

# Coeliac Disease and Other Food Sensitivities

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# Objectives

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## 01 Recognise

Modern adult phenotypes and extra-intestinal disease.

## 02 Diagnose

Use serology, biopsy, histology and HLA testing well.

## 03 Differentiate

Separate coeliac disease from mimics, allergy and intolerance.

## 04 Escalate

Approach non-response, refractory disease and malignancy risk.

# Case: Mr C.M.

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## Presentation

16-year-old African male referred to adult GI  
Longstanding diarrhoea, weight loss and stunting  
Absent secondary sexual characteristics  
Angular stomatitis; crusted buttock lesions, not typical DH

## Context and course

Limited-resource background  
Strict GFD attempted, but not fully affordable or feasible  
Prednisone and azathioprine tried  
No complete symptom resolution; never achieved full GFD adherence

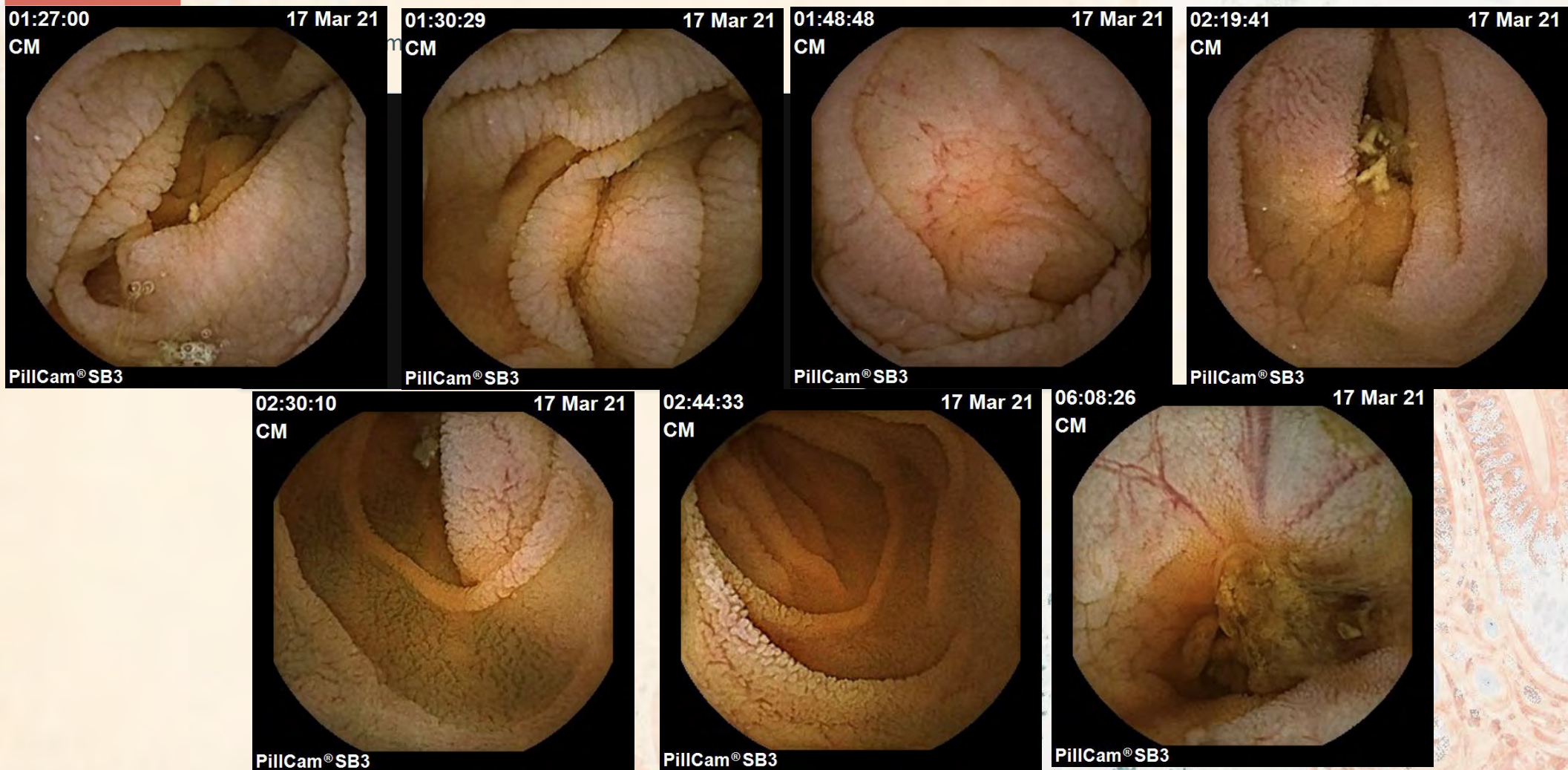
## Bloods and serology

Hb 10.2 g/dL; MCV 76.4 fL  
Ferritin 49; transferrin saturation 8%  
B12 65 pmol/L  
Total IgA normal  
tTG-IgA equivocal, later positive 21 U/mL

## Endoscopy and histology

Gastroscopy: atrophic gastritis; D2 macroscopically normal  
Colonoscopy: colon normal  
Terminal ileum: flattened villi; no ulceration, erosion or erythema  
TI biopsy: mild villous atrophy, crypt hyperplasia and increased IELs  
Marsh 3A; colonic biopsies normal

# Capsule endoscopy findings Mr CM



Patient capsule endoscopy stills supplied for teaching case.

# Definitions:

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## Coeliac disease

A chronic, immune-mediated small-intestinal enteropathy precipitated by dietary gluten in genetically predisposed people.

## Refractory coeliac disease

Persistent malabsorptive symptoms and villous atrophy after more than 12 months of a strict gluten-free diet.

## Potential coeliac disease

Positive coeliac serology with normal or near-normal duodenal mucosa.

## Gluten-related disorders

An umbrella term for coeliac disease, wheat allergy, and non-coeliac gluten or wheat sensitivity.

# Epidemiology: the 1% disease with an iceberg problem

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**~1%**

Estimated global prevalence, with major regional variation.

**2-3%**

Reported in high-prevalence countries such as Sweden.

## The epidemiology has changed

- A north-south prevalence gradient is described.
- No longer just a childhood malabsorption syndrome.
- Peak childhood incidence has shifted from 1-2 years to 5-8 years.

# Genetics: HLA is necessary, not sufficient

HLA-DQ2/DQ8 is a gatekeeper for coeliac disease, not a diagnosis.

**~100%**

of patients carry HLA-DQ2 or HLA-DQ8.

**30-45%**

of the general population also carry these haplotypes.

**3-4%**

of carriers eventually develop coeliac disease.

## Geography changes the pre-test probability

- HLA-DQ2/DQ8 are uncommon in East Asia and Japan; coeliac disease is also less common.
- African data are heterogeneous: North Africa/Saharawi populations show stronger HLA-wheat signals.
- Sub-Saharan data remain limited; DQ2 is reported around 5-10%, with true incidence uncertain.

# Coeliac disease in Africa: uncommon, or under-recognised?

The African signal is uneven: genotype, wheat exposure and diagnostic access all matter.

**1.1%**

Estimated African seroprevalence in global meta-analysis.

**5.6%**

Endomysial antibody positivity reported in Sahrawi children.

Higher wheat consumption and greater HLA-DQ2 frequency likely raise both risk and detection.

## Sub-Saharan evidence gap

Historically considered rare in Central Africa; now better framed as a major knowledge gap.

# Coeliac disease in South Africa: genetic risk is present

A SANBS transplant donor/recipient study found HLA susceptibility haplotypes across all population groups.

**n=5,746**

Potential organ donors and recipients typed through the South African National Blood Service.

**19.8%**

Overall HLA-DQ2.5/DQ8 prevalence; lower than ~30% reported in many Western populations.

## Population-group gradient

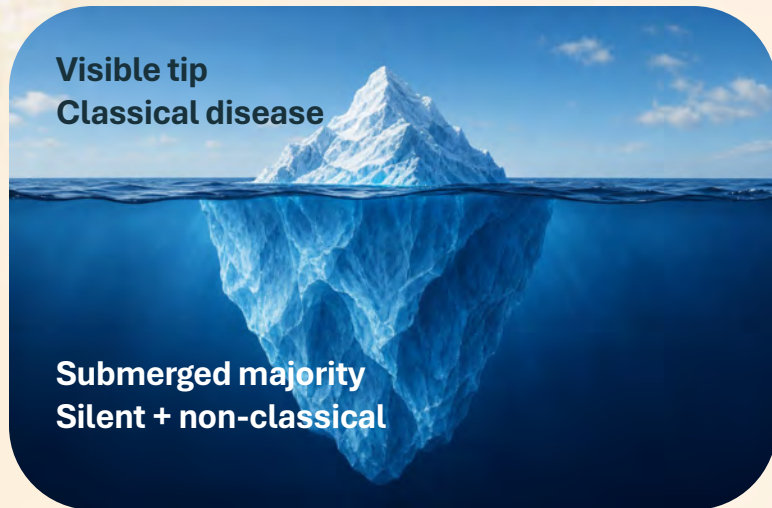
White 28.6%; coloured 22.0%;  
Indian 17.4%; black 15.9%.

## High-risk genotypes are not absent

DQ2.5 homozygosity or DQ2.5 plus DQ8: 1.7% of black and 2.2% of white participants.

**Question raised: underdiagnosis, silent disease, or lower penetrance of genetic risk?**

# Who gets missed? The submerged phenotype



**~70% may sit below the clinical waterline**

**In some European screening studies, diagnosed: undiagnosed cases were about 1:7.**

## **Asymptomatic**

Positive serology and enteropathy, but no volunteered symptoms. Often found through risk-group screening.

## **Non-classical or minor symptoms**

Iron deficiency, fatigue, arthralgia, headaches, enamel defects, short stature, raised transaminases, ataxia or neuropathy.

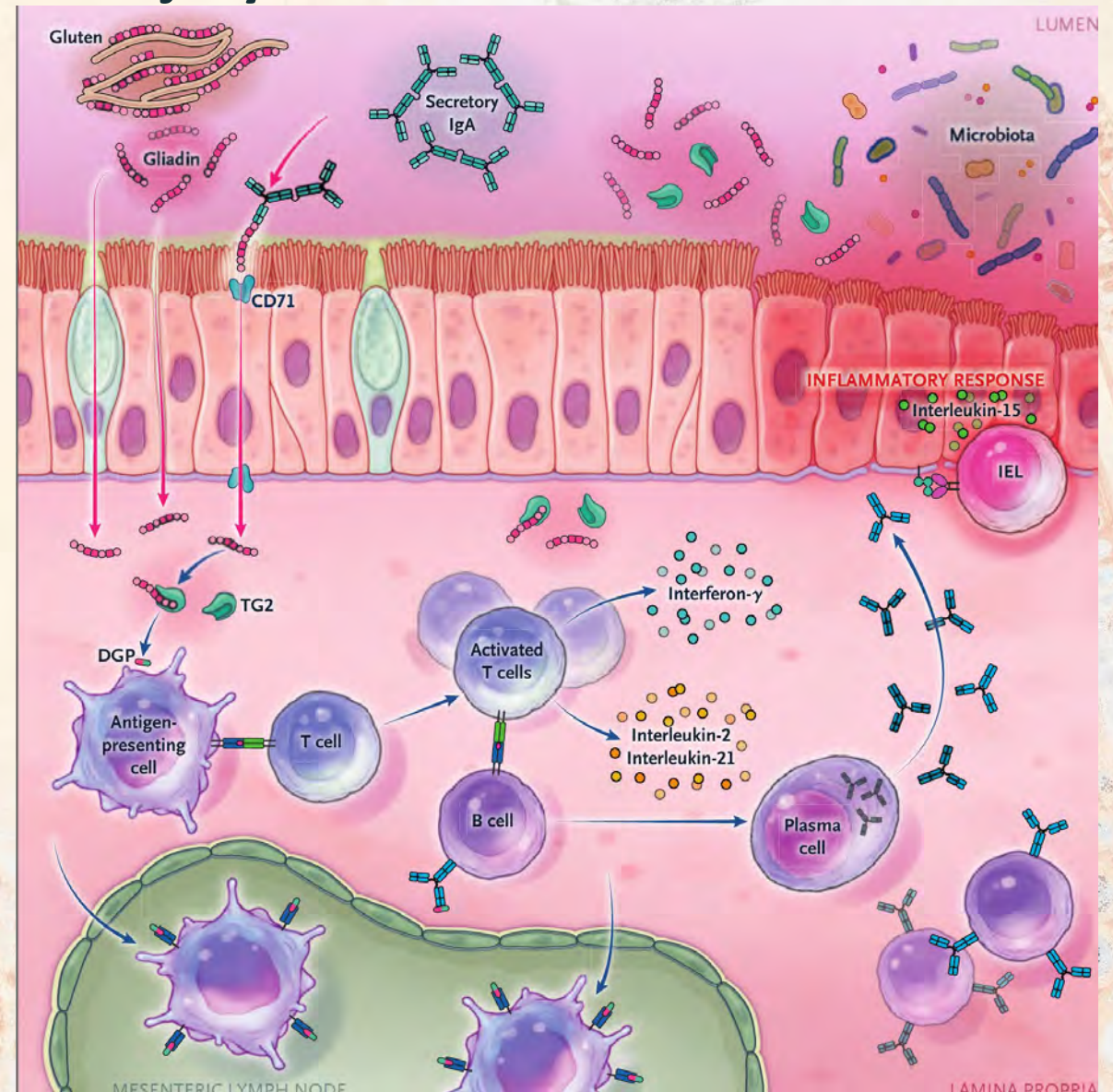
## **Not necessarily benign**

Untreated disease is linked with osteoporosis, impaired growth, infertility and higher malignancy risk.

# Pathogenesis: gluten, TG2 and mucosal injury

## Core sequence

1. Gluten peptides persist and cross the epithelium
2. TG2 deamidates gliadin peptides
3. HLA-DQ2/DQ8 present DGP to CD4+ T cells
4. Cytokines and B-cell responses amplify injury
5. IEL cytotoxicity drives villous atrophy



# Clinical presentation

## Classical manifestation

- Chronic diarrhoea
- Poor appetite
- Weight loss
- Abdominal distension
- Poor nutritional status
- Coeliac crisis

## Non-classical form

- Recurrent abdominal pain
- Bloating
- Diarrhoea or constipation
- Persistent iron deficiency
- Chronic fatigue
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- Hypertransaminas aemia
- Short stature
- Dermatitis herpetiformis
- Nutritional deficiencies
- Arthralgia or arthritis
- Alopecia
- Recurrent stomatitis
- Dental enamel defects

## Subclinical CD

- No clinical manifestations
- Usually identified through screening
- Intestinal damage still occurs
- Part of the hidden burden of disease
- About 70% escape diagnosis and treatment on average

# Gastrointestinal manifestations and malabsorption

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## Domain / Clinical features

### **Upper GI**

Nausea, vomiting, abdominal pain, bloating.

### **Lower GI**

Chronic diarrhoea, steatorrhoea, weight loss.

### **Children**

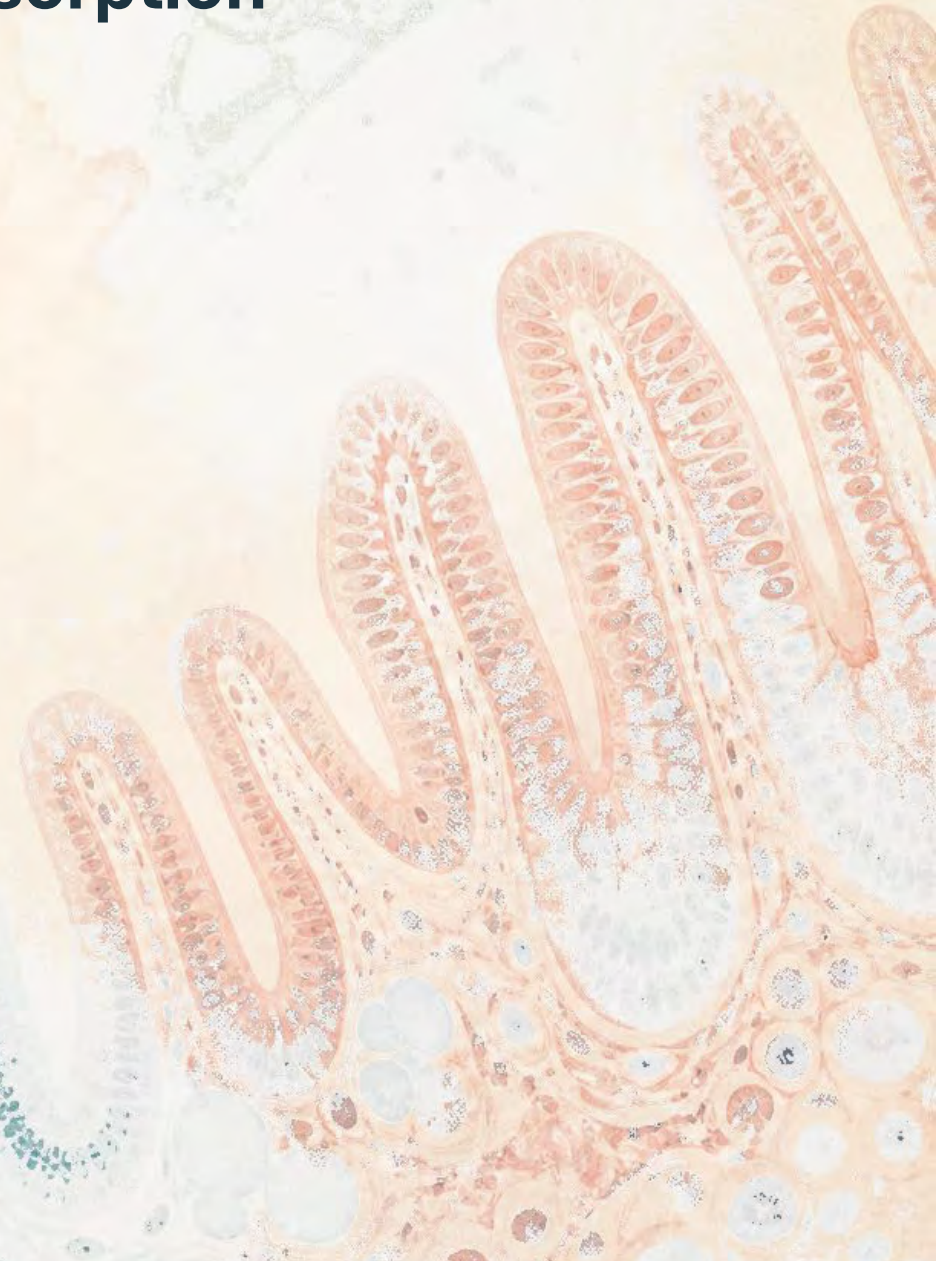
Growth failure, short stature, delayed puberty.

### **Malabsorption**

Carbohydrate/lactose, fat, and protein malabsorption.

### **Deficiencies**

Iron, vitamin B12, folate, copper, and other micronutrients.



# Associated autoimmune and genetic conditions

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## Endocrine disorders

- Type 1 diabetes: coeliac disease in about 5.1-6.0%.
- General population: about 1%.
- Autoimmune thyroid disease, especially Hashimoto's thyroiditis.

## Genetic syndromes

- Down syndrome.
- Turner syndrome.
- Williams syndrome.

## Other autoimmune associations

- Sjogren's syndrome, systemic lupus erythematosus, IgA nephropathy.

# Malignancies associated with coeliac disease

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## **Lymphoma**

Non-Hodgkin lymphoma; key entity is enteropathy-associated T-cell lymphoma (EATL).

## **Small bowel**

Small-intestinal adenocarcinoma.

## **Upper aerodigestive**

Reported associations with head and neck cancers and oesophageal cancer.

**Risk is most clinically relevant in persistent villous atrophy, refractory disease, and older patients.**

# Who should be tested?

## 1. Suggestive symptoms

Classic malabsorption: diarrhoea, steatorrhoea, weight loss or growth failure.  
Non-classical: bloating, abdominal pain, fatigue, joint pain or headaches.

## 2. High-risk asymptomatic groups

First-degree relatives of patients with coeliac disease.  
People with autoimmune disease or genetic predisposition, even if minimally symptomatic.

## 3. Endocrine and autoimmune disorders

Type 1 diabetes.  
Autoimmune thyroid disease: Hashimoto thyroiditis or Graves disease.  
Sjogren syndrome.

## 4. Gastrointestinal or liver disorders

Irritable bowel syndrome, microscopic colitis, inflammatory bowel disease.  
Autoimmune gastritis, autoimmune hepatitis, or unexplained liver enzyme elevation.

## 5. Genetic conditions

Down syndrome.  
Turner syndrome.  
Williams syndrome.

## 6. Extra-intestinal manifestations

Iron deficiency anaemia, dermatitis herpetiformis, dental enamel defects, recurrent aphthous stomatitis.  
Gluten ataxia, peripheral neuropathy, hyposplenism, delayed menarche, premature menopause or chronic fatigue syndrome.

# Serology: TTG-IgA, total IgA, EMA and DGP

**First-line test: tTG-IgA plus total IgA, while the patient is eating gluten.**  
**A gluten-reduced diet can make both serology and biopsy falsely reassuring.**

## tTG-IgA

- Best first-level screen in normal IgA
- High sensitivity and specificity in active disease
- High titres strongly predict villous atrophy
- Use a validated laboratory assay

## EMA-IgA

- Very high specificity
- Operator-dependent immunofluorescence
- Useful as confirmation or in unclear cases
- Less suited to routine first-line adult screening

## IgG tests

- Use if total IgA is deficient
- IgG-TG2 and/or IgG-DGP
- DGP is useful in IgA deficiency and young children
- Negative IgG does not fully exclude if suspicion is high

**Practical rule: do not order broad antibody panels routinely; discordant or borderline results need context, repeat testing, HLA testing, biopsy or gluten challenge.**

# Interpreting serology: titres, false negatives and false positives

**First question: is the patient eating gluten?**

**Gluten restriction can rapidly reduce the sensitivity of both serology and biopsy.**

## Titre changes probability

High tTG-IgA, especially  $\geq 10 \times$  ULN, strongly predicts villous atrophy. Low-positive results need confirmation, context and usually biopsy.

## False negatives

IgA deficiency, reduced gluten intake, mild or patchy disease, CVID or immunosuppression. If suspicion remains high, do not dismiss disease.

## False positives

Usually low-level tTG. Consider autoimmune or chronic liver disease, other autoimmunity/T1DM, infection or inflammation. EMA or repeat testing can clarify.

## Practical rule

Measure total IgA with tTG-IgA. If IgA deficient, use IgG-DGP and/or IgG-tTG. Discordant results need biopsy, HLA testing, or gluten challenge rather than a shortcut.

# Testing must happen on gluten: the pre-test diet problem

## Do not start a gluten-free diet before testing

Reduced gluten intake can lower antibody titres and allow mucosal healing enough to make serology or biopsy falsely negative.

### If already gluten-free

- Check HLA-DQ2/DQ8 first
- Negative HLA makes coeliac disease very unlikely
- If positive/compatible, discuss a supervised gluten challenge

### Minimum challenge

$\geq 3$  g gluten/day for 6 weeks

Higher dose or longer duration improves certainty if tolerated. Usually followed by biopsy.

### Bread equivalent

One medium wheat bread slice varies: about 2-5 g gluten

Practical target: 1-2 slices daily for 6 weeks to reach  $\geq 3$  g/day.

**Keep gluten in the diet until serology and, where needed, duodenal biopsy testing is complete.**

Sources: ESSCD/UEG 2025; BSG 2014; Clinician's Guide to Gluten Challenge 2024.

# Endoscopy: most mucosa looks normal, but markers matter

## Important limitation

A normal-looking duodenum does not exclude coeliac disease.

Most patients have a grossly normal endoscopic appearance, so duodenal biopsy remains essential for accurate assessment.

## Primary visual markers of villous atrophy

- Scalloping of duodenal folds.
- Reduction or loss of number and height of Kerckring folds.
- Nodular or mosaic mucosa, sometimes cracked or cobblestoned.
- Flattened mucosa, reflecting underlying villous atrophy.



# Scalloping of duodenal folds and absent Kerckring folds

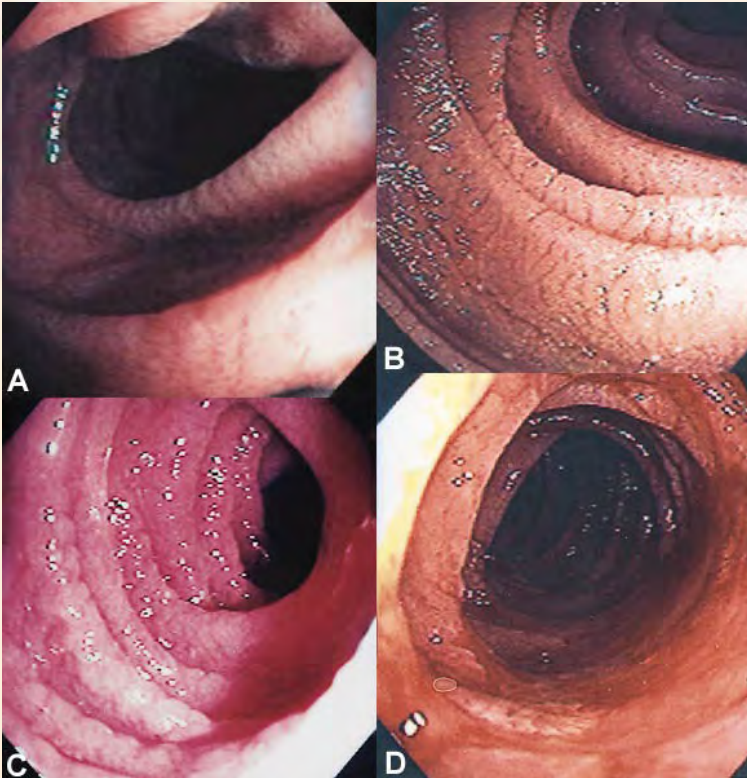


Figure 2. Endoscopic Appearance of the Descending Duodenum after Maximal Insufflation. Patients were described as having a normal number of Kerckring's folds (A), a reduced number (B), or a complete loss of such folds (C).

Image: Shah et al. All that scallops is not celiac disease. *Gastrointest Endosc.* 2000;51:717-720.

# Nodular or mosaic mucosa

**Nodular or mosaic mucosa**  
**Cracked or cobblestoned surface pattern.**  
**Irregular mucosal texture can reflect villous blunting with intervening grooves or nodularity.**

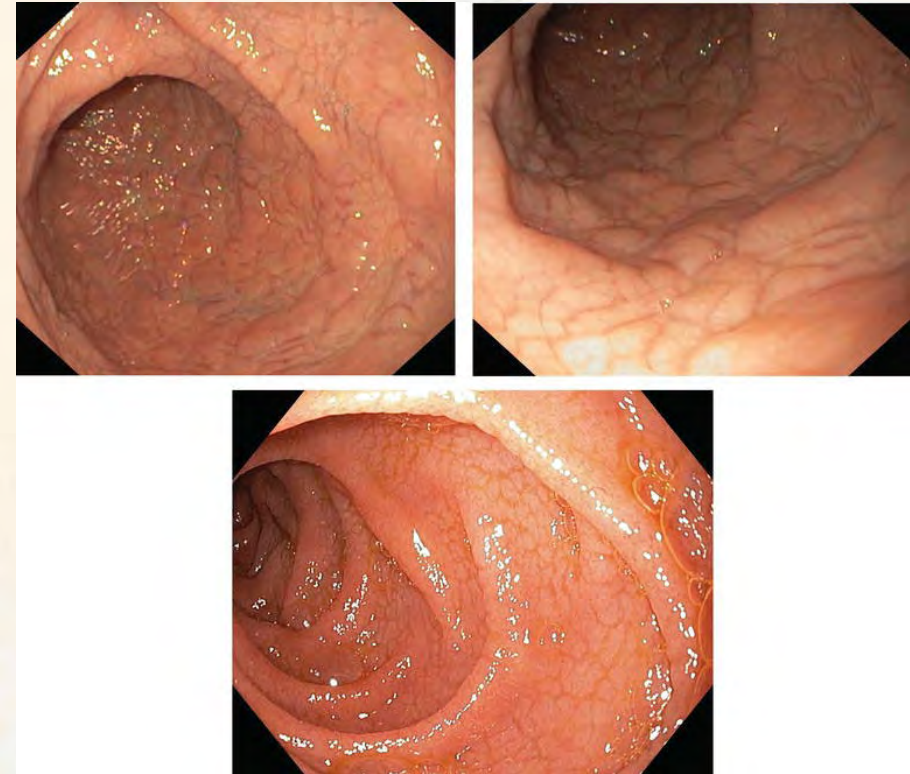


Image: Balaban, Popp & Jinga. Novel Endoscopic Techniques in Celiac Disease. IntechOpen, 2017, Fig. 7.

# Advanced endoscopic techniques for villous atrophy

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## Enhance villous pattern recognition

- Immersion technique: water in the duodenal lumen floats villi and can make atrophy easier to see.
- Chromoendoscopy: indigo carmine or methylene blue can outline villous architecture.
- Narrow-band imaging: highlights mucosal and vascular patterns without dye.

## When to think beyond standard endoscopy

Video capsule endoscopy gives a whole-small-bowel view.

Reported sensitivity is around 89%, but its main role is evaluating complications: refractory disease, ulcerative jejunoileitis, or suspected malignancy.

# Duodenal biopsy: number, site and orientation

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**Biopsy even when the duodenum looks normal: coeliac lesions are often patchy.**

Step / Recommendation

## **Number and site**

At least 4 biopsies from distal duodenum plus 2 from the duodenal bulb.

## **Sampling logic**

Multiple sites improve yield because villous atrophy can be patchy.

## **Technique**

Single-bite biopsies help achieve optimal tissue orientation.

## **Specimen handling**

Ideally process samples individually; keep bulb and distal duodenum in separate vials.

**Why separate bulb biopsies? Brunner glands reduce villous height and can complicate interpretation if mixed with distal duodenal samples.**

# Histology: Marsh classification and what the report must say

The modified Marsh classification remains the reference framework for grading coeliac enteropathy.

Modified Marsh criteria

Marsh 0 - Normal mucosa.

Marsh I - Increased intraepithelial lymphocytes; normal villous architecture.

Marsh II - Increased IELs with crypt hyperplasia.

Marsh IIIA - Partial villous atrophy.

Marsh IIIB - Subtotal villous atrophy.

Marsh IIIC - Total villous atrophy.

Report essentials: orientation, villous height-to-crypt depth ratio, IEL count, crypt hyperplasia, villous atrophy, and Marsh stage.

## Histology: Marsh lesions under the microscope

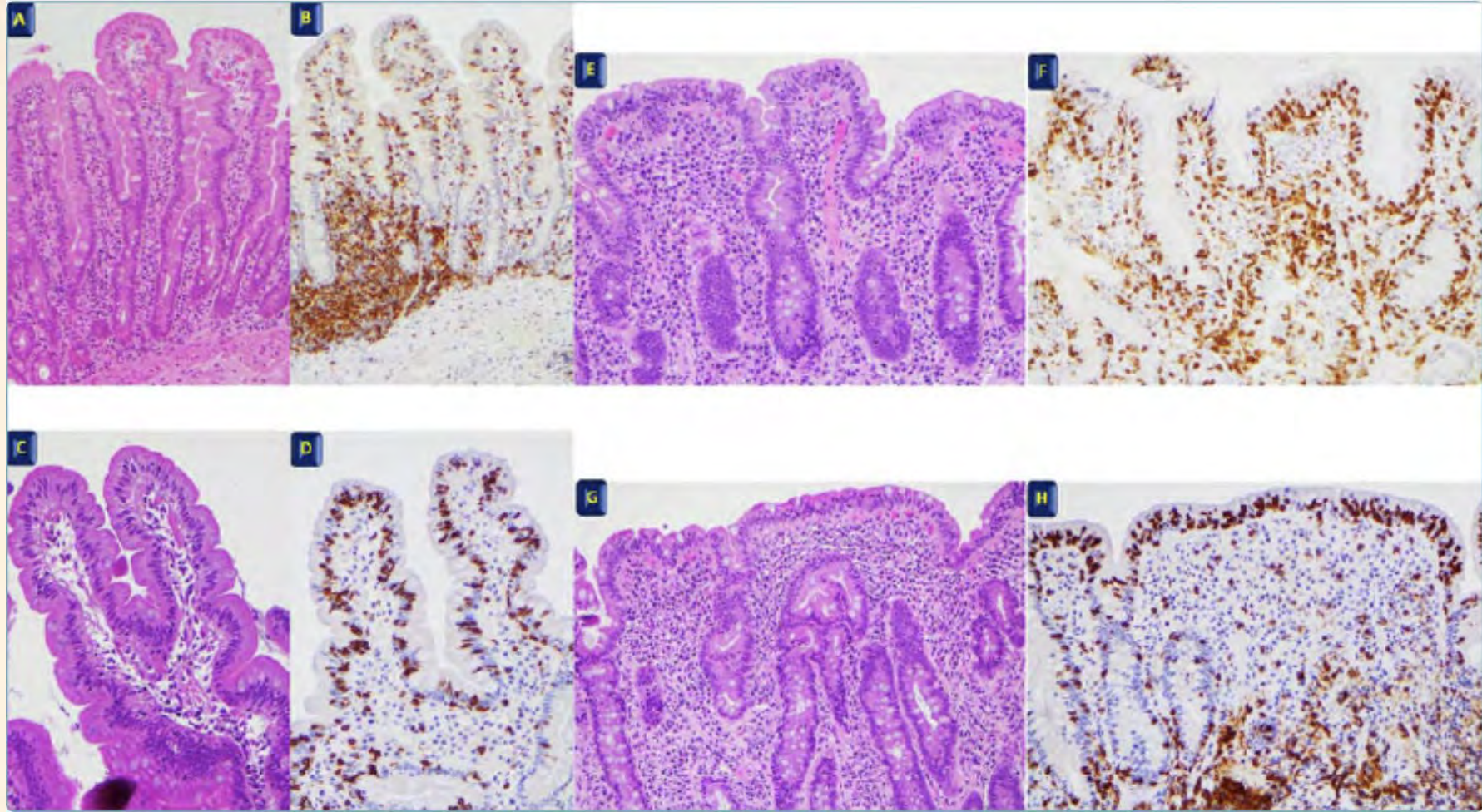


Image: Villanacci et al. Celiac disease: histology-differential diagnosis-complications. *Pathologica*. 2020;112:186-196. PMID: PMC7931573.

# Villous atrophy is not always coeliac disease

Villous atrophy is a pattern, not a diagnosis. Anchor interpretation to serology, drug exposure, immune status, geography, infection risk and histological clues.

## Infective / tropical

Tropical sprue  
Giardiasis  
HIV enteropathy  
Whipple disease

## Immune deficiency

CVID  
Hypogammaglobulinaemia  
Combined immunodeficiency

## Drug related

Olmesartan and other  
sartans  
Mycophenolate  
Methotrexate  
NSAID-associated injury

## Inflammatory / immune

Autoimmune enteropathy  
Crohn's disease  
Eosinophilic enteritis  
Peptic duodenitis

## Structural / rare sprues

Collagenous sprue  
Radiation enteritis  
Environmental enteropathy

## Malignant / pre-malignant

Enteropathy-associated T-cell lymphoma  
Pre-infiltrative intestinal T-cell lymphoma

# No-biopsy diagnosis in adults: evidence, guidelines and caution

## Children: strongest evidence base

- tTG-IgA  $\geq 10 \times$  ULN can support a reliable no-biopsy diagnosis
- Add positive EMA on a second sample: PPV ~99.8%
- Avoids unnecessary invasive procedures
- IgA deficiency: biopsy still required

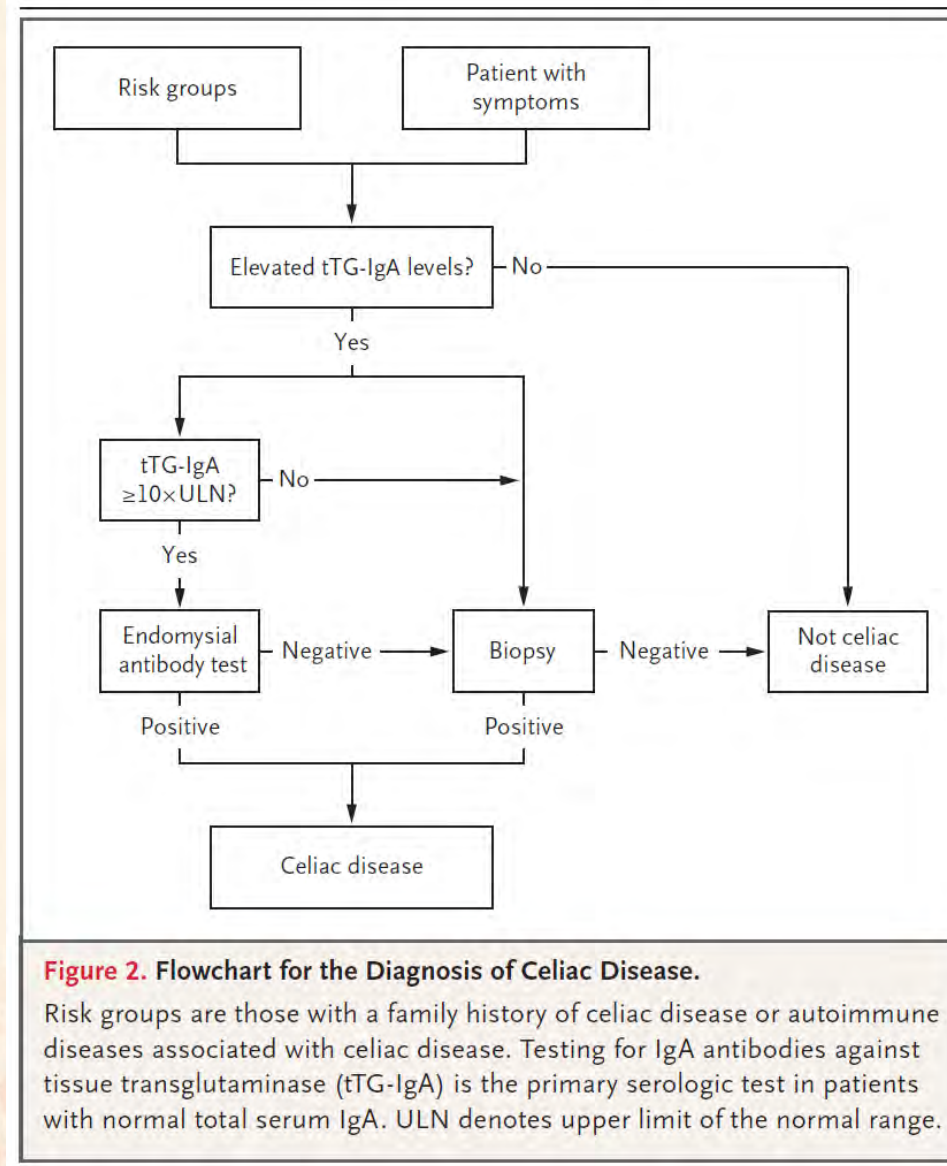
## Adults: biopsy remains the safeguard

- Histology is crucial if tTG-IgA  $< 10 \times$  ULN
- Excludes malignancy, serious mimics and severe adult enteropathies
- Villous atrophy may predict future complications, including EATL
- Endoscopy is generally well tolerated
- Index biopsy gives a baseline for mucosal healing
- High antibody titres are less frequent in adults

## ESsCD/UEG 2025: a conditional adult option

Selected adults  $< 45$  years with IgA anti-TG2  $\geq 10 \times$  ULN may be offered no-biopsy diagnosis after repeat serologic confirmation, shared decision-making and no red flags.

# A practical adult diagnostic algorithm



# Seronegative coeliac disease and its mimics

## 1. First define the problem

Seronegative villous atrophy = villous atrophy with negative coeliac serology.

Before labelling SNCD, confirm gluten exposure, total IgA/IgG-based tests, biopsy adequacy and pathology review.

## 2. When is it seronegative coeliac disease?

Rare: about 2-5% of coeliac disease cases.

Requires HLA-DQ2 or DQ8, exclusion of other enteropathies, and clinical plus histological response to a gluten-free diet.

## 3. Mimics to exclude

Infective / tropical: Giardia, tropical sprue, Whipple disease, TB/MAC, SIBO, HIV enteropathy.

Drug or treatment related: olmesartan/other ARBs, NSAIDs, mycophenolate, methotrexate, colchicine, chemotherapy, radiation, immune checkpoint inhibitors.

Immune / inflammatory: CVID, IgA deficiency, autoimmune enteropathy, eosinophilic gastroenteritis, Crohn disease, collagenous sprue.

Serious pathology: EATL/MEITL, IPSID, GVHD, amyloidosis.

**Practical rule: if HLA-DQ2/DQ8 is absent, seronegative coeliac disease is very unlikely; if present, continue the mimic work-up before committing to a lifelong diagnosis.**

# Management begins at diagnosis

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The first visit should translate a diagnosis into a safe diet, baseline risk assessment and a follow-up plan.

## 1. Expert dietitian

- Start education early
- Label reading and hidden gluten
- Cross-contamination at home and work
- Practical substitutes that fit culture, budget and access

## 2. Baseline assessment

- Weight, symptom burden and malabsorption markers
- FBC, ferritin, folate/B12, vitamin D, calcium, zinc and LFTs
- Correct deficiencies and document comorbid autoimmune disease

## 3. Risk prevention

- Bone density in adults or high-risk patients
- Consider pneumococcal, Hib and meningococcal vaccination in adults
- Agree 3-6 month review before the patient leaves

**Key point: prescribing “gluten-free” is not the same as treating coeliac disease.**

# Gluten-free diet: effective, but imperfect

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The diet induces remission for most patients, but the intervention is lifelong, socially difficult and nutritionally easy to get wrong.

## What to exclude

- Wheat, barley, rye and related grains
- Spelt, kamut, emmer, einkorn and triticale
- Gluten-free foods should contain <20 ppm gluten

## Oats are nuanced

- Most patients tolerate uncontaminated oats
- Introduce after clinical response and tTG-IgA normal or near-normal
- Use certified gluten-free oats; monitor symptoms and serology

## Why adherence fails

- Hidden gluten in sauces, soups, dressings and processed foods
- Cross-contamination, restaurants and workplace meals
- Cost, social isolation and dietary hypervigilance

**Nutrition watch: fibre, calcium, iron, folate and vitamin intake can fall on a poorly planned GFD.**

# Monitoring response: four signals, four timelines

Symptoms, antibodies and mucosal healing do not normalize in lockstep, so follow-up needs more than one marker.

## Clinical response

Review at 3-6 months, then 6-9 months, 1 year and yearly.

Track symptoms, weight and extraintestinal features.

## Serology

Use the same tTG-IgA assay where possible.

A falling titre is expected; normalization may take >2 years.

## Nutrition and bone

Repeat abnormal baseline tests.

Check FBC, iron/folate, vitamin D, zinc and weight; assess bone density in adults/risk groups.

## Histology

Serology poorly predicts persistent villous atrophy.

Consider biopsy after 12-24 months if symptoms, positive serology, anaemia or malabsorption persist.

**Emerging tool: urine or stool gluten immunogenic peptides may detect recent inadvertent exposure, but timing matters.**

# Persistent symptoms: work through the common causes first

Persistent symptoms are common; the first question is not “is this refractory?” but “what is still driving symptoms or injury?”

## 1. Recheck the diagnosis

Was the original diagnosis secure?

Review serology, biopsy quality, gluten exposure at testing and alternative enteropathies.

## 2. Audit gluten exposure

Expert dietitian review is central.

Look for hidden gluten, cross-contamination, oats and restaurant/workplace exposure.

## 3. Decide if mucosa is healed

Persistent villous atrophy changes the pathway.

Repeat biopsy if symptoms, malabsorption, anaemia or serology remain concerning.

## 4. Look for coexistence

If mucosa heals, think IBS/DGBI, lactose intolerance, SIBO, pancreatic insufficiency, microscopic colitis or IBD.

**Red flags: weight loss, hypoalbuminaemia, worsening anaemia, fever, obstruction, bleeding or severe malabsorption.**

# Non-responsive coeliac disease: separate activity from symptoms

Non-responsive disease is a working problem, not a final diagnosis: identify gluten exposure, slow healing, mimics and complications.

## Most common explanation

- Ongoing gluten ingestion or cross-contamination
- May be silent yet still damage mucosa
- Dietitian review beats self-report alone

## If biopsy is normal

- Think coexisting functional or malabsorptive disorders
- IBS/DGBI, lactose intolerance, SIBO
- Pancreatic insufficiency or microscopic colitis

## If villous atrophy persists

- Confirm strict GFD for at least 12 months
- Exclude Crohn disease, autoimmune enteropathy, medications and other mimics
- Refer for RCD work-up and IEL phenotyping

**Escalate early when malabsorption is severe or recurrent: diarrhoea, weight loss, anaemia and hypoalbuminaemia are not “IBS until proven otherwise”.**

# Refractory coeliac disease: clinical presentation and complications

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Both RCD I and II can present with severe malabsorption; type II is typically more aggressive.

## Typical patient

Usually presents after age 40-50 years.

## Symptoms

Chronic diarrhoea, profound weight loss.

## Malnutrition

Severe malnutrition, anaemia, hypoalbuminaemia.

## Ulcerative jejunoileitis

Multifocal inflammatory ulcerations and strictures; rare in RCD I, reported in about 30% of RCD II.



# Refractory coeliac disease: type I vs type II

**RCD = persistent or recurrent malabsorptive symptoms with villous atrophy despite a strict gluten-free diet for at least 12 months.**

## Type I

- Normal IEL phenotype: surface CD3+ and CD8+.
- Polyclonal T-cell population.
- Usually better prognosis.

## Type II

- Aberrant IELs: surface CD3-/CD8-, intracellular CD3+.
- Clonal TCR-gamma rearrangement.
- Higher risk of EATL and poorer prognosis.

**First-line for both: open-capsule budesonide. Typical regimen: 9 mg/day as opened 3 mg capsules, to deliver drug proximally.**

# Refractory coeliac disease type I: treatment

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## Treatment approach

- Confirm true gluten-free diet adherence first.
- Open-capsule budesonide is first-line.
- Azathioprine can be used as steroid-sparing immunosuppression.
- Systemic steroids may be needed in selected cases.

## Elemental diet

- Amino-acid based liquid formula with complete macro- and micronutrition.
- Used short-term to reduce antigen exposure and support nutrition.

# Refractory coeliac disease type II: treatment and risk

RCD II is often resistant to conventional therapy and has a poor prognosis because of progression risk to EATL.

## Therapeutic options

- Often resistant to azathioprine and steroids.
- JAK inhibition is being explored; tofacitinib is one candidate.
- Cladribine and cyclosporine have been used in specialist settings.
- No definitive second-line regimen is established.
- Autologous stem-cell transplant may be considered if other therapies fail.

## Investigational biologics

Monoclonal antibodies targeting IL-15 and CD52 are under investigation.

# Complications

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Severe recurrent symptoms, malnutrition, bleeding or obstructive features should prompt small-bowel assessment and specialist review.

## Ulcerative jejunoileitis

Multifocal inflammatory ulceration and stricturing of the small bowel.

Rare overall, but classically linked to RCD type 2; Lancet 2022 reports ulcerative jejunitis in around 30% of RCD2 patients.

## EATL

Aggressive T-cell non-Hodgkin lymphoma, usually intestinal and often jejunal.

Often represents the end-stage of RCD type 2; suspect with weight loss, pain, fever, obstruction, bleeding or worsening hypoalbuminaemia.

## Small-bowel adenocarcinoma

Uncommon, but increased in coeliac disease; most cases involve jejunum or duodenum.

Clinical clues include abdominal pain, persistent iron deficiency anaemia, occult/overt bleeding and obstructive symptoms.

**Practical threshold: unexplained deterioration on a strict GFD deserves imaging or capsule/enteroscopy, not reassurance.**

# Emerging therapies: plausible adjuncts, not replacements

No non-dietary drug is approved for routine coeliac disease care; the realistic near-term target is protection from inadvertent gluten exposure.

|                            |                                                                                                                                                  |                                                                                           |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Gluten degradation         | Latiglutenase reduced IEL rise and symptom worsening during gluten challenge; histology signal remains modest.                                   | Murray et al., <i>Gastroenterology</i> 2022; <i>BMJ</i> 2025                              |
| TG2 inhibition             | ZED1227 attenuated gluten-induced mucosal injury across three doses in a phase 2 gluten-challenge trial.                                         | Schuppan et al., <i>NEJM</i> 2021; <i>BMJ</i> 2025                                        |
| Immune tolerance           | TAK-101 reduced gluten-specific IFN-gamma T-cell response by 88%; mucosal protection trend did not reach significance.                           | Kelly et al., <i>Gastroenterology</i> 2021; <i>BMJ</i> 2025                               |
| Barrier modulation         | Larazotide improved symptoms in phase 2, but phase 3 was discontinued after interim analysis due to poor efficacy                                | Leffler et al., <i>Gastroenterology</i> 2015; <i>CedLara update</i> 2022; <i>BMJ</i> 2025 |
| Cytokine / immune blockade | Anti-IL-15 and related biologic strategies are biologically attractive, especially in complicated disease, but not established for routine care. | <i>Lancet</i> 2022; <i>BMJ</i> 2025                                                       |

Clinical message: keep the GFD central; reserve drug therapy discussion for trials, refractory disease or future adjunctive use.

# Food reactions are not all allergy

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## Food allergy

Immune reaction to a food protein; may be IgE-mediated, non-IgE or mixed.

## Food intolerance

Non-immune and often dose-related: enzyme deficiency, FODMAP effect, pharmacologic or toxic reaction.

## Coeliac disease

Autoimmune enteropathy triggered by gluten in genetically susceptible patients.

## NCWS

Reproducible wheat-triggered symptoms after coeliac disease and wheat allergy are excluded.

# IgE-mediated food allergy: immediate reactions

The diagnostic clue is rapid, reproducible, objective symptoms after exposure to a specific food.

## Timing and systems

Minutes to 2 hours

- Skin: urticaria, angioedema, flushing
- Respiratory: rhinitis, wheeze
- GI: pain, vomiting, diarrhoea
- CV: hypotension, collapse

## Anaphylaxis clues

- Multi-system involvement
- Respiratory compromise
- Hypotension or syncope
- Symptoms after tiny amounts
- Cofactors can lower the reaction threshold

## Testing principle

- Skin-prick or serum specific IgE shows sensitisation
- Sensitisation is not the same as clinical allergy
- Oral food challenge when the diagnosis is uncertain

**A positive IgE test without a compatible history should not trigger broad dietary restriction.**

# Non-IgE and mixed gastrointestinal food allergy

These syndromes are usually delayed and GI-predominant; standard IgE tests may be negative.

## Non-IgE patterns

- Delayed: hours to days
- GI-predominant symptoms
- FPIES: repetitive vomiting, lethargy, pallor, hypotension
- Enteropathy/proctocolitis: chronic diarrhoea, bleeding or poor growth

## Mixed IgE/non-IgE

- Eosinophilic oesophagitis
- Eosinophilic gastritis or gastroenteritis
- Food trigger may be one part of a broader atopic phenotype
- Diagnosis often needs endoscopy and histology

## How to prove it

- Pattern recognition first
- Targeted elimination, not broad avoidance
- Objective response and relapse on reintroduction
- Specialist challenge if severe reactions are possible

**Do not use negative IgE testing to dismiss a convincing delayed GI allergy phenotype.**

# Wheat allergy: how it presents

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Think allergy when wheat exposure causes rapid, objective, immune-mediated reactions rather than chronic IBS-like symptoms alone.

## IgE ingestion allergy

Minutes to 2 hours

- Urticaria, angioedema, oral itch
- Rhinitis, wheeze, asthma
- Abdominal pain, vomiting, diarrhoea
- Hypotension or anaphylaxis

## Cofactor-dependent

Wheat-dependent exercise-induced anaphylaxis

- Wheat plus exercise, NSAIDs, alcohol or infection
- May tolerate wheat without the cofactor
- Consider omega-5 gliadin testing

## Other wheat-allergy phenotypes

- Baker's asthma or rhinitis from flour inhalation
- Contact urticaria
- EoE/eosinophilic gastroenteritis
- FPIES, enteropathy or proctocolitis

**Work-up: history and timing first; skin-prick or serum wheat-specific IgE support sensitisation, while supervised oral food challenge is reserved for uncertainty.**

# Non-coeliac wheat sensitivity: diagnosis of exclusion

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## Required exclusions

- Coeliac disease while on gluten
- Wheat allergy: history + IgE testing
- Major organic GI disease
- Reproducible symptoms on wheat exposure

## Typical presentation

- Intestinal
- Bloating, abdominal pain
  - Diarrhoea or altered bowel habit
- Extra-intestinal
- Fatigue, headache, brain fog
  - Musculoskeletal symptoms

## What might trigger it?

- Gluten itself
- Fructans / FODMAPs
- Amylase-trypsin inhibitors
- Wheat germ agglutinins

Mechanisms remain uncertain: gut-brain axis, microbiome, permeability and innate immune activation.

**Key distinction: unlike coeliac disease, NCWS has no consistent HLA-DQ2/DQ8 association and no recognised malignancy-risk phenotype.**

# Oral tolerance: why most food proteins are ignored

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The normal gut response to food is active tolerance, not passive ignorance.

## Barrier and sampling

- Mucus and epithelial integrity limit exposure
- Secretory IgA binds luminal antigens
- Dendritic cells sample food antigens in a non-inflammatory context

## Regulatory response

- Regulatory T cells suppress effector responses
- IL-10 and TGF-beta support tolerance
- Microbiome metabolites help maintain mucosal immune balance

## When tolerance fails

- Sensitisation can produce allergy
- Coeliac disease is autoimmune loss of tolerance to gluten/TG2 biology
- NCWS may involve innate, neural or fermentable carbohydrate pathways

**This explains why the same food exposure can map to allergy, autoimmunity, intolerance or sensitivity.**

# Practical approach to suspected food reaction

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Start with phenotype before testing: timing, reproducibility, objective features and the food dose matter.

## 1. Timing

Minutes-2 h: IgE allergy  
Hours-days: non-IgE or intolerance  
Chronic wheat symptoms:  
exclude coeliac first

## 2. Exclude danger

Anaphylaxis, wheeze,  
hypotension, weight loss,  
bleeding, anaemia or  
hypoalbuminaemia need  
targeted work-up

## 3. Test narrowly

Coeliac serology on gluten  
Specific IgE only when history  
fits  
Avoid broad IgG food panels

## 4. Prove relevance

Diet diary  
Targeted elimination  
Structured reintroduction or  
supervised challenge when risk  
is high

**The safest endpoint is a named mechanism and a targeted plan, not an expanding list of avoided foods.**

# Five points to leave with

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The practical danger is not knowing the rare complications; it is missing the common patterns that should trigger the diagnosis and follow-up.

**1. Coeliac disease is common but missed. Classic diarrhoea and weight loss are only the visible tip.**

**2. Diagnosis must be made properly and on gluten. In adults, serology plus endoscopy and biopsy remain the gold standard.**

**3. Villous atrophy is not always coeliac disease. Remember the differential.**

**4. Management is more than just a gluten-free diet.**

**5. Refractory disease is rare, but missing it is life-threatening.**

# References

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