults carry these permissive alleles, which are necessary but not sufficient for CD diagnosis. Absence of these genes essentially excludes CD as it has a >99% negative predictive value.[14] In those on a GFD with a permissible allele, a gluten challenge is the next step. In the future, rising IL measurements (in particular IL-2, 8, 10) hours into a single-dose gluten challenge may prove useful as an early, sensitive diagnostic marker to detect gluten-specific T-cells' recall response in CD and to distinguish it from NCGS.[36,37]

Treatment

The treatment for CD is a strict lifelong gluten-free diet and regular follow-up. Dietary modification has benefits including resolution of symptoms, normalization of serology, healing of intestinal villi, and reduction in

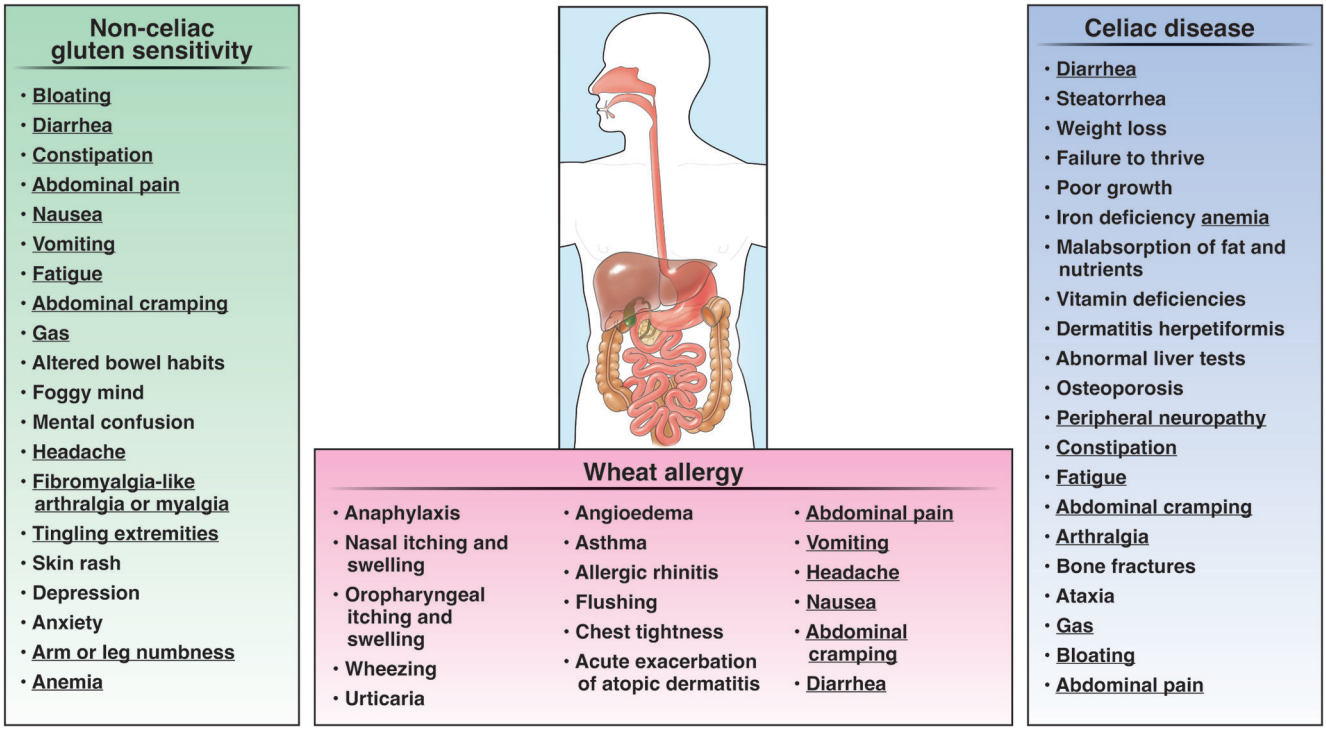

Figure 1. Symptoms of gluten-related disorders.

morbidity and mortality. A majority of patients experience substantial and rapid symptom improvement; in one survey of patients with biopsy-proven CD, abdominal pain and bloating improved from a pre-diet level of >70% to a post-GFD level of <5%.[38] Antibody concentration is expected to decrease after implementation of dietary treatment.[39] One study of 2245 patients with CD showed just 1% with positive TTG antibodies after 5

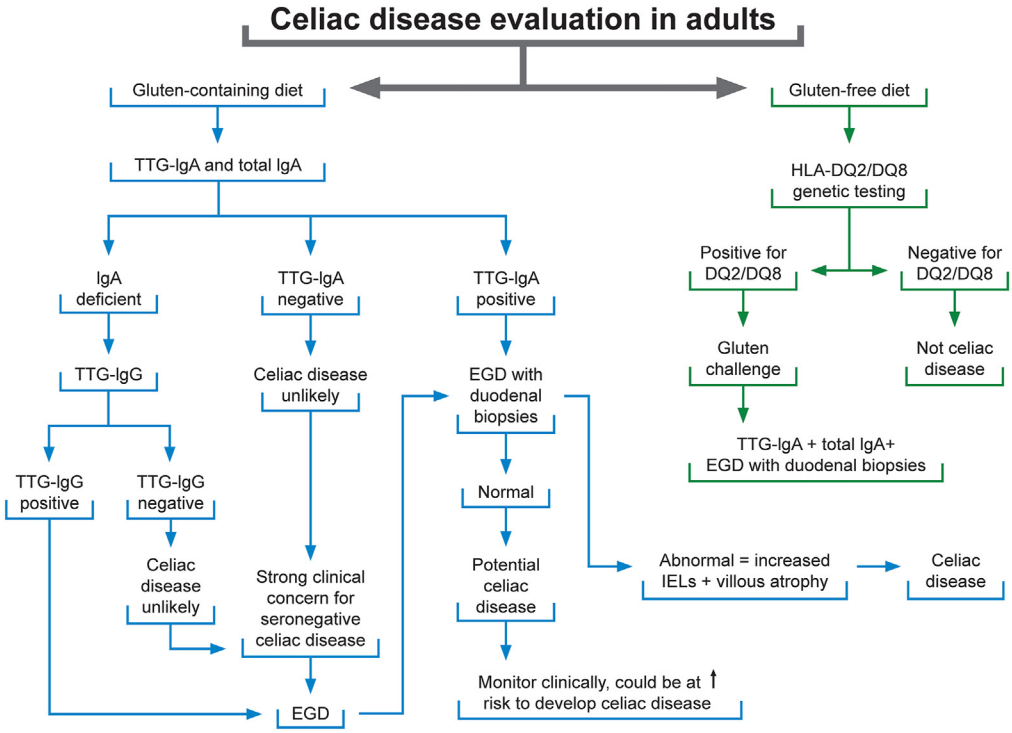

Figure 2. Celiac disease testing algorithm for adults. EGD, Esophagogastroduodenoscopy. *Adapted from the 2023 ACG guidelines for celiac disease: Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol 2023;118:59–76.

years on a GFD.[40] Mucosal recovery can take months to years, and dietary compliance is a key factor.[41] A celiac dietitian with expertise in the GFD is a vital part of the multidisciplinary team.

High-quality care also includes testing first-degree family members, screening for osteoporosis, updating age-appropriate vaccines (streptococcal pneumonia), and discussing mucosal healing as the treatment goal in adults.[15] Although regular follow-up with a dietitian should be offered to improve dietary adherence, guidelines do not yet support the use of gluten detection devices in food or biospecimens of patients with CD.[15] Technology may not yet distinguish between trivial and clinically significant gluten exposure. Although gluten fragments in stool and urine have promise for spot-checking gluten exposure, the overall role of this novel tool in clinical practice requires more study. Routine laboratory work at diagnosis in addition to baseline serology (TTG) should include a complete blood count, alanine and aspartate aminotransferase, iron, ferritin, folate, and vitamins (A, D, E, B12) and micronutrients (zinc, copper).[15,42] Any abnormal values should be followed for correction. Thyroid function in the form of thyroid stimulating hormone level should be checked to screen for other immune issues. If symptoms suggest other autoimmune disease, appropriate screening and referral when indicated should be pursued. A baseline dual-energy x-ray absorptiometry is advised to assess bone health.[15] The GFD and longitudinal follow-up remain the foundation of care of patients with CD.

Although a GFD is effective treatment for CD, it has its challenges. Expense, social isolation, vigilance, cross-contamination, and taxing disease burden with resultant impact on quality of life are concerns for patients. Because of these limitations of the GFD, patients, physicians, and the scientific community alike have an interest in non-dietary therapies for CD. Universities are exploring ways to modify or pretreat gluten. There are a number of emerging treatments that target various steps in celiac pathogenesis that offer hope (Table 1). There are many preclinical, phase I, and phase II drugs being studied, but the most advanced candidates for treatment have started phase III trials. Different agents under investigation include Latiglutenase (ALV-003, IMGX-003), an oral combination of proteases to help digest gluten proteins to neutralize their toxicity.[43,44] Other oral enzyme supplements to degrade gluten include TAK-062, AN-PEP, and STAN1.[43] Larazotide acetate (AT-1001) targets transit affecting tight junction modulators to restore intestinal barrier function.[45] TTG inhibition (ZED/TAK1227) shows promise.[46] Inhibitors of HLA-based immune activation (DONQ52) and gluten sequestering (AGY, BL-7010, scFv) are being explored.[43] Therapies affecting the gut microbiome (probiotics), cytokine release, lymphocyte recruitment, autoantibody generation, IL-15 signaling blockade (tofacitinib, AMG 714, Hu-Mik-β-1), and gluten tolerization (KAN-101, NexVax2, TIMP-GLIA, *Necator americanus*) are also potential therapeutic pathways.[43] These therapies under investigation represent adjuvant treatments, but not alternatives to the GFD.

Complications

Prior to discovering the trigger of gluten, CD was a deadly diagnosis with a historic mortality rate of 14.5% on average.[47] There remains a small increased mortality risk in patients with CD compared with the general population.[48] Rates of small intestine adenocarcinoma are higher in those with CD, but absolute risk is low.[49] Patients with persistent villous atrophy are at increased risk of lymphoproliferative malignancies including enteropathy-associated T-cell lymphoma.[50] Ongoing villous atrophy is found to be predictive of bone disease including hip fracture.[51] Iron deficiency anemia can continue in patients with CD despite a GFD.[52] The ultimate goal in the treatment of CD is healing of villi.[15] This process is gradual with a median time of 3.8 years to achieve villi of normal height based on a follow-up study of >200 adults.[53] Persistence of increased intraepithelial lymphocytes is not uncommon, but it lacks the clinical significance of ongoing villous atrophy.

Refractory CD should be suspected in patients with confirmed CD and persistent or recurrent symptoms despite following a GFD for >12 months after the exclusion of overt malignancy and other more common causes for symptoms such as gluten contamination.[54] Refractory CD is relatively rare, estimated to occur in just 1% of CD patients.[54] Clinical assessment of refractory CD requires repeat intestinal biopsy with special studies such as flow cytometry, immunohistochemistry, and T-cell receptor rearrangement to distinguish between subtypes.[55] Type 1 refractory CD is characterized by a normal intraepithelial lymphocyte population and type 2 is defined by the presence of an aberrant, clonal intraepithelial lymphocyte population (worse prognosis due to risk for ulcerative jejunoileitis or lymphoma). Aberrant/clonal intraepithelial lymphocytes are characterized by lack of expression of surface CD3 and CD8 molecules with normal intracellular CD3 expression.[56] They also express NKp46 (cut-off >25 NKp46+ intraepithelial lymphocytes per 100 epithelial cells) and show clonal T-cell receptor (TCR) gene rearrangements.[57] A flow cytometry is highly reliable for detection of aberrant/clonal intraepithelial lymphocytes with a diagnostic cutoff of 20% for prediction of subsequent lymphomagenesis.[58] Immunohistochemistry and T-cell receptor rearrangement studies are also helpful but less reliable for characterization of subtype due to several limitations related to the presence of a more diverse small intestinal T-cell receptor gene repertoires in CD and false-positive tests.[59,60] Careful evaluation of clinical presentation, histology, and immunophenotypic findings is necessary for a correct diagnosis and classification of refractory CD.[61]

Table 1. Selected Novel CD Therapies in Development

Novel agent	Phase of clinical trial	NCT identifier (related trials)	Mechanism	Efficacy	Adverse events
Latiglutenase	2b	NCT03585478 (NCT00959114, NCT01255696, NCT01917630, NCT00626184, NCT00669825)	Enzymatic gluten degradation in stomach	Reduction of gluten-induced intestinal mucosal damage and symptom severity (abdominal pain, bloating, tiredness)	No serious events, no differences with placebo, 52% of all patients had 1 event of mild severity, nausea (18%), distention (16%), diarrhea (16%) most common
Triticum Monococcum	2	NCT02220166	Form of wheat	No change in urinary lactulose/rhamnose ratio (measure of intestinal permeability)	Fewer adverse events reported in triticum group, mainly nausea, abdominal pain, bloating, graded as mild or moderate
AN-PEP	2	NCT00810654 (NCT04788797)	Enzymatic gluten degradation derived from aspergillus niger	Not effective in preventing mucosal damage induced by 7 g/day 2-week gluten challenge	No serious adverse events, no withdrawals, complaints reported were gastrointestinal and did not differ between groups
Bifidobacterium Infantis	2	NCT03271138 (NCT01257620)	Epithelial cell protection from gliadin damage using probiotic	Celiac symptom index improved in those with highest symptom burden compared with placebo, shift in stool microbiota profile	No differences in adverse events between two groups
Larazotide	2b	NCT01396213 (NCT00620451, NCT00889473, NCT00492960, NCT03569007)	Tight junction modulation to prevent intestinal permeability	Reduced symptoms shown by average on-treatment celiac disease GSRS score	Safety comparable with placebo at all dose levels, GI symptoms were most frequent, no serious adverse events
Necator Americanus	2a	NCT00671138 (NCT01661933)	Immune system regulation by inhibiting TH1 immune response	No obvious benefit on celiac pathology, wheat challenge caused deterioration in duodenal Marsh score	Transiently painful enteritis in 5 of 10 patients, chronic infection asymptomatic, no effect on hemoglobin levels
TAK-101	2a	NCT03738475	Induction of gluten-specific tolerance	Reduced INF-gamma, protected against villous height:crypt depth deterioration, no change in IELs	No serious adverse events, no clinically meaningful changes in vital signs or labs up to 8 mg/kg dose

Table 1. Continued

Novel agent	Phase of clinical trial	NCT identifier (related trials)	Mechanism	Efficacy	Adverse events
AMG 714	2a	NCT02637141 (NCT00433875)	IL-15 monoclonal antibody	Did not prevent mucosal injury during gluten challenge, but improvement in clinical symptoms like diarrhea	No serious adverse events, many patients experienced GI symptoms and injection site reactions in both groups
Nexvax2	2	NCT03644069	Immunotherapy recognizing CD4 T-cells	Study discontinued after planned interim analysis, no reduction in acute gluten-induced symptoms	Serious adverse events (renal infarct, PE, asthma exacerbation, appendicitis, infection) in 2% of intervention and 4% of control patients
KAN-101	1	NCT04248855	Induction of immune tolerance to gliadin using a liver-targeting glycosylation signature conjugated to a deamidated gliadin peptide	Acceptable safety profile, rapid systemic clearance, no accumulation on repeat dosing	Mild to moderate adverse events occurred, most commonly nausea, vomiting, diarrhea, abdominal pain, no serious adverse events, dose-limiting toxicities, or deaths occurred
Zed1227	2	2017-002241-30[a] (2014-003044-13, 2015-005283-42)[a]	Transglutaminase 2 inhibitor	Attenuation of gluten-induced duodenal mucosal injury (villous height:crypt depth, change in IEL density) and improved symptom and quality of life scores	Incidences were similar across groups, headache, nausea, vomiting, diarrhea, and abdominal pain reported, 8% of patients in highest dose group with rash
TAK-062	1	NCT03701555	Oral gluten endopeptidase	Well-tolerated, rapidly and effectively degrades large amounts of gluten in complex meals (97%-99% degraded of 1-6 g doses at 20-65 minutes post-dose)	Well-tolerated, headaches, nausea, abdominal distention reported, no serious adverse effects or deaths occurred

Note: Table was developed using PubMed for randomized controlled trials and clinicaltrials.gov for completed studies on celiac disease and interventional studies in phases 2 to 4. If more than one study was reported, the one with the most advanced stage with complete results was included. List of novel agents is not exhaustive. No results posted or publications available for STAN1, BL-7010, CCX282-B in humans.
GI, Gastrointestinal; GSRS, Gastrointestinal Symptom Rating Scale; IEL, intraepithelial lymphocytes; PE, pulmonary embolism.
[a]European Union registration identifier.

Non-celiac Gluten Sensitivity

Definition and Epidemiology

NCGS is a term encompassing the symptomatic and immunological manifestations precipitated by gluten-containing food ingestion in those where CD has been previously excluded.[1] In contrast to CD, people with NCGS lack elevations in celiac-specific antibodies and enteropathy. It is also a distinct entity from wheat allergy. It is formally defined by the Salerno consensus of experts in the field as discussed below in the diagnosis section. The exact component triggering symptoms has yet to be identified, and fructans or protein alpha-amylase-trypsin inhibitors may have a causal role.[62-64] Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in particular are gaining traction as the culprit, and in response, NCGS is also referred to as non-celiac wheat sensitivity. The diagnosis of NCGS relies on a clear relationship between gluten ingestion and symptoms. This entity was first described in 1978, but the precise prevalence is unknown.[65] What is known, is that between 1.7% and 7% of people, depending on geographic location, follow a GFD for reasons other than CD.[66,67] A vast majority, 82% according to one study, do so before seeking any medical advice.[68]

Pathophysiology

Although an exact mechanism is yet to be elucidated, it is hypothesized that the innate but not adaptive immune response may play a part in NCGS (Figure 3). Toll-like receptors in the intestinal mucosa are expressed at higher rates in NCGS compared with patients with CD.[69] It is also purported that damage to intestinal epithelial cells enables microbial translocation and immune system activation.[70] Patients with NCGS exhibit milder differences in intestinal histology such as villous height (shorter than controls, 600 vs 900 μm), median intraepithelial lymphocyte numbers (23 vs 14 in controls), and lower villous-to-crypt ratios indicating a response to a luminal antigen.[71]

Given the lack of clarity in NCGS pathogenesis, scientists have considered the causal role of other food components. These non-gluten entities include amylase-trypsin inhibitors (ATIs), wheat germ agglutinins, and fructans (a FODMAP). ATIs are a family of proteins that regulate starch metabolism during seed development and germination. They function as natural pesticides. ATIs stimulate innate immunity and have been shown to increase intestinal inflammation in mouse models.[72] ATIs are the source of allergen in baker's asthma.[73] Wheat germ agglutinins are a family of carbohydrate binding proteins in the lectin group. Studies in mice show wheat germ agglutinins provoke IL-4 and IL-13 release, increase inflammation, disrupt epithelial integrity, and increase synthesis of proinflammatory cytokines.[74] Fructans are polymers of fructose (6-carbon monosaccharide) that are osmotically active, thereby causing fluid retention and are rapidly fermented by gut bacteria in the colon. Any or all of these additional composites in wheat may contribute to symptoms in NCGS.

Clinical Presentation

NCGS is capable of a multifaceted clinical presentation just like CD (Figure 1). Abdominal pain, bloating, and

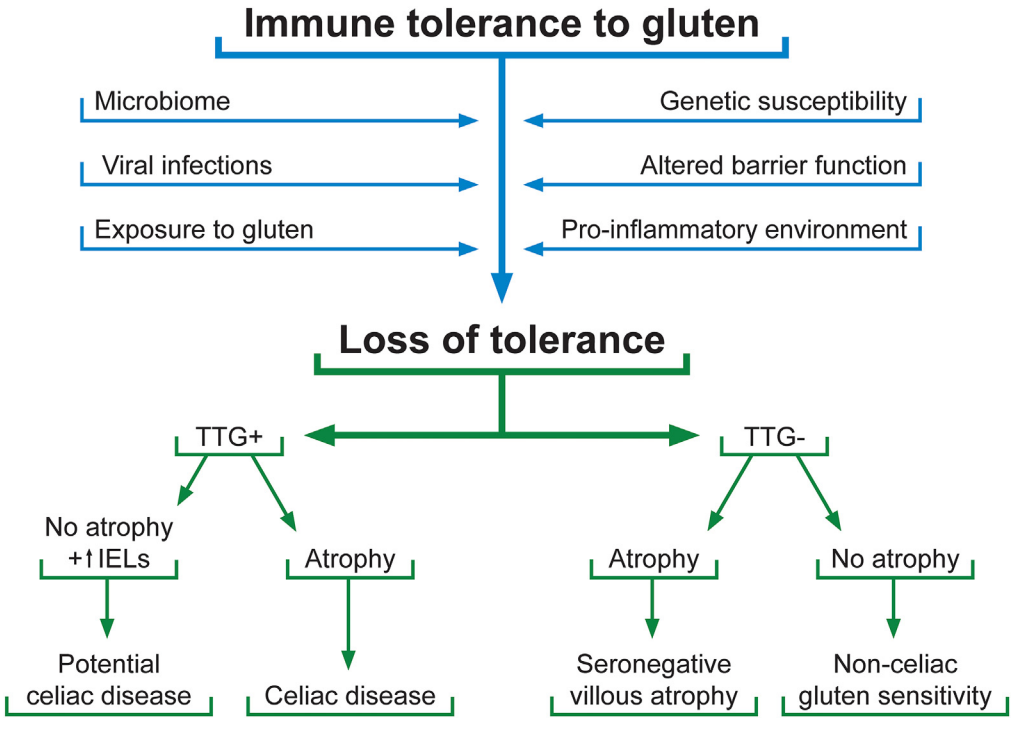

Figure 3. Immune tolerance in role of gluten-related disorders.

irregular bowel movements predominate for gastrointestinal symptoms, but systemic symptoms including fatigue (36%), headache (32%), "foggy mind" (42%), neuropathy (17%), and dermatitis (33%) have been reported among numerous others.[75] Additional intestinal symptoms may include borborygmi, increased flatus, fecal urgency, feeling of incomplete evacuation, eructation, nausea, vomiting, and heartburn or acid regurgitation.[76]

Diagnosis

Proper evaluation for and exclusion of CD and wheat allergy are paramount (serology, biopsy, allergy workup, and potentially genetic testing). Objective diagnostic tests for NCGS are lacking. The Salerno consensus describes a methodology to diagnose NCGS.[76] This involves a 6-week trial of gluten avoidance where symptoms improve then a double blind, placebo-controlled gluten challenge of 8 g/day.[76] Ideally the vehicle (muffin, bar, capsule) for gluten delivery is FODMAP-free and contains a standard amount of ATIs. A 1-week challenge occurs with gluten or placebo, then a 1-week washout of strict GFD, followed by crossover to a 1-week challenge of the other.[76] A 30% decrease in the modified Gastrointestinal Symptom Rating Scale between gluten and placebo diagnoses NCGS.[76] The complexity, length, and need for double-blinding limit the Salerno consensus's utility in clinical practice. However, the nocebo effect can influence results of open challenges. Symptoms triggered by gluten-containing foods with resolution on a gluten-free diet after exclusion of CD and wheat allergy may suggest the clinical diagnosis of NCGS (Table 2). The differential of irritable bowel syndrome (IBS) should be considered, especially if gastrointestinal symptoms are predominant and responsive to gluten-free or low-FODMAP diets. It has been reported in an Italian study that 41 of 44 patients with NCGS exhibit a decline in antigliadin (AGA) IgG after initiation of the gluten-free diet; although interesting in that it suggests a causal role for gluten, AGA positivity is only present in about one-half of patients with NCGS.[77,78] In patients with IBS, if AGA-IgG was positive those individuals were more likely to experience improvement in diarrhea (75% vs 38%; $P = .01$).[79]

Treatment

Limiting gluten in the diet is agreed upon for those with NCGS; what remains ambiguous is how strictly and for how long—a less stringent diet that is gluten-limited as opposed to gluten-free may be adequate.[42] Instruction on the GFD by a dietitian and regular follow-up are the authors' practice. For those who do not respond to the GFD, the diagnosis of NCGS cannot be confirmed, a low FODMAPs diet may be reasonable.

The GFD is lower in fiber and of suboptimal nutritional quality as GF foods are not fortified in iron, thiamine, niacin, riboflavin, and folate. They also have added sugar, fat, and salt compared with gluten-containing counterparts. As such, depending on the clinical scenario, we consider testing hemoglobin A1c and lipid panels. Body weight is carefully monitored, and a high index of suspicion is needed for nutritional deficiencies based on symptoms. Consider rechallenge with gluten in the future, after 1 to 2 years on a GFD, with help of a dietitian and gastroenterologist. Trial and error can be used to determine a tolerable dose of gluten. To our knowledge, there are no current drugs in development for NCGS likely owing to the ambiguity surrounding the pathogenic cascade; however, endopeptidases and microbiome-based therapies aimed at reducing gluten toxicity theoretically could benefit these patients.

Table 2. Proposed Criteria for Clinical Diagnosis of NCGS

Symptoms
• Digestive and extra digestive symptoms that occur after eating gluten-containing foods (stereotypic response or pattern of symptoms)
Work-Up
• Complete evaluation for celiac disease (negative TTG-IgA on gluten-containing diet) • Complete evaluation for wheat allergy (skin prick test negative, IgE wheat negative, referral to allergist if necessary) • Normal duodenal biopsy or increased intraepithelial lymphocytes
Treatment
• Improvement of symptoms on gluten-free diet

Note: Adapted from Ellis A, Linaker BD. Non-coeliac gluten sensitivity? Lancet 1978;1:1358-9.
IgE, immunoglobulin E; NCGS, non-celiac gluten sensitivity; TTG-IgA, tissue transglutaminase antibody immunoglobulin A.

Complications

NCGS lacks most of the consequences of CD because of the absence of enteropathy. It is not associated with malabsorption or malignancy.

Wheat Allergy

Definition and Epidemiology

Wheat allergy is characterized by an immunoglobulin E (IgE)-mediated response to wheat proteins. A reaction can be elicited through ingestion (food allergy) or inhalation (respiratory allergy or baker's asthma or wheat-dependent exercise-induced anaphylaxis). There are also non-IgE mediated food allergies characterized by eosinophil infiltration and inflammation outside the scope of this review. Wheat allergy is more common in children than adults and is outgrown in around 65% of

Table 3. Comparison of CD and NCGS

	CD	NCGS	Wheat allergy
Description	Immune-mediated enteropathy	Non-allergic, immune reaction to gluten	Allergic, immune-mediated
Epidemiology	1%	?	0.2%
Pathophysiology	Innate and adaptive immune response to gluten	Unclear, innate immune response, increased toll-like receptor expression	IgE-mediated response
Symptom onset	Days to weeks	Hours to days	Minutes to hours
Consequences	Villous atrophy (decrease in the villous height to crypt depth ratio below the normal range of 3-5:1), increased IELs (>25 IELs per 100 epithelial cells), damage to the small intestine, long-term complications	No villous atrophy, may have increased IELs or normal histology in small intestine	No villous atrophy, some cases result in anaphylaxis
Gluten ingestion	Required to trigger response	Likely required to trigger response	Wheat required to trigger allergic response
Genetics	HLA DQ2/DQ8 required	Variable, no requirement	No requirement
Diagnosis	Serology and duodenal biopsy	Evaluation of response to 6 weeks of GFD and 2 weeks of placebo/gluten challenge[a]	Serum wheat IgE, skin prick testing, evaluation by allergist
Treatment	Strict GFD	Limiting gluten in diet to tolerated amount	Epinephrine pen, avoidance

CD, Celiac disease; GFD, gluten-free diet; HLA, human leukocyte antigen; IELs, intraepithelial lymphocytes; IgE, immunoglobulin E; NCGS, non-celiac gluten sensitivity.
[a]Salerno criteria for research and clinical trials (less helpful in clinical practice).

kids by the time they turn 12.[73] Exact epidemiology is unknown but estimates range from 0.2% to 1%.[73]

Pathophysiology

IgE-mediated reactions are classically reproducible, immediate, and food-specific. Wheat allergy symptoms are caused by mediator release (histamine, leukotrienes, and platelet activator factor) from basophils and mast cells.[73] IgE production results from a breach of oral wheat tolerance. T-helper 2 cell dysregulation is responsible for sensitization and B-cells produce IgE antibodies.[73] Allergens in wheat include gliadin, peroxidase, serine proteinase inhibitor, ATIs, and others.[73]

Clinical Presentation

Symptoms of wheat allergy include hives or urticaria, rash, angioedema, gastrointestinal symptoms (abdominal pain, vomiting), respiratory symptoms, allergic rhinitis, asthma, and in some cases anaphylaxis.[73] Onset of symptoms are often immediate and can be minutes to within 3 hours of exposure to wheat. Wheat-dependent exercise-induced anaphylaxis happens during intense exercise and occurs in affected individuals within a few (typically 1-3) hours of wheat ingestion.[73] Baker's asthma or rhinitis is an occupational disease that occurs more commonly in atopic patients with high levels of wheat allergen exposure for hours duration throughout the day.[73]

Diagnosis

Serum wheat IgE level and skin prick tests are useful in diagnosis, coupled with the clinical history of wheat-induced symptoms; there is a difference between asymptomatic sensitivity suggested by a positive test and inability to tolerate wheat based on severity of symptoms after exposure.[73] Subjects with grass pollen sensitivity have been shown to have cross reactivity with wheat flour protein.[73] There is no exact level or degree of elevation of IgE that predicts true allergy. For a precise diagnosis, a medically supervised standardized oral food challenge is required.[73] For baker's asthma, a bronchial challenge with nebulized aqueous flour or inhalation of wheat flour dust is used, and a 20% drop in forced expiratory volume over 1 second during spirometry is diagnostic.[73]

Treatment

The mainstay of treatment is avoidance of wheat and inhaled wheat allergens. Regular follow-up with an allergist is advised. For those with wheat-dependent exercise-induced anaphylaxis, prevention strategies including exercise avoidance after wheat ingestion are recommended and access to emergency medication.[73] In

cases of anaphylaxis, an epinephrine pen is a lifesaving treatment (0.3 mg autoinjector intramuscular lateral thigh injection) and should be followed by emergency room evaluation.[73] Other emerging treatments may include sublingual or oral immunotherapy, and epicutaneous immunotherapy for gradual desensitization.[73]

Complications

Other than anaphylaxis, IgE-mediated wheat allergy is often benign in adults.

Summary

CD, NCGS, and wheat allergy share some similarities, but exhibit important clinical differences (Table 3). Their multiple possible presentations make diagnosis difficult, and therapy being dietary, without a pharmacologic option, leads to challenges in treatment. When approaching a patient in clinic with gluten-related symptoms, consider the differential diagnosis including CD, NCGS, and wheat allergy. Recall the definitions covered in this narrative review, consider the likelihood of diagnosis given epidemiology, and characterize their clinical phenotype. Perform a proper and guideline-directed evaluation for CD (Figure 2); only after this status is known, implement dietary measures accordingly. Finally, follow these patients clinically for symptomatic improvement, development of complications, concomitant-related conditions, and routine high-quality care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.09.042.

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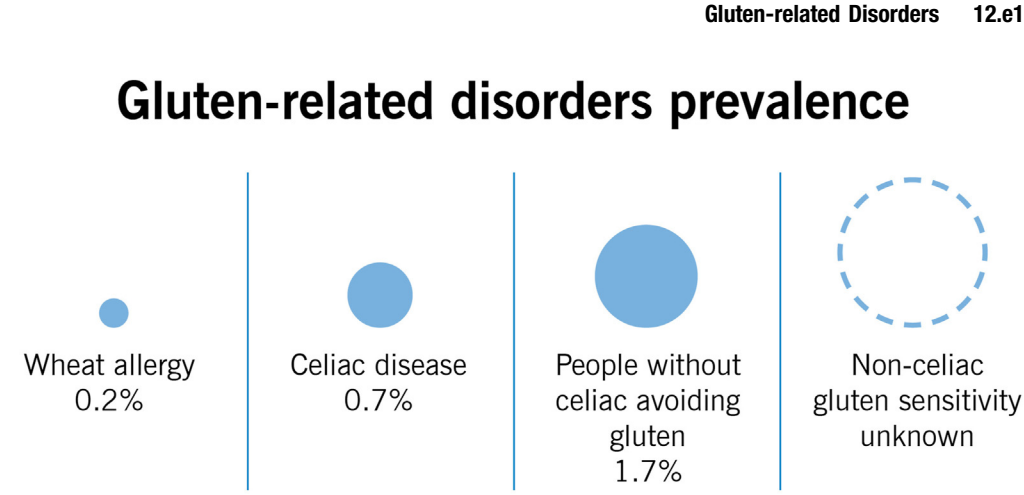

Supplementary Figure. Epidemiology of gluten-related disorders.