Celiac disease

Bible Class 02-24-2021

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Most relevant literature for the ESEGH

- Diagnosis and management of adult coeliac disease: guidelines from the **BSG** (doi:10.1136/gutjnl-2013-306578, 2014)

- **ACG** clinical guidelines: Diagnosis and management of celiac disease (doi:10.1038/ajg.2013.79, 2013)

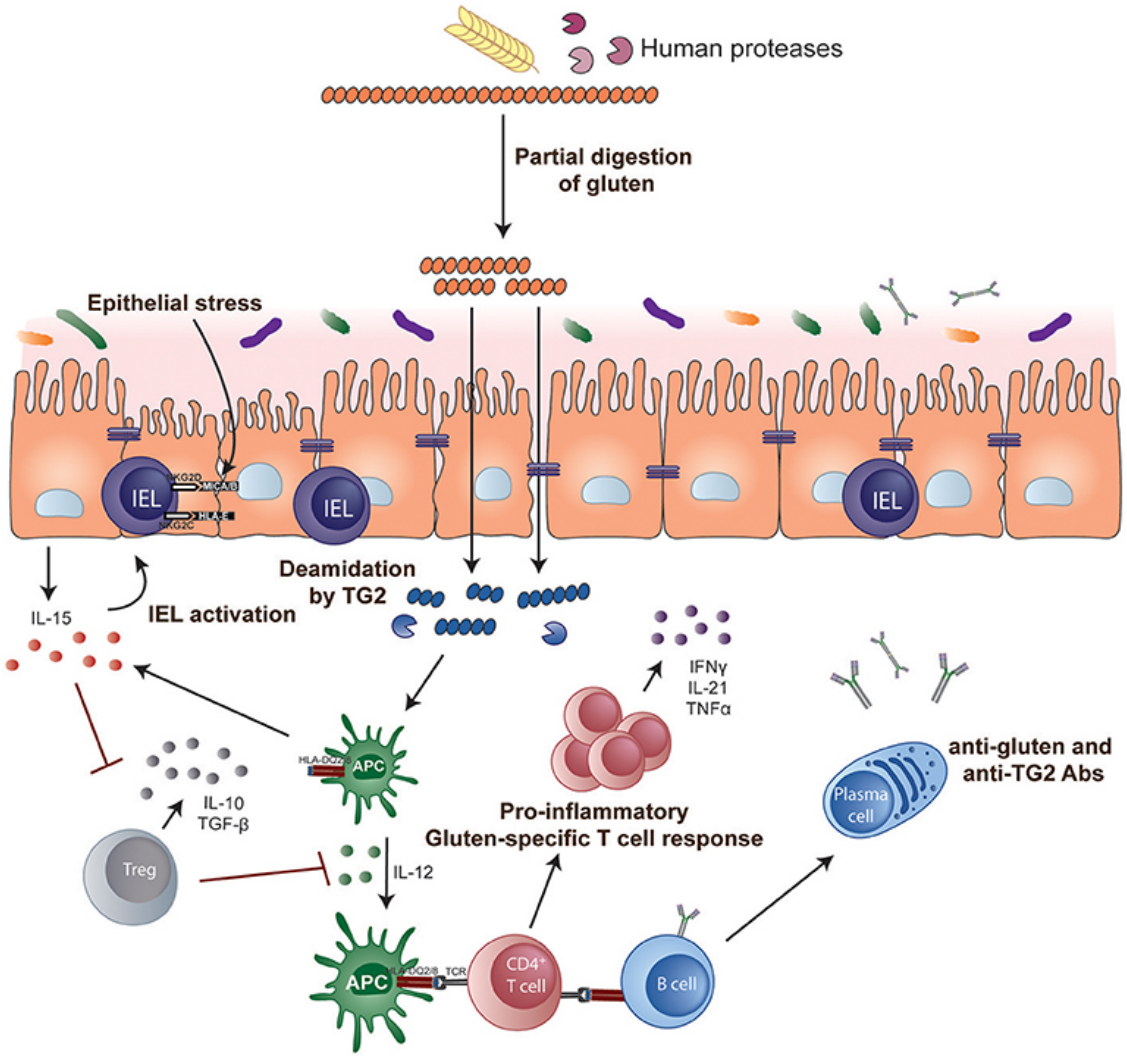
Background and clinical manifestations

What is CD?

- A chronic **small intestinal** **immune-mediated** enteropathy precipitated by **exposure to dietary gluten** in **genetically predisposed** individuals
  (Oslo definitions of CD, Gut. 2013)

- **Not CD:** Non-celiac gluten sensitivity (NCGS)
  Wheat intake → clinical symptoms, but CD excluded

Key steps in CD pathogenesis



Gluten-reactive T cells

Intraepithelial lymphocytes

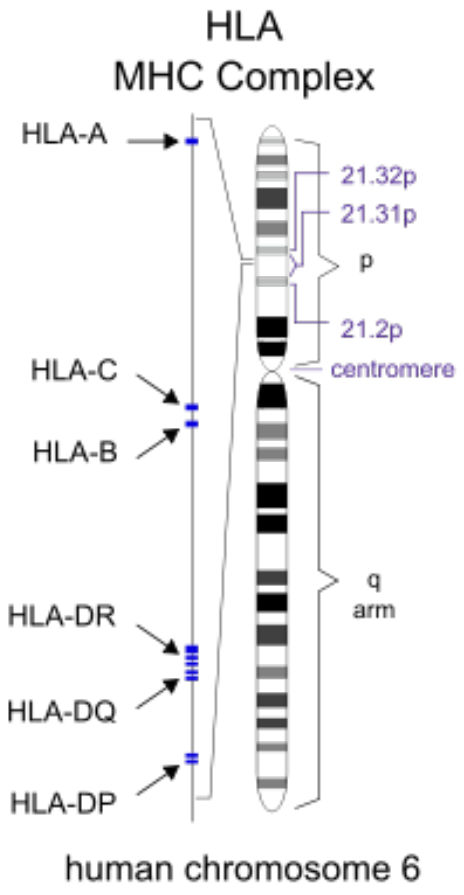
- TCRαβ^{+} CD8^{+}CD4^{-} or TCRγδ^{+} CD8^{-}CD4^{-}
- Can lyse epithelial cells, especially after IL-15 stimulations

Anti–tTG IgA producing plasma cells

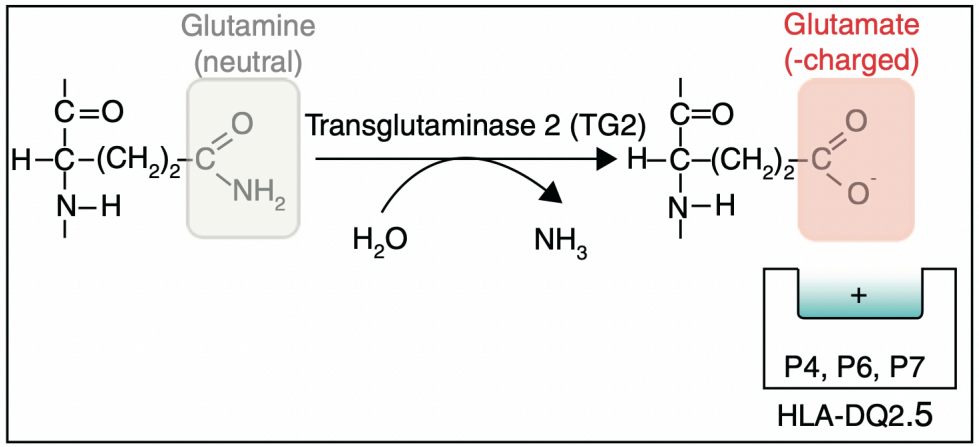
- Autoantibodies not just “bystanders”, can modify IEC differentiation/permeability

Tye-Din J., Galipeau H.J., Agardh D. Front. Pediatr., 21 November 2018

Genetics of CD? Mechanism?



- Strong association with
  - HLA-DQ2.5 (prevalence in Caucasians 13%)
  - HLA-DQ8 (prevalence in Caucasians 10%)
- Rarely
  - HLA-DQ2.2 or HLA-DQ7
- Non-HLA loci play a minor role

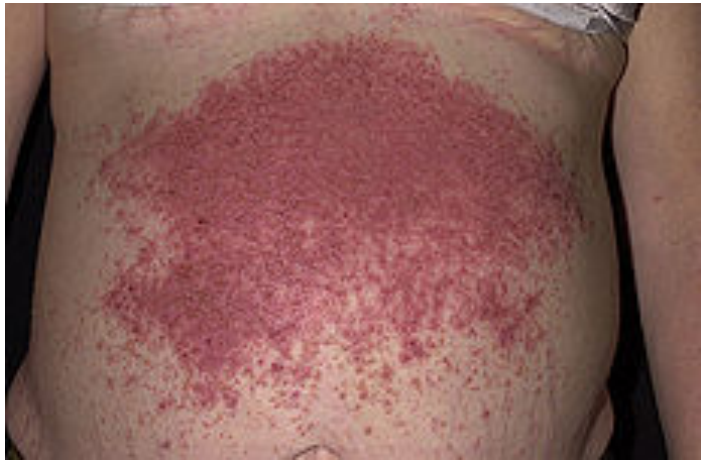


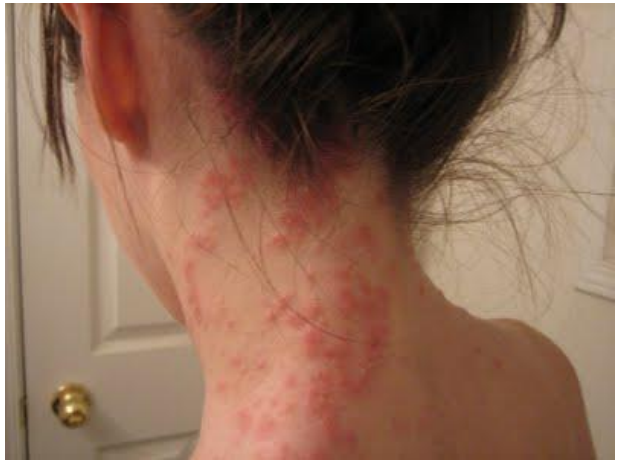
What are typical & possible symptoms of CD?

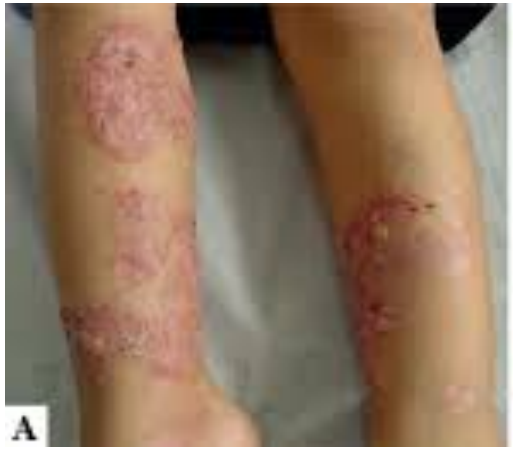
- **Classical CD**
  - Malabsorption (diarrhea, abdominal pain)
  - Weight loss
  - Failure to thrive

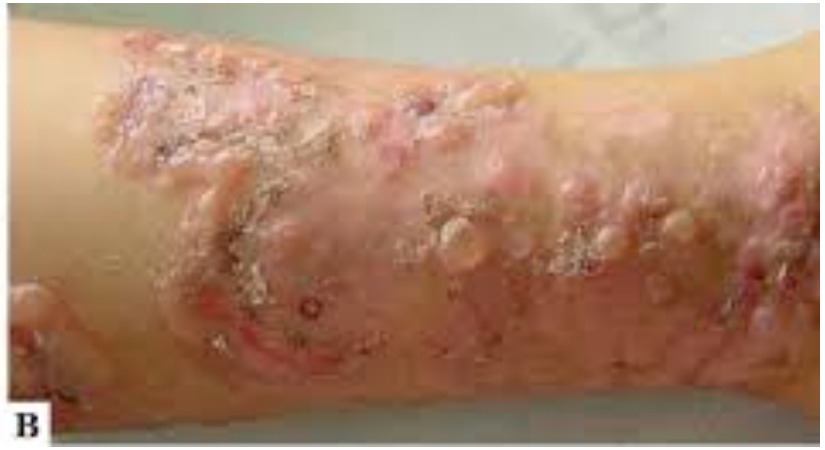
- **Non-classical CD**
  - Anemia
  - Osteomalacia/osteoporosis
  - Liver disease
  - Neuropsychiatric symptoms (neuropathy, ataxia, depression)
  - Aphthous ulcers
  - Dermatitis herpetiformis
  - Lymphoma

What is Dermatitis herpetiformis?









- Intensely pruritic papules and vesicles
- Grouped ("herpetiform") arrangements
- Typical onset 30–40y, M>F
- Histo: Dermal IgA deposits
- <10% have malabsorption but 70% have villous atrophy

Diagnostics in CD

Who should be tested for CD?

- Population prevalence of CD: 0.5–1%

- High-risk patients (prevalence 2–5%)
  - Classic CD symptoms
  - Iron deficiency anemia
  - Type 1 diabetes
  - Osteoporosis
  - Elevated liver enzymes w/o diagnosis
  - First-degree relatives of CD patients with **any** abdominal symptoms (prevalence up to 10%)

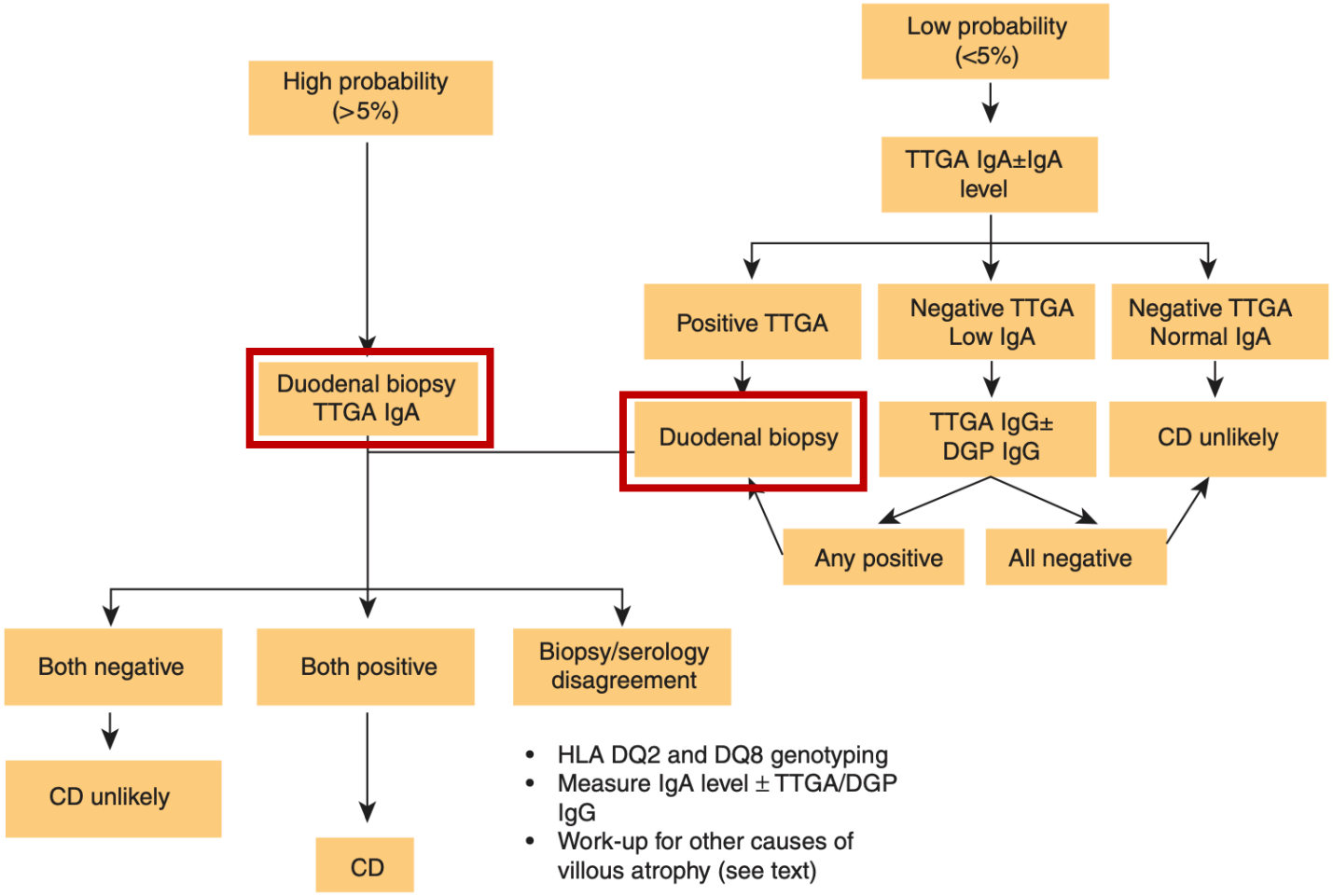
Which serological tests for CD are available?

Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

Test	Sensitivity (Range)	Specificity (Range)	Comments
	percent		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test
IgG anti-tTG antibodies	Widely variable (12.6–99.3)	Widely variable (86.3–100)	Useful in patients with IgA deficiency
IgA antiendomysial antibodies	>90.0 (82.6–100)	98.2 (94.7–100)	Useful in patients with an uncertain diagnosis
IgG DGP	>90.0 (80.1–98.6)	>90.0 (86.0–96.9)	Useful in patients with IgA deficiency and young children

Fasano A., Catassi C. NEJM 2012

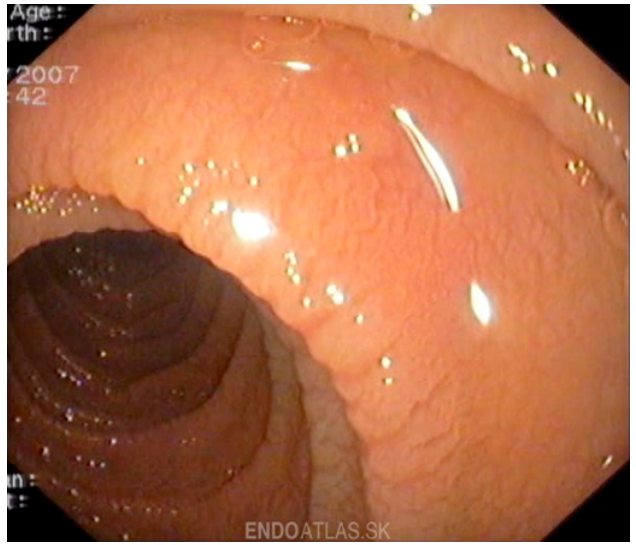
What is the recommended diagnostic algorithm for CD in adults?

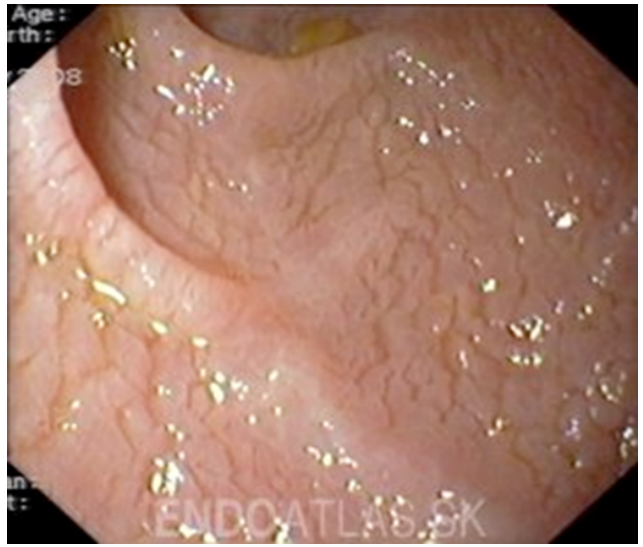


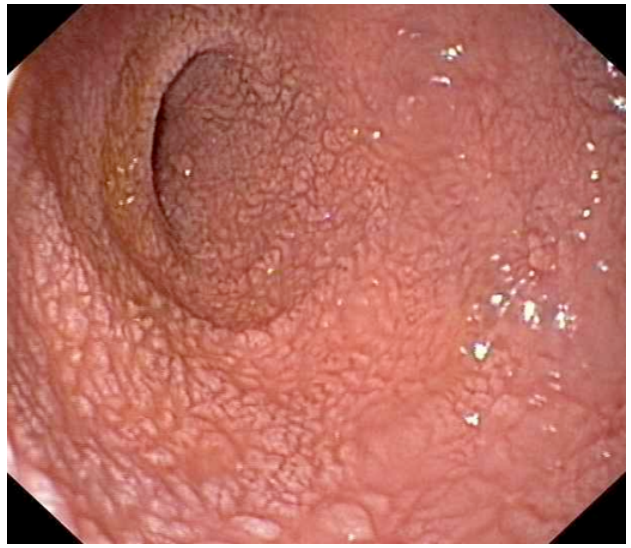
- All tests should be done on a gluten-containing diet
- Selective IgA deficiency is relatively common in CD (2–3%)
  → anti-TTG / DGP IgG
- In children <2y: combine anti-TTG IgA with anti-DGP IgA/IgG

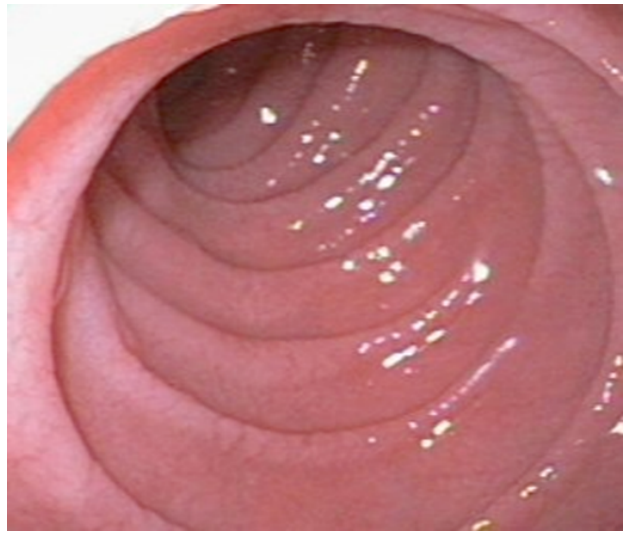
What is the endoscopic appearance of CD?

Scalloping
Mud-Cracking
Mosaic
Atrophy





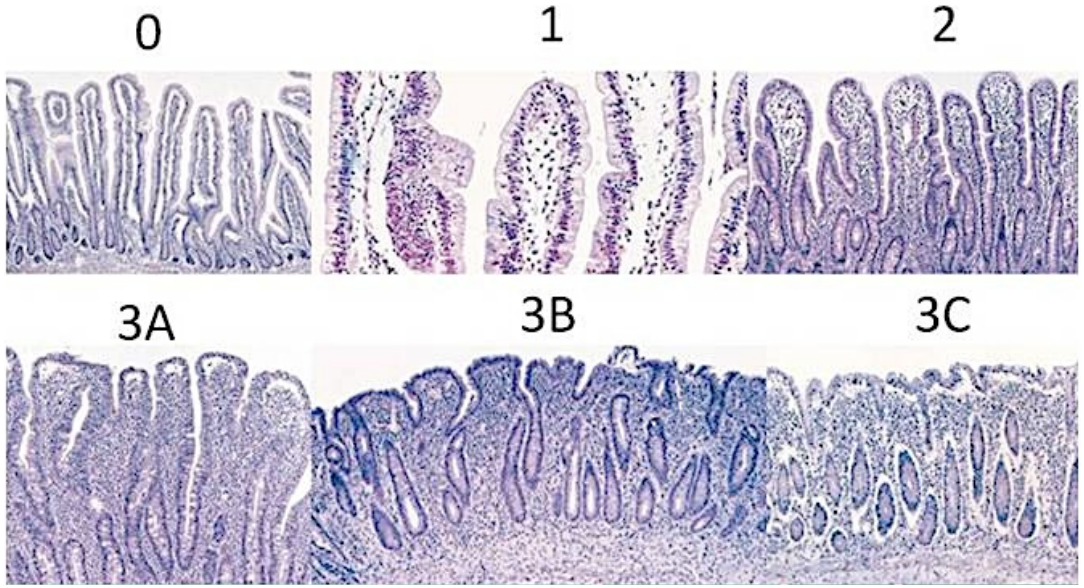




How to take biopsies?

- At least 6 duodenal biopsies (4 × distal, 2 × bulb)
  - Reason: patchy disease, 9–13% show atrophy restricted to the bulb
- Pathologists prefer biopsies taken with jumbo forceps and taken individually
- Diet should contain gluten (ask patients!)
- If suspicion for CD is high: ignore negative serology

Histologic hallmarks of CD? Classification?



Marsh modified (Oberhuber)	Histologic criterion			Corazza
	Increased intraepithelial lymphocytes[a]	Crypt hyperplasia	Villous atrophy	
Type 0	No	No	No	None
Type 1	Yes	No	No	Grade A
Type 2	Yes	Yes	No	
Type 3a	Yes	Yes	Yes (partial)	Grade B1
Type 3b	Yes	Yes	Yes (subtotal)	
Type 3c	Yes	Yes	Yes (total)	Grade B2

[a] >40 intraepithelial lymphocytes per 100 enterocytes for Marsh modified (Oberhuber); >25 intraepithelial lymphocytes per 100 enterocytes for Corazza.

Which diseases can mimic CD histology?

Table 2 Histological mimics of CD in seronegative patients—conditions to be considered for investigation in an appropriate clinical context

Duodenal histology: normal architecture and increased IELs (≥25/100 enterocytes) or villous atrophy±increased IELs (≥25/100 enterocytes)		
Immune disorders	Common variable immunodeficiency syndrome Glomerulonephritis Hypogammaglobulaemia IgA deficiency	
Autoimmune disease These patients may have concurrent CD, check serology and HLA status if appropriate*	Autoimmune enteropathy (adults and children) Graves' disease* Haemolytic anaemia Hashimoto's thyroiditis* Multiple sclerosis Psoriasis	Rheumatoid arthritis Sjögren's syndrome* Systemic lupus erythematosus Thymoma-associated autoimmune enteropathy Type I diabetes mellitus*
Hypersensitivity/non-gluten protein intolerance	Non-coeliac gluten sensitivity Protein intolerance (cows' milk, soy, eggs, peanuts, cereals)	
Infection	AIDS Cryptosporidium Giardiasis *Helicobacter pylori* gastritis† Postinfectious diarrhoea	Small intestinal bacterial overgrowth Tropical sprue Tuberculosis (including atypical TB) Viral Whipple's disease (for example, HIV)
Drugs	Chemotherapy Non-steroidal anti-inflammatory drugs Olmesartan Mycophenolate mofetil	
Neoplasia	Enteropathy-associated T-cell lymphoma Immunoproliferative small intestinal disease Refractory CD type 2 CD 4 T-cell proliferation	
Other	Abetalipoproteinaemia Collagenous colitis Collagenous duodenitis Crohn's disease	Eosinophilic gastroenteritis Glycogen storage disease Microscopic colitis Radiation enteritis Small bowel ischaemia

When should HLA testing be performed?

- **Not** routinely in initial diagnosis (PPV only 12%, NPV >99%)

- Good uses
  - Discrepant serology and histology
  - Equivocal histology (Marsh I or II) in seronegative patients
  - First degree relatives of CD patients
  - Patients who are self-treated on a gluten-free diet

Management of CD

Which dietary advice would you give to CD patients?

Patients may have secondary lactose intolerance

- Distilled alcoholic drinks are gluten-free
- Oats may be ok, but
  - Limit consumption to 50g/d
  - Long-term safety unclear
- Medication usually contains minimal gluten and does not need to be avoided
- Individual gluten tolerance variable, < 10–30 mg/d seems to be safe in the majority of patients (doi:10.1111/j.1365-2036.2004.01961.x)

Refer all patients to a dietician

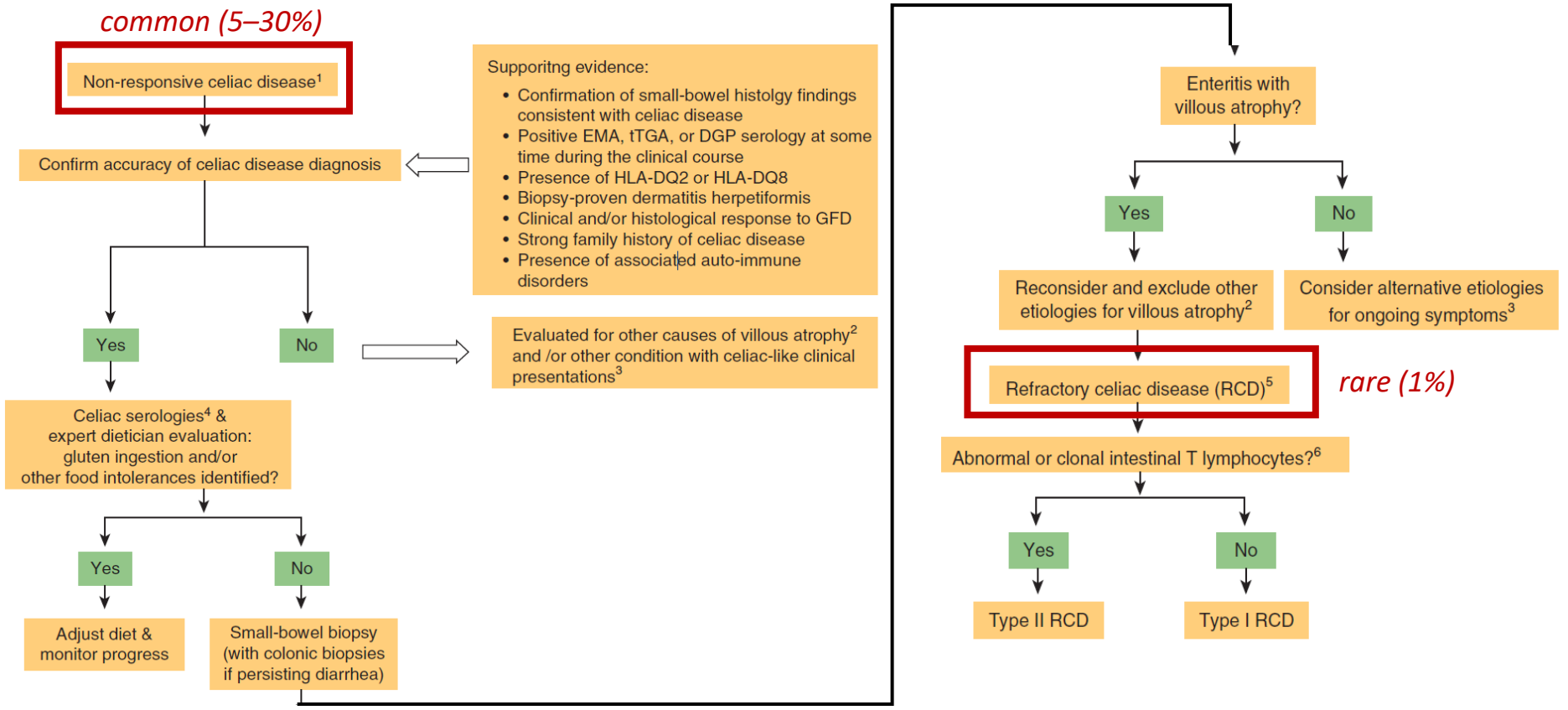
What else to do for CD patients?

- Test for **deficiencies in micronutrients**
  - Vitamin A, D, E, B12, Folic acid
  - Calcium, Copper, Zinc, Iron
- Rule out **associated diseases**
  - TSH, liver enzymes, fasting glucose
- Prevent **bone loss**
  - Perform DXA scan in all CD patients
  - Ensure adequate calcium intake >1000 mg/d
- Give **pneumococcal vaccine**
  - Optimal choice of vaccine unclear.
  - Safest option seems to be PCV13 then PPSV23

How to follow up CD patients?

- All CD patients should be monitored regularly for symptoms, adherence to GFD and complications
- **Serology**
  - All CD markers are gluten-dependent. Persistently positive serology after 1y is infrequent (1%) and suggests gluten intake.
  - But: Negative serology does confirm mucosal healing
- **Biopsy**
  - Follow-up biopsies should not be performed routinely, but in patients lacking clinical response despite GFD
- **Associated diseases** (e.g. nutrient deficiencies, bone loss)

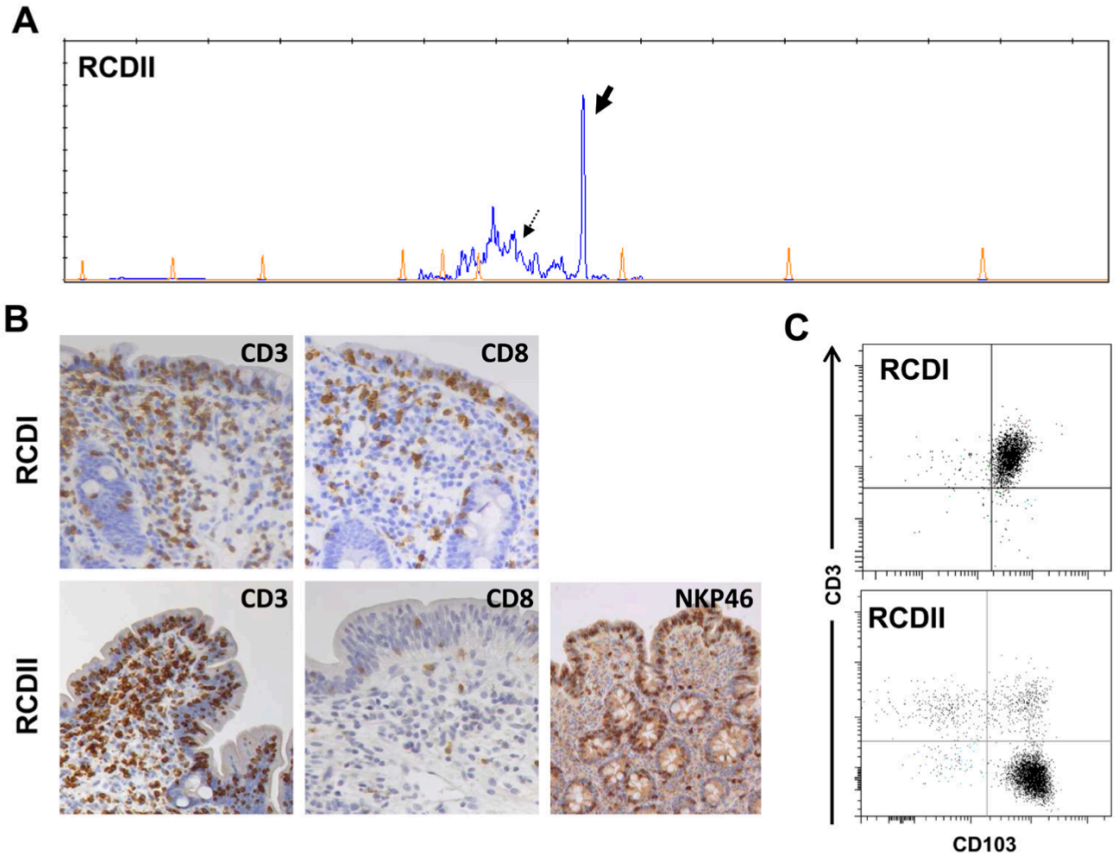
What is non-responsive (vs refractory) CD?



Reasons for
NRCD that is not RCD:

- **Gluten intake (35–50%)**
- Microscopic colitis
- SIBO
- Food intolerances
- Pancreatic exocrine insufficiency
- Wrong diagnosis

What is refractory CD?



Confirmed CD that is refractory to strict GFD
(i.e. usually negative serology)

	RCD1	RCD2
IEL phenotype	$CD3^+$ $CD8^+$	$CD3^-CD8^-$ $NKP46^+$
TCR	Polyclonal	Clonal
Ulcerative jejunitis	Rare	Common (→ Small-bowel work-up)
Progression into EATL	Rare	Common
5y survival	80–90%	40–50%
Treatment	Steroids, thiopurines	Chemotherapy Auto-SCT

Malamut G., Cording S. and Cerf-Bensussan N. doi:10.12688/f1000research.18701.1

ESEGH MCQs

MCQ 1

A 24-year-old woman presented with a 3-month history of lethargy, fatigue and weight loss. She had abdominal bloating and passed loose stools.

On examination, there were no abnormal findings.

Investigations:

haemoglobin	85 g/L (115–165)
MCV	70 fL (80–96)
white cell count	11.0 × 10^9/L (4.0–11.0)
platelet count	164 × 10^9/L (150–400)
serum ferritin	9 µg/L (15–300)
serum vitamin B_{12}	180 ng/L (160–760)
red cell folate	86 µg/L (160–640)
serum albumin	35 g/L (37–49)
serum IgG	7.2 g/L (6.0–13.0)
serum IgA	0.1 g/L (0.8–3.0)
serum IgM	0.3 g/L (0.4–2.5)
anti-tissue transglutaminase IgA antibodies	0 U/mL (<15)

What is the most appropriate next step in management?

A: CT scan of abdomen

B: duodenal biopsy

C: faecal elastase estimation

D: lactulose–hydrogen breath test

E: small bowel barium studies

MCQ 2

A 35-year-old woman presented for investigation of possible coeliac disease. She had been found to have raised anti-tissue transglutaminase antibodies on routine testing after the recent diagnosis of coeliac disease in her brother.

Examination showed no abnormal signs.

An upper gastrointestinal endoscopy was normal and duodenal biopsies were taken.

What histological feature on the duodenal biopsy specimen would most strongly support a diagnosis of coeliac disease?

A: eosinophilic infiltration

B: intraepithelial lymphocytosis

C: lymphangiectasia

D: neutrophil infiltration

E: plasma cell infiltration

MCQ 3

A 64-year-old man gave an 8-month history of sweats, fevers, arthralgia, back pain, weakness, presyncope, weight loss and diarrhoea. He also had a history of seronegative arthropathy.

On examination, he was malnourished with a distended abdomen.

Investigations:

stool microscopy and culture	negative
upper gastrointestinal endoscopy	normal
colonoscopy	normal
histology of duodenal (D3) biopsies	subtotal villous atrophy with increased intraepithelial lymphocytes and periodic acid–Schiff-positive staining of macrophages

What is the most likely diagnosis?

A: amyloidosis

B: coeliac disease

C: Crohn's disease

D: giardiasis

E: Whipple's disease

MCQ 4

A 54-year-old woman was referred with diarrhoea. She had a 9-month history of passing about six painless, foul-smelling stools per day, with weight loss and borborygmi. Her medical history included gastrooesophageal reflux disease, and type 1 diabetes mellitus (since the age of 13) complicated by proliferative retinopathy, peripheral neuropathy and renovascular disease. She was being treated with insulin, omeprazole, aspirin and simvastatin. She was a non-smoker and did not drink alcohol.

On examination, her abdomen was distended, with no masses or tenderness.

Investigations:

haemoglobin	105 g/L (115–165)
white cell count	5.0×10^9/L (4.0–11.0)
platelet count	350×10^9/L (150–400)
serum vitamin B_{12}	100 ng/L (160–760)
red cell folate	750 µg/L (160–640)
serum albumin	33 g/L (37–49)
serum total bilirubin	18 µmol/L (1–22)
serum alkaline phosphatase	300 U/L (45–105)
haemoglobin A_{1c}	112 mmol/mol (20–42)
serum 25-OH-cholecalciferol	30 nmol/L (>50)
ultrasound scan of abdomen	normal

What is the most likely diagnosis?

A: coeliac disease

B: Crohn's disease

C: intestinal bacterial overgrowth (SIBO)

D: lactose intolerance

E: pancreatic insufficiency

MCQ 5

A 40-year-old woman presented with abdominal distension and diarrhoea three to six times daily, with occasional incontinence. She had been told many years previously that she had irritable bowel syndrome. She had lost 8 kg in weight over the previous 6 months.

On examination, her temperature was 38.2°C and there was palpable hepatosplenomegaly.

Investigations:

haemoglobin	102 g/L (115–165)
MCV	92 fL (80–96)
white cell count	14.6 × 10^9/L (4.0–11.0)
ESR	86 mm/1st h (<20)
serum CRP	23 mg/L (<10)
anti-tissue transglutaminase IgA antibodies	31 U/mL (<15)

What is the most appropriate next investigation?

A: capsule endoscopy

B: colonoscopy

C: CT scan of chest, abdomen and pelvis

D: MR enteroclysis

E: push enteroscopy

MCQ 6

A 53-year-old woman with a history of hypothyroidism and celiac disease is seen in the outpatient clinic for diarrhea of 1-year duration. She is having 10 liquid stools per day with occasional episodes of incontinence. She was seen 2 years ago for bloating and occasional diarrhea, when upper endoscopy revealed flattening of villi in duodenum and biopsies confirmed a diagnosis of celiac disease. Her bloating improved with GFD and there was improvement of diarrhea as well. Repeat EGD last month showed normal villi and biopsies were normal, but she continues to have diarrhea on a GFD. Her tissue transglutaminase is now normal. Colonoscopy was performed revealing normal colonic mucosa and terminal ileums biopsies were obtained. Her only medication is L-thyroxin.

What is the most likely cause of her diarrhea?

A. Ulcerative colitis
B. Celiac disease
C. Microscopic colitis
D. IBS-D
E. Laxative abuse