

**MINISTRY OF HEALTHCARE OF UKRAINE
HSEEU "Ukrainian Medical Stomatological Academy"**

"Approved"
at the meeting of internal
medicine №1 department
Head of Department
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Protocol № 2 from 15.09.2016

**GUIDELINES
FOR STUDENTS
INDEPENDENT WORK
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Basics of Internal Medicine
<i>Content module</i>	Fundamentals of diagnostics, treatment and prevention of gastroenterological diseases
<i>Study subject</i>	Chronic diseases of the small intestine: celiac disease and other enteropathy. Chronic diseases of the colon: non-specific colitis and irritable bowel syndrome.
<i>Course</i>	IV
<i>Faculty</i>	of foreign students training

Poltava 2016.

1. **Relevance of the topic:** **Gluten enteropathy** is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined *gluten intolerance*, diffuse atrophy of mucous membrane, and leads to generalized malabsorption. About 20% of patients diagnosed with irritable bowel syndrome or with microscopic (lymphocytic) colitis have celiac disease. **Irritable bowel syndrome (IBS)** is a functional bowel disorder. The world-wide prevalence of IBS is 11,2%. Inflammatory bowel disease refers to two chronic idiopathic inflammatory disorders, **ulcerative colitis and Crohn's disease**. These disorders are diagnosed by characteristic clinical, endoscopic, and histologic features. Inflammatory bowel disease occurs worldwide.

2. **The main goal:** To be able to assess the typical clinical picture of intestinal disorders, to determine tactics of treatment and prophylaxis.

Specific goals:

- To select the information indicating the presence of intestinal disorders in a patient from the data history;
- To create a scheme of diagnostic search;
- To identify the signs of intestinal disorders in an objective study of the patient (general examination, palpation, percussion, auscultation)
- To analyze and interpret the changes in the results of the laboratory and instrumental methods of investigation, depending on the course of the disease;
- To formulate and justify a preliminary diagnosis of intestinal disorders according to classification;
- To conduct differential diagnostics of diseases with the similar clinical picture;
- To develop a strategy of treatment depending on the disease and the existing complications;
- To provide medical care;
- To assess the patient's prognosis and to propose a plan of preventive actions;
- To apply deontological communication skills with patients.

3. Basic knowledge, abilities, skills (interdisciplinary integration)

Discipline	To know	To be able to
Anatomy	The structure of the gastrointestinal tract, blood supply, innervation	
Histology	The structure of the wall of the intestines in health and disease	To interpret results of lower endoscopy with biopsy
Regional anatomy	Interposition of the gastrointestinal organs	
Physiology	Indicators of gastrointestinal tract function, its value	To determine the function of gastrointestinal organs
Morbid anatomy	Changes in the structure of the wall of intestines	
Radiology	Radiological changes	Analyze the radiological picture of the abdominal cavity
Propaedeutic	Symptomatology of intestinal	Conduct an objective examination of

therapy	disorders and their complications	the patient, analyze the clinical and laboratory results
Pharmacology	The mechanism of action, indications and contraindications for the prokinetics, antibiotics, antidiarrheal drugs, antispasmodics, 5-aminosalicylic acid, topically active and systemically active corticosteroids, immunosuppressives, anti-TNF- α antibodies	Prescribe the drugs of these groups

4. Do the tasks for independent work during preparation for classes.

4.1. The list of key terms, parameters, characteristics:

Term	Definition
Gluten enteropathy	is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined <i>gluten intolerance</i> , diffuse atrophy of mucous membrane, and leads to generalized malabsorption.
EMA, anti-tTG	antiendomysial and anti-tissue transglutaminase antibodies that are associated with celiac disease
Irritable bowel syndrome	is a functional bowel disorder in which recurrent abdominal pain occurs at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits.
Ulcerative colitis	is a heterogeneous chronic inflammatory bowel disorder that may affect the colon and rectum.
Crohn's disease	is a heterogeneous inflammatory transmural, granulomatosis bowel disorder that may affect different sites of the gastrointestinal tract.
Toxic megacolon	is the clinical term for an acute toxic colitis with dilatation of the colon which occurs when inflammation spreads into the deeper layers of colon.

4.2. Theoretical questions for the lesson:

1. Give the definitions of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome.
2. Specify the risk factors of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome.
3. Name the pathophysiological mechanisms of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome.

4. Name the diagnostic criteria of celiac disease, non-specific colitis, Crohn's disease and irritable bowel syndrome.
5. What are the endoscopic characteristics of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome?
6. Modern classification of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome.
7. Specify the principles and features of celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome pharmacotherapy according to modern recommendations.
8. What lifestyle modifications should be recommended for patients with celiac disease, enteropathy, non-specific colitis, Crohn's disease and irritable bowel syndrome?

4.3. Practical tasks that are performed in class:

1. Etiology of celiac disease is:

- 1) bacteria
- 2) NSAIDs
- 3) genetic reason**
- 4) chemical damage

2. The only available treatment for celiac disease is:

- 1) a strict lifelong gluten-free diet**
- 2) corticosteroids
- 3) probiotics
- 4) antibiotics

3. Irritable bowel syndrome is a functional bowel disorder in which recurrent abdominal pain occurs:

- 1) at least 3 days per week during the past 1 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.
- 2) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months**
- 3) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 9 months before diagnosis and symptoms should be present during the last 3 months.
- 4) at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 1 year before diagnosis and symptoms should be present during the last 6 months.

4. Inflammatory bowel disease refers to:

- 1) enteritis
- 2) IBS
- 3) ulcerative colitis and Crohn's disease**
- 4) all mentioned

5. A cobblestone mucosa on lower endoscopy makes the doctor think about:

- 1) Non-specific ulcer colitis
- 2) Bacterial colitis
- 3) Crohn's disease**

4) IBS

6. Transmural inflammation is distinctive feature for:

1) Non-specific ulcer colitis

2) Bacterial colitis

3) Crohn's disease

4) IBS

7. 5-aminosalicylic acids include:

1) prednisolone

2) budesonide

3) mesalazine

4) azathioprine

8. Anti-TNF- α antibodies include:

1) budesonide

2) sulfasalazine

3) azathioprine

4) infliximab

9. Drug therapy of the acute flare of Crohn's Disease, mild activity:

1) "Salofalk" 3-4,5 g/day

2) "Budenofalk" 60 mg/day

3) Prednisolone 60 mg/day

4) Azathioprine 2-3 mg/kg/day

10. Topical forms in proctitis and left-sided ulcerative colitis can be treated with:

1) Budesonide per os 8-12 mg a day

2) Budesonide per rectum 2-4 mg a day

3) Antibiotics

4) Mesalazine per rectum 3-4 mg/kg/day

Topic Content

CELIAC DISEASE

Synonyms: Gluten-sensitive enteropathy, Gluten enteropathy, Non-tropical sprue.

Definition. **Gluten enteropathy** is a chronic progressive immune-mediated intestinal inflammatory disease that is characterized by genetically determined *gluten intolerance*, diffuse atrophy of mucous membrane, and leads to generalized malabsorption.

Classification. Classic form (active form with gastrointestinal symptoms), non-classic (when gastroenterological symptoms are minimal or absent, but there are extra intestinal symptoms) and asymptomatic.

Epidemiology. Most common in the Irish, British, and other northern European populations. Screening studies for the antiendomysial (EMA) and anti-tissue transglutaminase (anti-tTG) antibodies that are associated with celiac disease suggest a prevalence in white populations of about 1%. About 20% of patients diagnosed with irritable bowel syndrome or with microscopic (lymphocytic) colitis have celiac disease.

Etiology. Genetic disease, associated with HLA-DQ2 and HLA-DQ8. Autosomal-dominated. Disease manifests only after peroral gliadine consumption. High-risk groups for

celiac disease include first-degree relatives and individuals with type 1 diabetes mellitus, autoimmune thyroid disease, primary biliary cirrhosis, Turner's syndrome, or Down syndrome.

Pathogenesis. *Gluten* is a protein of gramineous plants (cereals) such as wheat, barley, rye. *Gliadin* is alcohol-soluble component of gluten, which can be produced from gluten by pathologic proteolysis and trigger intestinal inflammation in susceptible individuals. A 33-mer peptide that is a natural digestion product of α 2-gliadin may be important in the pathogenesis of celiac disease. This peptide resists terminal digestion by intestinal brush-border proteases and contains three previously identified antigenic epitopes. It also reacts with tissue transglutaminase and stimulates human leukocyte antigen (HLA)-DQ2-restricted intestinal T-cell clones from individuals with celiac disease.

One group of scientists considers that celiac disease is an immune mediated injury to enterocytes accompanied by serum antibodies to gliadin.

tTG (the autoantigen recognized by EMA) may enhance intestinal inflammation by deamidation of select glutamine residues in gliadin to negatively charged glutamic acid. In the deamidated form, most gliadin peptides have a higher binding affinity for DQ2 and are more potent stimulants of glutensensitized T cells. Villous atrophy may be caused by inflammation that is triggered by γ -interferon released from DQ2- or DQ8-restricted CD4 T cells in the lamina propria. Alternatively, intraepithelial lymphocytes may directly kill intestinal epithelial cells under the influence of IL-15 released from stressed enterocytes.

The other theory is genetically determined fermentative deficiency that leads to inability to ferment gluten to non-toxic fractions.

Clinical features. Celiac disease usually manifests early in life, at about 2 years of age (after wheat has been introduced into the diet), or later in the second to fourth decades of life, but it can occur at any age. It can be characterized by absent gastrointestinal symptoms and a wide spectrum of non-intestinal manifestations that can involve any organ of the body, and very frequently may be completely asymptomatic.

Classical symptoms are:

- watery diarrhea (is caused by many mechanisms, including a decreased surface area for water and electrolyte absorption, the osmotic effect of unabsorbed luminal nutrients, an increased surface area for chloride secretion (crypt hyperplasia), and the stimulation of intestinal fluid secretion by inflammatory mediators and unabsorbed fatty acids),
- abdominal distention,
- flatulence,
- fatigue,
- weight loss, growth retardation,
- malabsorption: iron, mineral and vitamin deficiency.

Adults with celiac disease often present with anemia or osteoporosis without diarrhea or other gastrointestinal symptoms. These individuals most likely have proximal disease that impairs iron, folate, and calcium absorption but an adequate surface area in the remaining intestine for absorption of other nutrients.

Other extraintestinal manifestations of celiac disease include rash (dermatitis herpetiformis), neurologic disorders (peripheral neuropathy, ataxia, epilepsy), psychiatric disorders (depression, paranoia), reproductive disorders (infertility, spontaneous abortion), short stature, dental enamel hypoplasia, chronic hepatitis, or cardiomyopathy.

Diagnosis. The diagnosis of celiac disease is made by characteristic changes found on a small intestinal biopsy specimen and improvement when a gluten-free diet is instituted.

An upper endoscopy with biopsy of the duodenum (beyond the duodenal bulb) or jejunum is performed to obtain multiple samples (four to eight) from the duodenum. It is the “gold standard” of celiac disease diagnosis. Mucosal flattening may be observed endoscopically as scalloped or reduced duodenal folds. Characteristic features found on intestinal biopsy include blunted or absent villi, crypt hyperplasia, increased intraepithelial lymphocytes, and infiltration of the lamina propria with plasma cells and lymphocytes. In some individuals, the only abnormal biopsy finding is increased intraepithelial lymphocytes. A hypoplastic mucosa indicates irreversible (end-stage) intestinal disease.

Serologic markers for celiac disease are useful in supporting the diagnosis or in screening, and in monitoring the response to a gluten free diet.

- ✓ EMA (anti-endomysial antibodies) immunoglobulin A (IgA) antibodies, detected by indirect immunofluorescence, are highly sensitive (90%) and specific (90 to 100%) for active celiac disease in skilled laboratory testing.
- ✓ The newer antideamidated gliadin (a biotinylated synthetic γ -gliadin peptide with glutamic acid substituted for glutamine) IgA and IgG antibody immunofluorometric assay has a sensitivity and specificity that approaches that of EMA.
- ✓ The anti-tTG (anti-transglutaminase antibodies) IgA antibody test, when obtained with a serum IgA level, is a cost-effective strategy for screening high-risk groups.
- ✓ **NB!** Patients with mild disease may have negative antibody studies. Anti-tTG, gliadin peptide, and EMA IgA antibodies tests are also negative in individuals with selective IgA deficiency. In these patients, anti-tTG or gliadin peptide IgG antibodies may be helpful in diagnosis.

HLA genotyping is useful to exclude the diagnosis of celiac disease in persons who lack the DQ2 or DQ8 gene.

- 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. Stool fat test may be ordered, to evaluate malabsorption.

Common complications. Iron deficiency, vitamin B12 and folate deficiency, osteoporosis, cancer, malnutrition, lactose intolerance, intestinal ulcers.

Differential diagnosis. Other causes of malabsorption are: immune conditions, hypersensitivity/allergy/eosinophilic gastroenteritis, infection, Whipple’s dis., tropical sprue, bacterial overgrowth, nutritional deficiencies, amyloidosis, lymphoma, lipid storage, short bowel. Diarrhea is common for infectious and non-infectious enteritis, IBS, lactase deficiency, diabetic enteropathy, different colitis.

Treatment. The only available treatment for celiac disease is a strict lifelong gluten-free diet in which the diseased person does not ingest any gluten. 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.

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

Deficiencies of vitamins and minerals should be replenished. 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.








Cobalamin deficiency is more common and usually corrects itself on a gluten-free diet. Symptomatic individuals require supplementation of vitamin B12.

IRRITABLE BOWEL SYNDROME

Definition. Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) in which recurrent abdominal pain occurs at least 1 day per week during the past 3 months and is associated with defecation or a change in bowel habits. Symptom onset should occur at least 6 months before diagnosis and symptoms should be present during the last 3 months.

Classification. IBS subtypes related to bowel habit abnormalities:

- 1) IBS with predominant constipation: More than 25% of bowel movements with Bristol stool form types 1 or 2 and less than 25% of bowel movements with Bristol stool form types 6 or 7. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually constipation (like type 1 or 2 in the picture of Bristol Stool Form Scale (BSFS)).
- 2) IBS with predominant diarrhea (IBS-D): more than 25% of bowel movements with Bristol stool form types 6 or 7 and less than 25% of bowel movements with Bristol stool form types 1 or 2. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually diarrhea (like type 6 or 7 in the picture of BSFS).
- 3) IBS with mixed bowel habits (IBS-M): more than 25% of bowel movements with Bristol stool form types 1 or 2 and more than 25% of bowel movements with Bristol stool form types 6 or 7. Alternative for clinical practice: Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea, using picture of BSFS).
- 4) IBS unclassified (IBS-U): Patients who meet diagnostic criteria for IBS but whose bowel habits cannot be accurately categorized into 1 of the 3 groups above should be categorized as having IBS unclassified.

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shape but lumpy
Type 3		Like a sausage but with cracks on surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid

Epidemiology. The world-wide prevalence of IBS is 11,2%. Prevalence rates are higher for women than for men; younger people are more likely to be affected than those older than age 50 years.

Etiological and risk factors. Factors that increase the risk of developing IBS include genetic, environmental, and psychosocial factors. Factors that trigger the onset or exacerbation of IBS symptoms include a prior gastroenteritis, food intolerances, chronic stress, diverticulitis, and surgery. IBS is associated with more psychiatric distress, sleep disturbance, “affective vulnerability,” and “over-adjustment to the environment.”

Pathogenesis. IBS is a multifactorial disorder with a complex pathophysiology. The resulting pathophysiologic mechanisms are variable and patient independent, and include altered gastrointestinal (GI) motility, visceral hyperalgesia, increased intestinal permeability, immune activation, altered microbiota, and disturbances in brain-gut function.

Diagnostic Criteria: recurrent abdominal pain, on average, at least 1 day per week in the last 3 months with symptom onset at least 6 months before diagnosis, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool.
3. Associated with a change in form (appearance) of stool.

Diagnosis. For the majority of patients, when diagnostic criteria for IBS are fulfilled and alarm features are absent, the need for diagnostic tests should be minimal.

The diagnosis of IBS should be made based on the following 4 key features: clinical history; physical examination; minimal laboratory tests; and, when clinically indicated, a colonoscopy or other appropriate tests.

Pain can be present anywhere throughout the abdomen, although it is more common in the lower abdomen. A history of disordered bowel habits (eg, constipation or diarrhea or both) should be identified, along with their temporal association with episodes of abdominal pain. Abdominal bloating is present in a majority of IBS patients; abdominal distention may be reported as well, although neither is required to make the diagnosis of IBS. Abnormal stool frequency (>3 bowel movements/day and <3 bowel movements/week) abnormal stool form (types 1-2 or 5-6 of the Bristol scale), excessive straining during defecation, defecatory urgency, feelings of incomplete evacuation, and mucus with bowel movements, although common in IBS, are not specific.

A physical examination should be performed in every patient evaluated for IBS. This reassures the patient and helps to exclude an organic etiology. An anorectal examination is mandatory to identify anorectal causes of bleeding, evaluate anorectal tone and squeeze pressure, and identify dyssynergic defecation.

The next step in the diagnosis of IBS is to perform limited laboratory studies, if not previously performed. A complete blood count (CBC) should be ordered, as the finding of anemia or an elevated white blood cell count warrants further investigation. A C-reactive protein or fecal calprotectin should be measured, as these tests are helpful in excluding IBD in patients with symptoms suggestive of nonconstipated IBS. If inflammatory markers are mildly elevated, but the probability of IBD is low, then tests should be remeasured before performing colonoscopy (if no other indication for colonoscopy exists). Inflammatory markers, including fecal calprotectin, may not be useful in patients with constipation symptoms. Routine thyroid tests are not indicated in all patients, but can be checked if clinically warranted. Serologic tests for celiac disease should be performed in patients with IBS-D and IBS-M who fail empiric therapy. Upper gastrointestinal endoscopy with duodenal biopsies should be performed if serologic tests for celiac disease are positive or if clinical suspicion is high; duodenal biopsies can also be used to identify tropical sprue, which can mimic IBS symptoms. Stool analysis

(bacteria, parasites, and ova) may be useful if diarrhea is the main symptom, especially in developing countries where infectious diarrhea is prevalent. A screening colonoscopy is indicated in patients 50 years and older in the absence of warning signs (45 years in African Americans), based on national recommendations. Colonoscopy is also indicated for the presence of alarm symptoms or signs, a family history of colorectal cancer and persistent diarrhea that has failed empiric therapy. Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis. Bile acid malabsorption may be the cause of persistent, watery diarrhea in some patients. If empiric therapy fails, scintigraphic evaluation (⁷⁵SeHCAT test) or postprandial serum C4 (7 α -hydroxy-4-cholesten-3-one) or fibroblast growth factor 19 are diagnostic options, although none are currently widely available. Breath tests to rule out carbohydrate malabsorption may be useful in some patients with IBS symptoms and persistent diarrhea.

Differential diagnosis. Inflammatory bowel disease, celiac disease, lactose and fructose intolerance, and microscopic colitis.

Treatment. Treatment should be based on symptom type and severity.

Lifestyle modifications that may improve IBS symptoms include exercise, stress reduction, attention to impaired sleep, dietary fiber supplementation remain a cornerstone of IBS management.

IBS-C therapy. Several peripherally acting agents are available to treat IBS-C symptoms. Lubiprostone (8 mg bid) is a lumenally acting prostone that selectively activates type 2 chloride channels. Linaclotide is a 14-amino acid peptide that acts as a guanylate cyclase C agonist (290 mg qd). Psyllium (up to 30 g/d in divided doses) can be recommended. Different probiotics may also benefit IBS patients.

IBS-D therapy. Loperamide (2-4 mg; when necessary, titrate up to 16 mg/d), a synthetic peripheral m-opioid receptor agonist that decreases colonic transit, and increases water and ion absorption, is commonly used to treat IBS-D patients. There is increasing evidence to support a role for bile acids (cholestyramine 9 g bid-tid; colestipol 2 g qd-bid; colestevlam 625 mg qd-bid) in the pathophysiology of IBS-D. The US Food and Drug Administration approved rifaximin (550 mg 3 times daily 14 days), a nonabsorbable antibiotic, for the treatment of IBS-D. Alosetron (0.51 mg bid), a highly selective 5-HT₃ antagonist, is effective at relieving pain and reducing stool frequency. Other 5-HT₃ antagonist can be useful too (Ondansetron 4-8 mg tid; Ramosetron 5 mg qd). Eluxadoline (100 mg bid) is a novel mixed m-receptor agonist/d-opioid receptor antagonist that has been developed as a treatment for patients with IBS-D. Small number of patients experienced sphincter of Oddi dysfunction or self-limited pancreatitis, so Eluxadoline should be used at the lower dose and with careful monitoring in patients who had a history of cholecystectomy or significant ethanol consumption.

Abdominal pain therapy. Smooth muscle antispasmodics (Dicyclomine 10-20 mg qd-qid; Otilonium 40-80 mg bid-tid; Mebeverine 135 mg tid) are used to treat abdominal pain and spasms in all IBS subtypes. Lubiprostone, Linaclotide, Alosetron, Peppermint oil (enteric-coated capsules, 250-750 mg, bid-tid) also have pain relieving activity.

Tricyclic antidepressant agents (Desipramine 25-100 mg qhs; amitriptyline 10-50 mg qhs) appear effective in treating IBS symptoms. Few data are available on the use of selective serotonin reuptake inhibitors in IBS (Paroxetine 10-40 mg qd; Sertraline 25-100 mg qd; Citalopram 10-40 mg qd). Psychological and behavioral treatments relate to helping patients control and reduce pain and discomfort and are seen as ancillary to or augmenting medical

treatments. Treatments include cognitive behavioral therapy, hypnosis, and various relaxation methods to reduce muscle tension and autonomic arousal believed to aggravate GI symptoms.

INFLAMMATORY BOWEL DISEASE

Definition. Inflammatory bowel disease refers to two chronic idiopathic inflammatory disorders, **ulcerative colitis and Crohn's disease**. These disorders are diagnosed by characteristic clinical, endoscopic, and histologic features.

Ulcerative colitis is a heterogeneous chronic inflammatory bowel disorder that may affect the colon and rectum.

Crohn's disease is a heterogeneous inflammatory transmural, granulomatosis bowel disorder that may affect different sites of the gastrointestinal tract.

Ulceration from Crohn's disease may be transmural and may occur anywhere in the gastrointestinal tract, most commonly in the distal ileum and proximal colon. The hallmark of ulcerative colitis is continuous ulceration starting in the rectum and limited to the colon. Approximately 10% of patients with inflammatory bowel disease have *indeterminant colitis*, a term used when Crohn's colitis cannot be differentiated from ulcerative colitis.

Epidemiology. Inflammatory bowel disease occurs worldwide, but the highest incidence is found in North America, the United Kingdom, and northern Europe. The incidence of Crohn's disease has risen slowly over time, although ulcerative colitis remains slightly more prevalent than Crohn's disease. Crohn's disease and ulcerative colitis may occur at any age. The peak incidence of Crohn's disease occurs between age 15 and 30 years of age, with a second peak in the seventh decade, more often in female patients. Ulcerative colitis also has a bimodal peak age distribution, with an initial peak between 20 and 40 years of age and second smaller peak beyond the seventh decade.

Etiological and risk factors. Crohn's disease and ulcerative colitis are polygenic disorders, for which family history is a risk factor. Although the trigger for inflammatory bowel disease is not known, three major pathways likely activate the disease: a genetic predisposition, immune dysregulation, and an environmental antigen.

The initial gene associated with Crohn's disease is NOD2/CARD15, located on chromosome 16 (16q12), and is expressed in intestinal epithelial Paneth cells, macrophages, and dendritic cells. Activation of NOD2 leads to activation of NF- κ B, which mediates transcription of numerous proinflammatory cytokines. A mutation in the leucine-rich domain of the NOD2 protein, which interacts with bacterial lipopolysaccharide, leads to failure in activation of NF- κ B and is associated with the development of Crohn's disease. Toll-like receptor-4 gene polymorphisms are associated with both Crohn's disease and ulcerative colitis. Polymorphisms of the interleukin-23 (IL-23) receptor gene are associated with ulcerative colitis and a varied risk of Crohn's disease. Human leukocyte antigen (HLA) class II polymorphisms, especially in HLA-DR molecules, may confer increased risk for ulcerative colitis and possibly Crohn's as well.

Cigarette smoking is associated with a worse prognosis in patients with Crohn's disease but an improved course in ulcerative colitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be associated with exacerbations of disease, although evidence for this is less definitive. Appendectomy has been suggested as protective against the development of ulcerative colitis. Diet does not clearly affect the course of inflammatory bowel disease.

Pathogenesis. A possible explanation is that the inability of the innate immune system to clear microbial antigens, combined with increased intestinal epithelial permeability to antigens,

eventually leads to an overactive adaptive immune response. Microbes likely play a part in the development of inflammatory bowel disease. Both Crohn's disease and ulcerative colitis are products of a dysregulated innate immune system that triggers T cells and a humoral response. TH17 cells, which are activated in Crohn's disease and ulcerative colitis, are stimulated by IL-23, which is produced by antigen-presenting cells. Variations in single-nucleotide polymorphisms of the gene encoding the receptor for IL-23 are associated with Crohn's disease.

Crohn's Disease. As a result of a dysregulated immune system, patients with Crohn's disease develop aphthous ulcers, which are superficial mucosal ulcers. As the disease progresses, the ulceration becomes deeper, transmural, and discrete; it may form a serpiginous pattern and may occur anywhere from the esophagus to the anus in a noncontinuous pattern. The most common location for ulceration is the ileocecal region. In some patients, chronic disease leads to the formation of fibrotic strictures, and approximately 30% of patients may develop fistulas. In early Crohn's disease, the histopathology is characterized by an acute inflammatory infiltrate in the lamina propria, with cryptitis, and crypt abscesses. Later in the disease process, the crypt architecture becomes distorted, with a lymphocytic infiltrate and a resulting branching and shortening of the crypts. Noncaseating granulomas, which are present in up to 15% of endoscopic biopsy specimens and as many as 70% of surgical specimens, are not unique to Crohn's disease but help confirm the diagnosis when other classic features are present. Surgical specimens also may show transmural intestinal wall inflammation and fat creeping on the serosal surface.

Ulcerative Colitis. In mild ulcerative colitis, the mucosa is granular, hyperemic, and edematous in appearance. As the disease becomes more severe, the mucosa ulcerates, and the ulcers may extend into the lamina propria. Ulcerative colitis starts in the rectum and may extend proximally in a continuous pattern, but it affects only the colon. Pseudopolyps may form owing to epithelial regeneration after recurrent acute attacks. With chronic disease, the colonic mucosa may lose the normal fold pattern, the colon may shorten, and the colon may appear narrowed. In early ulcerative colitis, the histopathology is characterized by epithelial necrosis, an acute inflammatory infiltrate in the lamina propria, cryptitis, and crypt abscesses. In chronic disease, a predominant lymphocytic infiltrate and distortion of crypt architecture are seen.

Classification. Periods: exacerbation, remission. All complaints should be mentioned in diagnosis.

Montreal classification (2005):

Crohn's Disease (CD).

- Subdivision of the group based on age
 - A1 - below or equal to 16 years;
 - A2 - 17 to 40 years;
 - A3 above 40.
- Subdivision of the group based on location
 - L1 - ileal,
 - L2 - colonic,
 - L3 - ileocolonic,
 - L4 - isolated upper disease.
- Subdivision of the group based on behavior
 - B1 - non-stricturing, non-penetrating,
 - B2 - stricturing,

- B3 - penetrating, p perianal disease modifier
- P – perianal disease.

Ulcerative Colitis (UC).

- Subdivision of the group based on extension

- E1 - Ulcerative proctitis, involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction);
- E2 - Left sided UC (distal UC), involvement limited to a proportion of the colorectum distal to the splenic flexure;
- E3 - Extensive UC (pancolitis), involvement extends proximal to the splenic flexure);

- Subdivision of the group based on severity

- S0 - Clinical remission, asymptomatic;
- S1 - Mild UC, passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR);
- S2 - Moderate UC, passage of more than four stools per day but with minimal signs of systemic toxicity;
- S3 - Severe UC, passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h).

NB! Additional classification of CD: inflammatory/fibrosenotic/with fistulas. By severity: severe (diarrhea more than 6 times a day, fever more than 37.5, pulse rate more than 90, anemia (Hb less than 75% of normal rate), BSR more than 50mm/h, intestinal complications); moderate (features between severe and mild); mild (diarrhea less than 4 times a day, normal temperature, normal pulse rate, anemia (Hb more than 100g/l), BSR less than 30 mm/h). Activity of process should be established by index of Best and CDAI index!

Additional classification of UC: acute/chronic. Activity should be evaluated by index of Mayo!

Clinical features.

Crohn's Disease. The terminal ileum is affected in about 70% of patients with Crohn's disease. Primary ileal disease occurs in 30% of patients, whereas ileocolonic disease occurs in 40%.

Symptoms may include abdominal pain, typically in the right lower quadrant, diarrhea, hematochezia, fatigue, palpated abdominal infiltrates, perianal fistulas and abscesses. With more severe disease, fever and weight loss may be present. Some patients may present with obstructive symptoms, such as abdominal pain, abdominal distention, and nausea. Only approximately 5% of patients develop Crohn's disease in the upper gastrointestinal tract, and esophageal Crohn's disease occurs in less than 2% of patients.

Fever may be present if there is an abscess.

Fistulas, which are internal tracks that can occur anywhere in the gastrointestinal tract and connect to various sites, occur in 20 to 40% of Crohn's patients. External fistulas, which present with symptoms of fluid discharge from the cutaneous opening, can be enterocutaneous, or perianal. Internal fistulas can be enteroenteric, rectovaginal, or enterocolonic.

Ulcerative Colitis. As with Crohn's disease, symptoms and signs of ulcerative colitis depend on the extent and severity of disease. At the time of diagnosis, 14 to 37% of patients have pancolitis, 36 to 41% have disease extending beyond the rectum, and 44 to 49% have proctosigmoiditis.

Symptoms include hematochezia, diarrhea, tenesmus, passage of mucus, urgency to defecate, and abdominal pain. In the setting of proctitis or proctosigmoiditis, patients may have constipation with difficulty defecating. With more extensive and severe colonic involvement, patients may also have weight loss and fever. Patients may also have nausea and vomiting because of abdominal pain, fatigue because of anemia, and peripheral edema because of hypoalbuminemia.

Physical Examination. Oral ulcers may be present in Crohn's disease. The location of abdominal tenderness usually reflects the location of intestinal involvement. In Crohn's disease, abdominal tenderness is classically in the right lower quadrant and may include fullness or a mass depending on the severity of inflammation. Peritoneal signs may occur when penetrating Crohn's disease causes intestinal perforation. Rectal examination may reveal skin tags, hemorrhoids, fissure, and fistulas.

Diagnosis. When diarrhea is the predominant symptom, the initial evaluation should include a thorough medical history, testing for infectious colitis, and screening for endocrine-metabolic disorders such as hyperthyroidism and hypocalcemia. Infections with organisms such as *Shigella*, *Amoeba*, *Giardia*, *Escherichia coli*, and *Campylobacter* can be accompanied by bloody diarrhea, abdominal cramps, and an endoscopic picture identical to ulcerative colitis. Stool studies are needed to diagnose or exclude these infections. If hematochezia or abdominal pain are the predominant symptom, the differential diagnosis is broad.

Endoscopic Evaluation. In a patient with symptoms suggestive of inflammatory bowel disease and no evidence for an infection to explain their symptoms, endoscopic evaluation is essential. Colonoscopy is the initial endoscopic test for patients who present with lower gastrointestinal symptoms such as diarrhea and hematochezia, except in the presence of acute severe peritoneal symptoms. Small bowel imaging (such as small bowel follow-through or computed tomography [CT] enterography) may also be needed to determine whether there is small bowel disease or to determine the distribution of disease. Capsule endoscopy is useful if all other endoscopic and radiologic testing is nondiagnostic, but Crohn's disease of the small bowel is still suspected. Findings on capsule endoscopy should be followed by endoscopy to obtain biopsies. Capsule endoscopy should not be performed if Crohn's disease is complicated by a known small bowel stricture.

Crohn's Disease. Early endoscopic findings in Crohn's disease include superficial small mucosal ulcers, also called aphthous ulcers. As the severity of Crohn's disease progresses, the ulceration becomes deeper and may become round, linear, or serpiginous. A cobblestone appearance of the mucosa is caused by intersecting longitudinal and transverse ulcers, with "stone" areas representing normal mucosa. Areas of ulceration, which are typically interspersed with normal "skip" areas, may occur anywhere from the esophagus to anus but are most common in the ileocecal region. Isolated colonic disease occurs in 25% of patients, and 60% will have rectal involvement, thereby making it at times difficult to differentiate from ulcerative colitis. The diagnosis of inflammatory bowel disease is contingent on accurate histopathology, so biopsy of the affected area is key. Findings of an inflammatory infiltrate in the lamina propria and distortion of the crypt architecture support the diagnosis. The diagnosis of Crohn's disease may be made by histopathology alone if noncaseating granulomas are seen, but granulomas are rarely found on endoscopic biopsies. The diagnosis of Crohn's disease is usually based on a combination of information gleaned from histopathology, colonoscopy, and small bowel imaging.

A skipped pattern of ulceration, ulceration in the small bowel or upper gastrointestinal tract or the presence of fistulas supports the diagnosis of Crohn's disease. Colonic and small bowel ulceration occur in several other disorders, including infections that may not be detected by routine stool studies (such as enterohemorrhagic *Escherichia coli*), vascular disorders, immune-related enterocolitis, neoplasia, diverticulitis, radiation, and medications such as NSAIDs.

Ulcerative Colitis. The diagnosis of ulcerative colitis is based on endoscopic findings and histopathology. Early in the disease process, patients develop diffuse mucosal erythema with loss of the normal mucosal vascular pattern. In mild disease, the mucosa may have a granular and edematous appearance. As the disease becomes more severe, the mucosa becomes more friable, bleeds easily when the mucosa is touched, and may eventually ulcerate. Endoscopic findings, which start in the rectum and may extend proximally in a continuous pattern, affect only the colon. Pseudopolyps may form owing to epithelial regeneration after recurrent attacks in patients with long-standing disease. With chronic disease, the colonic mucosa may lose its normal fold pattern, and the colon may shorten and appear narrowed. Features such as crypt distortion, continuous mucosal inflammation starting from the rectum, absence of granulomas, and absence of small bowel disease are all consistent with ulcerative colitis. Early in the disease process, chronic inflammatory findings, such as crypt distortion, may not be present, and the diagnosis may be more difficult to confirm.

Radiologic imaging is vital and should almost always be obtained when inflammatory bowel disease, particularly Crohn's disease, is suspected. Barium studies such as an upper gastrointestinal series, small bowel followthrough, and barium enema are usually necessary to diagnose fistulas and strictures in Crohn's disease. If Crohn's disease is suspected by colonoscopic examination, a small bowel follow-through is generally obtained to assess the extent, severity, and type of disease (strictures and fistulas) in the small intestine.

CT enterography and magnetic resonance imaging (MRI) enterography are alternatives to a small bowel follow-through. CT enterography may be preferred for the detection of abdominal abscesses, whereas MRI may be preferred for the detection of perineal abscesses and strictures.

Laboratory Findings. Anemia may result from chronic disease, blood loss or nutritional deficiencies of iron, folate, or vitamin B12. A modestly elevated leukocyte count is indicative of active disease, but a marked elevation suggests an abscess or another suppurative complication. The erythrocyte sedimentation rate and C-reactive protein are nonspecific serum inflammatory markers that are sometimes used to monitor the activity of disease. Hypoalbuminemia is an indication of malnutrition.

Serologic markers are supportive but may not be used independently to diagnose inflammatory bowel disease.

Complications.

	CROHN'S DISEASE	ULCERATIVE COLITIS
Ocular disorders (uveitis, episcleritis)	+	+
Arthropathy	+	+
Oral ulcers	+	-
Skin disorders (pyoderma gangrenosum, erythema)	+	+

nodosum)		
Nephrolithiasis	+	+
Primary sclerosing cholangitis	+	+
Bone disorders (osteoporosis, osteomalacia)	+	-
Thromboembolic disease	+	+
B12 deficiency	+	-
Toxic megacolon	More often	Rarely
Cancer	Less often	More often
Bleeding	+	+
Fistula	+	-
Stricture	+	-
Perianal disease (fissure, skin tags)	+	-

Differential diagnosis.

	CROHN'S DISEASE	ULCERATIVE COLITIS
Peak age of onset (years of age)	15-30, 2nd peak in the 7th decade	20-40, 2nd smaller peak beyond the 7th decade
Potential sites of gastrointestinal involvement	Esophagus to anus	colon
Skip areas	+	-
Transmural inflammation	+	-
Ulcers	Fissuring	Superficial
Wall	Thick	Thin
Dilatation	-	+
Type of ulceration	Usually discrete	Continuous
Fistula	+	-
Stricture	+	-
Perianal disease (fissure, skin tags)	+	-
Granulomas	+	-
Fibrosis	Marked	Minimal

Treatment. As the etiology of inflammatory bowel disease has not yet been clarified, casual therapy doesn't exist. Consequently, therapy is aimed to reduce or eliminate symptoms during the acute flare or exacerbation as well as to maintain remission. Surgery is employed in life-threatening situations and fistulas and abscesses.

The principal classes of drug used in both ulcerative colitis and Crohn's disease are: preparations which release (mesalazine) or split off (sulfasalazine) 5-aminosalicylic acid; topically active (budesonide) and systemically active corticosteroids (prednisolone, 6-methylprednisolone); immunosuppressives (azathioprine, methotrexate). In recent years, anti-TNF- α antibodies (infliximab, adalimumab, certolizumab and natalizumab) have been introduced

in the therapy. They can be successful in corticosteroid-refractory disease. Supportive medical therapy, such as antibiotics, antidiarrheal and antispasmodic medications, may also be used.

Crohn's Disease.

Drug therapy of the acute flare (CDAI>150)

- mild to moderate activity: mesalazine “Salofalk” 3-4,5 g/day and/or budesonide “Budenofalk” 9mg/day. Involvement of rectum and distal colon allows to prescribe mesalazine and corticosteroids topically (suppositories or –enemas);
- moderate to severe activity: prednisolone 60 mg/day 1 week, 40 mg/day 2nd week, 30 mg/day 3rd week, 25 mg/day 4th week, 20mg/day 5th week, 15 mg/day 6th week, 10mg/day 7th-26th week, gradual reduction after week 27.

Complicated courses of disease.

- Azathioprine 2-3 mg/kg/day;
- Antibiotics, e.g. ciprofloxacin;
- Metronidazole 500-1000 mg/day (7-10 days);
- Methotrexat;
- Anti-TNF- α antibodies. Infliximab (intravenous. Induction: 5 mg/kg IV weeks 0, 2, 6. Maintenance: 5 mg/kg IV q 8 wk 5 mg/kg);
- Mercaptopurini (1,5 mg/kg/day),

Therapy for remission.

- relaps prophylaxis with mesalazine 1,5-3 g/day;
- Azathioprine in patients with frequent flares;
- light full diet;
- Colestyramine with chologenic diarrhea;
- Antidiarrheals (codeine, lomotil, loperamide);
- stop smoking.

Ulcerative Colitis.

Drug therapy of the acute flare

- mild activity: mesalazine 3x0,5 g/day (granules or tablets) or 1x3 g/day (granules) or olsalazine 3-4x0,5 g/day or sulfasalazine 3-4x1 g/day. Topical forms in proctitis and left-sided colitis can be administered. For example, Budesonide “Budenofalk” per rectum 2-4 mg a day.
- moderate to severe activity: therapy like mild activity plus prednisolone initially 40-60 mg/day orally with weekly reduction of the daily dose by 10mg, later 5mg depending on clinical activity.
- severe activity: prednisolone dose initially 100mg or higher, divided into morning and evening dose, possibly intravenous.

Complicated courses of disease.

- Azathioprine 2-3 mg/kg/day;
- consideration of “curative” surgery.

Corticosteroids because their risks outweigh their benefits are not used long-term in treatment. Immunosuppressive medications such as azathioprine and biological agents such as infliximab and adalimumab are given only if people cannot achieve remission with 5-ASA and corticosteroids.

Therapy for remission.

- relaps prophylaxis with mesalazine 1-3 g/day orally or olsalazine 2x0,5 g/day or sulfasalazine 2x1 g/day (suppositories and enemas also effective with proctitis/left-sided colitis);
- light full diet.

Materials for self-control:**Situation tasks:**

1. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4°C, malnutrition, skin is pale and dry. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most probable diagnosis? What additional obligatory test is necessary?
2. A 35 y. o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is soft, a little bit painful in the left iliac region. Blood and urine are normal. What is the probable diagnosis? What treatment can be prescribed to improve quality of life of the patient?

Tests:

1. A 20-year-old woman has a 3-4 months history of bloody diarrhea; stool examination proved negative for ova and parasites; stool cultures negative for clostridium, campylobacter and yersinia; normal small bowel series; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Choose the most probable diagnosis:
 - A. Gastroenteritis
 - B. Ulcerative colitis
 - C. Carcinoid syndrome
 - D. Zollinger-Ellison syndrome
 - E. Granulomatous colitis
2. Patient D., 48 years old, complains of pain in the lateral part of abdomen, that diminishes after defecation with gases, alternation of diarrhea and constipations. In the anamnesis: dysentery 2 years ago. Palpation of abdomen is painful, with abdominal murmur of colon. What method of examination is the most informative to make up the diagnosis?
 - A. Rectoromanoscopy
 - B. Rectal finger exam
 - C. Colonoscopy
 - D. Coprocytogram in dynamics
 - E. US examination of abdominal cavity
3. A 2 y.o. boy was admitted to the hospital with weight loss, unstable discharges, anorexia, following the semolina's introduction (since 5 months). The child is adynamic, flabby, with pale dry skin, subcutaneous layer is emaciated. Distended and tensed abdomen, tympanitis on percussion of the upper part of the abdomen, splashing sounds, feces are foamy, light, foul. On coprocytogram: a lot of neutral fat. What is the cause of the disease?
 - A. Celiakia (celiac disease)

- B. Mucoviscidosis (cystic fibrosis)
- C. Intestinal dysbacteriosis
- D. Chronic enteritis
- E. Disaccharidase insufficiency

4. A 43 y.o. male complains of stomach pain, which relieves after defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?

- A. Irritable bowel syndrome
- B. Spastic colitis
- C. Colitis with hypertonic type dyskinesia
- D. Chronic enterocolitis, exacerbation phase
- E. Atonic colitis

5. A 24 y.o. male complains of abdominal spastic pain, which occurs after emotional stress, relieves with defecation, and is accompanied by abdominal winds, constipation and the feeling of incomplete evacuation. These symptoms have lasted for over 3 months. No changes in laboratory tests, GDS and colonoscopy. What is the most proper treatment of constipation?

- A. Antidepressants
- B. Antibiotics
- C. Lactulose
- D. Loperamide
- E. Fluocetine

6. A 33 y.o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid, without mucous and blood. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is soft, a little bit painful in the left iliac region. Blood and urine analyses are normal. What is the possible and the most proper treatment of diarrhea in this case?

- A. Loperamide
- B. Probiotics
- C. Antibiotics
- D. Lactulose
- E. Polyvitamins

7. Teenager, 14 years old, has complaints on diarrhea, weakness, weight loss. The condition worsened after taking of plenty of flour products. Such phenomena are observed from babyhood. Objectively: general state is satisfactory, body weight is reduced, physical development is delayed. The reason of the disease is:

- A. Deficit of lactase
- B. Invasion with intestinal worms
- C. Chronic pancreatitis, syndrome of maldigestion
- D. Dysbacteriosis of intestine
- E. Gluten enteropathy

8. A 55-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 7 kg weight loss over the previous month. Objectively: body temperature - 37, 9oC, malnutrition. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. What is the most likely treatment?

- A. Sulfasalazine
- B. Clarithromycin
- C. Probiotics
- D. Kreon
- E. Amoxicillin

9. A 33-year-old woman has a 3-4 months history of bloody diarrhoea; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Non-specific ulcer colitis was detected. Select drug group of basic therapy:

- A. Antibiotics
- B. Aminosalicylates
- C. Probiotics
- D. Biologic agents
- E. Immunomodulators

10. A 70 years old male patient complains of permanent dull pain in the mesogastral region, constipations. What obligatory examine method should be performed?

- A. Scintigraphy
- B. ERCPG
- C. Colonoscopy
- D. Liver biopsy
- E. X-ray of abdominal cavity

Correct answers for the situation tasks:

- 1. Non-specific ulcerative colitis. Colonoscopy.
- 2. Irritable bowels syndrome with predominant diarrhea. Loperamide 2 mg per os.

The answers for the tests:

1-B, 2-C, 3-A, 4-A, 5-C, 6-A, 7-E, 8-A, 9-B, 10-C.

Recommended literature:

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