Celiac disease

- Celiac disease is a chronic, immune-mediated enteropathy that is precipitated by dietary gluten in genetically predisposed individuals.

- Gluten is the commonly used term for the complex of water-insoluble proteins from wheat, rye, and barley that is harmful to patients with celiac disease.

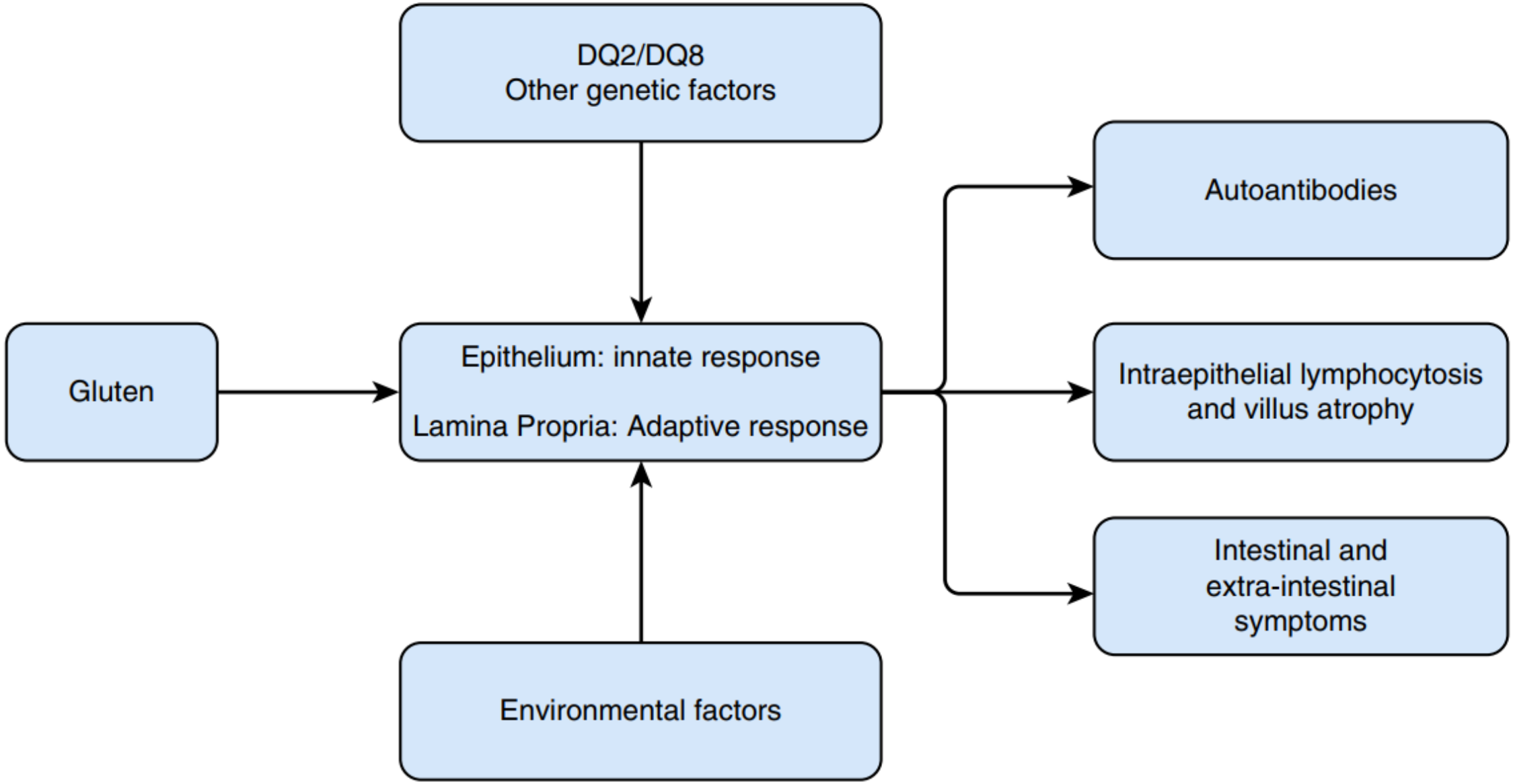
- The interaction of the water-insoluble protein moiety (gluten) of certain cereal grains with the mucosa of the small intestine in susceptible persons is central to the pathogenesis of celiac disease.

Epidemiology

- The estimated global prevalence of celiac disease based on serologic studies is approximately 1 percent.

- Epidemiologic studies using specific celiac serology testing indicate that celiac disease has a wide geographic distribution and affects individuals from multiple and diverse ethnic and racial backgrounds.

- Factors such as predominant HLA haplotype, timing of introduction of gluten into the diet, differences in the gliadin concentration of infant formulas, and interobserver variation in interpreting small intestinal biopsy findings might explain differences in prevalence.


DQ2/DQ8
Other genetic factors
Gluten
Epithelium: innate response
Lamina Propria: Adaptive response
Environmental factors
Autoantibodies
Intraepithelial lymphocytosis and villus atrophy
Intestinal and extra-intestinal symptoms

- In the past, celiac disease was perceived to be a pediatric disorder, but the diagnosis now is being made increasingly in adults.

- Currently, the **5th** decade is the most common age at presentation.

- 25% of cases diagnosed in patients older than 60 years.

- Other individuals at increased risk for celiac disease include (among several other autoimmune diseases):
  - Type 1 diabetes
  - Autoimmune thyroiditis
  - Down and Turner syndromes
  - Pulmonary hemosiderosis (moderate risk)

- Some authors have noted a female to-male ratio of 2:1, whereas others have reported equal prevalences in men and women. Most studies measuring diagnosed celiac disease, however, have found a female predominance, suggesting that men are more likely to remain undiagnosed.

- Concordance for celiac disease in first-degree relatives ranges between 8% and 18% and estimates for concordance in monozygotic twins range from 49% to 83%.

Terminology

- Celiac disease exhibits a wide spectrum of clinical presentations:
  - **Typical celiac disease** (now called **classical** celiac disease) denoted a clinical presentation with signs and symptoms of malabsorption, such as diarrhea, steatorrhea, weight loss, and nutritional deficiencies.
  - **Atypical celiac disease** and now termed **nonclassical** celiac disease (e.g., anemia, fatigue, abdominal bloating and discomfort, osteoporosis, infertility) .
  - **Asymptomatic celiac disease** (also called **silent** celiac disease) is usually identified by screening using celiac disease-specific serology and is characterized by duodenal villuos atrophy in individuals who lack symptoms or signs of celiac disease.

- **Potential celiac disease** denotes those with normal small intestinal histology who are at increased risk of developing celiac disease (usually identified by positive celiac disease-specific serology).

- **Latent celiac disease** was a previously used term for patients that presented with celiac disease in the past, usually diagnosed in childhood, but who recovered completely with a gluten-free diet and remained "silent" even once a normal diet was resumed.

- **Nonceliac gluten sensitivity** refers to symptoms or signs that develop upon gluten ingestion in people in whom a diagnosis of celiac disease has been excluded.

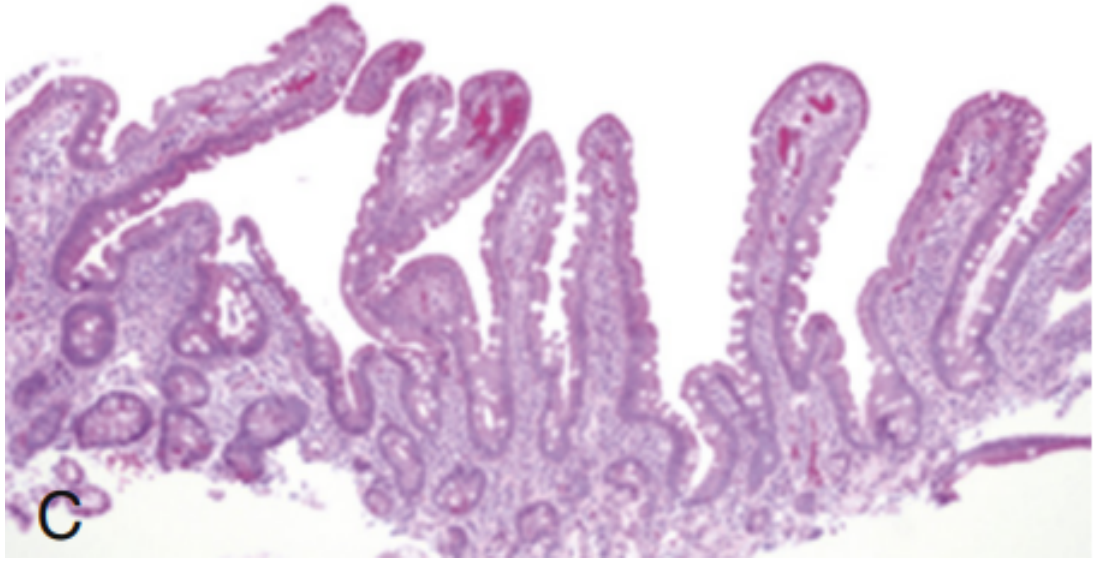
- **Refractory disease** defined by the persistence of symptoms and villous atrophy despite adherence to a gluten-free diet. Failure to improve on a gluten-free diet is mostly due to poor dietary compliance or other underlying malabsorptive disorders. However, in rare cases, diet-refractory celiac disease may be related to one of the following:
  - Non-malignant inflammation of the small intestine, possibly due to a high sensitivity towards minimal amounts of gluten (refractory celiac disease type 1 [RCD1]).
  - Semi-malignant inflammatory condition (RCD2).
  - Overt enteropathy-associated T-cell lymphoma (EATL).
  - Collagenous sprue, a very rare, little understood disorder, which is characterized by subepithelial collagen deposition [70].
  - Alternative diagnosis including autoimmune enteropathy, common variable immunodeficiency (CVID; IgG deficiency) or drug-induced villous atrophy.

PATHOLOGY

- Celiac disease affects the mucosa of the small intestine.

- Examination under magnification of the small intestinal mucosal surface in severe untreated celiac disease reveals a flat mucosal surface with complete absence of normal intestinal villi.

- Histologic examination of tissue sections :
  - Loss of normal villous structure (**villous atrophy**).
  - **Crypt hyperplasia** compensates for the absence or shortening of the villi.
  - **Intraepithelial lymphocytosis.**
  - **Chronic inflammatory cell infiltrate in the lamina propria.**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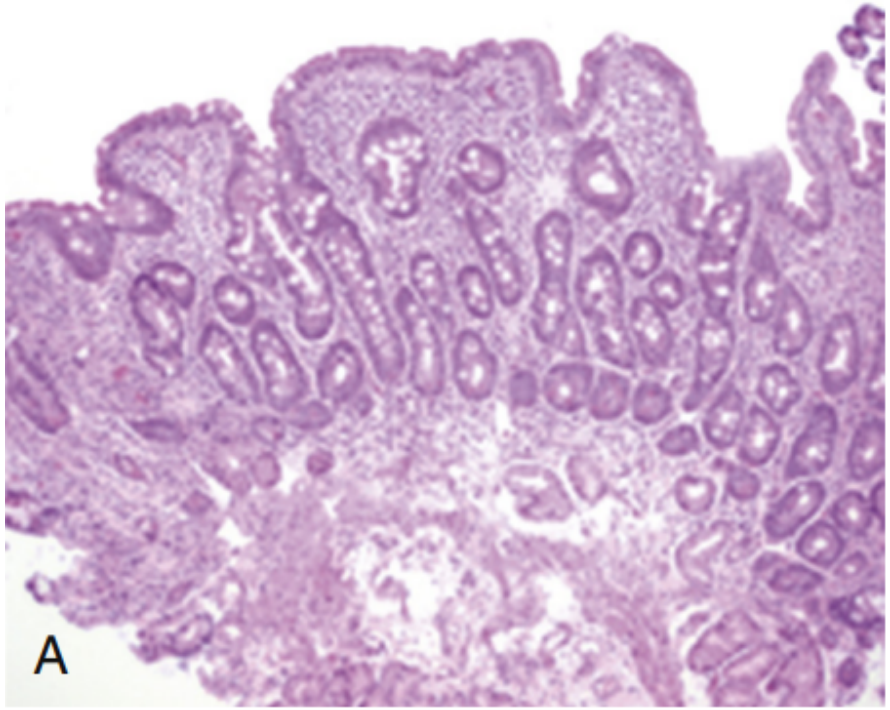
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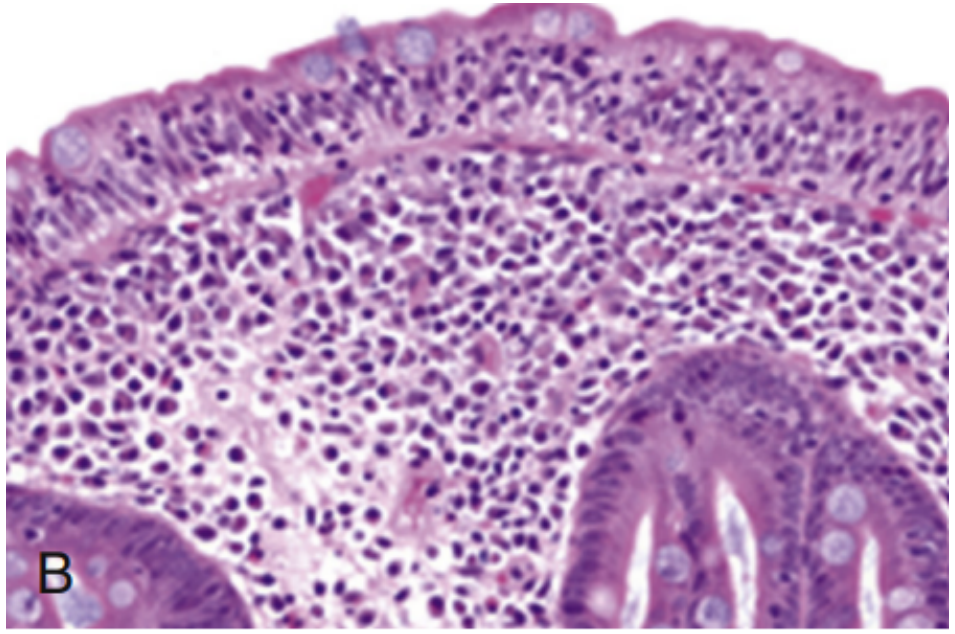
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Classification of celiac disease (MARSH CLASSIFICATION)

	Marsh 0	Marsh 1	Marsh 2	Marsh 3		
				3a	3b	3c
IEL Count*	<30/100	>30/100	>30/100	>30/100	>30/100	>30/100
Crypt Hyperplasia	Normal	Normal	Increased	+	+	+
Villous atrophy	Normal	Normal	Normal	Mild	Moderate	Total
	Pre-infiltrative	Infiltrative	Infiltrative-hyperplastic	Flat destructive		

IEL – intraepithelial lymphocytes. * Number of intraepithelial lymphocytes per 100 enterocytes.

CLINICAL MANIFESTATIONS

- Gastrointestinal manifestations:
  - Patients may present with classic signs, including diarrhea with bulky, foul-smelling, floating stools due to steatorrhea and flatulence.
  - These symptoms are paralleled by the consequences of malabsorption, such as weight loss, severe anemia, neurologic disorders from deficiencies of B vitamins, and osteopenia from deficiency of vitamin D and calcium.
  - The severity of histologic changes in the small bowel does not necessarily correlate with the severity of clinical manifestations.

- Extraintestinal manifestations:
  - **Mucocutaneous**
    - **Dermatitis herpetiformis**
      - common among patients with celiac disease.
      - development of multiple intensely pruritic papules and vesicles that occur in grouped ("herpetiform") arrangements.
      - The elbows, dorsal forearms, knees, scalp, back, and buttocks are among the most common sites for lesion development.

    - **Atrophic glossitis**
      - Oral lesions (erythema or atrophy) and a soreness or burning sensation of the tongue.

- **Metabolic bone disorders:**
  - Patients with celiac disease may have bone loss due to secondary hyperparathyroidism from vitamin D deficiency.
  - Osteomalacia due to vitamin D deficiency is also sometimes seen, although its prevalence is unknown.
  - In adults, loss of bone density in the peripheral skeleton may persist despite apparent normalization at axial skeletal sites after patients are on a gluten-free diet.
  - The risk of fractures is slightly increased in patients with celiac disease.
  - A higher prevalence of osteoarthritis has also been described in celiac disease.

- **Hematologic manifistations:**
  - **Iron deficiency anemia**
  - One study of 93 patients presenting for evaluation of iron deficiency anemia found 11 (12 percent) with small bowel biopsy findings compatible with celiac disease
  - The incidence was 20 percent in the subgroup of nonresponders to supplemental iron.
  - **Hyposplenism**
  - Several case reports have described hyposplenism in association with celiac disease ,the pathogenesis of which is unknown.

- **Neuropsychiatric manifistations:**
  - Several reports have described an association between celiac disease and neurologic or psychiatric symptoms including headache, peripheral neuropathy, ataxia, epilepsy, depression, dysthymia, and anxiety.

  - Peripheral neuropathies, characterized by burning, tingling, and numbness in hands and feet, have been described in up to 50 percent of patients with celiac disease and may precede its diagnosis.

  - In patients with celiac disease, neuropathies may also be associated with lymphoma and deficiencies of vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B12 (cobalamine), and E. However, vitamin deficiency syndromes are uncommon in the absence of severe and extensive small bowel involvement.

ASSOCIATED CONDITIONS

- **Selective IgA deficiency**
  - Selective IgA deficiency has been associated with celiac disease and has been detected in up to 8 percent of patients with celiac disease in some studies.

- **Autoimmune disease**
  - **Diabetes mellitus**
  - Celiac disease is closely associated with type 1 diabetes mellitus and polyglandular autoimmune syndrome type III (autoimmune thyroiditis combined with immune-mediated diabetes).
  - Type 1 diabetes and celiac disease share multiple genetic loci such as HLA-DR3, HLA-DQ2 (HLA-DQ8), and several genetic variations.

  - **Thyroid disease**
  - Hypothyroidism is more frequent than hyperthyroidism.

  - **Atopic dermatitis**
  - Patients with celiac disease (and their families) may also be more likely to have atopic dermatitis compared with the general population.

- **Gastrointestinal disease**
  - **Gastroesophageal reflux disease**
  - **Eosinophilic esophagitis**
  - **Inflammatory bowel disease**
    - more frequently with ulcerative colitis than Crohn disease.
    - the risk of IBD in patients with celiac disease was elevated 10-fold, while the risk of celiac disease in patients with IBD was comparable to controls.
  - **Microscopic colitis**
    - There is a 72-fold increased risk of microscopic colitis in patients with celiac disease, as compared with the general population.

- **Liver disease**
  - **Elevated aminotransferase**
    - Celiac disease may be associated with nonspecific mild to moderate chronic elevation in serum aminotransferase levels in 15 to 55 percent of patients (ALT is usually slightly greater than AST)
    - patients with cryptogenic elevations in aminotransferases, celiac serologies were positive in 6 percent and duodenal biopsies suggested celiac disease in 4 percent.
    - Serum transaminases normalized in 63 to 90 percent of patients within a year of initiating a gluten-free diet.
  - **Cholestatic and autoimmune liver disease**
    - Celiac disease has been associated with primary biliary cirrhosis (PBC).
- **Pancreatitis**
  - There is an increased risk of pancreatitis (both acute and chronic) in patients with celiac disease.

- **Menstrual and reproductive issues**
  - Women with celiac disease, most of them on a gluten-free diet, have similar overall fertility to the general female population
  - Women with untreated celiac disease may have later age of menarche, earlier menopause, secondary amenorrhea, recurrent miscarriage, spontaneous abortion, preterm delivery, and low birth weight.
  - Male infertility, characterized by abnormalities in sperm motility and morphology as well as a biochemical picture of androgen resistance (high serum testosterone and high luteinizing hormone [LH] concentrations), has been reported in celiac disease

- **Idiopathic pulmonary hemosiderosis**
  - Lane-Hamilton syndrome

- **Cardiovascular disease**
  - 5 percent of patients with autoimmune myocarditis or idiopathic dilated cardiomyopathy have unsuspected celiac disease
  - Patients with celiac disease may also be at increased risk for ischemic heart disease

- **Kidney disease**
  - Glomerular IgA deposition is common, occurring in as many as one-third of patients.
  - The great majority of affected patients have no clinical manifestations of kidney disease, perhaps because there is no associated activation of complement.

Diagnosis

- Individuals at **low** risk for celiac disease should undergo serologic testing.
  - Absence of suggestive signs or symptoms of malabsorption such as significant chronic diarrhea/ steatorrhea or weight loss
  - Absence of family history of celiac disease
  - Chinese, Japanese, or Sub-Saharan African descent
- Patients with positive serologic testing, should undergo an upper endoscopy with small bowel biopsy to diagnose celiac disease.
- The serum tissue transglutaminase (tTG)-immunoglobulin A (IgA) and endomysial (EMA)-IgA antibody tests have similar sensitivities.

- The specificities of the EMA IgA and tTG-IgA are high. Thus, their positive predictive values are high even in low-risk populations.

- The EMA-IgA test has the highest diagnostic accuracy but is more costly and less widely available than the tTG-IgA test.

- Combining several tests for celiac disease is not recommended in low-risk populations

- Individuals with **high** celiac disease probability
  - Individuals whose clinical presentation is highly suggestive for celiac disease such as chronic diarrhea/ steatorrhea with weight loss.
  - Individuals with both risk factors that place them at moderate to high risk of celiac disease and consistent gastrointestinal or extraintestinal symptoms/signs of celiac disease.

- Both serologic testing and small bowel biopsy (regardless of celiac specific serology results) should be performed in individuals with a high probability of celiac disease.

- Tissue transglutaminase (tTG)-IgA antibody is the single preferred test for detection of celiac disease in adults.

- We concurrently measure total IgA levels.

- In patients with IgA deficiency, we perform IgG-based testing with deamidated gliadin peptide (DGP)-IgG.

- An alternative approach is to perform both IgA- and IgG-based testing, in particular, tTG-IgA and DGP-IgG, in patients with a high probability of celiac disease.

- EMA-IgA is moderately sensitive and highly specific for untreated celiac disease (sensitivity 85 to 98 percent; specificity 97 to 100 percent, respectively).

- Anti-tTG antibodies are highly sensitive and specific for the diagnosis of celiac disease (sensitivity 90 to 98 percent; specificity 95 to 97 percent).

- The positive predictive value of a strongly positive TG2-IgA (>10 upper normal limit) combined with a positive endomysial antibody is approximately 100 percent.

- DGP-IgA has a sensitivity and specificity of 94 percent and 99 percent, respectively.

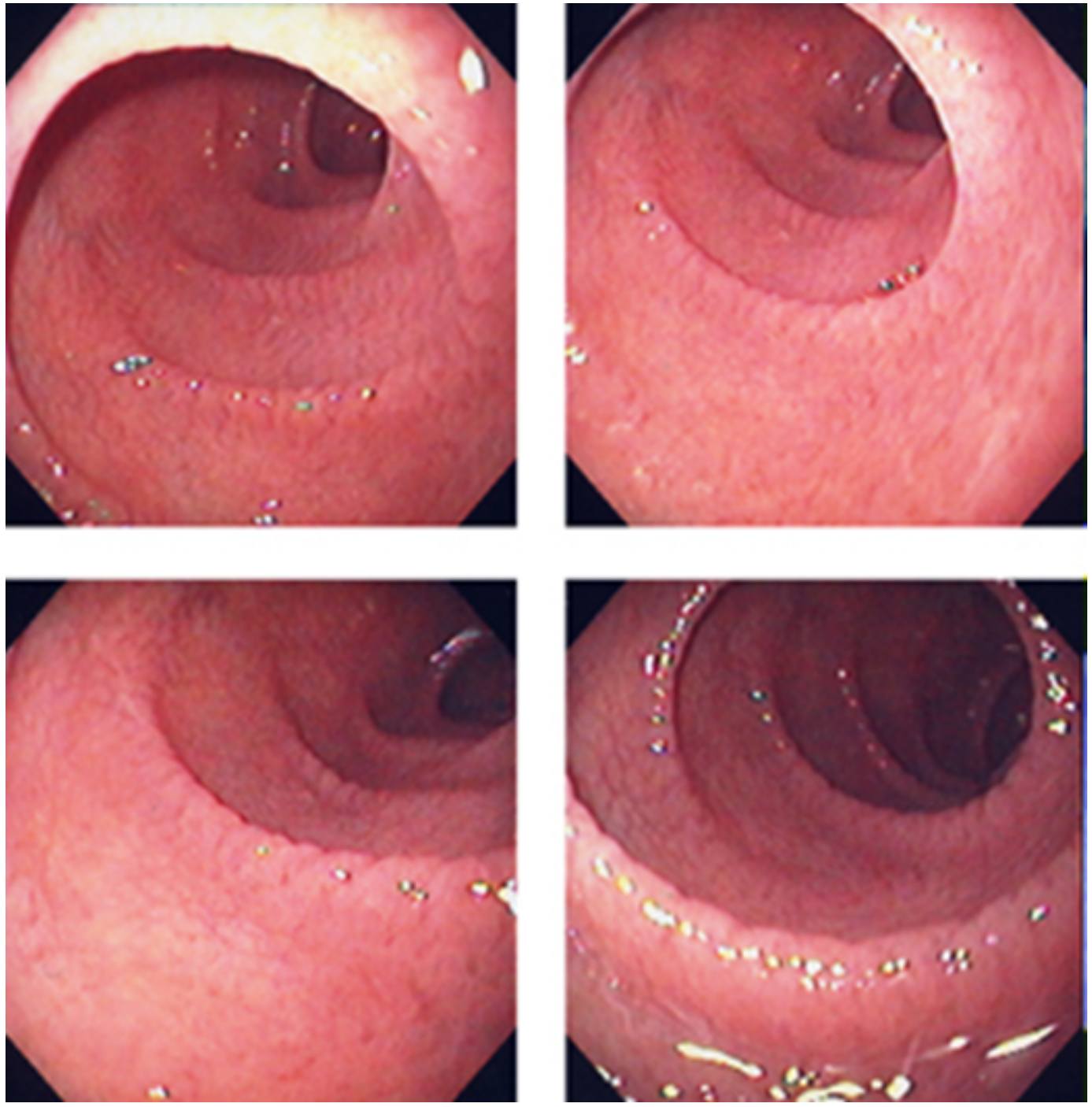
- The DGP-IgG has a sensitivity and specificity of 92 percent and 100 percent, respectively.

- The traditional antigliadin antibody tests (AGA-IgA and AGA-IgG) have lower diagnostic accuracy as compared with other serologic tests for celiac disease and are no longer recommended because they yield false-positive results in 15 to 20 percent of subjects tested.

- # Test interpretation
  - ## Positive serology
  - Individuals with positive serology require a small bowel biopsy to confirm the diagnosis.
  - Exceptions are patients with positive serology and biopsy-proven dermatitis herpetiformis in whom the diagnosis can be established without a small bowel biopsy.

  - ## Negative serology
  - Serologic studies are useful in excluding the diagnosis of celiac disease but cannot exclude celiac disease with 100 percent accuracy.
  - Negative celiac serologies in patients with celiac disease may be due to any one of the following:
    - **IgA deficiency**
    - **Low gluten/gluten-free diet**
    - **False negative**

- **Endoscopy with small bowel biopsy**
  - Atrophic appearing mucosa with loss of folds
  - Visible fissures
  - Nodularity
  - Scalloping
  - Prominent submucosal vascularity



- Endoscopic features suggestive of celiac disease have low sensitivity (59 to 94 percent).

- The reported specificity ranges from 92 to 100 percent.

- These findings may be seen with other disorders such as giardiasis, autoimmune enteropathy, and HIV infection.

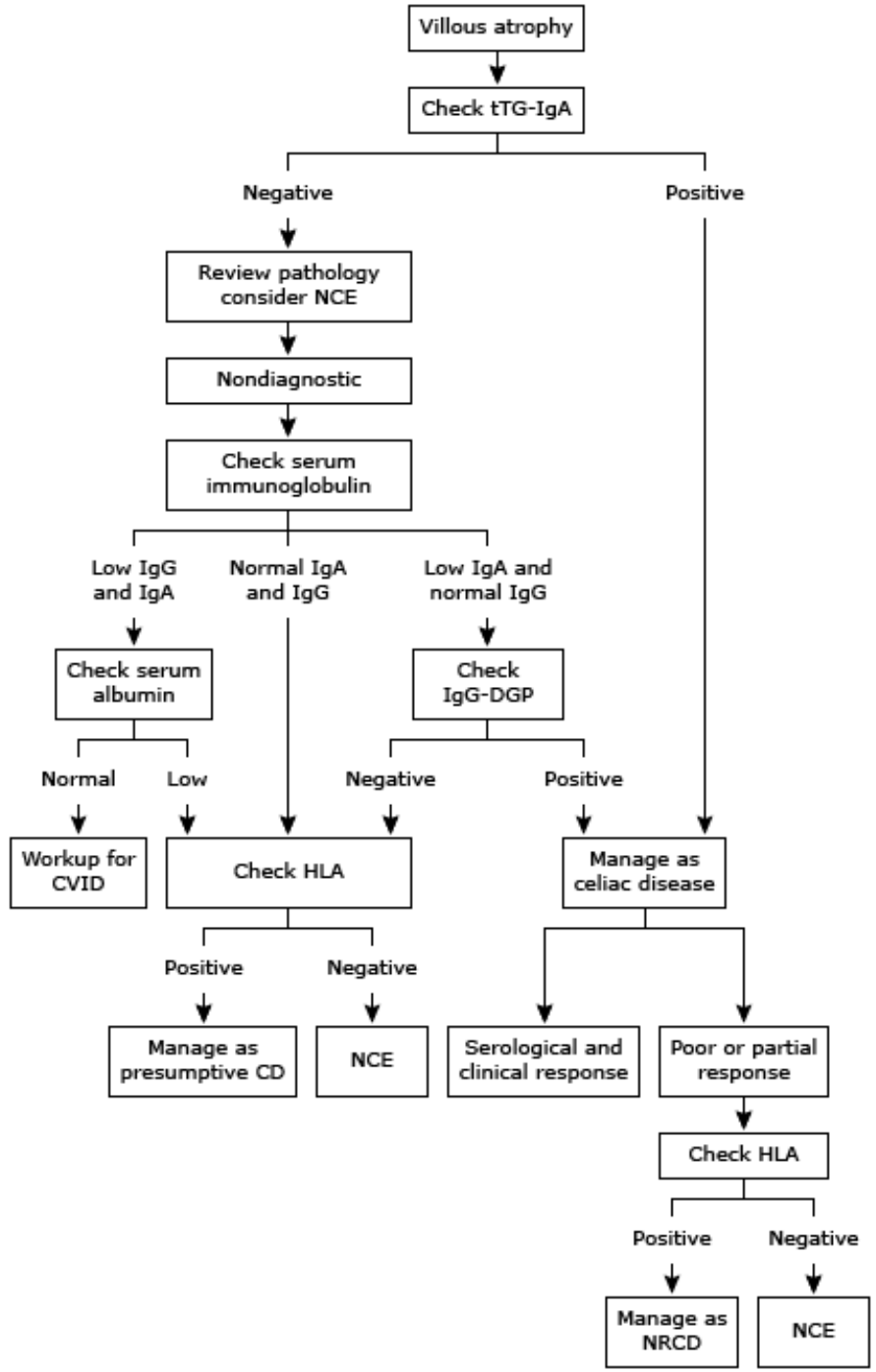
- Histology remains important in making a diagnosis of celiac disease, regardless of the endoscopic appearance.

Causes of small intestinal villous atrophy other than celiac disease

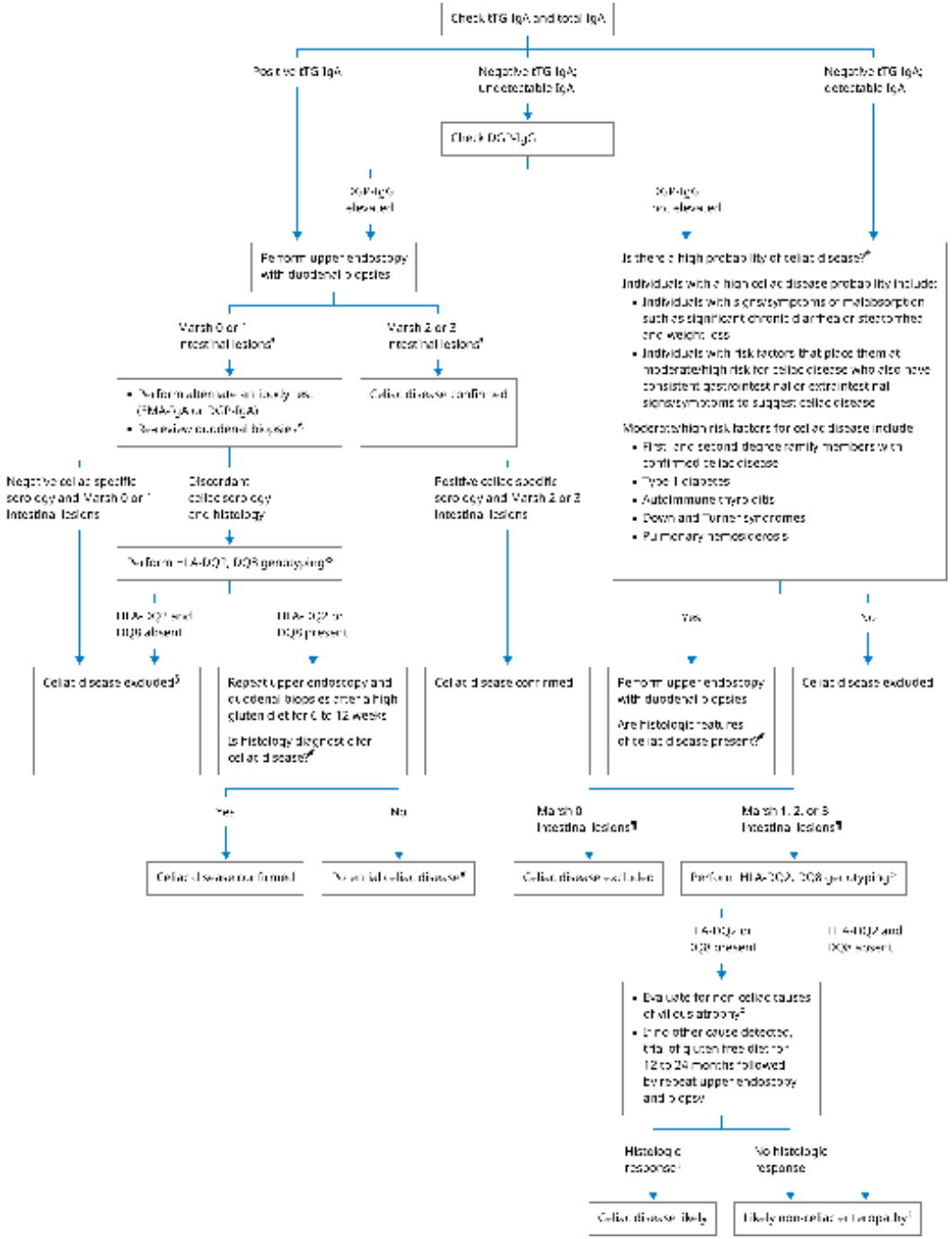
Small intestinal bacterial overgrowth
Crohn disease
Cow's milk or soy protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Intestinal lymphoma
Peptic duodenitis
Post-gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)
Medications (eg, olmesartan, NSAIDs)
Whipple disease
Malnutrition
Intestinal tuberculosis
Graft-versus-host disease

AIDS: acquired immunodeficiency syndrome; NSAIDs: nonsteroidal anti-inflammatory drugs.

Diagnostic algorithm for small intestinal villous atrophy


Villous atrophy
Check tTG-IgA
Negative
Positive
Review pathology consider NCE
Nondiagnostic
Check serum immunoglobulin
Low IgG and IgA
Normal IgA and IgG
Low IgA and normal IgG
Check serum albumin
Check IgG-DGP
Normal
Low
Negative
Positive
Workup for CVID
Check HLA
Manage as celiac disease
Positive
Negative
Manage as presumptive CD
NCE
Serological and clinical response
Poor or partial response
Check HLA
Positive
Negative
Manage as NRCD
NCE

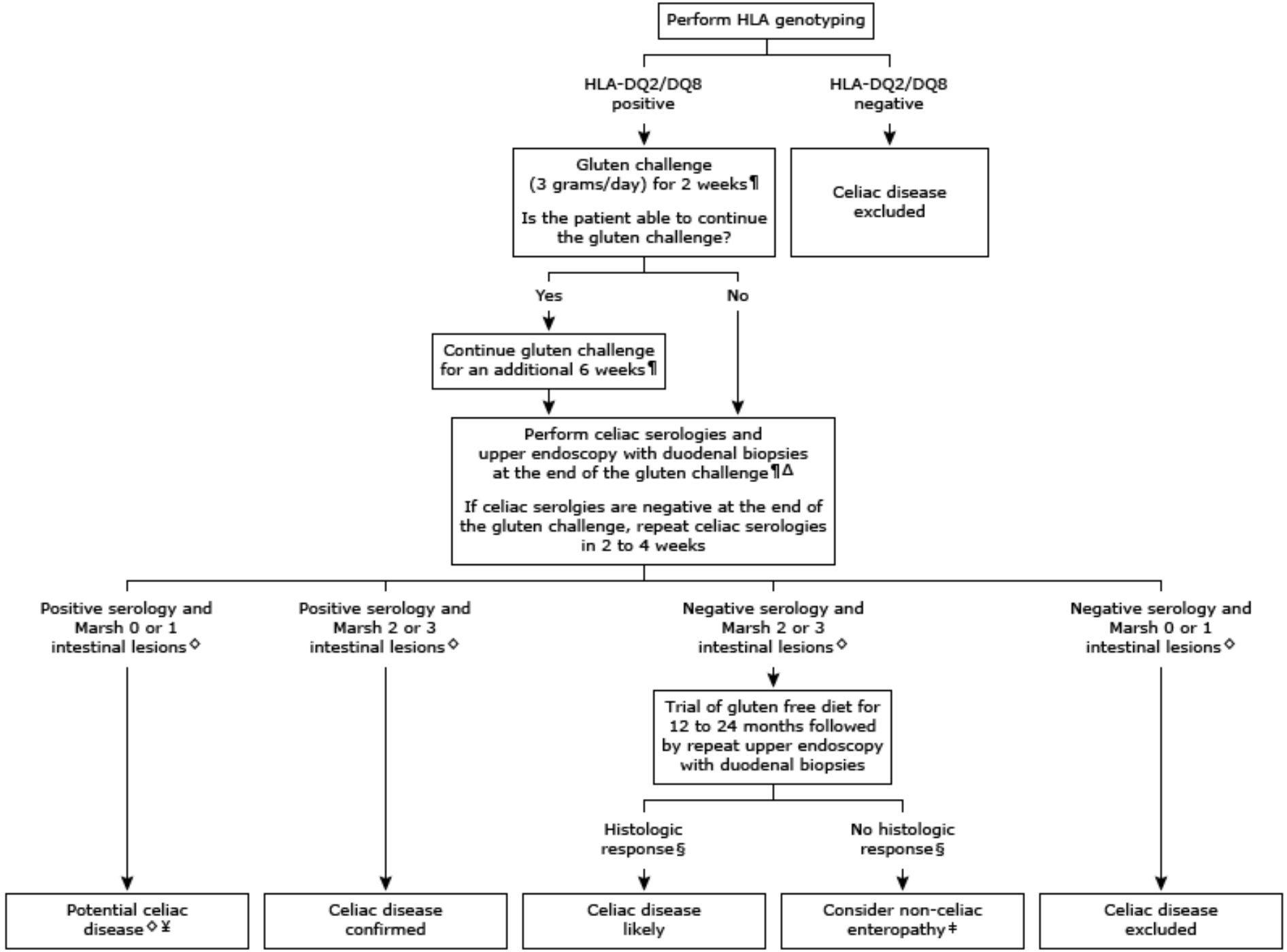
Diagnostic approach for suspected celiac disease in an adult patient on gluten containing diet


Check tTG IgA and total IgA
Positive tTG IgA
Negative tTG IgA; undetectable IgA
Negative tTG IgA; detectable IgA
Check DGP-IgG
DGP-IgG elevated
DGP-IgG not elevated
Perform upper endoscopy with duodenal biopsies
Is there a high probability of celiac disease?
Individuals with a high celiac disease probability include:
Individuals with signs/symptoms of malabsorption such as significant chronic diarrhea or steatorrhea and weight loss
Individuals with risk factors that place them at moderate/high risk for celiac disease who also have consistent gastrointestinal or extraintestinal signs/symptoms to suggest celiac disease
Moderate/high risk factors for celiac disease include:
First- and second-degree family members with confirmed celiac disease
Type 1 diabetes
Autoimmune thyroiditis
Down and Turner syndromes
Pulmonary hemosiderosis
Marsh 0 or 1 intestinal lesions
Marsh 2 or 3 intestinal lesions
Perform alternate serology (ie, tTG-IgA or DGP-IgA)
Repeat duodenal biopsies
Celiac disease confirmed
Negative celiac specific serology and Marsh 0 or 1 intestinal lesions
Discordant celiac serology and histology
Positive celiac specific serology and Marsh 2 or 3 intestinal lesions
Perform HLA-DQ2, DQ8 genotyping
HLA-DQ2 and DQ8 absent
HLA-DQ2 or DQ8 present
Celiac disease excluded
Repeat upper endoscopy and duodenal biopsies after a high gluten diet for 6 to 12 weeks
Is histology diagnostic for celiac disease?
Yes
No
Celiac disease confirmed
Not celiac disease
Yes
No
Perform upper endoscopy with duodenal biopsies
Are histologic features of celiac disease present?
Celiac disease excluded
Marsh 0 intestinal lesions
Marsh 1, 2, or 3 intestinal lesions
Celiac disease excluded
Perform HLA-DQ2, DQ8 genotyping
HLA-DQ2 or DQ8 present
HLA-DQ2 and DQ8 absent
Evaluate for non-celiac causes of villous atrophy
If no other cause detected, trial of gluten-free diet for 12 to 24 months followed by repeat upper endoscopy and biopsy
Histologic response
No histologic response
Celiac disease likely
Likely non-celiac enteropathy

- HLA testing in selected patients
  - The haplotypes HLA-DQ2 or DQ8 are present in almost all patients with celiac disease.
  - Testing for these haplotypes has a negative predictive value of greater than 99 percent, but positive predictive value is only around 12 percent because these haplotypes are common in the general population.

- HLA testing is useful only in ruling out celiac disease:
  - Patients with discordant celiac-specific serology and histology.
  - Patients who refuse upper endoscopy.
  - Evaluation of patients on a gluten-free diet with negative baseline serologies.
  - Patients with suspicion of refractory celiac disease where the original diagnosis of celiac disease remains in question.
  - HLA typing is sometimes performed in patients at high risk for celiac disease (eg, family history of celiac disease). A negative result will exclude celiac disease risk. This approach is most commonly used in at-risk children to obviate the need for periodic serology testing.

Diagnostic approach for suspected celiac disease in an adult patient on gluten free diet and negative baseline serologies


Perform HLA genotyping
HLA-DQ2/DQ8 positive
HLA-DQ2/DQ8 negative
Gluten challenge (3 grams/day) for 2 weeks¶
Is the patient able to continue the gluten challenge?
Celiac disease excluded
Yes
No
Continue gluten challenge for an additional 6 weeks¶
Perform celiac serologies and upper endoscopy with duodenal biopsies at the end of the gluten challenge¶Δ
If celiac serolgies are negative at the end of the gluten challenge, repeat celiac serologies in 2 to 4 weeks
Positive serology and Marsh 0 or 1 intestinal lesions◇
Positive serology and Marsh 2 or 3 intestinal lesions◇
Negative serology and Marsh 2 or 3 intestinal lesions◇
Negative serology and Marsh 0 or 1 intestinal lesions◇
Trial of gluten free diet for 12 to 24 months followed by repeat upper endoscopy with duodenal biopsies
Histologic response§
No histologic response§
Potential celiac disease◇¥
Celiac disease confirmed
Celiac disease likely
Consider non-celiac enteropathy‡
Celiac disease excluded

Management

- There are six key elements in the management of patients with celiac disease
  - Consultation with a skilled dietitian
  - Education about the disease
  - Lifelong adherence to a gluten-free diet
  - Identification and treatment of nutritional deficiencies
  - Access to an advocacy group
  - Continuous long-term follow-up by a multidisciplinary team

- A gluten-free diet is recommended in patients with celiac disease (classic disease, atypical celiac disease, and asymptomatic or silent celiac disease).

- Patients with latent celiac disease (positive IgA endomysial antibody, but normal small bowel biopsy) are not advised to be on a gluten-free diet but should continue to be monitored and rebiopsied if symptoms develop.

- The following dietary advice can be given to all patients:
  - Foods containing wheat, rye, and barley should be avoided.
  - Soybean or tapioca flours, rice, corn, buckwheat, and potatoes are safe.
  - Read labels on prepared foods and condiments carefully, paying particular attention to additives such as stabilizers or emulsifiers that may contain gluten.
  - Distilled alcoholic beverages and vinegars, as well as wine, are gluten free. However, beers, ales, lagers, and malt vinegars should be avoided.
  - Dairy products may not be well tolerated initially, since many patients with celiac disease can have secondary lactose intolerance.
  - Oats should be introduced into the diet with caution.

Foods and products that may contain gluten

Foods and products that may contain gluten

Frequently overlooked foods that may contain gluten and need to be verified:	NOT ALLOWED in any form:
▪ Brown rice syrup ▪ Breading and coating mixes ▪ Croutons ▪ Energy bars ▪ Flour or cereal products ▪ Imitation bacon ▪ Imitation seafood ▪ Marinades ▪ Panko (Japanese bread crumbs) ▪ Pastas ▪ Processed luncheon meats ▪ Sauces, gravies ▪ Self-basting poultry ▪ Soy sauce or soy sauce solids ▪ Soup bases ▪ Stuffings, dressing ▪ Thickeners (roux) ▪ Communion wafers ▪ Herbal supplements ▪ Probiotic products* ▪ Drugs and over-the-counter medications ▪ Nutritional supplements ▪ Vitamins and mineral supplements ▪ Play-Doh, crayons, paint, glue, paper mache – A potential problem if the child puts their hands on or in the mouth while playing; wash hands after using these products	▪ Wheat (einkorn, durum, faro, graham, kamut, semolina, spelt) ▪ Rye ▪ Barley ▪ Triticale ▪ Malt, malt flavoring, malt vinegar (are generally made from barley; verify the source)

* In 2015, a study of 22 commonly used probiotics revealed that 12 (55%) contained gluten, including 2 that were labeled gluten-free despite containing gluten levels higher than the 20 parts per million required for gluten-free labeling.[1]

Reference:

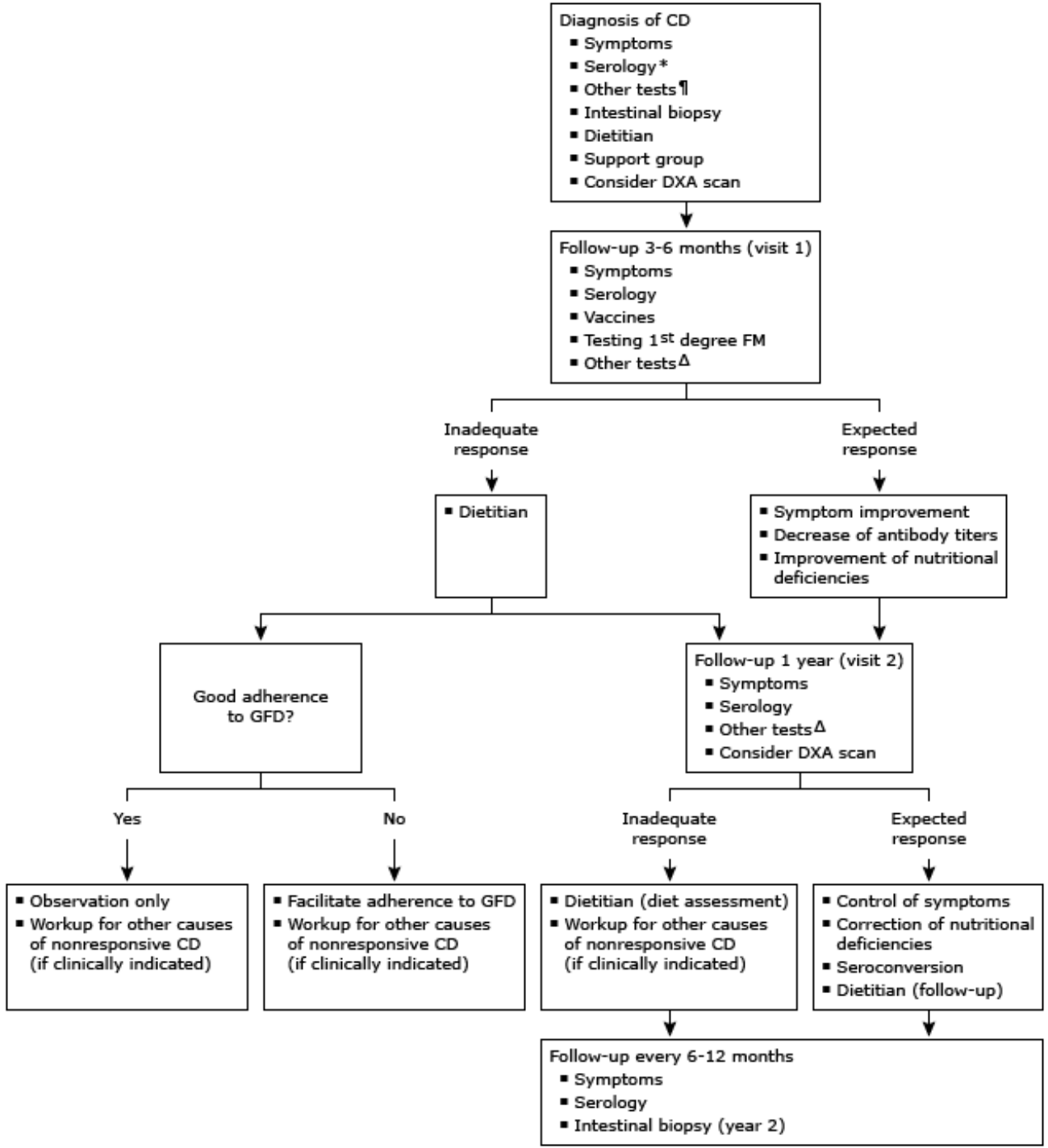
1. *Nazareth S, Lebwohl B, Voyksner JS, Green PH. Widespread Contamination of Probiotics With Gluten, Detected by Liquid Chromatography-Mass Spectrometry. Gastroenterology 2015; 148:S28.*

- **MONITORING THE RESPONSE TO A GLUTEN-FREE DIET**
  - Approximately 70 percent of patients have noticeable clinical improvement within two weeks
  - Patients be evaluated in three to six months following the initiation of a gluten-free diet at which time a complete blood count, folate, B12, iron studies, liver chemistries, and serologic testing should be performed.
  - IgA anti tissue transglutaminase (tTG) or IgA (or IgG) deamidated gliadin peptide (DGP) should be used to monitor the response to gluten-free diet.
  - We perform serologic testing 6 and 12 months after the initial diagnosis of celiac disease and annually thereafter.

- **Small bowel biopsy**
  - We perform a follow-up biopsy in adults after two years of starting a gluten-free diet to assess for mucosal healing.

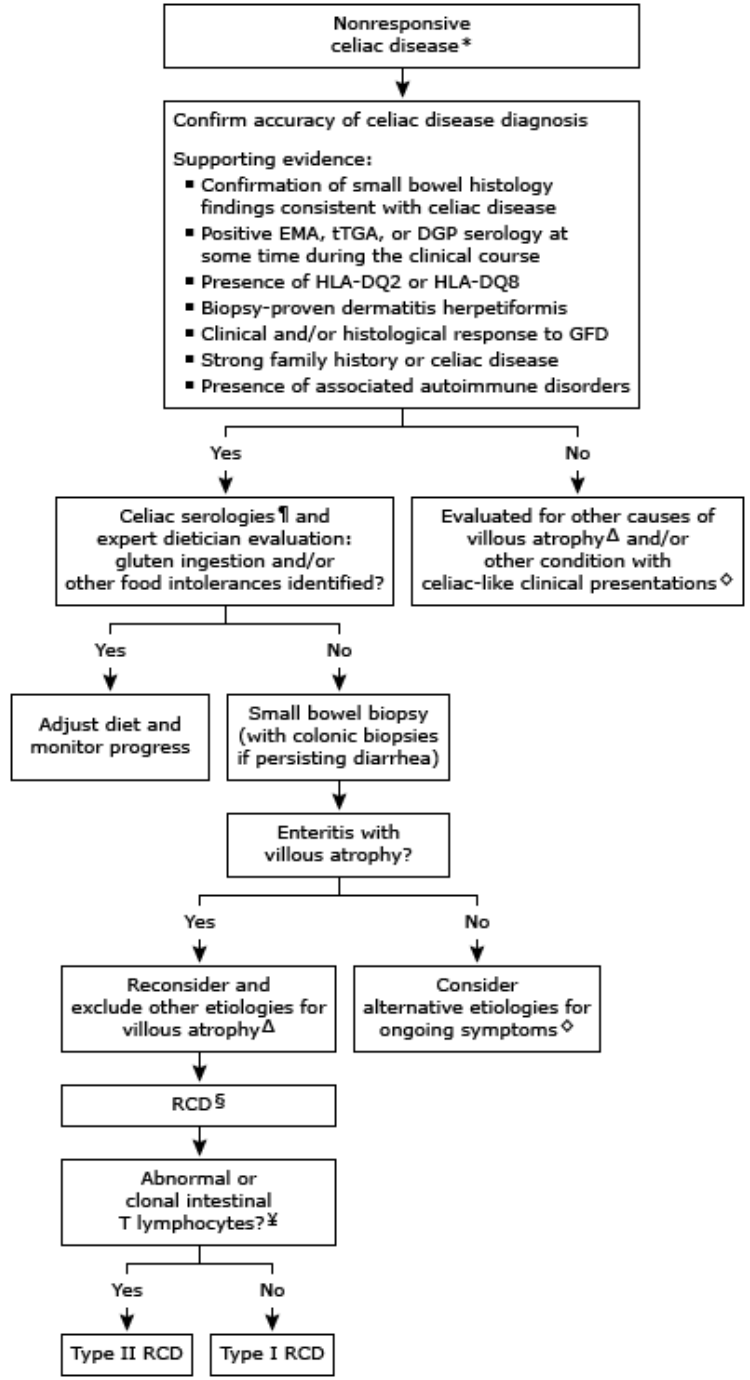
  - In patients with persistent Marsh 2 or more severe histologic lesions on re-biopsy, a follow-up upper endoscopy with biopsy should be performed in 12 months.

Approach to monitoring celiac disease


Diagnosis of CD
Symptoms
Serology*
Other tests¶
Intestinal biopsy
Dietitian
Support group
Consider DXA scan
Follow-up 3-6 months (visit 1)
Symptoms
Serology
Vaccines
Testing 1st degree FM
Other tests∆
Inadequate response
Expected response
Dietitian
Symptom improvement
Decrease of antibody titers
Improvement of nutritional deficiencies
Good adherence to GFD?
Follow-up 1 year (visit 2)
Symptoms
Serology
Other tests∆
Consider DXA scan
Yes
No
Inadequate response
Expected response
Observation only
Workup for other causes of nonresponsive CD (if clinically indicated)
Facilitate adherence to GFD
Workup for other causes of nonresponsive CD (if clinically indicated)
Dietitian (diet assessment)
Workup for other causes of nonresponsive CD (if clinically indicated)
Control of symptoms
Correction of nutritional deficiencies
Seroconversion
Dietitian (follow-up)
Follow-up every 6-12 months
Symptoms
Serology
Intestinal biopsy (year 2)

- **NON-RESPONDERS**
  - Non-responders are individuals who have persistent symptoms or serologic and/or histologic abnormalities after two years on a gluten-free diet.
  - 5 percent of individuals do not respond to a gluten-free diet
- Patients who do not respond to a gluten-free diet fall into five main categories:
  - Patients with poor compliance or inadvertent gluten ingestion (>90 percent)
  - Patients with clinical or histologic features that overlap with celiac disease but are caused by other disorders
  - Patients with concurrent disorders
  - Patients with refractory sprue
  - Patients with ulcerative jejunitis or intestinal lymphoma

An approach to the investigation of nonresponsive celiac disease and refractory celiac disease


Nonresponsive celiac disease*
Confirm accuracy of celiac disease diagnosis
Supporting evidence:
Confirmation of small bowel histology findings consistent with celiac disease
Positive EMA, tTGA, or DGP serology at some time during the clinical course
Presence of HLA-DQ2 or HLA-DQ8
Biopsy-proven dermatitis herpetiformis
Clinical and/or histological response to GFD
Strong family history or celiac disease
Presence of associated autoimmune disorders
Yes
No
Celiac serologies¶ and expert dietician evaluation: gluten ingestion and/or other food intolerances identified?
Evaluated for other causes of villous atrophyΔ and/or other condition with celiac-like clinical presentations◇
Yes
No
Adjust diet and monitor progress
Small bowel biopsy (with colonic biopsies if persisting diarrhea)
Enteritis with villous atrophy?
Yes
No
Reconsider and exclude other etiologies for villous atrophyΔ
Consider alternative etiologies for ongoing symptoms◇
RCD§
Abnormal or clonal intestinal T lymphocytes?¥
Yes
No
Type II RCD
Type I RCD

- Refractory sprue has also been subdivided into two immunologic categories
  - Type 1 in which there is a normal population of intraepithelial lymphocytes.
  - Type 2 in which there is an aberrant or premalignant population of intraepithelial lymphocytes based upon clonality analysis of T-cell receptors and immunophenotyping.
  - Type 2 can progress to enteropathy-associated T-cell lymphoma, which may present clinically as ulcerative jejunitis.
  - Patients with type 1 disease have a less severe presentation and a much better prognosis than patients with type 2 disease.
  - Refractory sprue (particularly type 2) can be severe and associated with progressive malabsorption and death in 55 percent of untreated cases.

- **OTHER ASPECTS OF MANAGEMENT**
  - Repletion of nutritional deficiencies
  - Medication absorption
  - Prevention of bone loss
  - Pneumococcal vaccination
  - Dermatitis herpetiformis
- **SCREENING FAMILY MEMBERS**

Thank You

Questions ??