Federal State Budgetary Educational Institution of Higher Education "North Ossetian State Medical Academy" of the Ministry of Health of the Russian Federation

INFLAMMATORY DISEASES OF THE INTESTINE

(a methodological manual for students of the V-VI courses of the Faculty of Medicine, residents and graduate students)

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The manual considers the etiology and pathogenesis of inflammatory bowel diseases from modern positions. The manual reflects the main achievements and world experience in the study of intestinal diseases over the past decades. Particular attention is paid to the aspects of timely correct diagnosis, issues of adequate drug therapy for inflammatory bowel diseases are highlighted.

CONTENT:

INTRODUCTION

Inflammatory bowel disease (IBD) - a general term that refers to a group of chronic inflammatory diseases of unknown etiology, in which the gastrointestinal tract is involved in the pathological process. Depending on the prevalence of the inflammatory process in the small or large intestine, various complications are possible, for example, the formation of stricture due to the development of tissue fibrosis, perforation and cancer. In addition, non-gastrointestinal organs, including the eyes, skin, joints, and liver, may be affected.

There are many predisposing factors that contribute to the development of IBD. They can be exogenous, such as smoking, diet, medication, geographic area, social status, stress, etc. Exogenous factors include genes, gut microbiota, gut wall permeability, and immune system status.

Currently, it is generally accepted to consider the following as the main components of the pathogenesis of IBD: environmental influences, genetic predisposition, intestinal microbiota, and the state of the immune system. These factors interact through mechanisms that are not fully understood, leading to the production of a large number of pro-inflammatory molecules such as cytokines, antibodies, enzymes, neuropeptides, reactive metabolites, etc.

The hypothesis that genotype is associated with the development of IBD has been put forward for a long time and was based on the observation that the likelihood of IBD is higher in relatives who have already developed these diseases. Despite this, real progress in the genetics of IBD has been relatively recent. In 2001, the first gene (NOD2) associated with Crohn's disease was described, and 5 years later, the second gene, the IL-23 cytokine receptor, was described. By 2011, about 100 genes associated with Crohn's disease and ulcerative colitis have been described, and more will be described in the next decade.

Of the 100 gene variants associated with IBD, some are associated only with ulcerative colitis, others only with Crohn's disease, and a number of genes are associated with both ulcerative colitis and Crohn's disease. This suggests the existence of both unique and common genetic abnormalities characteristic of Crohn's disease and ulcerative colitis.

Most of the genetic variations associated with IBD are associated with genes that mediate the immune/inflammatory response, bacterial recognition, processing, and barrier function of the intestinal epithelium. Some variations are found only in Crohn's disease, others only in ulcerative colitis, and some are found in both Crohn's disease and ulcerative colitis.

All autoimmune diseases, including IBD, result from a combination of environmental and genetic factors. However, the contribution of these two components is significantly different. In some diseases, such as psoriasis, the main role is played by the genetic factor, and the external factor is less important; in other diseases, such as multiple sclerosis, the genetic factor is less important, but external factors play a major role. In IBD, both environmental and genetic factors appear to play an equally important role.

The incidence of IBD worldwide is inversely proportional to the prevalence of infectious diarrhea. This clearly proves that improved sanitation, leading to the eradication of infections, also contributes to the onset of IBD.

Over the past 50 years, the incidence of infectious diseases has decreased and the incidence of autoimmune/chronic inflammatory diseases has increased. To explain the decline in the prevalence of infectious diseases and the rise in chronic inflammatory and autoimmune diseases over the past 50 years, the "hygiene hypothesis" has been proposed. According to the hygiene hypothesis, excessive hygiene (“clean” lifestyle) reduces the load on the immune system, and it loses its ability to resist new threats, producing long-lasting, but ineffective, inflammatory responses mediated by type 2 T-helpers. In contrast, exposure to infection and other factors early in life “trains” the immune system to respond with type 1 helper T cells.

Numerous external factors may predispose to IBD, including smoking, dietary habits, geographic and social status, lifestyle with multiple stressful situations, bacterial composition of the body, and especially the intestines, intestinal permeability, and appendectomy at an early age. External factors weaken the action of genes that regulate the immune response, or may directly affect the immune response. Depending on how long we are exposed to certain factors, the intestines can develop normal (physiological) inflammation or pathological inflammation, which is observed in IBD.

A modern diet rich in fats and proteins, but poor in carbohydrates, may be involved in the pathogenesis of IBD, but objective evidence supporting this theory has only recently appeared. Western countries tend to eat high-fat, high-protein foods, which can contribute to the development of IBD, while in less developed, carbohydrate-intensive countries, IBD is less common.

Health depends on many interactions between human cells and bacteria. The human body contains 10 times more bacterial cells than its own cells, and bacteria have 100 times more genes than humans. This means that the number and type of bacteria are the determining factors for whether the human body is healthy or not. Thus, mutually beneficial interactions between human and bacterial cells are necessary to be healthy.

Obesity is accompanied by changes in the gut microbiota and is a pre-inflammation condition. Antibiotics cause significant changes in both the composition of mucus and intestinal microflora. Antibiotic use may produce less mucus in the gut, abnormal composition of the mucosal layer, altered composition of the gut microbiota, increased permeability of the intestinal wall, and increased absorption of intestinal lumen contents. The combination of these pathological changes may predispose to the onset of IBD.

Recent evidence has shown that a certain type of gut bacteria, the so-called "segmented filamentous bacteria", induce the production of pro-inflammatory Th 17 cells in the gut. This observation suggests that the gut flora can directly influence the production of immune cells that cause inflammation in the gut.

In addition to segmented filamentous bacteria, there is evidence that different types of bacteria induce the production of different types of T cells in the gut; this is very important because it indicates that the composition of intestinal bacteria can control the development of a particular cell type in a particular place; some bacteria favor the generation of pro-inflammatory T cells, while others may promote the generation of pro-inflammatory cells. Therefore, the balance of bacteria may determine the balance of the gut immune system. Different types of gut bacteria can induce a balanced immune response (immune balance) or an unbalanced response, leading to the pro-inflammatory state characteristic of IBD (immune imbalance).

The two main forms of IBD, Crohn's disease and ulcerative colitis, are characterized by distinct immune profiles. Crohn's disease is a disease in which the immune profile is characterized by a predominance of Th1 cells that produce the cytokine interferon gamma and IL-17. Ulcerative colitis is a disease in which the immune profile is dominated by Th2 cells that produce the cytokines IL-5 and IL-13, but to a lesser extent IL-17. This difference is important because it indicates that Crohn's disease and ulcerative colitis are different diseases with different mechanisms of inflammation in the gut.

There is evidence that innate immunity is deficient in Crohn's disease. It has been suggested that impaired innate immune response in Crohn's disease may be due to impaired macrophage function. According to some researchers, macrophages do not produce enough cytokines, the supply of neutrophils is reduced, and the elimination of bacteria is impaired, at the same time it causes the formation of granulomas.

Inflammasomes are complex molecular structures that mediate inflammation. They are of particular importance in IBD, as evidence from experimental models indicates that inflammasomes are activated in IBD, and blocking them may be a new approach in the treatment of these diseases.

A new concept that contributes to the pathogenesis of many diseases is the concept of "exposome". The exposome is the totality of all external factors affecting the body during life. Because the body responds

to all external factors, their type, amount, and timing of exposure can be critical in initiating or maintaining IBD.

The body's response to exposomes is regulated by the "epigenome". The epigenome is a collection of DNA modulations induced by chromatin-modifying enzymes that determine the final expression of genes. This is critical because epigenetic changes serve as major regulators of the immune response, and these changes are sensitive to interventions that can help reduce inflammation.

In IBD, an early phase is detected, which is triggered by genes, microbes, external factors and the immune response, and the combination of these factors stimulate the onset of the inflammatory process in the intestine; then comes the late phase with more secondary factors such as the epigenome, damage-associated molecular patterns (DAMPs), neuropeptides, hormones, cell differentiation, etc. All of these factors contribute to the prolongation and maintenance of inflammation, which becomes chronic.

One of the reasons why IBD is so complex is that all the major components of IBD pathogenesis interact closely and modulate each other. External factors weaken the influence of genes, microbes and immune cells; genes control the immune response and indirectly influence the behavior of microorganisms; microorganisms have a modulating effect on the immune response and external factors in relation to the intestine; the immune response controls the type and number of bacteria and can also indirectly influence gene function.

IBD is a complex disease because all biological events are extremely numerous and complex in nature. This applies not only to inflammatory bowel disease, but to all autoimmune and immune-mediated disorders.

Currently, the basic concept of the pathogenesis of IBD is as follows:

• IBD is a range of diseases with different pathogenetic mechanisms, including changes in environmental factors, genetic predisposition, intestinal microflora and mucosal immune response;

• loss of immune tolerance to autologous intestinal flora is considered a central event in the pathogenesis of IBD, and changes in the microflora and immune response to it, apparently, is the main point for the control of inflammation;

• it is currently necessary to create a genetic, microbiological and immune portrait that would determine each form of IBD and their stage;

• The ultimate goal is to transform the complexity of IBD pathogenesis into an individualized picture of the disease.

NON-SPECIFIC ULCERATIVE COLITIS (NUC) is an inflammatory disease of unknown etiology that affects the mucous membrane of the rectum and colon with ulcerative-destructive changes, which has a chronic relapsing course, often accompanied by the development of life-threatening complications. The term "ulcerative colitis" was first introduced into the literature by Wilks and Moxon in 1859. It should be emphasized that ulcerative lesions of the colon mucosa are not always the basis for the diagnosis of ulcerative colitis.

Etiology and pathogenesis. IBD is still an idiopathic disease. The main pathogenic factors are:

• intestinal dysbacteriosis - a violation of the normal composition of the microflora in the large intestine, which has a local toxic and allergenic effect, and also contributes to the development of non-immune inflammation of the colon;

• violation of neurohumoral regulation of bowel function due to dysfunction of the autonomic and gastrointestinal endocrine system;

• a significant increase in the permeability of the colon mucosa for protein molecules and bacterial antigens;

• damage to the intestinal wall and the formation of autoantigens, followed by the formation of autoantibodies to the intestinal wall. Antigens of some strains of E. coli induce the synthesis of antibodies to colon tissue;

• the formation of immune complexes localized in the wall of the colon, with the development of immune inflammation in it;

• development of extraintestinal manifestations of the disease due to multifaceted autoimmune pathology.

Pathomorphology. The pathological process in ulcerative colitis begins in the rectum and spreads in the proximal direction, capturing the overlying layers of the intestinal wall, spreading to the entire colon and, in some cases, affecting the terminal ileum. There are no histological signs strictly specific for UC, most of them are detected in other intestinal infections caused by Shigella, Salmonella, Yersinia and HIV. The most typical histological sign of the disease is crypt abscesses.

Even in the period of remission, manifestations of inflammatory infiltration persist in the intestinal mucosa. Inflammation can be limited to the rectum (proctitis), rectum and sigmoid (proctosigmoiditis), spread to the entire left colon (left-sided colitis), or affect the entire colon (total colitis).

In the initial stage of the disease, ulcerative defects may not be. As the pathological process progresses, ulcers of various sizes and irregular shapes form in the mucosa. Ulcerative colitis is characterized by narrow long ulcers located along the muscle bands in two to three parallel rows. On examination, the bottom of small ulcers is clean, in large ones it is covered with a grayish coating of fibrin.

In severe cases, the mucous membrane is destroyed throughout, and the surface of the affected area of the intestine takes the form of an extensive bleeding ulcer. Extensive ulceration can penetrate into the muscular layer and the serosa. With a long chronic course of the disease, pseudopolyps are formed against the background of ulcerative defects.

In the period of remission, the mucous membrane is restored, but its atrophy, deformation of the crypts, and uneven thickening most often persist. Histological signs of UC provide the key to understanding the clinical manifestations of the disease. Thus, diarrhea occurs when the mucous membrane is damaged over a considerable extent and is unable to absorb water and electrolytes. Bleeding is the result of ulceration of the mucosa, overflow of the vessels of the colon mucosa with blood and the development of loose granulation tissue, well supplied with blood vessels. Due to the fact that in most cases the pathological process is limited to the mucous membrane and submucosal layer, fistulas, intestinal obstruction and perforations rarely occur.

To assess the prognosis of ulcerative colitis, it is important to characterize dysplastic changes in the intestinal mucosa:

1. With severe dysplasia.

2. With mild or moderate dysplasia.

3. Unclear about dysplasia.

4. Without dysplasia.

Clinic. The main clinical symptoms of UC include diarrhea and/or false urgency with blood, tenesmus and urgency with blood, tenesmus and urge to defecate, and nocturnal defecation. In a severe attack of UC, general symptoms may appear, such as weight loss, general weakness, anorexia, and fever.

Table 1. The main symptoms of ulcerative colitis

Possible symptoms of the disease in history	**Typical clinical symptoms at the time of examination**

• Episodes of diarrhea • Blood in the stool • Tenesmus • Extraintestinal symptoms (damage to the skin, mucous membranes, joints, eyes, etc.)	• Diarrhea • Blood in stool • Night defecation (more often with a pronounced activity of the process) • Tenesmus (often with proctitis and proctosigmoiditis) • Weight loss • Anemia • Extraintestinal symptoms

For UC, abdominal pain is moderate (spastic in nature), more often before a stool; with proctitis and proctosigmoiditis, diarrhea is absent, and frequent false urges can be combined with constipation or shaped stools.

A significant proportion of patients may have extraintestinal manifestations of the disease.

Autoimmune manifestations associated with the activity of the inflammatory process appear along with the main intestinal symptoms of exacerbation and disappear along with them during treatment. Autoimmune manifestations that are not associated with the activity of the process tend to progress regardless of the phase of the underlying disease (exacerbation or remission) and often determine a negative prognosis of the disease.

Intestinal complications of UC include intestinal bleeding, toxic dilatation and perforation of the colon, and colorectal cancer.

Table 2. Extraintestinal (systemic) manifestations

ulcerative colitis

Autoimmune associated with the activity of the disease:	**Autoimmune, unrelated disease activity:**	**Caused by prolonged inflammation and metabolic disorders.**
Arthropathy (arthralgia, arthritis) Skin lesions (erythema nodosum, pyoderma gangrenosum) Mucosal lesions (aphthous stomatitis) Eye involvement (uveitis, iritis, iridocyclitis, episcleritis)	Ankylosing spondylitis (sacroiliitis) Primary sclerosing cholangitis Osteoporosis, osteomalacia Psoriasis	Cholelithiasis Hepatic steatosis, steatohepatitis Thrombosis of peripheral veins, thromboembolism of the pulmonary artery Amyloidosis

The disease can begin suddenly in the form of moderate, severe and fulminant forms. In severe form, the disease occurs with severe profuse diarrhea, with heavy bleeding and subsequent development of toxic dilatation of the colon. The manifestation of the disease can be manifested by such extraintestinal lesions as arthritis, iritis, cholangitis, hepatitis. The course of the inflammatory process, considered more often as chronic, in some cases takes on an acute character. The extent of the colonic lesion may also vary.

UC is characterized by three leading symptoms: red blood during bowel movements, bowel dysfunction, and abdominal pain.

Isolation of blood during bowel movements is the first sign of the disease. Blood can be excreted with feces, mixed with mucus and pus, or in its pure form. With distal colitis, it is found mainly on the surface of the feces. When the proximal colon is affected, blood is mixed with feces. Its quantity varies widely - from streaks on the surface of feces to 300 ml or more with each act of defecation. In this case, a decrease in blood pressure is possible up to the development of collapse and hemorrhagic shock.

Impaired bowel function is the second important UC syndrome. Most patients complain of multiple unstable stools, which is the result of extensive damage to the mucous membrane and a decrease in the absorption of water and salts. Diarrhea has a different intensity - from loose stools with a frequency of 3-4 times a day to almost constant watery non-fecal discharge. Diarrhea is typical at night, as well as false urges to the bottom (tenesmus). At the same time, diarrhea itself is not a reliable criterion for the severity of the process. The severity of diarrhea in combination with the presence of red blood in the stool matters. In some patients, constipation is observed, which, as a rule, accompanies proctitis and sigmoiditis.

Mild UC is characterized by a satisfactory condition of patients. Pain in the abdomen is moderate and short-term. The chair is decorated, speeded up, up to 2-3 times a day. Blood and mucus are periodically found in the feces. In patients with UC, limited to the rectosigmoid colon, systemic manifestations such as fever, weight loss, and intoxication are very rarely noted. The clinical course is recurrent. The effect of treatment with salazopreparations is satisfactory. Relapses occur no more than 2 times a year. Remissions can be long (more than 2-3 years).

The moderate course of the disease is diagnosed if the patient has diarrhea. At the same time, the chair is frequent (up to 6-8 times a day), in each portion an admixture of blood and mucus is visible. Cramping pains in the abdomen have a greater intensity than with a mild form. There is an intermittent fever with a rise in body temperature up to 38C. Worried about intense general weakness. There may also be extraintestinal manifestations of the disease (arthritis, uveitis, erythema nodosum). The clinical course of NUC in the moderate form is recurrent or continuously recurrent, the effect of salazopreparations is unstable, hormones are prescribed during the exacerbation period.

Classification of ulcerative colitis.

According to the nature of the flow, there are:

1. Acute course (less than 6 months from the onset of the disease).

2. Chronic continuous course (absence of more than 6 months

periods of remission against the background of adequate therapy).

3. Chronic relapsing course (the presence of more than 6-month periods of remission).

Table 3. Montreal classification of UC by length

Proctitis	**The lesion is limited to the rectum**
Left-sided colitis	The lesion extends to the left flexure of the colon (including proctosigmoiditis)
total colitis	The lesion extends proximal to the left flexure of the colon (including subtotal colitis as well as total UC with retrograde ileitis)

The severity of the disease is generally determined by: the severity of the current attack, the presence of extraintestinal manifestations and complications, refractoriness to treatment, in particular, the development of hormonal dependence and resistance.

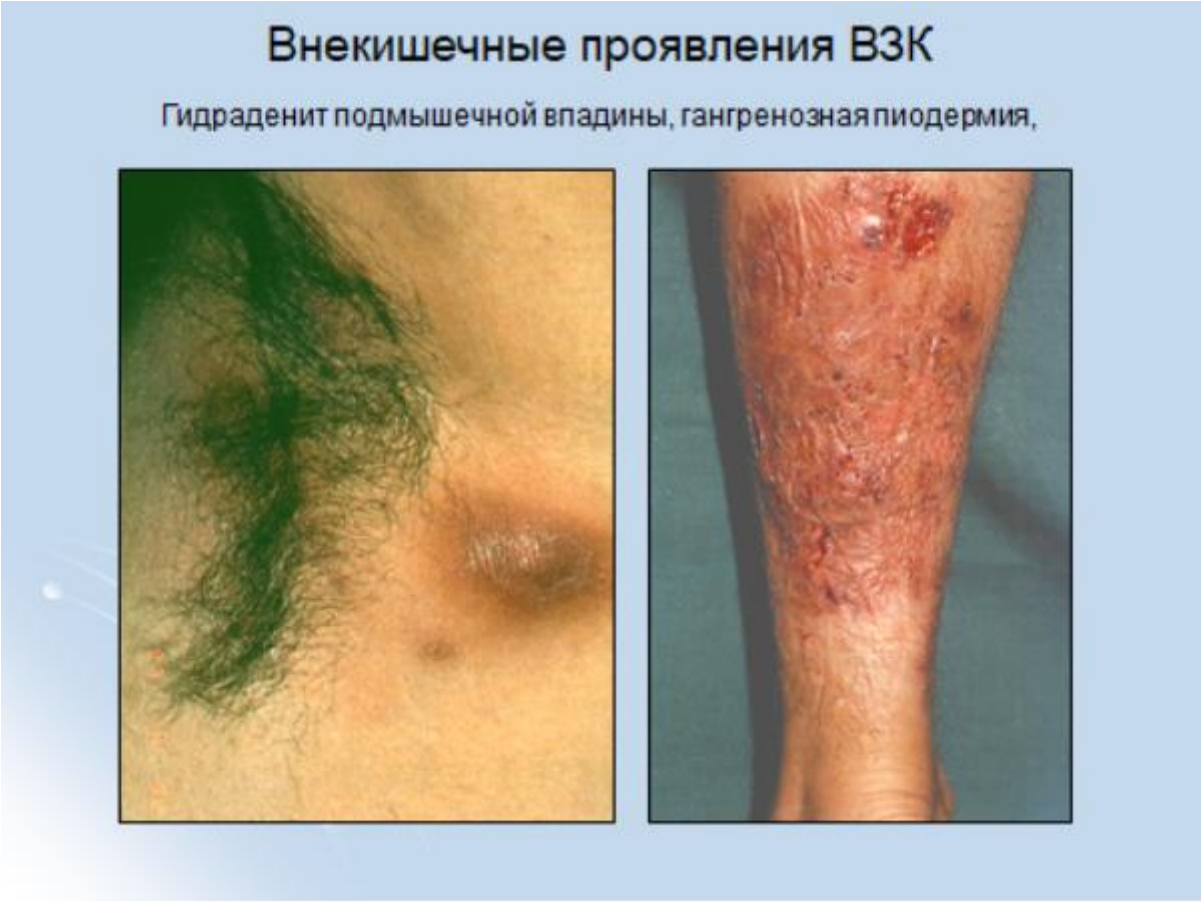


Table 4. UC attack severity according to Truelove-Witts criteria

	Light	**Moderate**	**Severe**
Frequency of bowel movements with blood	less than 4	more than 4 if:	more than 6 if:
Pulse	normal values	less than 90 bpm	more than 90 bpm or
Temperature	normal values	less than 37.5 C	over 37.5C or
Hemoglobin	normal values	over 105g/l	less than 105 g/l or
ESR	normal values	less than 30mm/h	more than 30 mm/h
Contact vulnerability of the colon mucosa	not available	are available	are available

In clinical practice, the so-called "super-severe or extremely severe attack" of UC is often encountered, characterized by diarrhea more than 10-15 times a day, an increasing drop in hemoglobin, fever above 38C, severe hypoproteinemia and electrolyte shifts, high levels of CRP.

Table 5. Attack severity according to UC activity index

(Mayo index)

Meaning	**0**	**1**	**2**	**3**

Stool frequency	обычная	1-2/day more than usual	3-4/day more than usual	5/day more than usual
Blood in the stool	not	veins	Visible blood	Predominantly blood
Mucosal condition	norm	Minimal activity (1 point on the Schroeder scale)	Moderate activity (2 points on the Schroeder scale)	Severe activity (3 points on the Schroeder scale)
General assessment of the condition by the doctor	norm	Satisfactory condition	Moderate condition	serious condition

Moderate and severe attacks are stated when the index value (the sum of scores for 4 parameters) is 6 or more.

Table 6. Classification of UC depending on endoscopic activity according to Schroeder)

0	**1 (minimum activity)**	**2 (moderate activity)**	**3 (expressed activity)**
Normal or inactive disease	Slight hyperemia, blurred vascular pattern. Slight contact vulnerability	Severe hyperemia, lack of vascular pattern, moderate contact vulnerability, erosion.	Spontaneous vulnerability, ulceration.

The classification of UC depending on the response to hormone therapy facilitates the choice of rational treatment tactics, since the goal of conservative treatment is to achieve stable remission with discontinuation of therapy:

Hormonal resistance:

1. In the case of a severe attack, the absence of positive dynamics from clinical and laboratory parameters, despite the use of systemic corticosteroids at a dose equivalent to 75 mg of prednisolone or 60 mg of methylprednisolone per day for more than 7 days; or

2. In the case of a moderate attack - maintaining the activity of the disease with oral administration of GCS at a dose equivalent to 60 mg of prednisolone for 2 weeks.

Hormonal addiction:

1. An increase in disease activity that occurred when the dose of corticosteroids was reduced after an initial improvement was achieved within 3 months from the start of treatment; or

2. The occurrence of a relapse of the disease within 3 months after the end of treatment with corticosteroids.

Diagnosis of ulcerative colitis.

1. Complete blood count - signs of anemia and inflammation (increased ESR). The white blood cell count is either normal or slightly elevated.

2. Blood biochemistry: increase in acute-phase parameters (fibrinogen, seromucoid, etc.). Dysproteinemia: hypoalbuminemia, hypergamma globulinemia. In severe cases - signs of electrolyte

imbalance and acid-base state. With autoimmune hemolysis - hyperbilirubinemia (indirect bilirubin). In hepatitis - an increase in the activity of transaminases.

3. Serology - antibodies against the colon mucosa, antiDNA antibodies, antibodies to red blood cells.

4. Bacteriology of feces: exclusion of acute intestinal infection, study of toxins A and B of C. difficile; determination of the nature of dysbacteriosis. A minimum of 4 stool samples is required to detect infection in 90% of cases. It is possible to study the level of fecal calprotectin.

5. Sigmoidoscopy is a necessary and, as a rule, sufficient diagnostic method. Endoscopically, the following criteria for colitis activity are distinguished:

• Minimum degree - edema, hyperemia, contact bleeding of the rectal mucosa.

• Moderate - signs of minimal severity plus multiple erosions, bloody mucus, no vascular pattern.

• The maximum degree - the mucosa is covered with fibrinopurulent plaque, when removed, a granular, diffusely bleeding surface is exposed. Multiple ulcers, pseudopolyps without signs of epithelialization. Rigidity of the intestinal wall and narrowing of its lumen.

6. Colonoscopy with ileoscopy. It allows to differentiate with other diseases of the colon, to clarify the prevalence, nature and degree of activity of the process, as well as to identify segmental forms of colitis. The most characteristic are continuous inflammation, limited to the mucous membrane, starting in the rectum and spreading proximal, with a clear border of inflammation. The endoscopic activity of UC is best reflected by contact vulnerability (bleeding on contact with the endoscope), the absence of a vascular pattern, and the presence or absence of erosions and ulcerations. The detection of persistent narrowing of the intestine against the background of UC requires the obligatory exclusion of colorectal cancer. Colonoscopy is contraindicated in severe cases of the disease, when there is a risk of perforation.

7. Biopsy of the colon mucosa:

• at the initial diagnosis;

• in case of doubts about the correctness of the previously made diagnosis;

• with a long history of UC (more than 7-10 years) - chromoendoscopy with targeted biopsy or stepped biopsy (from each part of the colon) to exclude epithelial dysplasia.

Microscopic signs of UC include deformity of the crypts (branching, multidirectionality, the appearance of crypts of different diameters, a decrease in the density of the crypts, "shortening of the crypts", the crypts do not reach the underlying layer of the muscular plate

8. X-ray examination:

• survey radiography of the abdominal cavity. It is used to detect perforation, toxic dilatation of the colon, in which a contrast study is contraindicated.

• irrigoscopy. Serrated contours of the intestine, disappearance of haustration, thickening of the folds, spotting of the relief, ulcerative niches, filling defects (pseudopolyps), uneven narrowing or shortening of the intestine are determined.

The study is carried out in the phase of attenuation of exacerbation and remission. In terms of information content, it is inferior to colonoscopy (especially in the diagnosis of the early stages of the disease).

9. Ultrasound examination of the abdominal cavity, retroperitoneal space, small pelvis;

10. If differential diagnosis is necessary or if it is impossible to conduct a full-fledged ileocolonoscopy, X-ray examinations are recommended:

• Magnetic resonance imaging (MRI) with bowel contrast;

• Computed tomography (CT) with bowel contrast.

Crohn's disease is a chronic relapsing disease of the gastrointestinal tract of unknown etiology, characterized by a transmural segmental granulomatous inflammatory lesion with the development of local and systemic complications.

The etiology and pathogenesis of the disease remain unclear. Predisposing causes that contribute to the occurrence of CD include:

• infection (viruses, atypical mycobacteria);

• tissue cytokines;

• mucous secretions;

• disturbed cellular immunity;

• food allergens;

• a diet high in refined sugar.

But these factors do not explain the undulating course of the disease (half of CD patients experience remissions that last for 5 years). There is evidence to support the importance of measles virus and immune mechanisms in the etiology and pathogenesis of CD.

The theory of the immune mechanism of CD development is based on the fact that frequent extraintestinal manifestations (for example, arthritis or pericholangitis) may be an autoimmune phenomenon and that treatment with corticosteroids and azathioprine is effective due to their immunosuppressive action. In patients with CD, humoral antibodies to intestinal cells, bacterial and viral antigens, E. coli and measles virus IgM class, to polysaccharides and a foreign protein can be detected.

In addition, a combination of CD with IgA deficiency has been reported. Immune complexes can also be considered as part of the group of factors responsible for the extraintestinal manifestations of CD. Many of the immune disorders disappear during the inactive period of the disease, which indicates their secondary specificity.

Pathomorphology. In Crohn's disease, any part of the gastrointestinal tract can be involved in the pathological process. The most frequently affected terminal segment of the ileum (85-90%).

The first microscopic signs of Crohn's disease are small focal "aphthoid" ulcerations of the mucosa. In the future, the inflammatory process progresses and involves all layers of the intestinal wall (transmural inflammation), the affected intestinal wall becomes edematous, thickens significantly. Deep tortuous and linear ulcerations appear on the mucous membrane of the affected intestine. The presence of multiple ulcerations with edema of the mucous membrane between them creates a characteristic picture of "cobblestone pavement", which is clearly visible during endoscopic examination. The corresponding sections of the mesentery are also involved in the pathological process, it thickens significantly, its adipose tissue extends to the serous surface of the intestine, an increase in mesenteric lymph nodes is characteristic.

Transmural inflammation of the intestine, deep ulcers, edema, fibrosis cause local complications of Crohn's disease - obstruction, external and internal fistulas, mesenteric abscesses.

The characteristic microscopic manifestations of Crohn's disease are:

• damage to all layers of the intestinal wall;

• swelling and infiltration by lymphocytes and plasma cells of the submucosal layer;

• hyperplasia of lymphatic follicles, Peyer's patches;

• granulomas consisting of large epithelial cells, multinucleated Langgans cells without signs of caseous decay (sarcoid-like granulomas). In Crohn's disease, the affected areas of the intestine alternate with normal ones.

The clinical picture of Crohn's disease depends on the localization and prevalence of the process, on the variant of the course - acute or chronic.

The acute form of Crohn's disease is observed less frequently, as a rule, while the pathological process is localized in the terminal segment of the ileum:

• increasing pain in the right lower quadrant of the abdomen;

• nausea, vomiting;

• diarrhea, often mixed with blood;

• flatulence;

• fever, often with chills;

• thickened painful terminal segment of the ileum;

• leukocytosis, increased ESR.

Common symptoms in CD (regardless of the localization of the process):

1. Most patients have 4 main symptoms; fever, diarrhoea, abdominal pain and BW drop. Pain in the abdomen in terms of localization and intensity may resemble appendicitis or yersinia ileitis, but a careful study of the development of the disease makes it possible to identify the symptoms preceding this period of the disease and differentiate them.

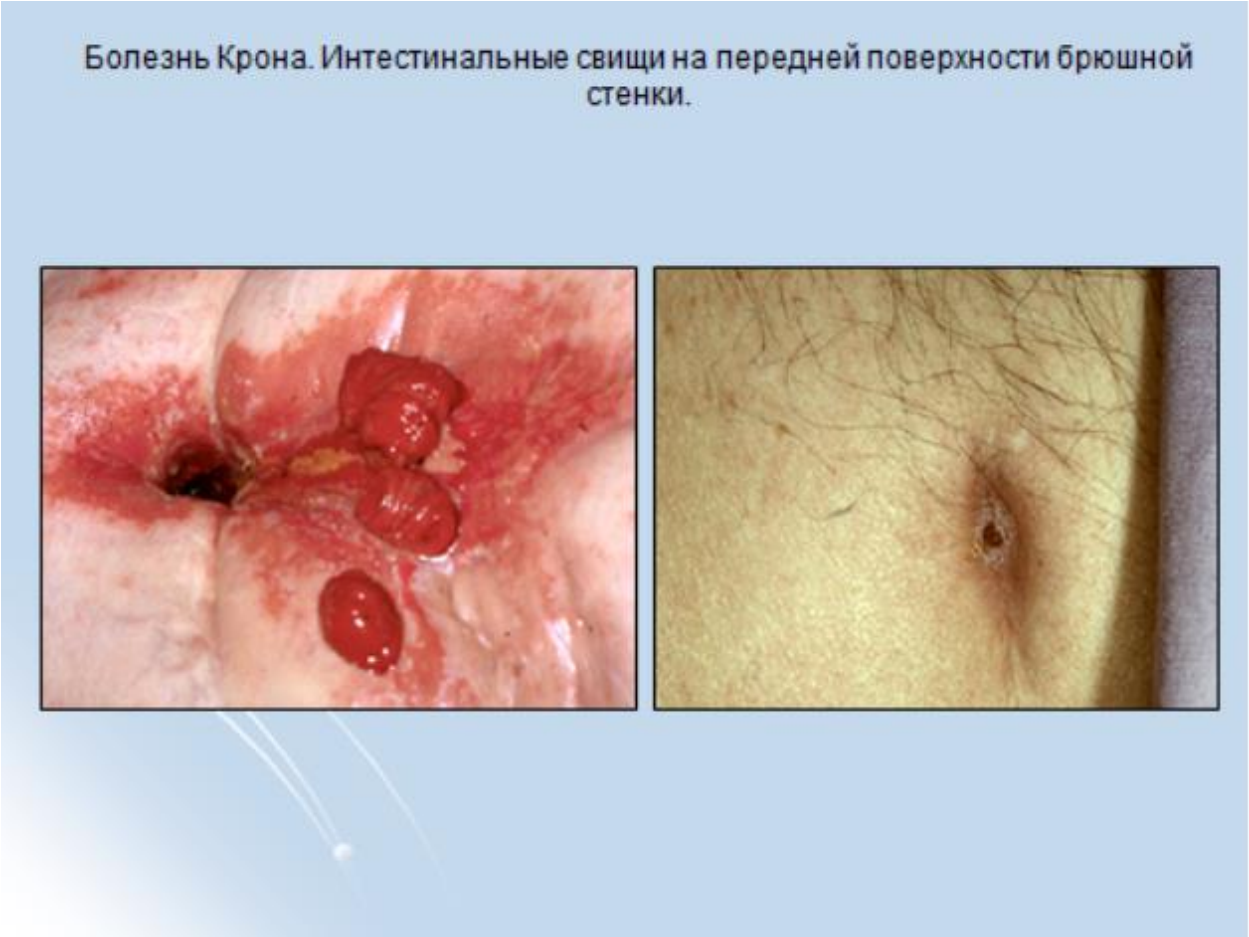
2. Fever, anorexia, weakness, lethargy and fatigue are typical of the active stage of the disease.

3. With CD, there is often a drop in BW due to anorexia without diarrhea and abdominal pain.

4. The clinic is closely related to the anatomical localization and activity of the process.

The chronic form of Crohn's disease is the most common.

small intestine localization. General symptoms are caused by intoxication and malabsorption syndrome: weakness, malaise, decreased performance, subfebrile temperature, weight loss, edema due to protein loss, hypovitaminosis (bleeding gums, cracks in the corners of the mouth, pellagrozny dermatitis, deterioration of twilight vision), pain in the bones and joints (depletion of calcium salts), trophic disorders (dry skin, hair loss, brittle nails), adrenal insufficiency (skin pigmentation, hypotension), thyroid gland (lethargy, puffiness of the face), gonads, parathyroid glands (tetany, osteomalacia, bone fractures), pituitary gland (polyuria with low urine density, thirst).



Local symptoms:

• Periodic, later constant dull pains (with damage to the duodenum - in the right epigastric region, jejunum - in the left and middle abdomen, ileum - in the right lower quadrant of the abdomen).

• The stool is semi-liquid, liquid, frothy, sometimes with an admixture of mucus and blood.

• When stenosis of the intestine - signs of partial intestinal obstruction (cramping pain, nausea, vomiting, gas and stool retention).

• On palpation of the abdomen - soreness and tumor-like formation in the terminal ileum, with other parts affected - pain in the umbilical region.

• Formation of internal fistulas opening into the abdominal cavity and external fistulas opening into the lumbar and inguinal regions.

• Possible intestinal bleeding.

Localization in the large intestine (granulomatous colitis).

Main clinical symptoms:

• Pain in the abdomen of a cramping nature that occurs after eating and before defecation. There may also be constant pain during movement, torso tilts (due to the development of the adhesive process). Pain is localized along the large intestine.

• Severe diarrhea (liquid or mushy stools up to 10-12 times a day with an admixture of blood). Some patients have a pronounced urge to defecate at night or in the morning.

• Paleness, dryness of the skin, decrease in its turgor and elasticity.

• When examining the abdomen, a decrease in the tone of the muscles of the anterior abdominal wall is revealed, palpation along the colon is accompanied by significant pain. The sigmoid colon is most often defined as a tourniquet, which is explained by infiltration of its wall.

• 80% of patients have anal fissures. Features that distinguish them from ordinary cracks: different localization, often multiple in nature, significantly less pain, lethargy of granulations, absence of rigid cicatricial edges, sphincter spasm.

• In digital examination, if the walls of the anal canal are involved in the process, edematous tissues are palpated, it is often possible to determine a decrease in the tone of the sphincter. After removing the finger, there is gaping of the anus and leakage of intestinal contents, usually purulent-bloody.

• An important diagnostic feature is intestinal fistulas and abdominal infiltrates. Fistulas of the rectum in Crohn's disease, even with prolonged existence, are rarely accompanied by scarring and are most often surrounded by infiltrative tissues with a polypoid-altered, infiltrated mucosa in the region of the internal opening and flaccid "labial-protruding" granulations around the external opening.

Extraintestinal manifestations of Crohn's disease are divided into three main groups.

1. Manifestations corresponding to the activity of the pathological process in the intestine, due to immunobiological processes and activation of the microbial flora: peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum. These complications are observed more often with damage to the large intestine.

2. Manifestations that are genetically associated with the HLA B27 genotype: ankylosing spondylitis, sacroiliitis, uveitis, primary sclerosing cholongitis.

3. Lesions directly related to the pathology of the intestine itself:

• kidney stones arising in connection with impaired uric acid metabolism, alkalinization of urine and excessive absorption of oxalates in the intestines;

• malabsorption syndrome;

• gallstones formed due to impaired reabsorption of bile salts in the ileum;

• secondary amyloidosis, which develops against the background of a long-term inflammatory and purulent process.

Diagnosis of Crohn's disease.

1. KLA: anemia, leukocytosis, increased ESR.

2. LHC: decrease in the content of albumin, iron, increase in α2- and γ-globulins, ALT, sometimes bilirubin.

3. Immunological blood test: an increase in the number of immunoglobulins, circulating immune complexes, a decrease in the number of suppressor T-lymphocytes. ASCA IgA.

4. Coprological analysis: an admixture of blood and mucus is macroscopically determined, in the absence of clearly visible blood - an increased number of red blood cells, always a positive reaction to latent blood and soluble protein, many epithelial cells and leukocytes.

5. FGDS: allows you to identify lesions of the upper gastrointestinal tract. Damage to the esophagus is extremely rare, manifested by inflammation of the mucous membrane of the esophagus, sometimes ulceration. The diagnosis is specified by histological examination of biopsy specimens of the esophageal mucosa. The defeat of the stomach is observed only in 5-6.5% of patients, and the most characteristic is an isolated lesion of the antrum of the stomach or a combination of lesions of the stomach and the initial part of the duodenum. The defeat of the stomach is manifested by an infiltrative inflammatory process

with ulceration in the center. The diagnosis is specified by histological examination of biopsy specimens of the gastric mucosa.

6. Endoscopic examination of the intestine (sigmoidoscopy, colonoscopy). Sigmoidoscopy is informative in cases where the rectum is involved in the pathological process (in 20% of patients). The most significant fibrocolonoscopy with a biopsy of the intestinal mucosa.

In the initial stage of the disease, against the background of a dull mucous membrane, erosion-aphthae are visible, surrounded by whitish granulations. Mucus and pus are visible on the walls of the intestine in its lumen. As the disease progresses and the activity of the process increases, the mucous membrane thickens unevenly, takes on a whitish appearance, large ulcers appear, often longitudinally located, and there is a narrowing of the intestinal lumen (a “cobblestone” pattern). During the period of greatest activity, the inflammatory process spreads to all layers of the intestinal wall, including the serous membrane, and fistulas are formed. In the future, cicatricial constrictions form at the site of ulcers-cracks.

7. Microscopic examination of mucosal biopsies: the biopsy should be carried out in such a way that the submucosal layer is included in the biopsy, because in Crohn's disease the process begins in it and then spreads transmurally.

• the submucosal layer is most affected, to a lesser extent - the mucous membrane;

• inflammatory cell infiltrate is represented by lymphocytes, plasma cells, histiocytes, eosinophils, against which sarcoid-like granulomas with giant Langgans cells are determined.

8. X-ray examination of the intestine: irrigoscopy is performed in the absence of rectal bleeding. The characteristic symptoms of Crohn's disease are:

• segmental lesions of the colon;

• the presence of normal sections of the intestine between the affected segments;

• uneven bowel contour;

• longitudinal ulcers and mucosal relief, resembling a "cobblestone pavement";

• narrowing of the affected areas of the intestine in the form of a "cord";

X-ray examination of the small intestine is most appropriate to carry out with the introduction of barium through a probe behind the ligament of Treitz. X-ray signs of damage to the small intestine are the same as those of the large intestine.

9. Laparoscopy: carried out mainly for the purpose of differential diagnosis. The affected sections of the intestine, primarily the terminal ileum, look hyperemic, thin, edematous; there are also thickening and enlargement of the mesenteric lymph nodes.

Table 7. Differential diagnostic differences

Crohn's disease and non-specific ulcerative colitis

signs	**Crohn's disease with localization in the large intestine (granulomatous colitis)**	**non-specific** **ulcerative colitis**
Depth of damage to the intestinal wall	Transmural lesion	The inflammatory process is localized in mucous membrane and in the submucosal layer
bloody stool	Maybe, but less often than in ulcerative colitis	Typical sign
Rectal injury	Rare (20% of cases)	Often
Pathological change around the anal holes	Characteristic	Are rare
External and internal fistulas	Characteristic	not typical

Determination of a tumor-like formation on palpation of the abdomen (adhesive adhesions of loops)	Characteristic	not typical
Ileocecal lesion	Characteristic	not typical
Relapse after surgical treatment	Often	Usually does not happen
Endoscopic data: Aphthae	Characteristic	not typical
Longitudinal ulcers	Characteristic	not typical
Continuous Defeat	rare	Characteristic
Microscopy of intestinal biopsy specimens - the presence of an epithelial (sarcoid-like) granuloma	Characteristic	not typical

Table 8. Differential diagnosis of diseases occurring with symptoms of chronic recurrent diarrhea.

The nature of the stool	**Частота стула**	**Peculiarities**	**Differential Diagnosis**	**Nosological form**
Mushy, mucilaginous, profuse, frothy.	1-3	Penetration of the flora of the large intestine into the small intestine, pH<5.2	Postenteritis syndrome	Condition after viral, bacterial, fungal enteritis or enterocolitis.
Watery, mushy, sometimes with mucus and blood, copious	1-5	With damage to the small intestine and malabsorption. X-ray roughness of the intestine, stenosis	Nonspecific enterocolitis	Granulomatous enterocolitis (Crohn's disease)
Mushy, mucus-bloody	3-10	Endoscopy: ulceration, late polyposis on the background of chronic inflammation of the mucous membrane	-	Ulcerative colitis.
Mushy, mucus-bloody	1-5	Positive tuberculin test	Specific enterocolitis	Tuberculosis of the intestine
mushy, slimy	1-7	Pathogen detection	-	Giardiasis, amoebiasis
mushy, sometimes frothy	1-4	pH<5.2; lactose (sucrose) load does not increase blood glucose levels	Enzymatic diarrhea	Hereditary or acquired deficiency of disaccharidases

Mushy, watery, often copious	2-5	Symptoms of malabsorption, PAS-positive inclusions in intestinal cells	-	Whipple disease
Mushy, shiny, plentiful	1-3	Chronic recurrent respiratory tract infections. Sweat test: >70mmol/l sodium	Digestive disorder	cystic fibrosis
Mushy, shiny, plentiful	1-3	Short stature. Sweat test normal	-	Shwachman's syndrome
Mushy, shiny, plentiful	1-5	Increased activity of amylase and lipase in the blood. Sweat test normal	-	Acute and chronic pancreatitis
Normally formed, bold, shiny	0-1	Increased appetite, no dystrophy	selective disorder of digestion	Congenital lipase deficiency
Mushy or decorated, shiny	1-2	Jaundice	-	Bile acid deficiency in hepatopathy
Mushy	1-5	Dystrophy, hypoproteinemic edema	-	Enterokinase or trypsinogen deficiency
Profuse, shiny, offensive	1-3	Anti-gluten (gliadin) antibodies, multifactorial anemia	Malabsorption	celiac disease
Liquid with an admixture of mucus	3-10	Elevated IgE, pH normal, slightly reduced	-	Allergy to cow's milk

Activity score.

In CD, it is important to determine whether the severity of the symptoms of the disease is associated with activity or with complications.

However, there are difficulties in assessing the activity of the disease, which can be resolved by an integrated approach to solving this problem.

1. Clinical signs: anorexia, weight loss, weakness, fever, tachycardia - indicate the activity of the disease, but similar symptoms can join as a result of superinfection, and therefore these signs in this situation will only be indirectly related to the activity of the CD process.

2. Laboratory signs of activity: low serum albumin, severe anemia, increased ESR, the presence of CRP, a sharp increase in platelet count.

3. Radiographic signs of activity: ulcers (aphthous, spike-like, slit-like), fistulas, cobblestone mucosa.

4. Endoscopic and histological signs (when examining a biopsy specimen) of activity: a visible ulcer, granulomas and other specific elements, but the site of the main process in CD may not be available for endoscopic examination (terminal ileum).

5. Ultrasound of the abdominal cavity: thickening of the intestinal loops, inflammatory infiltrate, abscess.

6. Relapses of symptoms of the disease as a manifestation of the activity of the process. CD is a chronic relapsing and progressive disease, and therefore some studies are repeated throughout the year, since the assessment and classification of symptoms are important. Some of the studies, such as x-rays, need to be limited and used only for special indications, such as suspected acute intestinal obstruction, to decide on indications for surgery.

Colonofibroscopy is indicated if "colonic" symptoms join, and EFGDS - if the symptoms that appear are presumably due to damage to the upper digestive tract.

If the attached symptoms differ from the previous ones, i.e. are not stereotypical, it is necessary to assume other reasons and conduct appropriate studies:

1. Examine the kidneys and urinary tract.

2. Take an abdominal x-ray to detect subacute intestinal obstruction.

3. Perform an ultrasound to detect gallstones, nephrolithiasis and hydronephrosis.

4. Carry out a lactulose-hydrogen breath test to detect bacterial overgrowth syndrome.

With a recurrence of symptoms, it is also necessary to determine what they are associated with: with an exacerbation of the old process or with the appearance of the process in a new place.

Treatment. Patients with newly diagnosed UC and CD, with a clinical exacerbation of the disease, need hospitalization to determine the complex of therapeutic measures due to the frequent presence of metabolic and hematological disorders. Therapy of IBD is also the main method of dealing with their extraintestinal manifestations. The new concept of IBD therapy is based on the idea that this disease usually begins at birth, and its latent course before the onset of clinical manifestations is due to various external events (exposome). Therefore, life "before IBD" and "after IBD" corresponds to the early and late stages of the disease. Each phase of IBD may be associated with different pathogenic events and mediated by different immune components.

Currently, it is still common practice in clinical practice to start treatment with less powerful drugs and then increase the dose or switch to another drug if, over time, it turns out that the prescribed treatment is ineffective. During this time, the disease can progress from an early to a late stage with the development of resistance to all drugs. This suggests that the prolonged use of immunosuppressive drugs with a gradual increase in dose in the treatment of IBD may contribute to the development of chronic inflammatory bowel disease.

1. Diet. In the acute phase - tables No. 4, No. 4b (mashed food). In remission - table number 4v. In some patients, diarrhea can be eliminated with a gluten-free diet (wheat, rye, barley products are excluded).

In severe cases, they resort to parenteral nutrition, use protein hydrolysates (aminopeptide, casein hydrolyzate, etc.), amino acid mixtures (alvezin, polyamine, vamin, etc.), glucose, lipid preparations (intralipid, lipofundin), solutions containing electrolytes (potassium chloride, magnesium sulfate, sodium chloride, etc.), vitamins, iron preparations.

2. Sulfanilamide preparations. In 30-50 years. of the last century, ulcerative colitis was accompanied by significant mortality. The situation changed radically only after effective drugs appeared in the arsenal of doctors - SULFASALAZIN and its analogues, as well as corticosteroid hormones.

The therapeutic effect of sulfasalazine is due to 5-ASA, and sulfapyridine plays a modest role as a "carrier" that ensures the delivery of the drug to the colon. This served as the basis for the creation of new drugs. They contain only 5-ASA and are free from the toxic side effects of sulfasalazine. Preparations of this group (salofalk, mesacol, salosan, tidikol) are prescribed in the same therapeutic doses as sulfasalazine and its analogues.

Side effects of sulfasalazine - anorexia, nausea, vomiting; skin rash, exfoliative dermatitis, epidermal necrolysis; cyanotic, icteric shade of the skin; headache, dizziness, weakness, malaise; abdominal pain, diarrhea, arthralgia; bronchospasm; eosinophilia; hepatitis; pancreatitis; paresthesia; anemia, leukemia, thrombocytopenia, agranulocytosis.

Preparations of 5-aminosalicylic acid and today occupy a leading place in the induction and maintenance of remission of mild and moderate forms of inflammatory diseases of the colon.

Salase derivatives of sulfanioamides (sulfasalazine, salazopyridazine, salazodimethoxine). They have antibacterial and anti-inflammatory action. Assigned to 0.5 g 1 hour before meals with alkaline drink (soda, milk, mineral water) 4 times a day. With good tolerance of the drug, the dose increases to 6-8 g, and in the absence of effect, up to 10-12 g (for 5-7 days). In most patients, a dose of 3-4 g per day is sufficient. Improving the general condition, reducing the secretion of mucus and blood and blood occurs in the first 5-8 days of treatment. The sigmoidoscopy picture improves at 3-4 weeks. The dose of the drug, as the signs of exacerbation subside, is gradually reduced to maintenance (1-1.5 g / day), which is recommended to be taken as anti-relapse therapy for a long time (up to 1 year or more).

With damage to the sigmoid and rectum, sulfasalazine is used in the form of microclysters (1-3 g of the drug dissolved in 50-100 ml of isotonic sodium chloride solution) or in suppositories (0.5-1.0 g each with cocoa butter at night for 3-4 weeks). Salazopyridazine is injected into the rectum in 30 ml of 5% suspension - 1-2 times a day for 1-2 months. Rectal administration of salazosulfa preparations is combined with their oral administration.

Mesalazine with 3 types of coating is registered on the Russian pharmaceutical market:

• from the euhydrate - L (salofalk): the release of mesalazine occurs gradually throughout the intestine with an optimum pH> 6.0 (25-30% in the terminal ileum and 70-75% in the colon);

• from ethylcellulose (pentase): the maximum release of mesalazine is observed at pH=1.0 (20% of the active substance in the stomach, 25-30% in the terminal small intestine, 25-30% in the colon and 25-30% of the drug can remain in microspheres and be excreted along with feces);

• from acrylic (mesacol): the release of mesacol occurs at pH>6.0, with at least 90% of the active substance being released within 15 minutes.

3. Glucocorticosteroids. Glucocorticosteroids are a pathogenetic treatment for severe forms of the disease. They alter the progression of leukocytes and lymphocytes, reduce leukocyte adhesion and chemotaxis, inhibit phagocytosis, inhibit the release of inflammatory mediators, reduce the expression of immunorecognizable molecules and adhesion molecules, inhibit antibody production, and inhibit cell-mediated cytotoxicity.

Indications:

a) acute course;

b) severe, life-threatening forms;

c) moderate forms with the ineffectiveness of 2-week treatment with salazopreparations;

d) chronic forms in cases of insignificant influence of other methods of treatment;

e) systemic (extraintestinal) manifestations;

e) intolerance to salazopreparations.

In severe and acute cases, intravenous or intramuscular administration of 50-150 mg of hydrocortisone twice during the first days is preferable. Subsequently, prednisolone is prescribed orally (30-60 mg / day).

In cases of moderate severity, treatment with prednisolone begins with a dose of 0.015-0.02 g. If there is no effect, it is increased by 0.005 g. Every 5-7 days (0.03-0.04 g of the drug is usually sufficient). Upon reaching the effect, the dose is gradually reduced to a maintenance dose - 0.005-0.015 g per day, which patients take for 2-4 months.

In distal forms of ulcerative colitis, prednisolone is initially prescribed rectally by drop: 25-30 mg in 30-50 ml of warm saline sodium chloride solution or in suppositories - 0.015 in the morning and evening after a stool. It should be emphasized that rectally administered glucocorticoids cause fewer side effects compared to oral administration, although their plasma concentration is identical at an equal dose of the administered drug.

Significant progress in the treatment of IBD has been achieved with the introduction of "new" steroids into healthcare practice. They are synthetic drugs with changes in C16, C17 and C21 (budesonide, fluticasone, prednisolone-21 phosphate, betamethasone-17 valerate, etc.), which therefore have high receptor affinity, low absorption capacity and high first pass metabolism. This group of drugs inhibits the hypothalamic-pituitary-adrenal system much less. The absence of inhibition of the pituitary-adrenal system in new corticosteroids is currently considered as the most significant feature in the treatment of patients with UC and CD.

Long-term therapy with systemic corticosteroids may be accompanied by side effects such as obesity (before the development of Cushingoid syndrome), arterial hypertension, osteoporosis (up to pathological fractures), diabetes mellitus, erosive and ulcerative lesions of the stomach and intestines with the development of bleeding. The development of side effects with the use of topical corticosteroids is very rare.

4. Immunosuppressants. The autoimmune nature of IBD causes an increased interest of clinicians in the use of cytostatics in this pathology. Shown in severe cases of the disease, when salazopreparations and glucocorticosteroids are ineffective.

Azathiopyrine 0.15-0.25 g per day or mercaptopurine 0.1 g per day are prescribed (usually in combination with glucocorticosteroids). A more promising immunosuppressant in the treatment of IBD is cyclosporine (Sandimmun). Cyclosporine is prescribed in enemas at a dose of 250 mg in suspension with methylcellulose and sorbitol. Intravenous administration of cyclosporine at a high dose (4 mg/kg) causes remission in 60-80% of patients with severe ulcerative colitis.

5. Biological therapy. Now that understanding has improved

mechanisms of IBD, modern therapeutic methods are based on the functioning of various metabolic pathways and molecules that are activated during the inflammatory process in the intestine. These methods can affect secreted cytokines (eg, tumor necrosis factor), cytokine receptors, chemokines, and cell adhesion molecules.

This method can be considered pathogenetically based, as opposed to empirical, based on the non-specific anti-inflammatory effect of drugs such as sulfasalazine, 5-aminosalicylic acid (5-ASA), or immunosuppressive drugs such as azathioprine or methotrexate. To date, various types of antibodies have been developed for the treatment of IBD to neutralize various pro-inflammatory molecules, in particular, tumor necrosis factor (TNF). Biological (anticytokine) therapy is based on the use of natural or chimeric biologically active molecules as drugs that block various stages of the inflammatory response in the tissue. Since the 90s of the last century, Remicade (Infliximab) has come into practice.

Remicade is a chimeric compound based on hybrid mouse and human IgG1 monoclonal antibodies. The effect is due to the neutralization of only one (key) inflammatory mediator TNFα. The initial dose is 5 mg / kg, the drug is administered during the induction course at 2 and 6 weeks after the first injection. With a maintenance course - every 8 weeks (after the induction course). Remicade is prescribed for steroid-dependent patients (more than one course of steroid therapy per year), with resistance to steroids and immunosuppressants, in the presence of side effects of steroids and immunosuppressants.

Various antibodies have also been developed against T-cell activation molecules and receptors. These include daclizumab and basiliximab, antibodies to the IL-2 receptor, abatacept, to coactivation molecules, and vizilizumab, to components of the CD3 receptor on T cells.

Infliximab can lead to mucosal healing and restoration of its normal histological pattern in Crohn's disease, which can be considered as a result of tumor necrosis factor neutralization. Infliximab can also be used in Crohn's disease to close fistulas. Infliximab is highly effective in the treatment of skin complications of IBD, such as pyoderma gangrenosum.

Tumor necrosis factor is not only a pro-inflammatory molecule, but also an important link in the fight against infection, and its blocking can have a negative impact on the immune system. Thus, blocking the tumor necrosis factor with the help of biological preparations can lead to the transition of tuberculosis into the active phase.

Treatment with biological drugs may be accompanied by some complications (from moderate to severe). These include injection site reactions, delayed-type hypersensitivity reactions, antibody and autoantibody formation, development of autoimmune diseases, active tuberculosis, opportunistic infections, abnormal liver function tests, malignant neoplasms and lymphomas, cardiovascular and neurological disorders, and even death. Biological drugs are selective immunosuppressants, monoclonal antibodies directed against tumor necrosis factor - Infliximab (Remicade), Golimumab (Simponi).

6. In case of a threat of development of toxic dilatation of the intestine, antibiotics (clindamycin, cefobid, ampicillin) are connected to the treatment. If toxic dilatation persists for 24 hours, patients are referred for surgical treatment.

7. Microclysters with warm fish oil or vegetable oil (peach, olive, sea buckthorn, rosehip), with antipyrine, solutions of collargol, novocaine, linseed infusion, chamomile.

8. Means for the treatment of intestinal dysbacteriosis.

9. Enzyme preparations that do not contain bile acids (pancreatin, trienzyme, mezim-forte, etc.).

10. Sedatives, tranquilizers, neuroleptics, antidepressants according to indications.

11. Effective repeated courses of hyperbaric oxygenation.

12. Surgical treatment. In severe cases that are not amenable to conservative treatment, a total or partial colonectomy is performed. Absolute indications for surgery are incessant bleeding, expansion of the colon, perforation and cancerous degeneration.

Treatment of ulcerative colitis.

Proctitis:

Light and moderate attack (1 attack or relapse): suppositories with mesalazine 1.0 - 2.0 g / day. The duration of the therapeutic response is up to 2 weeks. The duration of the induction course is 6-8 weeks;

If the treatment is ineffective, add - rectal forms of corticosteroids (suppositories with prednisolone 5-10 mg x 1-2 times a day);

If treatment is ineffective, add - oral forms of mesalazine - 3.0 - 4.0 g / day.

Mild and moderate attack (1 attack or relapse): systemic steroids (prednisolone 0.75 mg / kg + AZA 2 mg / kg or 6-MP 1.5 mg / kg; suppositories with prednisolone 5-10 mg x 1 are additionally acceptable 2 times a day; when remission is achieved, maintenance therapy is AZA 2 mg/kg or 6-MP 1.5 mg/kg for at least 2 years.

In the absence of effect: systemic steroids (prednisolone 0.75 mg / kg + AZA 2 mg / kg or 6-MP 1.5 mg / kg; suppositories with prednisolone 5-10 mg x 1-2 times a day are additionally acceptable; upon reaching remission maintenance therapy -AZA 2 mg/kg or 6-MP 1.5 mg/kg for at least 2 years.

Left-sided and total UC:

Light attack (1 attack or relapse): oral mesalazine tablets 3 g/day (or sulfasalazine 4 g/day) in combination with mesalazine enemas 2-4 g/day (depending on endoscopic activity), or mesalazine microbeads 3 g/day ., therapeutic response - up to 2 weeks. The duration of the induction course is 6-8 weeks.

If the treatment is ineffective, add rectal forms of corticosteroids (microclysters with a suspension of hydrocortisone 125 mg x 1-2 times a day).

When remission is achieved, maintenance therapy with mesalazine tablets 1.5 g / day orally + mesalazine in enemas 2 g x 2 times a week or mesalazine microgranules 1.5 g / day for at least 2 years. It is acceptable to prescribe sulfasalazine 3 g instead of mesalazine.

Medium attack. If there is no effect from 5-ASA - systemic steroids - prednisolone 1 mg / kg + AZA 2 mg / kg or 6-MP 1.5 mg / kg; with a good response, maintenance therapy with AZA 2 mg/kg/day or 6-MP 1.5 mg/kg for at least 2 years. If there is no effect within 8-12 weeks - infliximab 5 mg/kg at 0, 2, 6 weeks + AZA 2 mg/kg. Maintenance therapy with AZA or 6-MP + infliximab for at least 12 months every 8 weeks. In any clinical situation, an additional rectal administration of mesalazine 2-4 g or hydrocortisone 125 mg is recommended. If 1 attack was stopped by systemic steroids, then in case of relapse it is recommended to prescribe the same dose immediately in combination with AZA or 6-MP, maintenance therapy should be carried out with AZA or 6-MP.

Heavy attack. Systemic steroids (based on prednisolone): orally 1.5 mg/kg/day (no more than 3 weeks) or IV prednisolone 2 mg/kg/day, or hydrocortisone succinate (hemisuccinate) 400 mg daily for 7 days. Additionally, enemas with mesalazine 2-4 g per day or hydrocortisone 125 mg / day. With a good effect, after 7 days, transfer to oral prednisolone 1 mg / kg / day, followed by a dose reduction of 5 mg per week until complete cancellation.

• When reducing the dose of steroids to 30-40 mg, add mesalazine 3 g

• When remission is achieved, maintenance therapy is mesalazine 1.5-2g for 2 years. It is acceptable to prescribe sulfasalazine 3 g instead of mesalazine.

Antibiotics: 1st line - metronidazole + fluoroquinolones (ciprofloxacin, ofloxacin) IV for 10-14 days; 2nd line - cephalosporins in/in 7-10 days;

In the absence of the effect of steroid therapy after 7 days, it is shown:

• infliximab – induction course at 0,2,6 weeks 5 mg/kg or

• cyclosporine A in / in or orally 2 or 4 mg / kg with monitoring

blood concentrations after 1 week

• When responding to an infliximab induction course, maintenance

therapy is carried out with infliximab (1 infusion 1 time in 8 weeks not

less than 12 months in combination with AZA 2 mg/kg)

• If the effect of cyclosporine therapy after 7 days - switch to AZA 2

mg/kg (against a therapeutic dose of steroids) with a gradual withdrawal of steroids over 12 weeks

• Maintenance therapy with AZA 2 mg/kg for at least 2 years

• If there is no response to ciclosporin after 7 days or after 2 infliximab infusions, surgical treatment should be discussed.

INDICATIONS FOR SURGERY FOR ULCERATIVE COLITIS

I. Complications of ulcerative colitis

• Intestinal bleeding

• Toxic dilatation of the colon

• Colon perforation

II. Ineffectiveness of conservative therapy

• Hormonal resistance

• Hormonal dependence

III. Malignancy (colorectal cancer) against the background of ulcerative colitis

Hormone-resistant form: With adequate conservative therapy (prednisolone 2 mg / kg / day; erythromass, proteins, amino acids; infusions (50-70 ml / kg / day); broad-spectrum antibiotics) - no effect for 3 weeks - increase or persistence of severity intestinal symptoms, intoxication and metabolic disorders.

Hormone-dependent form: The need for continuous hormone therapy for more than 6 months to prevent reactivation of colitis (dose-dependent form).

Ineffectiveness or severe side effects when taking immunosuppressants (azathioprine, methotrexate, cyclosporine)

The constant threat of the development of complications of hormonal therapy (osteoporosis, steroid diabetes, arterial hypertension, infectious complications).

Treatment of Crohn's disease.

Terminal ileitis, ileocolitis:

I. Light flow (with low activity)

1 attack

• Mesalazine at least 4 g/day.

or

• Budesonide at a dose of 9 mg (3 mgx 3 times) up to 16 weeks with a gradual decrease.

Therapy is carried out until clinical remission is achieved (IAKB < 150)

• Maintenance therapy - mesalazine 2 g for at least 12 months.

• Budesonide at a dose of 9 mg (3 mg x 3) up to 16 weeks with a gradual decrease until clinical remission is achieved

• Maintenance therapy - mesalazine 2 g for at least 12 months.

II. Moderate (with moderate activity)

1 attack

• Budesonide at least 9 mg per day;

• in the absence of effect after 4 weeks. systemic

steroids (prednisolone 1 mg/kg orally, budesonide is discontinued)

• Antibiotics: rifaximin 400 mg x 2 times 7-10 days (up to 4 weeks) orally or metronidazole 1.5 g per day IV + fluoroquinolones (mainly) parenterally for 10-14 days.

Evaluation of the effectiveness of treatment after 2-4 weeks

• With a positive response - maintenance therapy - mesalazine 2 g for at least 12 months.

• If there is no effect, add azathioprine 2-2.5 mg/kg (if it is intolerant or ineffective, methotrexate 25 mg per week IM up to 16 weeks

• When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years

CD relapse

• Budesonide 9 mg daily or systemic steroids 1 mg/kg + azathioprine 2 mg/kg

• Antibiotics: rifaximin 400 mg x 2 times 7-10 days (up to 4 weeks) orally or metronidazole IV + fluoroquinolones (mainly) parenterally 10-14 days

Evaluation of effectiveness after 2-4 weeks

When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years.

III. Severe course (with high activity)

1 attack or relapse

• Systemic steroids 1.5 mg/kg (prednisolone or methylated analogs in terms of prednisolone) + azathioprine 2-2.5 mg/kg

• Antibiotics mandatory (metronidazole + fluoroquinolones

(mainly) in / in 10-14 days, if necessary, change the antibiotic (rifaximin).

Performance evaluation after 2 weeks

• If yes, reduce steroids, keep azathioprine at the same dose.

• When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years

• If there is no effect, add methotrexate 25 mg/week. i/m

or

• Infliximab (Remicade) 5 mg/kg IV (induction course - 3 infusions: 0, 2 and 6 weeks)

• Discusses surgical treatment.

Assessment of response to infliximab at the time of the 2nd or 3rd infusion

• In the absence of effect - surgical treatment

• When remission is achieved, maintenance therapy with infliximab every 8 weeks for at least 1 year or azathioprine 2 mg/kg for at least 2 years.

- Treatment of Crohn's disease of the colon (except for the anorectal zone):
- Mild flow (with low activity)
- 1 attack or relapse
- • Mesalazine (only Pentasa) at least 4 g/day.

- • Maintenance therapy - mesalazine (Pentasa) 2 g for at least 1 year.
- Moderate (with moderate activity)
- 1 attack
- • Systemic steroids 1 mg/kg
- • Antibiotics: oral rifaximin or IV metronidazole + fluoroquinolones
- (1 attack or relapse
- • Mesalazine 4 g or (equivalent to 8 g sulfasalazine)
- • Maintenance therapy - sulfasalazine 2 g
- or mesalazine 1-1.5 g
- • Possibly probiotics (non-pathogenic saccharomycetes,
- preparations of lactobacilli)
- Moderate (with moderate activity)
- 1 attack
- • Systemic steroids 1 mg/kg (prednisolone or methylated analogues in
- in terms of prednisolone);
- • Antibiotics: oral rifaximin or IV metronidazole + fluoroquinolones
- (mainly) parenterally 10-14 days.
- Evaluation of effectiveness after 2-4 weeks
- • If positive - maintenance therapy - mesalazine
- 2 g or sulfasalazine 2 g for at least 12 months.
- • If no effect, add azathioprine 2 mg/kg
- (if it is intolerant or ineffective - methotrexate 25 mg
- per week i / m up to 16 weeks);
- • When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years
- relapse
- • Systemic steroids 1 mg/kg (prednisolone or methylated analogues
- in terms of prednisolone) + azathioprine 2 mg/kg
- • Antibiotics: rifaximin by mouth for 7-10 days or
- IV metronidazole + IV fluoroquinolones 10-14 days
- Evaluation of effectiveness after 2-4 weeks
- When remission is achieved, maintenance therapy is azathioprine 2 mg/kg for at least 2 years.
- Crohn's disease of the small intestine (except terminal ileitis):
- Mild flow (with low activity)

- Mesalazine (only Pentasa) 4 g / day. 10-14 days.
- Evaluation of effectiveness after 2-4 weeks
- • With a positive response - maintenance therapy - mesalazine (Pentasa) 2 g for at least 12 months.
- • If there is no effect, add azathioprine 2 mg/kg (if it is intolerant or ineffective, methotrexate 25 mg per week IM up to 16 weeks.
- • If necessary - nutritional support (enteral nutrition)
- • When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years
- relapse
- • Systemic steroids 1 mg/kg + azathioprine 2 mg/kg
- • Antibiotics: rifaximin 200 mg x 3 times 7-10 days orally metronidazole IV +
- fluoroquinolones (mainly) parenterally 10-14 days;
- • If necessary - nutritional support (enteral nutrition).
- Evaluation of effectiveness after 2-4 weeks
- When remission is achieved, maintenance therapy: azathioprine 2 mg/kg for at least 2 years.
- Severe course (with high activity)
- 1 attack or relapse
- • Systemic steroids 1.5 mg/kg (prednisolone or methylated analogs
- in terms of prednisolone) + azathioprine 2-2.5 mg/kg
- • Antibiotics are mandatory (metronidazole + fluoroquinolones (mainly) IV for 10-14 days, if necessary, change the IV antibiotic.
- • Nutritional support (enteral tube feeding).
- Performance evaluation after 2 weeks
- • If yes, reduce steroids, keep azathioprine at the same dose.
- • When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years,
- with prolonged remission, a transition to Pentasa is possible
- • If there is no effect, add methotrexate 25 mg/week. i/m
- or
- • Infliximab 5 mg/kg (induction course)
- • In the absence of effect - surgical treatment
- • When remission is achieved, maintenance therapy with infliximab every 8 weeks for at least 1 year or azathioprine 2 mg/kg for at least 2 years.
- Intestinal bleeding.
- Diagnosis: control of hemoglobin, hematocrit, dynamic scintigraphy, hemodynamic monitoring, control of stool volume.

- • Treatment tactics: massive hormonal therapy (prednisolone 2 mg/kg/day), blood transfusions (500.0 ml of erythrocyte mass/day)
- • Indications for surgery: loss of more than 100 ml of blood per day, lack of positive dynamics of hemoglobin on the background of blood transfusion within 48 hours, hypotension.
- Toxic dilatation of the colon.
- Diagnosis: dynamic radiography of the abdominal organs (control of the degree of expansion of the colon).
- • Tactics of treatment: massive hormonal therapy (prednisolone 2 mg/kg/day), the introduction of protein drugs, endoscopic decompression of the colon.
- • Indications for surgery: expansion of the colon more than 9 cm with ineffective decompression, recurrence of toxic dilatation, impossibility to exclude covered perforation.
- Severe course (with high activity)
- 1 attack or relapse
- • Systemic steroids 1.5 mg/kg (prednisolone or methylated analogs in terms of prednisolone) + azathioprine 2-2.5 mg/kg
- • Antibiotics are mandatory (metronidazole + fluoroquinolones (mainly) IV parenterally for 10-14 days, if necessary, change the antibiotic - rifaximin.
- Performance evaluation after 2 weeks
- • If yes, reduce steroids, keep azathioprine at the same dose.
- • When remission is achieved, maintenance therapy with azathioprine 2 mg/kg for at least 2 years
- • If there is no effect, add methotrexate 25 mg/week. IM or infliximab 5 mg/kg IV (induction course - 3 infusions: 0, 2 and 6 weeks)
- • Discusses surgical treatment.
- Assessment of response to infliximab at the time of the 2nd or 3rd infusion
- • In the absence of effect - surgical treatment
- • When remission is achieved, maintenance therapy with infliximab every 8 weeks for at least 1 year or azathioprine 2 mg/kg for at least 2 years.

The severity of CD is difficult to assess, unlike ulcerative colitis. To this end, it is necessary to conduct appropriate studies and analyze their results.

A severe exacerbation is characterized by the presence of the following symptoms: the appearance of a serious patient, vomiting, febrile fever, tachycardia more than 90 beats / min, the severity of laboratory signs (increased ESR, CRP, leukocytes, albumin less than 35 g / l). In the presence of such manifestations of CD, patients need urgent hospitalization for urgent therapeutic measures, including:

1. In / in the introduction of fluids and electrolytes, especially potassium, since patients are often dehydrated.

2. In / in the introduction of hydrocortisone (initial dose of 100 mg 3 times a day).

3. Inside metronidazole (Trichopolum, etc.) 500 mg 3 times a day. The indication for prescribing the drug is its specific effect and the need to eliminate intestinal infection with opportunistic microflora inherent in this disease.

4. Blood transfusions to eliminate anemia, which is often quite significant (the level of Hb should be raised to 10 g/%).

5. If the patient has anorexia and severe dyspepsia (nausea, etc.), then you should refrain from forcible food intake, but at the same time ensure fluid intake.

6. In / in the introduction of hydrocortisone continues for 5 days, and as soon as vomiting stops and it becomes possible to take drugs orally, immediately in / in the introduction of hydrocortisone is replaced by oral administration of 4 mg of prednisolone per day.

7. The results of treatment are evaluated by the timing of the disappearance of symptoms (stool frequency, abdominal pain, anorexia, dyspepsia, abdominal tenderness, fever, tachycardia), laboratory parameters (Hb, CRP, ESR, albumin, electrolytes).

8. If no improvement occurs against the background of intravenous administration of hydrocortisone and other agents, then complications should be ruled out and the refractoriness of the disease should be taken into account. In this case, surgical treatment may be indicated.

9. When a clinical remission of the disease occurs, it is recommended to conduct appropriate studies in order to evaluate the results of treatment.

Indications for discharge of the patient are: the disappearance of dyspeptic and pain syndromes, restoration of appetite, stabilization of weight and other subjective and objective studies. 2 weeks after discharge, it is advisable to analyze the results of outpatient treatment.

10. If the remission of the disease persists on an outpatient basis, then after 2 weeks the dose of prednisolone must be reduced to 20 mg per day, against the background of ongoing remission, after 4 weeks, a further decrease in the dose of the drug by 5 mg every 2-4 weeks continues until it is completely cancelled. A more rapid reduction in the dose of the drug may be the cause of early relapse. Maintenance steroid therapy in CD is usually not carried out, except in cases where remission does not stabilize and the tendency to exacerbate with a decrease in the dose of the drug or its withdrawal persists.

Alternative treatment to steroid therapy.

1. Sulfasalazine 2 g per day (under the influence of intestinal microflora, it breaks down in the colon into sulfonamide and 5-aminosalicylic acid, which is the active ingredient of the drug). The drug can be used in combination with corticosteroids if the process is localized in the colon, but the benefit of such combined treatment is difficult to assess. Maintenance therapy with sulfasalazine in CD is possible only in those patients who have achieved remission under its influence and have a good tolerability of the drug. When the process is localized in the small intestine, convincing evidence of the effectiveness of this approach to the drug treatment of CD has not been obtained.

2. Mesalazine (mesalazine, salofalk and other synonyms) at 1200 mg per day is an alternative drug to sulfasalazine if the process in CD is localized in the small intestine.

3. Azathioprine (Imuran and other synonyms) at the rate of 2-2.5 mg per 1 kg of BW per day is prescribed in combination with steroids when a stable remission of the disease does not occur when taking steroids. The duration of taking azathioprine is at least a month. Longer treatment is determined empirically. With long-term use of azathioprine, it is necessary to conduct a blood test every 4-6 weeks, counting the number of granulocytes and platelets.

4. Metronidazole (tinidazole, trichopol and other synonyms) 400-500 mg per day is used in combination with steroids for perianal lesions or when there is a concomitant infection (dysbacteriosis, etc.). Metronidazole, according to the indicated indications, can be combined with other antibacterial drugs, for example, with ciprofloxacin (500 mg 2 times a day), to improve the results of treatment.

5. Cyclosporine (5-10 mg per 1 kg BW per day) is recommended to be used in combination with corticosteroids, but only in specialized medical institutions.

New goals for IBD treatment - not only clinical remission:

• Normalization of the quality of life

• Induction and maintenance of stable remission and withdrawal of steroids

• Prevention of complications, hospitalizations and surgical treatment

• Endoscopic remission

• Decreased mortality

Over the past 70 years, IBD therapy has evolved from empirical non-specific methods to a pathophysiology-based approach. Many drugs developed over this long period of time are still used today.

In the future, when the complex pathogenesis of IBD is better understood, and the existence of an individual patient response is proved, the ideal method of treating IBD will be selected for each patient, and this approach can rightfully be called personalized therapy.

Tests:

1. What is the leading theory of the occurrence of non-specific ulcerative colitis:

a) psychogenic

b) immunological

c) infectious

d) vascular

2. NUC is:

a) non-specific destructive inflammatory lesion of the large intestine;

b) specific ulceration of the large intestine

c) granulomatous inflammation of the colon

d) parasitic lesion of the large intestine

3. Morphological substrate of NUC:

a) chronic erosion or ulcer

b) specific granuloma

c) lymphocytic granuloma

d) narrowing of the intestinal lumen due to the growth of the mucous membrane

4. Endoscopic manifestations of UC in the acute phase:

a) ulceration and hyperemia of the intestinal mucosa

b) narrowing of the intestinal lumen

c) total atrophy of the intestinal mucosa

d) hemorrhoids

5. Name the characteristic clinical symptom of UC:

a) vomiting red blood

b) pain in the solar zone, passing after eating

c) blood in the stool

d) heartburn

6. The most informative way to diagnose UC:

a) passage of barium through the small and large intestines

b) colonoscopy

c) ultrasound scan of the intestine

d) thermography of the abdominal organs

7. Characteristic changes in the coprogram in NUC:

a) muscle fibers + starch grains

b) vegetable and muscle fibers + mucus

c) erythrocytes + leukocytes + mucus

d) plant fibers + muscle fibers + cholesterol crystals

8. Treatment of chronic ulcerative colitis begins with:

a) B vitamins

b) salazopyridazine

c) DOXA

d) protein hydrolysates

9. Crohn's disease is:

a) specific ulceration of the intestinal mucosa

b) non-specific ulceration of the intestinal mucosa

c) granulomatous inflammation of the digestive tract

d) parasitic lesions of the small and large intestines

10. Morphological substrate of Crohn's disease:

a) severe erosion

b) chronic erosion

c) lymphocytic granuloma

d) specific granuloma

11. Crohn's disease affects:

a) mucous membrane

b) submucosal layer

c) muscular and serous layers

d) all layers

12. The most common complication of Crohn's disease:

a) rectal bleeding

b) strictures and internal fistulas

c) malignancy

d) intestinal paresis

13. The drug of choice for the treatment of severe chronic ulcerative colitis:

a) prednisone

b) imodium

c) ftalazol

d) infliximab

14. Endoscopic sign of chronic nonspecific ulcerative colitis:

a) contact bleeding

b) persistent narrowing of the intestinal lumen

c) intestinal atony

d) mucosal atrophy

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