UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
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Diseases of small intestine

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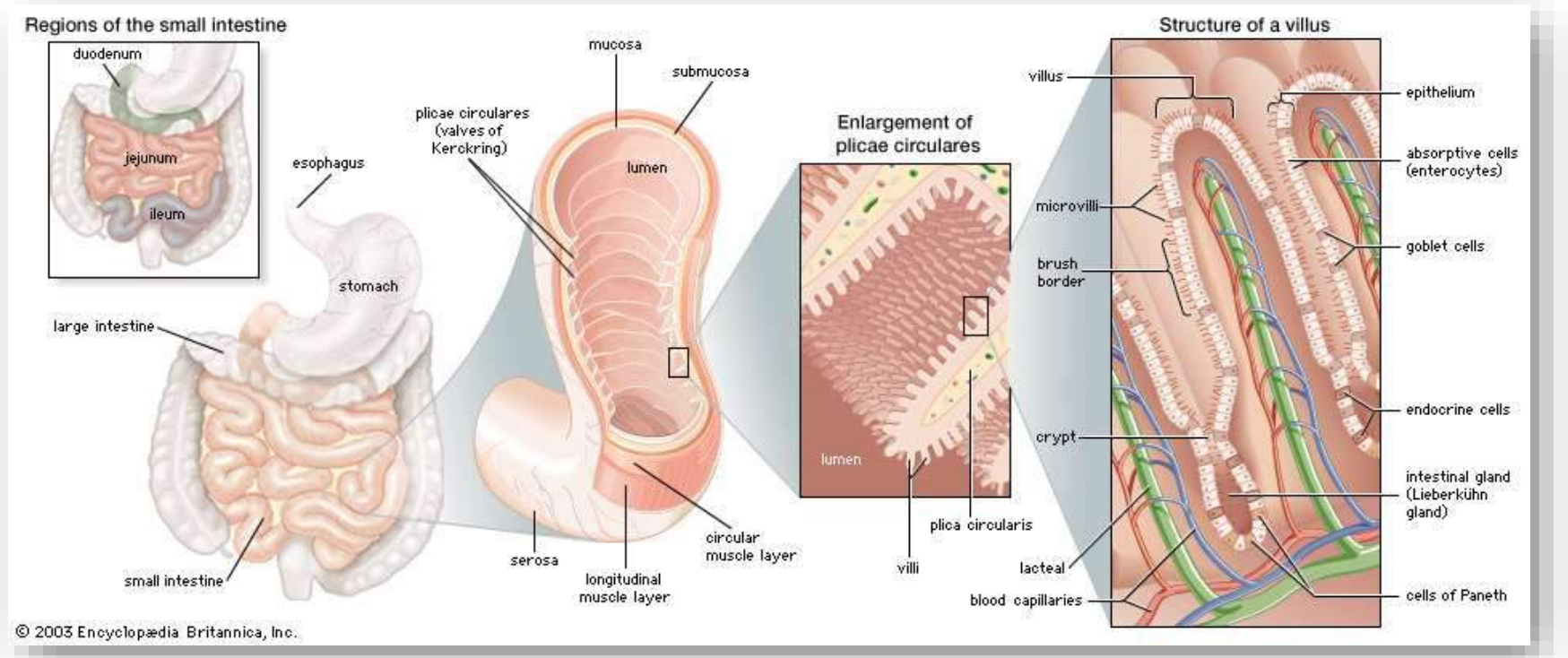
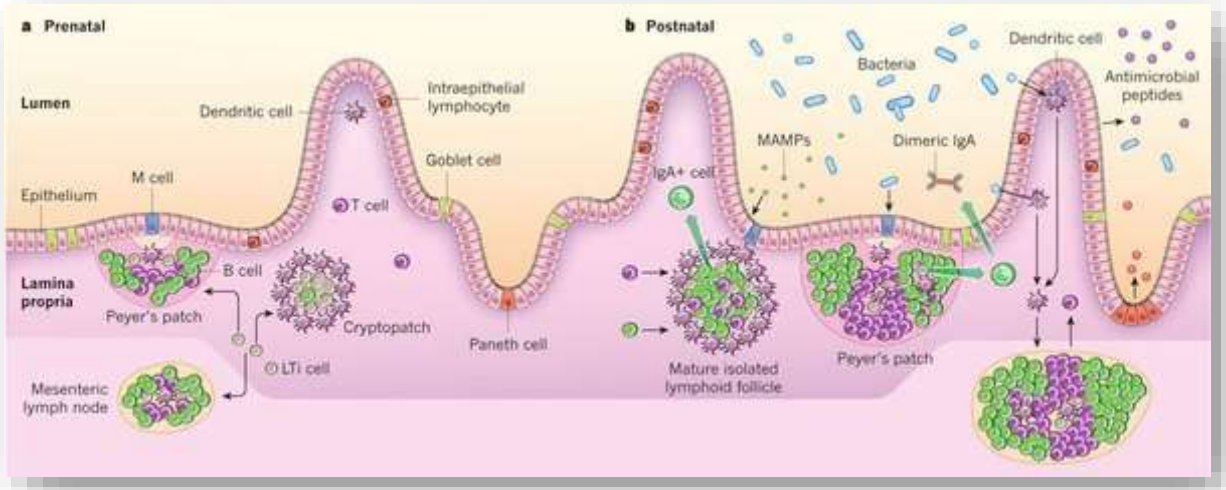
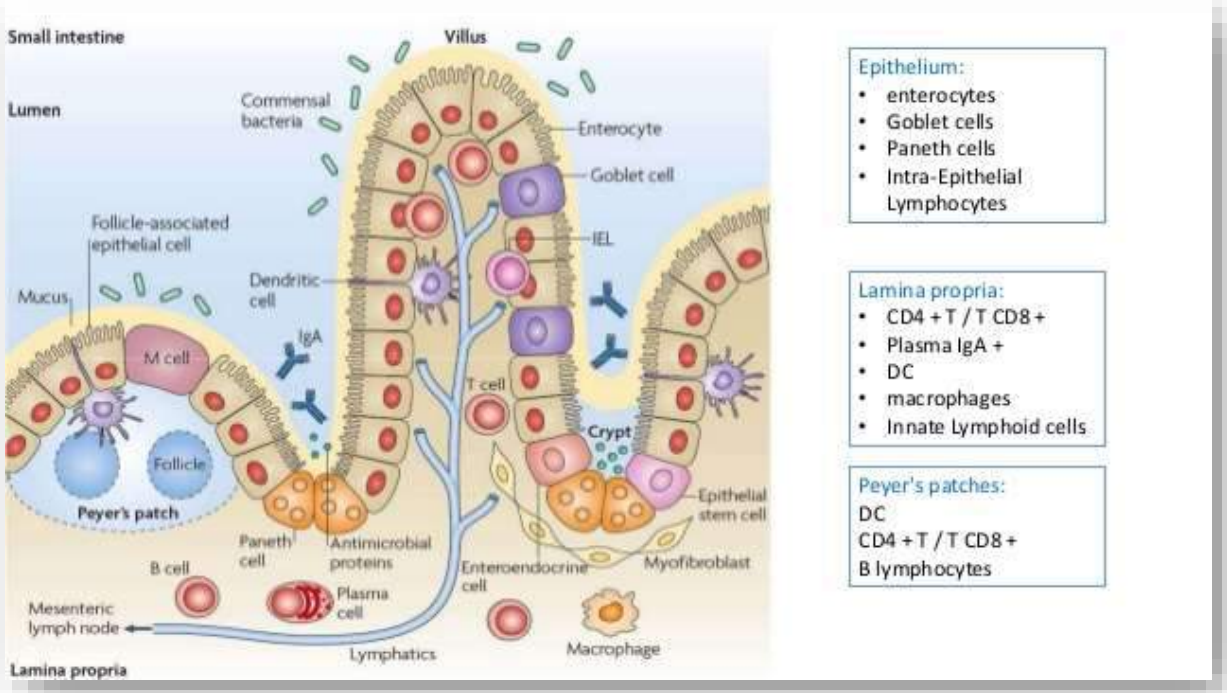
Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Small bowel anatomy



Small bowel immune system

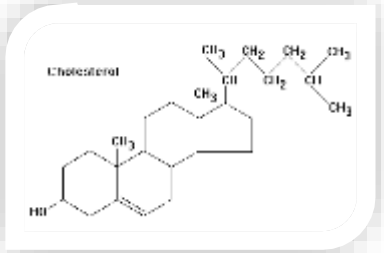


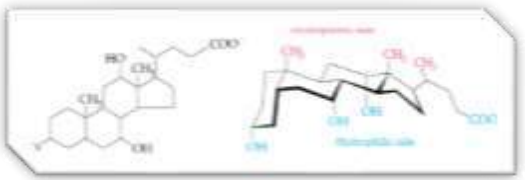


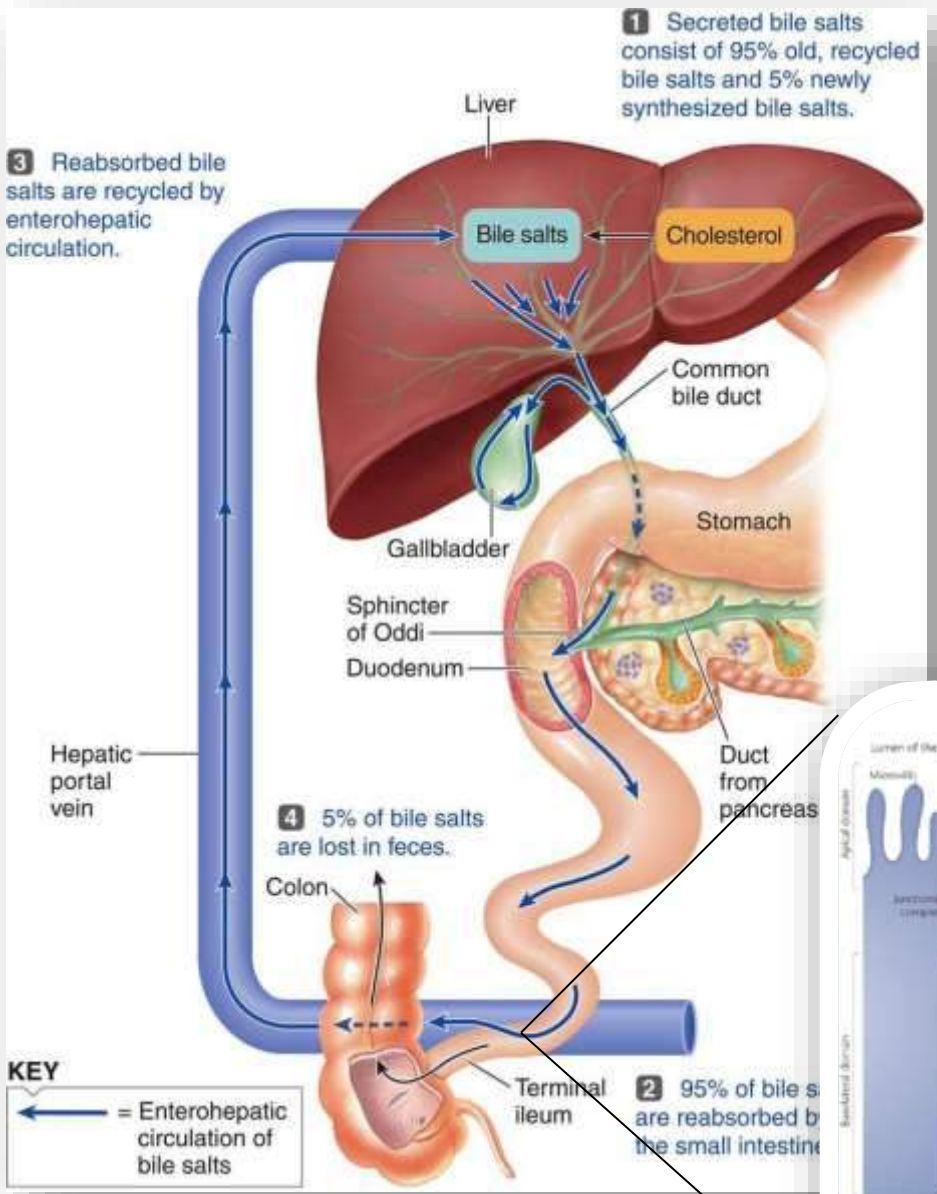
Epithelium:
- enterocytes
- Goblet cells
- Paneth cells
- Intra-Epithelial Lymphocytes

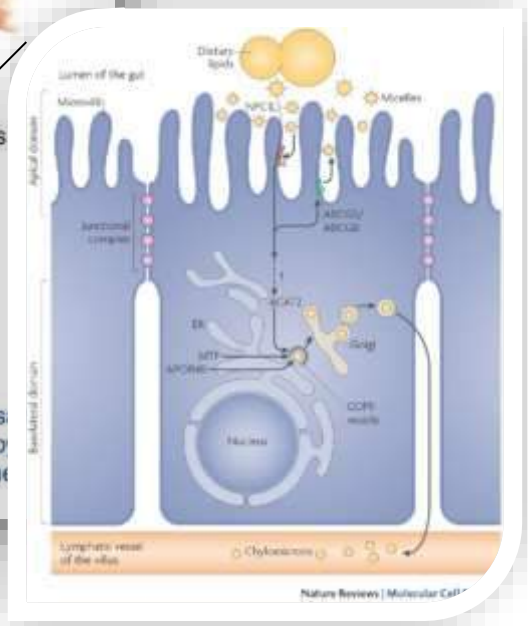
Lamina propria:
- CD4 + T / T CD8 +
- Plasma IgA +
- DC
- macrophages
- Innate Lymphoid cells

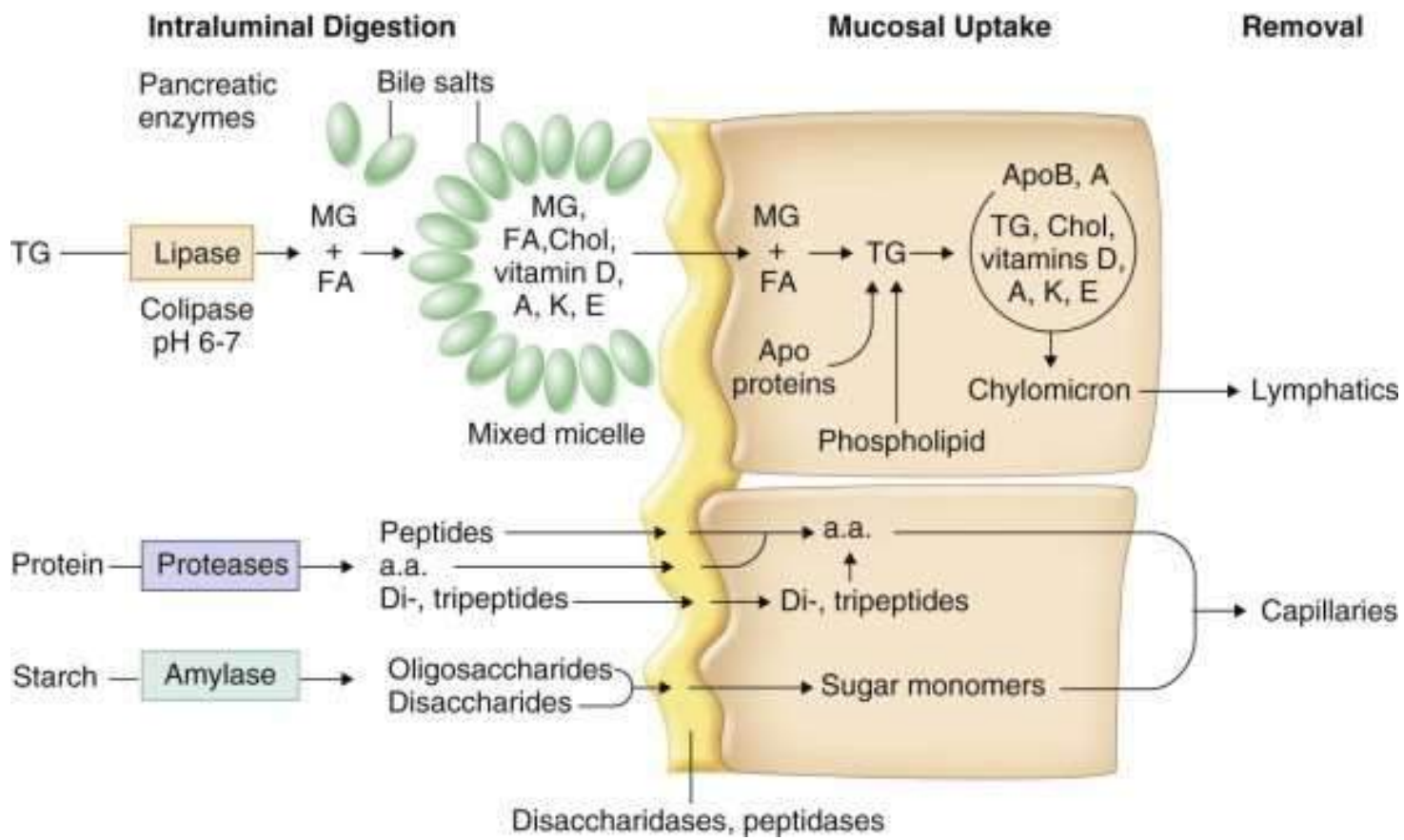
Peyer's patches:
DC
CD4 + T / T CD8 +
B lymphocytes


Cholesterol

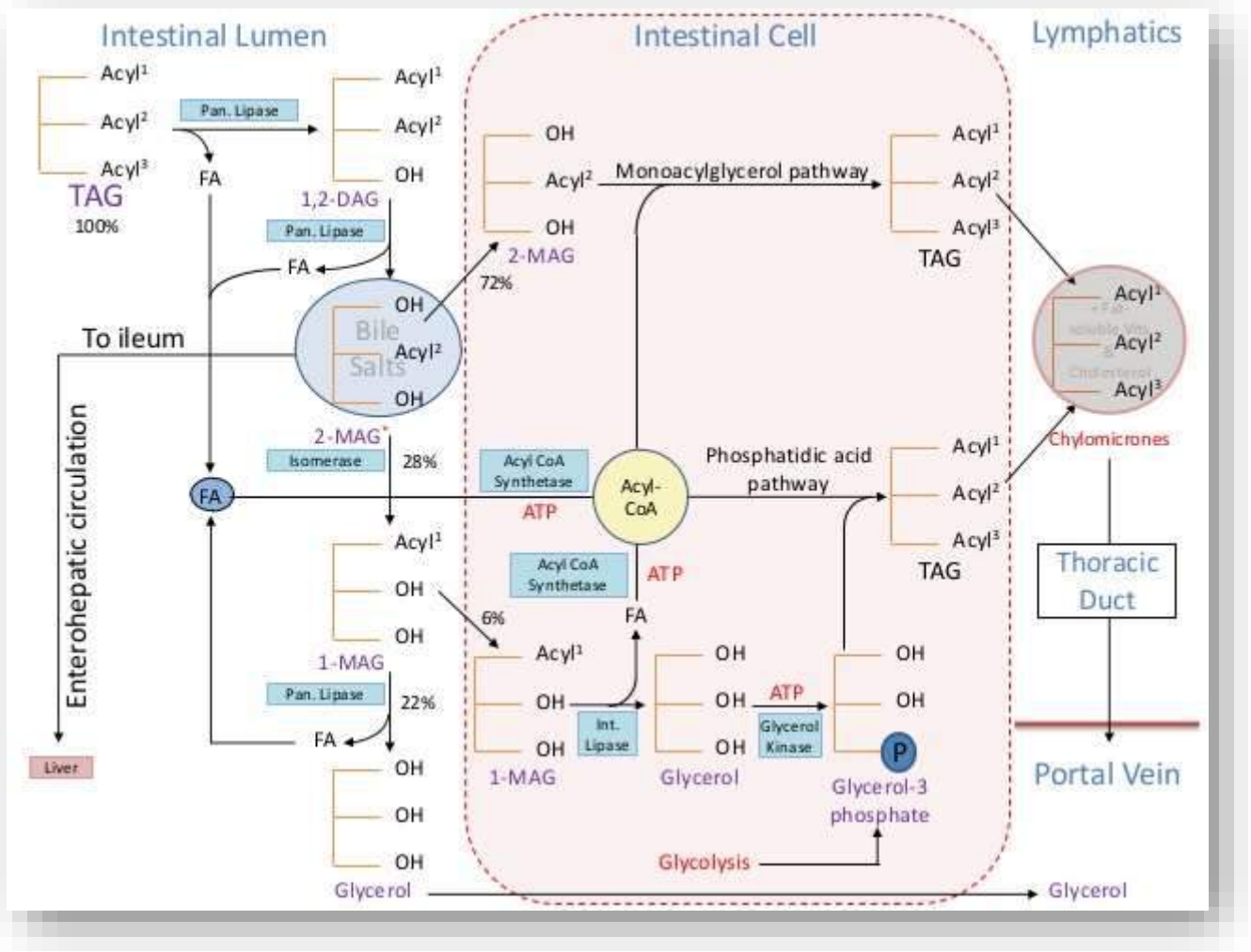



1 Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.
Liver
3 Reabsorbed bile salts are recycled by enterohepatic circulation.
Bile salts
Cholesterol
Common bile duct
Gallbladder
Stomach
Sphincter of Oddi
Duodenum
Hepatic portal vein
Duct from pancreas
4 5% of bile salts are lost in feces.
Colon
Terminal ileum
2 95% of bile s
are reabsorbed b
the small intestine
KEY
= Enterohepatic circulation of bile salts

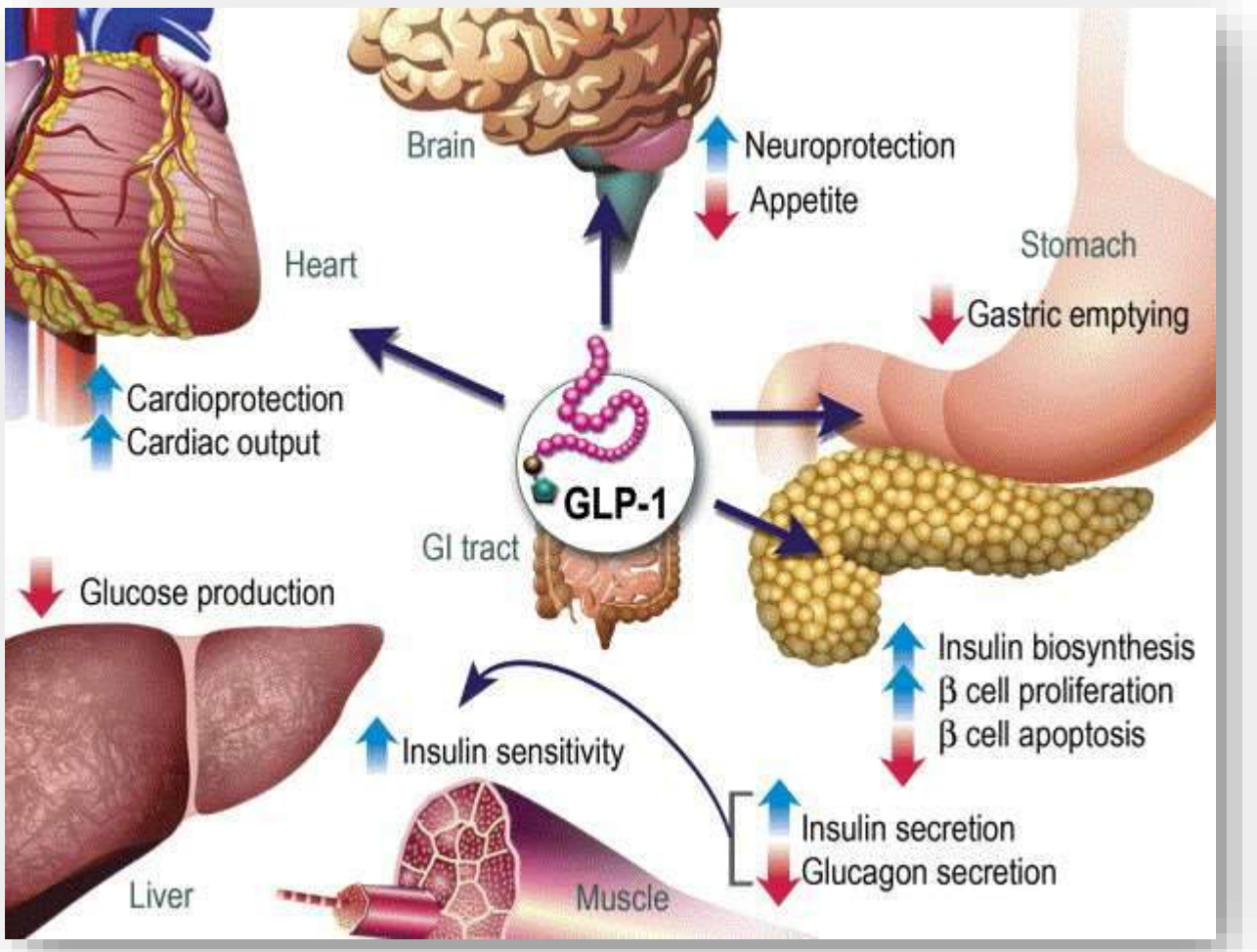



Intraluminal Digestion
Mucosal Uptake
Removal
Pancreatic enzymes
Bile salts
TG
Lipase
Colipase
pH 6-7
MG
+
FA
MG,
FA,Chol,
vitamin D,
A, K, E
Mixed micelle
MG
+
FA
TG
ApoB, A
TG, Chol,
vitamins D,
A, K, E
Apo
proteins
Phospholipid
Chylomicron
Lymphatics
Protein
Proteases
Peptides
a.a.
Di-, tripeptides
a.a.
Di-, tripeptides
Capillaries
Starch
Amylase
Oligosaccharides
Disaccharides
Sugar monomers
Disaccharidases, peptidases

Lipid absorption



Glucose –endocrine axis



Malabsorption syndrome

Malabsorption

- Disorders of absorption constitute a broad spectrum of conditions with multiple etiologies and varied clinical manifestations.
- Almost all of these clinical problems are associated **with *diminished* intestinal absorption** of **one or more dietary nutrients** and are often referred to as the ***malabsorption syndrome*.**

- Malabsorption is a clinical term that encompasses defects occurring during the **digestion and absorption** of food nutrients

- Impairment can be of single or multiple nutrients depending on the abnormality.

Malabsorption

Two main pathogenetic mechanisms lead to malabsorption :

- **Maldigestion (luminal mechanisms)**
- **Malabsorption (parietal mechanisms)**

Maldigestion (luminal mechanisms)

Pathophysiologic Mechanism	Malabsorbed Substrate(s)	Representative Causes
Maldigestion		
Conjugated bile acid deficiency	Fat Fat-soluble vitamins Calcium Magnesium	Hepatic parenchymal disease Biliary obstruction SIBO with bile acid deconjugation Ileal bile acid malabsorption CCK deficiency
Pancreatic insufficiency	Fat Protein Carbohydrate Fat-soluble vitamins Vitamin B_{12} (cobalamin)	Congenital defects Chronic pancreatitis Pancreatic tumors Inactivation of pancreatic enzymes (e.g., ZES)
Reduced mucosal digestion	Carbohydrate Protein	Congenital defects (see Table 104-10) Acquired lactase deficiency Generalized mucosal disease (e.g., celiac disease, Crohn's disease)
Intraluminal consumption of nutrients	Vitamin B_{12} (cobalamin)	SIBO Helminthic infections (e.g., *Diphyllobothrium latum* infection)

Malabsorption (parietal mechanisms)

Malabsorption		
Reduced mucosal absorption	Fat Protein Carbohydrate Vitamins Minerals	Congenital transport defects (see Table 104-10) Generalized mucosal diseases (e.g., celiac disease, Crohn's disease) Previous intestinal resection or bypass Infections Intestinal lymphoma
Decreased transport from the intestine	Fat Protein	Intestinal lymphangiectasia Primary Secondary (e.g., solid tumors, Whipple's disease, lymphomas) Venous stasis (e.g., from heart failure)
Other Mechanisms		
Decreased gastric acid and/or intrinsic factor secretion	Vitamin B_{12}	Pernicious anemia Atrophic gastritis Previous gastric resection
Decreased gastric mixing and/or rapid gastric emptying	Fat Calcium Protein	Previous gastric resection Autonomic neuropathy
Rapid intestinal transit	Fat	Autonomic neuropathy Hyperthyroidism

Malabsorptive disorders can be categorized into:

1-Generalized mucosal abnormalities

resulting in multiple nutrient malabsorption

2-Specific nutrient disorder

(carbohydrate, fat, protein, vitamin and mineral malabsorption)

Specific nutrient malabsorptive disorder

Carbohydrate malabsorption

- lactase deficiency (congenital, secondary)
- Congenital sucrase-isomaltase deficiency
- Glucose- galactose malabsorption

Protein malabsorption

- Enterokinase deficiency
- Amino acid transport defect

(eg; Hartnup disease)

Fat malabsorption

-Pancreatic exocrine insufficiency (cystic fibrosis, shwachman diamond syndrome, chronic pancreatitis)

-liver and biliary disorders

- Abetalipoproteinemia

Mineral and vitamin malabsorption

-Congenital chloride diarrhea

-Congenital sodium absorption defect

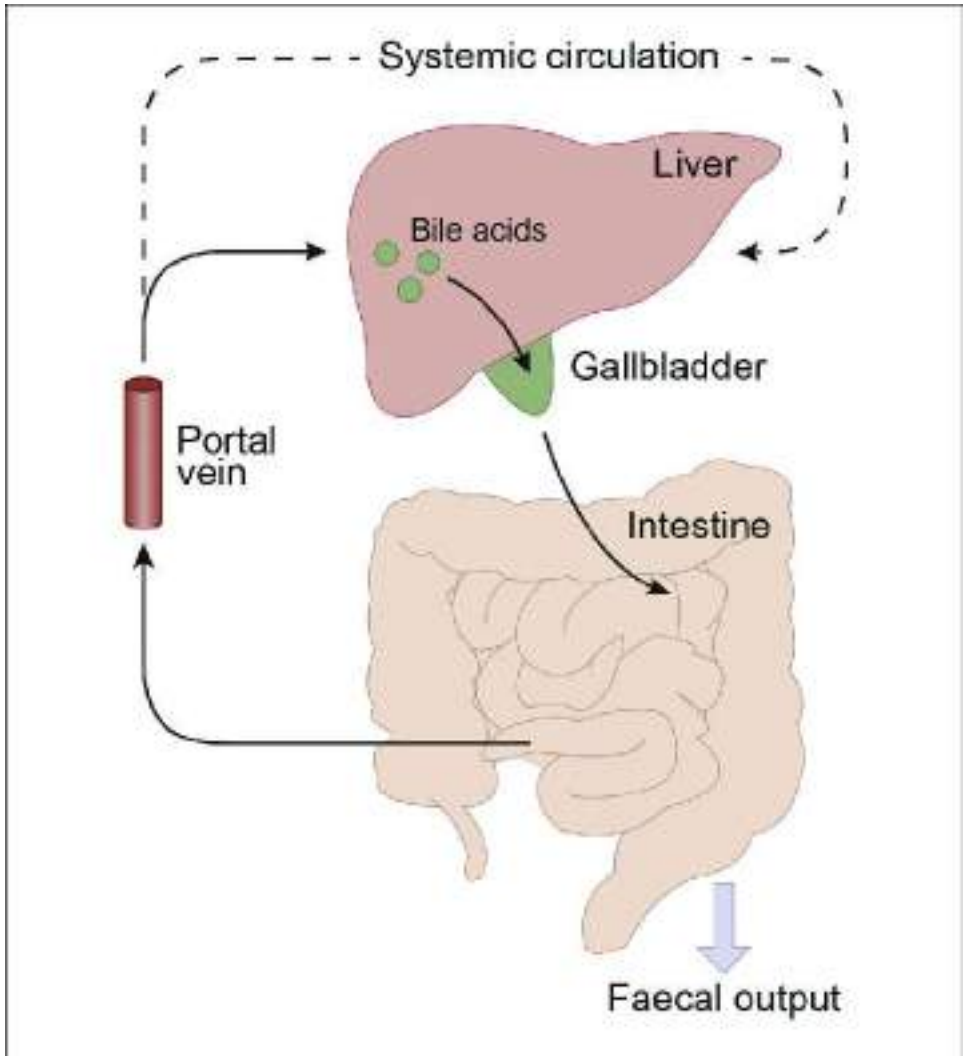
-Acrodermatitis enteropathica

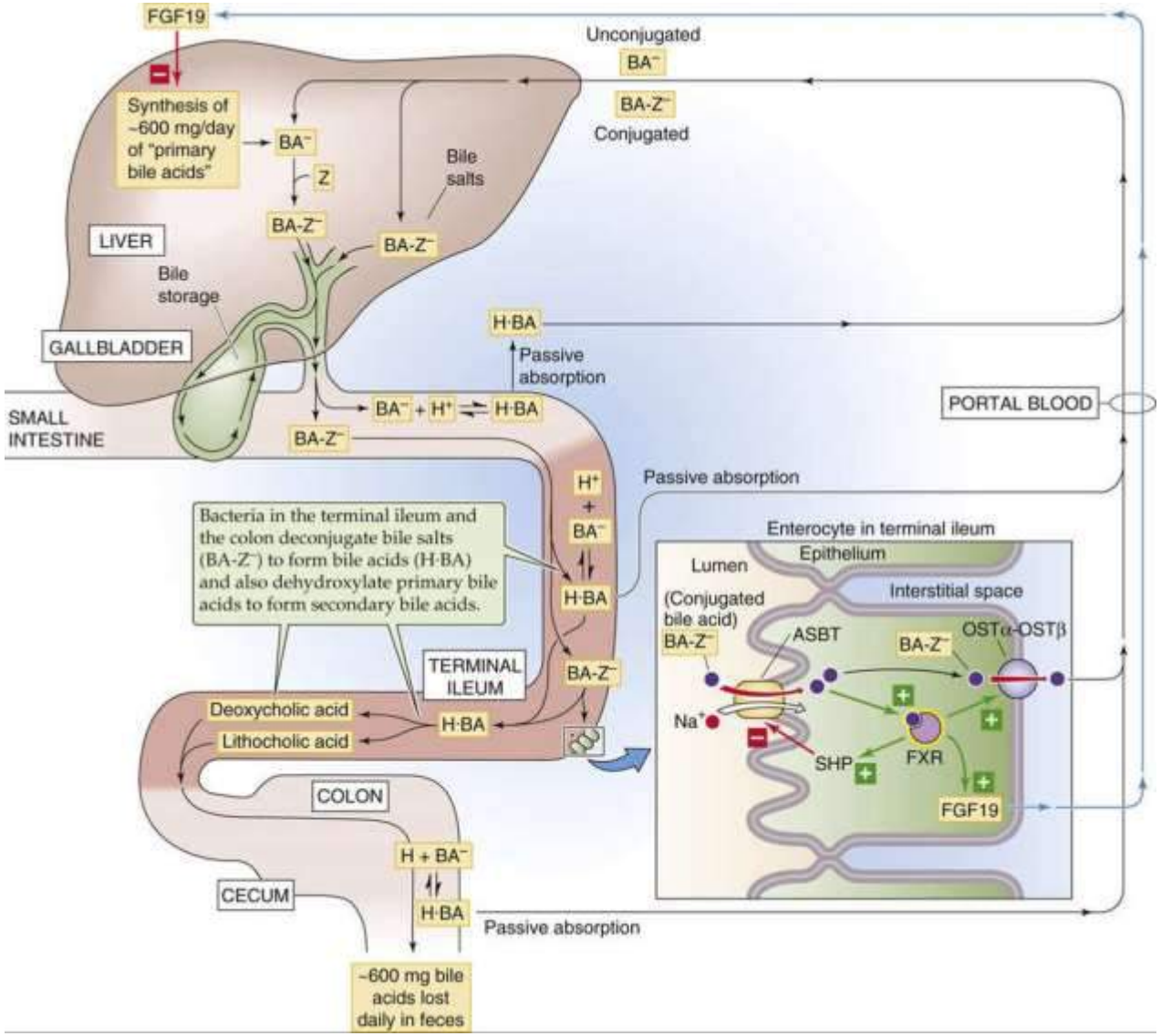
-Menke disease

-Vitamin D dependent rickets

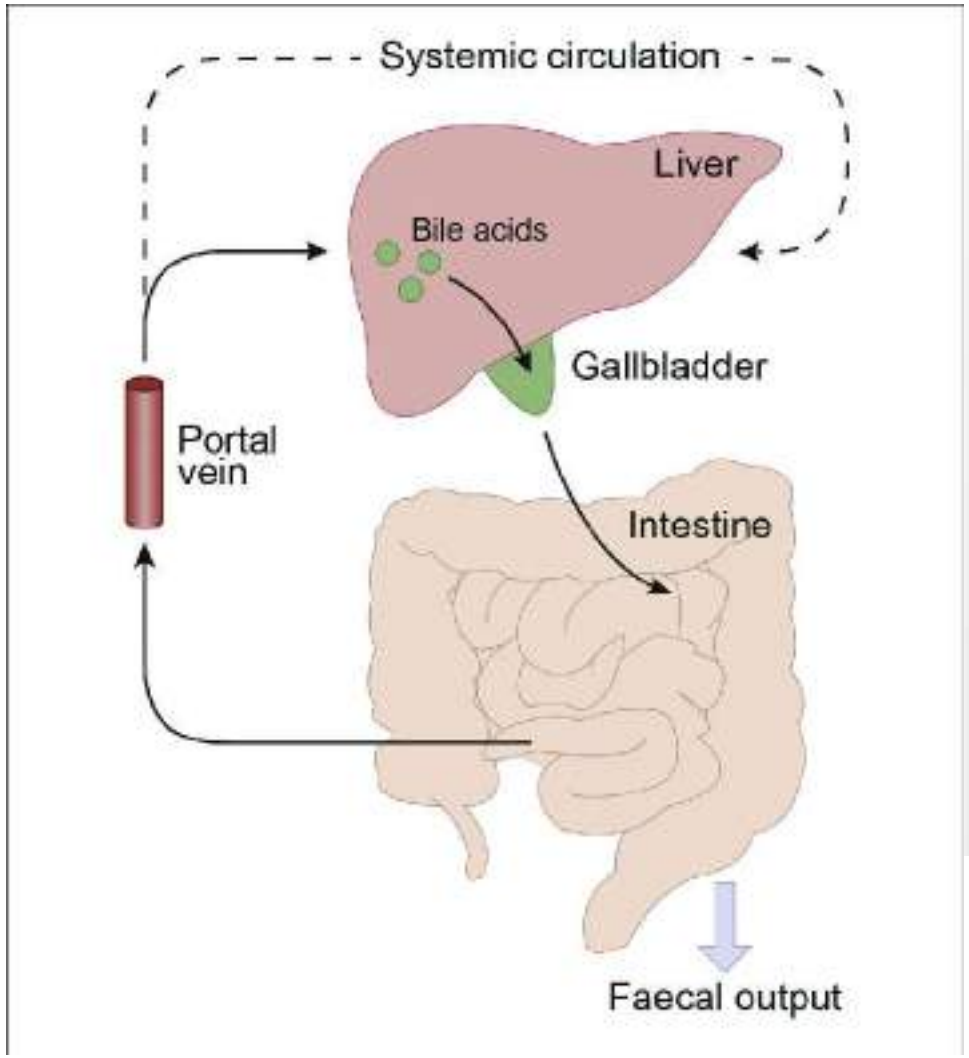
-Vitamin B12 malabsorption

Specific nutrient malabsorptive disorder : bile acid disorders





Specific nutrient malabsorptive disorder : bile acid disorders



Classification of BAM	Etiology
Type 1 Ileal dysfunction (secondary BAM)	Ileal Crohn disease, ileal resection • Results in failure to reabsorb BAs at the distal ileum leading to BA spillover into colon
Type 2 Idiopathic BAM/primary bile acid diarrhea	Unknown cause • No consistent inherited abnormality in transporter proteins • Mechanisms may arise from defect in negative feedback (FGF19) regulation in the synthesis of BAs, leads to overproduction of BAs
Type 3 Other conditions	Postcholecystectomy, postvagotomy, celiac disease, bacterial overgrowth, pancreatic insufficiency (chronic pancreatitis and cystic fibrosis) • May involve alterations in small intestinal motility, altered BA cycling, or composition of ileal contents

Adapted from reference 27. BA Bile acid; FGF Fibroblast growth factor

Drugs that might induce malabsorption

TABLE 104-9 Drugs and Dietary Products That Cause Malabsorption

Substance	Substrate Malabsorbed	Suggested Mechanism
Acarbose	Carbohydrate	Inhibition of α-glucosidase
Antacids	Phosphate, iron, vitamin A	Luminal binding of substrates
Azathioprine	Generalized malabsorption	Villus atrophy
Biguanide (metformin)	Cobalamin, folate, glucose	Reduced ileal absorption of intrinsic factor (IF)-cobalamin complex; inhibition of intestinal glucose or folate absorption
Carbamazepine	Folate	Inhibition of intestinal folate absorption
Cholestyramine	Fat, fat-soluble vitamins, bile acids	Binding of conjugated bile salts
Colchicine	Fat, xylose, nitrogen, cobalamin, carotene	Mucosal damage and villus atrophy at high doses (impaired processing of IF-cobalamin receptor [the cubilin-amnionless complex])

Sleisenger & Fordtran's Gastrointestinal and liver disease. 11th Edition - 2020

Drugs that might induce malabsorption

TABLE 104-9 Drugs and Dietary Products That Cause Malabsorption—cont'd

Substance	Substrate Malabsorbed	Suggested Mechanism
Contraceptives, oral*	Folate	Inhibition of pteroylpolyglutamate hydrolase (folate conjugase)
Ethanol	Xylose, fat, glucose, nitrogen, thiamine, cobalamin, folate	Mucosal damage; decreased disaccharidase activity; decreased pancreatic exocrine function and bile secretion
Fiber, phytates	Iron, calcium, magnesium, zinc	Chelation
Glucocorticoids	Calcium	Inhibition of calcium absorption
H2RAs	Cobalamin	Impaired release of food-bound B_{12} owing to reduced gastric acid and pepsin secretion (and reduced IF secretion)
Laxatives, irritant type (phenolphthalein, bisacodyl, anthraquinones)	Fat, glucose, xylose	Washout effect; toxic effect on mucosa
Methotrexate	Folate, fat, cobalamin, xylose	Mucosal damage; inhibition of intestinal folate transport
Methyldopa†	Generalized malabsorption	Mucosal damage
Neomycin	Fat, nitrogen, fat-soluble vitamins, cobalamin, mono- and disaccharides, iron	Mucosal damage; disruption of micelle formation

Drugs that might induce malabsorption

Olestra*	Fat-soluble vitamins	Binding of fat-soluble vitamins
Orlistat	Fat, fat-soluble vitamins	Inhibition of pancreatic lipase
Para-aminosalicylate	Fat, cobalamin, folate	Unknown
Phenytoin	Folate, calcium	Inhibition of folate and calcium absorption owing to luminal alkalinization; impaired vitamin D metabolism
PPIs*	Cobalamin, calcium?, magnesium?	Impaired release of food-bound cobalamin by pepsin owing to reduced gastric acid secretion; SIBO
Pyrimethamine	Folate	Competitive inhibition of intestinal folate absorption
Somatostatin analogs (e.g., octreotide)	Fat	Inhibition of hepatobiliary bile acid secretion; inhibition of pancreatic enzyme secretion; inhibition of CCK release
Sulfonamides and sulfasalazine	Folate	Inhibition of pteroylpolyglutamate hydrolase and folate transport
Tetracycline	Calcium	Precipitation of luminal calcium
Thiazides	Calcium	Decreased 1,25 dihydroxyvitamin D synthesis
Triamterene*	Folate	Competitive inhibition of intestinal folate absorption

Malabsorption syndrome

Clinical manifestations

TABLE 104-3 Symptoms and Signs of Malabsorption and Relevant Pathophysiology

Symptom or Sign	Pathophysiologic Explanation
Gastrointestinal	
Diarrhea	Osmotic activity of carbohydrates or short-chain fatty acids Secretory effect of bile acids and fatty acids Decreased absorptive surface Intestinal loss of conjugated bile acids: Ileal resection Severe ileal mucosal disease Congenital defects of the ileal sodium-bile acid cotransporter
Abdominal distention, flatulence	Bacterial gas production from carbohydrates in colon, SIBO
Foul-smelling flatulence or stool	Malabsorption of proteins or intestinal protein loss
Pain	Gaseous distention of intestine
Ascites	Protein loss or malabsorption
Musculoskeletal	
Tetany, muscle weakness, paresthesias	Malabsorption of vitamin D, calcium, magnesium, and phosphate
Bone pain, osteomalacia, fractures	Protein, calcium, or vitamin D deficiency; secondary hyperparathyroidism
Cutaneous and Mucosal	
Easy bruisability, ecchymoses, petechiae	Vitamin K deficiency, vitamin C deficiency (scurvy)
Glossitis, cheilosis, stomatitis	Vitamin B complex, vitamin B_{12}, folate, or iron deficiency
Edema	Protein loss or malabsorption
Acrodermatitis, scaly dermatitis	Zinc and essential fatty acid deficiency
Follicular hyperkeratosis	Vitamin A deficiency
Hyperpigmented dermatitis	Niacin deficiency (pellagra)
Thin nails with spoon-shaped deformity	Iron deficiency
Perifollicular hemorrhage	Malabsorption of vitamin C
Spiral or curly hair	Malabsorption of vitamin C
Other	
Weight loss, hyperphagia	Nutrient malabsorption
Growth and weight retardation, infantilism	Nutrient malabsorption in childhood and adolescence
Anemia	Iron, folate, or vitamin B_{12} deficiency
Kidney stones	Increased colonic oxalate absorption
Amenorrhea, impotence, infertility	Multifactorial (including protein malabsorption, secondary hypopituitarism, anemia)
Night blindness, xerophthalmia	Vitamin A deficiency
Peripheral neuropathy	Vitamin B_{12} or thiamine deficiency
Fatigue, weakness	Calorie depletion, iron and folate deficiency, anemia
Neurologic symptoms, ataxia	Vitamin B_{12}, vitamin E, or folate deficiency

Malabsorption syndrome

Diagnosis

Malabsorption

There is no specific test for malabsorption.

- Investigation is guided by symptoms and signs.
- 1. Blood tests
- 2. Fecal fat study to diagnose steatorrhea
- 3. Endoscopy Biopsy of small bowel
- 4. Breath test H_2 and C_{13} with lactose or glucose

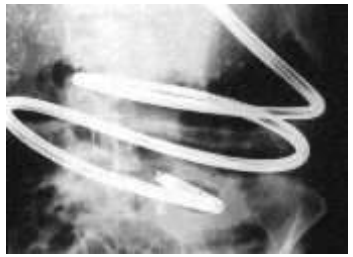
Malabsorption; blood tests

TABLE 104-4 Useful Laboratory Tests for Patients with Suspected Malabsorption and for Establishing Possible Nutrient Deficiencies

Test	Comment(s)
Blood Cell Count	
Hematocrit, hemoglobin	Decreased in iron, vitamin B_{12}, and folate malabsorption or with blood loss
Mean corpuscular hemoglobin or mean corpuscular volume	Decreased in iron malabsorption; increased in folate and vitamin B_{12} malabsorption
White blood cells, differential	Decreased in vitamin B_{12} and folate malabsorption; low lymphocyte count in lymphangiectasia
Biochemical Tests (Serum)	
TGs	Decreased in severe fat malabsorption
Cholesterol	Decreased in bile acid malabsorption or severe fat malabsorption
Albumin	Decreased in severe malnutrition, lymphangiectasia, protein-losing enteropathy
Alkaline phosphatase	Increased in calcium and vitamin D malabsorption (severe steatorrhea); decreased in zinc deficiency
Calcium, phosphorus, magnesium	Decreased in extensive small intestinal mucosal disease, after extensive intestinal resection, or in vitamin D deficiency
Zinc	Decreased in extensive small intestinal mucosal disease or intestinal resection
Iron, ferritin	Decreased in celiac disease, in other extensive small intestinal mucosal diseases, and with chronic blood loss
Other Serum Tests	
Prothrombin time	Prolonged in vitamin K malabsorption
β-Carotene	Decreased in fat malabsorption from hepatobiliary or intestinal diseases
Immunoglobulins	Decreased in lymphangiectasia, diffuse lymphoma
Folic acid	Decreased in extensive small intestinal mucosal diseases, with anticonvulsant use, in pregnancy; may be increased in SIBO
Vitamin B_{12}	Decreased after gastrectomy, in pernicious anemia, terminal ileal disease, SIBO, and infection with *Diphyllobothrium latum*
Methylmalonic acid	Markedly elevated in vitamin B_{12} deficiency
Homocysteine	Markedly elevated in vitamin B_{12} or folate deficiency
Citrulline	May be decreased in destructive small intestinal mucosal disease or intestinal resection
Stool Tests	
Fat	Qualitative or quantitative increase in fat malabsorption
Elastase, chymotrypsin	Decreased concentrations and output in exocrine pancreatic insufficiency
pH	Less than 5.5 in carbohydrate malabsorption

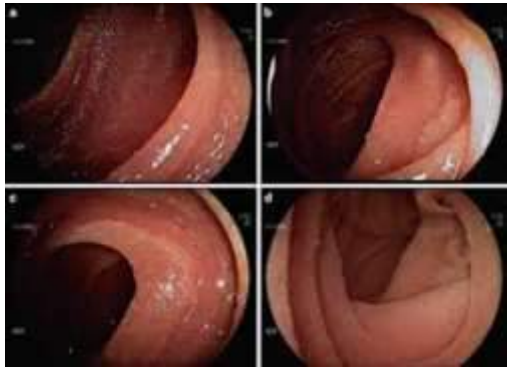
Endoscopy

- **Gross morphology – gives diagnostic clue**
  - Reduced duodenal folds and scalloping of duodenal mucosa – celiac disease
    - Use of vital dyes to identify villous atrophy
- **Biopsy – to establish Dx**
  - For patients with documented steatorrhea or chronic Diarrhea
- **Lesions – classified in to three**
  - Diffuse,specific e.g. Whipple's Disease
  - Patchy, specific – Crohn's D., lymphoma infectious causes
  - Diffuse,non-specific – celiac sprue, Tropical sprue autoimmune enteropathy
- **Suspected distal pathology** - push enteroscopy wireless capsule endoscopy

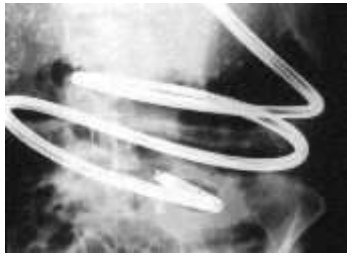


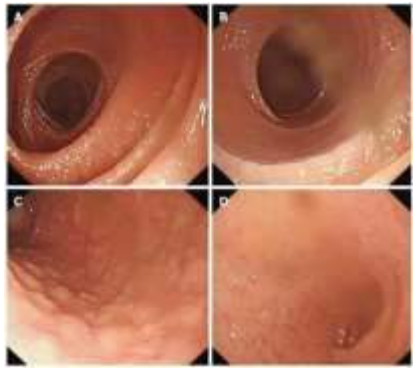
Endoscopy

Upper endoscopy

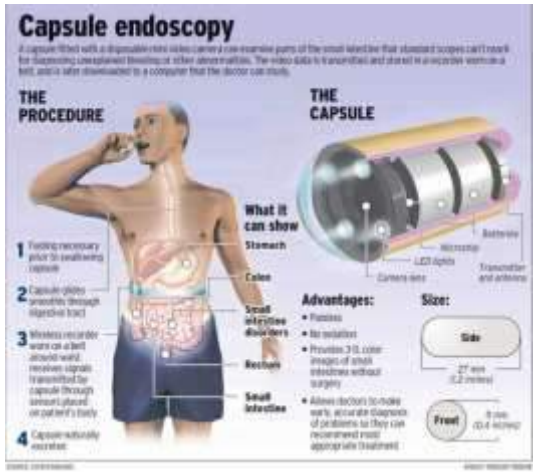


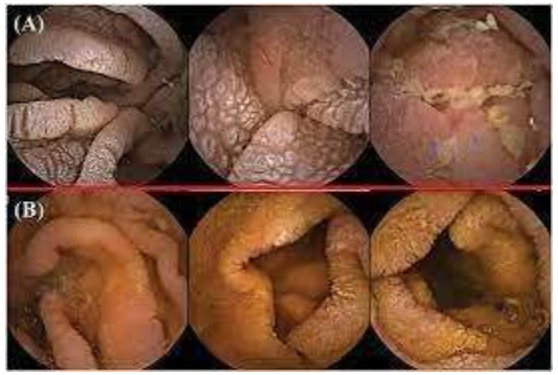
Enteroscopy





Capsule endoscopy



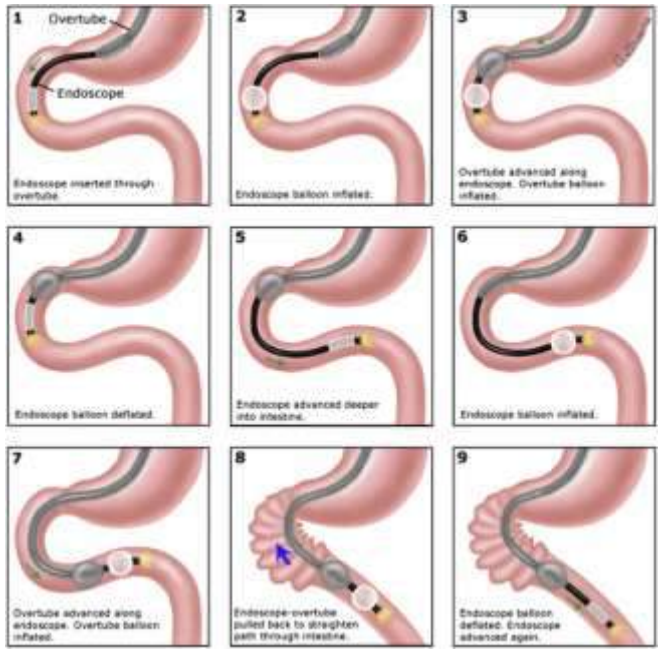


Biopsy

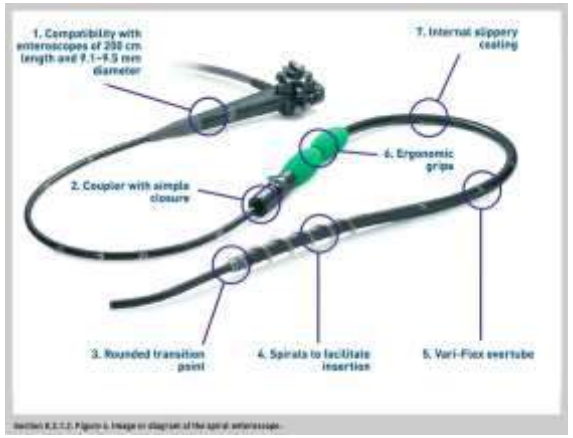
Endoscopy

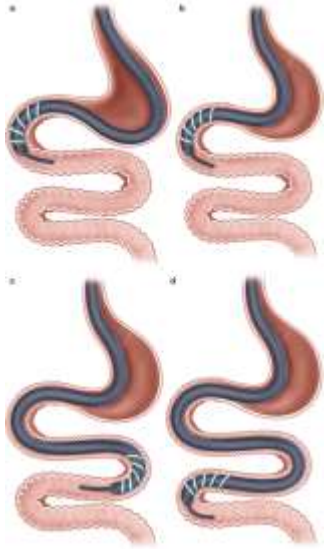
Enteroscopy: technique

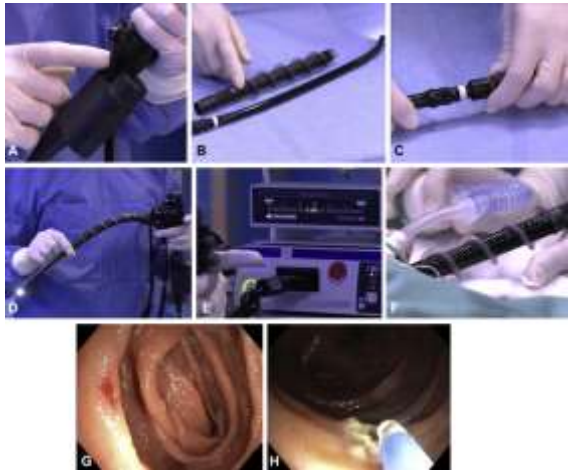
dual balloons



spiral



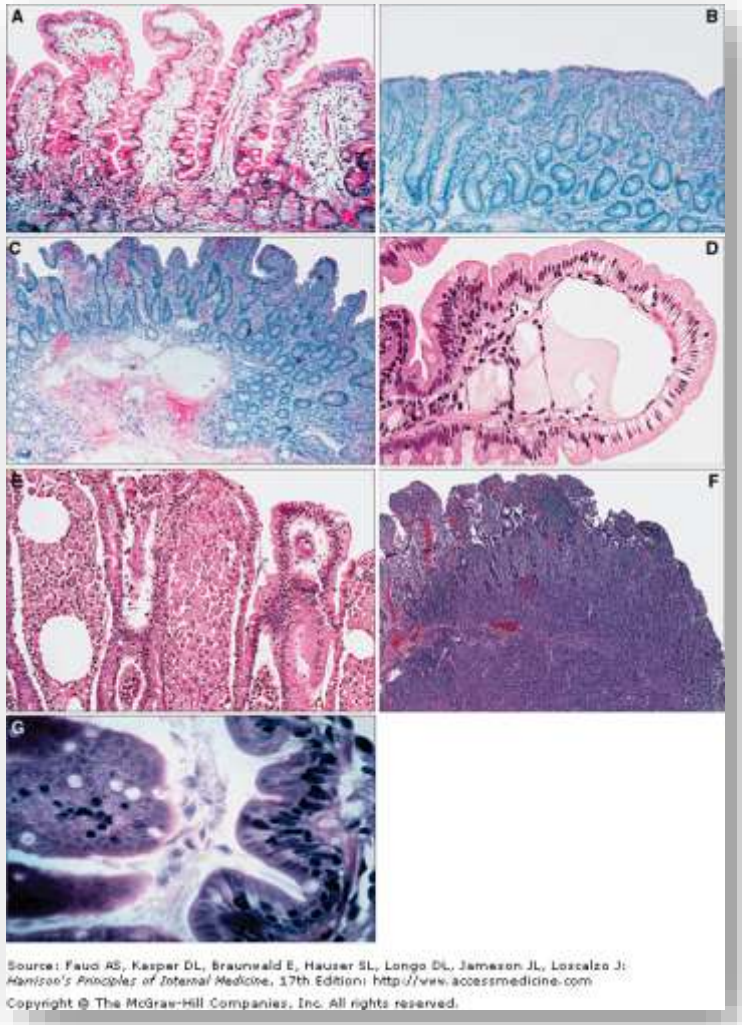




Small Bowel Biopsy

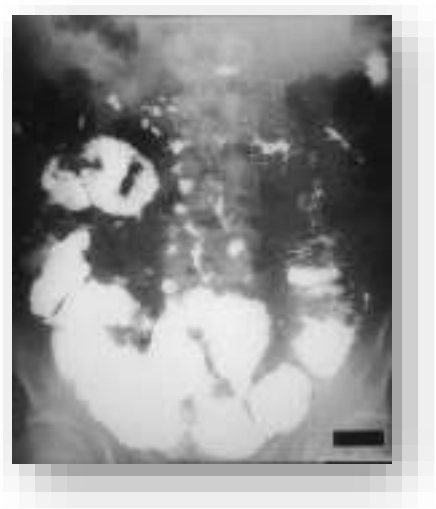
Causes of villous atrophy in the duodenum

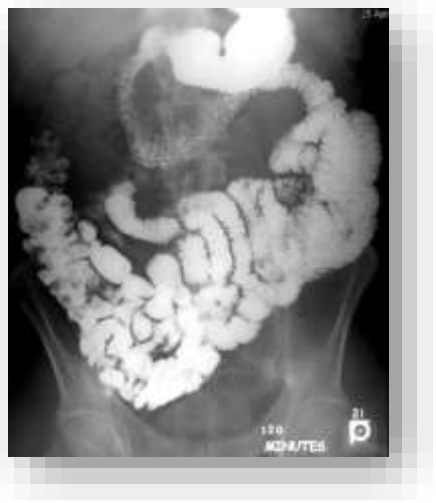
- **Celiac disease**
- Tropical sprue
- Small-bowel bacterial overgrowth
- Autoimmune enteropathy
- Hypogammaglobulinemic sprue
- Drug-associated enteropathy (e.g., olmesartan)
- Whipple disease
- Collagenous sprue
- Crohn's disease
- Eosinophilic enteritis
- Intestinal lymphoma Intestinal tuberculosis
- Infectious enteritis (e.g., giardiasis)
- Graft versus host disease
- Malnutrition
- Acquired immune deficiency syndrome enteropathy



Barium studies

- **Important information about the gross anatomy and morphology of SB**
  - Upper GI series with small bowel follow through
  - Duodenal tube, double contrast study by passing a tube into proximal SB and injecting barium+ methylcellulose





- **Normal study doesn’t exclude small bowel disease**

Tests for steatorrhea

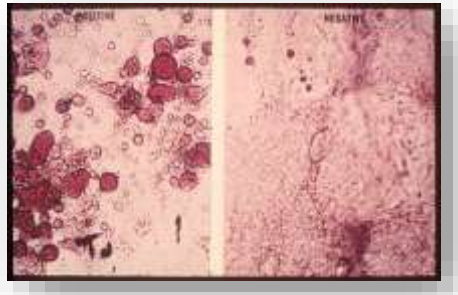
Quantitative test

Gold standard test of fat malabsorption, with which all other tests are compared. Requires ingestion of a high-fat diet (100 g) for 2 days before and during the collection.

Stool is collected for 3 days. Normally, <7 g/24 hr is excreted on a high-fat diet

Qualitative tests Sudan lll stain

Detect clinically significant steatorrhea in >90% of cases



Sudan stain of a stool sample for fat. Many fat droplets per medium-power field (×40) constitute a positive test result.

The nuclear magnetic resonance method determines the percentage of fat in the stool (normal, <20%).

The test depends on an adequate fat intake (100 g/day).

There is high sensitivity (90%) and specificity (90%) with fat malabsorption of >10 g/24 hr. Sensitivity drops with stool fat in the range of 6-10 g/24 h

D-xylose test

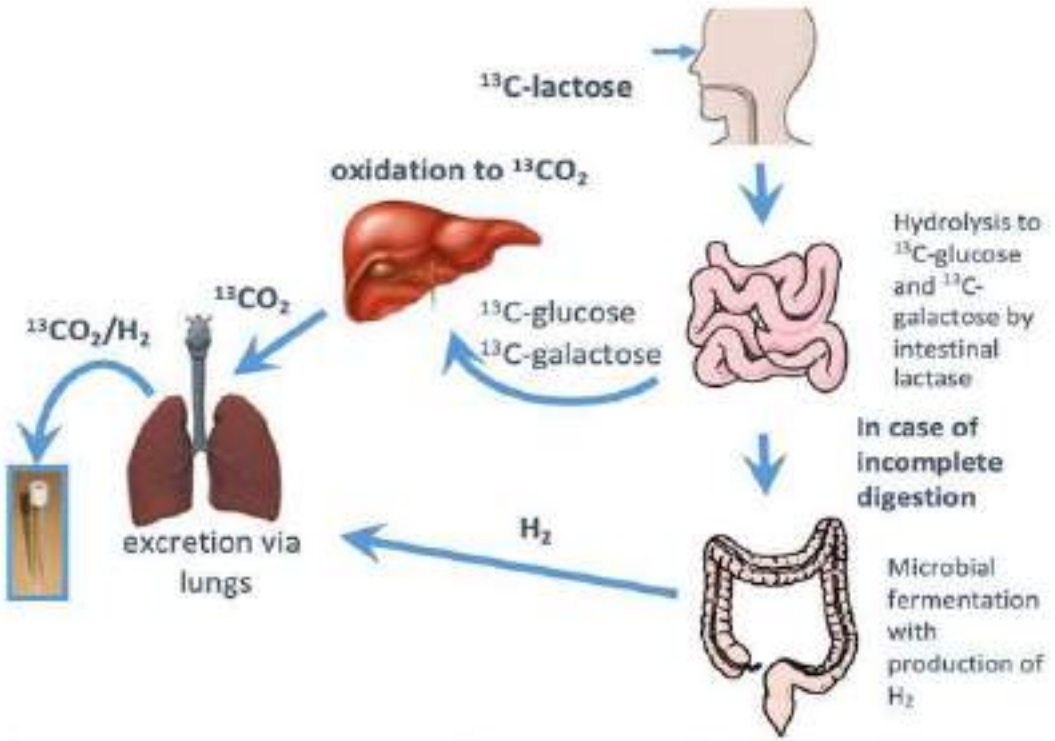
A Pentose monosacharide absorbed exclusively at the proximal small bowel

Is used to distinguish **mucosal malabsorption*** from **malabsorption due to pancreatic insufficiency**.
An oral dose of D-xylose (25 g/500 mL water) is administered, and D-xylose excretion is measured in a 5-hr urine collection.

Normally, **>4 g of D-xylose is excreted in the urine over 5 hr.** The test also may be positive in bacterial overgrowth owing to metabolism of D-xylose by bacteria in the intestinal lumen.

False-positive test results occur with renal failure, ascites, and an incomplete urine collection. Blood levels at 1 and 3 hr improve
sensitivity.
May be normal with mild or limited mucosal disease.

* The main cause of mucosal malabsorption is the celiac disease

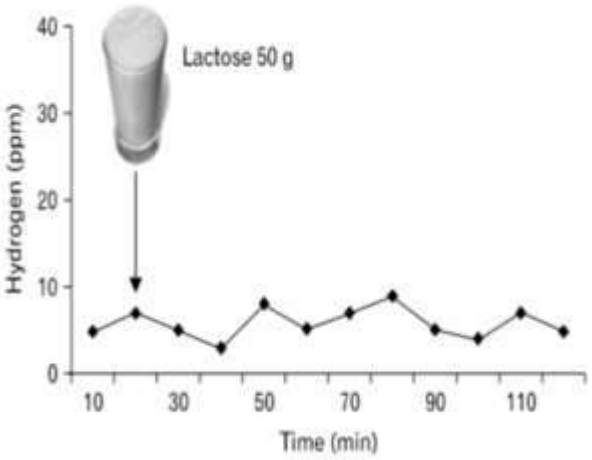


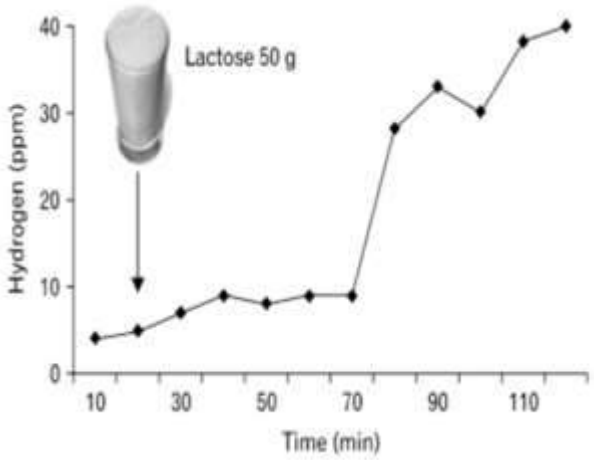
$^{13}CO_2$-excretion	H_2-increase	Interpretation
> cut-off for normal lactose digestion*	<20 ppm	Normal lactose assimilation
> cut-off for normal lactose digestion*	>20 ppm	Lactose malabsorption or SIBO
< cut-off for normal lactose digestion*		Lactase deficiency

*cut-off for normal lactose digestion : cum $^{13}CO_2$ excretion over 4h >14.5% of administered dose ^{13}C

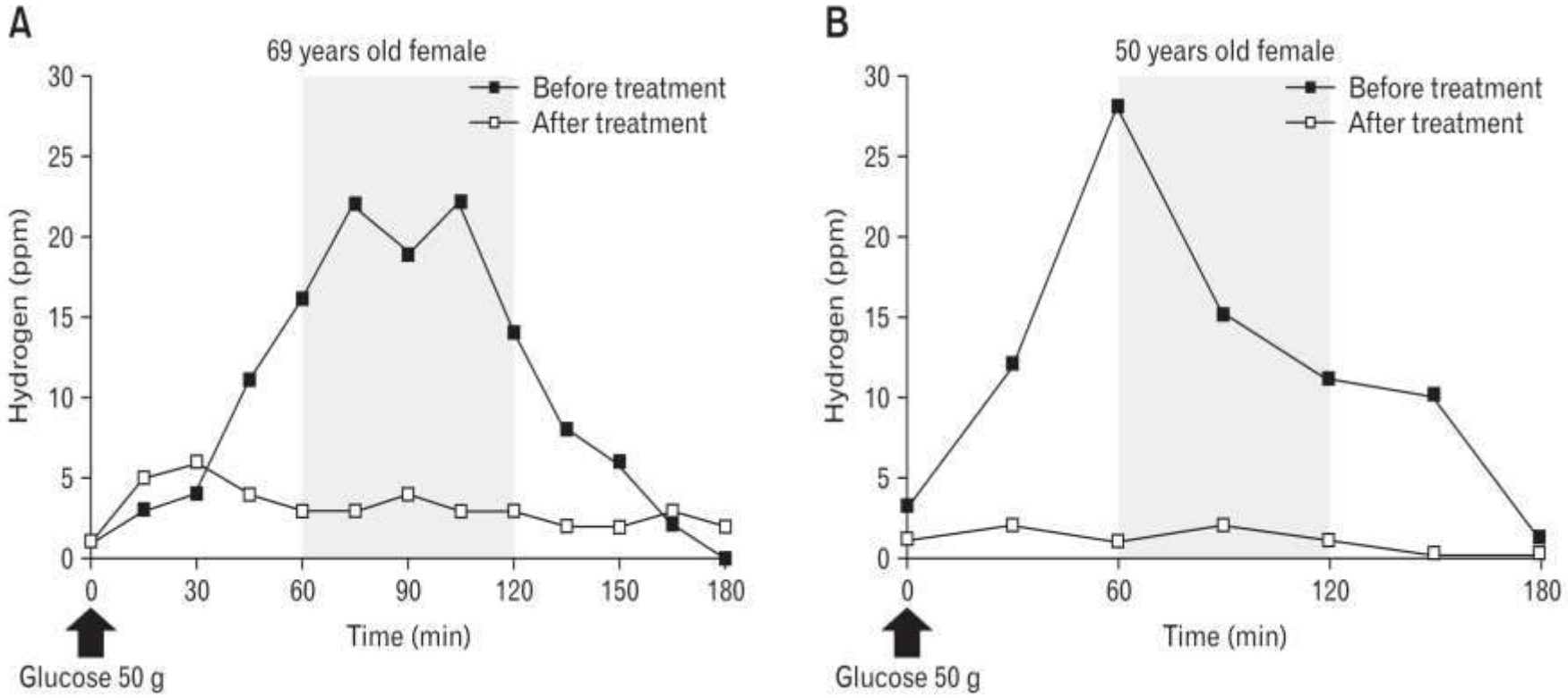
- **Carbohydrate malabsorbtion**
  - Lactose tolerance test
    - P.o. 50 gm lactose
    - Blood glucose at 0,60,120 min.
    - BG <20mg/l + dev't of Sxs – diagnostic

Breath tests Co_2 and H_2 (H2 also detects bacterial overgrowth)





Bacterial overgrowth (SIBO)



Lactose malabsorption

Glossary with definitions related to lactase deficiency,

Concept		Definition
CONGENITAL LACTASE DEFICIENCY	CLD	Very rare genetic disorder (typically frameshift mutations) leading to lack of expression of lactase and severe symptoms immediately after birth
LACTASE NON-PERSISTENCE	LNP	Decrease of intestinal lactase expression in the first two decades of life. Phenotype in most individuals worldwide (biological wildtype)
LACTASE PERSISTENCE	LP	Continued expression of intestinal lactase expression beyond infancy; dominant phenotype in Western countries.
LACTASE DEFICIENCY	LD	Inability to digest large amounts of lactose due to low lactase expression in the small intestine
LACTOSE MALABSORPTION	LM	Passage of lactose into the large intestine as a consequence of LD or other pathology (eg, rapid transit)
PRIMARY LACTOSE MALABSORPTION		Lactose malabsorption due to lactase non-persistence (dominant phenotype worldwide).
SECONDARY LACTOSE MALABSORPTION		Lactose malabsorption due to lower lactase expression, typically in the setting of intestinal inflammation (may be reversible).
LACTOSE INTOLERANCE	LI	Appearance of typical intestinal symptoms such as abdominal pain, bloating, diarrhoea in individuals with LM after lactose ingestion determined by appropriate testing (ideally blinded testing).
FUNCTIONAL LACTOSE INTOLERANCE		Symptoms of LI on lactose challenge in individuals without lactose malabsorption.
SELF-REPORTED LACTOSE INTOLERANCE	SLI	History of LI symptoms without formal testing of either LM or LI.

Lactose malabsorption

The ability to digest lactose during the period of breast-feeding is essential to the health of the infant as demonstrated by congenital lactase deficiency that is fatal if not recognized very early after birth.

However, following the first few months of life, **lactase activity starts to decrease (lactase non-persistence**).

In most humans, this activity declines following weaning to undetectable levels as a consequence of the normal maturational down-regulation of lactase expression

Lactose malabsorption

The exceptions to this rule are the descendants of populations that traditionally practice cattle domestication maintain the ability to digest milk and other dairy products into adulthood.

The frequency of this "**lactase persistence trait**" is high in northern European populations (>90% in Scandinavia and Holland), decreases in frequency across southern Europe and the Middle East (~50% in Spain, Italy and pastoralist Arab populations) and is low in Asia (~1% in China) and most of Africa (~5%–20% in West African agriculturalists); although it is common in pastoralist populations from Africa (~90% in Tutsi, ~50% in Fulani)

Lactose malabsorption: main causes

Congenital lactase deficiency (alactasia), **which is extremely rare**, is due to the inheritance of 2 defective alleles of the LCT gene.

The infant can suffer from watery diarrhoea after being fed with breast milk or food containing milk, and it can become a severe condition, as the shortage of nutritive ingredients can lead to growth delay, dehydration, and alkalosis; infants with congenital lactase deficiency were not expected to survive before the 20th century, when adequate lactose-free milk substitutes were not readily accessible.

Primary lactase deficiency (adult-type hypolactasia) is caused by the non-persistence of lactase, with enzyme levels progressively reducing starting from the age of 2–5 years, depending on ethnicity

Secondary hypolactasia involves the loss of the lactase enzyme due to other clinical conditions affecting the intestinal tract. Since this enzyme is found on the apex of the duodenal villus, all pathological conditions involving the microvilli can result in the reduction of lactase. Once the primary problem is resolved, lactose-containing products can often be consumed normally. Clinical conditions leading to secondary hypolactasia include:

- severe malnutrition
- **celiac disease**
- **inflammatory bowel diseases (Crohn's disease, ulcerative colitis)**
- bacterial or viral enteritis (e.g., rotavirus), and parasitic disease (e.g., giardiasis, cryptosporidiosis)
- actinic enteritis
- some pharmacological treatments (kanamycin, neomycin, polymycin, tetracycline, colchicine, and other chemotherapeutic drugs)
- some post-surgical conditions, such as stagnant loop syndrome or short bowel syndrome

Lactose malabsportion: prevalence

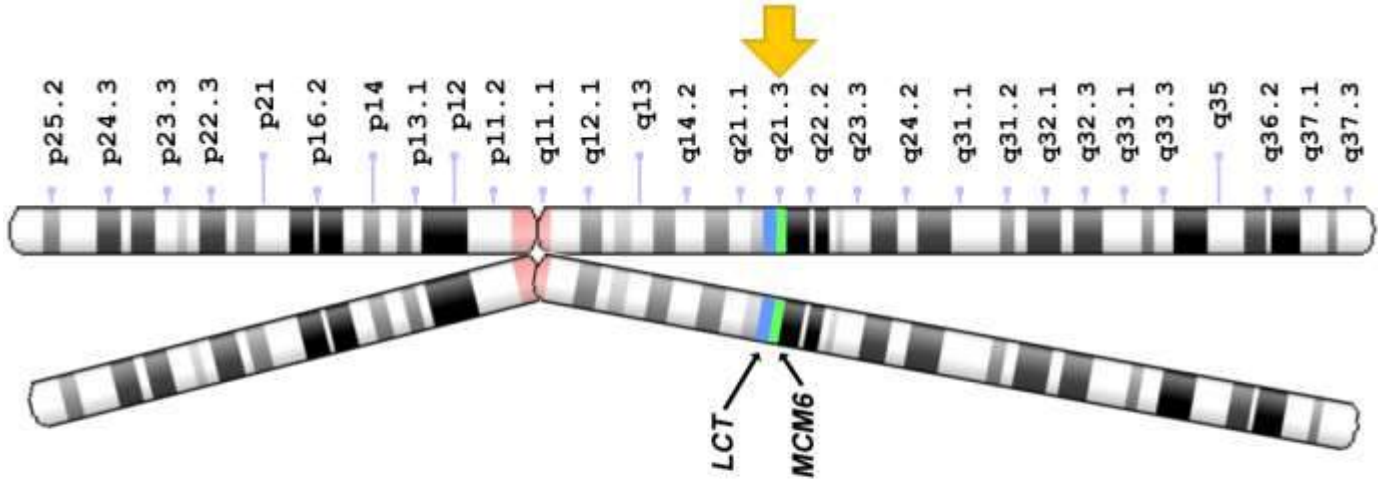
The estimated the prevalence of LM worldwide at 68% with higher rates reported for genetic tests than hydrogen breath tests (HBTs). LM is lowest in Nordic countries (<5% in Denmark) and highest in Korean and Han Chinese populations (approaches 100%).

Testing for LI is more complex and would require standardised hydrogen breath testing in large, carefully selected populations and, for this reason, the prevalence of LI is unknown.

Lactase gene

Gene: LCT

The small intestinal enzyme lactase (also called **lactase-phlorizin hydrolase**) is made of 1927 amino acids, **is encoded by the gene lactase (*LCT*)** on the long arm of chromosome 2 (2q.21-22), and has two enzymatic activities: **a lactase hydrolase activity and a phlorizin hydrolase activity**.



Lactose malabsorption

The molecular mechanism causing lactase reduction **is not attributable to polymorphisms within the lactase gene itself or within its promoter (55 kb within 70 kb, long arm of chromosome 2 (2p.21q) 17 exons).**

However, there **is a close correlation between lactase persistence and two polymorphisms, C/T_{13910} and G/A_{22018} upstream from the lactase gene, in the minichromosome maintenance complex component 6 (MCM6)** gene. Further on the CC/GG being associated with lactase non-persistence and lactose intolerance.

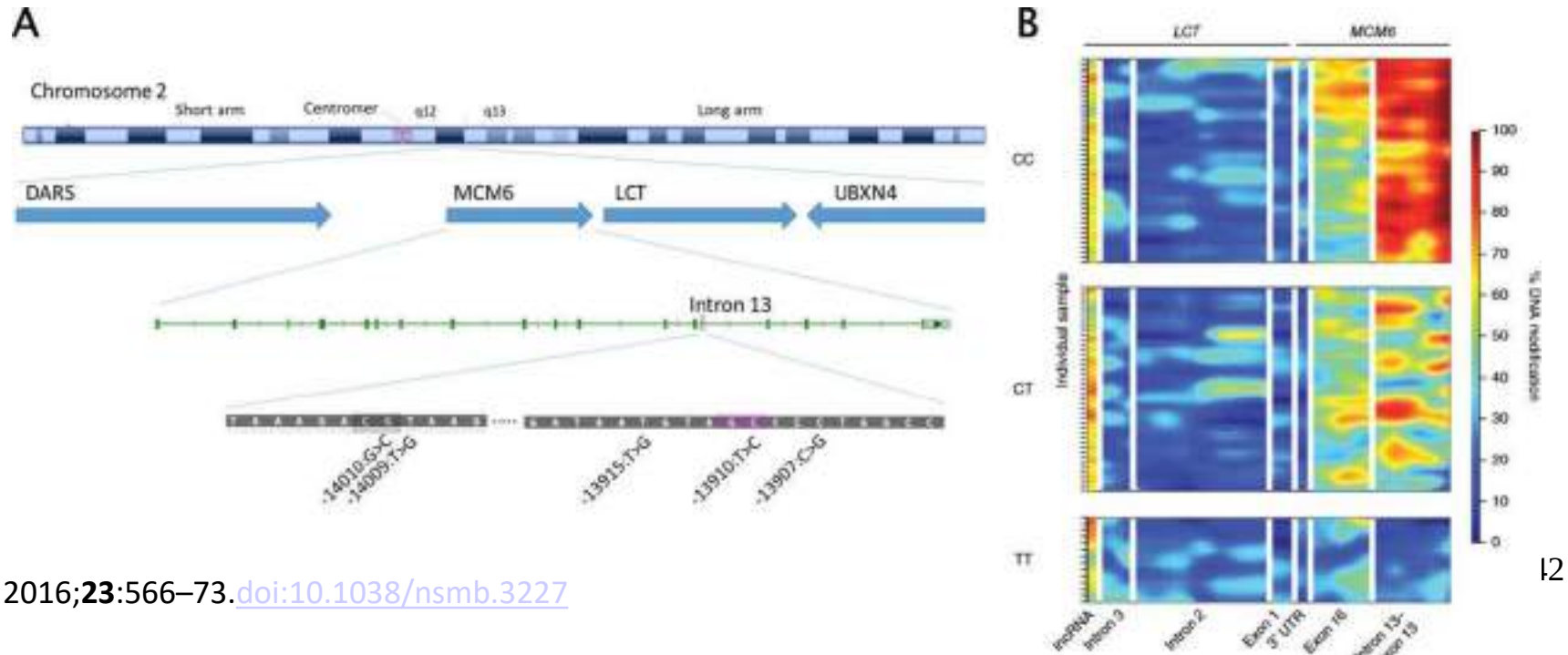
Genetics of lactose malabsorption.

(A) Organisation of the lactase genetic locus on chromosome 2. The positions of the lactase gene (LCT) and the neighbouring genes aspartyl-tRNA synthetase (DARS), minichromosome maintenance complex component 6 (MCM6) and UBX domain-containing protein 4 (UBXN4) are indicated.

(B) Polymorphisms relevant for lactose malabsorption are located within intron 13 of the MCM6 gene, upstream of the lactase gene.

(C) (B) Differential levels of methylation of intron 13 of MCM6 and the LCT gene in individuals with genetic lactose malabsorption (**LCT –13910:C/C), lactose tolerance (LCT –13910:T/T)** and the clinically silent, physiologically **intermediate genotype LCT –13910:C/T.**

Hypermethylation (red colour) results in genetic silencing of the respective gene. (Labrie *et al 2016*).



Nat Struct Mol Biol 2016;**23**:566–73.doi:10.1038/nsmb.3227

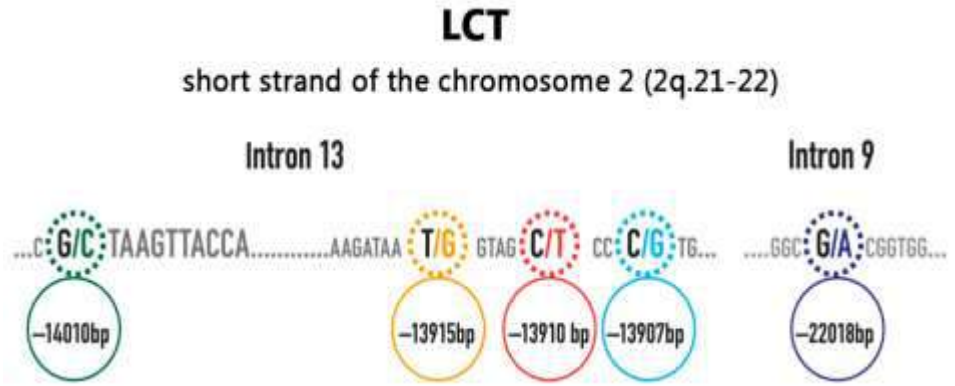
Lactase gene

In Caucasian populations, the persistence or non-persistence of lactase expression is strictly associated with the **single nucleotide polymorphism (SNP) C/T-13910** located upstream of the LCT-encoding gene (rs4988235).

This polymorphism emerges in the CC, CT, or TT variants .

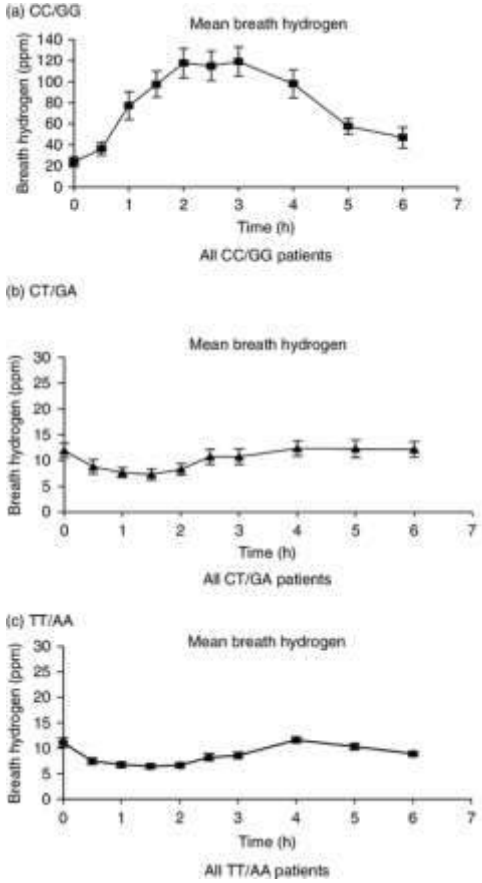
It was demonstrated that in Caucasians, **the CC variant is excellent as a predictor of the decline of intestinal** lactase, and it is thus associated with hypolactasia, whereas the genotype **TT is a predictor of the persistence of lactase activity.**

The presence of the CT genotype is characterized by the presence of intermediate levels of lactase expression, which are usually adequate for lactose digestion.



Tishkoff, S.A.; Reed, F.A.; Ranciaro, A.; Voight, B.F.; Babbitt, C.C.; Silverman, J.S.; Powell, K.; Mortensen, H.M.; Hirbo, J.B.; Osman, M.; et al. Convergent adaptation of human lactase persistence in Africa and Europe. *Nat. Genet.***2007**, *39*, 31–40.

Lactose malabsorption



CC hypolactasia (non-persistent LCT)

CT Intermediate

TT persistent LCT

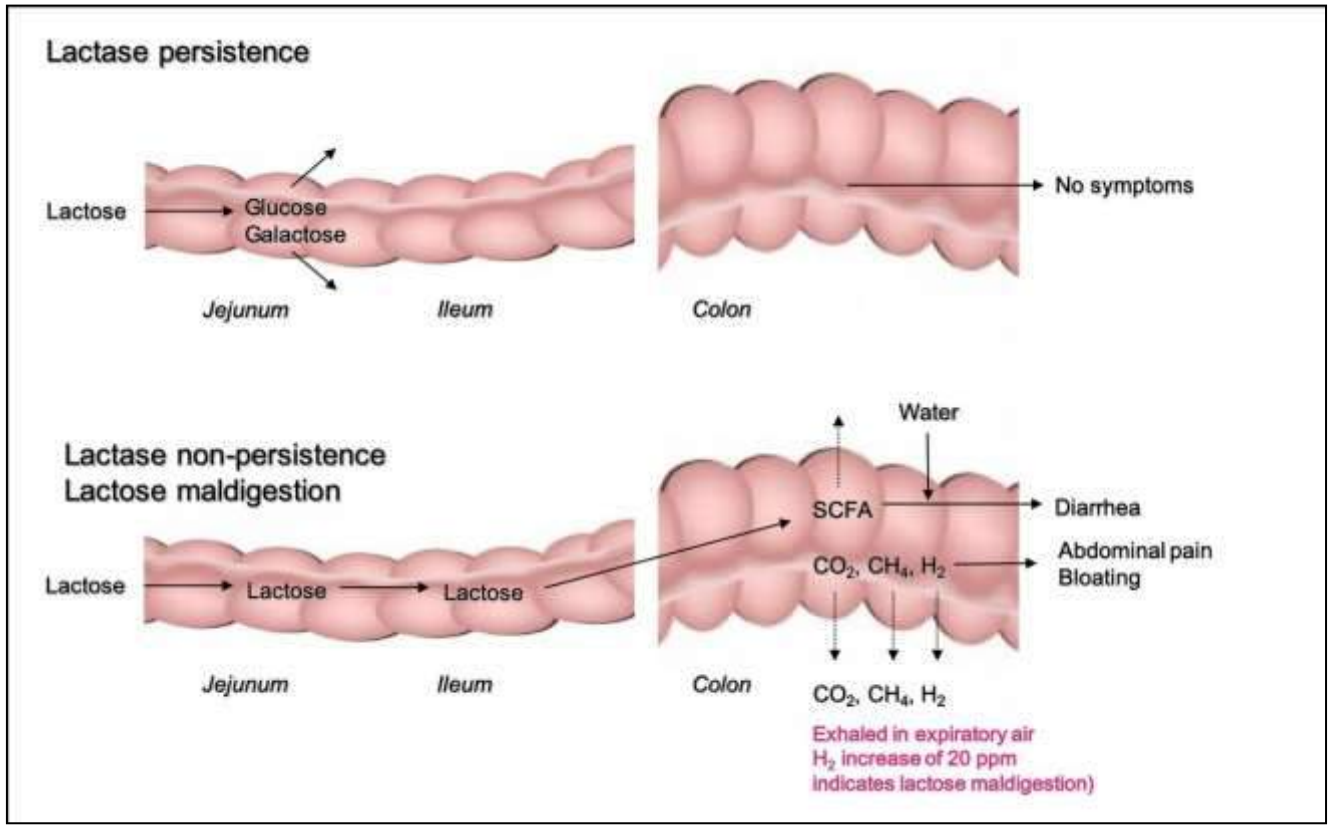
Effect of 50 g lactose on breath hydrogen in the three principal genetic groups.

Boxes represents CC/GG lactase non-persistent genotype, breath hydrogen >20 ppm above the nadir at 30 minutes and continues throughout the testing period. Triangles represent CT/GA heterozygous lactase persistent genotype showing a rise in breath hydrogen >20 ppm above the nadir after sampling above 300 minutes. Diamonds represent **TT/AA homozygous lactase persistent genotyped patient** in which the breath hydrogen does not rise above 20 ppm throughout the testing period of 360 minutes.

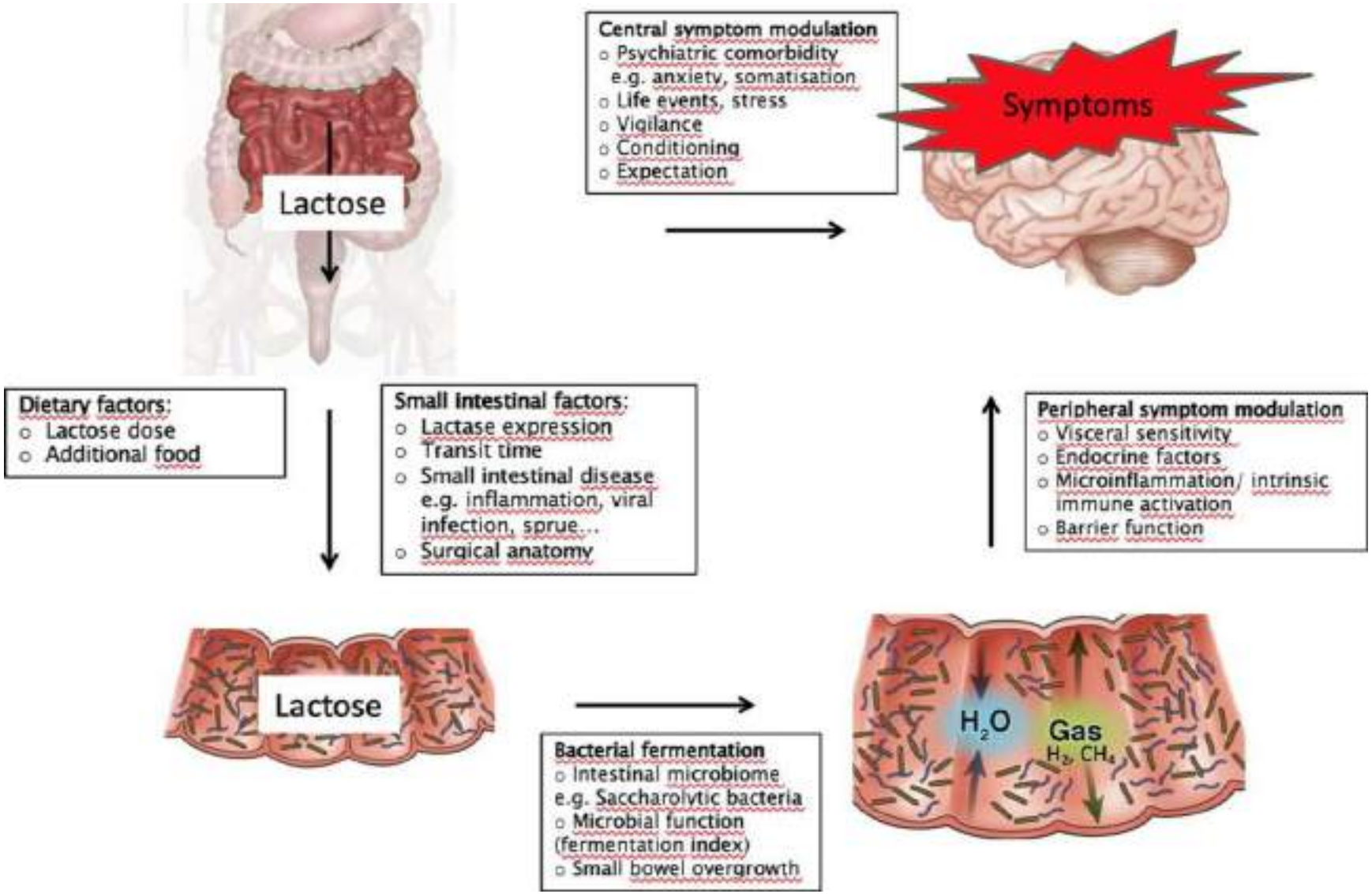
Clinical relevance of lactose intolerance

- **Lactose intolerance is defined as symptoms on lactose exposure in individuals with lactose malabsorption**.
- Most individuals with lactose malabsorption tolerate a dose of **at least 12 g lactose** (corresponding to 250 mL of milk) without problems. Larger doses may be tolerated if consumed with food or spread over a whole day.
- Symptoms of lactose intolerance depend on the strength of the stimulus (ie, lactose dose) and the presence of visceral hypersensitivity, as observed in many patients with IBS.
- Treatment options for lactose intolerance include a low-lactose diet, oral lactase enzyme replacement, prebiotics that produce bacterial lactase in the colon and, potentially, prebiotics that adapt the colonic microbiota.
- Intolerance of low–moderate lactose doses often indicates the presence of IBS. Such individuals are sensitive to a range of poorly absorbed, fermentable foods (‘FODMAPs’). Effective dietary treatment in this group requires not a low-lactose but a low-FODMAP diet.
- FODMAP, fermentable oligosaccharide, disaccharide and monosaccharide and polyols.

Lactose intollerant



Lactose malabsorption



Most frequently reported gut-related and systemic symptoms in patients with lactose intollerance

Symptoms of Lactose Intolerance		Frequency (% of Total)
GUT-RELATED SYMPTOMS	Abdominal pain	~100
	Gut distension	~100
	Borborygmi	~100
	Flatulence	~100
	Diarrhoea	70
	Constipation	30
	Nausea	78
	Vomiting	78
SYSTEMIC SYMPTOMS	Headache	86
	Loss of concentration	82
	Tiredness	63
	Muscle pain	71
	Joint pain/stiffness	71
	Mouth ulcers	30
	Increased frequency of micturition	<20

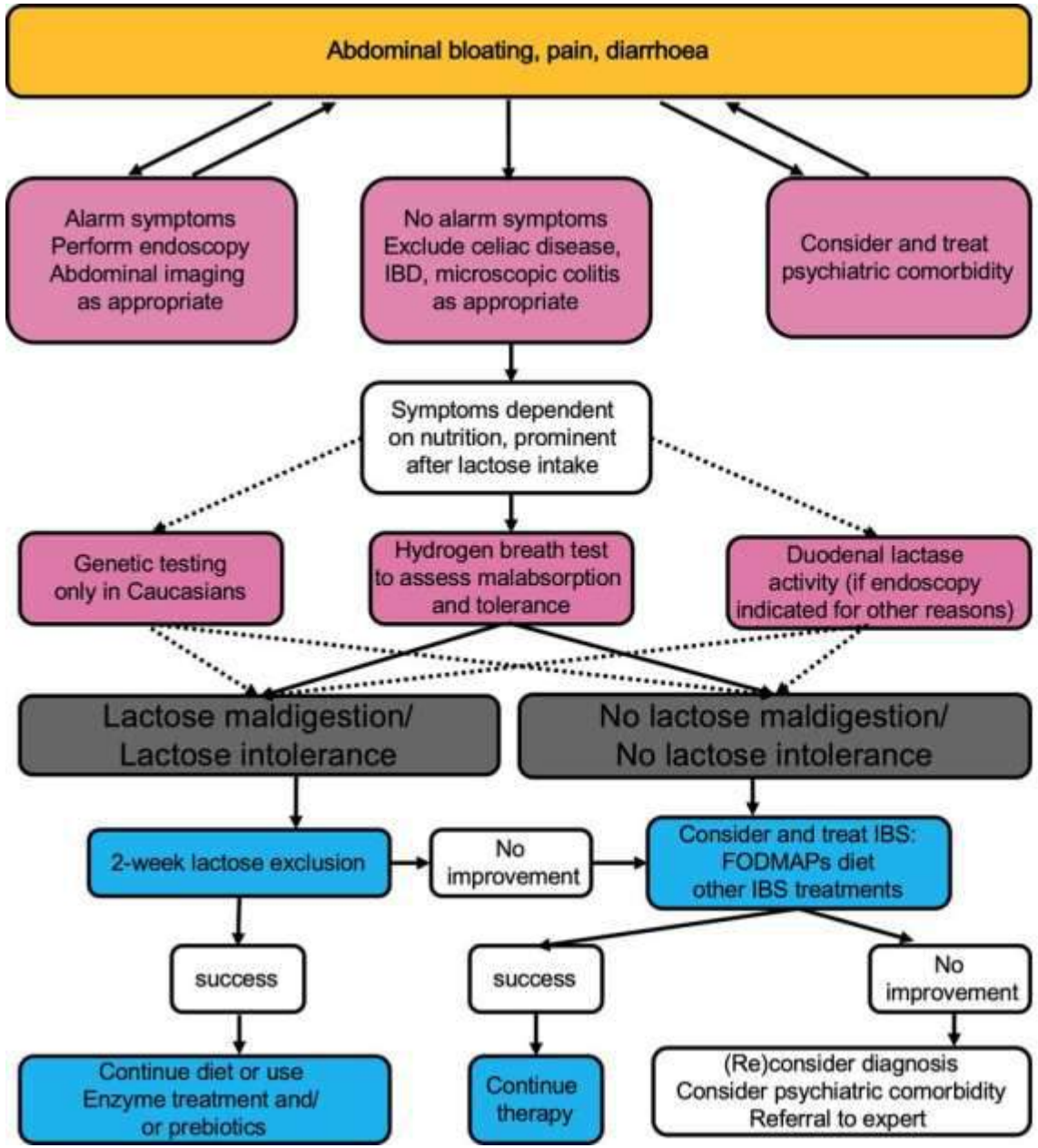
Lactose malabsorption: diagnosis

- Diagnosis of lactose malabsorption can usually be made on the basis of the history, supported by dietary manipulation.

- Diagnostic tests range from changes in **breath hydrogen levels** to biopsy of the small bowel.

- The measurement of **breath hydrogen after ingestion of 25 to 50 g of lactose is more sensitive and specific than the lactose tolerance test**

Summary of Available Tests for Assessing Lactose Malabsorption/Intolerance				
	Lactose Tolerance Test	**H_2-Breath Test (HBT)**	**Genetic Test**	**Lactose Activity at Jejunal Brush Border**
Test principle	Increase of glycaemia after lactose challenge	Increase of H_2 in expirate after lactose challenge	Assessment of 13910C/T polymorphism	Lactase enzymatic activity in bioptic sample
Cut-off criterion	<1.1 mmol/L within 3 h	>20 ppm within 3 h	C:C13910 Lactase non-persistence phenotype	<17–20 IU/g
Availability	Excellent	Good	Good	Rare
False positives	Rapid GI-transit, impaired glucose tolerance	Rapid GI-transit, SIBO	Rare (<5%) in Caucasians	Most likely, rare
False negatives	Fluctuations in glycaemia	Non-H_2-producers, full colonic adaptation	All causes of secondary lactose malabsorption	Patchy enzyme expression
Secondary causes	Cannot be excluded	Cannot be excluded, kinetics of H_2-increase can be suggestive	Cannot be excluded	Can be excluded (histopathology during same procedure)
Symptoms assessment	Possible	Possible	Not possible	Not possible
Cost	Lowest	Low	Medium	Highest
Comment	Low sensitivity and specificity	Method of choice for assessment of primary and secondary lactose intolerance	Method of choice for assessment of primary lactase deficiency in Caucasians	Invasive and expensive testing


Abdominal bloating, pain, diarrhoea
Alarm symptoms
Perform endoscopy
Abdominal imaging
as appropriate
No alarm symptoms
Exclude celiac disease,
IBD, microscopic colitis
as appropriate
Consider and treat
psychiatric comorbidity
Initial assessment
Symptoms dependent
on nutrition, prominent
after lactose intake
Genetic testing
only in Caucasians
Hydrogen breath test
to assess malabsorption
and tolerance
Duodenal lactase
activity (if endoscopy
indicated for other reasons)
LM diagnostic
+/- symptom
assessment
Lactose maldigestion/
Lactose intolerance
No lactose maldigestion/
No lactose intolerance
2-week lactose exclusion
No
improvement
Consider and treat IBS:
FODMAPs diet
other IBS treatments
Therapy
success
success
No
improvement
Continue diet or use
Enzyme treatment and/
or prebiotics
Continue
therapy
(Re)consider diagnosis
Consider psychiatric comorbidity
Referral to expert

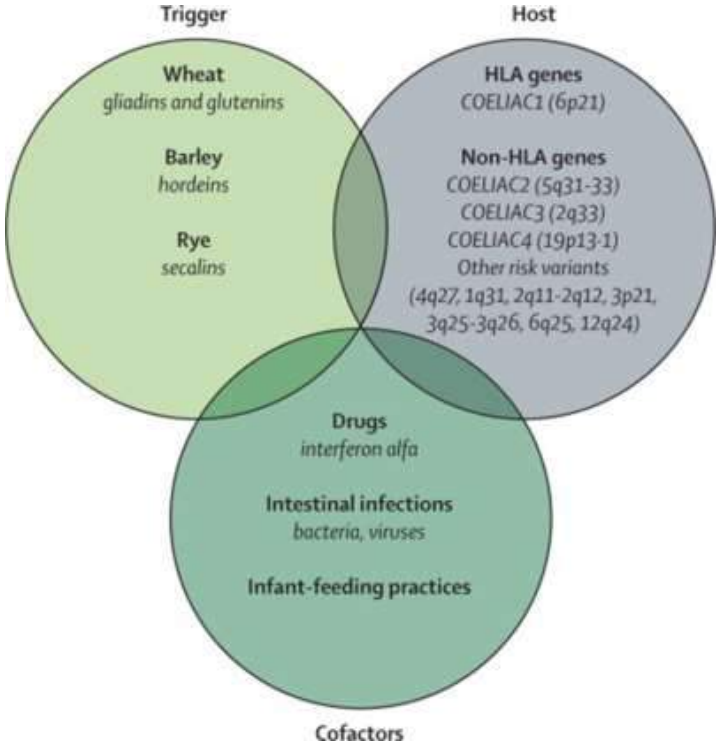
Celiac Disease

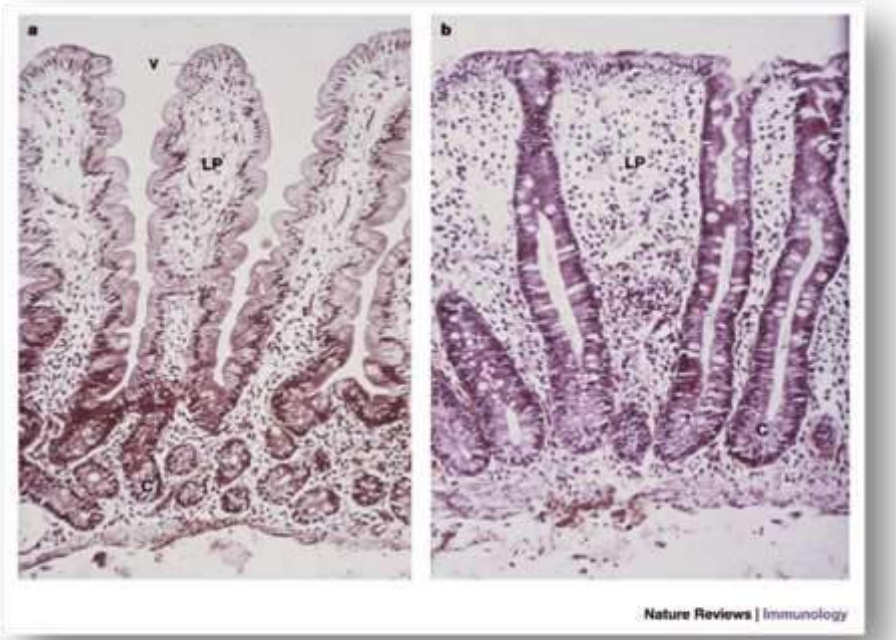
	Celiac Disease	Non-Celiac Gluten Sensitivity	Wheat Allergy
Definition	Genetic, autoimmune disorder; gluten ingestion triggers damage to small intestine	Intolerance to gluten or other wheat components without damage to small intestine	Immune response to one or more of the proteins found in wheat (can include gluten)
Gastrointestinal symptoms	Diarrhea, bloating, abdominal pain	Diarrhea, bloating, abdominal pain	Nausea, vomiting, diarrhea, bloating, irritation of mouth or throat
Extra-intestinal findings (e.g. anemia, bone loss)	Weight loss, malnutrition, iron deficiency, dental caries, bone loss, skin issues, neurological disorders, liver dysfunction, joint pain, hair loss, fatigue	Brain fog, neurological disorders, joint pain, fatigue	Hives, rash, nasal congestion, eye irritation, difficulty breathing
Positive antibody test	Yes	Variable	No
Abnormal intestinal biopsy	Yes	No	No
Treatment	Strict adherence to a gluten free lifestyle	Adherence to a wheat free/gluten free diet (level of adherence variable)	Strict adherence to a wheat free lifestyle

Fasano A, Sapone A, Zevallos V, Schuppan D. Nonceliac gluten sensitivity. Gastroenterology. 2015 May;148(6):1195-204. doi: 10.1053/j.gastro.2014.12.049.

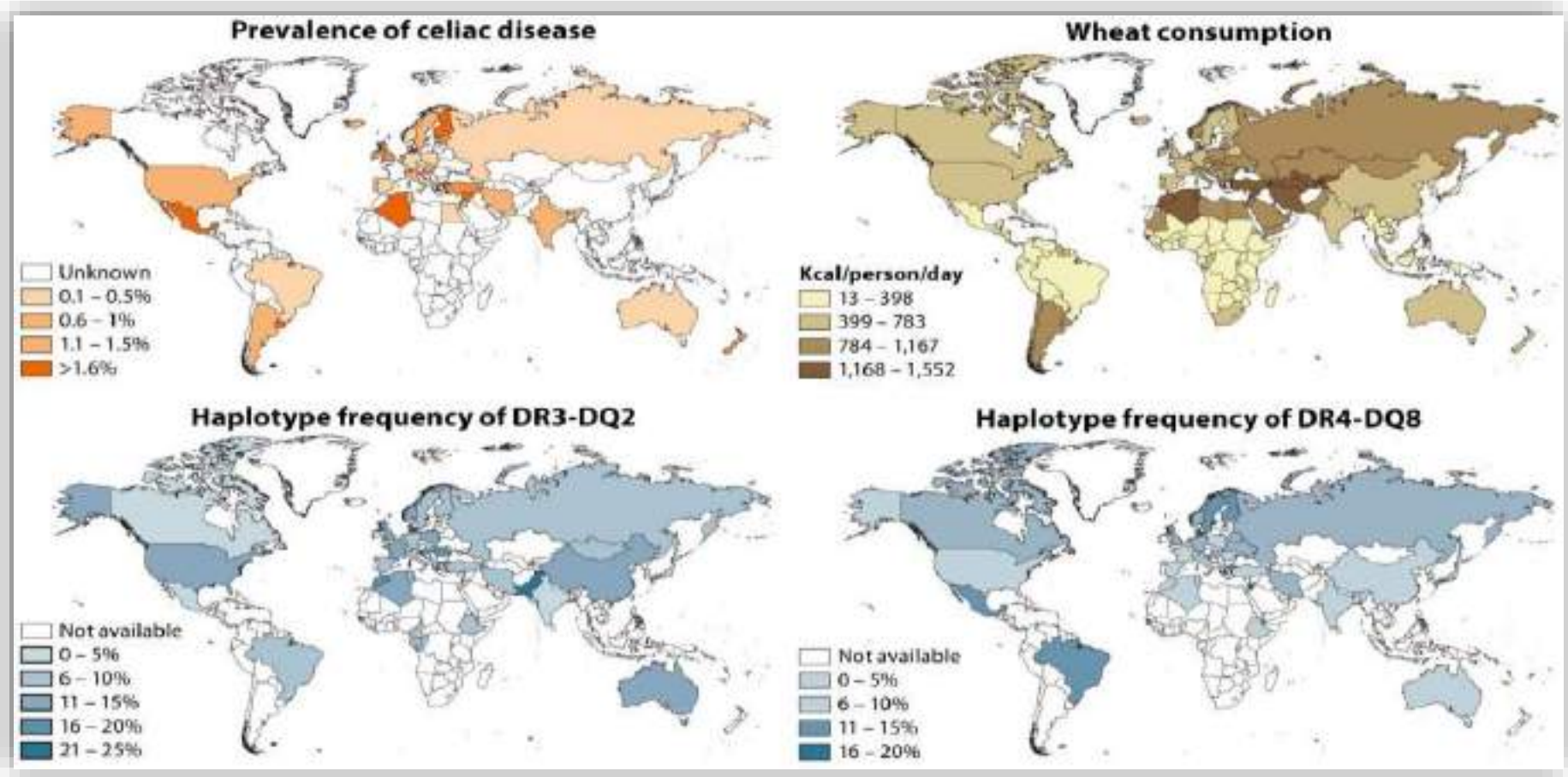
Celiac Disease

The celiac disease as an (auto)- immune disorder that is triggered by an environmental agent (**the gliadin component of gluten**) in genetically predisposed individuals

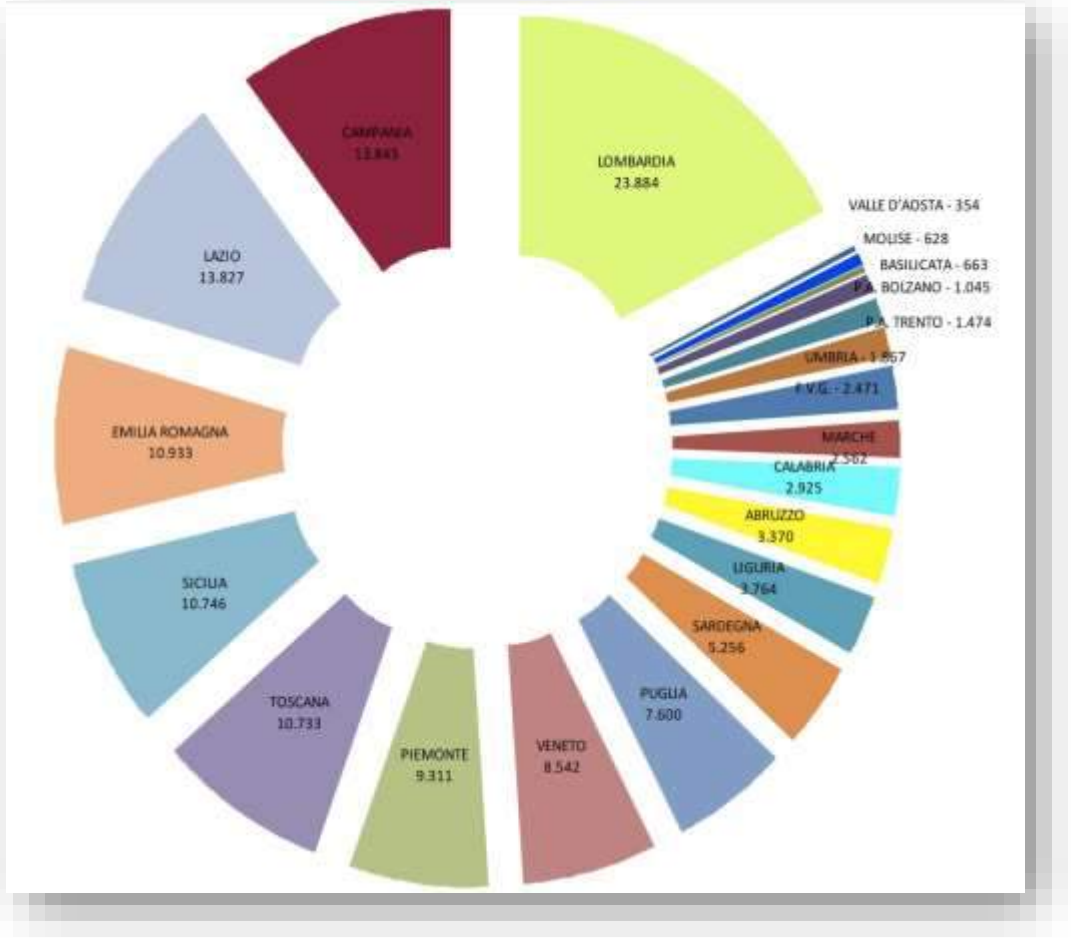




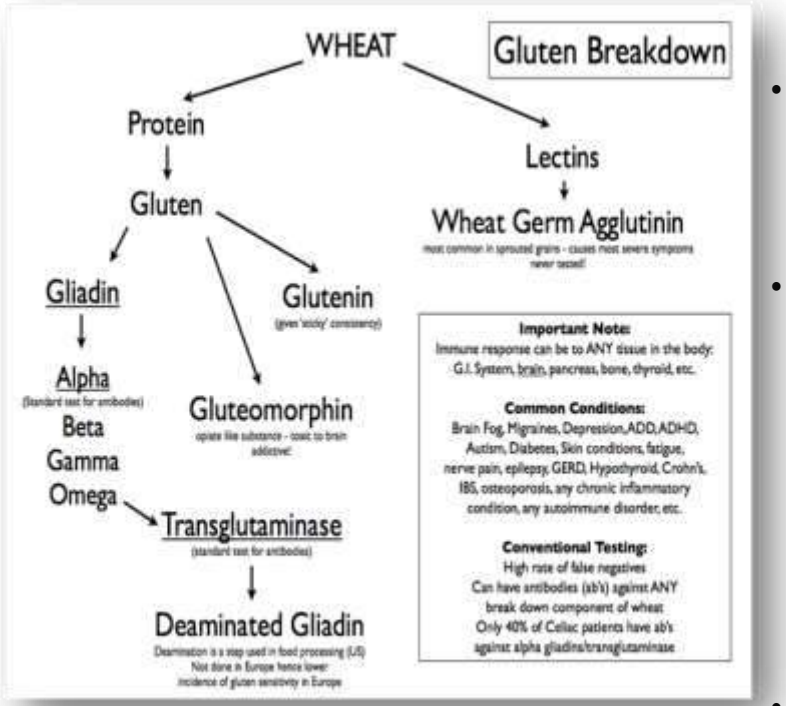
Celiac Disease



La celiachia è l'*intolleranza* alimentare più frequente a livello mondiale con una prevalenza stimata intorno all'1%, considerando sia la fascia degli adulti sia quella dei bambini. Nella popolazione italiana, cha dai dati ISTAT risulta essere al 2013 di 60.340.328, il numero teorico di celiaci dovrebbe essere intorno ai **600.0000** contro i **135.800 effettivamente diagnosticati**.



Gliadin



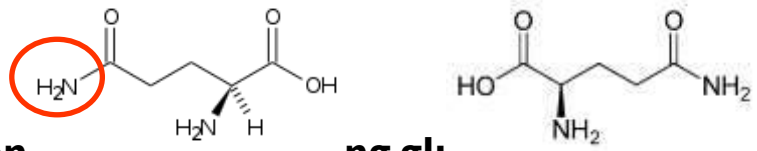
- **Gluten is a storage protein** that remain after starch is washed from wheat-flour dough, and can be roughly separated into two fractions—gliadins and glutenins.
- **Gluten proteins** have a complex chemistry and are responsible for the baking properties of wheat—water absorption capacity, cohesivity, viscosity, and dough elasticity.
- Analysis of **gliadin has identified more than a hundred components** that can be grouped into four main types (ω5-, ω1,2-, α/β-, γ-gliadins). The immunogenicity and toxicity of several gliadin epitopes has been established. A distinction exists between a peptide being immunogenic or toxic. Lymphocyte-based systems are used to assess immunostimulatory properties and, so far, all peptides that are immunostimulatory in vitro are toxic when tested in vivo.
- **Glutenins** can be divided into groups of high molecular weight and low molecular weight. Immunogenicity and toxicity in the high-weight group have been shown. Storage proteins (prolamines), with a similar aminoacid composition to the gliadin fractions of wheat, have been identified in barley (hordeins) and rye (secalines), and show a close relation to the taxonomy and toxic properties of wheat cereal that affect people with coeliac disease.

Celiac Disease

Tissue transglutaminase (tTg or Tg2)

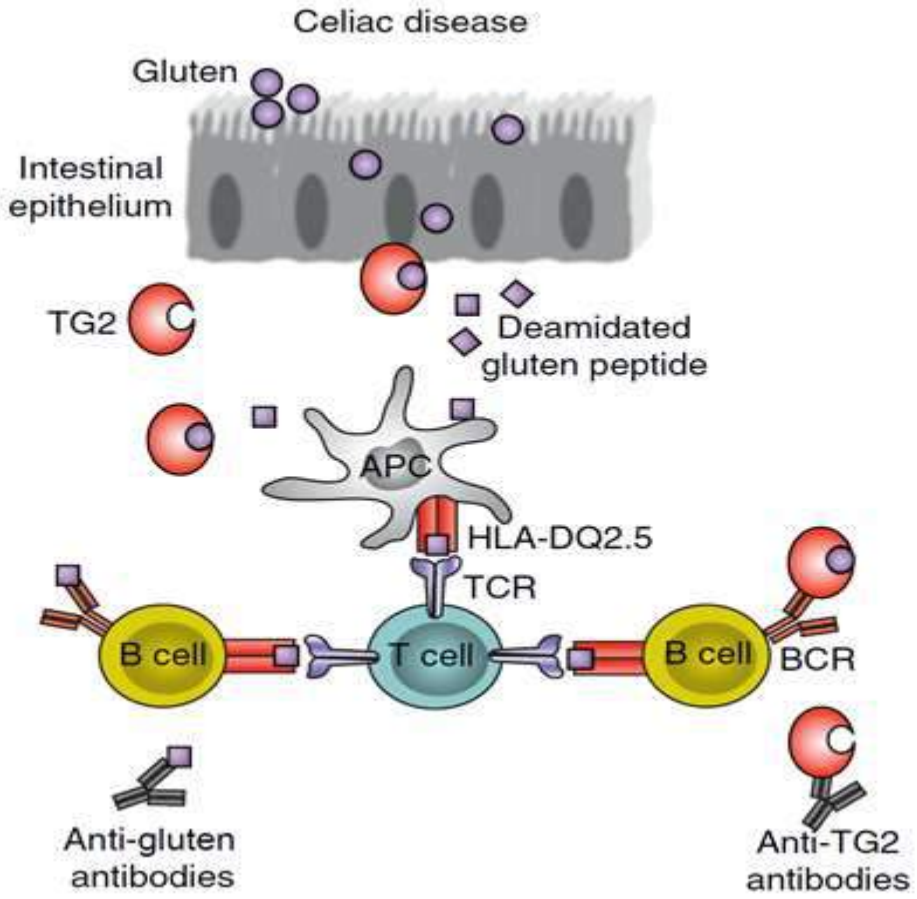
- is a calcium-dependent, ubiquitous enzyme that catalyses post-translational modification of proteins and is released during inflammation, could have at least **two crucial roles** in coeliac disease: **as the main target autoantigen *for antiendomysial antibodies* and *htTg antibodies*,** and as a **deamidating enzyme that raises the immunostimulatory effect of gluten.**

- Expression and activity of tissue transglutaminase are raised in the mucosa of patients with coeliac disease, where, by deamidating **glutamine to glutamic acid**, **this enzyme makes gliadin peptides negatively charged and therefore more capable of fitting into pockets of the DQ2/DQ8 antigen-binding groove.**



- **Additional functions of the enzyme in coeliac disease con ng gluten peptides, thus forming supramolecular complexes**, and catalysing either the binding of gluten peptides to interstitial collagen or the incorporation of histamine into gluten proteins (transamidation).
- All of these actions contribute to the formation of a wide range of T-cell-stimulatory epitopes that might be implicated in different stages of the disease. The α2-gliadin-33mer fragment is the most immunogenic because it harbours six partly overlapping DQ2-restricted epitopes.

Transglutaminase



Tissue transglutaminase modifies gluten peptides into a form that may stimulate the immune system more effectively. These peptides are modified by tTG in two ways, deamidation or transamidation.

Deamidation is the reaction by which a glutamate residue is formed by cleavage of the epsilon-amino group of a glutamine side chain. Transamidation, which occurs three times more often than deamidation, is the cross-linking of a glutamine residue from the gliadin peptide to a lysine residue of tTg in a reaction which is catalysed by the transglutaminase. Crosslinking may occur either within or outside the active site of the enzyme. The latter case yields a permanently covalently linked complex between the gliadin and the tTg. This results in the formation of new epitopes which are believed to trigger the primary immune response by which the autoantibodies against tTg develop.

Amino acid sequences of immunotoxic gluten peptides and their specificity for TG2 mediated deamidation [51, 104]

Amino Acid Sequence Immunotoxic Gluten Peptides	TG2 Specificity k_{cat}/K_M ($min^{-1}mM^{-1}$)
LQLQPF(PQPQLPY)$_3$PQPQPF	440
QLQPFPQPQLPYPQPQS	260
PQPQLPYPQPQLPY	300
QLQPFPQPQLPY	66
PQQPQQSFPQQQRP	61
γ-Fibrinogen Peptide	
TIGEGQQHHLG	63

Immunotoxic deamidated gluten epitopes and their EC_{50} for binding to the HLA-DQ2 and –DQ8 antigen receptors [57, 105, 106]

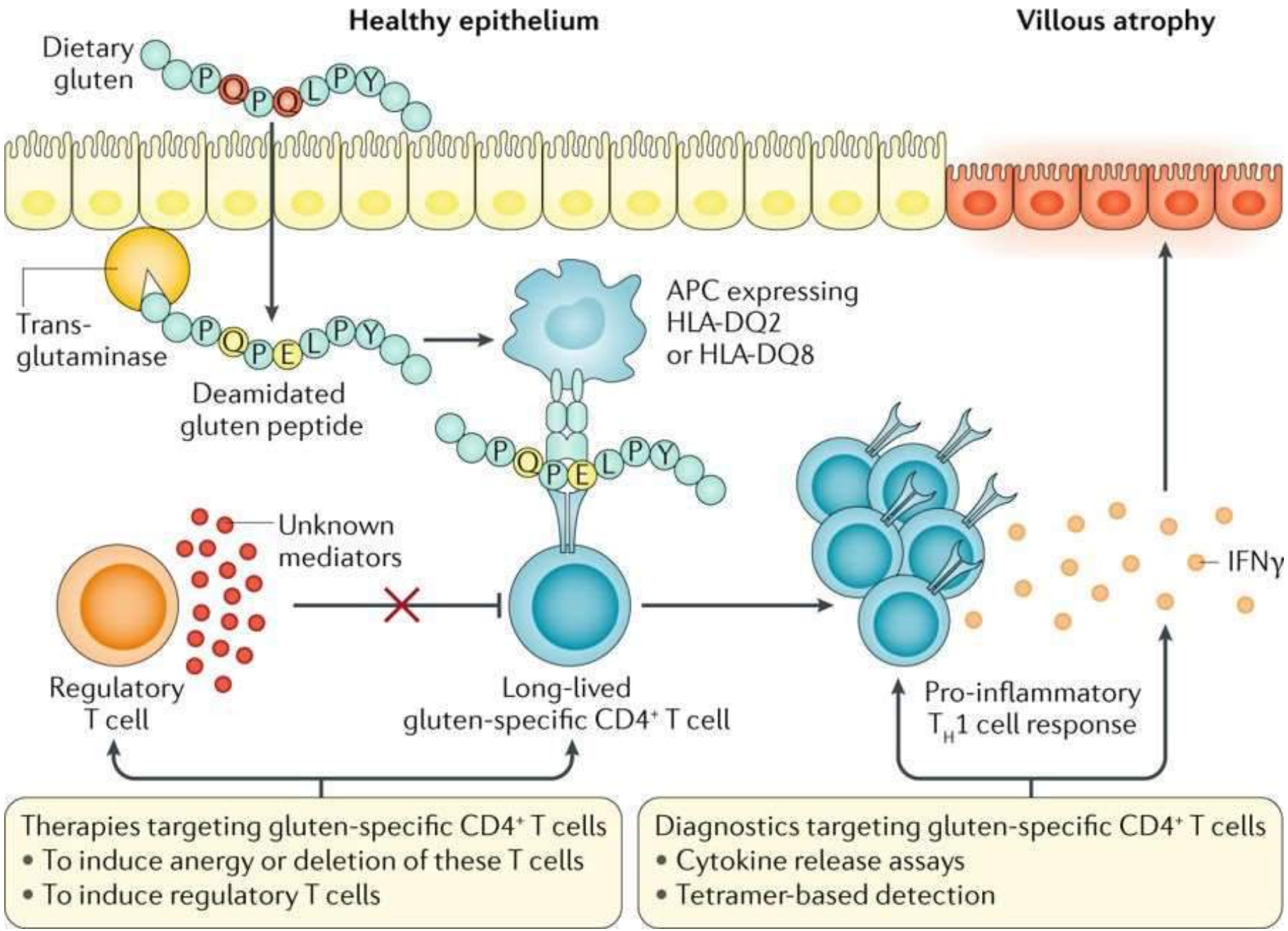
Gluten Peptide Immunotoxic Core		HLA-DQ2 Binding	HLA-DQ8 Binding
Gluten Epitope	Sequence	EC_{50} (μM)	EC_{50} (μM)
Gliadin-α2	PQPELPYPQ	15	-
Gliadin-α9	PFPQPELPY	8	-
Gliadin-α20	FRPEQPYPQ	30	-
Glu-5	EXPEQPQQF	100	-
Gliadin-γ2	PYPEQPEQP	65	-
Gliadin-γ1	PQQSFPEQE	14	-
Gliadin-γ30	IIQPEQPAQ	10	-
Glt-17	PFSEQEQPV	25	-
Gliadin-α1	EGSFQPSQE	-	~2

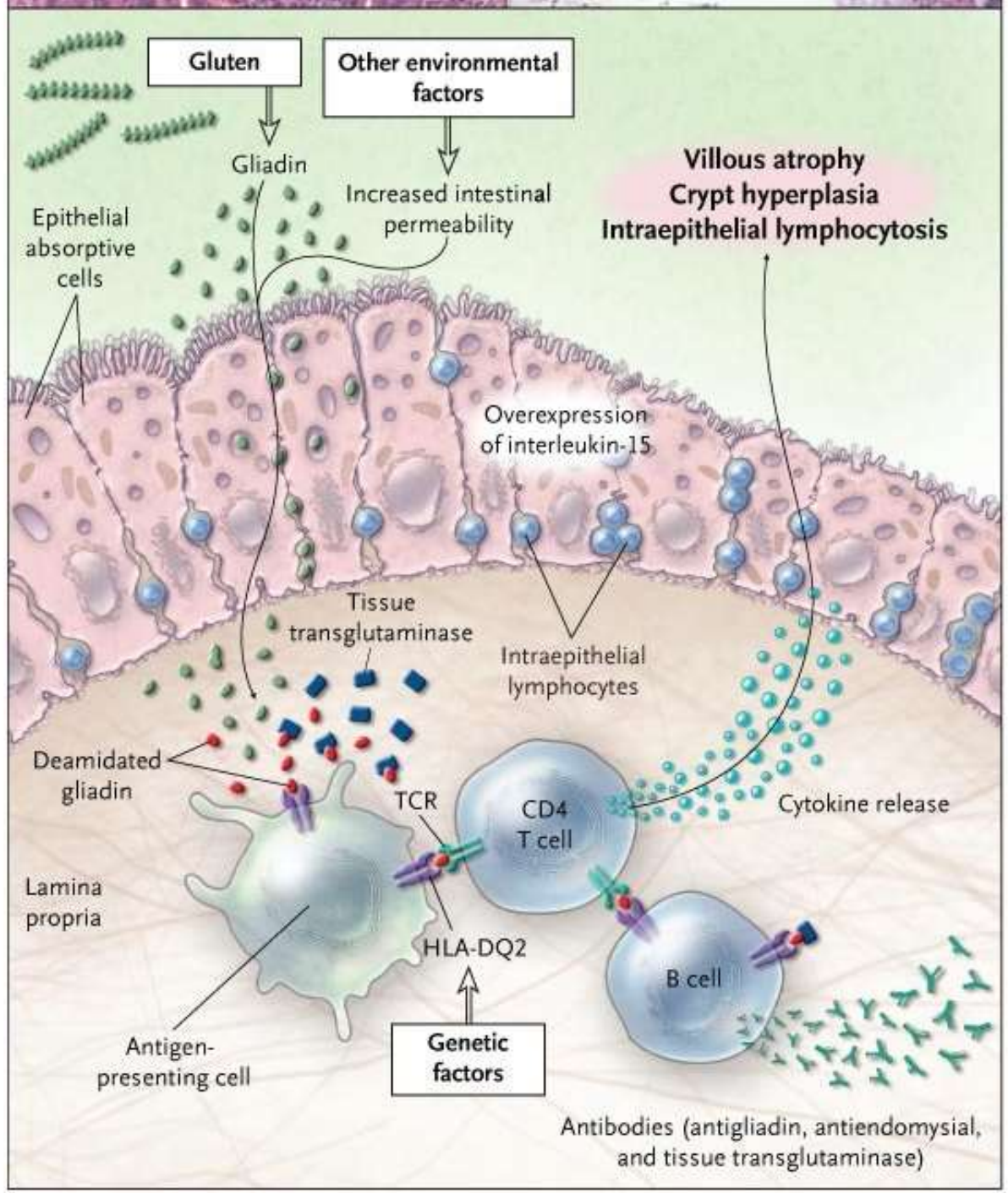
Celiac Disease

Gluten peptides

after crossing the epithelium into the lamina propria, are **deamidated by tissue transglutaminase (tTg or Tg2) and then presented by DQ2+ or DQ8+ antigen-presenting cells to pathogenic CD4+ T cells.**

Once activated, the **CD4+ T cells drive a T-helper-cell type 1** response that leads to the development of coeliac lesions—namely intraepithelial and lamina propria infiltration of inflammatory cells, crypt hyperplasia, and villous atrophy


Healthy epithelium
Villous atrophy
Dietary gluten
P Q P Q L P Y
Trans-glutaminase
P Q P E L P Y
Deamidated gluten peptide
APC expressing HLA-DQ2 or HLA-DQ8
P Q P E L P Y
Unknown mediators
IFNγ
Regulatory T cell
Long-lived gluten-specific CD4+ T cell
Pro-inflammatory T_H1 cell response
Therapies targeting gluten-specific CD4+ T cells
• To induce anergy or deletion of these T cells
• To induce regulatory T cells
Diagnostics targeting gluten-specific CD4+ T cells
• Cytokine release assays
• Tetramer-based detection


Gluten
Other environmental factors
Gliadin
Increased intestinal permeability
Villous atrophy
Crypt hyperplasia
Intraepithelial lymphocytosis
Epithelial absorptive cells
Overexpression of interleukin-15
Tissue transglutaminase
Intraepithelial lymphocytes
Deamidated gliadin
TCR
CD4 T cell
Cytokine release
Lamina propria
HLA-DQ2
B cell
Antigen-presenting cell
Genetic factors
Antibodies (antigliadin, antiendomysial, and tissue transglutaminase)

Genetic

- The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and / or DQ8) genes

- HLA-DQ2 and / or DQ8 genes are necessary (No DQ2/8, no Celiac Disease!) but not sufficient for the development of the disease

Celiac disease: HLA genes

Celiac disease **is a multigenic disorder**, in which the most dominant genetic risk factors are the genotypes encoding the HLA class II molecules

HLA-DQ2 encoded by ***HLA-DQA1* 0201 & 0501***
HLA-DQB1*0201 & 0501

HLA-DQ8 encoded by ***HLA-DQA1* any* and**
***HLA-DQB1*0301 and 0302*.**

Individuals are predisposed to celiac disease if they have any of the following results:

- **DQ2-positive** (HLA-DQA1*0501 or *0505 **and** HLA-DQB1*0201 or *0202)
- **DQ2-positive** (HLA-DQA1*0501 or 0505 **or** HLA-DQB1*0201 or 0202)
- **DQ8-positive (**HLA-DQA1*0301 **and** HLA-DQB1*0302)

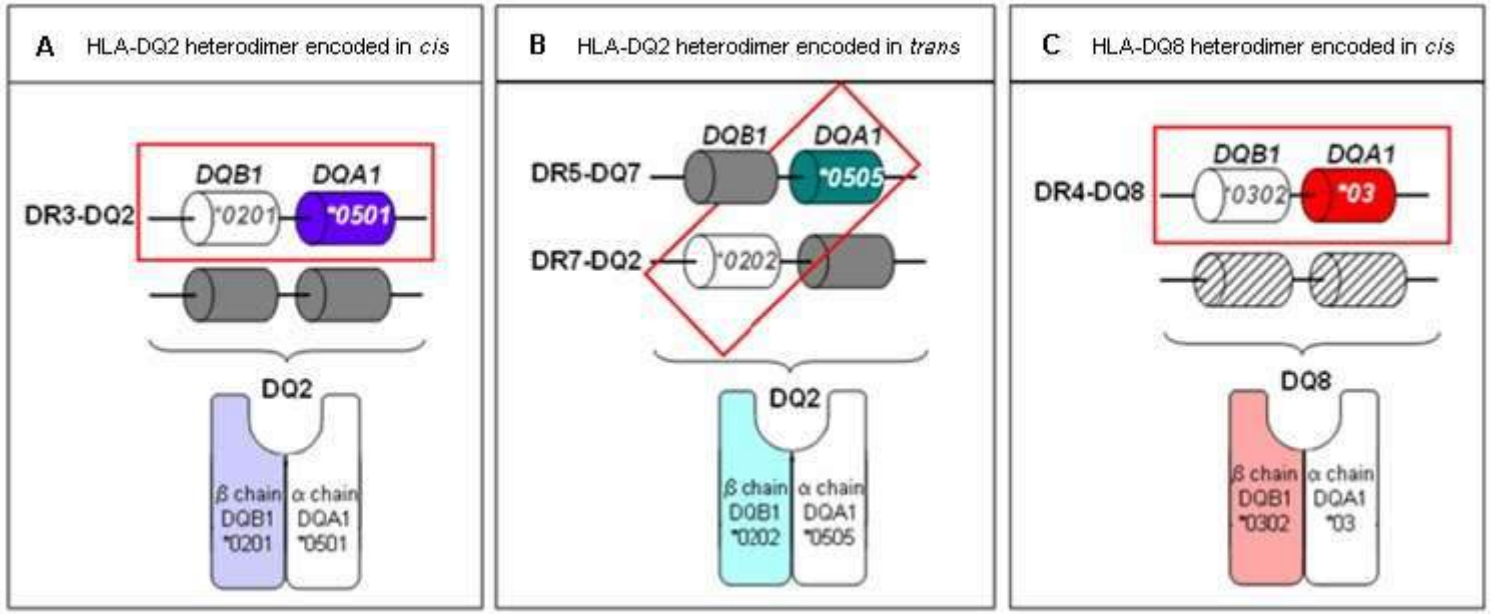
Deamidated gliadin peptides have a **high binding affinity t**o **HLA-DQ2 and HLA-DQ8** molecules, but not to other HLA class II molecules, which explains the immunogenicity of **gluten in carriers of HLA-DQ2 and HLA-DQ8**.

Celiac disease: HLA genes

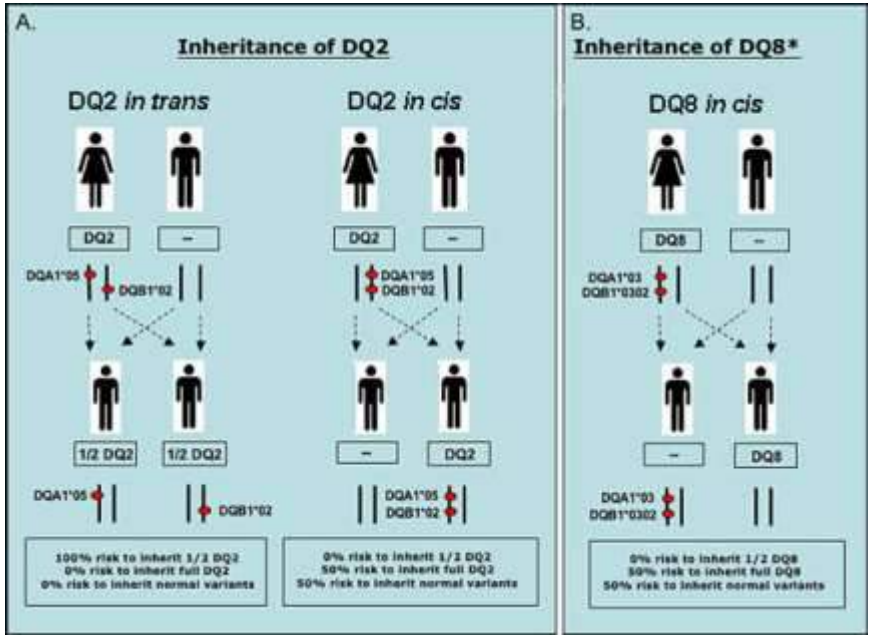
The presence of these HLA alleles is necessary but not sufficient to cause celiac disease.

- DQ2 is found in more than **90%** of individuals with celiac disease and in 20%-30% of the general population
- A small percentage of individuals with celiac disease have **either** an *HLA-DQA1* sequence variant (*0501 or *0505) **or** an *HLA-DQB1* sequence variant (*0201 or *0202), but not both (i.e., only half of the DQ2 heterodimer).
- DQ8 is found **in 5%-10%** of individuals with celiac disease and approximately 10% of the general population

A correlation has been found between **homozygosity** for the genes encoding the HLA-DQ2 molecule and the development of serious complications of celiac disease, in particular **RCD** and EATL (**enteropathy associated T cell lymphoma)**, which implies a gene–dose effect



Formation of DQ2 and DQ8



- A. **The DQ2 molecule**, consisting of the α-chain protein encoded by the HLA-DQA1*0501 allele and the β-chain protein encoded by the HLA-DQB1*0201 allele on the same parental chromosome (i.e., **in cis configuration).**
- B. **The DQ2 molecule**, consisting of the α-chain protein encoded from the HLA-DQA1*0505 allele and the β-chain protein encoded by the HLA-DQB1*0202 allele on separate parental chromosomes (i.e., **in trans configuration).**
- C. **The DQ8 molecule**, consisting of the β-chain protein encoded by the HLA-DQB1*0302 allele and the α-chain protein encoded by the HLA-DQA1*03 allele on the same parental chromosome (i.e., in **cis configuration**).

Celiac disease: genetic non HLA

Currently, **several susceptibility loci not related to HLA have been identified by genome-wide association studies**

each of which is estimated to be associated with only a small risk of developing celiac disease.

Most of these loci contain immune-related genes.

Table 1 | **Coeliac disease susceptibility loci**

Locus*	Most likely candidate gene(s)	Function of proteins encoded by candidate gene(s)	Probable immune function	Associated with type 1 diabetes?	Refs
6p21	*HLA*	MHC is important for antigen presentation	Yes	Yes	11
2q33	*CTLA4*	CTLA4 is a receptor on T cells for CD80 and CD86 and is a negative regulator of T cell activation	Yes	Yes	119
4q27	*IL2* and *IL21*	IL-2 is a growth factor for T cells; IL-21 is a cytokine that enhances B cell, T cell and NK cell functions	Yes	Yes	14
1q31	*RGS1*	RGS1 is involved in cell signalling and is expressed by intraepithelial lymphocytes	Yes	Yes	15
2q12	*IL1R1*, *IL18R1* and *IL18RAP*	The α-chain and β-chain of the IL-18 receptor are encoded by *IL18R1* and *IL18RAP*, respectively; IL-18 promotes interferon-γ production	Yes	Yes	15
3p21	*CCR1*, *CCR3*, *CCR2* and *CCR5*	The chemokine receptors CCR1, CCR3, CCR2 and CCR5 are encoded at this locus; there are probably two independent coeliac disease risk factors at this locus	Yes	Yes	15
3q25	*IL12A*	The p35 subunit of the cytokine IL-12 is encoded at this locus; IL-12 favours T_H1 cell differentiation	Yes	No	15
3q28	*LPP*	Unknown	No	No	15
6q25	*TAGAP*	TAGAP is expressed by activated T cells and is important for modulating cytoskeletal changes	Yes	Yes	15
12q23	*SH2B3*	Lymphocyte adaptor protein (LNK) is encoded at this locus and is involved in signalling in lymphocytes, including T cells	Yes	Yes	15
18p11	*PTPN2*	The T cell protein tyrosine phosphatase is a negative regulator of inflammation	Yes	Yes	19
6q23	*TNFAIP3*	TNFαIP3 is a zinc-finger protein that inhibits nuclear factor-κB activity and tumour necrosis factor-mediated programmed cell death	Yes	Yes	120
2p13	*REL*	REL is a component of the nuclear factor-κB transcription complex	Yes	No	120

CCR, CC-chemokine receptor; CTLA4, cytotoxic T lymphocyte antigen 4; IL, interleukin; LPP, LIM domain containing preferred translocation partner in lipoma; NK, natural killer; PTPN2, protein tyrosine phosphatase, non-receptor type 2; R, receptor; RAP, receptor accessory protein; RGS1, regulator of G protein signalling 1; TAGAP, T cell activation RhoGTPase activating protein; T_H1, T helper 1; TNFAIP3, tumour necrosis factor, α-induced protein 3. *The odds ratios of the strongest associated markers of the non-HLA loci range from 0.7–1.4.

Celiac Disease:
Clinical Manifestations

Celiac Disease: Clinical Manifestations in Children

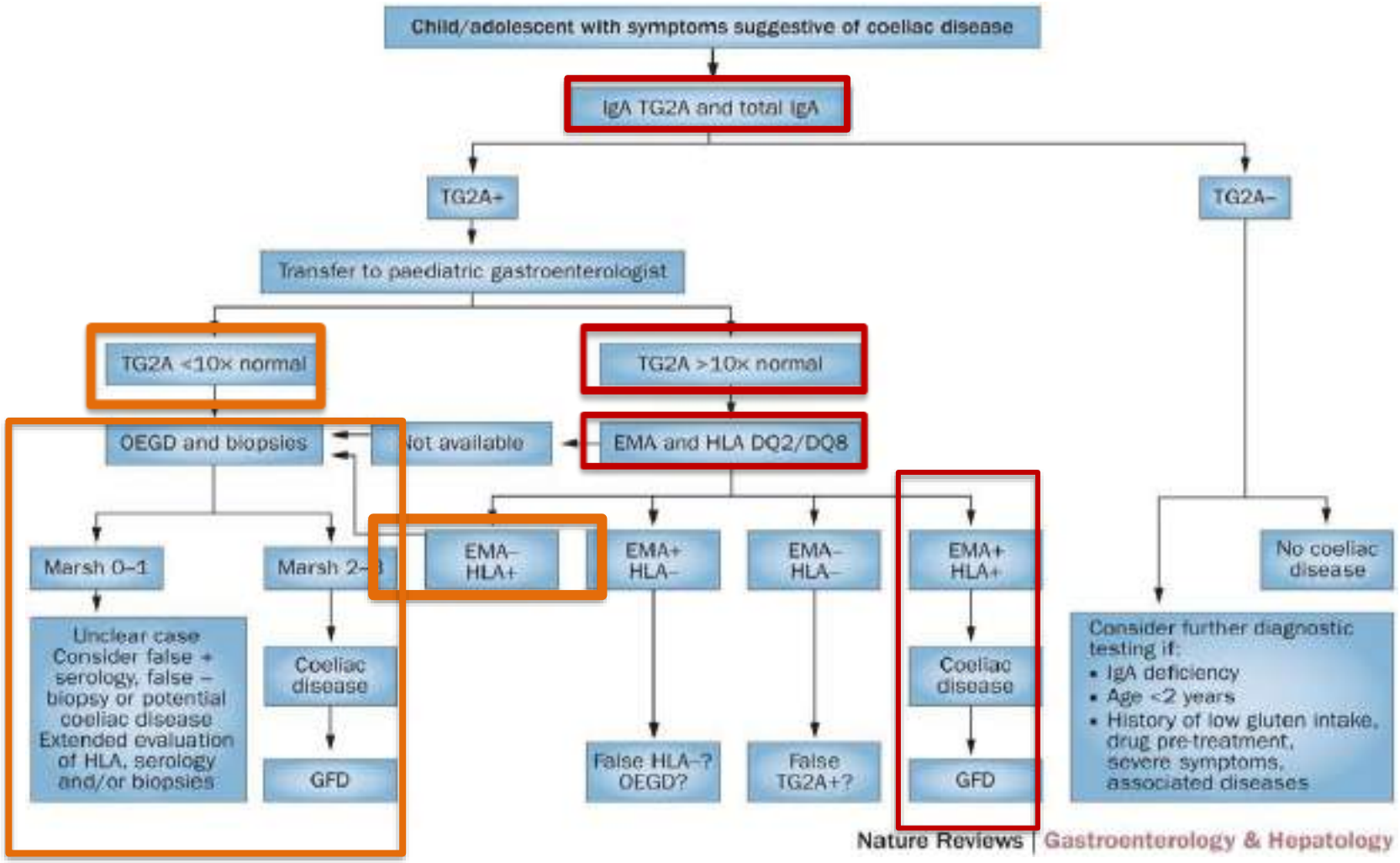
The classical presentation is in children after weaning and introduction of cereals into the diet:

- Failure to thrive
- Apathy
- Pallor
- Anorexia
- Muscle wasting with generalized hypotonia
- Abdominal bloating and distention
- Soft, bulky, clay-colored, offensive stools

Celiac Disease: Clinical Manifestations in Children

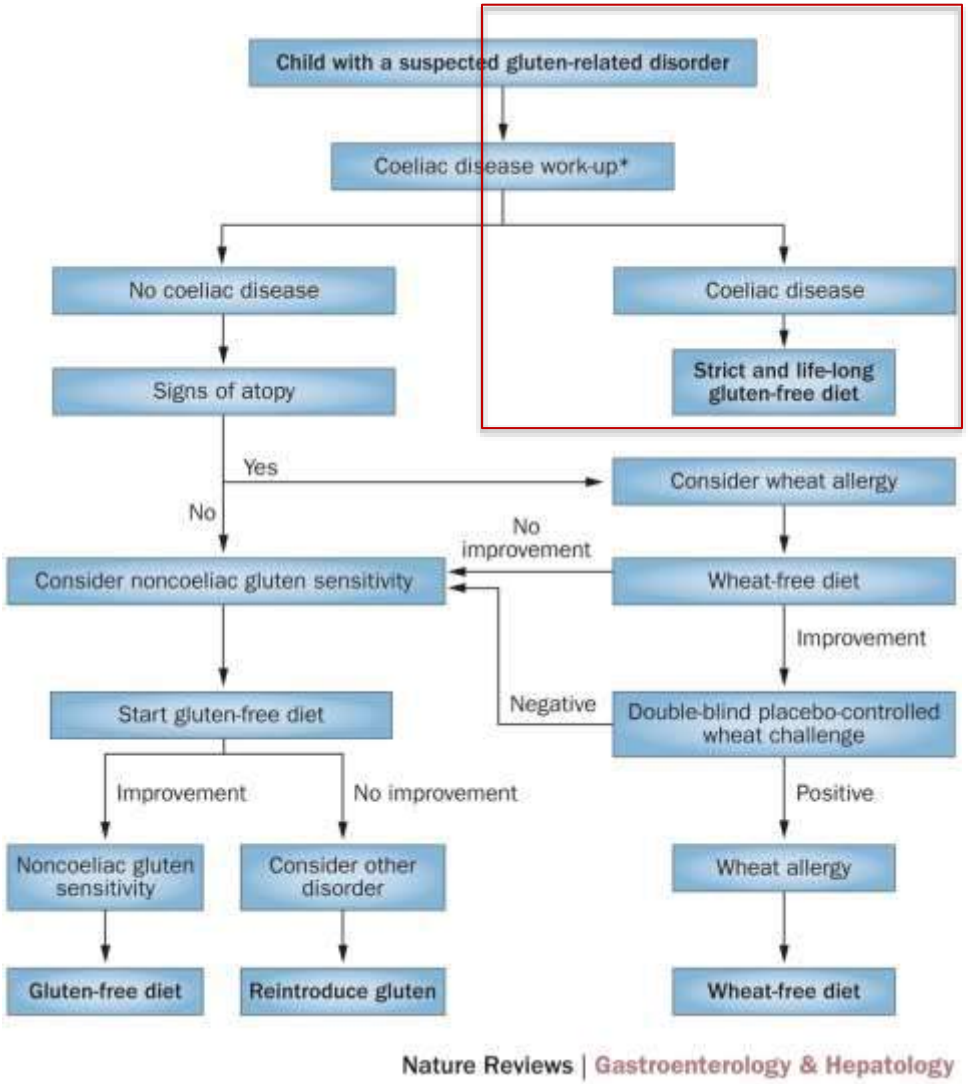
Symptoms and signs at presentation	Overall prevalence (%)
Iron deficiency with anemia	29
Iron deficiency without anemia	27
Recurrent Abdominal Pain	24
Mood Changes	17
Recurrent Aphthous Stomatitis	11
Poor appetite	10
Recurrent diarrhea	9
Short stature	7
Abdominal distension	5
Constipation	2
Pubertal delay	2
Hypoalbuminemia	2

ESPGHAN algorithm for the diagnosis of coeliac disease in children and adolescents with symptoms



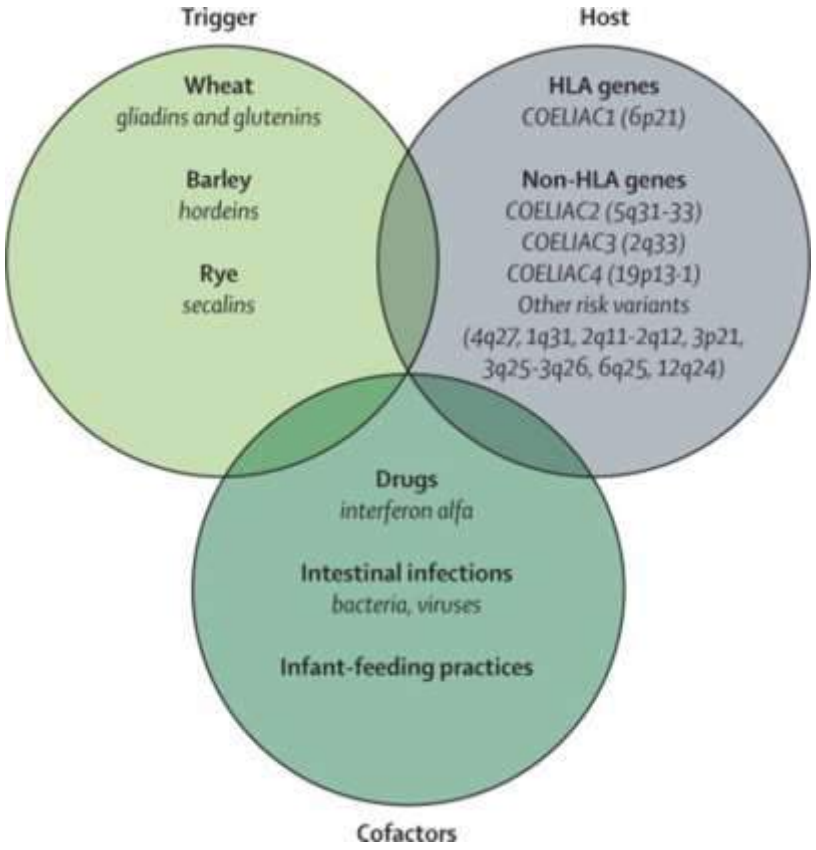
Vriezinga, S. L. *et al.* (2015) Coeliac disease and gluten-related disorders in childhood
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.98

Figure 1 Flow-chart of the diagnostic process in a child with a suspected gluten-related disorder



Vriezinga, S. L. *et al.* (2015) Coeliac disease and gluten-related disorders in childhood
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.98

Celiac Disease: Clinical Manifestations in Adults



- Majority of individuals were diagnosed in their 4th to 6th decades.
- Women predominated (2.9:1)- the female predominance was less marked in the elderly.
- **Diarrhea** was the main presenting symptom occurring in 50%.
- **36% had a previous diagnosis of irritable bowel syndrome.**
- Symptoms were present a mean of 11 years before diagnosis.

Green PHR, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001;96:126–131.

Celiac Disease in adult

Symptoms And Complications Associated with Celiac Disease*

Gastrointestinal
Recurring abdominal pain
Bloating
Gas
Chronic diarrhea
Constipation

Systemic
Persistent anemia
Chronic fatigue
Weight loss
Osteopenia, osteoporosis
Fractures
Amenorrhea
Infertility
Muscle cramps
Discoloration and loss of Tooth enamel

Autoimmune Associations
Dermatitis herpetiformis (DH)
Aphthous stomatitis/ulcers
Peripheral neuropathy, ataxia
Epilepsy
Arthritis
Thyroid disease
Sjogren's syndrome
Chronic active hepatitis, Primary biliary cirrhosis, Sclerosing Cholangitis

Malignancies
Non-Hodgkin lymphoma (intestinal and extra intestinal, T- and B-cell types)
Small intestinal Adenocarcinoma
Esophageal carcinoma
Papillary thyroid cancer
Melanoma

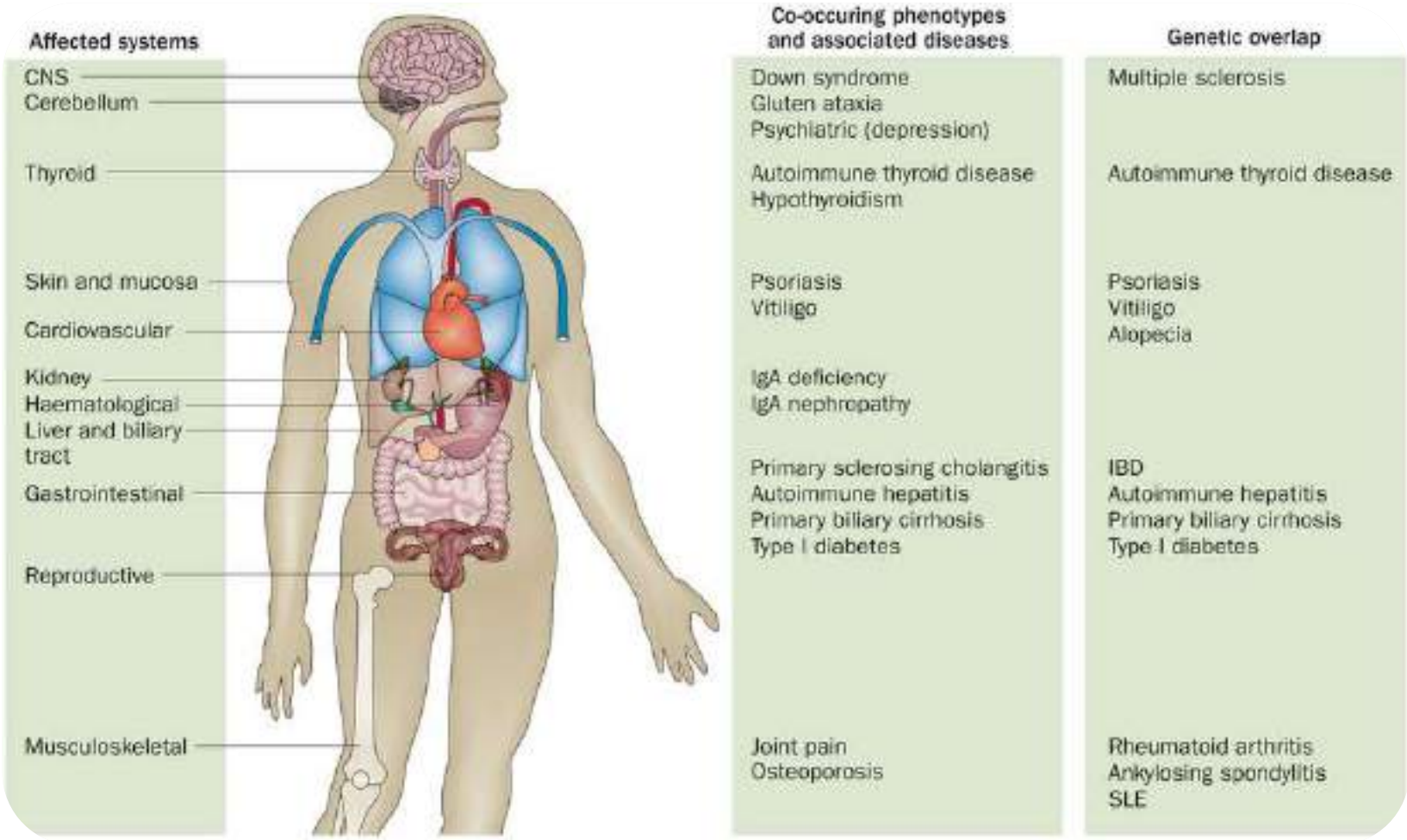
Spectrum of Celiac Disease

Few if any GI symptoms — **Marked GI symptoms**

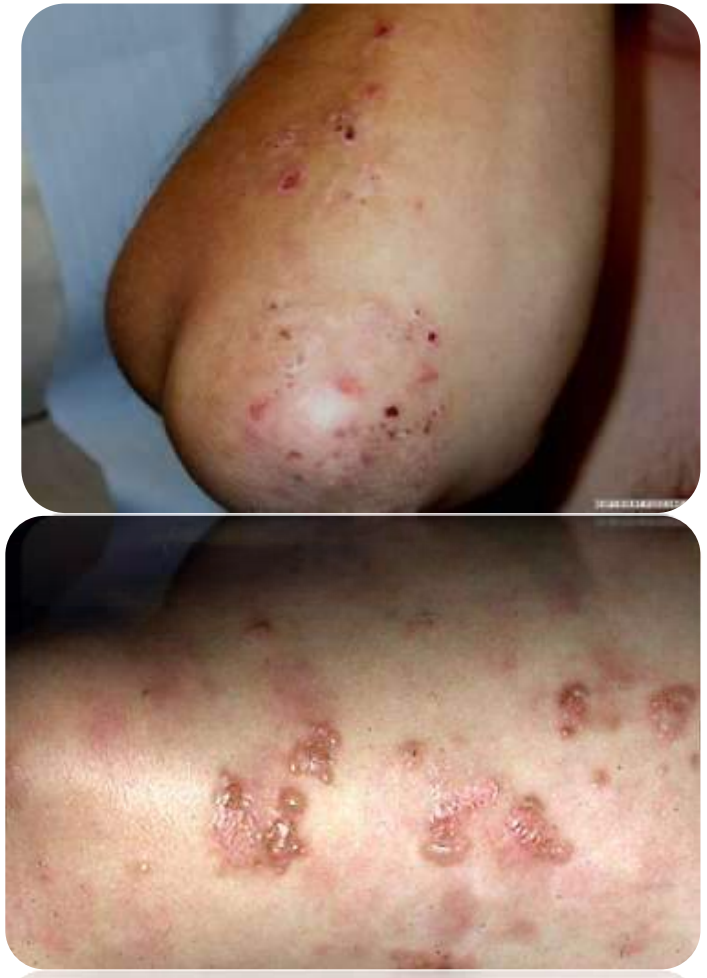
Fatigue
Depression, irritability
Menstrual irregularity
Weakness
Infertility
Neurologic Complaints

Diarrhea
Bulky, Pale, Foul stools
Abdominal Distension, Bloating
Abdominal cramps
Weight loss
Loss of or increased appetite

Autoimmune diseases



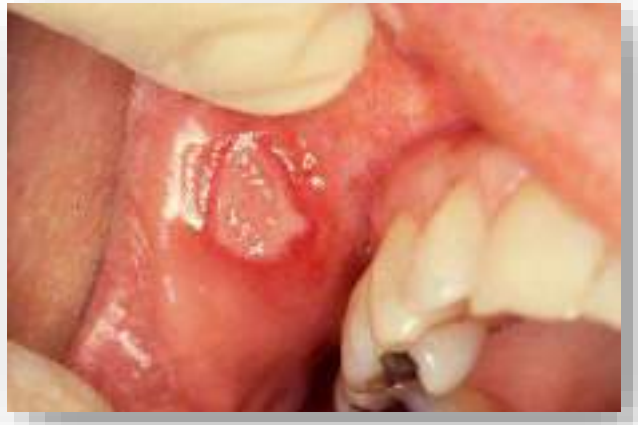
Celiac Disease:
Dermatitis Herpetiformis

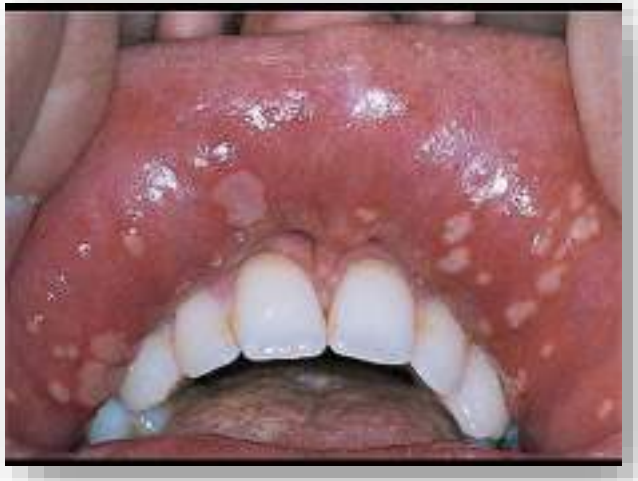


Symmetric vesicles, crusts and erosions distributed over the extensor areas of the elbows, knees, buttocks, shoulders and scalp, with a tendency to grouping of individual lesions

It has been reported that up to 10 percent of individuals with celiac will also have dermatitis herpetiformis

Celiac Disease: Associated Disorders





- Aphthous stomatitis- unexplained oral ulcers have been reported as the sole presenting feature
- Glossitis, angular stomatitis, and cheilosis have also been associated

Celiac Disease: Type 1 Diabetes

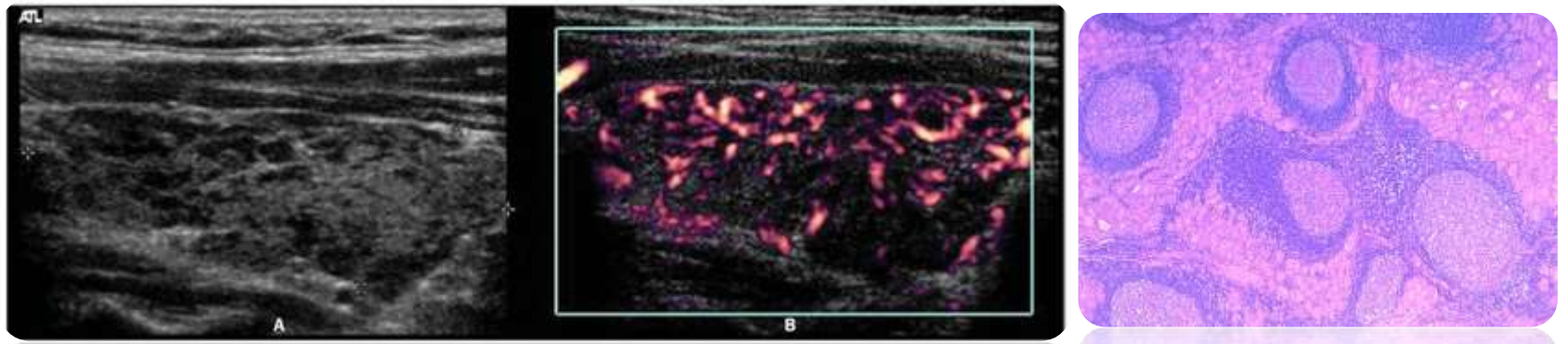
- An association between CD and type 1 diabetes mellitus (T1DM) has been recognized for decades

- Several studies in children and adults, have shown that there is a **1.5% to 7%** prevalence of CD in type 1 diabetes

- A community-based study of type 1 diabetics of all ages in Olmsted County, MN, revealed that 6.5% had celiac disease.

Celiac Disease:
Autoimmune Thyroid Disease

- Approximately 5-6% of the patients with celiac disease also had autoimmune thyroid disease (Hashimoto'a thyroiditis)

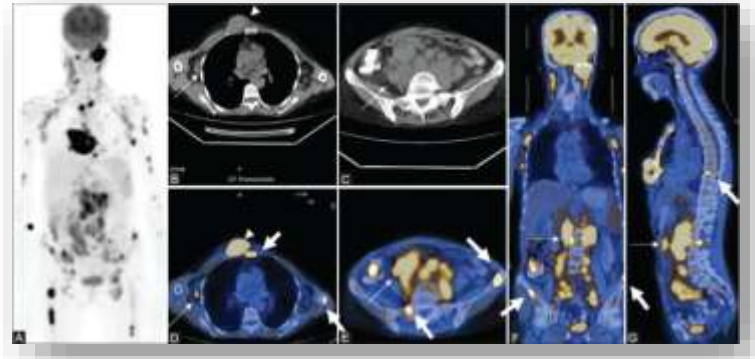


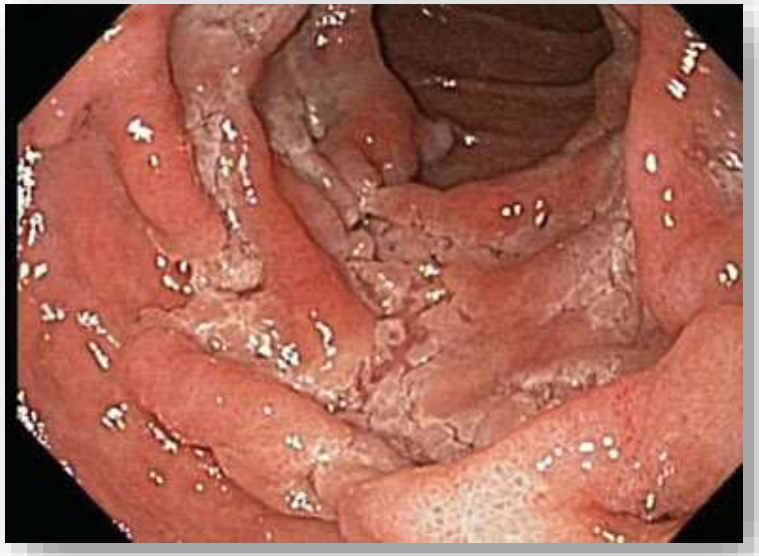
Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, is an autoimmune disease in which the thyroid gland is gradually destroyed. Some people eventually develop hypothyroidism with its accompanying weight gain, feeling tired, constipation, depression, and general pains

Celiac Disease: Neuropsychologic Features

- Depression- 10.6%
- Epilepsy- 3.5%
- Migraine headaches- 3.2%
- Anxiety- 2.6%
- Suicidal tendency- 2.1%
- Carpal tunnel- 1.8%
- Myopathy- 1.5%

Celiac Disease: Malignancies



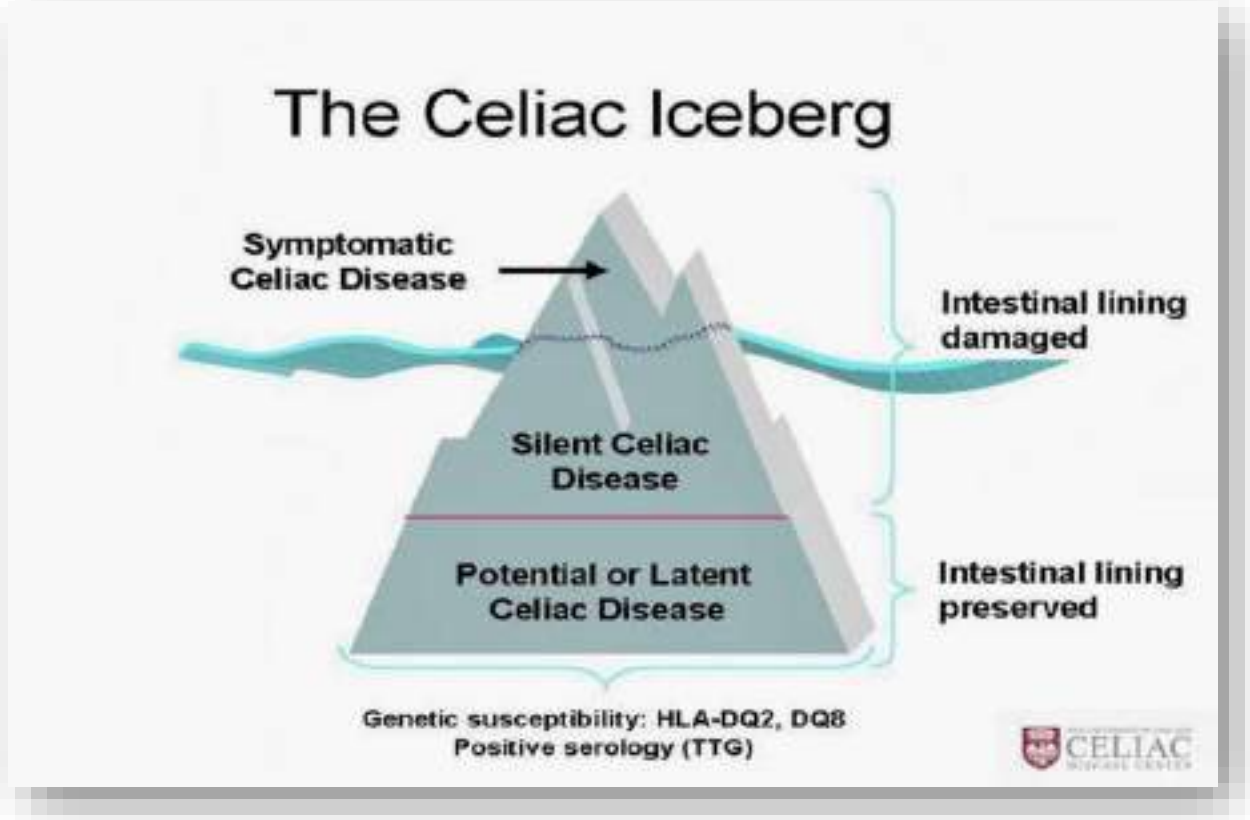


Malignancy	Overall Relative Risk
All cancers	2 to 3
Enteropathy -associated T-cell lymphomas	30 to 40 (w/o gluten free diet)
Small intestinal adenocarcinoma	83
Mouth, pharynx, esophagus cancer	23 (w/o gluten free diet)

American Gastroenterological Association, Ciclitra, PJ, Gastroenterology 2001; 120: 1526.

Classification of Celiac Disease

- Classical celiac disease
- Silent celiac disease
- Latent celiac disease



Diagnosis of Celiac Disease

Clinical & Laboratory Findings

Serologic testing

Small Intestines Mucosal Biopsy

Gluten Re-challenge

Diagnosis of Celiac disease: Serologic Testing

Serologic tests used to diagnose celiac:

- IgA and IgG anti-deamidated-gliadin antibodies
- IgA and IgG tissue transglutaminase antibodies
- IgA endomysial antibodies

Diagnosis of Celiac disease: Anti-tissue Transglutaminase Ab

- The antigen against which antiendomysial antibodies are directed is a tissue transglutaminase (tTG or TG2)
- IgA anti-tTG antibodies testing by ELISA are considered easier to perform and less costly than the immunofluorescence assay used to detect IgA endomysial antibodies.
- **Anti-tTG antibodies are both highly sensitive and specific**

Diagnosis of Celiac disease: IgA Endomysial Antibodies

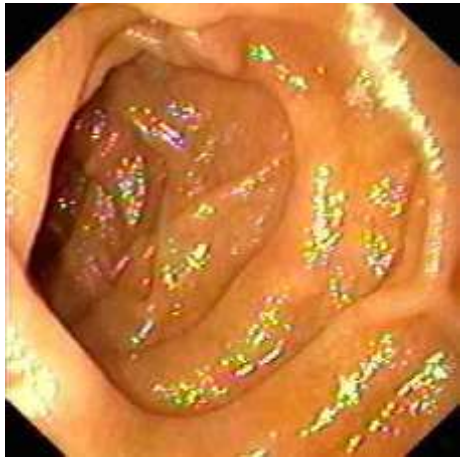
- Endomysial antibodies are directed against tTG bind to connective tissue surrounding smooth muscle cells

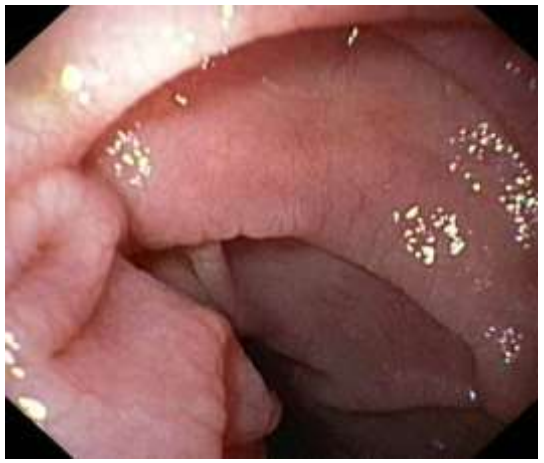
- IgA endomysial antibodies bind to the endomysium, producing a characteristic staining pattern, which is visualized by **indirect immunofluorescence**.

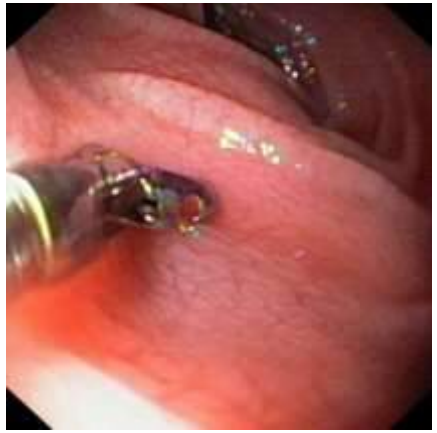
- **IgA endomysial antibody testing is moderately sensitive and highly specific for untreated celiac disease**

Diagnosis: Endoscopy

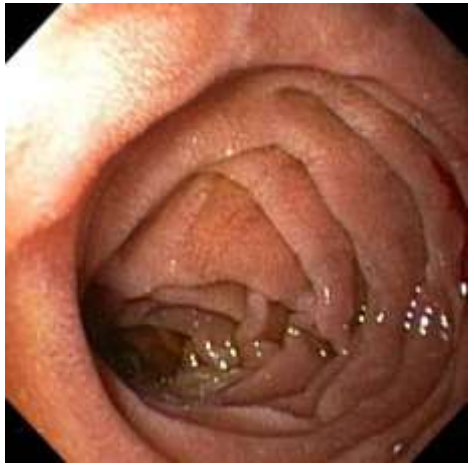
Normal

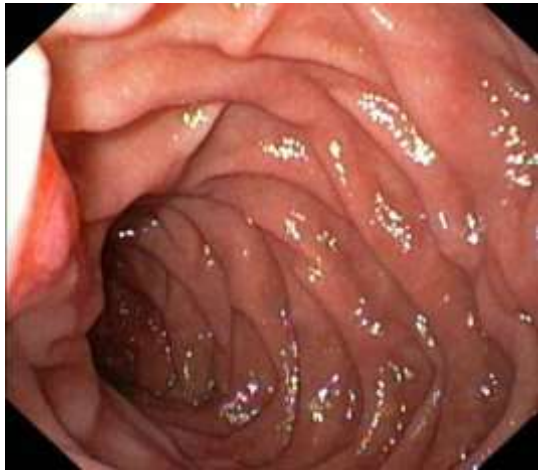






Celiac





Marsh's classification

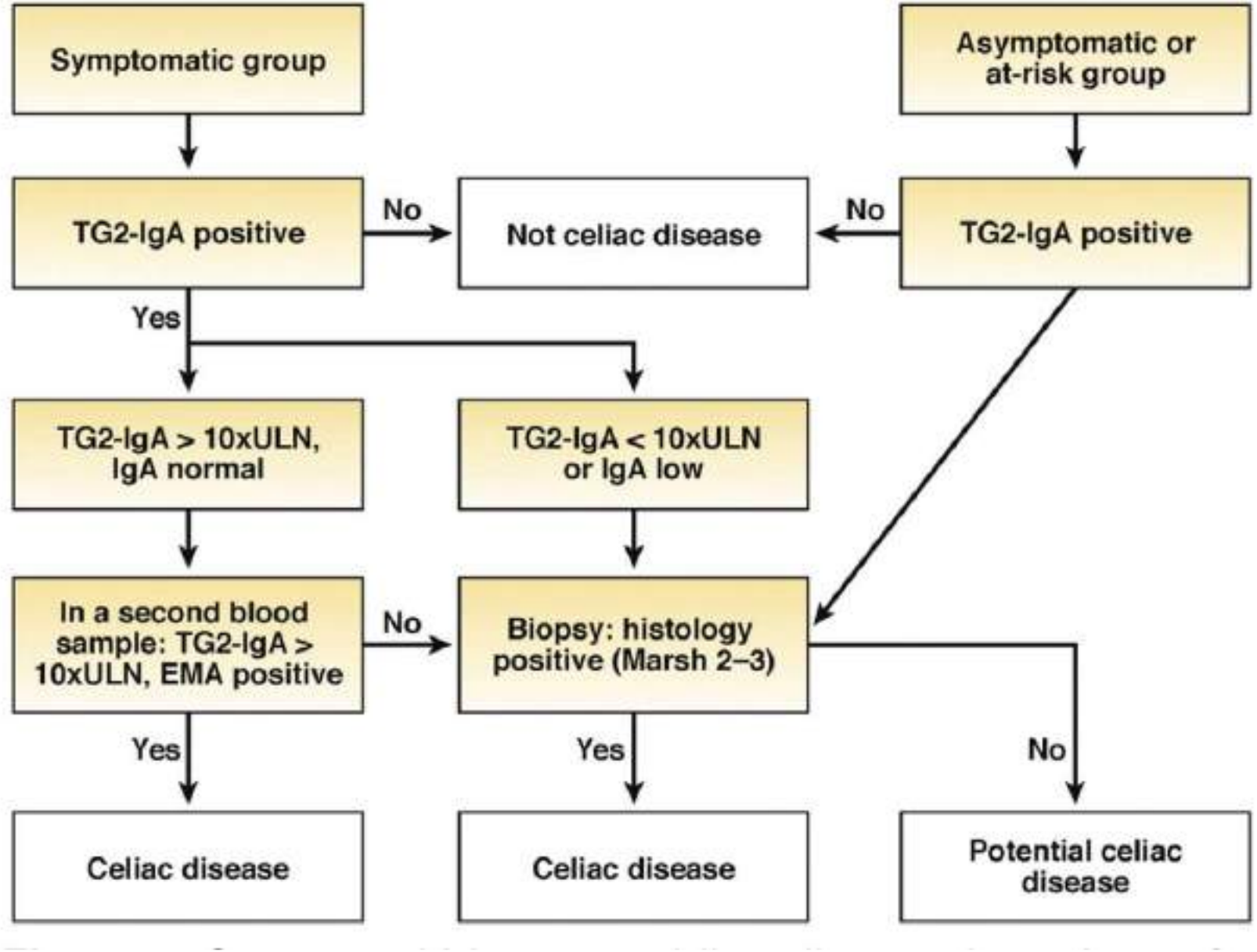
Stage 0
Preinfiltrative mucosa; 5% of patients with CD have small intestinal biopsy speciments that appear normal.

Stage I°
Increase in the number of intraepithelial lymhocytes (IELs) to more than 30 per 100 enterocytes.

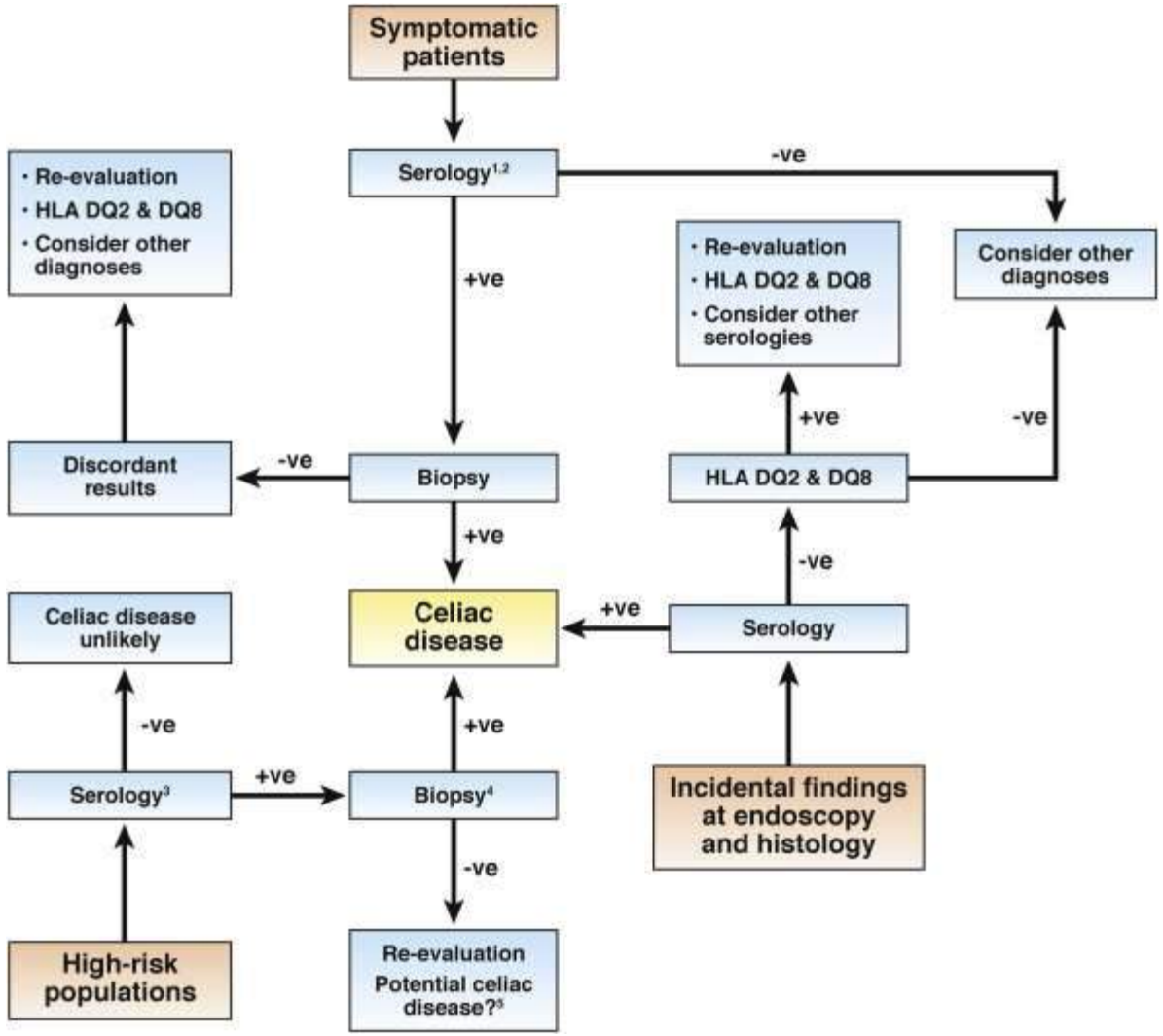
Stage II°
Criptic hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height.

Stage III°
Villous atrophy; A partial, B subtotal, C total.
This lesion is characteristic of, but not diagnostic for, CD and can also been seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies..

Algorithm for diagnosis of uncomplicated celiac disease



Celiac disease diagnosis



Treatment

Treatment consists of a lifelong gluten-free diet.

Wheat, rye, and barley grains should be excluded from the diet.

Rice and corn grains are tolerated.

Oats (if not contaminated by wheat grain) are tolerated by most.

Early referral to a reputable celiac support group or website is often helpful in maintaining dietary compliance.

Owing to secondary lactase deficiency, **a lactose-free diet** should be recommended until symptoms improve.

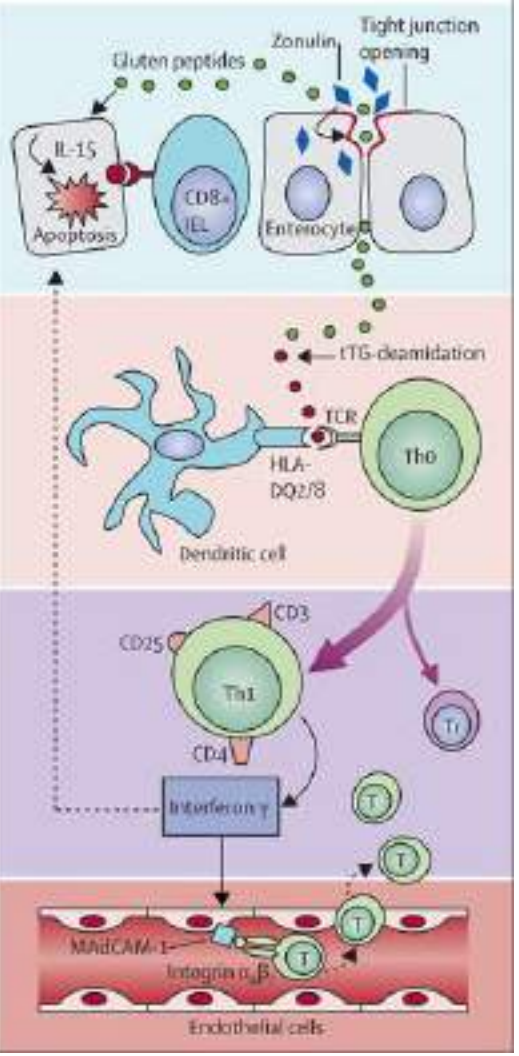
Bone densitometry should be performed on all individuals with celiac disease because up to 70% have osteopenia or osteoporosis.

Patients with diarrhea and weight loss should be screened for vitamin and mineral deficiencies. Documented deficiencies of vitamins and minerals should be replenished and women of childbearing age should take folic acid supplements.

Bone mass often improves on a gluten-free diet alone. Patients with vitamin D or calcium deficiency should receive supplements with the dose monitored by 25-OH vitamin D levels and a 24-hour urine test for calcium.

Therapy

Target	Therapeutic agent	Mechanism of action
Gluten peptides	Prolyl endopeptidases (PEP)	Cleavage of proline-rich and glutamine-rich gliadin peptides in safer sequences
Zonulin	Zonulin receptor antagonist (AT-1001)	Prevention of epithelial translocation of gluten peptides into the lamina propria
Interleukin 15	Anti-interleukin 15 antibody (AMG714)	Reduced cytolytic activity of intraepithelial lymphocytes against epithelial cells with consequent decrease of enterocyte apoptosis
Tissue transglutaminase	Tissue transglutaminase inhibitors	Blockade of deamidation and subsequent immunological potentiation of gluten peptides
HLA-DQ2/DQ8 molecules	DQ2/DQ8 inhibitors	Blockade of presentation of gluten peptides with consequent silencing of gluten-reactive T cells
Dendritic cells	Peptide vaccines	Manipulation of dendritic cells in order to make them a vehicle for peptide vaccines
Interferon γ	Anti-interferon γ antibody (fontolizumab)	Down-regulation of the Th1-mediated inflammatory response
T cells	Anti CD3 antibody (visilizumab), anti CD4 antibody (cM-T412), anti CD25 antibody (daclizumab)	Silencing of gluten-reactive T cells
Type 1 regulatory T cells (Tr)	Human recombinant interleukin 10 (Tenovil)	The interleukin-10-mediated expansion of type 1 regulatory T cells may suppress the immune response to gliadin
Adhesion molecules	Anti-integrin α_4 antibody (natalizumab); anti-integrin $\alpha_4\beta_7$ antibody (MLN-02); integrin α_4 antagonist (T-0047)	Blocking the cognate interaction between integrin $\alpha_4\beta_7$ expressed on lymphocytes and MADCAM-1 expressed on mucosal endothelial cells may decrease lymphocyte recruitment in the gut



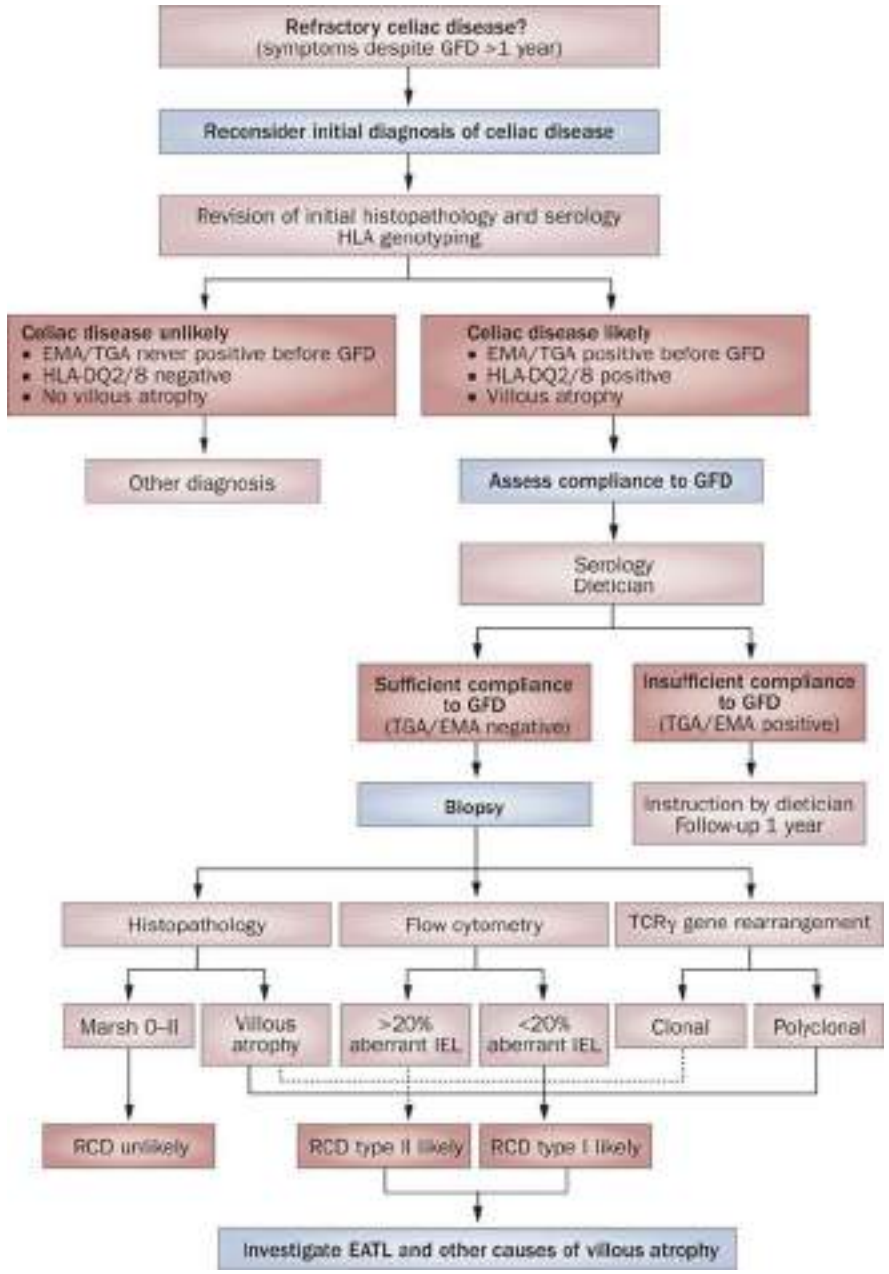
Celiac disease: refratory celiac disease

Refractory celiac disease (RCD) is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6–12 months in the absence of other causes of non-responsive treated celiac disease and overt malignancy.

Symptoms are often severe and require additional therapeutic intervention besides GFD.

RCD can be classified as **type 1 (normal intraepithelial lymphocyte phenotype), or type 2 (defined by the presence of abnormal** [clonal] intraepithelial lymphocyte phenotype).

Algorithm for diagnosis of refractory celiac disease



Tack, G. J. *et al*. (2010) The spectrum of celiac disease: epidemiology, clinical aspects and treatment *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2010.23

Celiac disease refractory disease

	Disease Category	
Clinical Criteria	RCD type 1	RCD type 2
Abnormal immunophenotype of IELs with loss of normal surface markers CD4, CD8, and T-cell receptor: either >50 % by immunohistochemistry or >20–25% by flow cytometry	No	Yes
T-cell receptor chains (γ or δ) clonal rearrangement by molecular methods (<15% in normal state)	No	Yes
Clinical or histological response to steroids or other immunosuppressive drugs or biologics	Yes	Variable
Lymphoma-genesis potential (especially T cell lymphoma development)	**Rare**	**Frequent**

Celiac disease:
refratory celiac disease

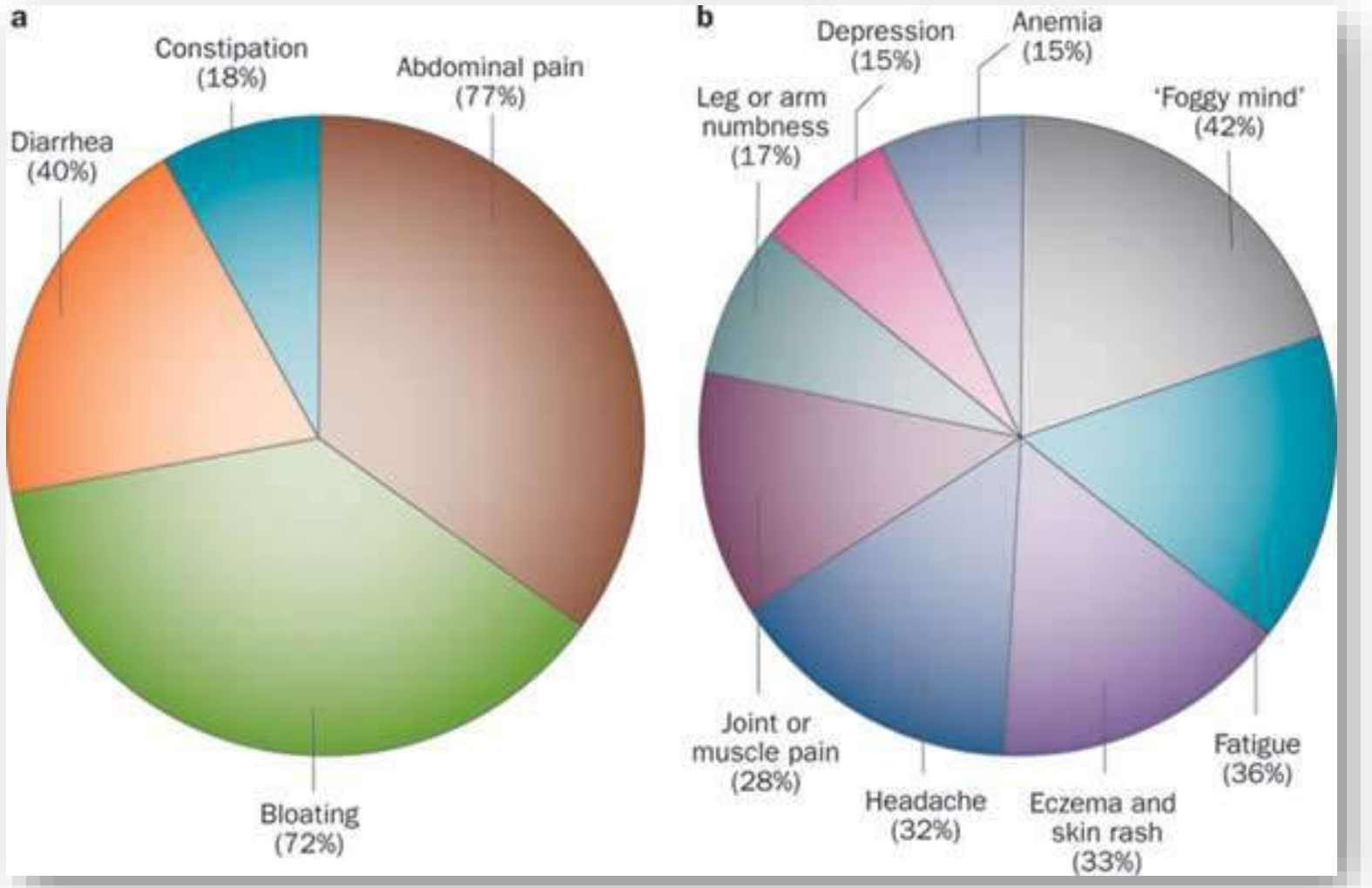
Prednisone (0.5–1 mg/kg/day), **budesonide** (9 mg/day), or a combination of prednisone and azathioprine (2 mg/kg/day) are clinically effective to induce clinical remission and mucosal recovery in most patients with RCD type Clinical response to steroids is observed in the majority (~75%) of patients with RCD type 2, however mucosal recovery is infrequent and progression to EATL is not prevented Steroid- dependence is observed in most patients with RCD type 1 or RCD type 2.[15]

Gluten sensitivity

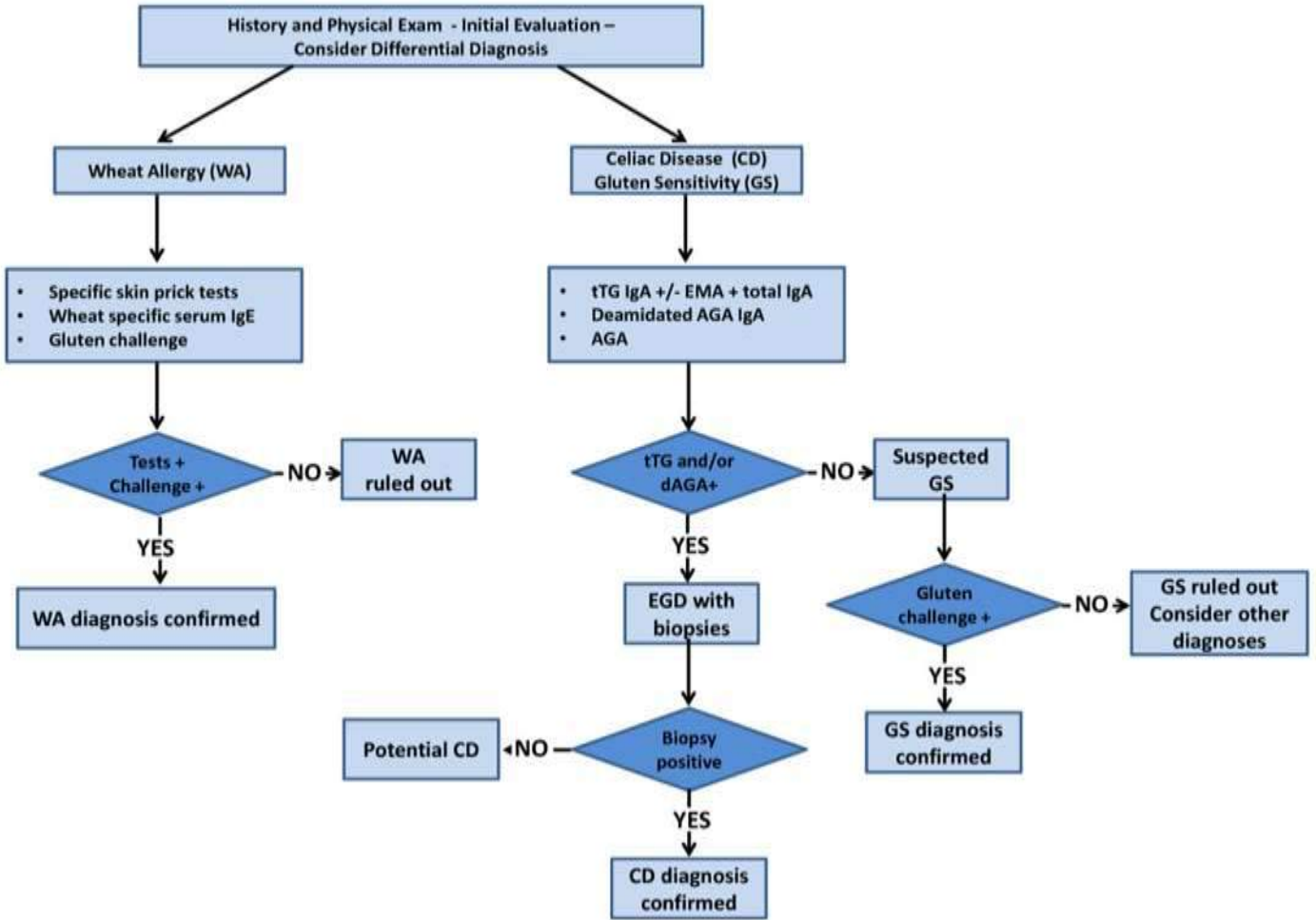
Unlike celiac disease, gluten sensitivity is not associated with ***serious conditions*** (referring to – autoimmune, cancer, osteoporosis, infertility, and neurological disease).

Common symptoms of gluten sensitivity include abdominal pain similar to irritable bowel syndrome, fatigue, headaches, “foggy mind” or tingling of the extremities.

Gluten sensitivity



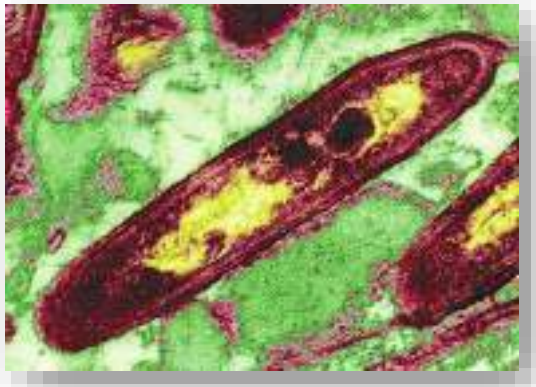
The spectrum of wheat-associated diseases

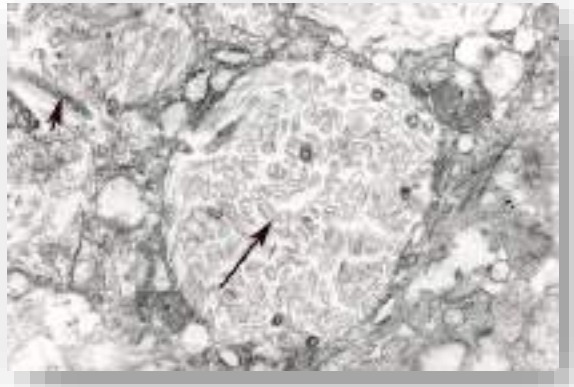


Wipple’s disease

Whipple's disease is a rare systemic infectious disease caused by the bacterium Tropheryma whipplei.

First described by George Hoyt Whipple in 1907 and commonly considered as a gastrointestinal disorder, Whipple's disease primarily causes malabsorption, but may affect any part of the human body, including the heart, brain, joints, skin, lungs and the eyes





Tropheryma whipplei, is a Gram positive Actinobacteria but is commonly found to be Gram negative or Gram-indeterminate when stained in the laboratory.

Whipple's Disease: Epidemiology

- Rare:
- Predilection for males of European ancestry.
- 8:1 Men:Women.
- Mean age 50 years.
- Majority have occupational exposure to soil or animals.

Lancet **361**: 239 (2003)
Clin Microbiol Rev **14**: 561 (2001)

Pathogenesis /Immunology

- Host immune deficiency and possibly secondary immune down regulation are responsible
- Source of transmission is unknown - likely per oral
- The bacteria most commonly invades the intestinal lamina propria and the vacuoles of "foamy" macrophages
- Tissue macrophages are unable to kill and clear *T.whipplei.*
  ↓ CD11b on macrophages mediates intracellular degradation of ingested bacteria
- *This deficiency in killing then causes Whipple's disease*

Common clinical syndromes that suggest the possible diagnosis of Whipple's disease include

Table 2. Demographic and Clinical Features of Classic Whipple's Disease.*

Feature	Patients with Whipple's Disease
	no./total no. (%)
Male sex	770/886 (87)
Arthralgia or arthritis	244/335 (73)
Diarrhea	272/335 (81)
Weight loss	223/240 (93)
Fever	128/335 (38)
Adenopathy	174/335 (52)
Melanoderma	99/240 (41)
Neurologic signs†	33/99 (33)
Ocular signs†	6/99 (6)
Pleural effusion	26/190 (14)

* Data are from reports on seven case series, all published since 1960, by Chears et al.,[22] Enzinger and Helwig,[16] Kelly and Weisiger,[23] Maizel et al.,[24] Dobbins,[15] Fleming et al.,[25] and Durand et al.[21] Total numbers refer to the total number of patients evaluated for Whipple's disease. The ages of the patients at diagnosis ranged from 1 to 83 years.

† Supranuclear ophthalmoplegia is included as a neurologic sign but not as an ocular sign. Two patients presented with supranuclear ophthalmoplegia.

- **Chronic diarrhea** with Vitamin or iron deficiency anemia, hypoalbuminemia, and relative lymphopenia should increase the level of suspicion associated with f**ever of unknown origin**, and **migratory polyarthropathy**, **progressive central nervous system disease** with myoclonus or ophthalmoplegia, and generalized lymphadenopathy.

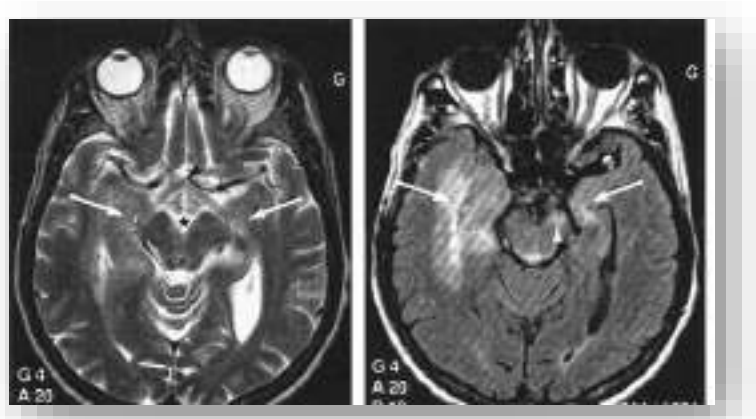
Clinical: CNS Features

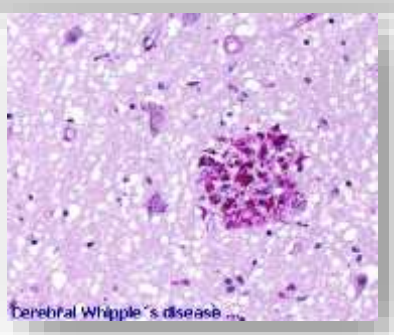
- 21–43% of cases of Whipple's disease have neurologic symptoms
- 43% - 100% have central nervous colonization
- Characteristic triad:
  - **Dementia**
  - **External opthalmoplegia***
  - **Facial myoclonus**
- Oculomasticatory myorhythmia (OMM) is diagnostic.
- CNS colonization may serve as a repository for bacteria and a mechanism for CNS relapse

*Drooping eyelids (ptosis), which can affect one or both eyelids,
and weakness or paralysis of the muscles that move the eye (ophthalmoplegia).

CNS Features

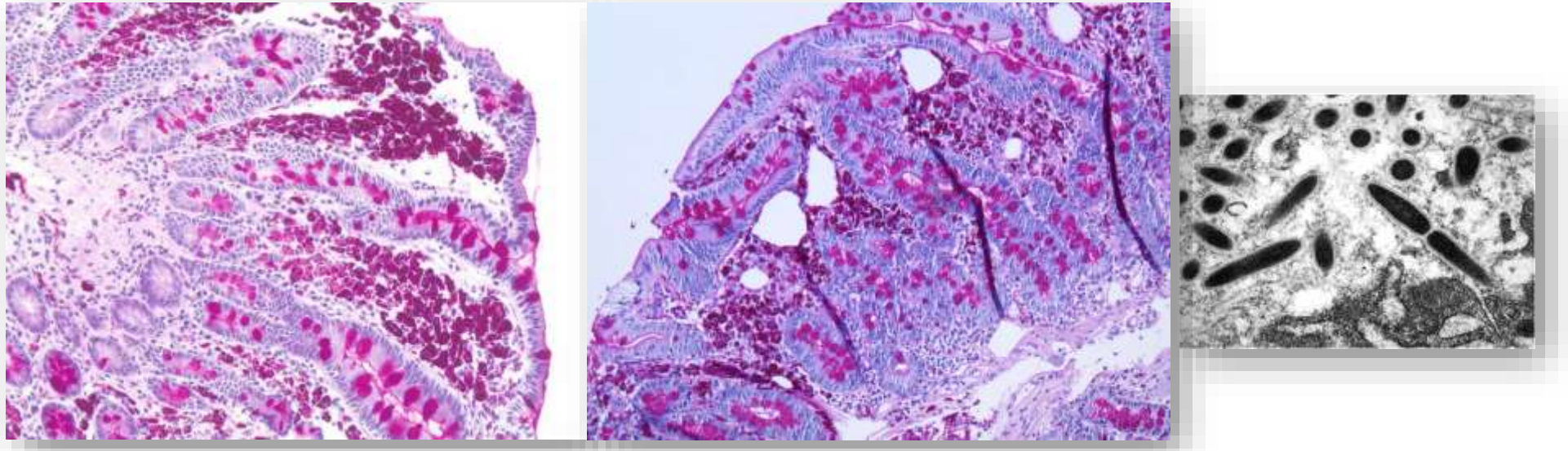
- **Imaging:**
  - generalized cerebral atrophy, scattered small chalky nodules in cortical and subependymal gray matter (true granulomas that contain PAS-positive foamy macrophages)
  - Areas of intense demylination resembling MS
  - Micro-infarcts





Intestinal biopsy

The hallmark of Whipple's disease is the histopathological finding of macrophages containing diastase-resistant **p-aminosalicylic acid (PAS)-**positive material, which are ***Tropheryma whipplei*** bacteria or partly digested remnants.



Recommended therapy for Whipple's disease.

Timing	First choice	Alternative
Initially (first 10–14 days)	Pen G (6–24 million U iv q.d.) plus Stm (1 g im q.d.) or third-generation cephalosporin (e.g., Ctri 2 g iv q.d.)	TMP-SMZ (160 mg/800 mg po b.i.d.)
Long term (~1 year)	TMP-SMZ (160 mg/800 mg po b.i.d.)	Dox (100 mg po b.i.d, Cfix (400 mg po b.i.d.), or Pen V potassium (500 mg po q.i.d.)

NOTE. Dox, doxycycline; Cfix, cefixime; Ctri, ceftriaxone; Pen, penicillin; Stm, streptomycin; TMP-SMZ, trimethoprim-sulfamethoxazole.

Strausbaugh L J et al. Clin Infect Dis. 2001;32:457-463