Celiac Disease
Updates for primary care providers

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Disclosures

I have no disclosures.

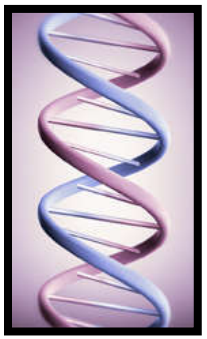
Objectives

1. Recognize typical and atypical presentations of celiac disease.
2. Name 5 non-gastrointestinal manifestations.
3. Know what tests to order based on age.
4. Identify hidden sources of gluten to avoid.
5. Be able to direct patients to appropriate resources.

Definition

- Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.

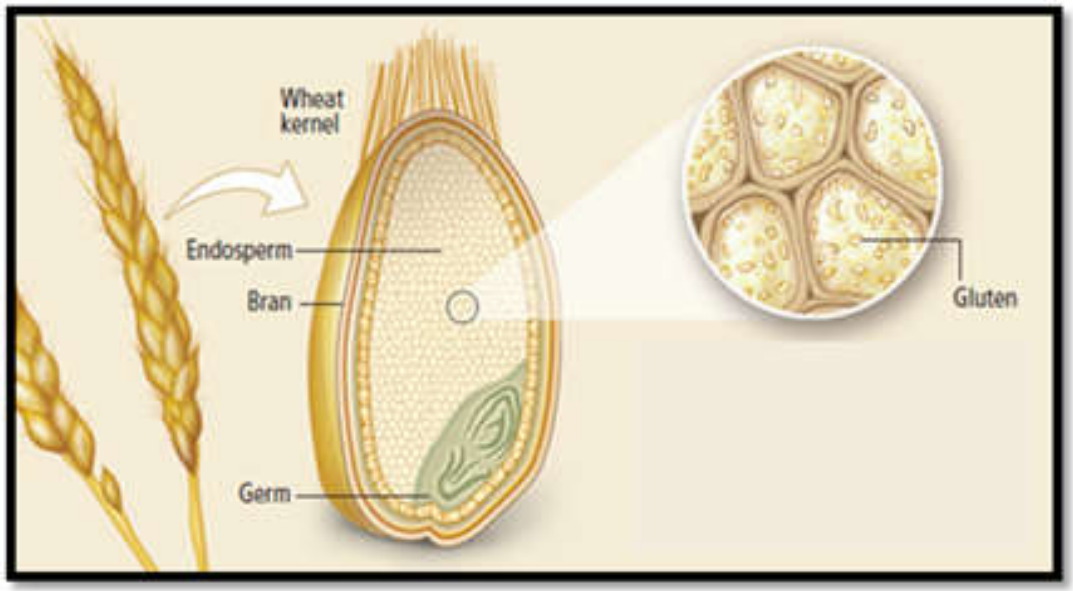
- It occurs in symptomatic patients with gastrointestinal and non-gastrointestinal symptoms, and in some asymptomatic individuals.



Definition

"Does gluten even exist?"

Gluten is a group of proteins which occur with starch in the endosperm of various cereal grains.

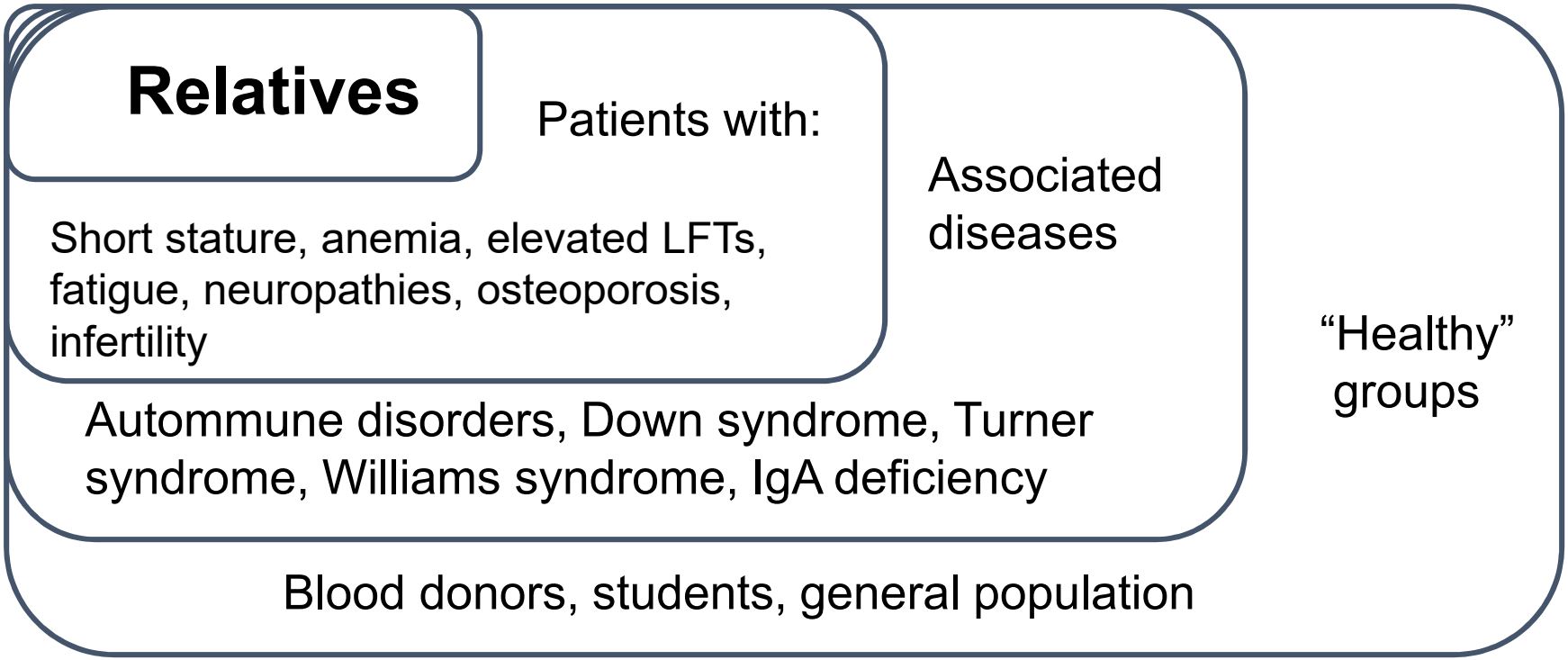


Epidemiology

The Changing Celiac Epidemiology

The availability of sensitive serological markers made it possible to discover Celiac Disease even when the clinical suspicion was low.

"Mines" of Celiac Disease Were Found Among:



Celiac Disease

- Higher incidence in certain populations:

  - **Type 1 diabetes**
  - **Down syndrome**
  - **Turner syndrome**
  - **Williams syndrome**
  - **Selective IgA deficiency**
  - **First degree relatives of individuals with celiac disease**

CD in Genetic Disorders

- Down Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8%
- IgA Deficiency: 7%
  - Can complicate serologic screening

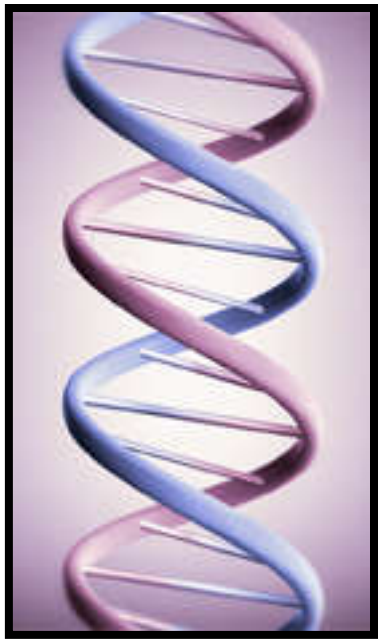
Prevalence in USA

- Healthy population: 1:133
- 1st degree relatives: 1:20
- 2nd degree relatives: 1:24 to 1:39

Fasano, et al, *Arch of Intern Med*, Volume 163: 286-292, 2003

Pathogenesis

Pathogenesis

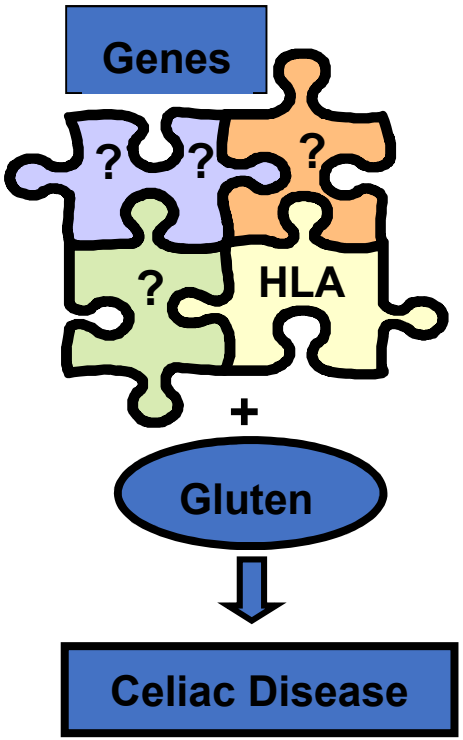


- Genetic predisposition
- Environmental triggers
  - Dietary
  - Non-dietary?

Genetics

- The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and/or DQ8) genes
  - 90-95% of CD patients have **HLA-DQ2**
  - ~5% are **HLA-DQ8**
- Other genes (not yet identified) account for 60% of the inherited component of the disease
- HLA-DQ2 and/or DQ8 genes are necessary **(No DQ2/8, no Celiac Disease!)** but not sufficient for the development of the disease

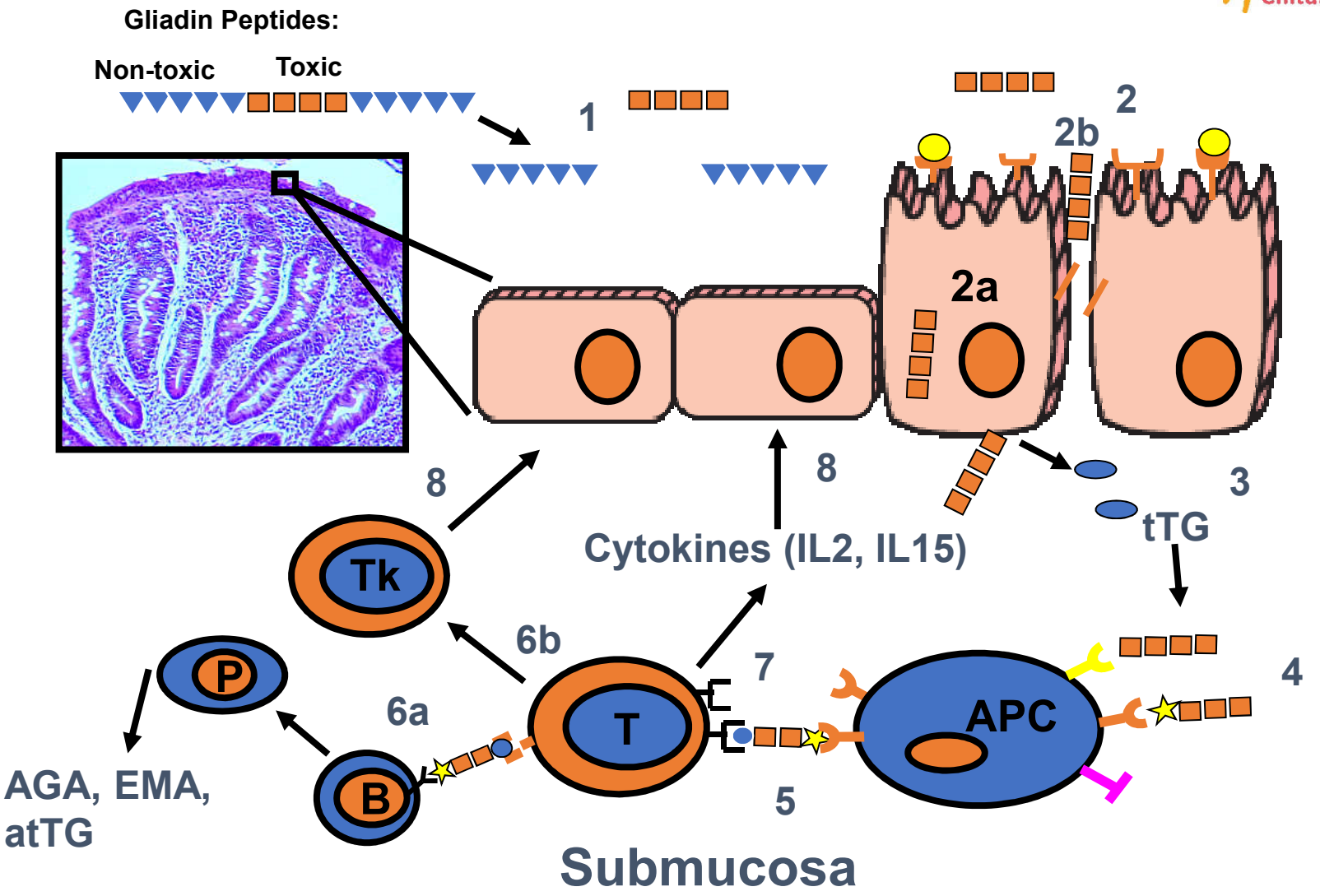
(30-40% of the Caucasian population have the HLA-DQ2 haplotype but only 1% develops CD)



Genetics

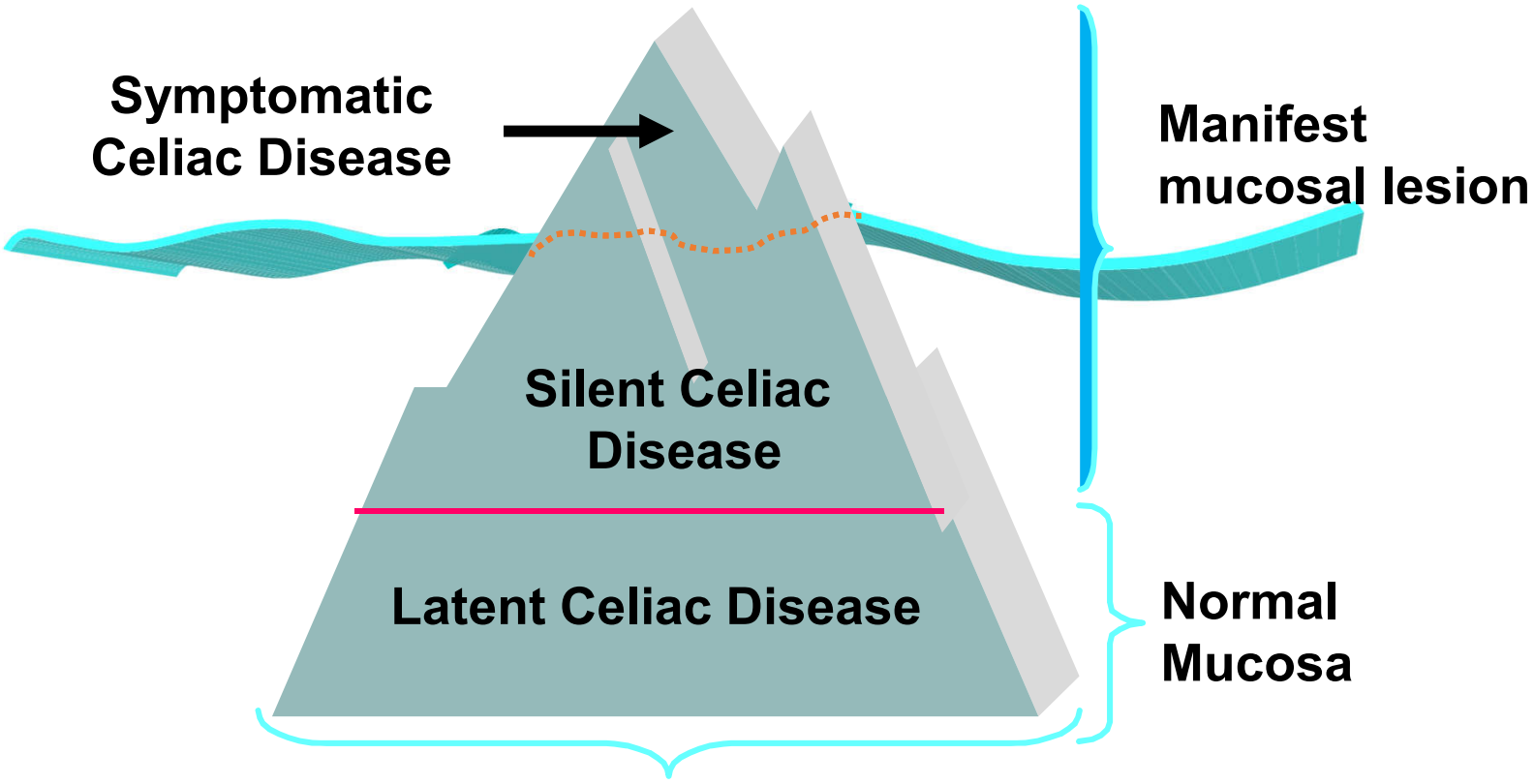
- Concordance in monozygotic twins is 70%
- Concordance in HLA-identical siblings is 30-40%, suggesting other genes involved
- 10% of patients with celiac disease have an affected first degree relative

Intestinal Lumen



Clinical Manifestations

The Celiac Iceberg



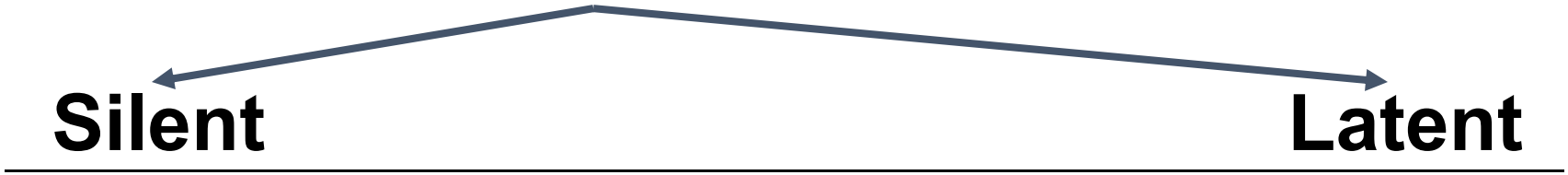
Genetic susceptibility: DQ2, DQ8
Positive serology

Asymptomatic CD

Silent:

- Minimal or no symptoms
- "Damaged" mucosa
- Positive serology
- Usually identified by screening asymptomatic individuals from groups at risk such as:
  - First degree relatives
  - Down syndrome patients
  - Type 1 diabetes patients

Asymptomatic CD



Latent:

- No symptoms
- Normal mucosa
- Usually identified by following asymptomatic individuals after detecting positive serology
- Under the "right" circumstances, develop mucosal changes (± symptoms)

Asymptomatic CD

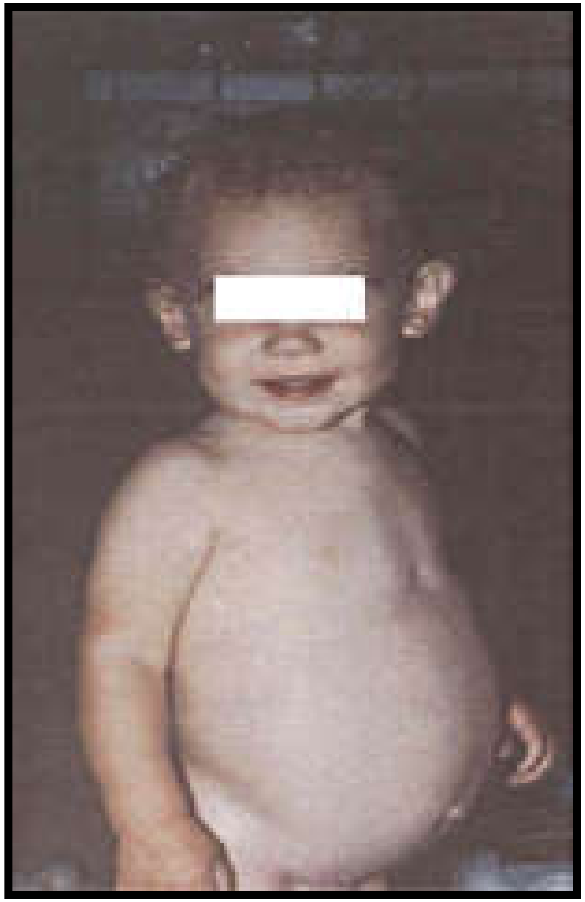
- Silent celiac disease should be treated
- Latent celiac disease can be followed without a gluten-free diet (GFD)
  - Treatment with a GFD can be considered in latent celiac disease, particularly in the presence of other risk factors, such as:
    - Type 1 diabetes
    - Down syndrome
    - Turner syndrome
    - Williams syndrome
    - Selective IgA deficiency
    - Autoimmune thyroiditis
    - First degree relative with celiac disease

Gastrointestinal Manifestations ("Classic")

- Abdominal distension
- Abdominal pain
- Chronic or recurrent diarrhea
- Anorexia
- Vomiting
- Failure to thrive or weight loss
- Irritability

Rarely: Celiac crisis

"Classic" Celiac Disease



Non-GI Manifestations

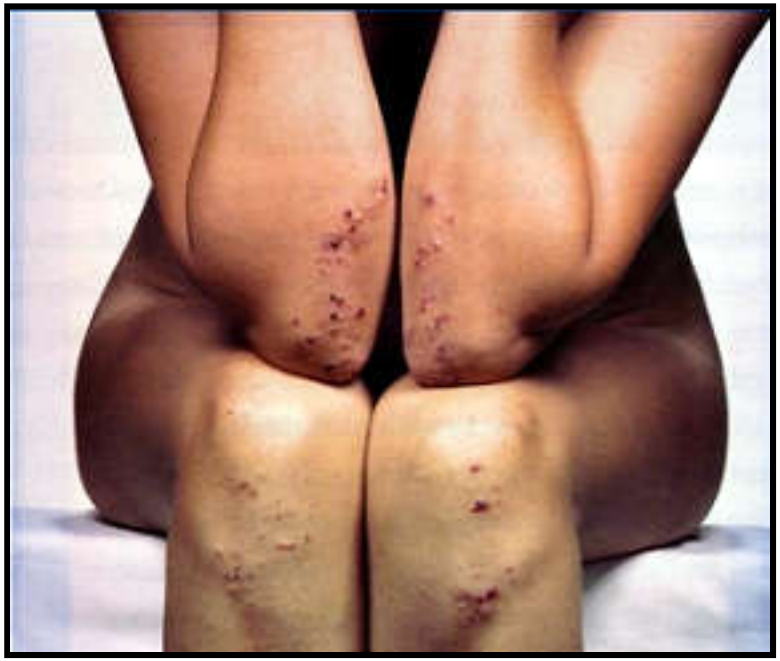
- Seen more commonly in older child to adult

- Dermatitis herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short stature
- Delayed puberty

- Iron-deficiency anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

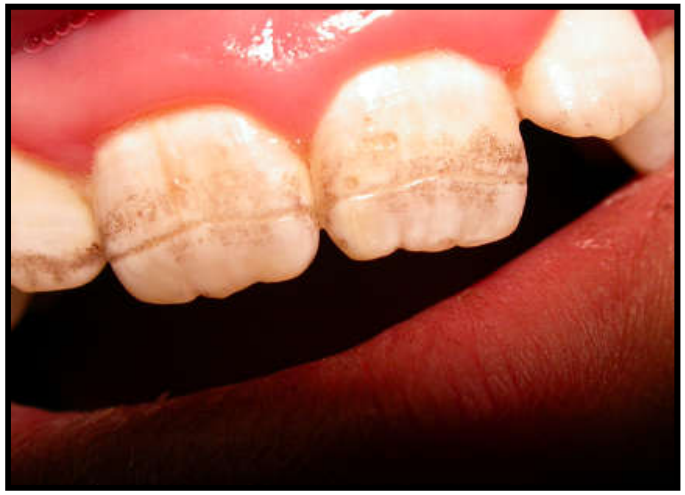
Dermatitis Herpetiformis

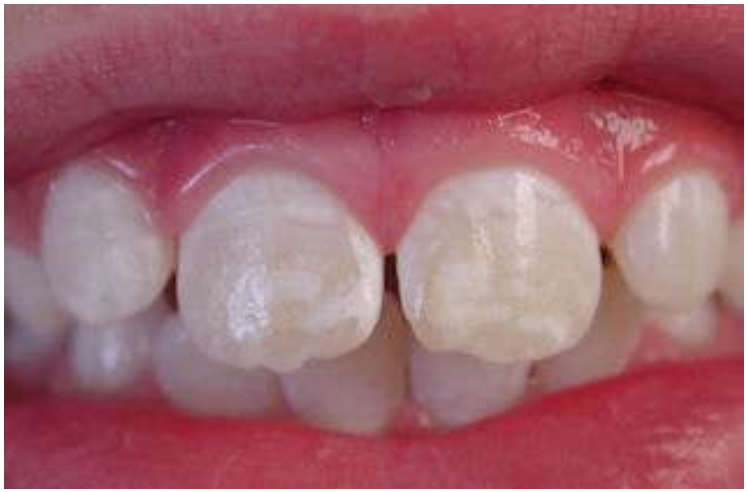
- Erythematous macule > urticarial papule > tense vesicles
- Severe pruritus
- Symmetric distribution
- 90% no GI symptoms
- 75% villous atrophy



Garioch JJ, et al. *Br J Dermatol*. 1994;131:822-6.
Fry L. *Baillieres Clin Gastroenterol*. 1995;9:371-93.
Reunala T, et al. *Br J Dermatol*. 1997;136-315-8.

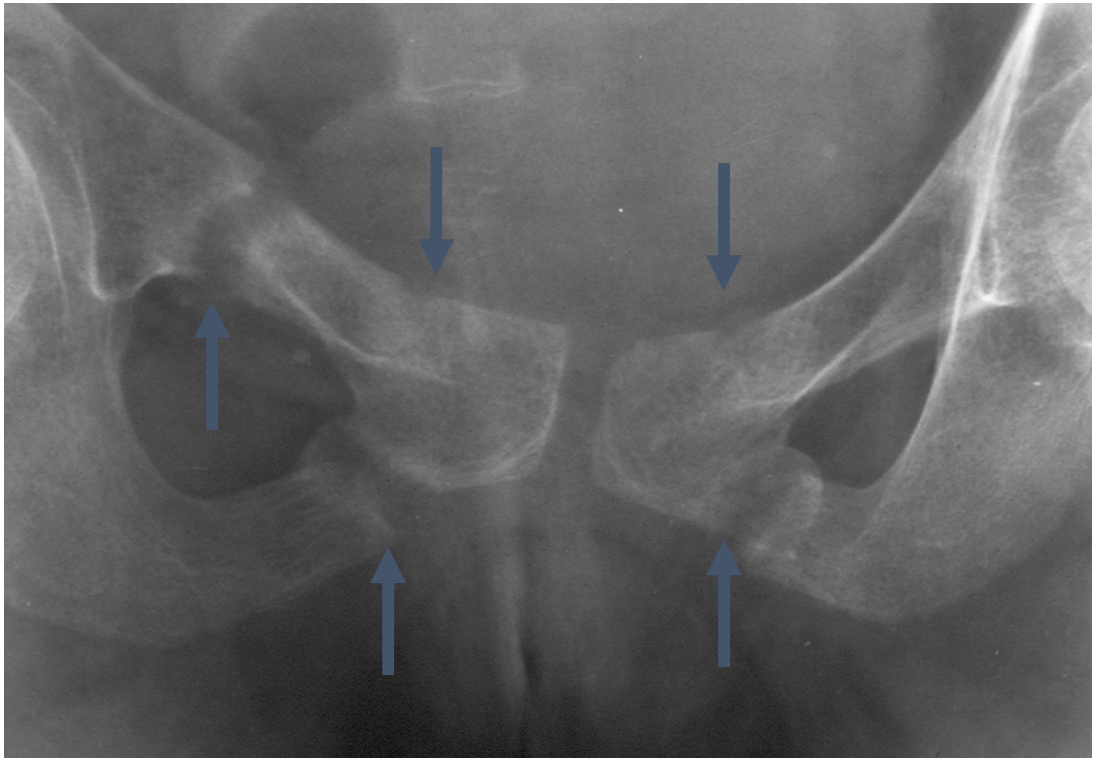
Dental Enamel Defects





Involve the secondary dentition.
May be the only presenting sign of Celiac Disease.

Osteoporosis



Low bone mineral density improves in children on a gluten-free diet.

Short Stature/Delayed Puberty

- Short stature in children / teens:
  - ~10% of short children and teens have evidence of celiac disease
- Delayed menarche:
  - Higher prevalence in teens with untreated Celiac Disease

Iron Deficiency Anemia Resistant to Oral Fe

- Most common non-GI manifestation in some adult studies
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- In children with newly diagnosed Celiac Disease:
  - Anemia is common
  - Little evidence that Celiac Disease is common in children presenting with anemia

Hepatitis

- Up to 9% of adults with elevated ALT, AST may have silent Celiac Disease
- Liver biopsies in these patients showed non-specific reactive hepatitis
- Liver enzymes normalized on gluten-free diet

Arthritis and Neurological Problems

- Arthritis in adults
  - Fairly common, including those on gluten-free diets
- Juvenile chronic arthritis
  - Up to 3% have Celiac Disease
- Neurological problems
  - Epilepsy with cranial calcifications in adults

Other Complications if Left Untreated

- Recurrent stomatitis
- Fertility problems
- **Small bowel adenocarcinoma**
- **T-cell lymphoma**

Diagnosis

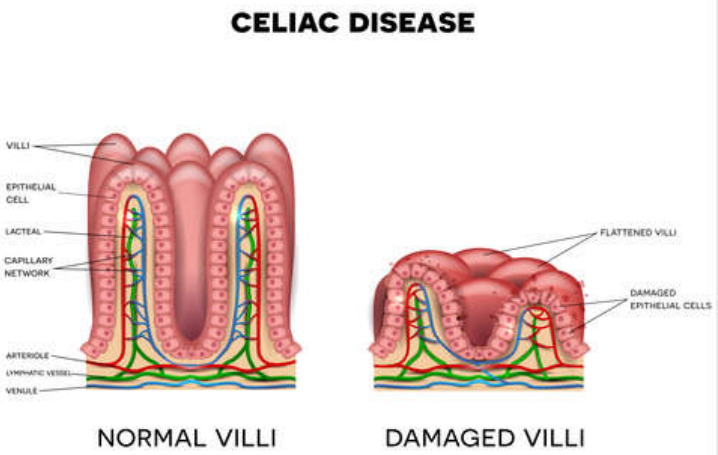
Diagnosis

- Confirm diagnosis before treating
  - Diagnosis of Celiac Disease mandates a strict gluten-free diet for life
    - Following the diet is not easy
    - QOL implications
- Failure to treat has potential long term adverse health consequences
    - Increased morbidity and mortality

Diagnosis

- Pt must be on a gluten-CONTAINING diet prior to EGD, consuming at least 1-2 slices of bread per day
  - If previously gluten free, then needs at least 8-12 weeks of gluten challenge
  - A gluten challenge is not recommended <3 yo, during puberty or if pregnant

Diagnosis



- Diagnosis of Celiac Disease requires:
  - Characteristic small intestinal histology in a symptomatic child
  - Complete symptom resolution on gluten-free diet
- Serological tests may support diagnosis
- Select cases may need additional diagnostic testing

ESPGAN working group. Arch Dis Child 1990;65:909

Serological Tests

Role of serological tests:

- Identify symptomatic individuals who need a biopsy
- Screening asymptomatic "at risk" individuals
- Supportive evidence for the diagnosis
- Monitoring dietary compliance

Serological Tests

- Antigliadin antibodies (AGA)
- Antiendomysial antibodies (EMA)
- Anti-tissue transglutaminase antibodies (tTG)
- Deamidated gliadin antibodies
- HLA typing

Antigliadin Antibodies

- Antibodies (IgG and IgA) to the gluten protein in wheat, rye and barley
- Advantages
  - Relatively cheap & easy to perform
- Disadvantages
  - Poor sensitivity and specificity

Endomysial Antibody (EMA)

- IgA based antibody against reticulin connective tissue around smooth muscle fibers
- Advantages
  - High sensitivity and specificity
- Disadvantages
  - Operator dependent
  - Expensive & time consuming
  - False negative in young children
  - False negative in IgA deficiency

Tissue Transglutaminase (tTG)

- IgA based antibody against tissue transglutaminase
- Advantages
  - High sensitivity and specificity
  - Not operator dependent (ELISA/RIA)
  - Relatively cheap
- Disadvantages
  - False negative in young children
  - False negative in IgA deficiency
  - Possibly less specific than EMA
- Qualitative vs. quantitative
- Note that there is a IgA and an IgG version

Deamidated Gliadin Peptide Antibodies

- Newer generation of gliadin antibody testing
- Increased sensitivity and specificity over traditional gliadin antibody testing
  - Similar to tTG antibody testing
  - DGPA-IgG superior to DGPA-IgA
  - **May be superior in children under age 2**

Serum IgA Level

- Check IgA levels with celiac disease serology in all symptomatic individuals
- Individuals with IgA deficiency are at increased risk for celiac disease
- IgA-deficient individuals will have negative tTG-IgA & EMA-IgA
- **Consider IgG based tests (tTG-IgG or DGPA-IgG) in IgA deficiency**

Serological Test Comparison

	Sensitivity %	Specificity %
AGA-IgG	69 – 85	73 – 90
AGA-IgA	75 – 90	82 – 95
EMA (IgA)	85 – 98	97 – 100
tTG (IgA)	90 – 98	94 – 97
DGPA (IgG)	80 – 90	95 – 99

*All antibody tests normalize on gluten-free diet

Farrell RJ, and Kelly CP. Am J Gastroenterol 2001;96:3237-46.

HLA Tests

- HLA alleles associated with celiac disease
  - DQ2 found in 95% of celiac patients
  - DQ8 found in remaining patients
  - DQ2 found in ~30% of general population

- Value of HLA testing
  - **High negative predictive value**
  - Negativity for DQ2/DQ8 excludes diagnosis of celiac disease with 99% confidence

Schuppan. Gastroenterology 2000;119:234
Kaukinen. Am J Gastroenterol 2002;97:695

HLA Tests

Potential role for DQ2/DQ8

- Asymptomatic relatives
- Down, Turner & Williams syndrome
- Type 1 diabetes
- Patients already on gluten-free diet

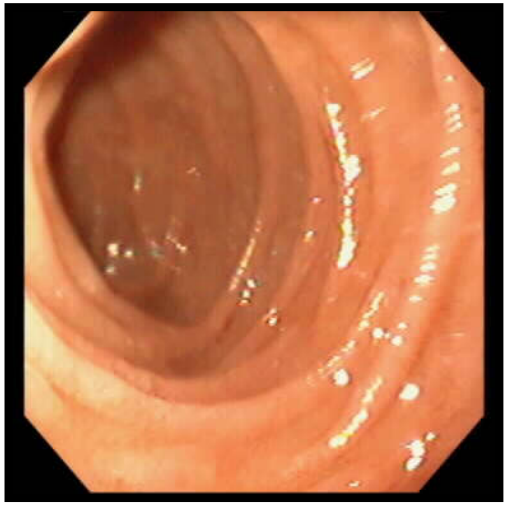
Endoscopy (EGD)

- Allows biopsy of duodenum to look for characteristic histologic changes
- Also allows evaluation of other parts of upper GI tract
- Gold standard for diagnosis*

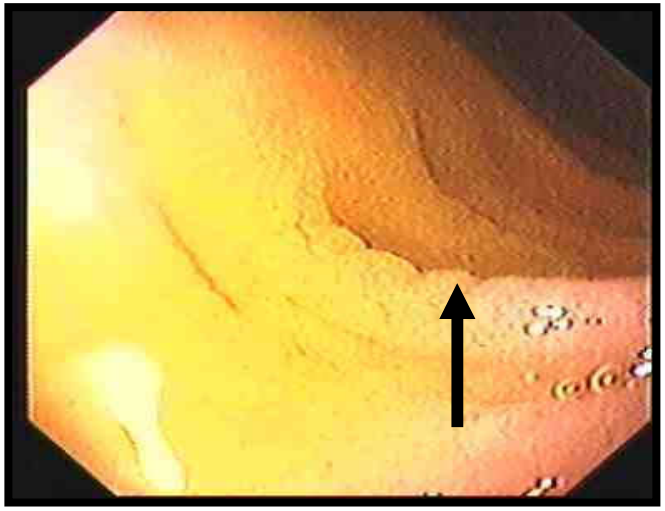
*EGD findings normalize on gluten-free diet

- Some are starting to advocate skipping EGD in the most compelling clinical cases (typical presentation, very high antibody levels)

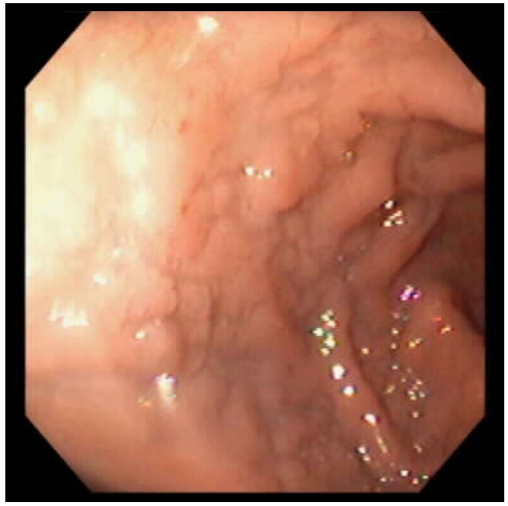
Endoscopic Findings



Normal Appearing

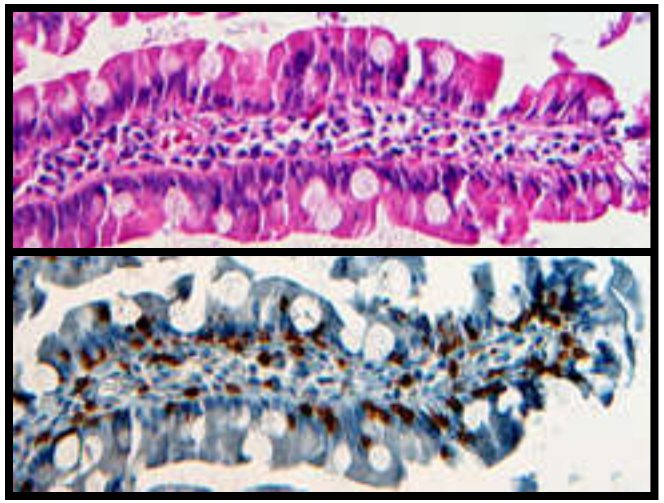


Scalloping



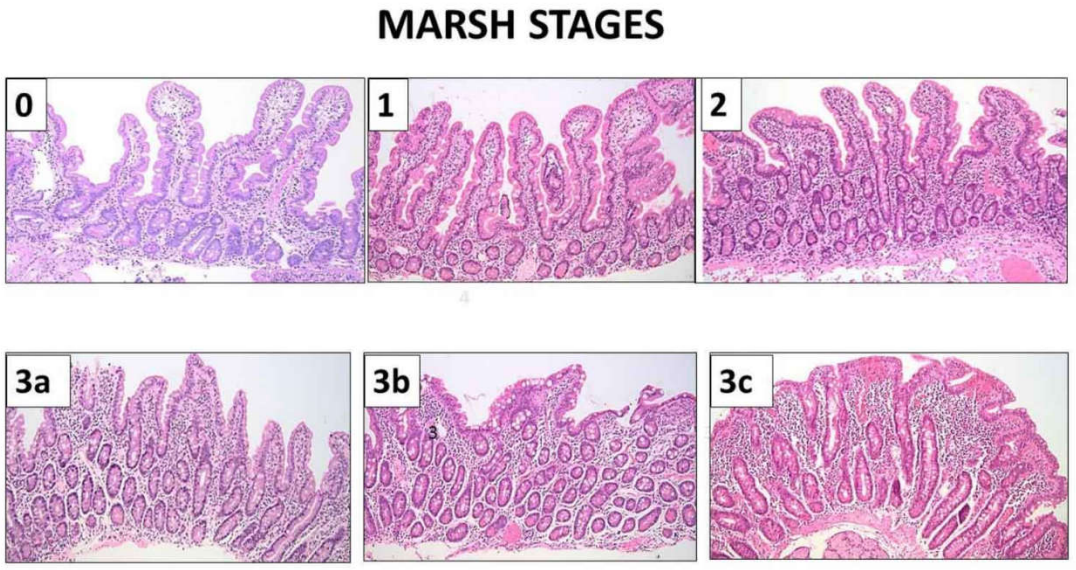
Nodularity

Biopsy Findings



- Histologic Features:
  - Increased IEL's (>30/100 enterocytes)
  - Change from columnar to cuboid
  - Cellular infiltrate in the lamina propria
  - Crypt elongation and hyperplasia
  - Progressive villous flattening

Histological Features



0	Normal mucosa
1	Increased number of intraepithelial lymphocytes, usually exceeding 20 per 100 enterocytes
2	Proliferation of the crypts of liberkuhn
3	Variable villous atrophy
3a	Partial villous atrophy
3b	Subtotal villous atrophy
3c	Total villous atrophy
4	Hypoplasia of the small bowel architecture

Horvath K. Recent Advances in Pediatrics, 2002.

Treatment

Treatment

- Only treatment for celiac disease is a gluten-free diet (GFD)
  - Strict, lifelong diet
  - Avoidance of
    - Wheat
    - Barley
    - Rye

How Much Gluten is Too Much?

- 50 mg/day for 3 months enough to induce histologic changes
- 10 mg/day was considered a "gray area"
- Complete gluten restriction is the only way to ensure safe diet
  - Even on GFD, there is potential for exposure through cross-contamination

Catassi C, *et al*. Am J Clin Nutr 2007

Gluten-Containing Grains to Avoid

Wheat	Bulgar	Filler
Wheat Bran	Couscous	Graham flour
Wheat Starch	Durum	Kamut
Wheat Germ	Einkorn	Matzo
Flour/Meal	Barley	Emmer
Semolina	Barley Malt/ Extract	Faro
Spelt	Rye	Triticale

Hidden Sources of Gluten

- Malt or malt-flavoring
- Soy sauce (unless specifically labeled as gluten-free)
- Worcestershire sauce
- Latin names:
  - *Triticum vulgare* (wheat)
  - *Hordeum vulgare* (barley)
  - *Secale cereale* (rye)
  - *Triticale* (cross between wheat and rye)
  - *Triticum spelta* (spelt, a wheat variety)

Hidden Sources of Gluten

Gluten Free Apps

Find Me Gluten Free

iPhone rating: 4.9 stars

Android rating: 4.5 stars

Price: Free with in-app purch

Eating out when you're gluter
you have Find Me Gluten Fre
restaurants filtered to your sp
breakfast. Check out location
directions or a number to mal
bookmark your favorites and
popular chain restaurants.

Sift Food Labels

iPhone rating: 4.6 stars

Android rating: 3.8 stars

Price: Free with in-app purchases

Overwhelmed by complicated, confusing ingredient l
Use the barcode scanner in the Sift Food Labels app
accurate, simple information, including any ingredient
may be banned in other countries. The app is especia
helpful in supporting gluten-free nutrition and other li
diets.

The Gluten Free Scanner

iPhone rating: 4.6 stars

Android rating: 3.5 stars

Price: Free with in-app purch

This simple app makes findin
The barcode scanner provide
more information and greater
has over 500,000 products a
for gluten in all of your favorit

Celiac Disease Diet Tips & Gluten Free Foods Help

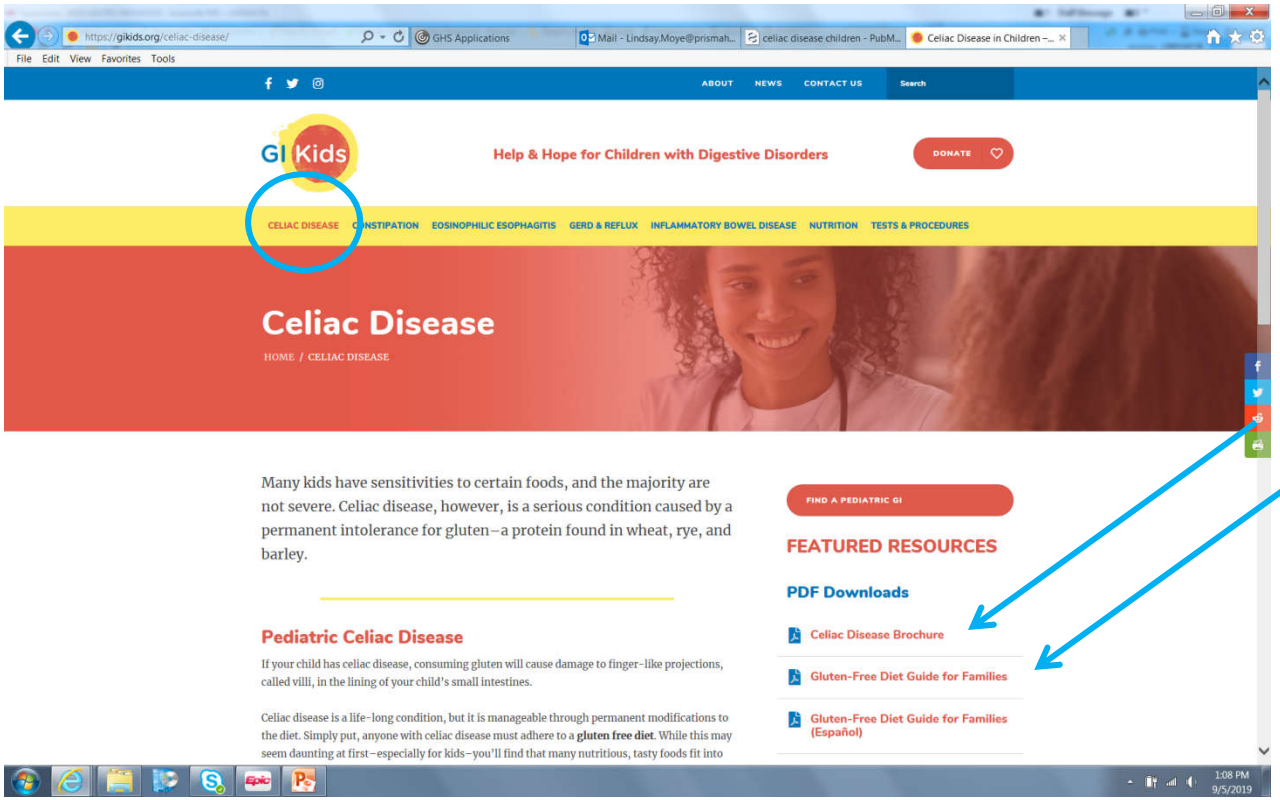
Android rating: 4.2 stars

Price: Free

Learn the ins and outs of managing celiac disease or
sensitivity with this comprehensive app. It includes
information about symptoms and diagnosis, treatmen
foods to eat, foods to avoid, and common foods with
gluten. Need more? Contact the app's dietitians direc
answers to your questions.

Resources

- GIkids.org > Celiac



Follow Up/Monitoring

- Recheck tTTG IgA levels– these should start to fall by 3–6 months but can remain elevated (even despite adequate dietary adherence)
- Persistently elevated antibodies or ongoing symptoms should prompt referral to a dietitian for assessment of adherence and reinforcement of advice
- Repeat EGD after 12–24 months of a gluten-free diet, particularly if there are ongoing symptoms or if celiac antibodies remain elevated

Follow Up/Monitoring

- Check CBC, LFTs, iron, vitamin B12, vitamin D and calcium
- Screen for other associated conditions if clinically relevant (type 1 diabetes, autoimmune thyroid disease)
- Recommend celiac screening for first-degree relatives
- Consider evaluating bone mineral density

The Future of Celiac

- Enzyme therapy
- Engineered grains
- Immunomodulatory strategies
- Correction of intestinal barrier defects

*As difficult as it is, GFD is effective and safe and will likely not be surpassed by future treatments

Bad News and Good News

- Bad news:
  - Life-long gluten sensitivity
  - Minimal amounts perpetuate the disease
    - No cheating!
  - Untreated disease may be asymptomatic but still lead to complications

- Good news:
  - One of the few chronic diseases that can be managed completely by diet
  - Lots of foods are naturally gluten-free
  - More and more good gluten-free alternatives

Take Home Points

- Celiac disease is more prevalent than most people think
- First degree relatives and certain populations are at much higher risk
- tTG IgA and total IgA adequate in most cases
  - Also consider DGPA IgG in children <2
- Tell parents not to start the gluten-free diet until testing is complete!
- Direct parents to helpful resources
- Untreated disease may be asymptomatic but still lead to complications

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PrismaHealth.org