Celiac disease

73RD MCGILL ANNUAL REFRESHER COURSE FOR FAMILY PHYSICIANS

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Disclosures

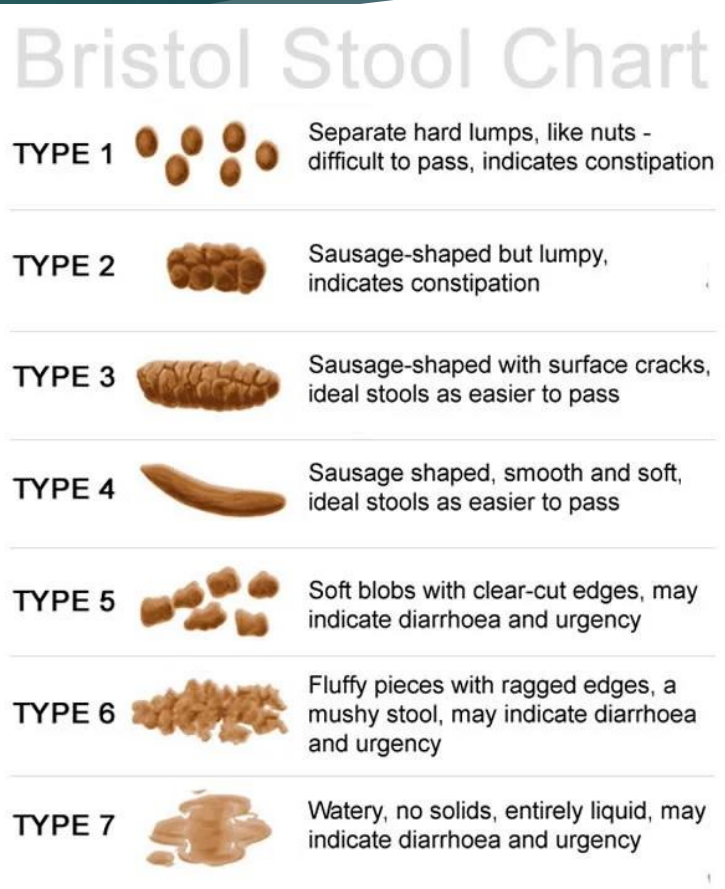
- No conflicts of interest to disclose

Learning objectives

- As a result of attending this session, participants will be able to:
  - Define the different clinical presentations of celiac disease
  - Understand diagnostic tests for celiac disease
  - Identify complications of celiac disease

Case 1

- 35F comes to see you for worsening constipation over the last year.
  - PMHx: depression
  - Meds: citalopram
  - FMHx: Grave's disease (mother), Crohn's disease (sister)
  - Habits: non smoker, rare alcohol, non vegetarian diet
  - HPI: Notices some constipation x years. This has progressed over the last year. She has hard stools and bowel movements (BM) q2-3 days. She strains regularly. She has occasional bloating. She complains of mild cramps that resolve when she passes a BM
  - She denies any weight loss, blood in the stools, or diarrhea. She denies upper GI symptoms. She has regular periods that are not abundant.



Case 1

- Physical examination
  - Looks well, weight 140 lb, BMI 26
  - Abdomen soft, non distended
  - Non tender
  - No rash

- Laboratory findings
  - **Hgb 107, MCV 78**, plt 221, WC 5.5
  - **Ferritin 5 and iron saturation of 0.05**
  - TSH normal
  - B12 normal
  - **ALT 55, AST 65,** Bili, ALP normal, INR normal

Case 1

- You diagnose her with iron deficiency anemia.
- You proceed to tell her that you want to rule out celiac disease (CD). She tells you that it is impossible because she can eat gluten without any symptoms and that she has no family history of celiac.

- **What are presenting features of celiac disease?**
- How prevalent is celiac disease?

Clinical presentation

- Clinical presentation of celiac disease
  - Classical (50-60%) vs non-classical presentation
  - Intestinal vs extra-intestinal manifestations
- Other signs or symptoms include
  - Vague abdominal symptoms, reflux esophagitis, EoE, neuropathy, ataxia, depression, lymphoma
  - Liver biochemical abnormalities can occur in 40% of patients with new diagnosis of celiac

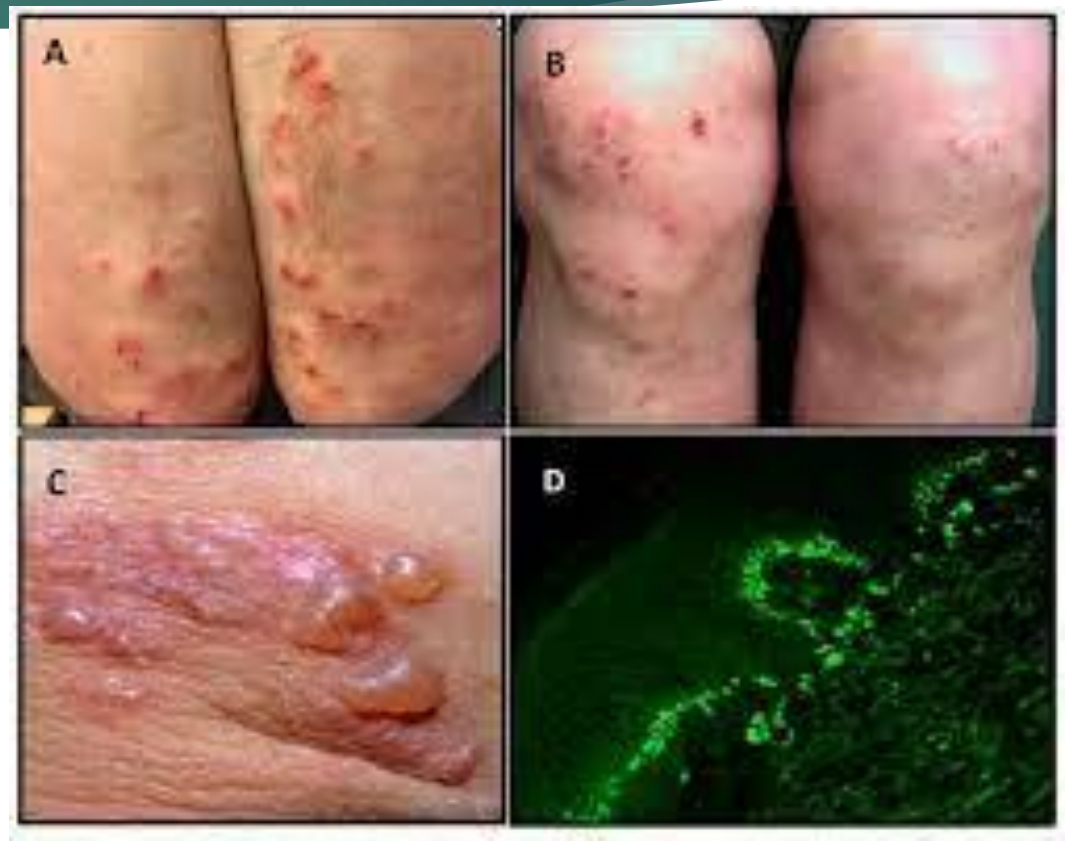
Table 1 **Most frequent clinical manifestions of celiac disease.**

	Intestinal	Extraintestinal
Classical	Diarroea	Iron deficiency anaemia
	Failure to thrive	Muscle waisting
	Weight loss	Oedema
	Bloating	
Non classical	Chronic abdominal pain	Short stature
	Abdominal distension	Delayed puberty
	Constipation	Amenorrhea
	Vomiting	Irritability, unhappiness
		Chronic fatigue
		Epilepsy
		Peripheral neuropathy
		Joint/muscle pain
		Elevated aminotransferases
		Aphtous stomatitis
		Recurrent miscarriages
		Reduced bone mineral density

Raiteri, World J Gastro 2022;28:154-175
Al-Toma, United European Gastroenterology Journal 2019; 7(5) 583–613

Dermatitis herpetiformis

- Cutaneous manifestation of celiac
- Vesicular pruritic rash on elbow, knees and buttock
- IgA deposition
- Responds to gluten free diet



Reunala Nutrients 2018;10, 602

Malabsorption

- Steatorrhea, weight loss, diarrhea, nutrient and vitamin deficiency
- Maldigestion vs malabsorption

Case 1

- You diagnose her with iron deficiency anemia.
- You proceed to tell her that you want to rule out celiac disease. She tells you that it is impossible because she can eat gluten without any symptoms and that she has no family history of celiac.

- What are presenting features of celiac disease?
- **How prevalent is celiac disease?**

Epidemiology of celiac disease

- Disease frequency of about **0.6-1%** worldwide
  - US prevalence of 0.75% (1:133) in general population
  - Can occur across all age groups
  - F>M
- The prevalence of celiac is increasing
- Not only limited to Northern and Western Europe descent
  - Regional differences
  - Lowe in non-Hispanic blacks and Hispanics vs white individuals in the US

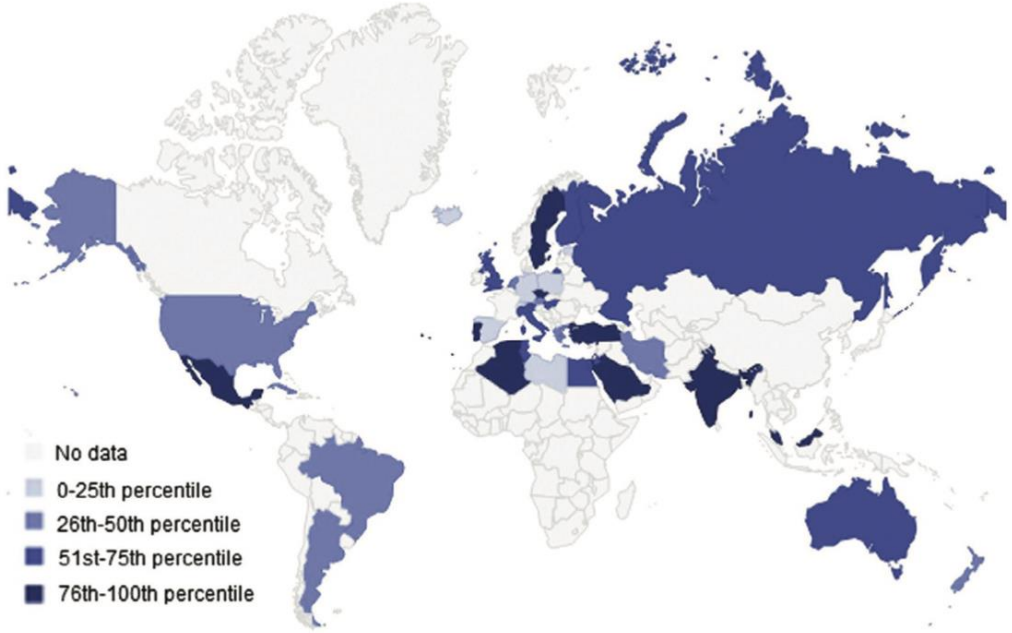


Figure 1.2 ***Country-wise seroprevalence of CeD; Countries are stratified into 4 groups of percentiles***

Rajput Celiac and gluten related disorder 2022, Chapter 1

Case 1

- Her sister who accompanied her to the appointment wants to know if she should be tested as well. She has no symptoms.

- **Who are at increased risk for celiac disease?**
- **What are indications to test for celiac disease?**

High-risk population

- **First degree relatives** of patients with celiac disease (risk of 7.5%)
- Patients with **auto-immune** conditions
  - **DM1** (up to 5-10% of pt with DM1 also have CD)
  - Auto-immune thyroid diseases
  - Auto-immune liver disease
- Association with **cryptogenic cirrhosis** (2.5%)
- Certain genetic conditions
  - IgA deficiency
  - Down syndrome
  - Turner syndrome

Table 1.2 Prevalence of CeD amongst extra-intestinal manifestations and high-risk groups.

Condition	Prevalence CeD % (95% CI)	
Iron deficiency anaemia [50]	3.2 (95% CI 2.6–3.9)	
Short stature [58]	All cause	7.4 (95% CI 4.7–10.6)
	Idiopathic	11.6 (95% CI 4.1–22.2)
Infertility [98]	All cause	2.3 (95% CI 1.4–3.5)
	Idiopathic	3.2 (95% CI 2–4.9)
Type 1 diabetes [61]	6 (95% CI 5–6.9)	
Osteoporosis [69]	1.6 (95% CI 1.1–2.0)	
Autoimmune thyroid disorder [63]	1.4 (95% CI 1–1.8)	
Cryptogenic cirrhosis [76]	2.50%	
Autoimmune hepatitis [80]	3.50%	
Unexplained transaminases [70]	4 (95% CI 1–7)	

Husby, gastroenterology, 2019:156:885-889
Rajput Celiac and gluten related disorder 2022, Chapter 1

Indications for celiac testing

- Patients with symptoms, signs of celiac disease (CD)
- 1st degree relative of CD
  - Test if they are symptomatic
  - Consider testing in asymptomatic 1st degree relative
  - Over rate of CD is up to 5-20%
- Unexplained transaminitis
- DM1
- Other high risk populations

European Society for the Study of Coeliac Disease (ESsCD) recommendations

CD serology is indicated: biopsy is needed only when serology is positive

(1) IBS
(2) Elevated otherwise unexplained liver transaminases
(3) Chronic GI symptoms without a family history of CD or a personal history of autoimmune disease
(4) Microscopic colitis
(5) Hashimoto's thyroiditis and Graves' disease
(6) Osteopenia/osteoporosis
(7) Unexplained ataxia or peripheral neuropathy
(8) Recurrent aphthous ulcerations/dental enamel defects
(9) Infertility, recurrent miscarriage, late menarche, early menopause
(10) Chronic fatigue syndrome
(11) Acute or chronic pancreatitis after excluding other known causes
(12) Epilepsy; headaches including migraines; mood disorders; or attention-deficit disorder/cognitive impairment
(13) Hyposplenism or functional asplenia
(14) Psoriasis or other skin lesions than DH
(15) Down's or Turner's syndrome
(16) Pulmonary haemosiderosis
(17) IgA nephropathy

Rubio-Tapia Am J Gastro 2013, 108:656-676
Al-Toma, United European Gastroenterology Journal 2019; 7(5) 583–613

Indications for testing despite negative serology

Endoscopy and duodenal biopsy even if CD serology is negative

(1) Chronic (non-bloody) diarrhoea
(2) Diarrhoea with features of malabsorption, especially weight loss
(3) Iron deficiency anaemia in absence of other causes
(4) GI symptoms with a family history of CD
(5) GI symptoms in patient with autoimmune disease or IgA deficiency
(6) Failure to thrive in children
(7) Skin biopsy-proven DH
(8) Patient with video capsule findings suggestive for villous atrophy
(9) Unexplained high output ileo-(colo-)stomy

Al-Toma, United European Gastroenterology Journal 2019; 7(5) 583–613

Case 1

- You proceed to test her for celiac disease

- **What serology to you order?**
  - **What are the available serologic tests?**
  - **What are complementary investigations you can order?**

  - **What if her IgA were low?**

Serology in celiac disease

- Most sensitive test (se 95%): **anti-tissue transglutaminase IgA (tTG IgA)**
  - Less specific especially with low levels
  - Anti-tissue transglutaminase **IgG** is less sensitive and less specific → only use with IgA deficiency
- Most specific test (sp 97-100%): **anti-endomysial IgA (EMA IgA)**
  - Less sensitive, costly, operator dependent
  - Can use to confirm celiac in equivocal cases
- Deaminated gliadin peptide (DGP) (IgA and IgG)
  - Slightly less sensitive and specific compared to tTG
- Anti-gliadin antibody
  - Lower sensitivity and specificity, poor performance for general population
- 2% of patients will be seronegative

Celiac serological tests

Table 2. Sensitivity and specificity of different serological tests.

Antigen	Antibody type	Sensitivity, % (range)	Specificity, % (range)
Gliadin	IgA	85 (57–100)	90 (47–94)
	IgG	80 (42–100)	80 (50–94)
Endomysium	IgA	95 (86–100)	99 (97–100)
	IgG	80 (70–90)	97 (95–100)
Tissue transglutaminase	IgA	98 (78–100)	98 (90–100)
	IgG	70 (45–95)	95 (94–100)
Deamidated gliadin peptide	IgA	88 (74–100)	90 (80–95)
	IgG	80 (70–95)	98 (95–100)

Al-Toma, United European Gastroenterology Journal 2019; 7(5) 583–613

IgA deficiency

- IgA deficiency occurs in 2-3% of celiac patients
- Use a combination
  - Antibody to **deaminated gliadin peptides IgG (DGP-IgG)**
  - Anti-tissue transglutaminase **IgG (tTG-IgG)**
- Pediatric population (< 2 year old): may have low IgA → measure both tTG-IgA and DGP-IgG

Case 1

- You see her in your office 3 months later to review her laboratory results.
  - IgA normal
  - tTG-IgA is 5 (negative)

- **What do you tell her at this stage?**
  - **Does she have celiac disease?**
  - **What do you need to confirm or rule out celiac disease**

Case 1

- Upon further questioning. She tells you she has been on a gluten free diet because she was worried about having celiac disease. She did her bloods after being on a gluten free diet for 2.5 months.

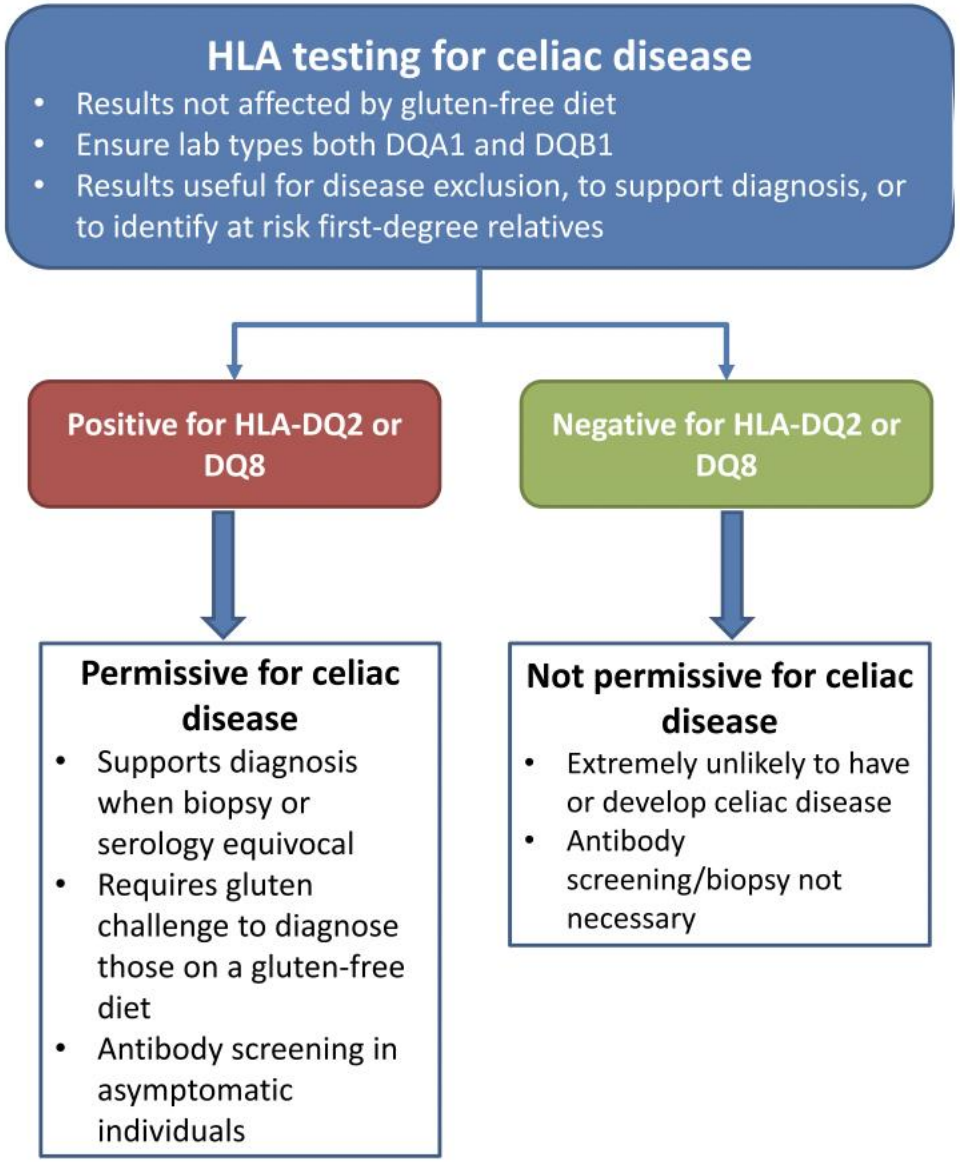
- **What is the next step in her diagnosis?**

HLA testing to rule out celiac disease

- Human lymphocyte antigen **(HLA) DQ2 or DQ8** present in the majority of patients with celiac disease
  - Celiac disease: 90-95% are DQ2 positive, 5-10% DQ8 positive, 3% (both DQ2/DQ8 positive)
  - Present in **30-40% of general population**
    - Only 4% of those who test positive will have celiac disease
  - Poor specificity
- Can be used **to rule out** celiac if it is negative **(NPV of >99%)**
- Do not use as first line diagnosis

HLA testing indications

- Rule out celiac in patient on a gluten-free diet
- Support diagnosis when biopsy or serology are equivocal
- Identify at-risk individuals (such as first degree relatives)



Brown, Am J Gastro 2019;114:1587-1592

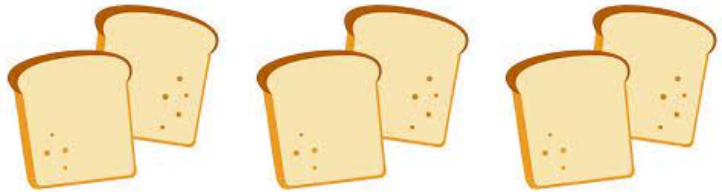
Case 1

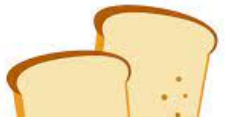
- Her results come back and her HLA DQ2 is positive and HLA DQ8 is negative

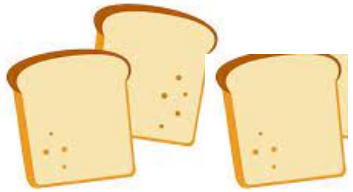
- **What is your next diagnostic step?**

Gluten challenge

- **Classic** gluten challenge
  - 8g-10g of gluten per day (4-6 slices of bread) x 6-8 weeks
  - Repeat serology after challenge
- **Modified** gluten challenge
  - Can be considered in patients <u>unable to tolerate</u> classic gluten challenge
  - 3g of gluten per day (1.5 slices of bread) x 2-4 weeks
  - Repeat serology after 2-4 weeks
    - If negative → extend gluten challenge x 8 additional weeks
      - If still negative at 12 weeks, celiac is less likely
    - If positive → request EGD and continue gluten
- AGA Clinical practice update on diagnosis and monitoring of celiac disease (Husby, Gastroenterology 2019)
  - **3 slices** of bread x 1-3mo

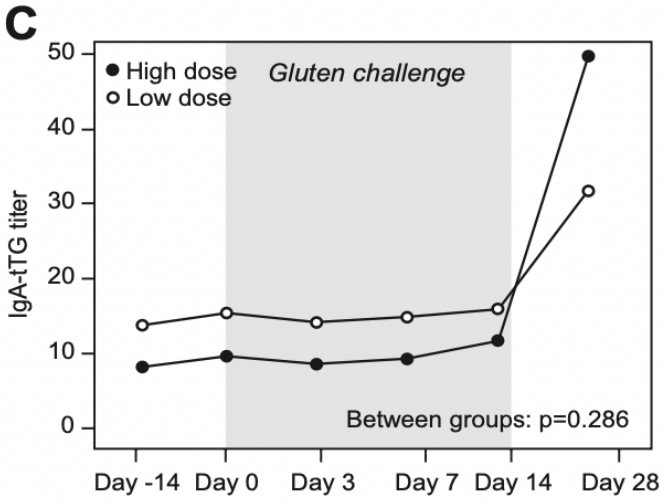


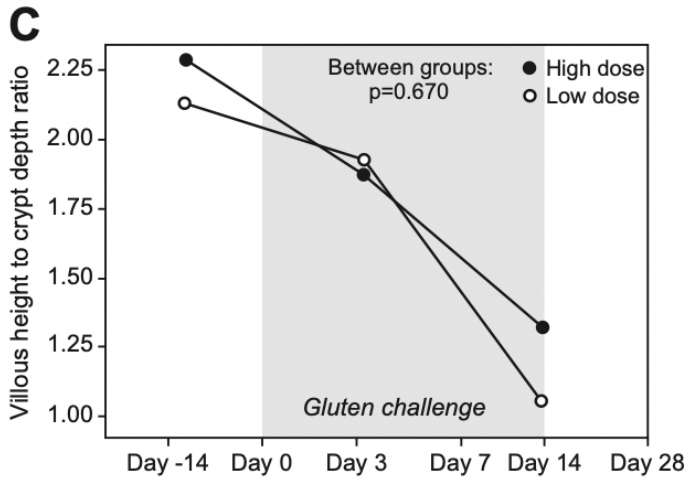




Gluten challenge

- Observational study of 20 patients with known celiac disease undergoing gluten challenge(Leffler Gut 2013)
  - By day 14, histologic changes appear
  - By day 28, tTG titers rise in both groups
  - After stopping gluten, symptoms resolve by 14 days
- There are no long term risks to gluten challenge
- Patients should be counselled during the process

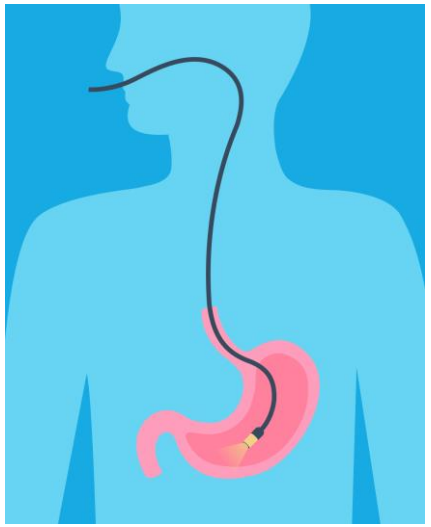




Leffler, Gut 2013:62:996-1004

Case 1

- The patient goes on a well tolerated the classic gluten challenge with 10g for 8 weeks. She noticed moderate increased in bloating and headaches but was able to continue the gluten challenge. The repeat her serology reveal an elevated **tTG-IgA of 92**. You wish to send her for a gastroscopy but the patient is anxious about the procedure.
- She would like to know if she can avoid the endoscopy given her high tTG-IgA titers and HLA results.
- **Can you diagnose celiac disease without histology?**



Biopsy avoiding diagnostic strategy for celiac

- In select population, diagnosis of celiac can be made without duodenal biopsy
  - Mostly adopted for **pediatric** population
- Requirements
  - Clinical symptoms of celiac
  - **Anti-TTG > 10x UNL**
  - Positive EMA-IgA
  - Positive HLA-D2/DQ8

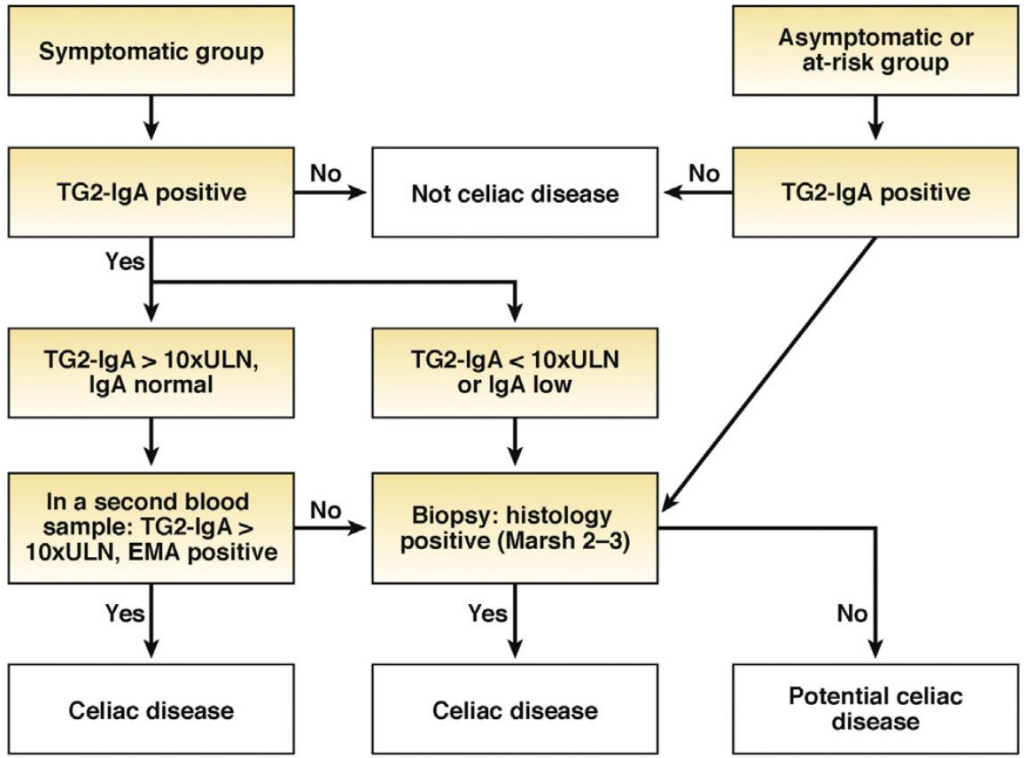


Figure 1. Suggested biopsy-avoiding diagnostic pathway for coeliac disease. On the right is the process for an asymptomatic or at-risk child. A positive anti-TG2 result should lead to biopsies and histological analysis for diagnosis. Potential celiac disease suggests further follow-up.

Husby, gastroenterology, 2019:156:885-889

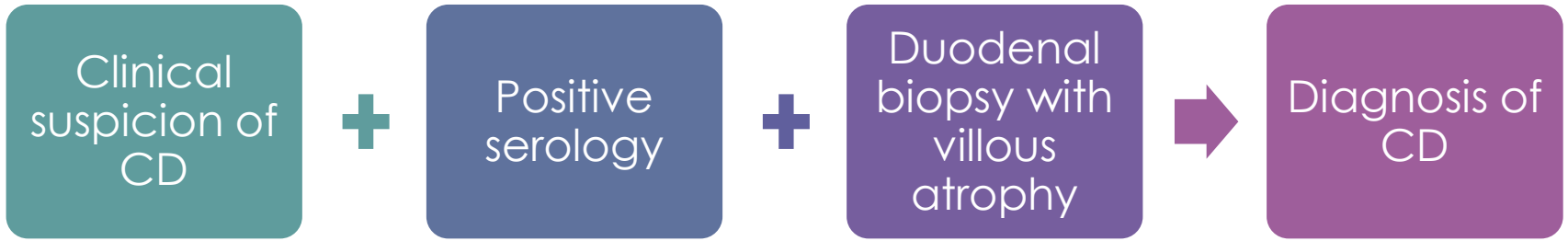
Histologic findings

- Allows to rule out other pathologies
- **What are we looking for on histology?**
  - Intra-epithelial lymphocytes (>25/hpf)
  - Crypt hyperplasia
  - Villous atrophy
  - Villous-crypt ratio
  - Marsh classification

- **What are some limitations of duodenal biopsies?**
  - Sampling error
  - Tangential positioning

Diagnosis of celiac disease

- Celiac is diagnosed using serology and histology in the right clinical context



Discordant results – positive serology and negative biopsy

- Confirm with pathologist
- Confirm gluten ingestion with patient
- **Potential celiac disease**
  - If other antibodies are positive (anti-EMA, anti –DGP) → increased probability of celiac disease
  - Management
    - Consider gluten free diet if symptomatic → Repeat biopsy on gluten free diet
    - If decide to stay on gluten → re-biopsy in 3-6month
- False positive
  - Usually less than 3x ULN (anti-tTG)
  - DDx: auto-immune disease, hypergammaglobulinemia, chronic liver disease, CHF, infectious enteritis

Diagnostic subtypes

- Potential celiac disease
- Seronegative celiac disease (or seronegative enteropathy)
- Refractory celiac disease

Seronegative enteropathy

- Definition: villous atrophy and negative serology (negative tTG, DGP, anti-EMA)
  - Compatible genetics
  - Response to gluten free diet
- Investigations
  - HLA testing
  - Rule out other causes of villous atrophy
- Gluten free diet
  - Repeat endoscopy after 1-3 years on a gluten free diet
  - Seronegative celiac disease is confirmed if improved histology on a gluten free diet

Leonard, Gastroenterology 2021; 160:427-444

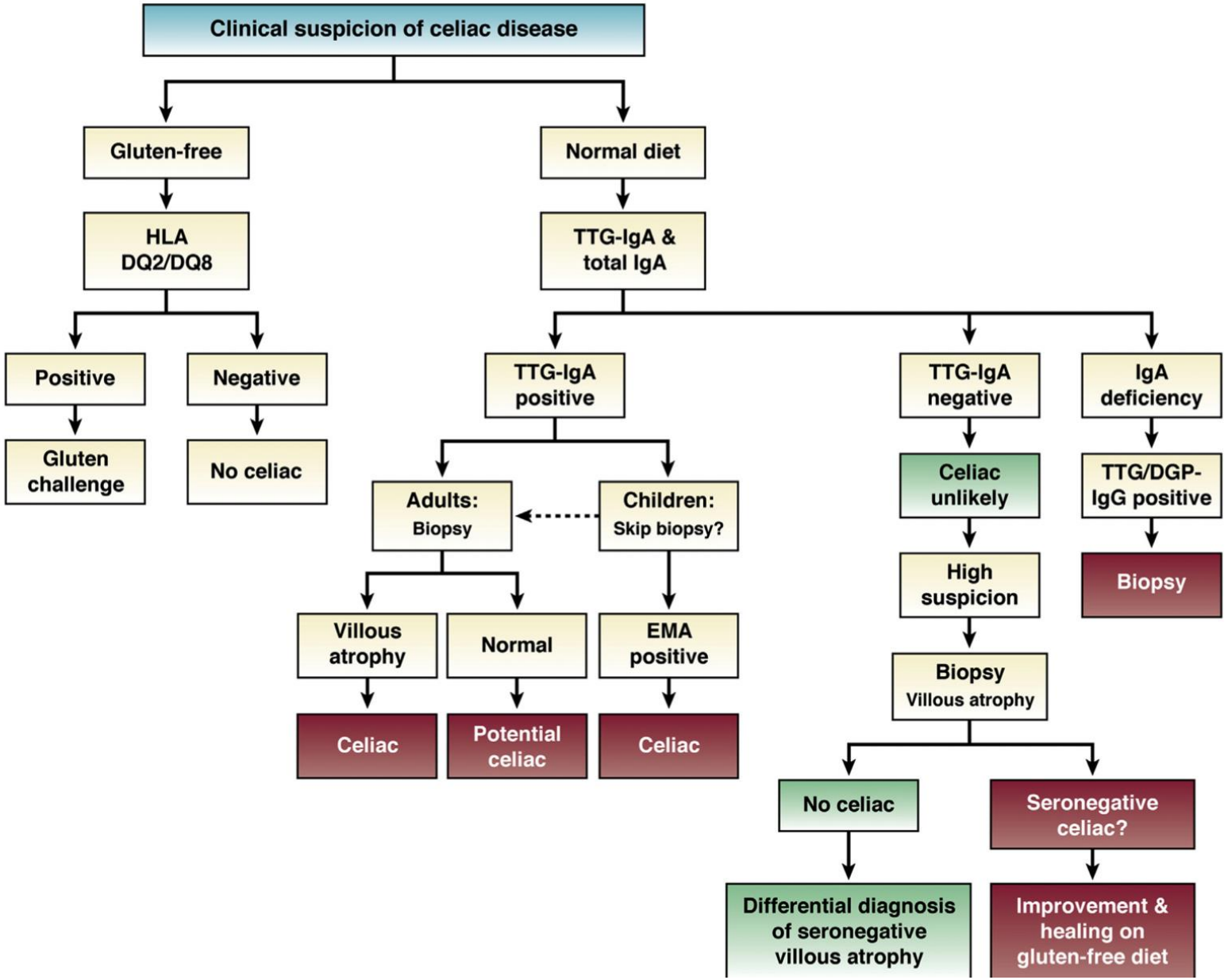
Other causes of villous atrophy and IEL

Intraepithelial lymphocytes

- H Pylori
- Medication (NSAIDs, PPI)
- Infections (viral GE, giardia)
- Autoimmune conditions (RA, SLE, Hashimoto, AI enteritis)
- Small intestinal bacterial overgrowth (SIBO)
- Common variable immune deficiency (CVID)
- Microscopic colitis
- Blind loop

Villous atrophy

- Infections (tropical sprue, giardia, Whipple's disease)
- Medication (**Olmesartan**, colchicine, immunosuppressant)
- Collagenous sprue
- Auto-immune enteritis
- CVID
- Crohn's disease
- Radiation, chemotherapy
- Eosinophiic gastroenteritis
- SIBO
- Nutritent deficiency
- Amyloidosis
- Intestinal lymphoma
- Intestinal TB



Husby, gastroenterology, 2019:156:885-889

Case 1

- The patient finally decides to undergo an EGD. There is scalloping and the pathology report show finding corresponding to Marsh 3a.
- You refer the patient to a nutritionist. In the meantime, she would like to know what she should avoid eating.
- **How to you counsel her for a gluten free diet?**

Gluten free diet

- Avoid gluten containing ingredients or "contains" claim
  - **Wheat (including spelt and kamut), barley, rye, gluten contaminated cereals***
  - *Oats are acceptable if specially produced "gluten free oats"
- Label reading
  - Avoid "may contain wheat"
  - Look for "gluten free" claim
    - Certifies <20 ppm of gluten content
    - Max gluten allowed is 10mg /day
- Look for logos that are "gluten free certified"

Gluten free diet

- Unsafe grains and foods
- Hidden sources of gluten
  - Candy, chocolate, alcohol, sauces, seasoning blends, potato chips, ice cream, deli meats, soups
- Cross-contamination
  - Kitchen organization
  - Food preparation

Unexpected sources of gluten. Canadian celiac association. https://www.celiac.ca/wp-content/uploads/2022/08/Unexpected-Sources-of-Gluten-Infographic.pdf

Limitations of gluten free diet (GFD)

- Non food sources of gluten
  - Body care product such as cosmetics, lotions, toothpaste that can be ingested
  - Medication containing gluten
- Nutritional deficiencies associated with GFD
  - Lower B vitamins, vitamin D, vitamin E, folate
  - Lower minerals such as iron, calcium, magnesium, zinc
  - Low complex carbohydrate and low fiber
  - Higher fat and sugar contents

Patient references

- Canadian celiac association: www.celiac.ca
- Coéliaque Québec: www.coeliaque.quebec
- www.beyondceliac.org
- www.celiac.org
- www.nationalceliac.org

Case 1

- Before leaving, the patient asks you what she will be expecting in terms for follow-up. **Will she need blood work or other investigations such as endoscopy?**

- CBC
- Iron studies
- Folate
- Vitamin B12
- Albumin
- LFTs
- INR
- Calcium
- Phosphate
- Vitamin D
- TSH
- Bone density (if risk factor or severe malabsorption)
- Weight/BMI
- Trace: zinc, Cu, Mn
- Vitamin A, E

Case 1

- The patient tells you that she had read about increased risks of lymphoma in patients with celiac disease. She would like to know if this is true and what are other complications of celiac disease.
- **Is she at increased risk for lymphoma?**
- **What are other complications of celiac disease?**

Complications of celiac disease

- Malabsorption
- Anemia
- Osteoporosis
- Refractory celiac disease
  - Type 1 and type 2 (higher risk for progression to lymphoma)
- Small bowel lymphoma
  - Enteropathy associated T-cell lymphoma (EATL)
- Small bowel adenocarcinoma

Nutritional deficiencies in celiac disease

- Iron deficiency
  - 2-5% of patient with iron deficiency anemia have celiac disease
- Vitamin D deficiency
  - From villous atrophy and fat malabsorption
  - Bone density in high risk patient
- Calcium deficiency
  - Secondary lactose intolerance
- B12 deficiency
- Folate deficiency
  - Low in GFD
- Other deficiencies:, zinc, copper, B6

Dennis Gastroenterol Clin N Am 2019; 48:53-72

Case 1

- At 6 month, you see her at a clinic follow-up.
- **What are elements do you include in your assessment?**

Case 1

- Your patient says she has a good compliance to gluten free diet. She eats out about once per week and asks for gluten free dishes. She has maintained her weight and has a good appetite. She denies any bloating diarrhea and weight loss.
- Her repeat labs are:
  - Hemoglobin 125, normal LFTs and iron studies are normal
  - tTG is 21 (positive) from prior level of 92
- **What is the next step in her management?**

Monitoring of celiac disease

- Assess for symptoms of CD and complications
- Review compliance to GFD
- Monitor celiac serology (most normalize by 2-3 years)
  - Good marker for GFD compliance
  - Poor sensitivity for villous atrophy
  - Gluten immunogenic peptide (GIP) to detect gluten exposure
- Bone density at diagnosis and q5yrs
- Assess for mucosal healing
  - May take 6-24mo
  - Consider EGD at 1-2 years
- Vaccination for hyposplenism (N Meningitis and H Influenza)

Follow-up intervals

Expert dietitian education
Anthropometry / BMI

Check:
- Coeliac serology
- Routine tests: Nutrient screen (Iron, vitamin B12, folate, vitamin D, calcium, phosphate + others as indicated); Liver enzymes; Thyroid function tests
- DEXA (at diagnosis, but not later than 30-35 years)

Join coeliac society
Immunisation
Family screening
Mental wellbeing

GP letter outlining follow-up plan

History – dietary progress and adherence; dietitian review if needed

Check that family screening, joining coeliac society and immunisation has been followed-up

Anthropometry / BMI

Check:
- Coeliac serology
- Routine tests (at 6 months if previously abnormal; at 12 months routinely)

Letter to update GP

History – dietary adherence; dietitian review if needed

Anthropometry / BMI

Check:
- Coeliac serology
- Routine tests

DEXA as indicated based on index result

Consider follow-up small intestinal biopsy after 2 years to confirm mucosal healing

Letter to update GP

Tye-Din Alimentary Pharmacology and Therapeutics, 2021;56:49-63

Conclusions

- The presentation of celiac disease includes classical and non-classical presentation as well and intestinal and extra-intestinal features.
- Screening for celiac should be performed in
  - patients with signs and symptoms suggestive of celiac disease
  - high-risk population1st degree relatives, DM1, auto-immune conditions)
- Serology with tTG-IgA and total IgA level should be used as first line for screening
- HLA DQ2 and DQ8 are good to rule out celiac disease
- Long term follow up is needed to ensure compliance and rule out complications

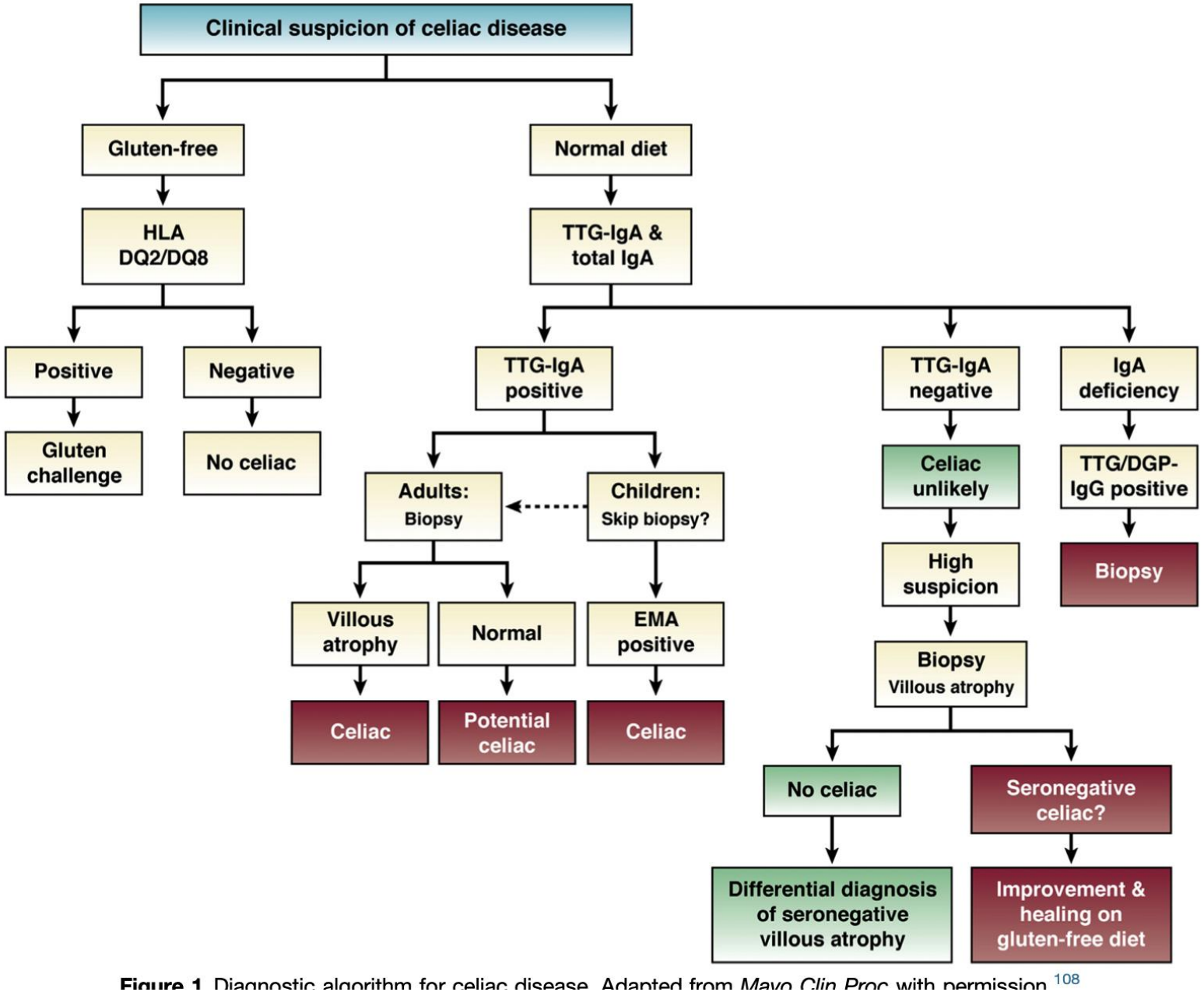


Figure 1 Diagnostic algorithm for celiac disease. Adapted from *Mayo Clin Proc* with permission.[108]

Husby, gastroenterology, 2019:156:885-889

Investigations

- CBC, B12, folate, iron studies, vitamin D, INR
- Ca, Mg, Phos
- Albumin, pre-albumin
- Fecal fat test
  - If high, do the 72hr stool collection
- Fecal elastase for pancreatic insufficiency
- Alpha-1-antitrypsin clearance for protein losing enteropathy
- Breath test
  - Specific carbohydrate malabsorption and SIBO
- Endoscopy
- Imaging

Table 2
Causes of malabsorption.

Causes of malabsorption	Entity	Specific diseases
Luminal phase		
Affecting absorptive surface	Short bowel syndrome	
	Intestinal mechanical obstruction	
	Intestinal fistula	
	Intestinal dysmotility	
	Small bowel mucosal disease	Crohn's disease
		Coeliac disease
		Radiation enteritis
		Autoimmune enteropathy
		Amyloidosis
		Giardiasis
		Tropical sprue
		Whipple's disease
	Bariatric surgery	
Deficiency of digestive enzymes/substrates	Digestive enzyme deficiency	Chronic pancreatitis
		Cystic fibrosis
		Gastrinoma (acid inactivation of lipase)
		Orlistat (inactivation of lipase)
	Decreased bile salts	Cirrhosis (decreased synthesis)
		Chronic cholestasis (impaired secretion)
		Bacterial overgrowth (bile salt deconjugation)
		Ileal disease or resection (increased losses)
	Specific nutrients	Pernicious anaemia (cobalamine/vitamin B 12)
Mucosal (absorptive) phase		
	Brush border enzyme deficiency	Lactase deficiency
	Enterocyte defect	Crohn's disease
		Coeliac disease
Transport phase		
	Lymphatic obstruction	Intestinal lymphangiectasia
		Tumour
		Infection
		Surgery

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