# NASPGHAN Clinical Report on the Diagnosis and Treatment of Gluten-related Disorders

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**ABSTRACT**

Dietary exclusion of gluten-containing products has become increasingly popular in the general population, and currently ~30% of people in the United States are limiting gluten ingestion. Although celiac disease (CD), wheat allergy (WA), and nonceliac gluten sensitivity (NCGS) constitute a spectrum of gluten-related disorders that require exclusion of gluten from the diet, together these account for a relatively small percentage of those following a gluten-free diet, and the vast majority has no medical necessity for doing so. Differentiating between CD, WA, and NCGS has important prognostic and therapeutic implications. Because of the protean manifestations of gluten-related disorders, it is not possible to differentiate between them on clinical grounds alone. This clinical report will compare and contrast the manifestations of gluten-related disorders, emphasize the importance of differentiating between these conditions, discuss initial and subsequent tests needed to confirm the diagnosis, and provide recommendations on treatment and follow-up for each condition.

**Key Words:** celiac disease, celiac disease serological tests, gluten-free diet, IgE-specific antibodies, nonceliac gluten sensitivity, wheat allergy

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Gluten, the major complex protein component of wheat, has a high concentration of glutamine and proline residues referred to as prolamins. Similar high concentrations of prolamins are found in barley and rye, and the term ''gluten'' is now loosely used to refer to the proteins found in all the 3 grains. Gluten is the major environmental factor that triggers celiac disease (CD) in genetically predisposed people, and strict exclusion of gluten by means of a gluten-free diet (GFD) for life is required for treatment of those in whom a diagnosis of CD is confirmed.

Recently, the possible role of gluten as a cause of symptoms in conditions other than CD has become of interest to both health care professionals and the lay public. Wheat allergy (WA) is 1 such condition that requires the exclusion of wheat protein from the diet. In addition, many people who do not have CD or WA suffer from a variety of symptoms that improve when they adopt a GFD. The term nonceliac gluten sensitivity (NCGS) is used to describe such individuals, and together with CD and WA these constitute a ''spectrum'' of gluten-related disorders.

What constitutes NCGS is the subject of some debate, and the prevalence of the condition is not known. Symptom response to the GFD in some patients is because of removal of the gluten per se, whereas in others it is attributed to the removal of other nonprotein components found in these grains, such as the fructans that belong to the category of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Compounding the confusion is the fact that adoption of a GFD has become the most popular dietary fad in the United States today, and the production of gluten-free foods has evolved into a multibillion dollar industry. Although the exclusion of gluten is essential for those with CD, WA, and possibly for some who have NCGS, it is believed that together these account for a relatively small percentage of people who are currently following a GFD, and the majority is doing so for personal and not medical reasons. Following a strict GFD is cumbersome and is associated with increased costs and possible risk for both nutrient deficiencies, and excessive weight gain in some patients because of the hypercaloric content of commercial gluten-free products (1). Gluten-free foods are not routinely fortified and have been associated with deficiencies of fiber, thiamine, folate, vitamin A, magnesium, calcium, and iron (2). Therefore, a GFD should be recommended only after careful consideration of the potential downside.

This clinical report will differentiate CD from WA and NCGS. For the purpose of this report, the term ''nonceliac gluten sensitivity'' is used to describe those patients in whom symptoms are related to ingestion of gluten and not those who respond to the removal of FODMAPs from the diet. The clinical manifestations of these conditions will be compared, and the identification of those in need of testing will be defined. The recommended initial tests to be used and how the diagnosis of each condition is confirmed will be described. Finally, the treatment for these conditions and the need for continued follow-up will be discussed.

## DEFINITION OF GLUTEN-RELATED DISORDERS

There are a number of definitions in use for CD, WA, and NCGS. By and large, all of them encompass the same basic principles. For the purpose of this report, the following definitions have been chosen for these conditions.

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## Celiac Disease

CD is an immune-mediated systemic disorder triggered by gluten and related prolamins present in wheat, barley, and rye that occur in genetically susceptible individuals who have the human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes. It is characterized by an inflammatory enteropathy with variable degrees of severity, a wide range of gastrointestinal and/or systemic complaints, and the presence of celiac-specific autoantibodies (3).

## Wheat Allergy

WA is a hypersensitivity reaction to wheat proteins mediated through immune mechanisms and involving mast cell activation. The immune response can be immunoglobulin E (IgE) mediated, non-IgE mediated, or a combination of both. WA is most commonly a food allergy, but wheat can become a sensitizer when the exposure occurs through the skin or airways (baker's asthma).

## Nonceliac Gluten Sensitivity

NCGS is a poorly defined syndrome characterized by a variable combination of intestinal and extraintestinal symptoms, typically occurring soon after the ingestion of gluten-containing foods and disappearing quickly upon their withdrawal, occurring in individuals where both CD and WA have been excluded (4).

# CLINICAL MANIFESTATIONS OF GLUTEN-RELATED DISORDERS

The clinical manifestations of gluten-related disorders are protean in nature and involve multiple organ systems. There is considerable overlap of symptoms between these conditions, which makes differentiation impossible on clinical grounds alone (Table 1).

TABLE 1. Common clinical manifestations of gluten-related disorders

| | Celiac | NCGS | WA |
|---|---|---|---|
| Time from exposure to symptoms | Hours-months | Hours-days | Minutes-hours |
| Gastrointestinal | | | |
| Diarrhea | X | X | X |
| Abdominal pain | X | X | X |
| Constipation | X | X | X |
| Gas/bloat/distention | X | X | X |
| Poor weight gain | X | X | X |
| Malodorous fatty stools | X | | |
| Vomiting | X | X | X |
| Extraintestinal | | | |
| Pubertal delay | X | | |
| Unexplained weight loss | X | X | X |
| Poor height gain | X | | |
| Bone/joint pain | X | X | X |
| Rash of DH | X | | |
| Eczema | | X | X |
| Hives/atopic dermatitis | | | X |
| Fatigue | X | X | X |
| Headache/migraine | X | X | X |
| Foggy mind | X | X | |
| Angioedema | | | X |
| Anaphylaxis | | | X |
| Respiratory | | | |
| Asthma | | | X |
| Cough | | | X |
| Postnasal drip, throat clearing, rhinitis | | | X |

DH = dermatitis herpetiformis; NCGS = nonceliac gluten sensitivity; WA = wheat allergy.

## Clinical Manifestations of CD

Gastrointestinal symptoms are still prominent, particularly in younger children. The onset of CD in infancy and very early childhood may have severe gastrointestinal manifestations resulting in malnutrition, failure to thrive, and in some patients a protein-losing enteropathy. Although these were relatively common presentations of CD in the past, they are rare nowadays.

Abdominal pain and distention with diarrhea or even frank steatorrhea are hallmarks of CD, but severe forms of these manifestations have become progressively less frequent, and milder forms are more common at initial presentation. Counterintuitively, severe constipation related to delay in orocecal transit time (5,6), possibly aggravated by disordered upper gastrointestinal motor function (7), can be the presenting manifestation in a significant number of children. Although CD is typically thought to be associated with weight loss or failure to gain weight, some children with CD are initially overweight or obese (8). Less common presentations include acute electrolyte disturbances, hypotension, and lethargy, and recurrent intussusception occurs more frequently in children with CD (9).

There are also numerous extraintestinal manifestations, and almost any body system can be involved. Older children and adolescents are more likely to present with nongastrointestinal symptoms (10–12), and previously used terms of ''typical'' and ''atypical'' to describe gastrointestinal and extraintestinal symptoms, respectively, are now considered obsolete and no longer recommended (13). The variable nature of the clinical manifestations, and the fact that CD may be asymptomatic, is believed to be largely responsible for the majority of people with CD remaining undiagnosed.

A mild elevation of serum liver enzymes is also well described as a presenting manifestation of CD in the pediatric age group and may account for up to 12% of children with unexplained hypertransaminasemia (14). The enzymes involved are alanine aminotransferase and aspartate aminotransferase, and typically these are elevated in the region of 2 to 3 times the upper limit of normal (ULN). Following institution of a GFD, the majority of affected patients will have normal transaminase levels within 4 to 8 months (14). In a small number, hypertransaminasemia persists despite strict adherence to a GFD. In these, additional workup should be considered to look for other causes of liver disease, such as autoimmune hepatitis, which can be associated with CD.

Anemia, most commonly as a result of iron deficiency, has been reported in 12% to 69% of newly diagnosed patients (15–18) and appears more prevalent in celiac patients with an atrophic mucosa compared with those with mild enteropathy (19). Linear growth failure as an isolated initial presentation of CD is well described and can be found in up to 10% of children undergoing investigation for short stature (20,21).

Dermatitis herpetiformis (DH) is considered a skin presentation of CD and is more common in adults or older teenagers. It is characterized by symmetrical, pruritic blisters followed by erosions, excoriations, and hyperpigmentation most commonly involving elbows (90%), knees (30%), shoulders, buttocks, sacral region, and face (22). The diagnosis of DH depends on demonstrating typical immunoglobulin A (IgA) deposits on skin biopsies (23).

Other manifestations include dental enamel hypoplasia (24), recurrent aphthous ulcers in the mouth, low–bone mineral density, and arthritis/arthralgia (25). Although children with low–bone

mineral density appear better able to correct this deficiency after starting the GFD, recovery can be delayed in some patients, whereas others are at risk for never achieving optimal bone density as they go through puberty (26,27).

There appears to be a slight increase in the frequency of neurological symptoms including headache, peripheral neuropathy, and seizures in CD (28–31). In 1 young adult with CD and epilepsy refractory to antiepileptic drugs, seizures were controlled with a GFD (32).

Adolescents with CD have been reported to have psychiatric issues including anxiety, recurrent panic attacks, hallucinations, depression, and an increased prevalence of suicidal behavior. There is some evidence that the GFD diet may help alleviate depression in adolescents with CD (33,34).

## Clinical Manifestations of WA

Food allergies most often involve the gastrointestinal system, skin, or respiratory tract. The clinical manifestations of WA range from swelling and itching of the lips or mouth, atopic dermatitis, hives, allergic rhinitis, and asthma to angioedema and anaphylaxis. Intestinal manifestations include abdominal pain, bloating, diarrhea, nausea, vomiting, and constipation. Other nonintestinal manifestations include fatigue, weight loss, joint pains, and headaches (35). Another possible clinical manifestation of WA is eosinophilic esophagitis (EoE). In this chronic condition, various food proteins, including wheat, serve as the trigger for a dysregulated immune response limited to the esophagus and causing infiltration of the mucosa and deeper layers with high density of eosinophils. The result of this inflammatory response is damage leading in some patients to edema, spasm, and stricture. Clinically, EoE presents with symptoms overlapping gastroesophageal reflux, and dysphagia, feeding aversions, and eventually food impaction.

Two additional clinical presentations deserve separate note: wheat-dependent, exercise-induced anaphylaxis (WDEIA) and baker's asthma. WDEIA is a rare form of anaphylaxis triggered when the consumption of wheat is followed within a short period of time by exercise. Omega-gliadins seem to play an important role in this condition, and aspirin is known to contribute to the occurrence and severity by enhancing intestinal permeability and enhanced antigen absorption.

In baker's asthma, sensitization to wheat proteins occurs through the inhalation of particulates in workers exposed to aerosolized flours. The clinical manifestations are chronic cough, asthma, and rhinitis, which improve when the exposure is avoided. In addition to ω-gliadins, the thioredoxin hB component has been identified as responsible triggers (36). Recently, a fungus-derived amylase, added to the flour to improve baking quality, has been identified as a responsible allergen in some patients.

## Clinical Manifestations of NCGS

Manifestations of NCGS are multisystemic and characterized by a variable combination of intestinal and extraintestinal symptoms (37–39). Similar to CD, NCGS is reported to affect different organs/systems, and symptoms can vary in severity. The latency between gluten ingestion and the onset of symptoms is often relatively short and may be within a few hours to days. This is somewhat different from WA in which onset of symptoms following exposure is often within minutes to hours and CD in which onset may be more prolonged and can vary from days to weeks. A relatively common reported presentation of NCGS resembles irritable bowel syndrome with symptoms of bloating, abdominal pain, and change in consistency and/or frequency of bowel movements. Differentiating between these conditions may be facilitated by those with NCGS more commonly describing additional extraintestinal symptoms, including headache or frank migraine, foggy mind, chronic fatigue, joint and muscle pain, tingling of the extremities, leg or arm numbness, eczema, anemia, and/or behavioral changes (37–39). The clinical features attributed to NCGS have mainly been described in the adult population, and there are little data for the pediatric population.

Because many people and parents of children with symptoms ascribed to NCGS have already suspected an association between gluten ingestion and onset or worsening of symptoms, some will self-treat with a GFD before seeking medical advice. Doing so is discouraged as the elimination of dietary gluten makes it difficult to differentiate CD from WA and NCGS.

# WHO SHOULD BE TESTED FOR GLUTEN-RELATED DISORDERS?

## Symptomatic Individuals

Because the manifestations of gluten-related disorders are so varied, diagnosis requires a high index of clinical suspicion. In addition, owing to the overlapping symptoms between CD, WA, and NCGS, these disorders cannot be distinguished from one another on the basis of clinical manifestations alone.

Children with symptoms consistent with gluten-related disorders, or who have self-identified relief of symptoms when avoiding gluten, should undergo testing for CD and/or WA before the elimination of dietary gluten. CD should be an early consideration in those with typical gastrointestinal symptoms such as chronic diarrhea, abdominal pain, distension, and weight loss (40). Testing should also be considered when no other cause for symptoms can be identified in those with less typical symptoms including, but not limited to, constipation, linear growth failure, anemia, fatigue, arthralgia, and elevated liver enzymes (Table 2). Testing for WA should be considered when there is a history of symptoms occurring shortly, or within a few hours, after consuming wheat products. Allergy testing is not always helpful, especially if EoE is suspected, and an endoscopy may be indicated. There is no test to identify people who may have NCGS. Before this condition can be considered, however, it is first essential to exclude CD and WA.

Differentiating CD from WA and NCGS is important because there are significant differences in potential long-term health consequences. People with CD are at increased risk for other autoimmune diseases such as autoimmune thyroiditis and

TABLE 2. Indications to consider CD testing

| Symptoms | Associated conditions |
|---|---|
| Abdominal pain | First-degree relatives of those with CD |
| Abdominal distension | Type 1 diabetes |
| Diarrhea | Autoimmune thyroid disease |
| Constipation | Autoimmune liver disease |
| Growth failure or deceleration | Trisomy 21 |
| Weight loss | Williams syndrome |
| Arthralgia | Turner syndrome |
| Elevated hepatic transaminases | IgA deficiency |
| Iron deficiency anemia | Juvenile chronic arthritis |
| Unexplained osteopenia | |
| Dental enamel defects | |
| Recurrent aphthous stomatitis | |
| DH | |

CD = celiac disease; DH = dermatitis herpetiformis; IgA = immunoglobulin A.

should be monitored for these. Those with symptomatic CD who do not follow a strict GFD have increased risk for mortality and relative increased risk for intestinal malignancies. On the contrary, those with WA and NCGS may be able to follow a less restrictive diet and have a lower risk for long-term adverse health outcomes. Although symptom relief following self-initiation of a GFD is evidence for the role of gluten, this is not diagnostic by itself. A gluten challenge should be considered in those who initiate a GFD before confirmatory diagnostic testing, given the significance of the long-term clinical implications. The decision to undertake a gluten challenge should be considered carefully in the context of each individual patient.

## Asymptomatic Individuals

Children belonging to groups known to be at increased risk for CD may initially have no symptoms, or very minor symptoms, despite having intestinal histologic changes that are characteristic for CD. Included in these groups are first-degree relatives of an index case, people with trisomy 21, Turner syndrome, Williams syndrome, and IgA deficiency, and those with other autoimmune conditions (Table 2). There is some debate as to whether people belonging to these at-risk groups should be tested for CD if they are totally asymptomatic. Guidelines from the pediatric societies recommend testing all such people beginning after the age of 3 years or at the time of initially diagnosing the associated condition (3,40). Those from the adult societies do not strongly advocate testing for all at-risk individuals but recommend that they be studied and tested if they ever develop any symptoms (41,42).

Potential benefits of early identification of CD in asymptomatic at-risk people include decreased morbidity and mortality, possible prevention of other autoimmune diseases, and an improvement in quality of life (43–45). There is some data suggesting that dietary adherence is better when the diagnosis is made in early childhood and that dietary adherence diminishes with advancing age at diagnosis (46,47).

Potential disadvantages of treating asymptomatic people identified with CD through screening programs include an adverse impact on their quality of life and the increased costs incurred with the GFD. Quality of life does not appear to be impaired in screen-detected children before GFD initiation (48). There are reports that adolescents perceive the diagnosis of CD and the need to adhere to the GFD, however, as having an adverse impact on their quality of life and social function (49). For these reasons, adolescents with screen-detected CD may be less compliant with a prescribed GFD even though many have serological evidence of ongoing active disease (50).

# INITIAL TESTING FOR GLUTEN-RELATED DISORDERS

## Celiac Disease

Commercial serological tests for both IgA and immunoglobulin G (IgG) antibodies against gliadin (AGA), endomysium (EMA), tissue transglutaminase (tTG), and deamidated gliadin peptides (DGPs) are available (Table 3). Serological tests for CD are dependent on the consumption of gluten, and avoidance of gluten before testing can result in a false-negative result. Although the exact duration of gluten consumption required before testing is not known, experts agree that the ingestion of $\geq$10 g of gluten (equivalent to 2 slices of whole wheat bread) per day for $\geq$8 weeks should allow for confident interpretation of the tTG antibody test result.

TABLE 3. Sensitivity and specificity of serological tests for CD

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Antigliadin antibody IgG (AGA-IgG) | 83–100 | 47–94 |
| Antigliadin antibody IgA (AGA-IgA) | 52–100 | 72–100 |
| tTG; tTG IgA (tTG-IgA) | 90–100 | 95–100 |
| Anti-EMA antibody IgA (EMA-IgA) | 93–100 | 98–100 |
| DGP; DGP IgA (DGP-IgA) | 80–91 | 91–95 |
| DGP; DGP IgG (DGP-IgG) | 88–95 | 86–98 |

AGA = antibodies against gliadin; CD = celiac disease; DGP = deamidated gliadin peptide; EMA = endomysium; IgA = immunoglobulin A; IgG = immunoglobulin G; tTG = tissue transglutaminase.

Present guidelines recommend the tTG-IgA antibody as the most cost-effective and reliable test to identify people who may have CD (3,40–42). Obtaining a serum IgA level at the same time should be considered to identify those who have selective IgA deficiency.

The tTG-IgA antibody is performed by means of an enzyme-linked immunosorbent assay or radio immune assay (RIA) method and is highly sensitive and specific (Table 3). The EMA-IgA is less sensitive than the tTG-IgA but slightly more specific. The EMA requires an immunofluorescent technique using monkey esophagus or human umbilical cord as the substrate. It is more expensive than the tTG and subject to interobserver variability, and thus is prone to false-negative results and, to a lesser extent, particularly at low titers, to false-positive results in inexperienced hands.

The AGA tests are both poorly sensitive and specific compared with the tTG and EMA, and prone to wide variability between laboratories. Therefore, AGA tests are not recommended for initial diagnosis of CD (1,40,41). DGP tests detect antibodies against synthetically derived peptides and perform better than the AGA tests. The DGP-IgG has comparable specificity but lower sensitivity than the tTG-IgA and EMA-IgA, whereas the DGP-IgA is both less sensitive and specific (Table 3).

Use of a panel of antibodies instead of a single tTG-IgA test is not recommended. Although this approach may be associated with a marginal increase in the sensitivity of the test, it decreases the specificity and significantly increases the costs (41,51).

## Special Considerations

### *IgA Deficiency*

Selective IgA deficiency is more common in people with CD than in the general population. With IgA deficiency, an IgG-based tTG, EMA, or DGP assay is required to test for CD (3,40). A positive IgG-based test for tTG, EMA, or DGP in a person with IgA deficiency is an indication for endoscopy with biopsy to confirm or exclude the diagnosis of CD. IgG antibody tests, however, are less accurate than IgA tests. Therefore, if there is a strong clinical suspicion for CD in an IgA-deficient person, an intestinal biopsy should be considered even if all serological tests are negative.

An isolated positive IgG-based test with negative IgA-based tests in an IgA-competent individual is unlikely to be because of CD (3). In such patients, other causes for symptoms should be considered and clarification on whether the subject has been avoiding gluten is required before recommending additional testing for CD.

### *Young Child*

Based on some studies, there is a possibility that the tTG-IgA and EMA-IgA tests may not be as accurate in the young child

(<2 years of age). Therefore, when testing for CD in a child <2 years of age, it is suggested that the tTG-IgA be combined with a DGP-IgG to improve the accuracy of the testing (3).

### Associated Autoimmune Conditions

People with other autoimmune conditions associated with CD, such as type 1 diabetes and autoimmune thyroiditis, can have transient mild elevation of antibodies to tTG-IgA that is nonspecific and not indicative of CD. In these patients, the EMA-IgA will be negative. It is not known exactly how high the tTG-IgA antibody level must be before it is considered sufficient to recommend intestinal biopsy, but based on expert opinion anything <3 times the ULN should be viewed with suspicion (52). If the tTG-IgA is <3 times ULN, consider obtaining an EMA-IgA first and only proceed to biopsy if the EMA is positive. If the EMA is negative, and there are no other concerning symptoms, it is acceptable to observe the patient and repeat the serological tests after 6 to 12 months.

### Concurrent Infections

Transient nonspecific elevations of tTG can occur during an acute infectious process. In these patients, the levels return to normal and remain so following the resolution of the infection (53). Caution is necessary when interpreting an elevated tTG obtained during any febrile illness. Repeat testing following complete recovery from any illness is advisable before recommending a diagnostic endoscopy with biopsies.

### HLA Tests

The HLA DQ heterodimers DQ2 and/or DQ8 are necessary for CD but not specific to people with CD, and can be found in up to 40% of the general population. Although there is evidence that people who are HLA DQ2 homozygous are at much higher risk, HLA testing should not be used as an initial diagnostic test for CD (41). Testing for HLA-DQ2/8 is best reserved for patients in whom there is a diagnostic dilemma, such as when there is a discrepancy between the serological and histologic findings or when a GFD has been started before any testing. In such patients, if neither HLA-DQ2 nor DQ8 is present, CD is highly unlikely, and an alternative diagnosis should be sought.

It has been recommended that the HLA test should be used as a first test when screening asymptomatic people at increased risk for CD such as family members of an index case (3). In those who are negative for both DQ2 and DQ8 alleles, no further testing for CD is needed, whereas in all other patients testing for tTG/EMA antibodies is needed to identify those who require intestinal biopsies to confirm the diagnosis. Currently, the HLA tests are expensive, and the cost-effectiveness of such a strategy has not been determined.

### Point-of-Care Tests

Rapid tests for tTG antibodies that can be used at the point of care (POC) have accuracy similar to that of tTG tests by laboratory detection (3). These POC tests do not allow for quantitative analysis of the antibody levels and therefore should not be used to replace laboratory testing. If a POC test is positive, the test should be repeated by means of a standard laboratory test before diagnosis and treatment of CD. In addition, a negative POC test performed by someone who has not been specifically trained to perform the test should be ignored and repeated by means of a laboratory test.

### Fecal Antibody Testing

Fecal tests for CD-associated antibodies are considered unreliable and should not be used under any circumstances to screen patients for CD (3).

## Wheat Allergy

Sensitization to wheat proteins can be demonstrated by the measurement of circulating IgE-specific antibodies against the suspected allergen and by skin sensitivity testing. The ImmunoCAP Specific IgE blood test, also called the CAP FEIA (fluorenzymeimmunoassay) test or Pharmacia CAP test, is the most commonly used method and has replaced the radioallergosorbent test as the preferred method to report quantitative detection of specific IgE antibodies. Systematic review of the accuracy of specific IgE determinations to identify WA demonstrated a pooled sensitivity of 83% (95% CI 69–92) and specificity of 43% (95% CI 20–69) (54).

Skin testing can be done either by prick or patch technique, and by intradermal injection. In the skin prick test (SPT), the allergen is placed on the skin, and a superficial prick is performed with a thin plastic probe or needle, so the solution penetrates the skin. A wheal reaction indicates sensitization. In the patch test, the allergen is applied in a well or patch that is kept in contact with the skin for 72 hours. A systematic review of the accuracy of skin tests to identify WA demonstrated a pooled sensitivity of 73% (95% CI 56–85) and specificity of 73% (95% CI 48–89) (54). Variability in results of patch testing is in part because of lack of standardization of the technique. Despite this, patch testing is felt by some to be useful for identifying certain delayed-type (ie, non-Ig-E mediated) allergic food reactions and may be helpful in the identification of food triggers in conditions such as EoE and dermatitis (55,56).

Intradermal tests for WA have been shown to be more sensitive than the SPT but are more likely to generate a false-positive test result. One problem with the SPT is the lack of specificity of the crude wheat extract used as the antigen. Many children with eczema have a positive SPT and yet do not display an allergic reaction when ingesting wheat. Use of more specific wheat components, such as α-amylase inhibitor or high molecular weight glutenins, need to be studied further before they can be recommended for clinical use.

## Nonceliac Gluten Sensitivity

There are currently no initial tests available to identify people who may have NCGS. There is a suggestion that those with NCGS are more likely to have an elevated AGA test or have the HLA DQ2 or DQ8 haplotype than healthy controls (37), but neither of these tests can be used to screen for NCGS with any degree of confidence. Instead, to consider the possibility of NCGS, it is first necessary to exclude both CD and WA on the basis of negative serological tests, normal histology, or negative SPT and serum IgE tests (37,57). Table 4 provides a comparison of initial testing for gluten-related disorders.

# CONFIRMING THE DIAGNOSIS OF GLUTEN-RELATED DISORDERS

## Celiac Disease

The diagnosis of CD is confirmed on demonstration of the characteristic changes in the histology of the small intestinal mucosa. Biopsies are obtained from the duodenum via an upper gastrointestinal endoscopy. Initially, the histologic changes may be

TABLE 4. Comparison of initial testing for the gluten-related disorders

| | CD | NCGS | WA |
|---|---|---|---|
| tTG IgA | +[†] | − | − |
| HLA DQ2/DQ8 | + | +/− | +/− |
| Small bowel biopsy with VA | + | − | − |
| ImmunoCAP Specific IgE[*] | +/− | − | + |
| SPT | +/− | − | + |

+/− indicates the test can be either positive or negative in these patients. CD = celiac disease; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgE = immunoglobulin E; NCGS = nonceliac gluten sensitivity; SPT = skin prick test; tTG = tissue transglutaminase; VA = villous atrophy; WA = wheat allergy.

[*]A positive ImmunoCAP wheat-specific IgE assay and SPT for wheat may coexist with a diagnosis of CD though not with NCGS, given that the latter is largely a diagnosis of exclusion.

[†]Positive for IgA-sufficient individuals.

patchy in distribution and confined to the duodenal bulb, so it is recommended that 1 or 2 biopsies be obtained from the bulb and ≥4 from the distal duodenum (3,40).

Documentation of the characteristic histologic findings of CD on small intestinal biopsy has been considered central to the diagnosis for decades. The cascade of immunologic events that follows ingestion of gluten in those predisposed to develop CD result in an inflammatory state causing derangement of the mucosal architecture. The characteristic microscopic features include infiltration of lymphocytes in the epithelium, increased density and depth of the crypts, and progressive flattening of the villi. This progression was first described by Marsh (58) in 1992, and his scoring system, from stage 0 (normal) to stage 3 (villus blunting), subsequently modified by Oberhuber et al (59), is now widely used by pathologists to diagnose CD.

It is important to note that these changes are not unique for CD and can be seen in other disease processes such as autoimmune enteropathy, food allergies (in children, particularly allergies to cow's milk and soy protein), Crohn disease, and a number of viral, bacterial, and parasitic infections. Therefore, in addition to the biopsy findings, the clinical history, results of the serological tests, and response to a strict GFD are all essential considerations to confirm a diagnosis of CD (60).

In 2012, the European Society of Gastroenterology, Hepatology and Nutrition published evidence-based guidelines for the diagnosis of CD in which it was suggested that a nonbiopsy diagnosis of CD could be considered in some circumstances (3). The recommendations included an option to forego the duodenal biopsy in children with classic symptoms of CD, a tTG-IgA > 10 times the ULN, a positive EMA-IgA on a separate blood sample, and the presence of HLA DQ2/8 haplotype. Under these circumstances, villous atrophy (Marsh 3) (58,59) of the duodenal mucosa is nearly always found. The subsequent resolution of symptoms with normalization of the tTG titer following institution of a GFD would serve to confirm the diagnosis. It is estimated that about half of the children eventually diagnosed with CD would fall into this category, thus potentially avoiding the risks associated with sedation and endoscopy and decreasing the cost of diagnosis. Although a nonbiopsy diagnosis of CD is desirable, there are potential risks associated with skipping the biopsy. There is currently no standardization of serological tests for CD in the United States, and marked variation in antibody levels between commercial assays when the same serum samples are tested has been documented (61–63). Consequently, it is possible that without biopsy confirmation, some children may be falsely diagnosed with CD and placed on treatment. Because a strict GFD is cumbersome, expensive, and has an adverse impact on the quality of life of the individual, it is important to confirm the diagnosis before recommending such a lifelong dietary change. Another possible disadvantage of a nonbiopsy diagnosis is the potential for missing additional gastrointestinal disorders (such as peptic esophagitis, EoE, *Helicobacter pylori* gastritis), which may occur as comorbidities in celiac patients and would not be diagnosed without an endoscopy (64).

In some patients with positive celiac antibodies (tTG-IgA and/or EMA-IgA), the histologic report on the small biopsy fails to confirm CD. In such cases, it is essential to first confirm that the patient was consuming adequate amounts of gluten and that the biopsies obtained were adequate in number, obtained from both the duodenal bulb, and more distal duodenum and were reviewed by a pathologist knowledgeable about CD. In addition, one should consider that factors such as tangential sectioning because of poor orientation of the specimen and inherent patchiness of small bowel lesions associated with CD may limit the ability to correctly interpret the biopsies. Other autoimmune conditions and inflammatory bowel disease should be considered (65–67) because these can have transient elevations of CD-associated antibodies. HLA typing may be helpful in these patients as if negative for both the HLA DQ2 and DQ8 risk alleles, CD is highly unlikely. Capsule endoscopy has been used in some patients to assess for gross evidence of mucosal disease more distally. In the event all these factors have been excluded as possible explanations, patients with positive celiac antibodies and normal histology represent cases of potential CD. Although knowledge of the natural history of such patients is limited, there is some evidence that with persistent ingestion of gluten a substantial number will develop the characteristic mucosal changes over time (68). In patients with potential CD who are symptomatic, it is reasonable to implement a GFD and monitor for both symptom resolution and normalization of the serological antibody levels. Under such circumstances, a diagnosis of CD is probable, but if there is any doubt it may be necessary to resort to a gluten challenge with repeat biopsies at some stage in the future. Those with potential CD who are truly asymptomatic and choose not to exclude gluten from their diet should be studied with repeat testing in the event they subsequently develop any symptoms.

## Wheat Allergy

Because both SPTs and tests for specific IgE antibodies have relatively poor sensitivity and specificity (54), confirmation of WA usually requires an oral food challenge. A double blind, placebo controlled (DBPC) challenge is the most accurate way of confirming the diagnosis of suspected food allergies. Extracting the relevant antigens from wheat to prepare the extracts to be used for the challenge, however, can be problematic. A DBPC challenge can be difficult to undertake and is best performed by those who have specialized expertise in the diagnosis and management of food allergies. In clinical practice, symptom resolution in response to dietary elimination of wheat is usually regarded as confirmation of the suspected diagnosis of WA.

## Nonceliac Gluten Sensitivity

Based on a recent consensus conference held in Salerno (Italy), confirming a diagnosis of NCGS is a 2-fold process involving assessment of the clinical response to the GFD in those patients who are ingesting an unrestricted diet and measuring the effect of reintroducing gluten in those patients who are on a GFD (69). It follows that a full diagnostic evaluation can only be started in the patient who is on a normal, gluten-containing diet. A simplified/shortened diagnostic procedure, however, may be adopted in

patients who are already on a GFD before being seen by a health care professional.

Based on the consensus conference recommendations (69), patients on an unrestricted diet should be evaluated with a questionnaire assessing baseline intestinal and extraintestinal symptoms. Patients should be reevaluated after 6 weeks of implementation of a GFD, even if improvement in symptoms is expected shortly after starting the GFD. According to the new consensus, a decrease of $\geq$30% from the baseline score is considered a symptomatic response (69).

For those already on a GFD, a placebo controlled double/single blind challenge with crossover would provide a high level of evidence for diagnosing NCGS in lieu of validated biomarkers. The challenge should involve the ingestion of gluten or placebo for 1 week followed by a 1-week washout of strict GFD and then crossover to a second 1-week challenge. The same questionnaire administered to patients on an unrestricted diet should be used for the blind challenge. Once again, a variation of $\geq$30% between the gluten and the placebo challenge should be detected to discriminate a positive from a negative result. The threshold of 30% decline in symptom score is somewhat arbitrary and needs scientific validation.

Patients who do not have recurrence of symptoms when challenged with gluten are unlikely to have NCGS. In these patients, other causes for the symptoms, such as ingestion of FODMAPS, should be considered.

## HOW DO WE TREAT GLUTEN-RELATED DISORDERS AND WHAT ARE THE THERAPEUTIC GOALS?

### Celiac Disease

The complete exclusion of dietary gluten for life is currently the only accepted treatment for children with CD. Strict adherence to a GFD is not easy as gluten is hidden in many processed foods. Therefore, dietary counseling from a dietitian who has expertise in the treatment of CD is an essential component of treatment.

Overall, the therapeutic goals of treatment for CD are symptom resolution, maintenance of normal growth and development, and resolution of the enteropathy. Persistence of symptoms and villous atrophy has been associated with long-term adverse health outcomes with increased morbidity, increased risks of malignancy, and increased mortality (70,71). In contrast to the adult population, mucosal recovery in children is generally more complete following the institution of a strict GFD (72). For this reason, repeat endoscopy with biopsies is not routinely recommended in children and is usually reserved for those with persistent unexplained symptoms.

A progressive decline with eventual normalization of the antibody levels on repeat serological testing during 12 to 24 months following the institution of a GFD is widely used as an indicator of dietary compliance and mucosal recovery. In people who are asymptomatic but identified to have CD on the basis of screening groups at increased risk for the condition, normalization of the CD serology is usually used to presume mucosal recovery. Similarly, in those diagnosed with CD based on abnormal serological tests alone, resolution of symptoms and normalization of the serological test is presumed to indicate mucosal recovery. In adults, normal tTG-IgA titers do not exclude the possibility of ongoing villous atrophy among treated patients (73). Conversely, a recent pediatric study demonstrated good correlation between adherence to a GFD, symptom resolution, normalization of the CD serological test, and mucosal healing (74,75). This, however, needs to be confirmed with additional studies before normal TTG levels can be considered a reliable indicator of mucosal healing in children.

### Wheat Allergy

Complete elimination of wheat-containing products is needed to treat WA. In those who manifest an anaphylactic reaction to wheat, dietary elimination should probably be permanent, although loss of sensitization has been documented in some patients. In children with predominantly gastrointestinal manifestations, tolerance for wheat can develop in $>$75% by adolescence. The time to developing tolerance has been correlated with the peak level of specific IgE titers. Tolerance developed at a mean age of 41.1 months when the peak IgE was $<$10, 44.5 months when the titer was between 10 and 19.9, 84.9 months with titers 20 to 49.9, and 84.8 months when the titer was $>$50. Rates of resolution of WA have been reported as 20% by age 4 years, 52% by 8 years, 66% by 12 years, and 76% by 18 years (76). Prospects for resolution of WA in children are significantly better than for peanut, tree nuts, or sesame allergies, in which tolerance can be expected in only $\sim$10% of children, and life-long intolerance is the norm for the majority. The decision on whether and when to challenge children with WA is best undertaken by an expert in food-related allergies.

### Nonceliac Gluten Sensitivity

Similar to CD and WA, the cornerstone of the treatment of NCGS is the elimination of gluten-containing food from the diet. Given the uncertainty on pathogenesis and trigger(s) of NCGS, it is not clear, however, how strict the diet needs to be, for how long the diet needs to be implemented, and how to monitor efficacy of the treatment other than by clinical response. Clinical experience suggests that patients affected by NCGS range from those who need to adhere to a strict GFD to those who can tolerate cross-contamination without clinical consequences. Another area of uncertainty is the possibility that some can ''outgrow'' NCGS. There is still insufficient data to determine whether this is a permanent condition (like CD) or temporary (like WA). In addition, the possibility that NCGS represents a number of unrelated disorders further complicates the ability to provide precise dietary recommendations. To date, there is no good evidence that either rye or barley have to be avoided in those diagnosed with NCGS.

## WHAT FOLLOW-UP IS NEEDED FOR THOSE WITH GLUTEN-RELATED DISORDERS?

### Celiac Disease

There are no published recommendations for follow-up of children diagnosed with CD. Long-term management should involve both a pediatric gastroenterologist, or pediatrician with experience in CD, and a dietitian with expertise in the GFD. In the first 1 to 2 years following diagnosis, more frequent follow-up visits may be needed to monitor for compliance with the diet, address concerns related to potential nutrient deficits, and ensure the resolution of symptoms (Table 5). In some patients, additional resources such as psychology may be needed to help children cope with their new diagnosis, and referral to a local CD support group may be beneficial.

Repeat determination of CD serological tests at 3- to 6-month intervals demonstrating a progressive decline in antibody levels suggests good compliance. Conversely, failure to demonstrate progressive decline in antibody levels, or an increase in these levels at any stage, requires careful review of the diet by a knowledgeable dietitian for continued overt or inadvertent gluten ingestion. Once the child is symptom free, and the antibody levels have returned to normal, follow-up visits may occur on an annual basis.

TABLE 5. Recommended testing and follow-up for children with CD

| Timing | Visit | Tests |
|---|---|---|
| At diagnosis | Physician, dietitian | CD serology (tTG-IgA, EMA-IgA)* |
| | | Complete blood count<br>Iron profile<br>Hepatic function panel<br>Thyroid tests (TSH, free T4)<br>Calcium<br>Vitamin D level |
| 3–6 mo after starting the GFD and every 6 mo thereafter until CD serology has normalized or other concerns have resolved | Physician† | CD serology (tTG-IgA or DGP-IgG) |
| | Dietitian (as necessary) | Additional testing based on clinical indication or previous abnormal results (eg, elevated liver enzymes) |
| Annually after symptom resolution and normalization of CD serology | Physician, dietitian† | CD serology (tTG-IgA or DGP-IgG) |
| | | Complete blood count<br>Thyroid tests (TSH, free T4)<br>Vitamin D level<br>Additional testing based on clinical indication. |

CD = celiac disease; DGP = deamidated gliadin peptide; EMA = endomysium; GFD = gluten-free diet; IgA = immunoglobulin A; IgG = immunoglobulin G; tTG = tissue transglutaminase; TSH = thyroid stimulating hormone.

*Other CD-specific antibodies may be relevant for individuals with IgA deficiency or lack of initial tTG IgA elevation.

†Participation of additional providers such as psychology may be necessary in conjunction with medical and dietary visits.

Although there are some recommendations regarding testing for nutrient deficiencies at the time of diagnosis, these are not based on any good evidence (41). The GFD may be deficient in micronutrients such as iron, folate, and B vitamins, and monitoring for micronutrient deficiency is a consideration. As people with CD are at increased risk for other autoimmune disorders such as autoimmune thyroiditis, monitoring for such conditions should also be considered.

Table 5 lists a suggested program for testing at diagnosis and on subsequent follow-up for children with CD. It is emphasized that this is not based on any evidence but has been developed on the basis of consensus and expert opinion.

## Wheat Allergy

Manifestations of WA involving the gastrointestinal system and skin are generally mild to moderate in severity and can usually be managed by a child's primary care physician. In more severe cases, referral to a subspecialist (gastroenterologist, dermatologist, or allergist) is warranted. The decision to perform a wheat challenge in these more severe cases is best made by an experienced allergist and should be undertaken under close supervision in a well-equipped medical facility with personnel trained to manage anaphylaxis.

## Nonceliac Gluten Sensitivity

Currently, there are no clear guidelines on standardized follow-up of patients diagnosed with NCGS who are following a GFD. In general, given the expected fairly rapid resolution of symptoms following the implementation of the diet, follow-up within 3 months from the beginning of the dietary treatment to confirm this has occurred is recommended. There are currently no data that can be used to provide recommendations on the need for, or frequency of, repeated follow-up visits in these patients. It is considered good clinical care to study these patients at regular intervals to insure they remain healthy and involve a dietitian in their care to make sure they are not at risk for nutrient deficiencies. It is also recommended that the continued need for ''strict'' avoidance of all gluten-related products should be reviewed following recovery because in some patients it may be possible to follow a less restrictive diet without the recurrence of symptoms. Any consideration to liberalize the diet does first require that the possibility of CD has been confidently excluded. Once again, this emphasizes the need for physicians to confirm the diagnosis of a specific gluten-related disorder before initiating treatment.

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## Infants and Alcohol

As early as the 4th century BCE, history has recorded incidences of wine and beer being fed to newborns:

> It is a common thing for convulsions to attack an infant. . .Mischievous regards this affection is wine, dark more than white and wine not diluted with water
>
> Aristotle (384–322 BCE), *On the History of Animals*, Book 7

Wine was perceived as a healthier source of fluid than plain water and generally was ''cut'' with water. Well into the apogee of the eastern Roman Empire (900–1100), white wine was the preferential drink for toddlers through adolescence. Following the Great Pestilence, wine fell into disfavor over beer (perhaps as a result of crop failures during the Little Ice Age, and the resulting dearth of grapes), and beer both in mainland Europe and the British Isles became the preferential fluid ingredient of pap.

> Infants are given with good result broth made of beer mixed with boiled bread and butter which is quite nourishing. Wine should not be given to infants, but in our parts beer is given to them with advantage.
>
> Daniel Sennert (1572–1637), *De Mulierum et Infantius Morbis*

> Gin also was given to children as a soporific, and its consumption by adults and children was a significant public health issue in England during the eighteenth century. In the 17th century, gin had been an expensive libation imported from the Netherlands. The British government encouraged domestic distillation through a series of legislation with large tax incentives. Gin then became locally produced and a very cheap source of alcohol; a penny's worth was sufficient to intoxicate the average adult. Consumption of gin in England rose from 527,000 gallons in 1685 to 11,000,000 gallons in 1750 . . . parents gave their infants and children as much as 60 ml of gin on a routine basis to sedate them. William Hogarth's (1697–1764) *Gin Lane* rendered visual expression of the social malady.
>
> A.R. and P.A. Colón, *A History of Children*

Engraving from *Gin Lane* (1751). Courtesy of Wikimedia Commons.

*—Contributed by Angel R. Colón, MD*