Update in celiac disease diagnosis (ESsCD 2025)

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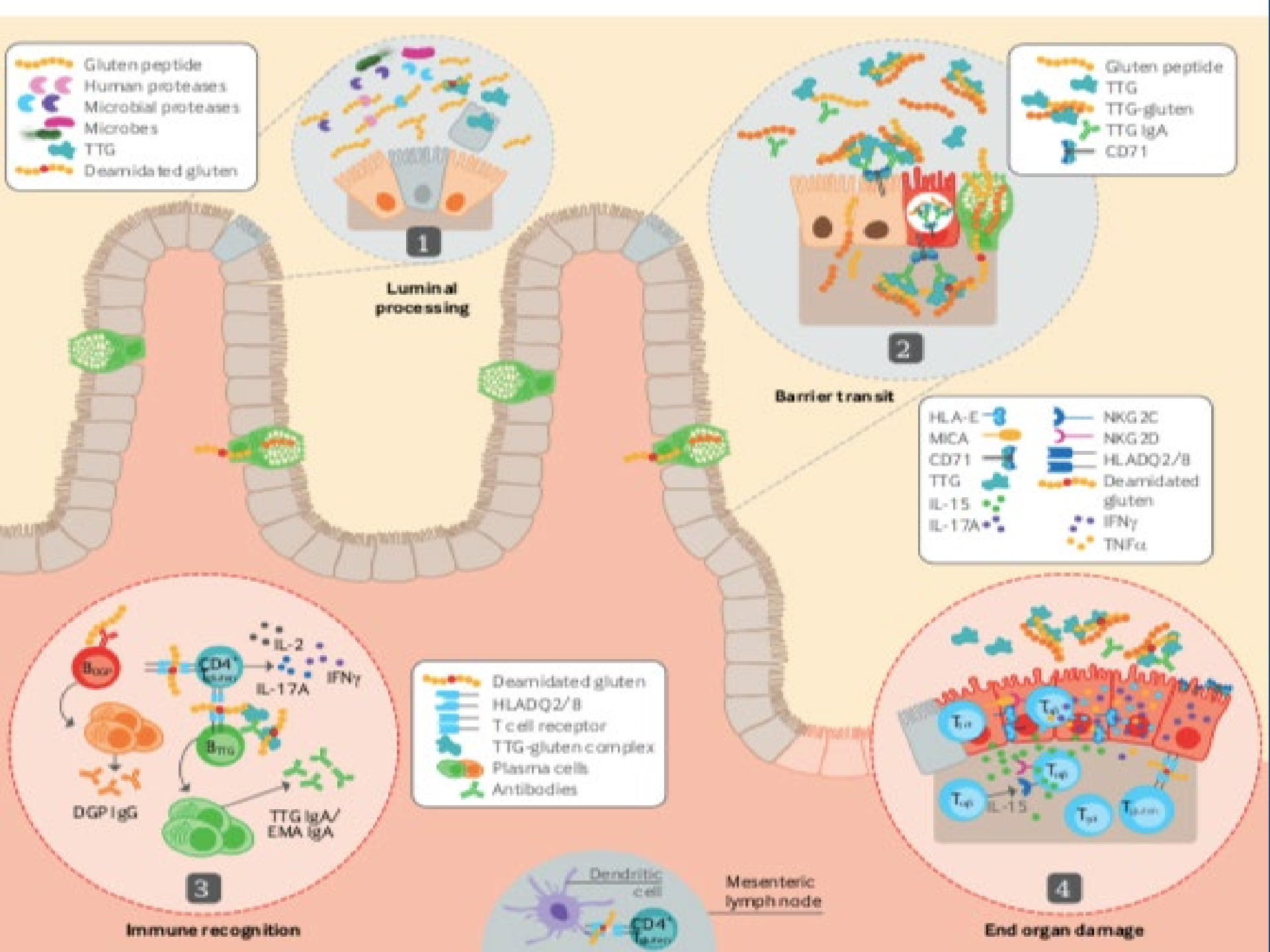

Gluten peptide
Human proteases
Microbial proteases
Microbes
TTG
Deamidated gluten
1
Luminal processing
Gluten peptide
TTG
TTG-gluten
TTG IgA
CD71
2
Barrier transit
HLA-E
MICA
CD71
TTG
IL-15
IL-17A
NKG 2C
NKG 2D
HLADQ2/8
Deamidated gluten
IFNγ
TNFα
IL-2
IL-17A
IFNγ
DGP IgG
TTG IgA/ EMA IgA
3
Immune recognition
Deamidated gluten
HLADQ2/8
T cell receptor
TTG-gluten complex
Plasma cells
Antibodies
IL-15
4
End organ damage
Dendritic cell
Mesenteric lymph node

- *Loss of gluten tolerance can occur at*

any age as a consequence of other triggers besides gluten.

- *(GI) infections, medications, and surgery have also known as trigger factors*

ACG 2023 : who should be tested ?

Patients with signs &symptoms suggestive CD:

- Intestinal and extraintestinal :
- Diarrhea, weight loss, abdominal pain and bloating, …..

unexplained elevated ALT, IDA.



	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



- Evaluation for CD could be considered in patients with unexplained dyspepsia after initial investigation.

- Consider obtaining duodenal BX in patients with dyspepsia who are undergoing EGD.

Prevalence of CD

- *overall occurrence is similar between males and females, diagnosis remains more frequent in females, with reported female-to-male ratios ranging from 2:1 to 1.5:1*



Some Clinical Aspects of CD

- DH*, share the same HLA haplotypes and improve following a GFD .*
- *Enteropathy similar to CeD have been reported in 75% with DH, and the remaining have minor changes consistent with possible latent CeD.*
- *Minor GI complaints are the most common*

Neuro-coeliac manifestations

- *Can be immune-mediated related to gluten: antibody cross reaction, deposition of immune-complex, direct neurotoxicity,*
- *and in severe cases, vitamins or nutrients deficiency*

Gluten ataxia (GA)

- *Most frequently reported in CeD.*
- *10% of patients with GA have GI symptoms but a third have enteropathy on biopsy .*

Gluten neuropathy

Is idiopathic neuropathy with positive serology. Presentations include:

- *Symmetrical sensorimotor axonal peripheral neuropathy*
- *Asymmetrical neuropathy*
- *Sensory ganglionopathy and small-fibre neuropathy*
- *Effect of a GFD on peripheral neuropathy is disappointing*

- *Gluten encephalopathy, temporal lobe epilepsy with hippocampal sclerosis, gradually progressive neurological disease and gluten sensitivity associated with white matter lesions, mimicking multiple sclerosis, have been described.*
- *Mild cognitive symptoms called 'foggy brain', which improves with GFD*

Concentration and attention difficulties

- *Episodic memory deficits*
- *word-retrieval problems*
- *Reduced mental acuity*
- *Episodes of confusion or disorientation*

- *Psychiatric disorders: Depression, bipolar disorder, apathy, excessive anxiety, schizophrenia, eating disorders, attention deficit/ hyperactivity disorder, autism and sleep disturbances, Anxiety disorders are usually reactive in patients with CeD and improve with a GFD*

Non-coeliac wheat sensitivity (NCWS):

- *characterized by (IBS)-like symptoms*
- *and extra-intestinal manifestations, occurring after ingestion of gluten-containing food, improving rapidly with gluten withdrawal and relapsing soon after gluten challenge.*

Diagnosis

- serology in low risk patients and only positive patients referred for EGD and BX for confirmation.
- In high risk patients (>5% probability of CD)
- We need both pathology and serology at the same time

High pretest probability > 5%

High pretest probability, EGD with biopsy should be done ,even with a negative serology.

Classic symptom

First degree relatives

Diabetics

Thyroid disease

Down and Terner syndrome, William

IgA deficiency

- *Serological Testing: IgA anti-tTG is primary screening test.*
- *Routine use of IgA EMA serology is no longer recommended,*

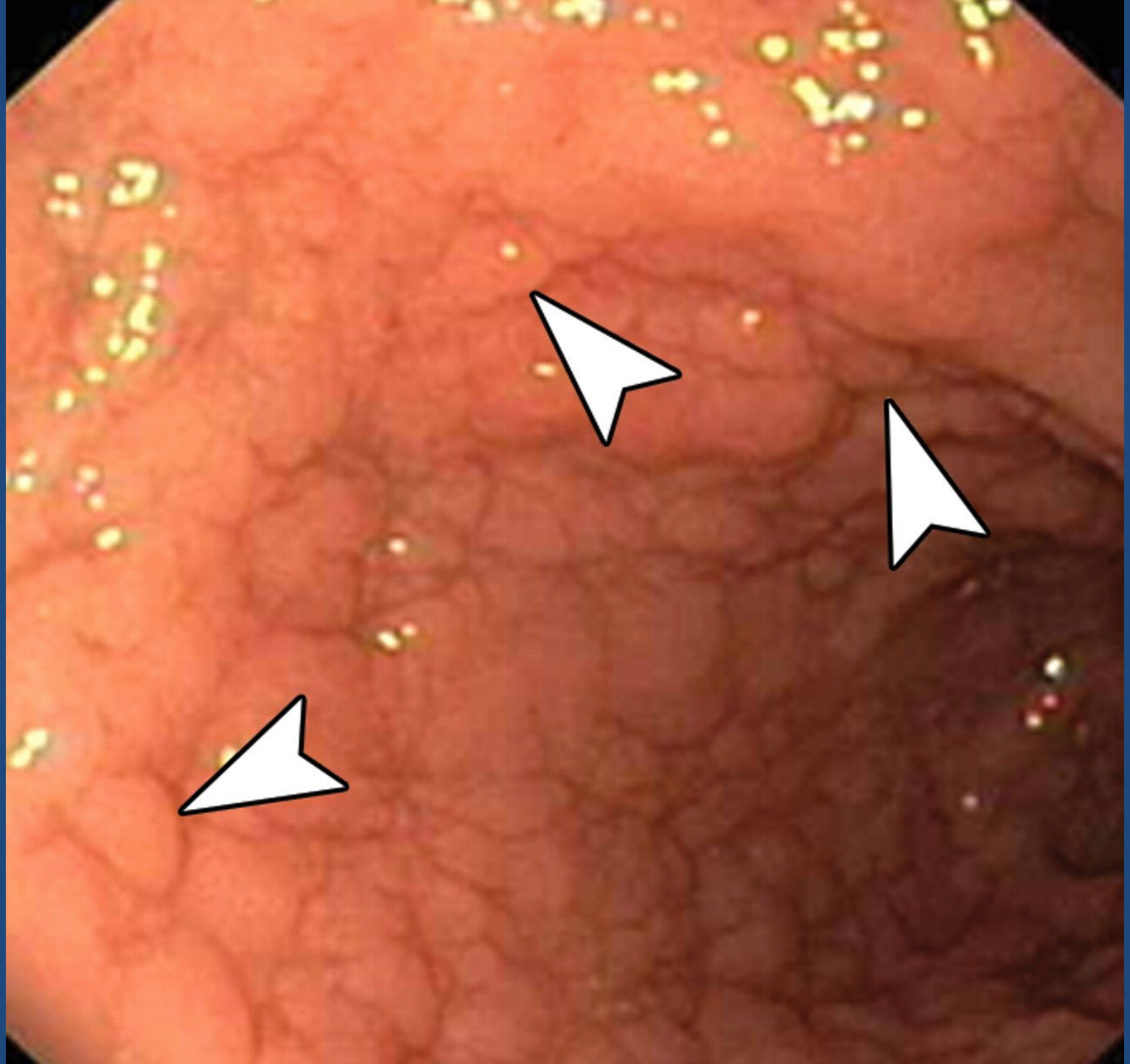
- Anti-tTG and -DGP assays, are based on the (ELISA)
- EMA assay is based on immunofluorescence
- Interobserver variability(operator dependent)
- EMA has more specificity

- *Routine use of multiple serological assays for initial screening is not supported by*
- *strong evidence and may unnecessarily increase cost and complexity.*

ESsCD 2025 and guidelines for the management of celiac disease: A systematic review.WJG 2022

Anti tTG

- Variety of manufacturers
- Some have better test characteristics than others
- Significant range in test accuracy, and switching assay may be considered if noting poor test performance



Endoscopy





United European Gastroenterology Journal

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GUIDELINE OPEN ACCESS

European Society for the Study of Coeliac Disease 2025 Updated Guidelines on the Diagnosis and Management of Coeliac Disease in Adults. Part 1: Diagnostic Approach

Abdulbaqi Al-Toma[1] | Fabiana Zingone[2,3] | Federica Branchi[4] | Annalisa Schiepatti[5,6] | Georgia Malamut[7,8] | Cristina Canova[9] | Isabella Rosato[9] | Honoria Ocagli[9] | Nick Trott[10,11] | Luca Elli[12,13] | Alina Popp[14] | Carmen Gianfrani[15] | Renata Auricchio[16] | Andra Neefjes-Borst[17] | David S. Sanders[10] | Christophe Cellier[18] | Chris J. Mulder[19] | Gerd Bouma[19] | Knut E. A. Lundin[20,21,22] | Ludvig M. Sollid[21] | Michael Schumann[4]

Diagnostic Approach

1.IgA anti tTG antibody as a single test for initial testing for CeD at any age.

2. Measure total IgA concurrently to exclude IgA deficiency.

3. Perform testing while the patient is on a GFD.

EMA *testing*

- *anti-EMA testing, highly specific, operator-dependent, less suitable for widespread initial screening.*
- *In diagnostically ambiguous situations - in patients with autoimmune or hepatic disorders -*
- *May provide added value and help avoid unnecessary duodenal biopsies*

- *Total IgA deficiency is defined by serum*
- *IgA levels < 7 mg/dL.*

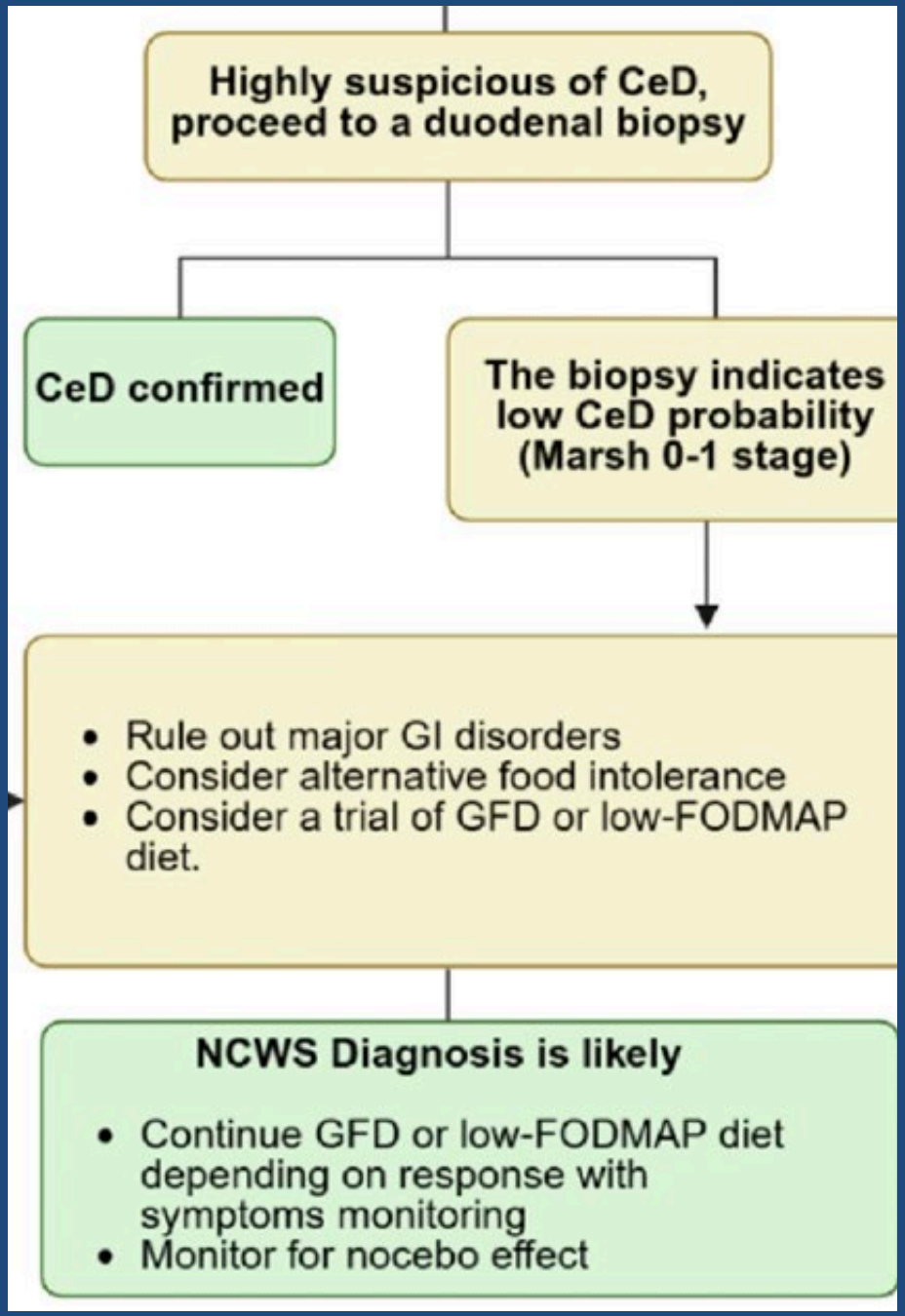
- *Partial ,when serum IgA levels are > 7 mg/dL, but below the lower limit of normal according to age*

in patients with IgA deficiency

- *IgG-based for serological testing of CeD*

(IgG anti-tTG or IgG anti-DGP) are required

- *Duodenal biopsies should be undertaken regardless of IgG serology results*


Highly suspicious of CeD, proceed to a duodenal biopsy
CeD confirmed
The biopsy indicates low CeD probability (Marsh 0-1 stage)
Rule out major GI disorders
Consider alternative food intolerance
Consider a trial of GFD or low-FODMAP diet.
NCWS Diagnosis is likely
Continue GFD or low-FODMAP diet depending on response with symptoms monitoring
Monitor for nocebo effect

Histopathology

- *Mucosal lesions have a patchy distribution. multiple BX (four biopsies from D2 and 1–2 from bulb) are needed.*
- *Bulb biopsies should be placed in a separate vial.*
- *when only bulb biopsied, Brunner's glands resulting in a reduced villous height.*
- *PUD and gastric metaplasia at bulb make diagnosis of CeD difficult*

Do the Sub-Classifications (A, B, C) of Marsh-III Stage in the Modified Marsh Classification Add Clinically Relevant Information?

- *While the sub-classifications (3A–3C) offer a more detailed description of mucosal damage, their clinical relevance in routine practice is limited*

Quantitative evaluation of BX

- *villous height-to-crypt depth (Vh:Cr) ratio and (IEL) density .*
- *A Vi:Cr ratio < 2 indicates villous atrophy and active disease, while treated patients with CeD typically have ratios > 3.*
- *A threshold change or healing of 0.4 in Vi : Cr or ≥ 30% in T-cell IEL density is considered clinically significant*

How Should Duodenal Biopsies Be Processed for Optimal Evaluation in CeD Diagnosis?

- *well-oriented duodenal biopsies are essential.*
- *Haematoxylin and Eosin (H&E) staining is recommended for routine diagnostic purposes.*

- *immunohistochemical (IHC) staining, including formalin-fixed staining such as CD3 and gamma delta, is more precise for identifying IELs in challenging or borderline cases*

- *The use of classification systems (the modified Marsh classification)*
- *Comprehensive pathology reporting*
- *Adequate biopsy sampling*

are essential components of high-quality diagnostic practice.

Report of pathology

- *Histological interpretation should be made by clinical and serological information whenever possible.*
- *The pathology reports should explicitly detail key parameters*
- *such as the number of biopsies received, the quality of orientation, Vi : Cr ratio, IEL count, and Marsh stage.*

- *In cases of diagnostic uncertainty, especially when assessing mild or borderline changes, obtain a second opinion to increase diagnostic confidence.*
- *Use of digital pathology platforms and AI is supporting and reducing interobserver variation*

Can Advanced Endoscopic Techniques Replace Standard Histopathology in the Assessment of Small Bowel Mucosal Damage in CeD?

- *While it may allow for biopsy-free diagnosis in some cases, CLE is costly, requires specialised equipment and expertise, and is not widely accessible*
- *further research is required to establish a standardized and validated classification system for its interpretation.*

Can the Diagnosis be made in Persistently Positive Serology But Architecturally Normal Duodenal Histology?

- *If these individuals carry the HLA-DQ2 and/or DQ8 haplotype, they may be classified as having potential coeliac*

False-positive tTG

- *In conditions such as hypergammaglobulinemia, autoimmune diseases, chronic liver disease, and enteric infections.*
- *Transient positive anti-tTG may be seen at the time of T1DM diagnosis.*

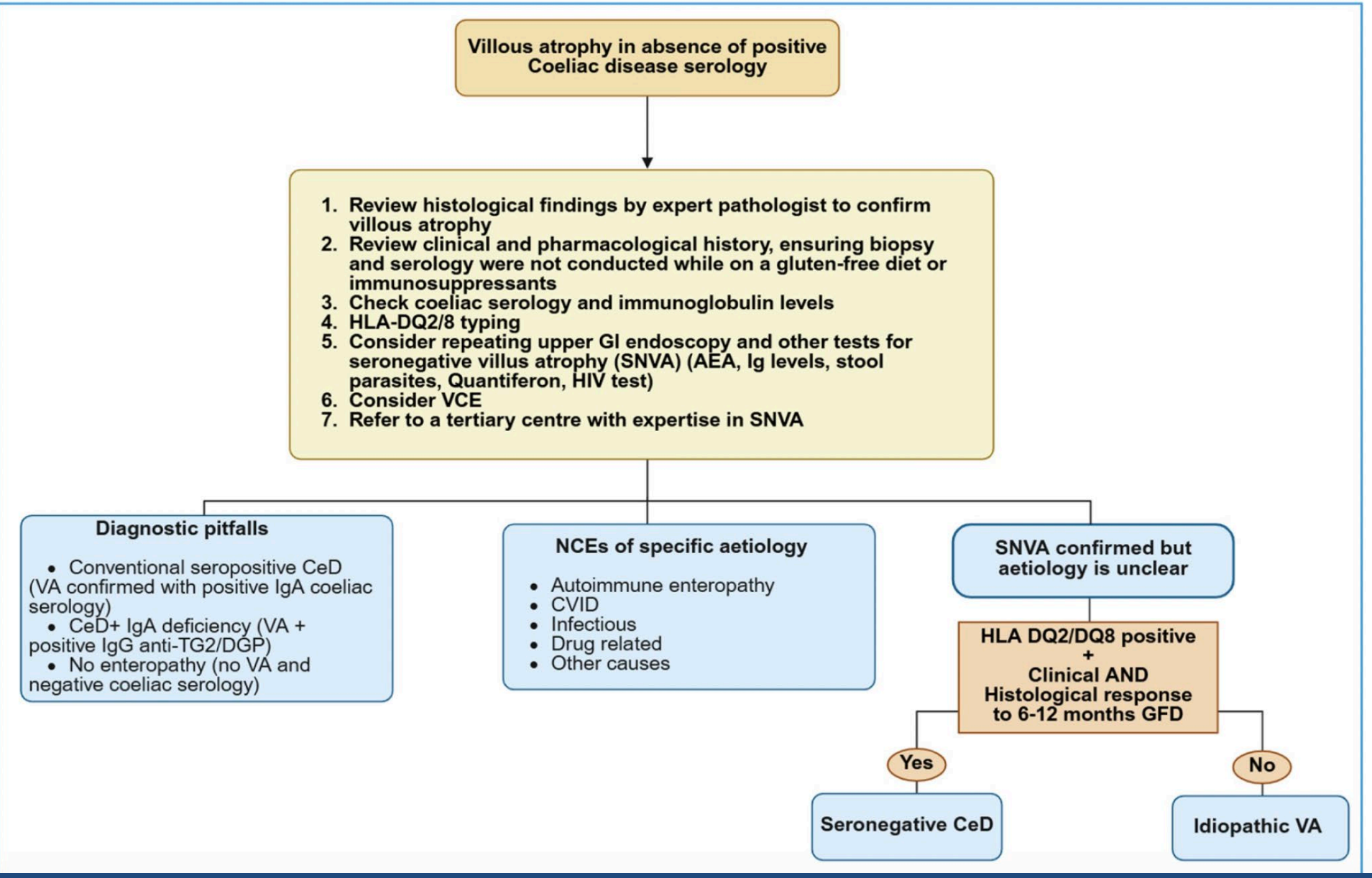
Marsh-I histology

- *Is non-specific and has been observed in 1.3%–6% of small-bowel biopsies :*
- *gluten-related disorders (CeD, NCWS),*
- *wheat allergy, HP infection and drug-related reactions.*
- *it may be secondary to (IBD), autoimmune conditions, immunoglobulin deficiencies, blood malignancies, infections and IBS*

What Is the Approach to Villous Atrophy in the Absence of CeD-Specific Serology

- *After excluding other causes of seronegative villous atrophy, diagnosis of CeD should rely on the clinical and histological response to a GFD in individuals with HLA-DQ2 or HLA-DQ8 haplotypes.*

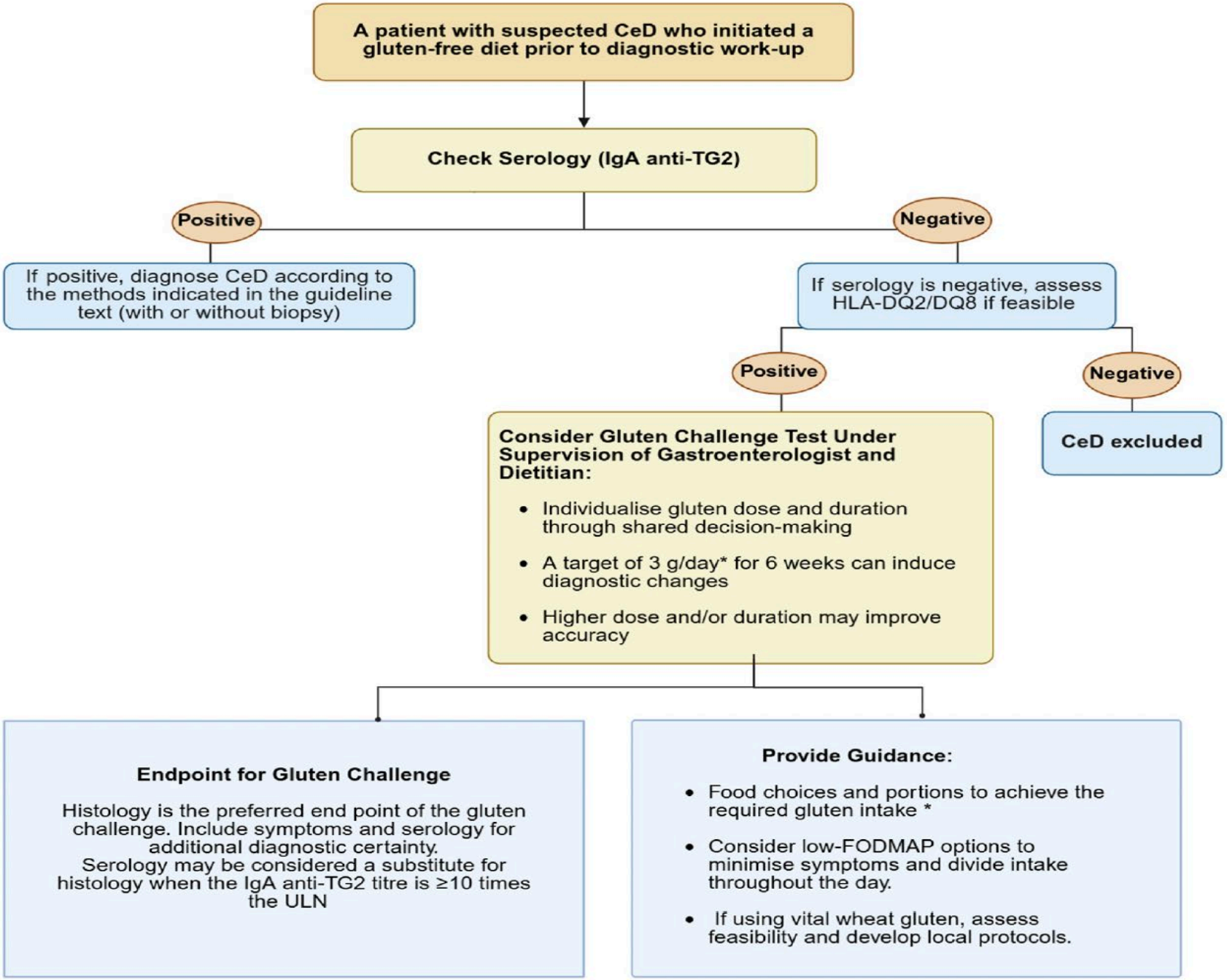
- *Duodenal histological assessment is endpoint for evaluating gluten challenge.*
- *Clinical symptom monitoring and serological testing may support diagnosis and enhance diagnostic certainty.*


Villous atrophy in absence of positive Coeliac disease serology
1. Review histological findings by expert pathologist to confirm villous atrophy
2. Review clinical and pharmacological history, ensuring biopsy and serology were not conducted while on a gluten-free diet or immunosuppressants
3. Check coeliac serology and immunoglobulin levels
4. HLA-DQ2/8 typing
5. Consider repeating upper GI endoscopy and other tests for seronegative villus atrophy (SNVA) (AEA, Ig levels, stool parasites, Quantiferon, HIV test)
6. Consider VCE
7. Refer to a tertiary centre with expertise in SNVA
Diagnostic pitfalls
• Conventional seropositive CeD (VA confirmed with positive IgA coeliac serology)
• CeD+ IgA deficiency (VA + positive IgG anti-TG2/DGP)
• No enteropathy (no VA and negative coeliac serology)
NCEs of specific aetiology
• Autoimmune enteropathy
• CVID
• Infectious
• Drug related
• Other causes
SNVA confirmed but aetiology is unclear
HLA DQ2/DQ8 positive + Clinical AND Histological response to 6-12 months GFD
Yes
No
Seronegative CeD
Idiopathic VA

- *In cases of serum IgA anti–tTG antibody titre ≥ 10 the ULN, serology may be considered an acceptable alternative to histological confirmation.*

- *Until more safety data are available, the no-biopsy approach should be limited to patients under 45 years with tTG >10 ULN*

- *ungraded expert opinion; Agreement: 95%*



** Example: Bread (white or wholemeal, 1 slice) contains 3.5 grams of gluten*

Drug and villous atrophy

- Olmesartan and other angiotensin inhibitors
- Azathioprine
- Micophenolate mophetile
- Methotrexate.

Idiopathic and temporary villous atrophy

- Acute and self- limiting forms of enteropathy with variable degree of villous blunting likely due to acute infective gastroenteritis.

- Transient VA resolving spontaneously within 6–12 months

Rebiopsy for assessing mucosal healing

- Repeat biopsy after 2 years of GFD to assess mucosal healing. Some suggest repeating biopsies only for persistent symptoms or serological abnormalities after 12 mo of GFD.
- Especially in patients >40 Y/O at diagnosis or with classical presentation, risk of complicated CD is higher.

Rubio-Tapia A, et al. Mucosal recovery after treatment with a GFD. Am J Gastroenterol 2010

Serological Investigation of Persistent Villous Atrophy in Celiac Disease

Changlin Gong, MD[1], Claudia Saborit, MD[1], Xin Long, MD, PhD[1], Ao Wang, MD[2], Beishi Zheng, MD[1], Howard Chung, MD[1], Suzanne K. Lewis, MD[2], Suneeta Krishnareddy, MD[2], Govind Bhagat, MD[2,3], Peter H.R. Green, MD[2,*] and Xiao-Fei Kong, MD, PhD[1,4,*]

Clinical and Translational Gastroenterology 2023

- 36.6% of patients had presence of villous atrophy at follow-up visit.
- Patients in this study with ongoing mucosal injury had a combination of gluten exposure, slow recovery, and refractory celiac disease.
- These data suggest substantial proportion of patients not achieving therapeutic goals.

If biopsies were normal but symptoms persist:

other associated causes of abdominal pain and diarrhea with celiac disease are considered:

- Lactose deficiency
- IBS
- Microscopic colitis
- BOG
- Fructose intolerance.


CD with persistent symptom by GFD
Confirm diagnosis
Confirm adherence to GFD
EGD and BX after 12 months
Atrophy
RCD,IBD ,CVID,….
No atrophy
CD+Other cause













