# All Things Gluten:
## Evaluation and Management of Celiac Disease and Non-Celiac Gluten Sensitivity

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## Disclosure

Consultant: AbbVie; Amgen

Speaker's Bureau: AbbVie; Pfizer; Takeda

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## Outline

- Small intestine function
- Gluten-related disorders
- Non-gluten-related disorders


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## Guidelines / Clinical Updates

Gastroenterology 2019;156:885–889

**AGA CLINICAL PRACTICE UPDATE**

**AGA Clinical Practice Update on Diagnosis and Monitoring of Celiac Disease—Changing Utility of Serology and Histologic Measures: Expert Review**

Steffen Husby,[1] Joseph A. Murray,[2] and David A. Katzka[2]

[1]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; and [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

656 PRACTICE GUIDELINES nature publishing group

CME

ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease

Alberto Rubio-Tapia, MD[1], Ivor D. Hill, MD[2], Ciarán P. Kelly, MD[3], Audrey H. Calderwood, MD[4] and Joseph A. Murray, MD[1]

Guidelines

OPEN ACCESS

Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology

Jonas F Ludvigsson,[1,2] Julio C Bai,[3] Federico Biagi,[4] Timothy R Card,[5] Carolina Ciacci,[6] Paul J Ciclitira,[7] Peter H R Green,[8] Marios Hadjivassiliou,[9] Anne Holdoway,[10] David A van Heel,[11] Katri Kaukinen,[12,13,14] Daniel A Leffler,[15] Jonathan N Leonard,[16] Knut E A Lundin,[17] Norma McGough,[18] Mike Davidson,[19] Joseph A Murray,[20] Gillian L Swift,[21] Marjorie M Walker,[22] Fabiana Zingone,[23] David S Sanders,[24] Authors of the BSG Coeliac Disease Guidelines Development Group

Gastroenterology 2021;160:437–444

**CLINICAL PRACTICE UPDATES**

**AGA Clinical Practice Update on the Evaluation and Management of Seronegative Enteropathies: Expert Review**

Maureen M. Leonard,[1,2] Benjamin Lebwohl,[3] Alberto Rubio-Tapia,[4] and Federico Biagi[5]

[1]Center for Celiac Research and Treatment, Division of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts; [3]Celiac Disease Center, Columbia University Irving Medical Center, New York, New York; [4]Division of Gastroenterology, Hepatology, and Nutrition, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio; and [5]Clinical Scientific Institutes Maugeri Scientific Institute for Research, Hospitalization and Healthcare, Gastroenterology Unit of Pavia Institute, University of Pavia, Italy

Gastroenterol 2019; 156:885-889
Am J Gastroenterol 2013; 108:656-676
Gut 2014; 63:1210-28
Gastroenterol 2021; 160:437-444

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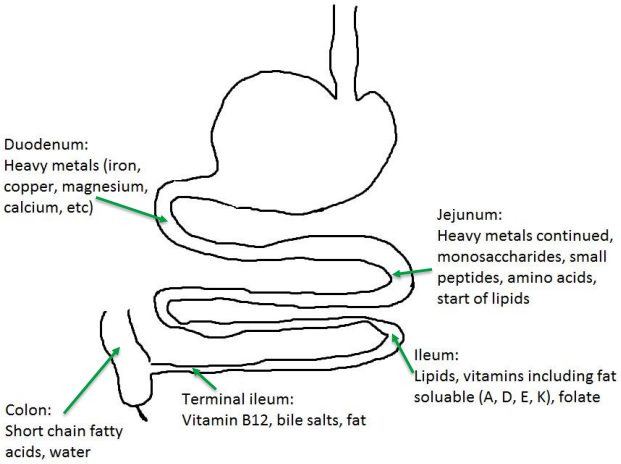
## Small Intestine- Absorption Overview

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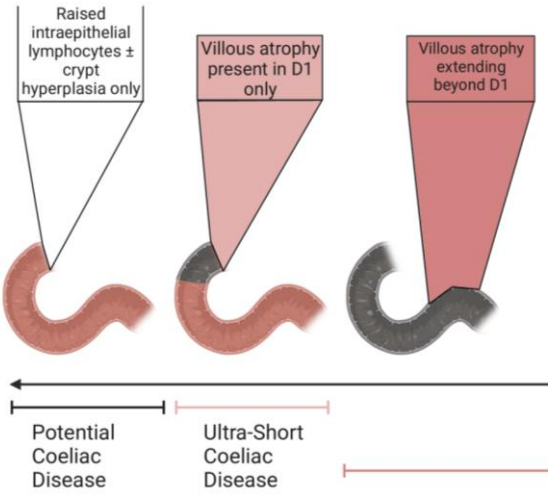
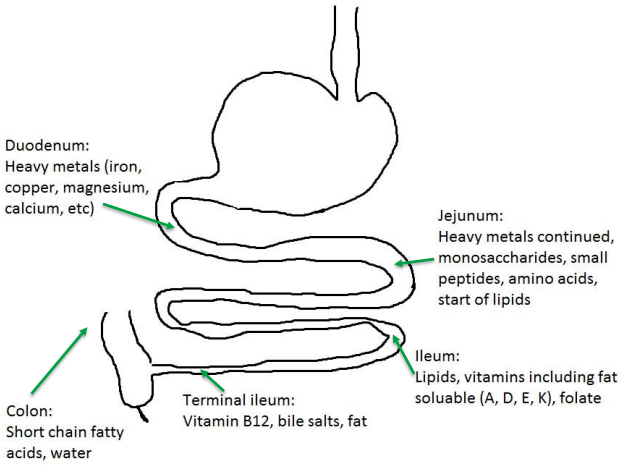
## Small Intestine- Absorption Overview

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Raju SA et al. Gut 2024;73:1124-1130

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# Celiac Disease

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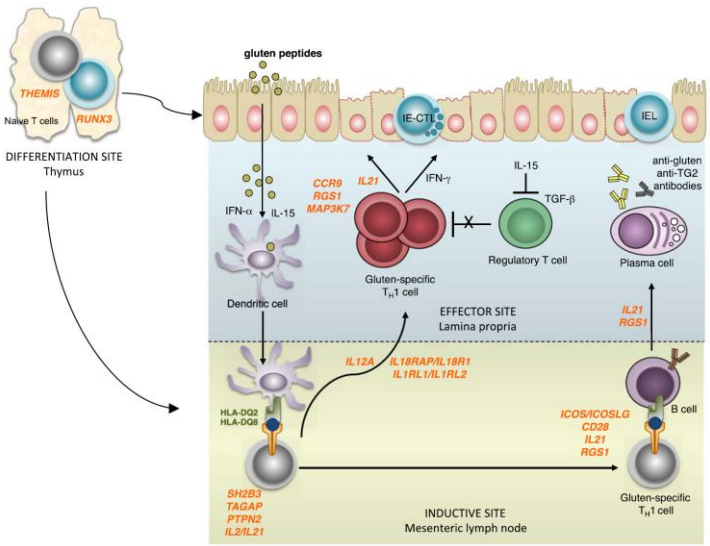
## Celiac Disease

- Inappropriate immune reaction
- Triggered by gluten exposure
- Genetic predisposition
- Small bowel inflammation (enteropathy)
- Wide variety of clinical symptoms
- ~1-2% prevalence




Bouziat et al. *Science*. 2017:44-50
Jabri and Sollid. J Immunol. 2017:3005-3014
Uche-Anya and Lebwohl. Curr Opin Gastroenterol. 2021:619-624

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## What Is Gluten?

- Found in wheat, rye, barley
- Protein (Latin- glue)
- Provides a flexible quality to baked goods

- Typically, well tolerated unless…
  - Allergy
  - Immune-mediated disease (celiac)
  - Non-celiac gluten sensitivity

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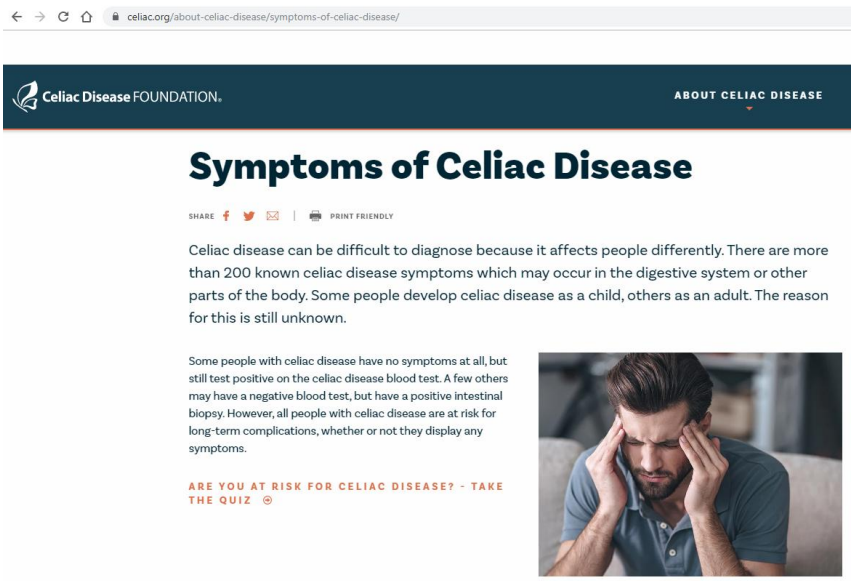
## When to Suspect Celiac?

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https://celiac.org/about-celiac-disease/symptoms-of-celiac-disease/ (accessed 1/27/2020)

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## When to Suspect Celiac?

- Common associated conditions
  - Gas/bloat
  - Diarrhea
  - "IBS"
  - Unexplained recurrent pancreatitis
  - Elevated liver transaminases
  - Oral aphthous ulcers
  - Weight loss
  - Growth failure
  - Iron deficiency anemia
  - Premature weight loss
  - Peripheral neuropathy
  - Thyroid disease
  - Down Syndrome
  - Turner Syndrome
- Less common associated conditions
  - Dyspepsia
  - Constipation
  - Abdominal pain
  - Infertility (both male/female)
  - Amenorrhea
  - Pulmonary hemosiderosis
  - Malabsorption of thyroid medication
  - Chronic fatigue
  - Epilepsy
  - Ataxia
  - Chronic arthralgia
  - "Brain fog"
  - Recurrent headache/migraine

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*Am J Gastroenterol* 2023; 118:5876

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## Dermatitis Herpetiformis

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https://celiac.org/about-celiac-disease/related-conditions/dermatitis-herpetiformis/ (accessed 12/30/2020)

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## Celiac Disease: Diagnosis

Histopathology*

Response to gluten-free diet

Serologic Markers*

HLA type

*On a gluten-containing diet

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Gastroenterol 2019; 156:885-889

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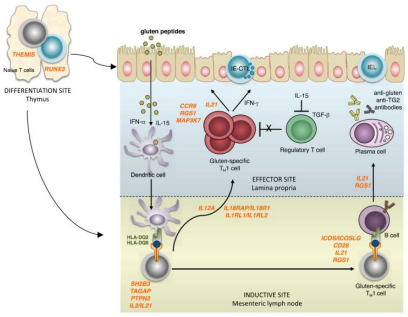
## Celiac Disease: Diagnosis




- Tissue Transglutaminase-2 (TTG) IgA
- Tissue Transglutaminase-2 (TTG) IgG
- Deamidated gliadin peptides (DGP) IgA
- Deamidated gliadin peptides(DGP) IgG
- Endomysial (EMA) IgA

Serologic Markers*

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## Celiac Disease: Antibodies

| | Sensitivity* | Specificity* |
|---|---|---|
| Tissue Transglutaminase (TTG) IgA | 95-100% | 95-100% |
| Tissue Transglutaminase (TTG) IgG | 60% | 98% |
| Deamidated gliadin peptide (DGP) IgA | 94% | 92% |
| Deamidated gliadin peptide (DGP) IgG | 92% | 100% |
| Endomysial IgA (EMA) | 85% | 97-100% |

* These numbers are all over the place in the literature

- False positives:
  - "idiopathic"
  - Elevated total serologic IgA or IgG
  - Other autoimmune diseases
  - Congestive heart failure
  - Chronic liver disease

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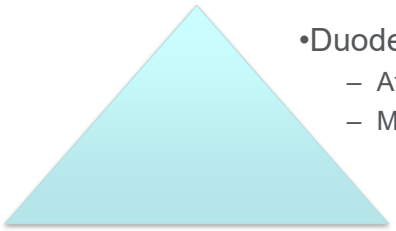
## Celiac Disease: Diagnosis

Histopathology*



- Duodenal Biopsies
  - At least 6 "bites" including two from bulb
  - Marsh Classification

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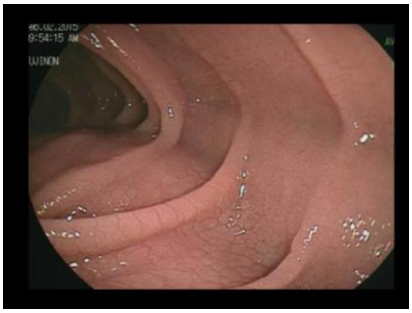
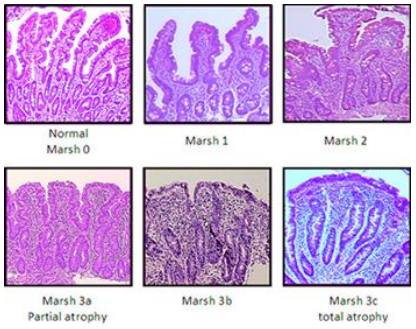
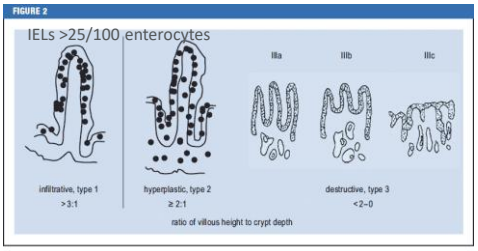
# Celiac Disease

- Duodenal Biopsies
  - At least 6 "bites" including bulb
  - Marsh Classification






**The mucosal lesions of celiac disease** (Marsh–Oberhuber classification): the histologic changes of the intestinal mucosa consist of lymphocytic proliferation in the epithelium and the lamina propria, crypt hyperplasia, and lower height of the villi. A type 2 or type 3 lesion is required for the diagnosis of celiac disease. Modified from (e16)

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Shuppan et al. *Dtsch Arztebl Int* 2013
https://www.massgeneral.org/children/news/newsarticle.aspx?id=4136 (accessed 7/29/19)

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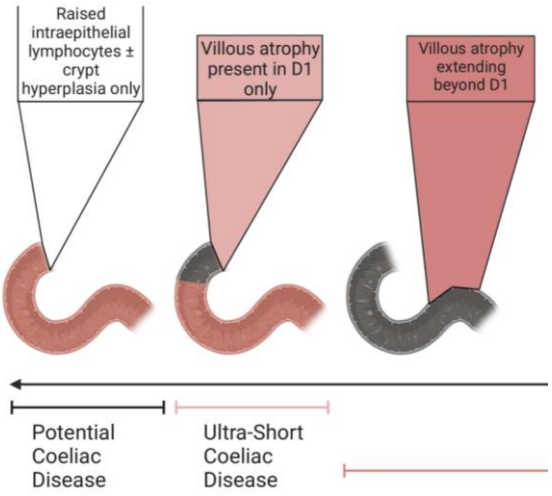
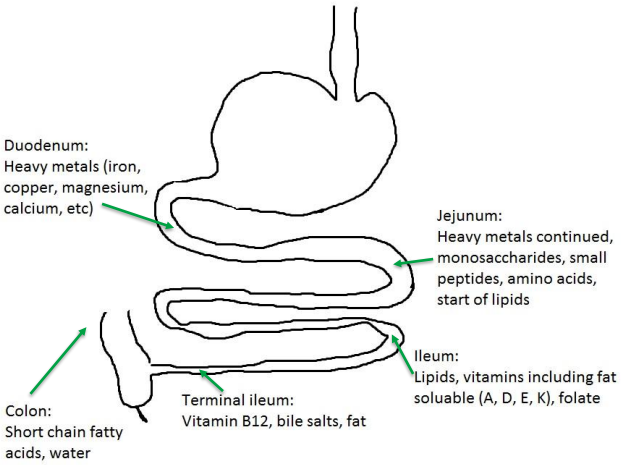
# Small Intestine- Absorption Overview

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Raju SA et al. Gut 2024;73:1124-1130

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## Similar Histology to Celiac Disease

- Medications (ARBs, NSAIDs, mycophenolate)
- Infection
  - Viral
  - Tropical sprue
  - Giardia
  - Whipple disease
  - Tuberculosis
  - HIV-related enteropathy
- Bacterial overgrowth
- Malnutrition in general
- Crohn's disease / Sarcoidosis
- Graft-vs-host disease
- Radiation enteritis
- Common variable immune deficiency (CVID)
- Peptic damage
- Eosinophilic gastroenteritis
- Autoimmune enteropathy
- Lymphoma

Am J Gastroenterol 2013; 108:656-676
Gastroenterol 2019; 156:885-889
Gastroenterol 2021; 160:437-444

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## Are Biopsies Necessary for All?

- European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Guideline
  - No biopsies needed if:
    - TTGA ≥ 10x upper limit of normal (ULN)
    - Positive EMA
- Meta-analysis in adults
  - Sensitivity 51% (95% CI, 42%–60%)
  - Specificity 100% (95% CI, 98%–100%)

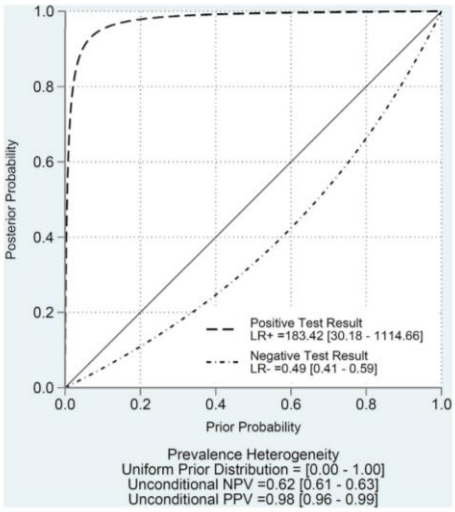


**Figure 4.** Probability modifying plot showing the unconditional PPV and NPV of IgA-tTG ≥10×ULN to identify patients with celiac disease. LR, likelihood ratio.

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Shiha MG et al. Gastroenterol. 2024;166:620-630
Husby S et al. J Pediatr Gastroenterol Nut. 2020;70:141-156

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## Celiac Disease: Diagnosis

- HLA-DQ2 or HLA-DQ8
- Very high negative predictive value
  - Testing on a gluten-free diet
  - Evaluating first degree family
  - Diagnostic challenges
- Not necessary to "secure" diagnosis



HLA type

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## Celiac Disease: Treatment

# Gluten-free Diet

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## Celiac Disease: Diagnosis

- Only effective treatment
- Monitor for:
  - Symptomatic response
  - Serologic improvement
  - Histologic response (conditional)


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Gastroenterol 2019; 156:885-889

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## Celiac Disease: Review of Diagnosis


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## CLINICAL PEARL

## BEFORE TESTING: VERIFY GLUTEN IN DIET

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## CLINICAL PEARL

## CELIAC DISEASE = DIETITIAN REFERRAL

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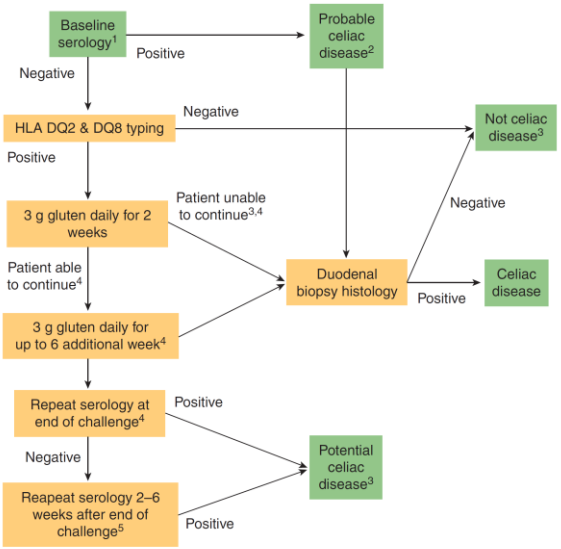
## Approach to Diagnosis - Celiac Disease (Gluten Free)

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Rubio-Tapia et al. *Am J Gastroenterol* 2013

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## Approach to Diagnosis - Celiac Disease (Gluten Free)- WBAIL-2


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Moscatelli et al. *Gastroenterol* 2025
https://celiac.org/2025/06/16/a-game-changer-for-celiac-diagnosis-il-2-blood-test-may-eliminate-the-need-for-gluten-challenges/ (accessed November 2, 2025)

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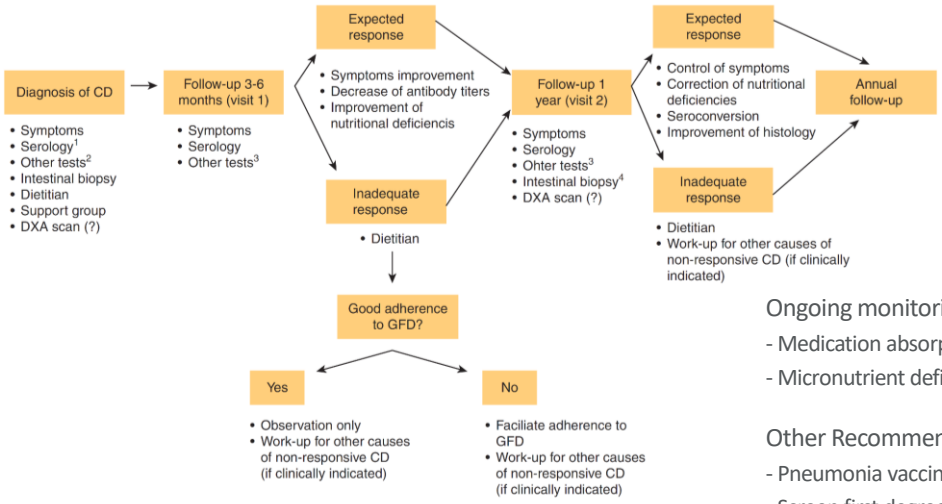
# Celiac Disease: Follow Up




Ongoing monitoring for:

- Medication absorption
- Micronutrient deficiencies (iron, b12, zinc, etc)

Other Recommendations:

- Pneumonia vaccine (hyposplenism)
- Screen first degree family members

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Am J Gastroenterol 2013; 108:656-676

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# Refractory Celiac Disease

- 12+ months of persistent/recurrent villous atrophy on a strict gluten free diet
- Prevalence 1-2%
- Type 1
  - Mucosal lymphocytes are identical (clonal) to Celiac disease
  - Treatment- steroids/azathioprine, ?mesalamine, symptom control, nutritional interventions
- Type 2
  - Mucosal lymphocytes are abnormal (premalignant→T-cell lymphoma)
    - CD3 T-cells lack CD8 expression
    - Oligoclonal T-cell expansion (lack of diversity)
  - Same therapy, less likely to work, usually need TPN
  - Poor prognosis

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Rubio-Tapla et al. Am J Gastroenterol 2013

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# Case Study/Question

22yo college senior on winter break tells his parents his semester did not go well. He notes trouble concentrating, decreased energy, and bloating when he drinks beer (which he does nightly). His sister was recently diagnosed with celiac disease and says she has similar symptoms when Talla exposed to gluten. Initial labs are notable for a hemoglobin 10.2 (normal 12.5-16) and MCV 78 (normal 80-99).



# What Is the Next Step?

A. Try a gluten-free diet for 6 weeks
B. Labs for celiac disease serologic markers
C. Upper endoscopy for duodenal biopsies
D. Colonoscopy to assess for inflammatory bowel disease
E. “Tough it out”

## Non-celiac Gluten Sensitivity

- No objective evidence of celiac disease
- Symptomatic response to gluten free diet
- Pathophysiology not well established
- Could be due to other foods beyond gluten
  - FODMAPs
  - Fiber
- Could be "IBS"

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Am J Gastroenterol 2013; 108:656-676
Am J Gastroenterol 2018; 113:421-430

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# Enteropathy ("Seronegative Enteropathy")

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CLINICAL PRACTICE UPDATES

# AGA Clinical Practice Update on the Evaluation and Management of Seronegative Enteropathies: Expert Review

Maureen M. Leonard,[1,2] Benjamin Lebwohl,[3] Alberto Rubio-Tapia,[4] and Federico Biagi[5]

[1]Center for Celiac Research and Treatment, Division of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts; [3]Celiac Disease Center, Columbia University Irving Medical Center, New York, New York; [4]Division of Gastroenterology, Hepatology, and Nutrition, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio; and [5]Clinical Scientific Institutes Maugeri Scientific Institute for Research, Hospitalization and Healthcare, Gastroenterology Unit of Pavia Institute, University of Pavia, Italy

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## Seronegative Enteropathy: Definition

- Some degree of villous atrophy (small bowel)
- Negative celiac serologies
  - Make sure to get both IgA/IgG serologic markers
- +/- Negative anti-endomesial antibody

- Could this still be celiac disease?
  - Seronegative celiac disease
    - Normal serologies with histologic improvement on gluten-free diet
  - IgA deficiency associated with celiac disease
    - With elevated IgG celiac serologies

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## Example #1

- 48yo with bloating and diarrhea
  - Stool tests for infection/inflammation all normal
  - EGD with villous blunting but no increased IELs
  - Colonoscopy normal
  - Celiac serologies (done after EGD) all normal, normal IgA
- Gluten-free diet initiated, no improvement in symptoms
- Frequently vacations in the Caribbean
  - Gluten resumed
  - Symptoms improved with 3 months of:
    - high dose folic acid (5 mg/day)
    - doxycycline 100 mg BID

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## Tropical Sprue

- Enteropathy/malabsorption likely from a water-borne infection
- More prevalent in waters around:
  - Caribbean: Dominican Republic, Haiti, Cuba, Puerto Rico
  - Arabian Sea / Gulf of Oman / Day of Bengal: India, Pakistan
- Need > 1 month exposure
- Diagnosis: exclusion (rule out other infectious agents, celiac, etc)
- Enteropathy can be seen throughout small bowel
- Treatment 3-6 months of:
  - Folic acid 5 mg/day
  - Tetracycline 250 mg QID or doxycycline 100 mg BID

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Gastroenterol 2021; 160:437-444
Am J Gastroenterol 2020; 115:492-497

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## Example #2

- 68yo with bloating, diarrhea, and weight loss
  - Stool tests for infection/inflammation all normal
  - EGD with villous blunting and increased IELs
  - Colonoscopy normal
  - Celiac serologies (done after EGD) all normal, normal IgA
- Gluten-free diet initiated, no improvement in symptoms
- Positive anti-enterocyte antibody
  - Gluten resumed
  - Symptoms improved within 2 weeks of:
    - Budesonide 9 mg (one opened/crushed, one opened, and one whole)

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## Autoimmune Enteropathy

- Immune-mediated damage to the small bowel
- Presents with: diarrhea/malnutrition
- Diagnosis:
  - Biopsies with few increased IELs, decreased goblet cells
  - Positive anti-enterocyte antibody (can be negative)
- Treatment:
  - Immunosuppression- steroids/immunomodulators, ?anti-TNF

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Am J Gastroenterol 2020; 115:492-497

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## Example #3

- 29yo with diarrhea and weight loss, recent diagnosis of CVID (Common Variable Immune Deficiency)
  - Stool tests for infection/inflammation all normal
  - EGD with "mild" villous blunting without increased IELs
  - Colonoscopy normal
  - Celiac serologies (done after EGD) all normal, noted low total IgA/IgG
- Gluten-free diet initiated, no improvement in symptoms
- Review of pathology shows no plasma cells
  - Gluten resumed
  - Symptoms improved within 2 weeks of:
    - Budesonide 9 mg (one opened/crushed, one opened, and one whole)

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## CVID-Related Enteropathy

- Common Variable Immune Deficiency (CVID)
- Etiology unclear
- Presents with: diarrhea/malnutrition
- Diagnosis:
  - Exclude GI infections
  - Biopsies with paucity of plasma cells
  - Low Ig levels (IgG AND either IgA or IgM)
- Treatment:
  - Steroids
  - IVIg unlikely to help with GI symptoms

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## Enteropathy Differential

- Medications (ARBs, NSAIDs, mycophenolate)
- Infection
  - Viral
  - Tropical sprue
  - Giardia
  - Whipple disease
  - Tuberculosis
  - HIV-related enteropathy
- Bacterial overgrowth
- Malnutrition in general
- Crohn's disease / Sarcoidosis
- Graft-vs-host disease
- Radiation enteritis
- Common variable immune deficiency (CVID)
- Peptic damage
- Eosinophilic gastroenteritis
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- Lymphoma

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## Pearls

- Celiac disease
  - *Essential* to know gluten exposure before testing
  - Multi-disciplinary approach: refer to a dietitian (knowledgeable about celiac)
  - Continue to follow up at least annually including serologies
- Non-celiac gluten sensitivity is real but not well understood
- Other diseases can look like celiac, but aren't celiac (and are treated differently)

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