

Is Wheat the Enemy?

Celiac Disease and the Gluten-Free Era.



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This is to acknowledge that Lisa Casey, MD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Casey will not be discussing off label uses in her presentation.

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Purpose and overview:

The clinical phenotype of celiac disease was first described 2000 years ago. Prevalence and incidence of the disease are increasing and the clinical phenotype is changing. Many persons with the disease remain undiagnosed and therefore untreated. Increasing health care provider awareness of the disease characteristics, diagnostic algorithms, and management is critical to improve diagnosis and patient outcomes.

This presentation will review relevant background and current evidence regarding the presentation, pathophysiology, diagnosis and management of celiac disease with attention to the current popularity of a gluten-free diet and its impact on celiac patients.

Educational objectives:

- 1) Introduce the concept of gluten sensitive disorders.
- 2) Become familiar with the changing clinical manifestations of celiac disease.
- 3) Learn a diagnostic algorithm for celiac disease.
- 4) Summarize available consensus regarding non-celiac gluten sensitivity.

Introduction

Simply put, a gluten-free diet is a diet completely devoid of wheat, rye, barley and products that may be cross contaminated in production with these grains. Historically, this diet was recommended for individuals with a diagnosis of celiac disease or a related dermatological disorder called dermatitis herpetiformis. Additional patients might be instructed to follow a modified version of this diet due to an Ig E mediated wheat allergy or another medical issue where gluten sensitivity was thought to contribute to their symptoms or disease process.

The term gluten encompasses a group of cereal grain storage proteins from wheat, rye, barley, corn and oat. Wheat proteins themselves are labeled according to their solubility and of the four major wheat proteins (globulins, minor albumins, prolamins and glutenins) the glutenins and prolamins – specifically the prolamin gliadin – are considered gluten. Wheat gluteins and other prolamins from the Triticeae family - rye secalins and barley hordeins - are the specific gluten peptides of interest in celiac disease. Structurally these peptides have a higher concentration of proline and glutamine than non-Triticeae gluteins, making them more resistant to degradation by gastric acid, brush border and pancreatic enzymes. This resistance to degradation suggested a role in their toxicity since they remain in the gut lumen as larger and more complex molecules. Gliadin is the best understood, having been separated electrophoretically into four major fractions with all four fractions demonstrating toxicity in celiac disease. Culturally, gluten plays a role of critical importance as the factor that gives bread the texture we understand as bread-like.

Wheat grain's introduction as a food source dates to approximately 10,000 years ago when humans transitioned from hunter-gatherers to an agrarian society. Wheat is thought to be the product of a cross between several different species of grass arising in the Tigris and Euphrates river valley, near modern day Iraq and Turkey. Archaeologists have found wheat at sites of human settlement dated to 8,000 years ago and the British museum has actual loaves of bread from Egypt estimated to be 5,000 years old. Ancient historians such as Socrates, Plato (400BC) and Pliny (70AD) described the rising cultural importance of wheat in antiquity and many modern religions continue to include wheat and bread in their rituals. Wheat, and consequently gluten, has become a dietary staple in much of the world providing approximately 20% of the world's calories. Nearly 1/3 of the foods found in American supermarkets contain some component of wheat – usually gluten or starch or both. Despite this presence, discussion relevant to the role of wheat in our modern diet appeared predominately contained to the scientific, agricultural and medical communities until the last decade.

In 2004, the plight of persons with celiac disease and food allergies was assisted when the US Food and Drug Administration Center for Food Safety and Applied Nutrition passed the Food Allergen Labeling and Consumer Protection Act (FALCPA) acknowledging the growing issue of food allergies and raising awareness. This act noted that eight common allergens accounted for about 90% of food allergies, additionally reporting that 2% of adults and approximately 5% of infants and young children in the United States suffer from food allergies leading to approximately 30,000 emergency room visits and at least 150 deaths (2004 statistics). The act acknowledged the challenge food allergy patients have in determining safe foods for consumption and required inclusion of derivatives of the main allergens in the labeling, including flavorings, colorings and additives and set deadlines for reporting on cross contamination standards. FALCPA also set the first basic standards for gluten-free labeling, raising

awareness of celiac disease as an immune mediated disorder with a medical indication for a gluten-free diet.

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106187.htm> accessed 11/10/2014

Thanks to improved technology and diagnostic methods, we have seen an increase in the diagnosis of celiac disease over the last decade. In addition, studies have demonstrated as much as a four-fold increase in prevalence of the disease over the last 50 years. Current prevalence of the disease in the United States is estimated at 1% of the population. In addition to celiac disease, with growing food allergy awareness, wheat allergy is estimated to affect approximately 0.4% of the population. Wheat allergy patients could be understood to appreciate an easily accessible gluten-free diet given this would inherently be wheat-free. Interestingly, as recently as 2009-2010 a prevalence study done by Rubio-Tapia et al using NHANES data (National Health and Nutrition Examination Survey) demonstrated a weighted prevalence of American persons on a gluten-free diet of only 0.63% - much less than the confirmed prevalence of celiac disease in the study and the majority of those patients on a gluten-free diet did not have celiac disease. The study also confirmed previous data suggesting more than 80% of patients that have celiac disease do not know they have celiac disease.

This leads us to “The gluten-free paradox” attributed to Daniel Leffler, director of the Celiac Center at Beth Israel Deaconess Medical Center in Boston:

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The gluten-free paradox:

“Many people on a gluten-free diet do not have celiac disease and many celiac patients have not been diagnosed and are not on a gluten-free diet. “

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Over the last 5 years, this gluten-free paradox does not appear to have substantially changed but a culture shift seems to have occurred. Gluten-free is suddenly everywhere. When celiac disease and other gluten sensitive disorders with a medical indication for a gluten-free diet are taken into account, even generous estimates suggest this represents less than a few percent of the American population and yet the gluten-free lifestyle is suddenly widely visible even in the popular media. In June, The Wall Street Journal referred to data from market research firm NPD Group in their assessment of the popularity of gluten-free reporting almost 30% of American adults surveyed are trying to eliminate or cut back on gluten in their diet. This seems a very high number, particularly in relationship to the above data from only 5 years ago, though it is hard not to notice that something is going on. Gluten-free food has suddenly become available everywhere from your local bistro to the neighborhood Wal Mart. The food industry has capitalized on the enthusiasm and gluten-free is now valued as a multi-billion dollar industry. As a reflection of cultural awareness, gluten-free has even passed that litmus test of popular culture – becoming fodder for the late night talk show hosts – making an appearances on The Tonight Show and Comedy Central’s popular adult comedy South Park. South Park became the first all gluten-free city in America this year with federal troops to support the satirical plight. Where did this phenomenon come from?

Several self-help books published beginning in 2011 might provide us with a clue. Wheat Belly was published by Cardiologist William Davis in 2011 and within a month became a New York Times bestseller. His book endorses a gluten-free diet to “lose weight and find your path back to health”, replacing the gluten containing foods with low glycemic index alternatives, strict avoidance of grains and avoidance of many other processed foods. This was followed in 2013 by Grain Brain from neurologist Dr. David Perlmutter. The “eating to prevent brain disease and Alzheimer’s” diet is also gluten-free, recommending avoidance of processed foods and emphasizing high fat intake and a low glycemic index. The books begin with a simple diet premise but take the advice and declarations to extremes only loosely linked to science. Dr. Davis believes that modern wheat is “Frankengrain created by genetics research and agribusiness” not at all like the wheat of 1950’s and 60’s calling it “as toxic and addictive as many drugs” and that gluten sensitivity “represents one of the greatest and most under recognized health threats to humanity.” Dr. Davis also asserts that “cutting edge research...has revealed that consumption of modern wheat is the first step in triggering autoimmune diseases such as type 1 diabetes, rheumatoid arthritis and multiple sclerosis.” Dr. Perlmutter declares that “brain dysfunction starts in your daily bread” and “modern grains are destroying your brain.” The vilification of wheat and gluten led by Drs. Davis and Perlmutter has created an empire founded on the premise that gluten is poison. Gluten-free has become the solution to a large culture of searchers looking for the newest cure for what ails.

What could be so bad about the popularity of gluten-free? For patients with celiac disease, there is a downside. Equal to the number of blogs touting the magical benefits of a gluten free diet are the blogs of celiac patients relating the woes of their delayed diagnosis, their social isolation, that they are not taken seriously by restaurants who think gluten free is a “fad” diet.

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Case 1.

JD is a 22 year old medical student. She fractured her wrist in an intramural volleyball game.

X-rays of the wrist show osteopenia.

No past medical, surgical, or social history. She takes no medications.

ROS: includes intermittent fatigue and oral ulcerations but no gastrointestinal complaints.

Hematocrit - 32%

Ferritin – 10

Vitamin D – low

Does she have celiac disease? Or does she need a multivitamin with iron and more sunlight?

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Case 2.

JD is a 51yo nurse.

CC: “I just feel like I am dying I am so exhausted all of the time. It wears me out to dry my hair.”

PMH and ROS: “stomach problems since I was a teenager, dental problems even though I floss, canker sores, food intolerances, allergies, intermittent dizziness, anxiety, bouts of depression, low vitamin D level, I had early menopause, migraines, joint aches, sometimes toes get tingly”

“Maybe I am just stressed out living with 3 teenagers and you know my husband’s bakery is getting busy with the holidays coming.”

Hematocrit – 32%

Ferritin – 10

Low vitamin D

Does she have celiac disease? Or does she need psychological counseling and vitamins?

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Celiac Disease in History

Reactions to gluten are not a new phenomenon. As far back as the first century AD, the Greek physician Aretaeus of Cappadocia first described a disease phenotype suggestive of celiac disease.¹ London Pediatrician Samuel Gee provided the first modern clinical description of celiac disease in 1888 – emphasizing both a suspected family link and a dietary trigger. Though a dietary culprit had long been hypothesized, confirmation did not come until the 1940’s. During the 1944 famine Dutch physicians led by William Dicke discovered that celiac children’s symptoms improved when wheat and rye were scarce, but the children quickly deteriorated when Allied food drops reintroduced bread into the Dutch diet.² Soon afterward, Charlotte Anderson and colleagues identified the gluten component as the toxic factor leading to mucosal damage. Since the identification of gluten as the trigger for celiac disease there has been steady progress understanding the immune mechanisms, symptoms and conditions associated with celiac disease and the identification of what appear to be other unique gluten sensitive disorders.

Pathophysiology of Celiac Disease

Celiac disease is an autoimmune disease triggered by dietary gluten found in wheat, rye and barley in genetically susceptible individuals. These three grains all belong to the same tribe called Triticeae. Both the disease activating peptides found in wheat – glutenins and prolamins called gliadins and the peptides in barley and rye, hordeins and secalins respectively are capable of activating disease. All of these peptides contain a high content of prolines and glutamines which makes them resistant to degradation by gastric acid, pancreatic and brush-border enzymes which lack the correct enteropeptidase.² The best understood is wheat gliadin. In patients with celiac disease, immune responses to gliadin fractions remaining in the intestinal lumen after ingestion and digestion promote an inflammatory reaction, primarily in the proximal small intestine, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. The response is mediated by both the innate and adaptive immune systems. Increased intestinal permeability (“leaky gut”) is frequently observed in celiac patients and allows transport of intact gliadin molecules through the small intestinal epithelium into the lamina propria. Tissue transglutaminase (tTG) deamidates the gliadin peptides in the lamina propria, increasing their immunogenicity. It remains unclear whether celiac patients have a baseline defect that causes them to have increased intestinal permeability or if

the altered permeability is triggered by an environmental factor such as infection with associated inflammation leading to increased secretion of intracellular tTG and the increased permeability. One current theory is that is that celiac disease patients have impaired intestinal permeability as a result of abnormal tight junction morphology. Tight junctions are theorized to be gluten responsive and open in the presence of gluten, which in celiac disease would allow the exposure of luminal antigens into the lamina propria. In the lamina propria, the deamidated gliadin peptides are bound to HLA class II molecules DQ2 or DQ8 on antigen presenting cells (APC). CD4+ T cells in the lamina propria recognize these complexes and produce pro-inflammatory cytokines triggering an inflammatory cascade and immune response. Based on cytokine studies, both the innate and adaptive immune systems are implicated in the damage triggered by gluten. The pathophysiology of celiac is still not completely understood but is thought to result from the interaction of genetic, environmental and immunologic factors.

Immune and Environmental Factors in Celiac Disease

Gluten is the primary trigger in celiac disease, which is believed by various mechanisms to activate both adaptive immunity and innate immune responses in the gut epithelium. The HLA haplotype HLA-DQ2 or HLA DQ8 or a variant must be present as the intermediary between deamidated gluten and the antigen presenting cell but this immune complex is not sufficient to develop celiac disease, other factors must be present. Epidemiologic studies have suggested timing of gluten introduction, cesarean delivery, breast feeding and recurrent childhood gastrointestinal infections³ as possible environmental factors. Differences in incidence of celiac disease in northern European countries was noted after a sharp but transient increase in celiac disease was reported between 1984 and 1996 in Sweden. A complex interplay of feeding practices was thought to be at work including timing of gluten introduction, amount of gluten given and whether or not breast feeding continued at the time of gluten introduction. Later studies have suggested early gluten introduction before 4 months, or introduction of gluten after 7 months of age might increase risk, as well as gluten introduction during weaning or larger amounts of gluten exposure. Summary recommendations remain confusing but suggest introduction of gluten in the window between 4-7 months of age and while still breast feeding is optimal. Studies are ongoing.⁴ Hypotheses that might explain the beneficial nature of breast feeding include avoidance of early gluten introduction, protection against infections, decreased immune response due to IgA antibodies in breast milk and possibly T-cell suppressive effects. Theories relating to mode of delivery are based on exposure to different bacterial species during birth – potential skin flora during cesarean delivery and maternal vaginal flora such as Lactobacillus and Prevotella - where there is a not well understood but slight increase in risk in those born by caesarian. A role for infections in the pathogenesis of celiac disease has been suggested for several decades, perhaps due to increased vulnerability of inflamed mucosa. This is most recently supported by a correlation between rotavirus infection frequency as gauged by serial rotavirus antibody titers and later development of celiac disease. There has been some interest in whether the wheat itself has changed but there does not seem to be compelling evidence in this regard. It is notable that there might be changes in bread baking techniques over time with more additives and certainly exposure is ubiquitous.

Genetic Factors

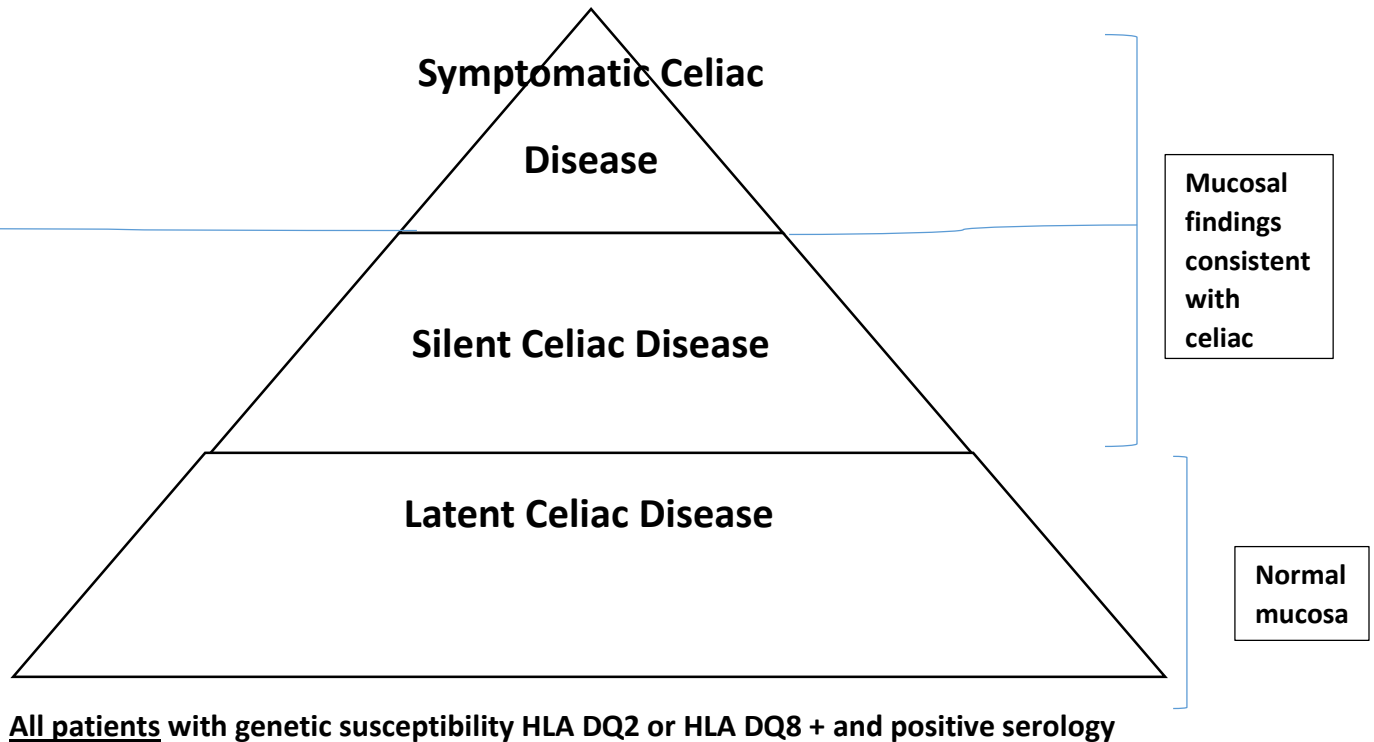
Celiac disease pathogenesis has a strong genetic component. Epidemiologic studies report up to 20% of first-degree relatives are affected by the disease with concordance rates of 75-80% with monozygotic

twins and 10% in dizygotic twins. The best characterized genetic susceptibility factors in celiac disease are the HLA class II genes HLA-DQ2 and HLA-DQ8 which present antigens to immune cells. Celiac disease does not develop unless a person has alleles that encode for these proteins but given they are common in the general population (20-30% depending on locale), they are necessary but alone are not sufficient for the development of the disease. The European General Cluster on Celiac Disease typed 1000 patients and found that while 96% had either HLA-DQ2 or HLA-DQ8 genes that 4% had neither. Almost all of these patients were found to have a variant HLA-DQ2 half heterodimer (only 0.4% fulfilled criteria for celiac disease in the absence of DQ2/ half heterodimer or DQ8). The presence of these HLA types varies geographically. The disease risk and clinical course may be able to be predicted based on which gene variants are present and their position. Liu et al in a recent paper studied 6403 children from the United States, Finland, Germany and Sweden with HLA haplotype DR3-DQ2 or DR4-DQ8 prospectively from birth with the primary end point being development of celiac disease autoimmunity, defined by presence of tTG antibodies on two consecutive tests at least 3 months apart with the secondary endpoint being development of celiac disease.⁵ Median follow up was 5 years and it was noted that children with the HLA haplotype DR3-DQ2, especially homozygotes, were at highest risk for celiac autoimmunity and subsequent development of celiac disease in early childhood confirming a gene dose effect as described in previous studies. Though more advanced immunological features of celiac disease are beyond the scope of the average practice, these markers are felt to have an important role in screening in terms of their high negative predictive value and perhaps in the future a more advanced role in determining who is a greatest risk and how early they should be screened for disease. It is emphasized that clear clinical disease should not be ignored in the case of a negative HLA-DQ2 or DQ8 given rare variants.^{2,6,7 8}

Clinical presentation

Celiac disease was for many years thought to be a predominately pediatric disease characterized by diarrhea and malabsorption with the earliest clinical guidelines for management to be found in the European Pediatric Gastroenterology literature. Between the 1950's and 1980's major advancements were made in understanding the pathogenesis, diagnosis and treatment with the development of ways to biopsy the small bowel and serological testing. The concept of the celiac iceberg was first noted in a small Italian study and is now widely used to express the numerous presentations and acknowledge the disparities between diagnosed and undiagnosed. In the diagram below, all patients have favorable genetic factors and would, if tested also have serological markers adequate for celiac disease diagnosis. The bottom third of the iceberg represents patients with normal mucosa or only mildly inflamed mucosa which does not meet criteria for diagnosis of celiac disease. These patients are asymptomatic and may represent a disease in evolution, or a clinical scenario such as a patient diagnosed in childhood who has normalized histology on regular diet perhaps experiencing a type of remission in adolescence (not well understood but described). It is important to emphasize that despite some reported cases of this sort of tolerance, celiac disease does not go away. Patients in the upper two segments have characteristic genetic, serological and histological findings for a diagnosis of celiac disease but are separated by clinical presentation and presence or absence of a diagnosis.

The celiac iceberg



Presenting symptoms ⁹

Oral ulcers	Depression, anxiety, mood swings
Tooth enamel erosion	Brain fog, difficulty concentrating
Frequent miscarriages	Eczema, skin rashes
Infertility	Chronic fatigue
Early menopause or delayed menses	Dizziness
GERD	Ataxia
Bloating	Numbness, tingling, peripheral neuropathy
Nausea, vomiting	Headaches, migraines
Diarrhea or constipation	Hair loss
Malabsorption	Osteoporosis, vitamin D deficiency
Joint pain, muscle or back pain	Iron deficiency anemia, B 12 or folate deficiency
Elevated liver enzymes	No symptoms

Additional presenting symptoms in children may also include vomiting, constipation, recurrent abdominal pain, growth issues, anemia, arthritis, neurological symptoms or no symptoms

It is now clear that the disease spans all demographics, has a widely variable presentation and the more common symptoms of presentation may vary depending on the region where the patient resides. ¹⁰ Presenting symptoms are no longer the classic symptoms of diarrhea, malabsorption. Half of American patients now present with atypical symptoms, including extra-intestinal symptoms or absence of symptoms. Improved testing methods and screening high risk populations has increased diagnosis and

also begun to identify these asymptomatic patients.¹¹⁻¹⁵ Research suggests that there are still large numbers of undiagnosed patients and for unclear reasons the prevalence of this disease is increasing.^{16,17 18,19}

Prevalence

Fasano and colleagues in a screening population evaluated 13, 145 subjects with antibodies, HLA typing and biopsy when feasible and established baseline celiac disease prevalence in the United States of 1:22 in first degree relatives, 1:39 in second degree relatives, 1:56 in symptomatic patients and 1:133 in low risk patients, which is similar to that seen in Europe.¹⁶ Prevalence is widely accepted to be increasing. Rubio-Tapia and colleagues performed a study designed to examine the long term effects of undiagnosed celiac disease. Blood samples from 9000 Air Force recruits between 1948-1954 were screened for tTG with plans to identify celiac disease patients and follow their outcomes. It was assumed that they would find a similar 1% from older samples but only 0.2% of cases were found to have positive antibodies. Comparison of samples was then performed with a demographically similar group of modern 20 and 70 year old men. In both modern groups, prevalence of 1% was maintained suggesting a more than a 4 fold increase since the 1950's.

Screening

In traditional practice, screening for celiac disease is triggered by gastrointestinal symptoms of diarrhea or malabsorption. Improved understanding of the disease and awareness of associated conditions has led to wider screening recommendations. These include screening relatives and persons with disease-associated disorders. Given people later diagnosed with celiac disease meet ROME III criteria for IBS, many European countries recommend ruling out celiac disease before giving a patient a diagnosis of IBS.^{20,21} There is a large volume of literature supporting a case finding approach to screening^{16,22-24} in which patients are sought based on associations and symptoms. This has demonstrated an increase in diagnosis up to 40 fold in some places.

US practice guidelines currently recommend testing patients with symptoms, signs or laboratory evidence of malabsorption, of a disorder for which celiac disease is a treatable cause, patients with a first degree relative having celiac disease with signs or symptoms and to consider testing first degree relatives in the absence of symptoms.²⁵ European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) screening recommendations acknowledge the progression of celiac disease from a rather uncommon enteropathy to a common multi-organ disease with a strong genetic predisposition. Their recommendations are similar to US adult recommendations but provide a very detailed list of associated symptoms and related diseases.²⁶

Commonly Associated Disorders

Autoimmune thyroid disease
Dermatitis herpetiformis
Type 1 diabetes
Autoimmune liver including biliary disease
Sjogren's syndrome
Williams syndrome
Down syndrome

Less well known associations from ESPGHAN: autoimmune myocarditis, idiopathic dilated cardiomyopathy, IgA deficiency, Addison disease, IgA nephropathy, sarcoidosis, primary hyperparathyroidism, alopecia areata, vitiligo, neurologic abnormalities including epilepsy, ataxia and neuropathy, atopy, inflammatory bowel disease, psoriasis and chronic urticaria, infertility.

The American College of Gastroenterology Guidelines for the Diagnosis and Management of Celiac Disease identify at least 26 different symptoms and conditions which celiac disease is found to be more common than in the general population and in which a gluten free diet might be found to be beneficial. Several are listed in the box at the right.

Metabolic bone disease
Iron deficiency anemia
Peripheral neuropathy
Growth failure
Dental enamel problems
Infertility
Amenorrhea
Chronic fatigue
Epilepsy or ataxia
Constipation
Recurrent abdominal pain
Recurrent oral aphthae

Recommended links:

www.celiacdisease.net

www.celiac.org

<http://gi.org/guideline/diagnosis-and-management-of-celiac-disease/>

http://journals.lww.com/jpgn/Fulltext/2012/01000/European_Society_for_Pediatric_Gastroenterology.28.aspx

Some researchers argue that we should be screening universally and it is cost effective to do so ^{27,28} pointing out the myriad manifestations of this illness and the extent of health care utilization prior to diagnosis which improves with management. It is widely recognized that celiac disease patients suffer a prolonged delay in diagnosis after the onset of symptoms, 4.4-10 years depending on the study.

World Health Organization criteria for diseases that warrant mass screening -
Consider celiac:

- Early clinical detection is difficult (may be highly variable or asymptomatic)
- The condition is common (at least 1% of the population)
- Screening tests are highly sensitive and specific (variable)
- Effective treatment is available (yes, the gluten free diet is very effective)
- Untreated disease can lead to complications (probably, yes).

Early clinical detection may be difficult in celiac disease given a highly variable or possibly asymptomatic presentation. The condition is felt to be common with accepted prevalence of at least 1% of the

population. Effective treatment is available with a gluten-free diet. Screening tests are available but their specificity and sensitivity is likely variable with wide usage. Tissue transglutaminase, for example, should have sensitivity and specificity approaching 95% range but this may be affected by differing testing manufacturers and there will inevitably be a reasonably high false positive rate. The other complicating factor is that the data remains mixed on the long term outcomes of untreated celiac disease.

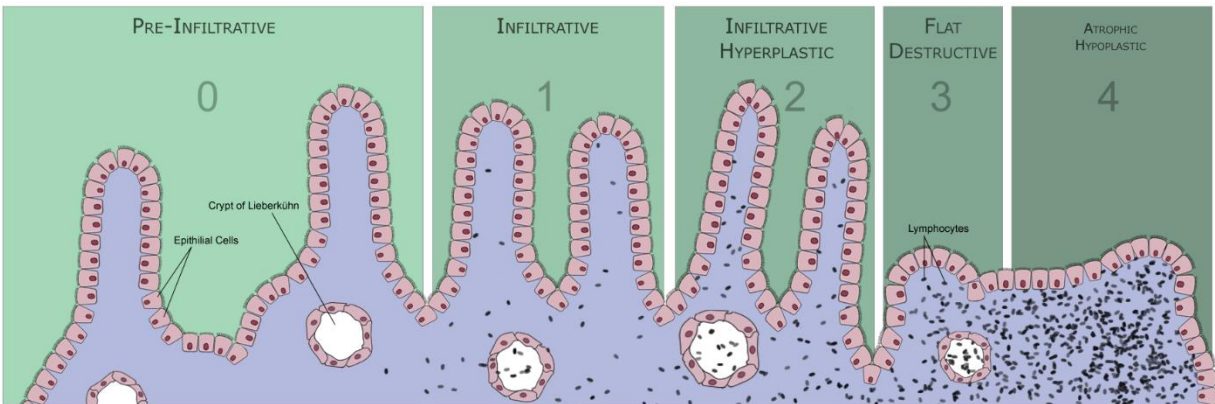
Are there long term risks for undiagnosed patients?

With continued gluten ingestion, resulting enteropathy may eventually lead to complications such as osteoporosis, anemia, infertility, vitamin deficiencies such as vitamin D, copper, zinc, B12, and folate deficiency and there is continued risk of developing small intestinal lymphoma with continued gluten ingestion. Quality of life issues also warrant mention as many studies regarding response to a gluten free diet after asymptomatic diagnosis (relatives, for example) note that patients report feeling better on a gluten-free diet even if they did not perceive their symptoms prior to diagnosis, having assumed they were normal. Long term there is increased risk of NHL, small bowel adenocarcinoma and esophageal cancer. Up to half of older patients with celiac disease are also felt to have what amounts to a functional asplenia - this is recognized in long term celiac disease and the issue of this risk has been raised in the undiagnosed. Rubio-Tapia and colleagues presented some of the most compelling mortality data for undiagnosed patients with their 2009 Warren Air Force Base study suggesting a significantly higher mortality for undiagnosed celiac disease patients which did not manifest until 15-20 years after the initial screen.

Diagnosis of Celiac Disease

Any method used to test for celiac disease must be performed on a **gluten-containing diet**. In the majority of patients, screening with IgA tTG is reasonable. In patients that are higher risk (symptoms, relatives with celiac disease) there is a slightly higher risk of selective IgA deficiency approximately 1%, and in celiac disease the prevalence of IgA deficiency is 2-3%. Many groups advocate adding a serum IgA level as a reasonable approach to the initial screen. Endomysium antibodies are highly sensitive and almost 100% specific for celiac disease but they are limited by high complexity, cost and not being widely available although these are sometimes also used as a confirmatory serology. A relatively new antibody to deamidated gliadin (DAG) has been shown to have high sensitivity and specificity and may be a useful adjunct to testing in children and patients that are otherwise seronegative, which appears to

occur in 10-15% of cases. Confirmation with biopsy remains the gold standard.



Characteristic biopsy findings include > 25-30 intraepithelial lymphocytes per 100 enterocytes (25 in modified criteria), villous atrophy, crypt hyperplasia and increased villous to crypt ratio. Original histology criteria known as the Marsh criteria is outlined in basic visual form above with Marsh - 0 being normal mucosa and with progressive appearance of intraepithelial lymphocytes and villous atrophy as reaches Marsh - 4. Criteria were later modified to March-Oberhuber criteria and along with Corazza-Villanacci criteria are routinely used in diagnosis by specialized pathologists. It is important to note that there is a very wide differential for the histological findings that also may be found in celiac disease, which emphasizes why celiac disease cannot be diagnosed histologically in the absence of appropriate serology and possibly genetic testing.

Differential Diagnosis of histology findings ²⁹

Normal villous architecture / increased IEL	Villous atrophy with / without increased IEL
Immune dysregulation – RA, SLE, thyroid, MS	Infections – tropical sprue, Giardia, Whipple disease, MAC
Autoimmune enteropathy	Refractory sprue
Food hypersensitivity – cow’s milk, soy, fish, eggs, rice, chicken	Autoimmune enteropathy, immune mediated enteropathy
Peptic ulcer disease	Immunodeficiency – CVID
Helicobacter pylori associated gastro-duodenitis	GVHD
Drugs – NSAIDs, PPIs	Inflammatory bowel disease – Crohn’s
Immunodeficiency - CVID	Drugs – mycophenolate, colchicine, olmesartan
Infections – viral enteritis, Giardia, Cryptosporidium	Chemo radiation therapy
GVHD	Immunomodulatory drug therapy
Inflammatory bowel disease	Eosinophilic gastroenteritis
Bacterial overgrowth, blind loop-syndrome	Bacterial overgrowth
Lymphocytic and collagenous colitis	EATL
Irritable bowel disease	Nutritional deficiency

The role for HLA testing is limited to special considerations in which ruling out disease is the best first step - see table below.

Appropriate uses for HLA testing in celiac disease – ACG guidelines
1) Seronegative patients with equivocal small bowel biopsy
2) Evaluation for celiac patients on a gluten-free diet that were never tested prior
3) Serology and histology do not match
4) Suspicion of refractory celiac disease when original diagnosis is in question
5) Assessment of celiac disease in patients with Down syndrome

Algorithm links:

<http://gi.org/guideline/diagnosis-and-management-of-celiac-disease/>

http://journals.lww.com/jpgn/Fulltext/2012/01000/European_Society_for_Pediatric_Gastroenterology,.28.aspx

http://www.mayomedicallaboratories.com/it-mmfiles/Celiac_Diagnostic_rev_092013_FINAL.pdf

Treatment of celiac disease

- C – Consultation with a skilled dietician
- E – Education about the disease
- L – Lifelong adherence to a gluten free diet
- I – Identify and treat nutritional deficiencies
- A – Access to an advocacy group / support group
- C – Continuous long term follow up by a multidisciplinary team

The gluten-free diet

The only currently recognized treatment for celiac disease is a strict gluten-free diet. This diet requires strict avoidance of wheat, rye, barley and any substance that might be cross contaminated with these grains. While there are a great deal of options that were not present even a few years ago there are limitations. Truly following a strict gluten free diet is not easy. It is socially isolating. It is still expensive. It is labor intensive. Even reusing water in which wheat pasta has been cooked can be dangerous. Many celiac patients report keeping an entirely gluten-free home or keeping a set of separate kitchen utensils, butter, jelly and other condiments to avoid cross contamination. There are patients that develop significant fear of contamination and being “glutened” given they are sensitive to even minute amounts of gluten. In addition to avoidance of triggering grains, many patients find they are lactose intolerant when they begin their gluten free diet – presumably some of this is a reflection of overall bowel damage – and find that they can later tolerate lactose after an interval of a gluten free diet to provide healing time. Oats are a different question – most celiac patients can tolerate oats provided that they are certified gluten free but there appear to be some patients who suffer cross reactivity with oat grain due to oat prolamins. Despite widely available gluten free diet instructions, it appears the best success comes from education and interaction with a skilled dietician and interaction with support networks. In addition to cost and accessibility, some additional pitfalls of the gluten free diet include inadequate

vitamins – gluten-free flour substitutes tend not to be vitamin enriched, inadequate fiber leading to issues with constipation, substitute foods are likely to be higher fat or sugar or processed to improve palatability. Weight gain can be common, both due to increased absorption of nutrients and the substitute foods noted above. Interestingly, European countries provide celiac patients a monthly stipend to account for increased cost of gluten-free food. Symptomatic improvement on a gluten-free diet can be seen in as little as 2 weeks and some patients report generally feeling better in as little as 48 hours.

Gluten containing foods – must read labels and learn the hidden sources:

Wheat, rye, barley flour	Sourdough	Commercial salad dressings
Breads	Malt flavoring	Non-dairy creamer
Breaded products	Some pharmaceuticals	Some canned vegetables
Many cereals	Spelt	Instant coffee/drink mix
Soy sauce	Graham flour	Many lunch meats/hot dogs
Pasta / semolina flour	Cream soups	Malted milk

Future treatment options

Numerous targets for therapy are being investigated from the wheat itself to the cellular and immune system level of gluten and human interaction. Wheat grain might be modified to produce wheat strains with lower immunogenicity. Gluten might be modified, either genetically as with wheat grains, possibly pre-treating flour with bacteria or enzymes to pre-digest gluten fragments down to smaller less immunogenic particles or supplementing with oral proteases to accomplish a similar goal. Oral proteases such as ALV003 are currently in clinical trials. Intraluminal therapies might act to bind gluten peptides, sequestering gluten with polymers or resins. Induction of tolerance has been explored with vaccination or experimental hookworm infection. Intestinal permeability is also targeted via Zonulin receptor antagonists modifying tight-junction characteristics. Additional therapies target specific aspects of the immune response directly.

Non-celiac gluten-sensitivity (NCGS)

Some of the intra and extra intestinal symptoms experienced by celiac disease patients in response to ingestion of gluten are also reported by individuals who do not have the typical serologic, histologic or genetic markers of celiac disease and who do not experience the immunoglobulin E serologic response associated with wheat allergy. The term non-celiac gluten sensitivity NSGS has been proposed to refer to the spectrum of conditions reported by these patients.

The possibility that gluten might lead to symptoms outside of classic celiac disease was first suggested in a small case series of 8 patients in 1980. These patients had chronic diarrhea and abdominal pain with dramatic relief on a gluten free diet and return of symptoms on re-challenge. Celiac disease was ruled out given absence of villous atrophy but jejunal cellular infiltrate was noted.³⁰ Celiac serology was only rudimentary at that time thus these patients might have been atypical celiacs but the idea took hold. Was it possible that celiac disease was being under-diagnosed in patients told they had irritable bowel syndrome or was there a gluten trigger to irritable bowel symptoms. Increased interest in this issue can be tracked in the medical literature for more than a decade but in 2011 Australian investigators Gibson

and Biesiekierski published a very important study. They evaluated 34 people with IBS reporting gluten sensitivity responding to a gluten free diet and subjected them to a carefully designed, double-blind, randomized, placebo-controlled gluten re-challenge trial. The important finding was that subjects receiving gluten had more symptoms documented on gluten exposure than placebo, providing objective data for the first time that perhaps non-celiac gluten sensitivity might be a factor in irritable bowel patient's symptoms.³¹ The following year Brottveit and colleagues asked the question whether self-described gluten-sensitive patients had more somatization, anxiety depression, quality of life issues or certain personality traits that might separate them from patients with celiac disease and explain their symptoms. Following an open label gluten challenge, gluten-sensitive, celiac and normal control patients were examined and there were no significant differences in any of the studied traits but wheat sensitive patients complained of more wheat related symptoms than celiac or control patients.³²

Numerous additional studies have been done in the last 3 years, but given the absence of a clear case definition or sensitive and specific serologies or biomarkers, it is very difficult to "study" these patients. Carroccio and colleagues, for example, reviewed all patients diagnosed with wheat sensitivity over a 10 year period in their institution and compared to celiac patients and matched controls – suggesting anemia, childhood food allergy, atopy, presence of first generation anti-gliadin antibodies (AGA – first generation celiac antibodies no longer used given low sensitivity and specificity for celiac disease) and positive basophil activation were clues but perhaps they were seeing 2 different phenotypes of NCGS.³³ Other studies have reported presence of AGA antibodies in half of patients designated NCGS as well as these patients being more likely to have + HLA-DQ markers than the average population (50% versus 30%). It has been suggested that 12% of NCGS patients have a first degree relative with celiac disease but it is not clear if this relationship led them to screening and into secondary care. Consensus clusters met in 2011 in London and again in 2013 in Munich to determine a loose definition to aid in further study.

- **Symptoms triggered by gluten and resolve on a gluten-free diet**
- **Intra and extra intestinal symptoms similar to celiac disease**
- **But**
 - **no malabsorption**
 - **no small bowel damage**
 - **no relationship to autoimmune disorders noted**
- **Celiac and Ig E mediated wheat allergy must be ruled out by accepted practices.**

In an attempt to solidify their earlier findings with a larger study, Australian investigators Gibson and Biesiekierski planned a larger double, blind, placebo-controlled gluten challenge but in the 2013 study there was more specific focus on gastrointestinal irritable bowel type symptoms and the baseline diet used was a low FODMAP diet with 4 different crossover arms – high gluten, low gluten, whey protein or control. Each patient encountered each arm. In this trial there was no significant response to gluten after being on the FODMAP diet raising the question once again of whether the gluten is really the issue or another dietary component. The FODMAP diet is named after fermentable, oligosaccharides, disaccharides, monosaccharides and polyols – these carbohydrates may not be well digested or absorbed and produce an osmotic reaction after transit through the small bowel into the colon producing diarrhea, constipation, bloating, gas and cramping in some patients. Authors suggested that perhaps the FODMAP diet was the key to all of the GI symptoms but acknowledged they tracked extra intestinal symptoms more aggressively in their prior study and did notice a trend toward more extra

intestinal symptoms in the gluten sensitive group. There is also the question as to whether the FODMAP diet changes the microbiome as the gluten-free diet has been show to do and whether this might not obscure the gluten sensitivity or whether this represents a different entity such as an alternate wheat carbohydrate sensitivity.

Non-celiac wheat sensitivity is where celiac disease was 40 years ago...

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