Celiac Disease Update

Dominic J. Nompleggi, M.D., Ph.D.
Associate Professor of Medicine and Surgery
Chief, Division of Gastroenterology
University of Massachusetts Medical School

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

What Is Celiac Disease?

- Celiac disease is a unique autoimmune disorder triggered by gluten.
- Originally considered a rare malabsorption syndrome of childhood.
- Now recognized as a common condition that may be diagnosed at any age and that affects many organ systems.
- This presentation discusses the pathogenesis, diagnosis, and management of the disease.

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Pathogenesis

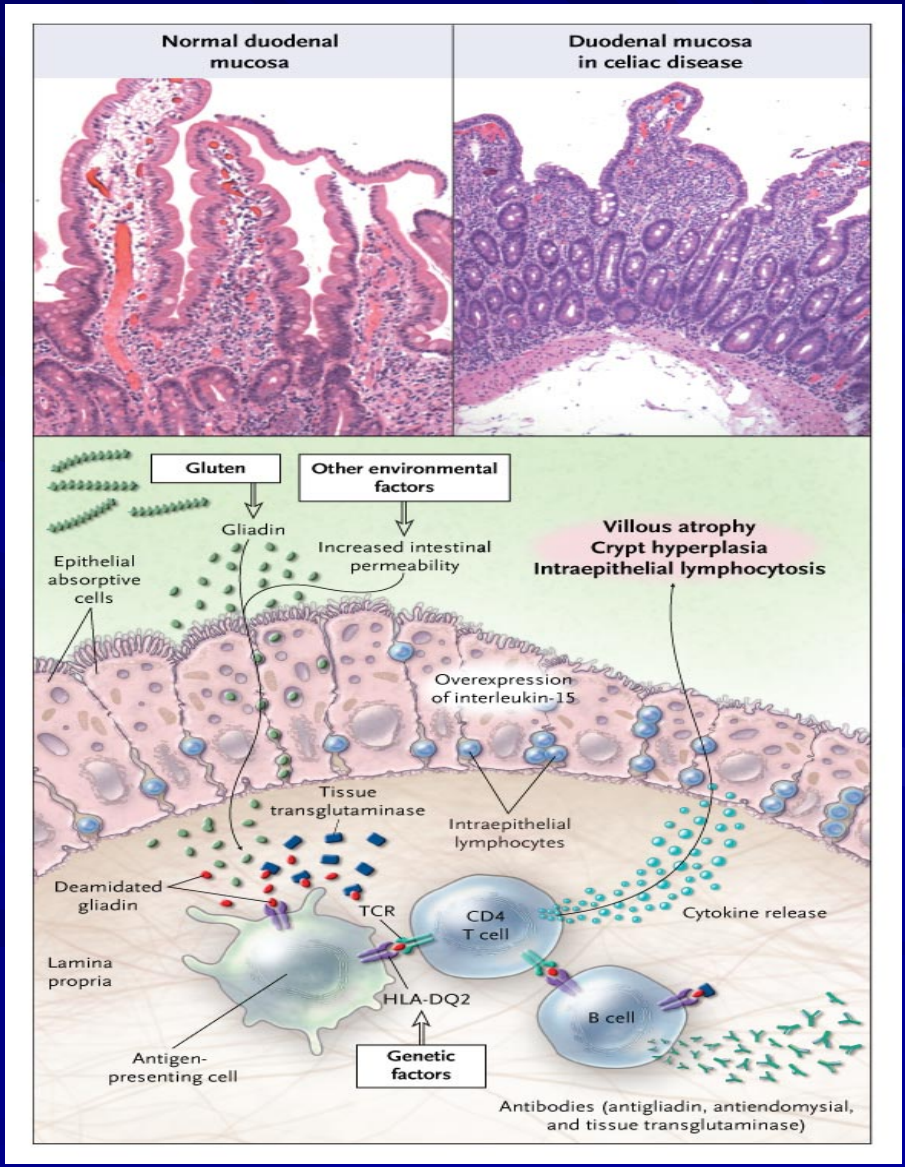
- The Role of Gluten
  - Celiac disease is induced by the ingestion of gluten-the entire protein component of wheat the gliadin fraction of gluten contains the bulk of the toxic components.
- Mucosal Immune Responses
  - Immune responses to gliadin fractions promote an inflammatory reaction primarily in the upper small intestine.
- Genetic Factors
  - Requires the alleles that encode for HLA-DQ2 or HLA-DQ8
- Environmental Factors
  - Protective effect of breast-feeding
  - Introduction of gluten < age 4

Gluten

- The gluten protein is poorly absorbed in the upper GI tract. The gliadin component is toxic.
- Gluten is derived from wheat, barley and rye.
- Gliadin fraction is resistant to degradation by gastric, pancreatic and intestinal brush-boarder proteases in the intestine.

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Interaction of Gluten with Environmental, Immune, and Genetic Factors in Celiac Disease



Genetic Factors

- Genetic background plays a key role in disposition to the disease.
- 90% of patients express the HLA-DQ2 haplotype compared to one third of the general population.
- 5% express the HLA-DQ8 haplotype
- These genes are necessary for the development of celiac disease.
- There is a 10% prevalence among first degree relatives.

Environmental Factors

- Play an important role in development of celiac disease.
- Breast feeding is protective.
- Introduction of gluten before age 4 increases the risk.
- Marginal risk after age 7 months.
- Certain infections increase the risk
  - Rotavirus

Epidemiology

- Rate in adults and children 1% of the population.
  - Regional differences 0.3% in Germany, 2.4% in Finland.
- Rates are increasing in many developing countries because of westernization of the diet.
  - China, India

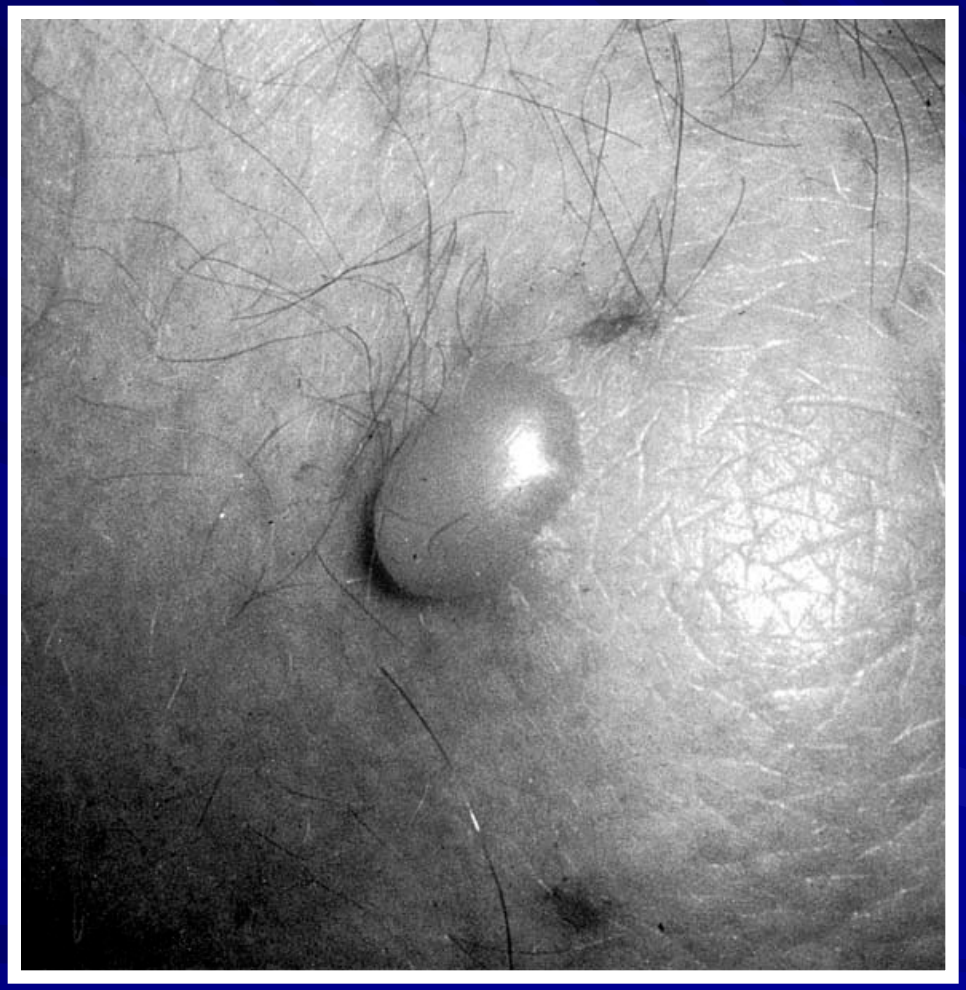
Clinical Manifestations

- Vary Greatly according to age.
  - Children-
    - Generally diarrhea, abdominal distention, failure to thrive, but constipation, vomiting, irritability and anorexia are common.
  - Older children and adolescents-
    - Extraintestinal manifestations-short stature neurologic symptoms or anemia.

Clinical Manifestations

- Adults
  - Two to three times more likely in women.
  - Autoimmune diseases more common in women.
  - Osteoporosis and iron deficiency diagnosed more often in women.
  - Female predominance decreases after age 65.
  - Historically diarrhea and abdominal pain most are the most common symptoms.
  - Dermatitis herpetiformis is rare.

Dermatitis Herpetiformis

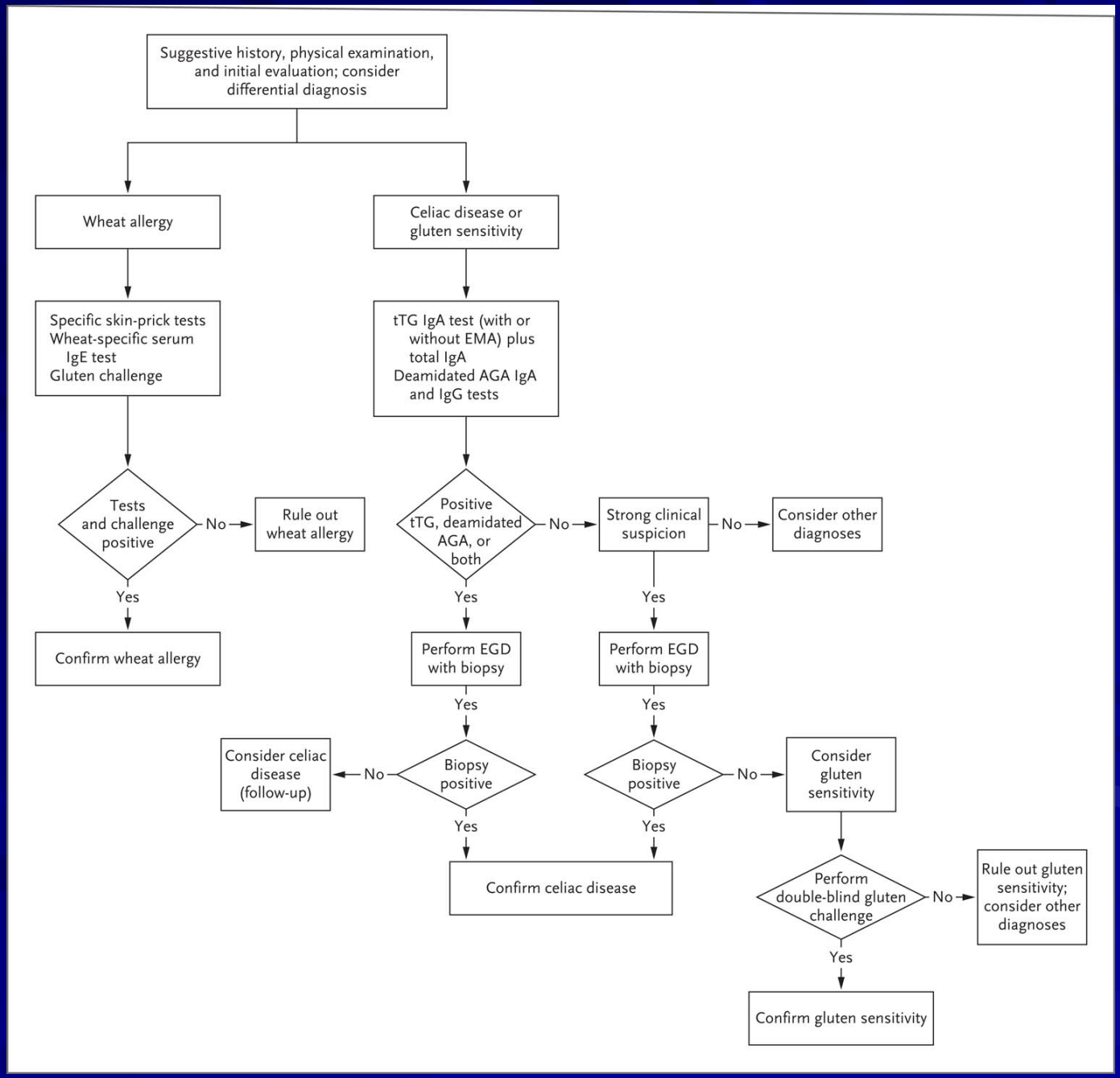


A skin blister on the elbow of a subject with dermatitis herpetiformis.

Diagnosis

- Often misdiagnosed as IBS.
- Increased surveillance among higher risk groups
  - Down Syndrome, Turner's Syndrome, Type 1 Diabetes.
  - Rate of diagnosis increased to 43% in one case study.

Differential Diagnosis of Gluten-Related Disorders



Serologic Tests

Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

Test	Sensitivity (Range)	Specificity (Range)	Comments
	percent		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test
IgG anti-tTG antibodies	Widely variable (12.6–99.3)	Widely variable (86.3–100)	Useful in patients with IgA deficiency
IgA antiendomysial antibodies	>90.0 (82.6–100)	98.2 (94.7–100)	Useful in patients with an uncertain diagnosis
IgG DGP	>90.0 (80.1–98.6)	>90.0 (86.0–96.9)	Useful in patients with IgA deficiency and young children
HLA-DQ2 or *HLA-DQ8*	91.0 (82.6–97.0)	54.0 (12.0–68.0)	High negative predictive value

* Data are from Husby et al.[28] and Giersiepen et al.[29] DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.

Fasano A, Catassi C. N Engl J Med 2012;367:2419-2426
Husby S, Kolezko S, et al. J Pediatr Gastroenetrol Nutr 2012;54:572
Giersiepen K, Leigemann M, et al. J Pediatr Gastroenetrol Nutr 2012;54:229-41

Interpretation of Antibody Tests

- The most sensitive antibody tests are the IgA class.
- Antigliadin no longer though sensitive enough to diagnose celiac disease in adults.
- The diagnostic standard is still the antiendomysial – approaches 100% accuracy but expensive.
- Tissue transglutaminase - > 90% accuracy but less expensive.

Interpretation of Antibody Tests

- Titers of endomysial and anti-tissue transglutaminase correlate with mucosal damage.
- Warning: IgA deficiency is 10 fold higher in this population – beware of false negatives.
- Check total IgA level in patients with a high clinical suspicion of disease-second line test.

Diagnosis Requirements

A duodenal biopsy showing:

- Intraepithelial lymphocytosis
- Crypt hyperplasia
- Villous atrophy

Biopsy confirmation is essential.

Positive response to a gluten free diet.

Who Should be Biopsied?

- Chronic Diarrhea of unknown etiology.
- Iron Deficiency Anemia
- Weight loss

Differential Diagnosis

Table 1. Causes of Villous Atrophy Other Than Celiac Disease.

Giardiasis
Collagenous sprue
Common-variable immunodeficiency
Autoimmune enteropathy
Radiation enteritis
Whipple's disease
Tuberculosis
Tropical sprue
Eosinophilic gastroenteritis
Human immunodeficiency virus enteropathy
Intestinal lymphoma
Zollinger–Ellison syndrome
Crohn's disease
Intolerance of foods other than gluten (e.g., milk, soy, chicken, tuna)

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Treatment of Celiac Disease

- Nutritional therapy is the only accepted treatment.
- Lifelong elimination of wheat, rye and barley.
- Oats not uniformly recommended because of contamination in growing, transportation and milling.
- Screening for osteoporosis.
- Testing and replacement of micronutrients:
  - Iron, vitamin B12, fat-soluble vitamins and calcium.

Table 2. Fundamentals of the Gluten-free Diet.

Grains that should be avoided

Wheat (includes spelt, kamut, semolina, triticale), rye, barley (including malt)

Safe grains (gluten-free)

Rice, amaranth, buckwheat, corn, millet, quinoa, sorghum, teff (an Ethiopian cereal grain), oats

Sources of gluten-free starches that can be used as flour alternatives

Cereal grains: amaranth, buckwheat, corn (polenta), millet, quinoa, sorghum, teff, rice (white, brown, wild, basmati, jasmine), montina (Indian rice grass)

Tubers: arrowroot, jicama, taro, potato, tapioca (cassava, manioc, yucca)

Legumes: chickpeas, lentils, kidney beans, navy beans, pea beans, peanuts, soybeans

Nuts: almonds, walnuts, chestnuts, hazelnuts, cashews

Seeds: sunflower, flax, pumpkin

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Response to Diet

- Clinical response within days to weeks.
- Histologic recovery can be weeks to years.
- Clinical or histologic improvement fails in –
  7 to 30%.
- The most common cause is dietary nonadherence.

Table 3. Problems of Dietary Adherence and Poor Response in Celiac Disease.

Reasons for poor adherence to a gluten-free diet
High cost
Poor availability of gluten-free products (in developing countries)
Poor palatability
Absence of symptoms when dietary restrictions not observed
Inadequate information on gluten content of food or drugs
Inadequate dietary counseling
Inadequate initial information supplied by diagnosing physician
Inadequate medical or nutritional follow-up
Lack of participation in a support group
Inaccurate information from physicians, dietitians, support groups, or Internet
Dining out of the home
Social, cultural, or peer pressures
Transition to adolescence
Inadequate medical follow-up after childhood
Causes of poorly responsive celiac disease
Incorrect diagnosis
Gluten ingestion (intentional or unintentional)
Microscopical colitis
Lactose intolerance
Pancreatic insufficiency
Bacterial overgrowth
Intolerance of foods other than gluten (e.g., fructose, milk, soy)
Inflammatory bowel disease
Irritable bowel syndrome
Anal incontinence
Collagenous sprue
Autoimmune enteropathy
Refractory celiac disease (with or without clonal T cells)
Enteropathy-associated T-cell lymphoma

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Refractory Celiac Disease

- Occurs in 5% of patients despite strict adherence to diet.
- Persistent symptoms and villous atrophy.
- Two types:

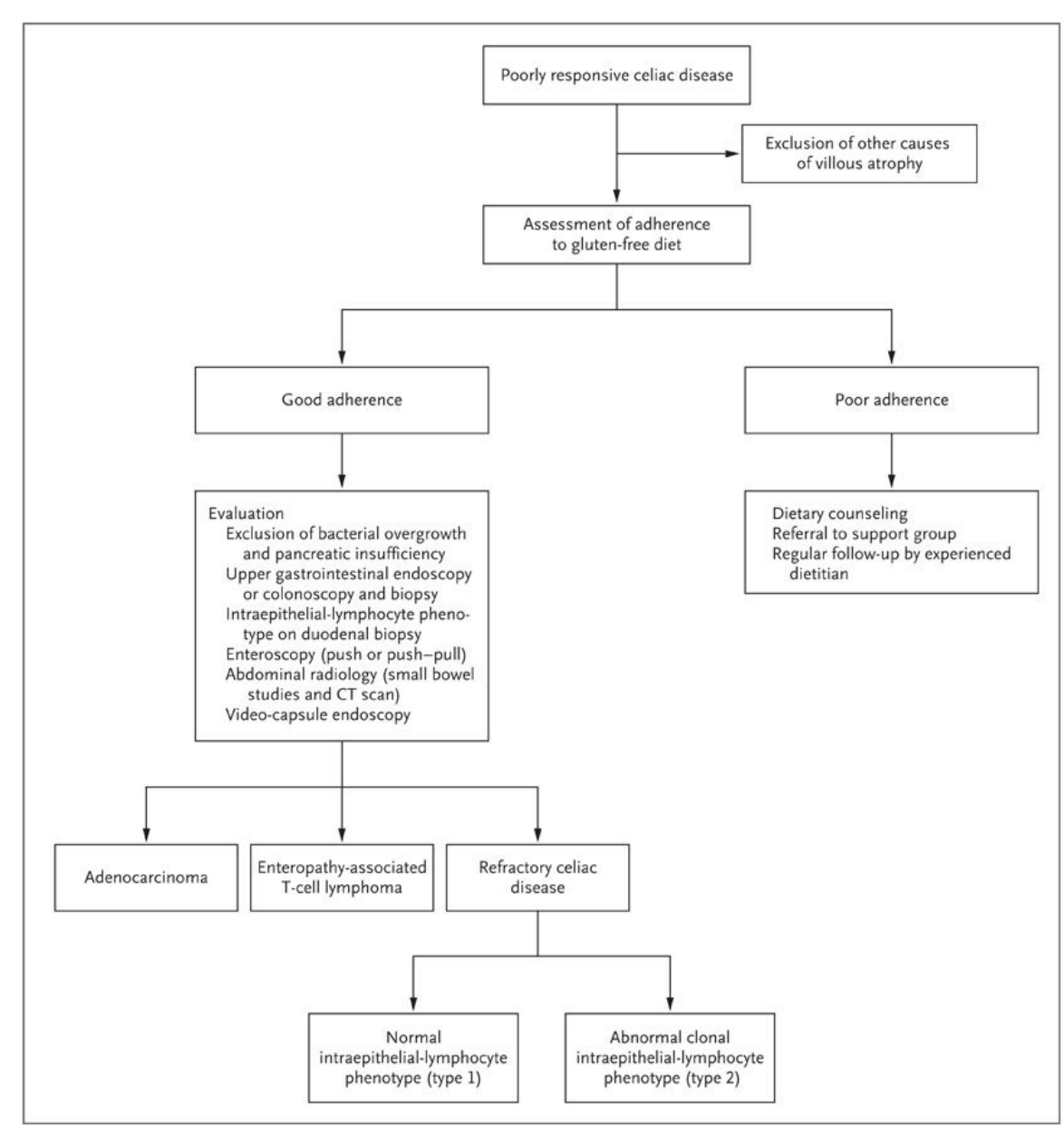
  Type 1

  Normal intraepithelial lymphocytes

  Type 2

  Clonal expansion of aberrant intraepithelial lymphocytes

Assessment Plan for patient with poorly responsive celiac disease



Treatment of Refractory Celiac Disease

Type 1

- Corticosteroids usually induce remission.
- Other immunosupressive drugs.

Type 2

- High risk for:
  - Ulcerative jejunitis
  - Enteropathy-associated T-cell lymphoma

Complications of Celiac Disease

Adenocarcinoma of the small intestine

- Twice the risk of the general population

T-cell or B-cell Lymphoma

- Intestinal or extraintestinal

Oropharyngeal, esophageal and colon Adenocarcinoma

Pancreatic and hepatobiliary cancers

Green PHR, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731-43

Gluten Sensitivity vs. Celiac Disease

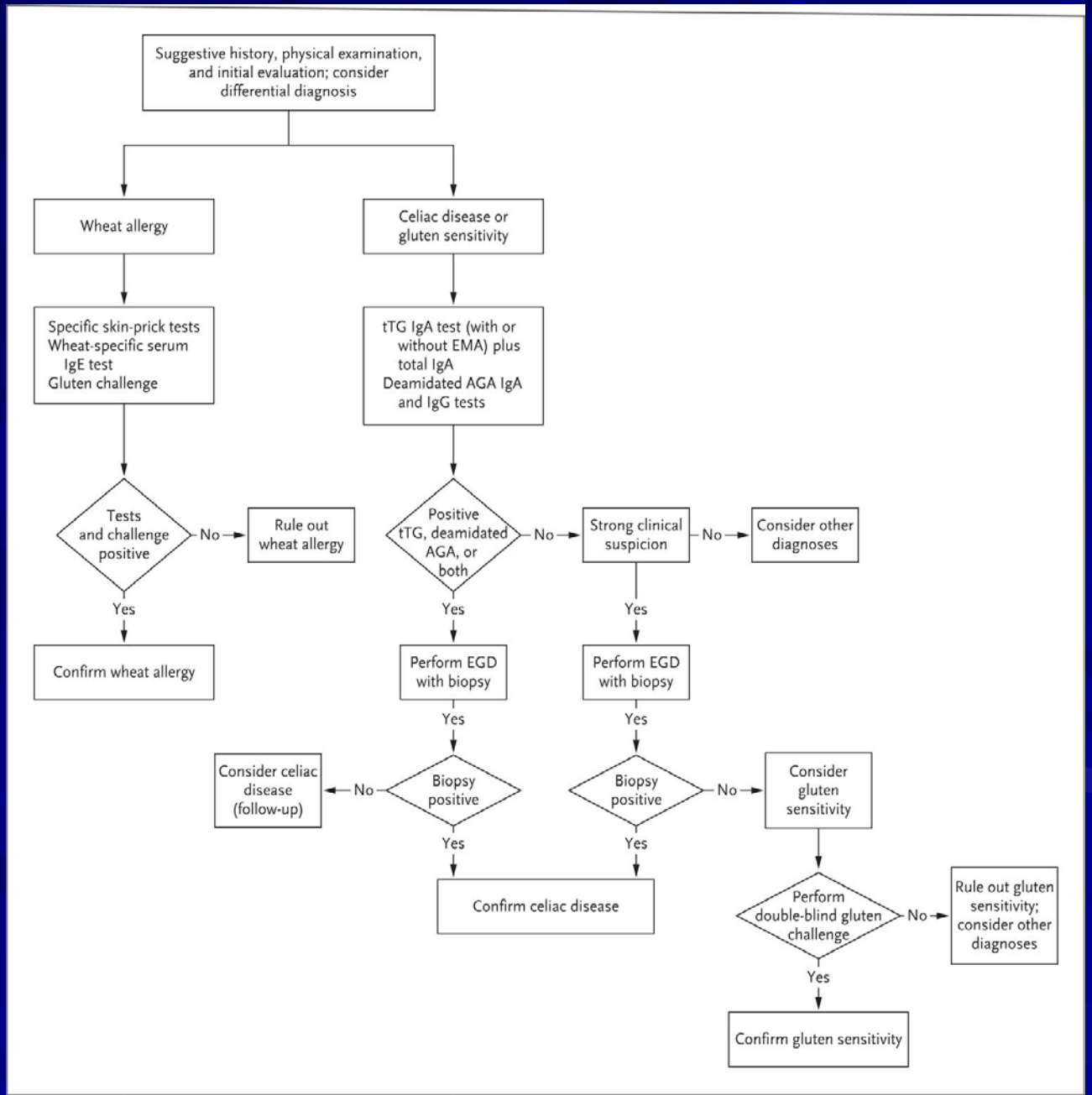
- Many people report gluten sensitivity and a response to a gluten-free diet.
- Media attention to the adverse effects of gluten on health promotes a gluten-free diet without medical supervision.
- Response to therapy alone is not diagnostic.
- Patients with wheat allergy and gluten sensitivity may benefit.

Fasano A, Catassi C. **Celiac Disease. N Engl J Med 2012;367:2429-26.**

Table 2. Clinical and Pathogenic Differences among Celiac Disease, Gluten Sensitivity, and Wheat Allergy.

Variable	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Interval between exposure to gluten and onset of symptoms	Weeks to years	Hours to days	Minutes to hours
Pathogenesis	Autoimmunity (innate and adaptive immunity)	Possibly innate immunity	Allergic immune response
HLA	Restricted to *HLA-DQ2* or *HLA-DQ8* (in approximately 97% of positive cases)	Not restricted to *HLA-DQ2* or *HLA-DQ8* (*HLA-DQ2*–positive, *HLA-DQ8*–positive, or both in 50% of patients)	Not restricted to *HLA-DQ2* or *HLA-DQ8* (*HLA-DQ2*–positive, *HLA-DQ8*–positive, or both in 35–40% of patients, similar to the general population)
Autoantibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in the intraepithelial lymphocyte count)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of gluten sensitivity and wheat allergy	Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of celiac disease and wheat allergy	Both intestinal and extraintestinal; gastrointestinal symptoms gastrointestinal symptoms not distinguishable from those of celiac disease and gluten sensitivity symptoms
Complications	Coexisting conditions; long-term complications	Absence of coexisting conditions and long-term complications	Absence of coexisting conditions; short-term complications (including anaphylaxis)

Gluten-Related Disorders



Summary of Celiac Disease

- Once considered a GI disorder of children
- Now known to affect different ages, races and ethnic groups.
- IgA anti-tissue transglutaminase is the preferred initial screening test
- Diagnosis confirmed by duodenal biopsy
- Cornerstone of treatment is a gluten-free diet
- Gluten sensitivity may occur in the absence of celiac disease.