

Supportive module 2 "Basics of diagnosis, treatment and prevention of major gastroenterological diseases"



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Supportive module 2: Basics of diagnosis, treatment and prevention of major gastroenterological diseases

Chronic Disease of the Small Intestine: Crohn's disease, Celiac disease

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

M. Yabluchansky, L. Bogun, L. Martymianova, O. Bychkova, N. Lysenko, N. Makienko
V.N. Karazin National University Medical School' Internal Medicine Dept.

Definition

Crohn's disease, Celiac disease

- Crohn's disease encompasses a multisystem group of autoimmune inflammatory disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation primarily affecting the gastrointestinal tract.
- Celiac disease (gluten-sensitive enteropathy) is an autoimmune inflammatory disorder of the small intestine that is precipitated by the ingestion of gluten, a component of wheat protein, in genetically susceptible persons and it is the result of the interaction between genetic and environmental factors.

Epidemiology

Crohn's disease, Celiac disease

- Crohn's disease with potential for systemic and extraintestinal complications can affect any age group, but the onset (diagnosis) is most common in the second and third decades; the incidence and prevalence in developed countries estimated to be 5/100,000 and 50/100,000, respectively.
- The prevalence of celiac disease is approximately one case per 250 persons.

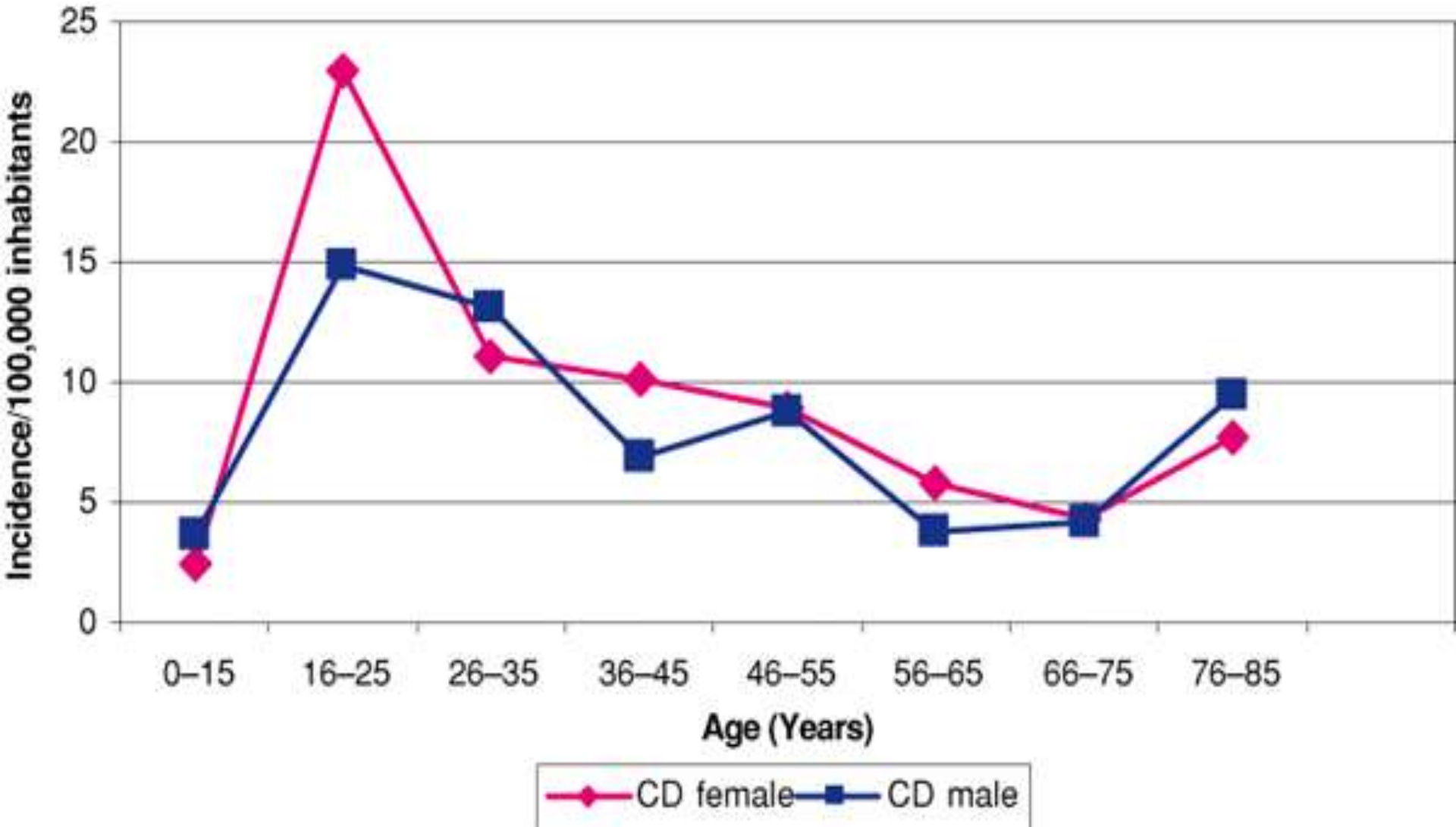
Epidemiology

Geographic Distribution of Crohn's disease



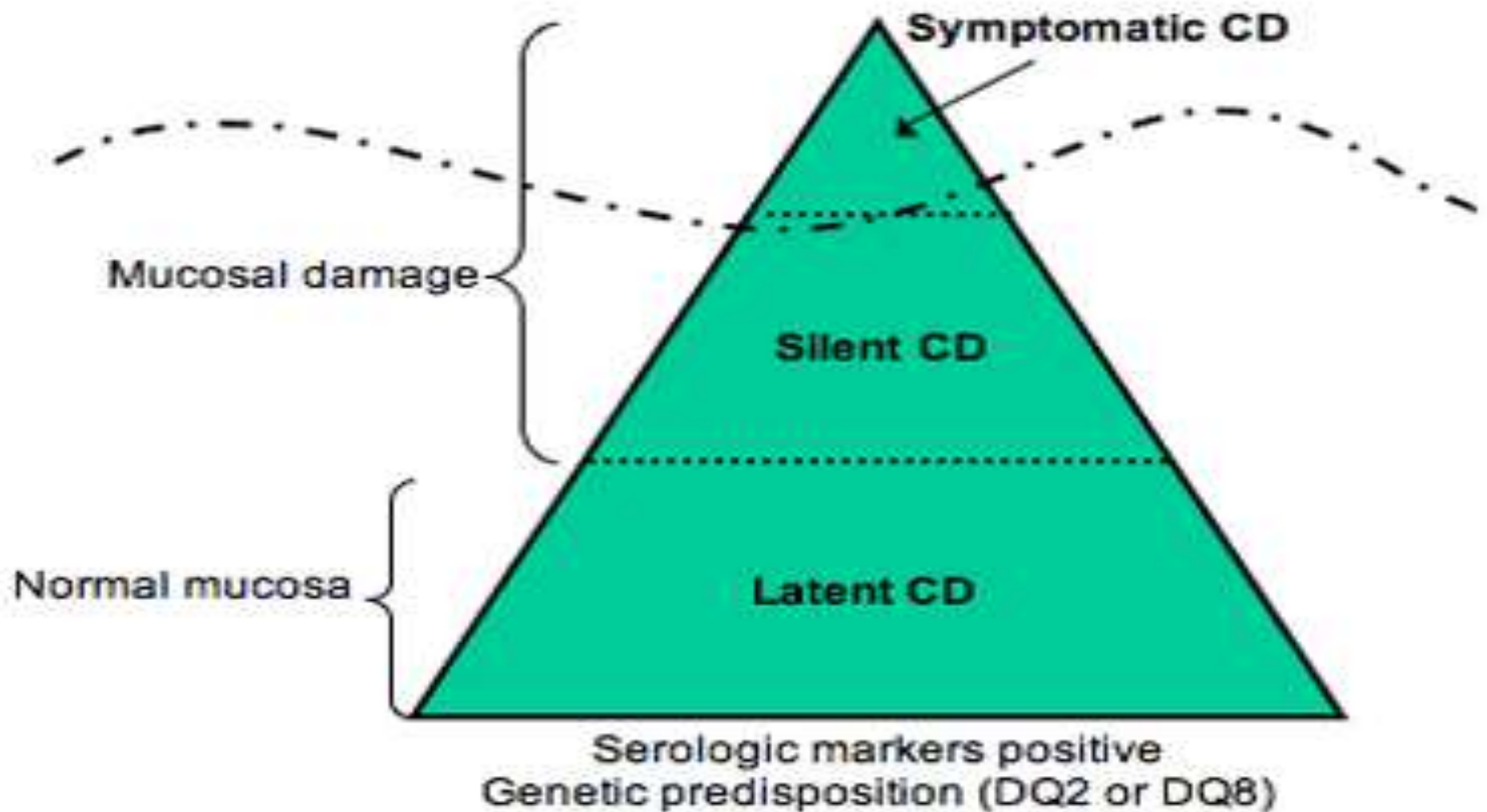
Epidemiology

Aged distribution of Crohn's disease



Epidemiology

The Celiac Disease Iceberg



Risk Factors & Etiology

Crohn's disease, Celiac disease

- The causes of Crohn's disease are not known, and a malfunctioning immune system, genetics, and environment may all play a part; risk factors may include (young) age, ethnicity (whites and Jews), family history (1 in 5 people with Crohn's disease has a family member with the disease), cigarette smoking, nonsteroidal anti-inflammatory medications, life in an urban area or in an industrialized country;
- The cause for celiac disease is unknown, and people of European descent and those with other autoimmune disorders are at increased risk for its developing; among genetic risk factors, the strongest association is with the HLA class II DQ region; nevertheless at least 39 non-HLA loci are associated with disease; gluten is the main trigger of the disease; a role for infectious agents and microbiota composition in disease development has also been proposed.

Mechanism

Crohn's disease 1

Key Players

- Genetics (Crohn's disease is genetically linked to celiac disease)
- Environmental factors (the increased incidence of Crohn's in the industrialized world indicates an environmental component)
- Immunobiology:
 - Microbiota (a causal role for *Mycobacterium avium* subspecies paratuberculosis)
 - Intestinal barrier
 - Microbial sensing, innate immunity, and autophagy
 - Adaptive immunity (Crohn's disease is a primary T cell autoimmune disorder and results from an impaired innate immunity) and leucocyte migration.

Mechanism

Crohn's disease 2

- Chronic inflammation from T-cell activation leading to tissue injury is implicated in the pathogenesis of Crohn disease
- The initial lesion starts as a focal inflammatory infiltrate around the crypts, followed by ulceration of superficial mucosa
- Inflammatory cells invade the deep mucosal layers and, in that process, begin to organize into noncaseating granulomas
- The granulomas extend through all layers of the intestinal wall and into the mesentery and the regional lymph nodes
- Neutrophil infiltration into the crypts forms crypt abscesses, leading to destruction of the crypt and atrophy of the colon
- Transmural inflammation results in thickening of the bowel wall and narrowing of the lumen

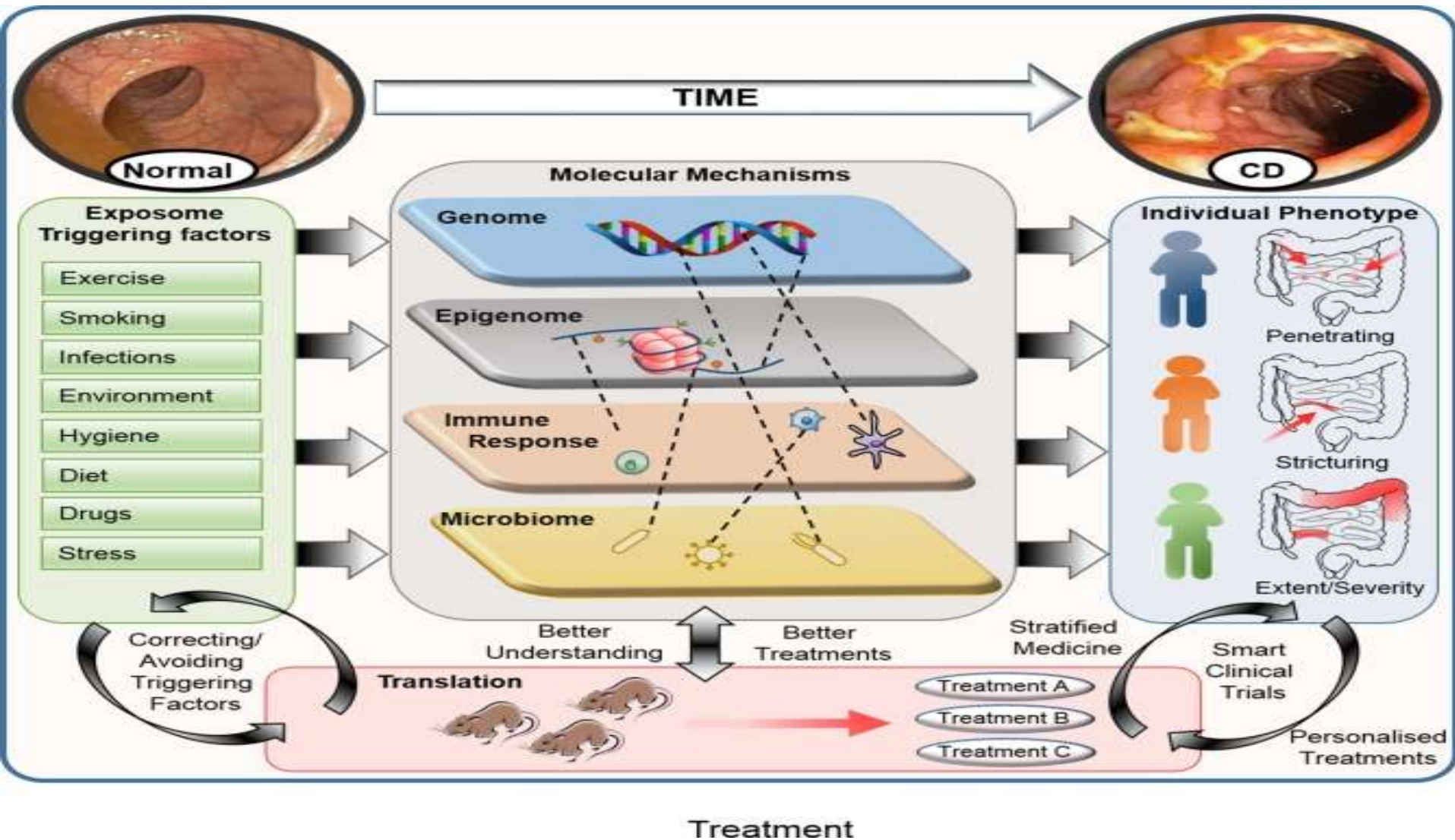
Mechanism

Crohn's disease 3

- Ulcerations are common and are often seen on a background of normal mucosa
- As disease progresses, it is complicated by obstruction or deep ulceration leading to fistulization by way of the sinus tracts penetrating the serosa, microperforation, abscess formation, and malabsorption
- Obstruction is intermittent and can often be reversed by means of conservative measures and anti-inflammatory agents but with further disease progression becomes chronic because of fibrotic scarring, luminal narrowing, and stricture formation
- Serosal inflammation causes adhesions; thus, free perforations are less common in Crohn disease than in other inflammatory bowel conditions.

Mechanism

Factors contributing to Crohn's disease



Mechanism

Celiac disease 1

- Celiac disease results from genetic abnormal immune response to gluten that leads to local activation of immune system
- As a result of immunological reactions with significant role of T lymphocytes (non proliferative activation of lamina propria CD4+ lymphocytes and proliferative activation of intra-epithelial TcR alpha/beta CD8+ and TcR gamma/delta lymphocytes) the inflammatory process with typical histopathological lesions develops
- In immunological reaction to gluten besides T lymphocytes other cells are involved (lymphocytes B, natural killer cells (NK), neutrophils, eosinophils, macrophages, mastocytes
- This intense local inflammatory reaction produces the villous flattening characteristic of gluten-sensitive enteropathy

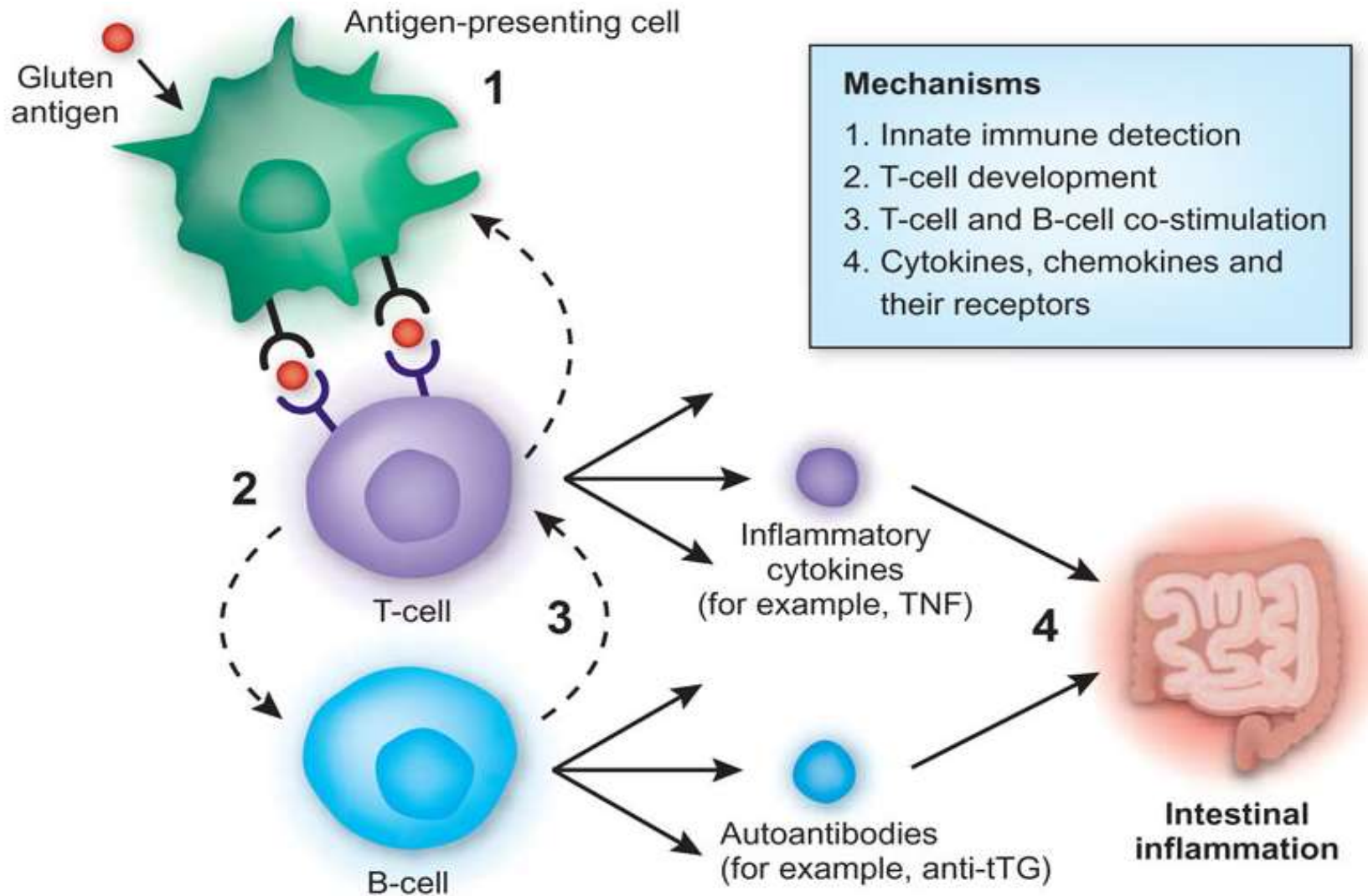
Mechanism

Celiac disease 2

- Malabsorption of micronutrients (e.g., vitamins and minerals) and macronutrients (e.g., protein, carbohydrate, fat) follows
- Small-bowel involvement is most prominent proximally and may be “patchy,” especially in patients with “silent” celiac disease (i.e., minimal or no symptoms) and those with dermatitis herpetiformis
- About 95% of patients with celiac disease exhibit specific Human Leukocyte Antigen (HLA) class II alleles DQA1*0501 and DQB1*0201
- Patients with type 1 diabetes, autoimmune thyroid disease, Sjögren's syndrome, primary biliary cirrhosis, Addison's disease, systemic lupus erythematosus, selective IgA deficiency, and alopecia areata may also exhibit similar genotypes and are at risk for gluten-sensitive enteropathy.

Mechanism

Genetic Pathways of Celiac disease



Classification

International Classification of Diseases

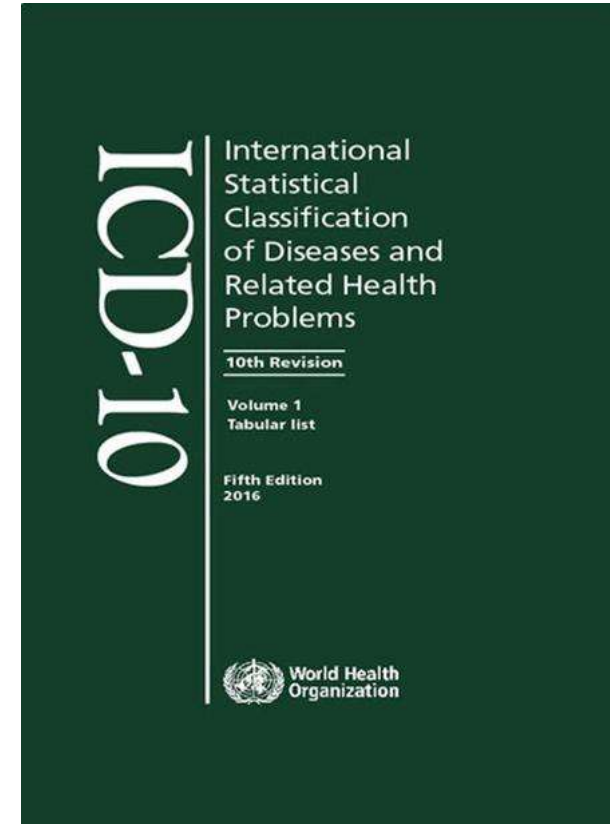
XI Diseases of the digestive

K50-K52 Noninfective enteritis and colitis

K50.0 Crohn disease of small intestine

K90-K93 Other diseases of the digestive system

K90.0 Celiac disease



Classification

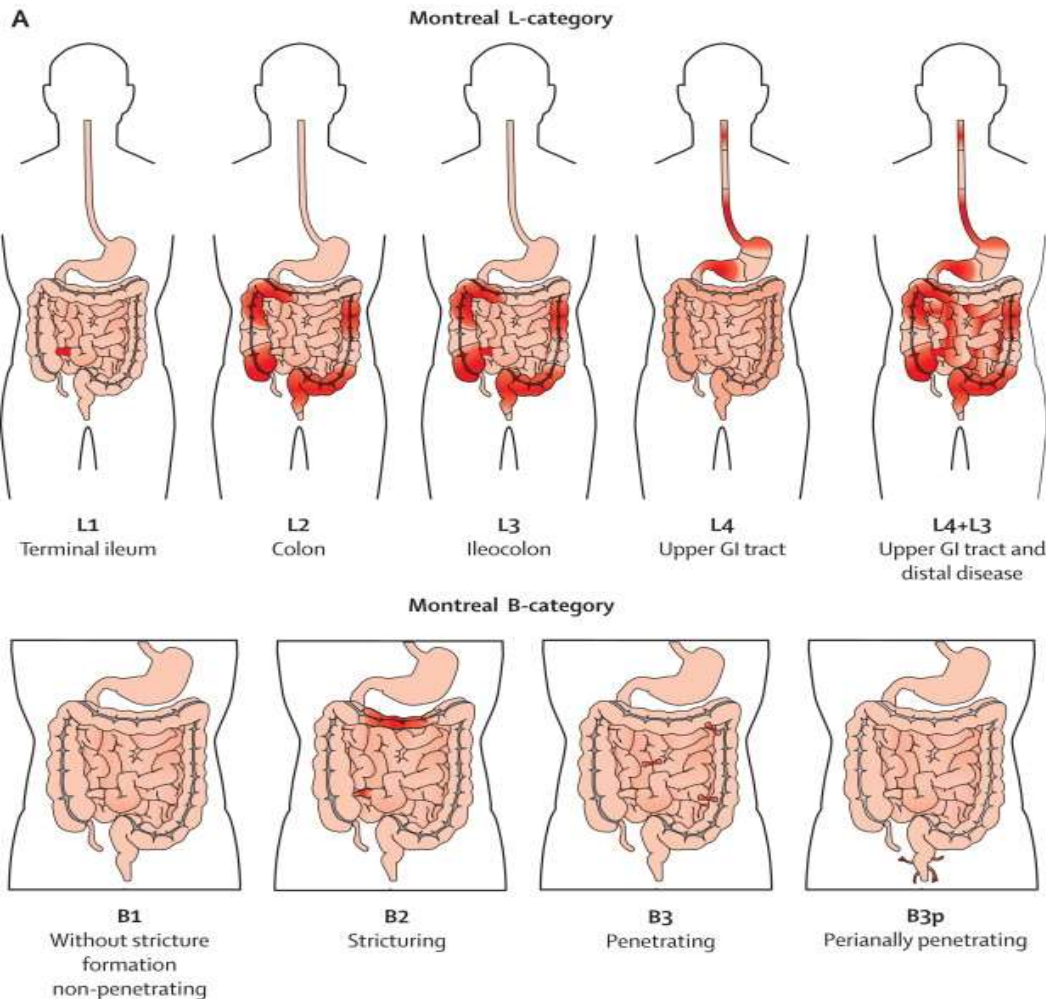
Vienna and Montreal classification for Crohn's disease

	Vienna (1998)	Montreal (2005)
Age at diagnosis	A1 below 40 y	A1 below 16 y
	A2 above 40 y	A2 between 17 and 40 y
Location		A3 above 40 y
	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
Behaviour	L4 upper	L4 isolated upper disease
	B1 non-stricturing, non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 structuring
	B3 penetrating	B3 penetrating
		p perianal disease modifier

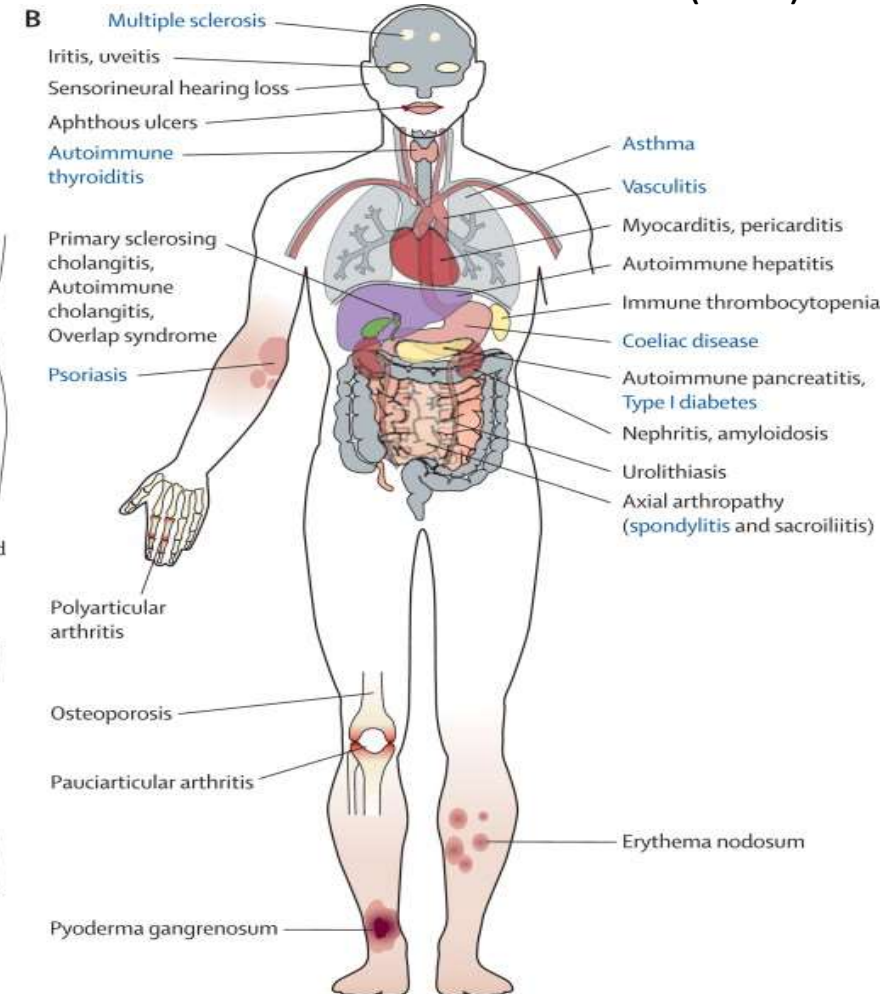
Classification

Phenotype of Crohn's disease

Montreal classification



Major extraintestinal manifestations and associated autoimmune disorders (blue)



Classification

The Crohn's Disease Activity

Classification	Patient Activity and Common Characteristics
Mild-to-moderate	Patient tolerates oral alimentation without dehydration, abdominal pain, obstruction, toxicity, or weight loss >10%
Moderate-to-severe	Patient nonresponsive to treatment of mild-to-moderate disease; has fever, weight loss, abdominal pain, nausea and vomiting (without obstructive findings), or significant anemia
Severe-fulminant	Patient receiving steroids and experiencing persistent symptoms; presents with high fever, significant weight loss, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia, or abscess formation
Remission	Patient asymptomatic, no inflammatory complications, or response to acute medical intervention (CDAI <150).

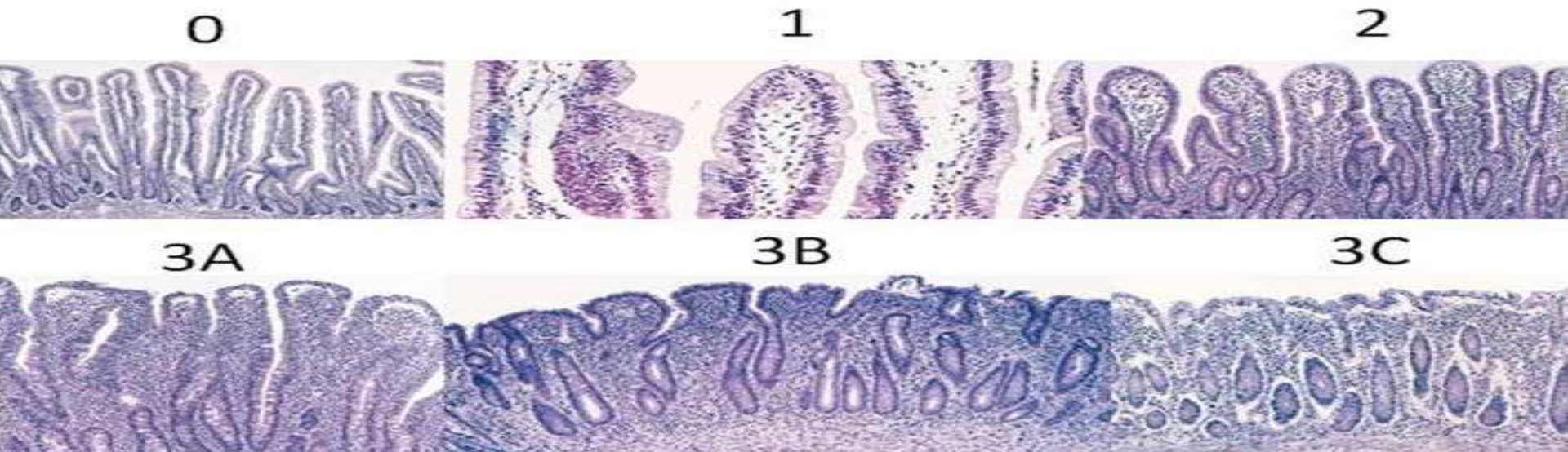
CDAI: Crohn's Disease Activity Index. Source: References 19, 20.

Classification

Marsh Grading of Celiac Disease

Marsh grade

- | | |
|----|---|
| 0 | Normal mucosa |
| 1 | Increased number of intraepithelial lymphocytes, usually exceeding 20 per 100 enterocytes |
| 2 | Proliferation of the crypts of Lieberkuhn |
| 3 | Variable villous atrophy |
| 3a | Partial villous atrophy |
| 3b | Subtotal villous atrophy |
| 3c | Total villous atrophy |
| 4 | Hypoplasia of the small bowel architecture |



Signs and Symptoms

Crohn's disease

- The characteristic presentation is abdominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction
- Other signs and symptoms of Crohn disease may include rectal bleeding; fever; weight loss, anorexia; nausea, vomiting; malnutrition, vitamin deficiencies; generalized fatigability; bone loss
- Psychosocial issues (e.g., depression, anxiety, and coping difficulty); pediatric patients may also experience psychological issues regarding quality of life and body image
- Growth failure in pediatric patients: may precede gastrointestinal symptoms by years.

Signs and Symptoms

Celiac Disease

- In infancy disease manifests as failure to thrive, diarrhea, abdominal distention, and developmental delay
- In adults, gastrointestinal tract involvement may manifest as diarrhea, constipation, or other symptoms of malabsorption (bloating, flatus, or belching)
- Fatigue, depression, fibromyalgia-like symptoms, aphthous stomatitis, bone pain, dyspepsia, gastroesophageal reflux, etc.
- Women comprise approximately 75 % of newly diagnosed disease cases and tend to have more clinically conspicuous disease.

History

Crohn's disease

- Patients with suspected Crohn disease should be evaluated initially by their primary care team, and symptoms should be elicited in detail
- Obtain a complete medical, surgical, social, and family history, and perform a detailed review of systems
- Preliminary laboratory data (e.g., inflammatory and anemia markers) may be helpful
- If Crohn disease is suspected, the patient should be promptly referred to a gastroenterologist for consultation.

History

Celiac Disease

- The manifestations of untreated celiac disease can be divided into gastrointestinal symptoms and extraintestinal symptoms
- Gastrointestinal symptoms include diarrhea due to maldigestion and malabsorption of nutrients (watery or semifformed stools, steatorrhea, flatulence, borborygmus, weight loss, weakness and fatigue, severe abdominal pain)
- Extraintestinal symptoms include anemia, a bleeding diathesis, osteopenia and osteoporosis, neurologic symptoms (motor weakness, paresthesias with sensory loss, and ataxia), skin disorders (including dermatitis herpetiformis), hormonal disorders (amenorrhea, delayed menarche, and infertility in women and impotence and infertility in men).

Physical Exam

Crohn's disease

- Vital signs are usually normal, though tachycardia may be present in anemic or dehydrated patients
- Chronic intermittent fever is a common presenting sign
- Abdominal findings may vary from normal to those of an acute abdomen
- In addition to local complications, various extraintestinal manifestations may be associated with Crohn disease, usually involving the skin, joints, mouth, eyes, liver, or bile ducts.

Physical Exam

Celiac Disease

- A protuberant and tympanic abdomen due to distention of intestinal loops with fluids and gas
- Weight loss, including muscle wasting or loose skin folds
- Orthostatic hypotension
- Peripheral edema
- Ecchymoses
- Hyperkeratosis or dermatitis herpetiformis
- Cheilosis and glossitis
- Peripheral neuropathy
- Chvostek sign or Trousseau sign.



Trousseau sign of latent tetany in hypocalcemia



Chvostek sign of a facial nerve tetany in hypocalcemia

Complications

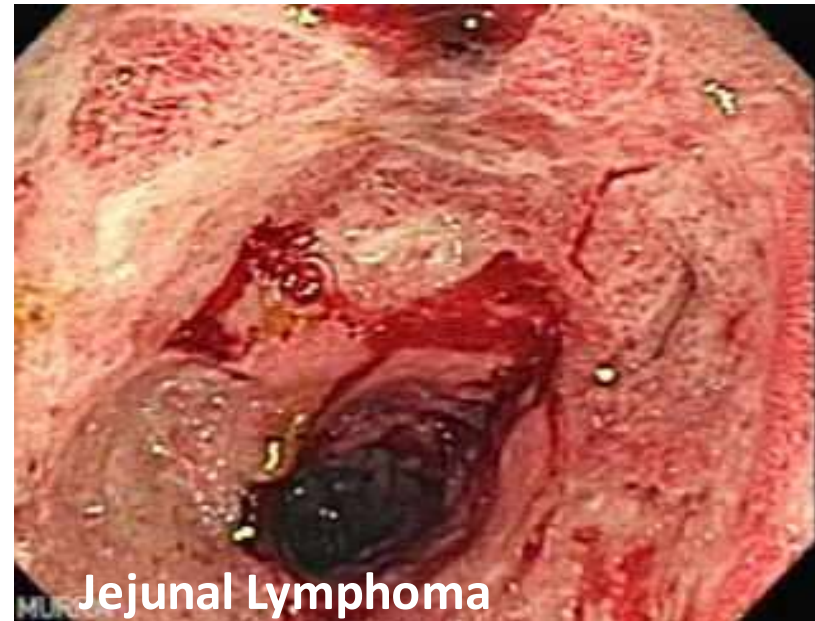
Crohn's disease

- The major significant complications include intestine obstruction, abscesses, free perforation and hemorrhage, which in rare cases may be fatal
- Obstruction occurs from strictures or adhesions that narrow the lumen, blocking the passage of the intestinal contents
- A fistulae develop between two loops of bowel, between the bowel and bladder, between the bowel and vagina, and between the bowel and skin
- Abscesses are walled off concentrations of infection, which can occur in the abdomen or in the perianal area
- Crohn's disease also increases the risk of cancer in the area of inflammation.

Complications

Celiac Disease

- Iron deficiency
- Lower prevalence of sexual satisfaction
- Osteoporosis
- Malignancy (lymphomas, carcinomas)



Diagnosis

Examination for Crohn's disease

- Vital signs: normal, but possible presence of tachycardia in anemic or dehydrated patients; possible chronic intermittent fever
- Gastrointestinal: may vary from normal to those of an acute abdomen
- Genitourinary: may include presence of skin tags, fistulae, ulcers, abscesses, and scarring in the perianal region; nephrolithiasis, hydronephrosis, and enterovesical fistulae
- Musculoskeletal: possible arthritis and arthralgia
- Dermatologic: may show pallor or jaundice, mucocutaneous or aphthous ulcers, erythema nodosum, and pyoderma gangrenosum
- Ophthalmologic: may reveal episcleritis; possible uveitis
- Growth delay: decreased growth velocity (eg, height), pubertal delay
- Hematologic: hypercoagulable state.

Diagnosis

Laboratory Tests, Imaging studies and Procedures in Crohn's disease

- Routine laboratory studies include CBC count, chemistry panel, liver function tests, inflammatory markers, stool studies, serologic tests; they may be used as surrogate markers for inflammation and nutritional status and to screen for deficiencies of vitamins and minerals
- Imaging studies include plain abdominal radiography, barium contrast studies, computed tomography (CT) and magnetic resonance imaging (MRI), nuclear imaging, fluorine-18-2-fluoro-2-deoxy-D-glucose scanning combined with positron emission tomography, etc.
- Procedures include endoscopic visualization and biopsy, colonoscopy, ileocolonoscopy, small bowel enteroscopy, interventional radiology.

Diagnosis

Blood Tests in Crohn's disease

- CBC may reveal anemia, which is caused by blood loss leading to iron deficiency or by vitamin B12 deficiency, caused by ileal disease impairing vitamin B12 absorption
- Serum iron, total iron binding capacity and transferrin saturation may be more easily interpreted in inflammation
- Erythrocyte sedimentation rate (ESR) and C-reactive protein help assess the degree of inflammation
- Testing for *Saccharomyces cerevisiae* antibodies (ASCA) and antineutrophil cytoplasmic antibodies (ANCA) help differentiate Crohn's disease from ulcerative colitis
- Low serum levels of vitamin D are associated with Crohn's disease
- Increasing levels of antilaminaribioside, antichitobioside, etc. may aid in the prognosis of Crohn's disease.

Diagnosis

Ordinary Findings in Crohn's disease

Terminal ileum involvement	Commonly
Colon involvement	Usually
Rectum involvement	Seldom
Bile duct involvement	No increase in rate of primary sclerosing cholangitis
Distribution of disease	Patchy areas of inflammation (skip lesions)
Endoscopy	Deep geographic and serpiginous (snake-like) ulcers
Depth of inflammation	May be transmural, deep into tissues
Stenosis	Common
Granulomas on biopsy	May have non-necrotizing non-peri-intestinal cryptgranulomas

Diagnosis

Stenosis in Crohn's disease



(A) MR enterography of Crohn's disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. (B) Ultrasound image of an intestinal stenosis in Crohn's disease.

Diagnosis

Ileal Crohn's disease



Resected ileum for a person with Crohn's disease.

Diagnosis

Serologic Tests in Celiac Disease

<i>ANTIBODY TEST</i>	<i>SENSITIVITY (%)</i>	<i>SPECIFICITY (%)</i>	<i>TIME COURSE</i>
IgA antiendomysial antibody	85 to 100	96 to 100	Antibody disappears within several months after institution of gluten-free diet.
IgA antitransglutaminase antibody	95	90	Limited data; correlated with IgA antiendomysial antibody in studies
IgA antigliadin antibody	53 to 100	65 to 100	More persistent than IgA antiendomysial antibody; may persist for 6 months or longer
IgG antigliadin antibody	57 to 100	42 to 98	Most persistent; may be detectable up to 12 months after institution of gluten-free diet
			False-positive tests reported in patients with Crohn's disease, wheat-protein allergy, and postdiarrhea states

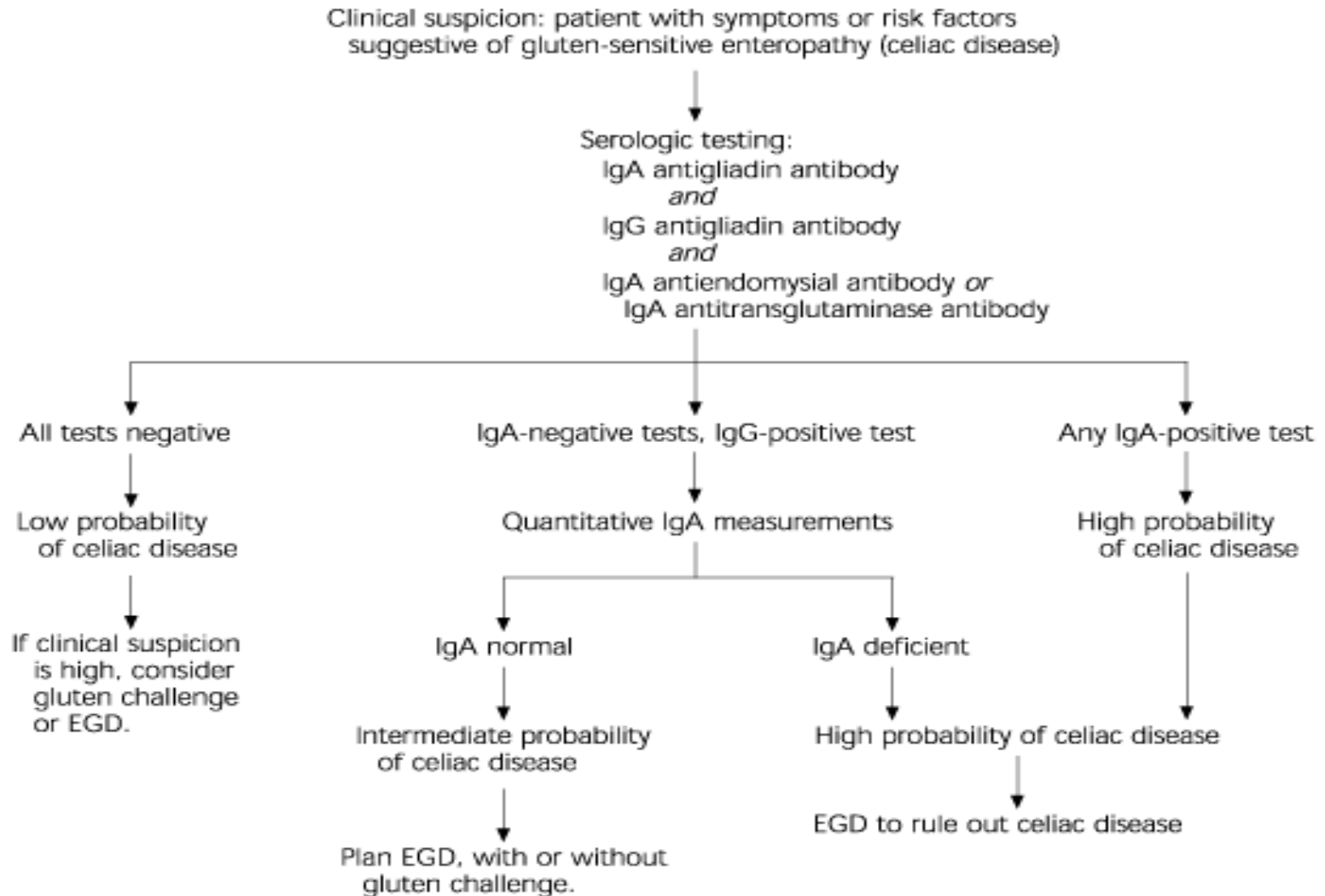
Diagnosis

Abnormal Laboratory Findings in Celiac Disease

<i>LABORATORY FINDING</i>	<i>PATHOPHYSIOLOGY</i>
Anemia	Iron deficiency; vitamin B ₁₂ and/or folate deficiency
Elevated alkaline phosphatase level	Osteoporosis, osteomalacia
Elevated aspartate transaminase and alanine transaminase levels	Minimal elevation common in celiac disease; presumably autoimmune
Decreased albumin level	Malnutrition
Elevated calcium level, decreased phosphate level	Vitamin D deficiency, secondary hyperparathyroidism
Thrombocytosis, leukocytosis	General inflammatory reaction
Coagulopathy	Decreased vitamin K absorption
Low high-density and low-density lipoprotein cholesterol levels	Decreased fat absorption, decreased hepatic lipoprotein production

Diagnosis

Algorithm for the Diagnosis of Celiac disease



Diagnosis

Other Conditions with Similar Symptoms as Crohn's disease and Celiac disease

- Intestinal tuberculosis
- Behçet's disease
- Ulcerative colitis
- Nonsteroidal anti-inflammatory drug enteropathy
- Irritable bowel syndrome
- Crohn's disease (for celiac disease)
- Celiac disease (for Crohn's disease)

Management

Lifestyle modification in Crohn's disease

- Lifestyle changes reduce symptoms, including dietary adjustments, elemental diet, proper hydration, and smoking cessation
- Diets that include higher levels of fiber and fruit are associated with reduced risk, while diets rich in total fats, polyunsaturated fatty acids, meat, and omega-6 fatty acids may increase risk
- Eating small meals frequently instead of big meals
- A food diary may help with identifying foods that trigger symptoms
- Some people should follow a low dietary fiber diet
- Some find relief in eliminating casein and gluten from their diets
- Fatigue can be helped with regular exercise, a healthy diet, and enough sleep.

Management

Patient Education

Education of patients and their families is encouraged and is extremely important in the treatment process.

Management

Pharmacotherapy of Crohn's disease

- 5-Aminosalicylic acid derivative agents (e.g., mesalamine rectal, mesalamine, sulfasalazine, balsalazide)
- Corticosteroids (e.g., prednisone, methylprednisolone, budesonide, hydrocortisone, prednisolone)
- Immunosuppressive agents (e.g., mercaptopurine, methotrexate, tacrolimus)
- Monoclonal antibodies (e.g., infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab)
- Antibiotics (e.g., metronidazole, ciprofloxacin)
- Antidiarrheal agents (e.g., loperamide, diphenoxylate-atropine)
- Bile acid sequestrants (e.g., cholestyramine, colestipol)
- Anticholinergic agents (e.g., dicyclomine, hyoscyamine, propantheline).

Management

Surgery of Crohn's disease

- Crohn disease has no surgical cure
- Surgical management of the terminal ileum, ileocolon, and/or upper gastrointestinal tract may include resection of the affected bowel, ileocolostomy or proximal loop ileostomy, drainage of any septic foci with later definitive resection, strictureplasty, bypass endoscopic dilatation of symptomatic strictures.

Management

Celiac disease 1

- At present, the only effective treatment is a lifelong *gluten-free* diet
- No medication exists that will prevent damage or prevent the body from attacking the gut when gluten is present
- Strict adherence to the diet allows the intestines to heal, leading to resolution of all symptoms in most cases and, depending on how soon the diet is begun, can also eliminate the heightened risk of osteoporosis and intestinal cancer and in some cases sterility
- The diet can be cumbersome; failure to comply with the diet may cause relapse
- Up to 5% of people have refractory disease, which means they do not improve on a *gluten-free* diet, and if alternative causes have been eliminated, steroids or immunosuppressants (such as azathioprine) may be considered in this scenario

Management

Celiac disease 2

- In many countries, *gluten-free* products are available on prescription and may be reimbursed by health insurance plans
- Gluten-free products are usually more expensive and harder to find than common gluten-containing foods
- The term *gluten-free* is generally used to indicate a supposed harmless level of gluten rather than a complete absence
- The European Commission issued regulations in 2009 limiting the use of "*gluten-free*" labels for food products to those with less than 20 mg/kg of gluten, and "very low gluten" labels for those with less than 100 mg/kg
- In the United States, the FDA issued regulations in 2013 limiting the use of "*gluten-free*" labels for food products to those with less than 20 ppm (one part per million = one part per 1,000,000 parts, one part in 10^6) of gluten.

Prognosis

Crohn's disease, Celiac disease

- Appropriate medical therapy helps patients with Crohn's disease to have a reasonable quality of life, with an overall good prognosis and an extremely low risk of a fatal outcome; most patients develop complications that require surgery, and postoperative clinical relapse occurs in a significant proportion
- Most patients who have celiac disease begin to feel better soon after starting the *gluten-free* diet; patients who begin a strict, *gluten-free* diet immediately after diagnosis have the best chance of living a healthy and active life; full recovery can take a few months to several years.

Prophylaxis

Crohn's disease, Celiac disease

- Crohn's disease can not be prevented
- Celiac disease can not be prevented; in the last years, several studies suggested a protective role of breast-feeding.

Abbreviations

ANCA - antineutrophil cytoplasmic antibodies

ASCA - *Saccharomyces cerevisiae* antibodies

CT – computed tomography

ESR - Erythrocyte sedimentation rate

IBD - inflammatory bowel disease

MRI - magnetic resonance imaging

NK - natural killer cells

ppm - one part per million

Diagnostic and treatment guidelines

[Gluten-Sensitive Enteropathy \(Celiac Disease\)](#)

[ESPEN guidelines on chronic intestinal failure in adults](#)

[Inflammatory Bowel Disease](#)

[Management of Crohn's Disease in Adults](#)

[Guidelines for the investigation of chronic diarrhea](#)

[Radiation-induced small bowel disease: latest developments and clinical guidance](#)

[Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease](#)