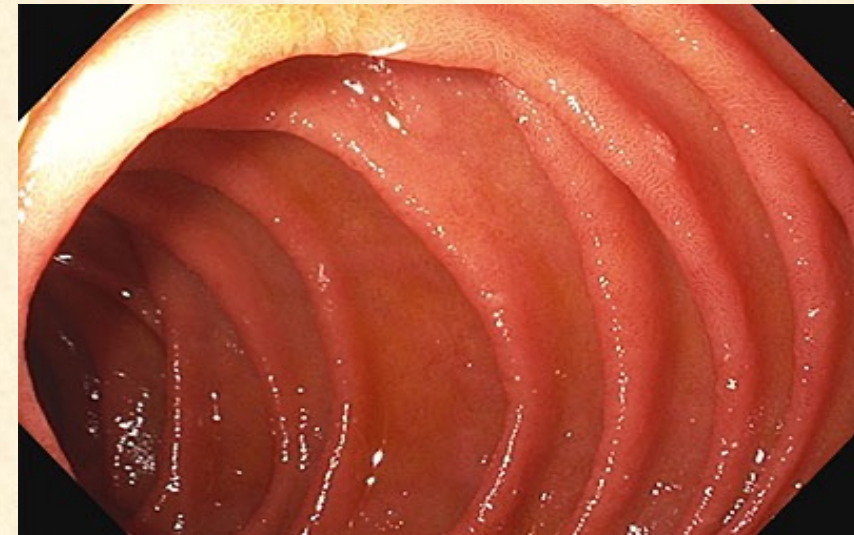




Celiac disease diagnostic & treatment challenges

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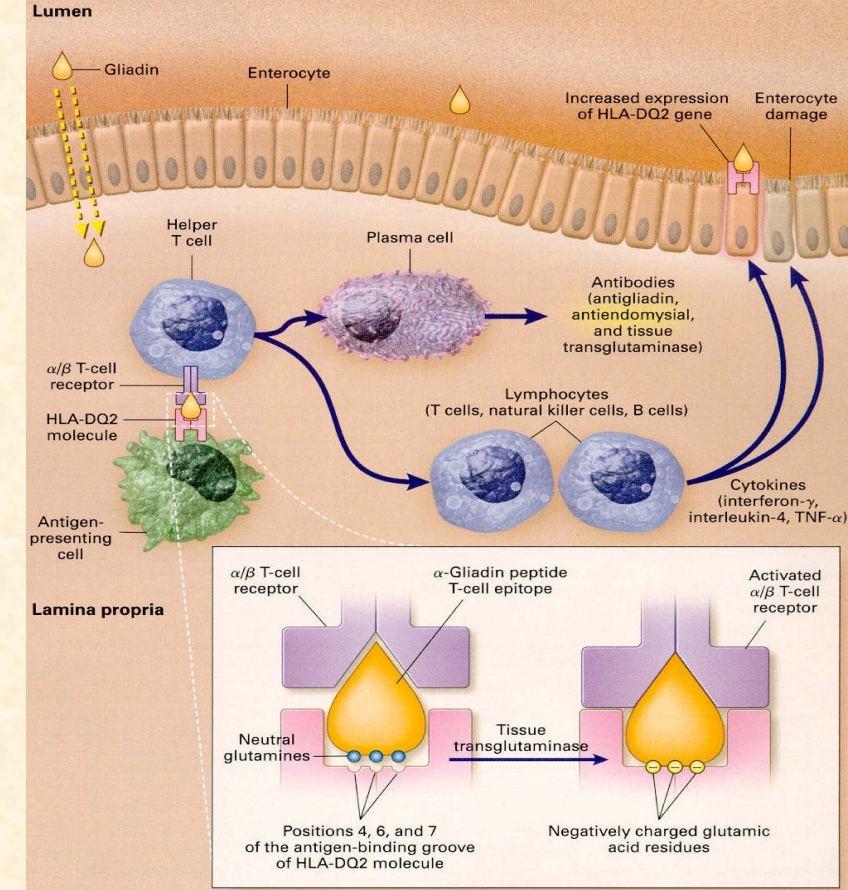
DEFINITION:

- Celiac Disease: an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals

- **PREVALENCE IN CHILDREN BETWEEN 2.5 AND 15 YEARS OF AGE:**

3 to 13 per 1000 children or approximately 1 in 300 to 1 in 80 children.

- Therefore, in a pediatric practice of 1500 children there are probably between 5 and 20 children with CD, either diagnosed or undiagnosed.



TESTING IS RECOMMENDED FOR CHILDREN WITH:

- DIARRHEA AND FAILURE TO THRIVE
- PERSISTENT GI SYMPTOMS INCLUDING RECURRENT ABDOMINAL PAIN, ANOREXIA, CONSTIPATION AND VOMITING
- DERMATITIS HERPETIFORMIS
- DENTAL ENAMEL HYPOPLASIA OF PERMANENT TEETH
- OSTEOPOROSIS
- SHORT STATURE
- DELAYED PUBERTY
- IRON-DEFICIENT ANEMIA RESISTANT TO ORAL IRON

ASYMPTOMATIC CHILDREN WITH CONDITIONS ASSOCIATED WITH AN

INCREASED PREVALENCE OF CELIAC DISEASE:

- **FIRST-DEGREE RELATIVES OF PATIENTS WITH CELIAC DISEASE**
- • AUTOIMMUNE THYROIDITIS
- • TYPE 1 DIABETES, • DOWN SYNDROME
- • SELECTIVE IMMUNOGLOBULIN A (IGA) DEFICIENCY
- • TURNER SYNDROME
- • WILLIAMS SYNDROME
- • JUVENILE CHRONIC ARTHRITIS
- • AUTOIMMUNE LIVER DISEASE

If screening is undertaken for **asymptomatic** individuals in these high-risk groups, testing should first be performed at **three years** of age or older and on a gluten-containing diet for at least one year

- . IF INITIAL RESULTS ARE NEGATIVE, SCREENING TESTS SHOULD BE REPEATED AT INTERVALS OR AT ANY TIME THAT SYMPTOMS DEVELOP.

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- THE OPTIMAL TIME INTERVAL FOR SUBSEQUENT TESTING HAS NOT BEEN STUDIED, BUT IN OUR PRACTICE,
- WE SCREEN **ASYMPTOMATIC** MEMBERS OF THESE GROUPS **EVERY THREE TO FIVE YEARS** DURING CHILDHOOD

SEROLOGY SCREENING TOOLS

Serological tests are fundamental for CD screening.

Measurement of **serum IgA antibodies to tissue transglutaminase (anti-tTG)** (or IgG class in subjects with IgA deficiency) is recommended for initial testing, owing its high sensitivity (94%), and specificity (97%), and excellent standardization.

CURRENT DIAGNOSTICS - SEROLOGY

Testing should be performed while on a gluten-containing diet.

Individuals previously started on a gluten-free diet without prior testing should resume a diet containing ideally **at least 3 g gluten/day** (equivalent to approximately one slice of bread daily) for **at least six weeks before undergoing antibody testing**, although the duration and amount of gluten required for diagnostic accuracy has not been fully clarified

Serologies may become **negative within weeks of beginning a gluten-free diet** but may take up to a year or even longer in some cases

- **Anti-endomysial antibodies** – Testing for anti-endomysial antibodies (EMA) is as accurate as tTG-IgA, but this test is more expensive and somewhat dependent on operator interpretation.
- . As a result, EMA is typically used as a second-line test to clarify the diagnosis in patients with equivocal results of tTG-IgA, including asymptomatic members of a high-risk group,
- EMA is an immunofluorescence test for IgA antibodies to endomysium, a structure of the smooth muscle connective tissue .
- **Deamidated gliadin peptide** – Deamidated gliadin peptide (DGP) also has good diagnostic accuracy and may be particularly useful for young children; this is a second-generation anti-gliadin antibody test .
- **Anti-reticulin antibodies** – Tests of anti-reticulin antibodies have reasonably high specificity, but lower sensitivity, and are no longer commonly used
- **Anti-gliadin antibodies** – Standard (first-generation) IgA or IgG anti-gliadin antibodies are considerably less reliable and are not recommended

Initial testing

- Testing for total IgA and TGA-IgA should be used for children with suspected CD, after checking that the child is consuming normal quantities of gluten.
- In children with low total IA concentrations (**low for age or <0.2 g/L above the age of 3 years**), an IgG-based test (**DGP, EMA or TGA**) should be performed as a second step.
- If initial testing suggests coeliac disease, the child should be referred to a pediatric gastroenterologist/coeliac disease specialist.

Deamidated gliadin peptide (DGP IgA and IgG):

- This test can be used to further screen for celiac disease in individuals with IgA deficiency, which affects 2-3% of patients with celiac disease, or people who test negative for tTg or EMA antibodies.
- For children younger than two years, tTG-IgA is the best initial test for IgA-sufficient children, as it is for older individuals, with >97 percent sensitivity for detecting celiac disease
- While tTG-IgA is at least as sensitive as DGP-IgG (except for patients with IgA deficiency) IgA deficiency in a patient may be indicative of other diseases that may **cause villus atrophy, such as giardiasis, small-bowel bacterial overgrowth (SIBO) or common variable immunodeficiency (CVID)**

Results of Celiac Disease Testing?

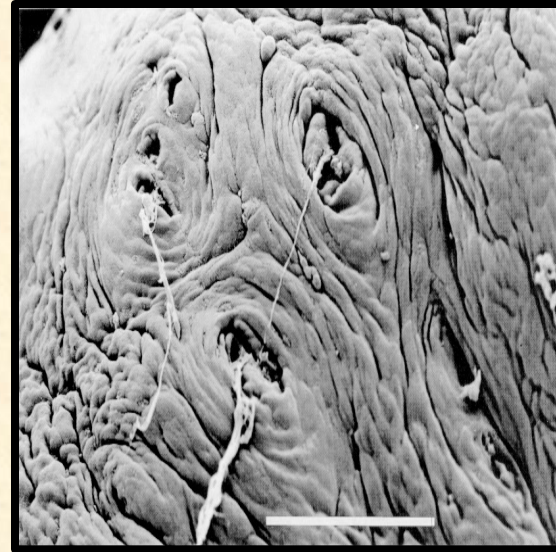
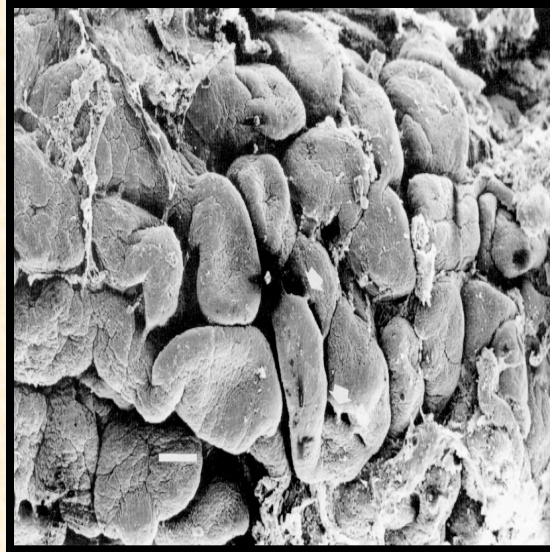
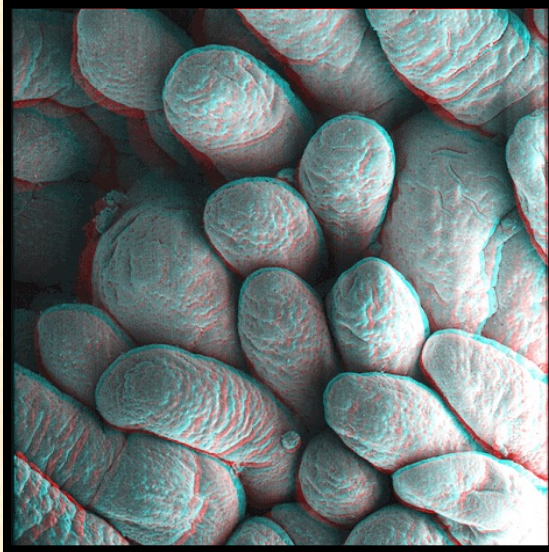
Positive Celiac Disease Assay

- Perform endoscopy with biopsy to confirm celiac disease while patient continues to consume gluten.
- Collect a minimum of 4 distal duodenal biopsies and 1-2 biopsies of duodenal bulb (preferably from 9 or 12 o'clock position).

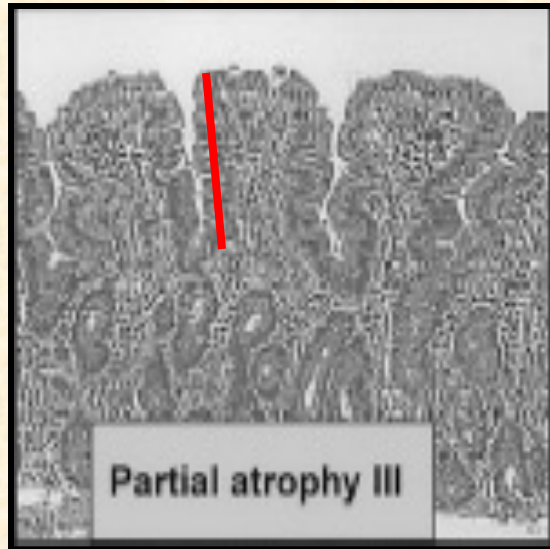
Intestinal Biopsy, pathology

- A less severe infiltrative lesion characterized by isolated infiltration of IEL, especially CD8+ T lymphocytes, within a structurally normal mucosa (so called Marsh 1 lesion)
- A hyperplastic lesion showing crypt hypertrophy (Marsh 2)
- A flat/destructive lesion with the greatly hypertrophied crypts and the characteristically flattened villi (Marsh 3a to 3c)

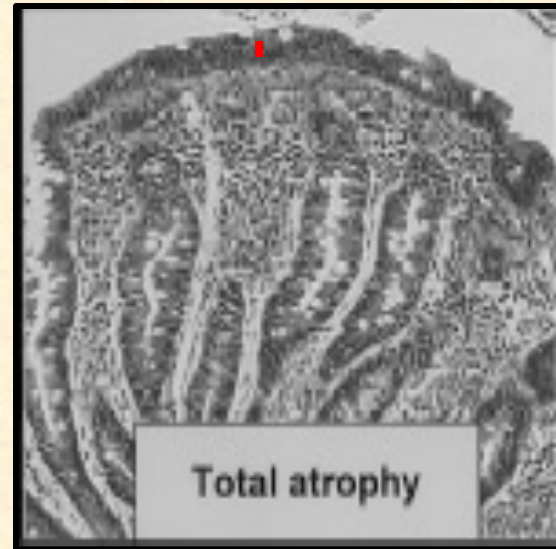
Progression of disease



Normal

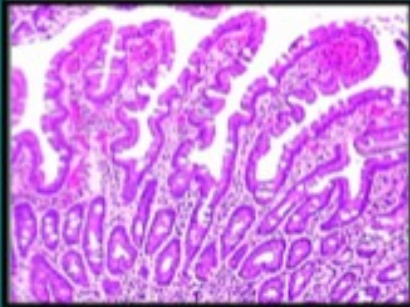


Partial atrophy III

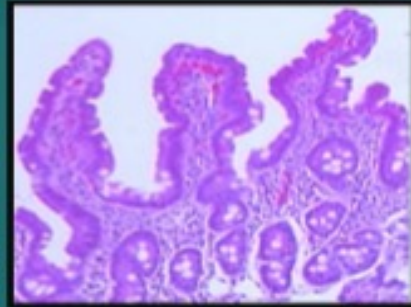


Total atrophy

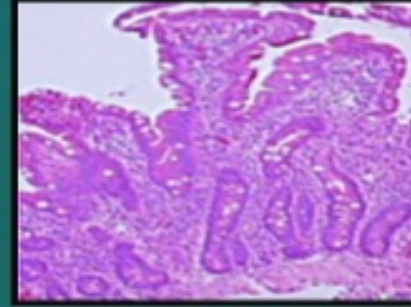
Histological Features



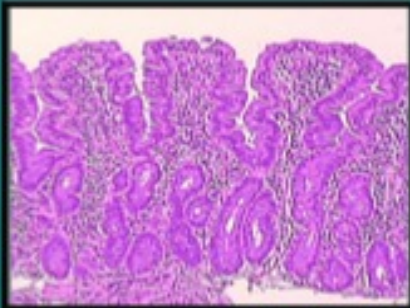
Normal 0



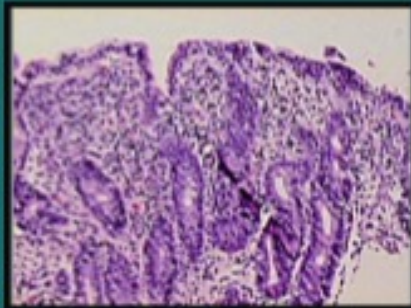
Infiltrative 1



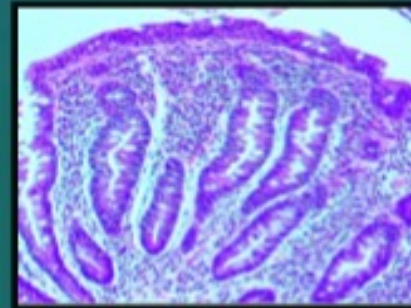
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

Biopsy Results

Marsh I or II

- This is an equivocal lesion which may still be consistent with celiac disease, though care should be taken in such cases prior to rendering the diagnosis.
- Confirm sufficient gluten intake.
- Review biopsies with an experienced pathologist;
- ensure proper orientation and exclude *Helicobacter pylori* infection and use of NSAIDs.
- Consider repeating serological assays at a different laboratory as variability may exist.
- Ensure that alternative explanations for the patient's symptoms and positive serologies have been excluded (e.g., IBD or other autoimmune disease).
- Consider HLA DQ2 (DQA1*05:01/05:05 and DQB1*02:01/02:02)/DQ8 (DQA1*03:01 and DQB1*03:02), genotyping.

HLA-testing

- HLA-testing is **not required** in patients with positive TGA-IgA,
- if they qualify for CD diagnosis with biopsies or
- if they have high serum TGA-IgA $\geq 10 \times \text{ULN}$ and EMA-IgA positivity.
- A negative test for HLA-DQ2 and/or -DQ8 indicates a very low risk of CD, while a positive result does not confirm the diagnosis.
- If no risk alleles are found, CD is unlikely.
- HLA testing and presence of symptoms are not obligatory criteria for a serology based diagnosis without biopsies.

no-biopsy approach

- for CD diagnosis is confirmed to be safe in children with high TGA-IgA values ≥ 10 times the upper limit of normal with accurate, appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample
- All patients who are IgA deficient and who are positive for an IgG based serological test should be biopsied.

THE MOST COST-EFFECTIVE AND HEALTHY WAY TO FOLLOW THE GLUTEN-FREE DIET IS TO SEEK OUT THESE NATURALLY GLUTEN-FREE FOOD GROUPS, WHICH INCLUDE:

- **FRUITS**
- **VEGETABLES**
- **MEAT AND POULTRY**
- **FISH AND SEAFOOD**
- **DAIRY**
- **BEANS, LEGUMES, AND NUTS**

Treatment



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

Sources of Gluten



- OBVIOUS SOURCES
 - Bread
 - Bagels
 - Cakes
 - Cereal
 - Cookies
 - Pasta / noodles
 - Pastries / pies
 - Rolls

HOW TO MONITOR?

1. Periodic visits for assessment of symptoms, growth, physical examination and adherence to the gluten-free diet
 - Measurement of **TTG 6 months after treatment** with a gluten-free diet is begun, and then approximately once a year if the patient has no symptoms
 - Measurement of TTG at any time after starting a gluten-free diet if the patient has persistent or recurring symptoms

- A complete blood cell count, micronutritional status (eg, hemoglobin, iron, vitamin B12, and vitamin D levels) and ALT measurements, should be performed after clinical evaluation at time of diagnosis.
- In a child with impaired growth at the time of CD diagnosis, catch-up growth in weight and height is usually expected within **six months** after starting the GFD, after which, depending on the patient's age and continuance of the diet for 1–2 years, expected height is reached.

- In the prepubertal/pubertal child, if significant catch-up growth in height is not reached within **1 year** after initiating GFD, despite strict dietary adherence,
- additional investigations and consultation with a pediatric endocrinologist are recommended to rule out other causes of short stature.

- Lack of decreasing IgA-TGA levels after 6–12 months on a GFD or
- persistently positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer.

For all patients, we monitor the following, as indicated

- Monitoring of growth (height, weight, and body mass index)
- Complete blood count
- Iron status (by measuring ferritin)
- Thyroid-stimulating hormone – Patients with celiac disease have substantially increased risk of autoimmune thyroiditis that increases with age
- Aspartate and alanine aminotransferases – Patients with celiac disease have an increased risk of autoimmune hepatitis
- Vitamin D status (by measuring 25-hydroxyvitamin D)

Laboratory testing for type 1 diabetes is not routinely needed but is appropriate for selected patients based on individual risk factors

Thanks for your attention

