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PROJECT: CLINICAL GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ULCERATIVE COLITIS

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Key words
o Biological therapy
o Inflammatory bowel disease
o Adults
o Glucocorticosteroids
o Diarrhea
o Immunosuppressants
o Mesalazine
o Ulcerative colitis

List of abbreviations:
5-ASA -5-aminosalicylic acid
AZA-azathioprine
MP-mercaptopurine
CD -Crohn's disease
CI -coincidence interval
CT-computed tomography
GCS-glucocorticosteroids
IARA-ileoanal reservoir anastomosis
MMS -multi matrix shell
MRI - magnetic resonance imaging
NSAIDs-nonsteroidal anti-inflammatory drugs
RCT-randomized controlled trial
UC -ulcerative colitis

TERMS AND DEFINITIONS

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucous layer.

Flare-up (relapse, attack) of UC – the appearance of typical symptoms of the disease in patients with UC in the stage of clinical remission, spontaneous or medically supported. In practice, the signs of clinical flare-up are frequent bowel movements, bloody stools and/or peculiar changes during colonoscopy.

Remission of UC – disappearance of the main clinical symptoms of the disease [1] and healing of the colon mucosa ("deep remission") [2].

Clinical remission of UC – no blood stools, no urgent and frequent bowel movements 3 times a day or less.

Endoscopic UC remission – absence of visible macroscopic signs of inflammation during colonoscopy.

Histological UC remission– no microscopic signs of inflammation.

1. BRIEF INFORMATION

1.1 Definition

Ulcerative colitis is a chronic disease of the colon characterized by immune inflammation of its mucous layer.

1.2 Etiology and pathogenesis

The etiology of inflammatory bowel diseases (IBD), including UC, is unclear: the disease develops as a result of a combination of several factors, including genetic predisposing factors, defects in congenital and acquired immunity, intestinal microflora and various environmental factors.

About 100 single nucleotide polymorphisms associated with UC have been described. This genetic background predisposes to changes in congenital immune response, autophagy, mechanisms of recognition of microorganisms, endoplasmic reticulocyte stress, epithelial barrier functions and adaptive immune response.

A key immune defect predisposing to the development of IBD is a lesion of the recognition of bacterial molecular markers (patterns) by dendritic cells, which leads to hyperactivation of signaling proinflammatory pathways.

Also, in IBD, there is a decrease in the diversity of intestinal microflora due to a decrease in the proportion of anaerobic bacteria, mainly Bacteroidetes and Firmicutes. In the presence of these microbiological and immunological changes, IBD develops under the influence of trigger factors, which include smoking, nervous stress, vitamin D deficiency, a diet with a low content of dietary fiber and an increased content of animal protein, intestinal infections, especially C.difficile infection.

The result of the mutual influence of these risk factors is the activation of T-helpers of the second type, hyperexpression of anti-inflammatory cytokines, first of all, tumor necrosis factor-alpha (TNF-alpha) and cell adhesion molecules. The result of these reactions is lymphoplasmocytic infiltration of the colon mucosa with the development of specific macroscopic changes and symptoms of UC.

In UC, only the large bowel is affected (except for retrograde ileitis), the rectum is necessarily involved in the process, inflammation is most often limited to the mucous layer (except for acute severe colitis) and is diffuse.

1.3 Epidemiology

According to foreign data, the incidence of UC is from 0.6 to 24.3 per 100,000 people, the prevalence reaches 505 per 100,000 people [3]. Data on the prevalence of UC in the Russian Federation are limited [4]. The prevalence of UC is higher in Northern latitudes and in the West.

The incidence and prevalence of UC in Asia is lower, however, increasing. Caucasians suffer from the disease more often than representatives of the Negroid and Mongoloid races. The peak incidence is observed between 20 and 30 years of life, and the second peak incidence is described at the age of 60-70 years old. The incidence is approximately the same in males and females.

1.4 ICD Coding 10

C51.0-Ulcerative (chronic) enterocolitis
C51.0-Ulcerative (chronic) ileocolitis
C51.0 - Ulcerative (chronic) proctitis
C51.0-Ulcerative (chronic) rectosigmoiditis
C51.4- Colon Pseudopolyposis
C51.5-Mucosal proctocolitis
C51.8-Other ulcerative colitis
C51.9- Ulcerative colitis, unspecified

1.5 Classification

Proper classification of UC by the extent of the lesions, the nature of the course, the severity of the attack and the presence of complications determines the type and form of drug administration, as well as the frequency of screening for colorectal cancer [5].

The Montreal classification is used to describe the extent of the lesions (Table 1), assessing the extent of macroscopic signs in colonoscopy.

Table 1. *The Montreal classification of UC according to extent of disease process [6]*

Proctitis	The extent of the disease is limited to the rectum

Left-sidedcolitis	The lesion extends to the left flexure of the colon (including proctosigmoiditis)
Totalcolitis	The lesion extends proximal to the left flexure of the colon (including subtotal colitis as well as total UC with retrograde ileitis)

The nature of the course allocate:

1. Acute course (less than 6 months from the onset of the disease).
2. Chronic continuous course (absence of more than 6-month periods of remission on the background of adequate therapy).
3. Chronic recurrent course (presence of more than 6-month periods of remission).

The severity of the disease in general is determined by: the severity of the current attack, the presence of extra-intestinal manifestations and complications, refractory to treatment, in particular, the development of hormonal dependence and resistance. However, in order to formulate a diagnosis and determine treatment modality, the severity of the current flare-up (acute attack) should be determined, for which simple Truelove-Witts criteria, usually used in everyday clinical practice, and the UC activity index (Mayo index), usually used in clinical trials, are used. There are mild, moderate and severe disease (Table 2 and 3).

Table 2. *UC severity according to Truelove-Witts criteria [7]*

	Mild	**Moderate**	**Severe**
Frequency of defecation with blood	<4	≥4 if:	≥6, if:
Pulse	Normal values	≤90 bpm	≤90 bpm or
Temperature		≤37.5°C	>37.5°C or
Hemoglobin		≥105 g/l	≥105 g/l Or
ESR (erythrocyte sedimentation rate)		≤30 mm/h	≤30 mm/h
Contact vulnerability of the mucous layer of the colon	No	Visible	Visible

In clinical practice, the so-called "super severe" or "extremely severe" attack of UC is often found, characterized by diarrhea more than 10-15 times a day, a progressive decrease of hemoglobin, fever above 38°C, severe hypoproteinemia, electrolyte shifts, high levels of CRP [8,9].

Treatment modalities of such colitis are different from the usual. In English literature, this condition is called "acute severe UC" [10].

Table 3. *The severity of the attack according to the UC activity index (Mayo index)*

Indexvalue	**0**	**1**	**2**	**3**
Stool frequency	Usual	On the 1^{st}-2^{nd}days more than usual	On the 3^{rd}-4^{th}days more than usual	On the 5^{th}day more than usual
Blood in the stool	No	Fibrilla	Visible blood	Mostlyblood
Condition of the mucous layer	Normal	Minimum activity (1 point on the Schroeder scale)	Moderate activity (2 points on the Schroeder scale)	Expressed activity (3 points on the Schroeder scale)
General assessment of the condition by the doctor	Normal	Satisfactory condition	The condition of moderate severity	Severe condition
Moderate and severe attacks are stated at the index value (the sum of estimates for 4 parameters) from 6 and above.				

The Schroeder mucosal assessment scale used in the Mayo index is shown in table 4 and is used to assess the endoscopic activity of UC.

Table 4. *Classification of UC depending on endoscopic activity (according to Schroeder) [11]*

0	**1 (minimum activity)**	**2 (moderate activity)**	**3 (expressed activity)**

Normal or inactive disease	Slight hyperemia, blurred vascular pattern. Easy contact vulnerability.	Severe hyperemia, absence of vascular pattern, moderate contact vulnerability, erosion).	Spontaneous vulnerability, ulceration.

Classification of UC depending on the response to steroid therapy facilitates the choice of rational treatment modality, since the goal of conservative treatment is to achieve stable remission with the cessation of therapy with glucocorticosteroids (GCS).

For these purposes are allocated:

1. Hormonal resistance:

a. In case of severe attack-no positive changes in clinical and laboratory indicators, despite the use of systemic corticosteroids at a dose equivalent to 2 mg/kg body weight of prednisolone per day for more than 7 days;

b. In the case of a moderate attack-maintaining the activity of the disease with oral administration of GCS at a dose equivalent to 1 mg/kg body weight of prednisolone for 2 weeks.

2. Hormone dependence:

a. Increase in disease activity resulting from a reduction in the dose of GCS after achieving initial improvement within 3 months from the beginning of treatment;

b. Relapse of the disease within 3 months after the end of treatment with GCS.

In formulating the diagnosis should reflect the nature of the disease, extent of lesions, severity of current attack or the presence of remission, the presence of hormonal dependence or resistance, and the presence of intestinal or extraintestinal complications of UC.

The following are examples of diagnosis formulations:

1. "Ulcerative colitis, chronic recurrent course, proctitis, moderate attack."
2. "Ulcerative colitis, chronic continuous course, left-sided lesion, moderate attack. Hormone dependence. Extra-intestinal manifestations (peripheral arthropathy)".
3. "Ulcerative colitis, chronic recurrent course, total lesion, severe attack. Hormonal resistance. Toxic megacolon."

1.6 Clinical picture

The main clinical symptoms of ulcerative colitis include diarrhea and / or false blood urges, tenesmus and imperative urge to defecate, and nocturnal defecation.

With a severe attack of UC, common symptoms such as weight loss, general weakness, anorexia, and fever may appear. The main symptoms are listed in table 5.

Table 5. *The main symptoms of ulcerative colitis*

Possible symptoms of the disease in history		**Typical clinical symptoms at the time of examination**	
✔ Episodes of diarrhea ✔ Admixture of blood in feces ✔ Tenesmus	✔ Extra-Intestinal symptoms (lesions of the skin, mucous layers, joints, eyes, etc.)	✔ Diarrhea ✔ Blood in the feces ✔ Night defecation (more often with expressed activity of the process)	✔ Tenesmus (more often in proctitis and proctosigmoiditis) ✔ Body weight loss ✔ Fever ✔ Anemia ✔ Extra-intestinal symptoms

For UC, unlike Crohn's disease (CD), abdominal pain is less specific and is moderate (spastic), more often before defecation; with proctitis and proctosigmoiditis, diarrhea may be absent, and frequent false urges may be combined with constipation or formed feces.

In a significant part of patients, extra-intestinal manifestations of the disease can be detected (Table6) [12].

Table 6. *Extra-intestinal (systemic) manifestations of ulcerative colitis*

Autoimmune activity-related diseases:	**Autoimmune, non-activity-related diseases:**	**Caused by prolonged inflammation and metabolic disorders:**
Arthropathy (arthralgia, arthritis) Skin lesions (erythema nodosum, gangrenous pyoderma) Mucosal lesions (aphthous stomatitis)	Ankylosing spondylitis (sacroileitis) Primary sclerosing cholangitis	Cholelithiasis Liver steatosis, steatohepatitis Peripheral vein thrombosis, pulmonary embolism

Eye lesions (uveitis, iritis, iridocyclitis, episcleritis)	Osteoporosis, osteomalacia Psoriasis	Amyloidosis

Autoimmune manifestations associated with the activity of the inflammatory process appear together with the main intestinal symptoms of flare-up and disappear with them during treatment. Autoimmune manifestations that are not associated with the activity of the process (in the English literature they are often called "concomitant autoimmune diseases") tend to progress regardless of the phase of the underlying disease (flare-up or remission) and often determine the negative prognosis of the disease.
Intestinal complications of UC include intestinal bleeding, toxic dilation and perforation of the colon, and colorectal cancer. Since these complications require more surgical treatment, they are discussed in detail in Section 3.2 " Surgical treatment».

2. DIAGNOSTICS

There are no unambiguous diagnostic criteria for UC. The diagnosis is made on the basis of a combination of anamnesis, clinical picture and typical endoscopic and histological changes.

2.1 Complaints and history of the disease

In all patients with suspected UC, it is recommended to pay attention to the frequency and nature of feces, the duration of these symptoms, the presence of blood in stools, the nature of abdominal pain [13,14].

Category of recommendations - B (level of evidence - 3)

- In all patients with suspected UC, a detailed history survey should be conducted, including, in particular, the collection of information on:
  - trips to southern countries [15].

Category of recommendations - B (level of evidence - 3)

  - medications taken (in particular, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)) [16].

Category of recommendations - B (level of evidence - 3)

  - smoking [17].

Category of recommendations - A (level of evidence - 1)

  - presence of inflammatory and malignant intestinal diseases in relatives [18].

Category of recommendations - B (level of evidence - 3).

2.2 Physical examination

- All patients with suspected UC are recommended to undergo mandatory physical examination [19-21]:
  – inspection of the perianal area;
  – finger examination of the rectum;

Category of recommendations - D (level of evidence - 5)

Comment. *Physical examination may reveal various manifestations of UC, including fever, peripheral edema, nutritional deficiencies, signs of perforation or toxic dilatation of the colon, and extra-intestinal manifestations.*

2.3 Laboratory tests

• For all patients, the recommended minimum laboratory tests are:
- Clinical blood analysis (hemoglobin, hematocrit [22,23] leukocytes, neutrophils, lymphocytes, monocytes [23,24,25], platelets [23], erythrocyte sedimentation rate (ESR) [26];
- Blood biochemistry (total protein, albumins [23], liver enzymes [27], electrolytes [28]);
- C-reactive protein [26,29];
- Coagulogram (fibrinogen) [30]

Category of recommendations - D (level of evidence - 5)

Comment. *At the clinical analysis of blood, anemia (iron deficiency, anemia of chronic disease), leukocytosis (on the background of chronic inflammation or on the background of steroid therapy), thrombocytosis can be diagnosed.*

Biochemical examination reveals electrolyte disturbances, hypoproteinemia (in particular, hypoalbuminemia), as well as an increase in alkaline phosphatase, which is a possible manifestation of primary sclerosing cholangitis associated with UC.

- In all patients with acute UC (at the first attack of the disease) it is recommended to perform bacteriological and microscopic examination of feces to exclude acute intestinal infection [17].

Category of recommendations - B (level of evidence - 3)

Comment. *With the debut of the disease and the recurrent attack both, it is recommended to study toxins A and B C. difficile (especially with a recent course of antibiotic therapy or hospital stay). This test is also recommended for severe development of resistance to therapy [31,32]. A minimum of 4 feces samples are required to detect infection in 90% of cases [33,34]. In severe and supersevere UC it is necessary to exclude cytomegalovirus (CMV) infection.*

- In all patients with suspected UC, it is recommended to study the level of fecal calprotectin in the primary differential diagnosis with functional intestinal diseases, as well as for non-invasive assessment of the activity of the inflammatory process in the intestine during treatment [35,36].

Category of recommendations - B (level of evidence - 2b)

- Patients with moderate and severe attacks of ulcerative colitis, as well as in the case of hormonal resistance or hormonal dependence, resistance to immunosuppressive therapy or biological therapy drugs, loss of effect on immunosuppressive therapy or biological therapy drugs are shown to conduct DNA cytomegalovirus in a biopsy from the affected areas of the large intestine by polymerase chain reaction [20,37].

Category of recommendations - B (level of evidence - 3)

Comment: *More than 5,000 copies/10^5 cells are considered to be a diagnostically significant titer.*

2.4 Instrumental diagnostics

Diagnosis of UC is mainly based on instrumental methods. To confirm the diagnosis, the following measures are necessary:

- Rectoromanoscopy is recommended for all patients with UC [19,38].

Category of recommendations - D (level of evidence - 5);

- Patients with severe UC attack are recommended to have a review x-ray of the abdominal cavity to exclude toxic dilatation and perforation of the colon; [39,40].

Category of recommendations - D (level of evidence - 5);

- All patients with suspected UC are recommended to undergo colonoscopy with ileoscopy to determine the location, extent, degree of activity of the inflammatory process [41].

Category of recommendations - A (level of evidence - 1);

Comment. *This is a mandatory procedure for the diagnosis of UC, as well as to make decision on colectomy.*

Endoscopic examination of the large intestine is the main method of diagnosis of UC, however, specific endoscopic signs are absent.

The most specific symptoms are continuous inflammation, limited by the mucous layer, beginning in the rectum and spreading proximally, with a clear border of inflammation.

The endoscopic activity of the UC is best reflected by contact vulnerability (spontaneous bleeding in contact with the endoscope), the absence of vascular pattern and the presence or absence of erosions and ulceration.

Detection of persistent narrowing of the intestine against the background of UC requires mandatory exclusion of colorectal cancer.

- All patients with suspected UC at the initial diagnosis, with doubts about the correctness of the earlier diagnosis, it is recommended to perform a biopsy of the colon mucosa [41,42].

Category of recommendations - A (level of evidence - 1);

Comment. *With a long history of UC (for more than 7-10 years) - chromoendoscopy with targeted biopsy or step biopsy (from each part of the colon) are recommended to exclude epithelial dysplasia.*

The recommended biopsy standard for diagnosis is to take biopsies of the mucous layer of the rectum and at least 4 other areas of the colon, as well as the mucous layer of the ileum.

Microscopic signs of UC include the deformation of the crypts (branching, diversity, appearance of crypts of different diameter, the density of the crypts, "the shortening of the crypts", the crypt does not

reach the underlying layer of muscularis propria of mucous layer), "irregular" surface of the mucosa in the biopsy specimen of the mucous layer, a decrease in the number of goblet cells, basal plasmacytosis, infiltration of the lamina propria of the mucosa, the presence of crypts abscesses and basal lymphoid clusters.

The degree of inflammatory infiltration usually decreases with distance from the rectum.

- Ultrasound examination of the abdominal cavity, retroperitoneal space, pelvis is recommended for all patients with suspected UC at the initial diagnosis, with doubts about the correctness of the earlier diagnosis, with a long history of UC, with suspected complications of UC, as well as to exclude the pathology of other abdominal organs [43,44].

Category of recommendations - C (level of evidence - 4);

- Radiological examinations are recommended for all patients with suspected UC if differential diagnosis is necessary or if full ileocolonoscopy is not possible:

- Magnetic resonance imaging (MRI) with contrast of the intestine [45,46];

Category of recommendations - D (level of evidence - 5);

In case of unavailability of expert evaluation or impossibility to perform MRI with intestine contrast, computed tomography (CT) with intestine contrast is recommended [47,48];

Category of recommendations - D (level of evidence - 5);

- For all patients with suspected UC if differential diagnosis is necessary or if it is impossible to perform a full ileocolonoscopy, MRI and CT, it is recommended to perform double-contrast barium enema examination to assess the extent of lesions in the colon, to clarify the presence of tumors, strictures, etc. [20,49].

Category of recommendations - D (level of evidence - 5);

Additional tests in the presence of indications can be:

- *transabdominal ultrasound scan of the small intestine and colon;*
- *transrectal ultrasound of the rectum and anal canal;*
- *fibrogastroduodenoscopy;*
- *videocapsularendoscopy;*
- *one-or two-balloon enteroscopy.*

2.5 Other diagnostics

Additional instrumental and laboratory tests are performed primarily for the purpose of differential diagnosis with a number of diseases.

These are infectious, vascular, drug, toxic and radiation lesions, as well as diverticulitis, etc.

At the next stage of differential diagnosis, verification of clinical diagnoses of UC and CD belonging to the IBD group is carried out.

Thus, the differential diagnosis of UC is carried out with Crohn's disease of the large intestine, acute intestinal infections (dysentery, salmonellosis, campylobacteriosis, yersiniosis, amoebiasis), parasitoses, antibiotic-associated intestinal lesions (pseudomembranous colitis caused by C.Difficile) [50], intestinal tuberculosis, systemic vasculitis, colon cancer, diverticulitis, microscopic colitis (collagen and lymphocytic) [51], radiation proctitis.

For the purpose of differential diagnosis and selection of therapy for extraintestinal manifestations of UC and comorbidities may be required consultation by:

- *Psychotherapist, psychologist (neurosis, planned surgery with the presence of stoma, etc.);*
- *Endocrinologist (steroid diabetes mellitus, adrenal insufficiency in patients on long-term hormone therapy);*
- *Dermatologist (differential diagnosis of erythema nodosum, pyoderma, etc.);*
- *Rheumatologist (arthropathy, sacroiliitis, etc.);*
- *Obstetrician-gynecologist (pregnancy).*

3. TREATMENT

3.1 Conservative treatment

3.1.1 Principles of therapy

Treatment modalities for UC include drug prescribing, surgical treatment, psychosocial support, and dietary recommendations.
The choice of conservative or surgical treatment depends upon the severity of the attack, extent of lesions of the large intestine, presence of extra intestinal manifestations, duration of anamnesis, efficacy and safety of past therapy and the risk of complications of UC [52,53].
The aim of therapy is to achieve and maintain steroid-free remission (discontinuation of GCS within 12 weeks after the start of therapy) [54], prevention of complications of UC, prevention of surgery, and with the progression of the process, as well as the development of life-threatening complications-timely appointment of surgical treatment.
Since the complete cure of patients with UC is achieved only by removing the substrate of the disease (colproctectomy), when remission is achieved, the non-operated patient must remain on constant maintenance (anti-relapse) therapy.
It should be noted that GCS can not be used as a maintenance therapy.
Recommendations on the choice of drugs for induction and maintenance of remission depending on the extent of the lesion and the severity of the attack are presented below [20].

3.1.2 Proctitis. Mild and moderate attacks.

- For this group of patients, it is recommended to prescribe suppositories with mesalazine (1-2 g/day) or rectal mesalazine foam (1-2 g/day) [55].

Category of recommendation – A (level of evidence - 1).
Comment. *The therapeutic response is assessed after 2 weeks [55]. With a positive response, treatment at these doses is prolonged to 6-8 weeks.*

- For this group of patients with ineffective treatment with rectal forms of mesalazine, it is recommended to administer rectal forms of GCS (rectal foam budesonide 2 mg per day, suppositories with prednisolone 10 mg x 1-2 times per day) with an assessment of the response after 2 weeks [56].

Category of recommendation - A (level of evidence - 1).

- For this group of patients with remission, it is recommended to conduct maintenance therapy-rectal mesalazine (suppositories or rectal foam) 1-2 g x 3 times a week in the form of monotherapy ("weekend" therapy) for at least 2 years [57].

Category of recommendation - A (level of evidence - 1).

- For this group of patients with ineffective local treatment, it is recommended to add oral forms of mesalazine granules, tablets, tablets in a multimatrix shell (MMS)) at a dose of 2.4-4.8 g/day [58].

Category of recommendation - B (level of evidence - 1).

- For this group of patients in the absence of the effect of oral forms of mesalazine, it is recommended to prescribe GCS at a dose equivalent to 0.5-0.75 mg/kg body weight of prednisolone tablets per day. It is also possible to prescribe topical steroids (budesonide MMS at a dose of 9 mg per day) [59].

Category of recommendation - B (level of evidence - 3).

- In this group of patients, in case of relapse requiring repeated administration of GCS, the combination of GCS with azathioprine (AZA) or mercaptopurine (MP) is recommended [59].

Category of recommendation - B (level of evidence - 3).
Comment.*ASA is prescribed at 2-2. 5 mg/kg, and 6-MP at 1.5 mg/kg. Local therapy (rectal foam budesonide 2 mg per day, suppositories with prednisolone 10 mg x 1-2 times per day) can be continued.*

- For this group of patients in achieving remission induced by GCS, is recommended maintenance therapy of AZA 2-2. 5 mg/ kg (or MP 1.5 mg / kg) for at least 2 years [59].

Category of recommendation - B (level of evidence - 3).

- In case of detection of cytomegalovirus DNA by polymerase chain reaction in the biopsy from the affected area of the colon mucosa, the patient is indicated for ganciclovir therapy at a dose of 5mg / kg 2 times a day for 14-21 days [20,60].

Category of recommendation – C (level of evidence - 4).

3.1.3 Proctitis. Severe course (develops extremely rarely).

- For this group of patients with severe ulcerative proctitis, is recommended intravenous GCS at a dose equivalent to prednisolone 1-2 mg / kg body weight per day in combination with local therapy with mesalazine (suppositories, rectal foam) or GCS (rectal foam budesonide 2 mg per day, suppositories with prednisolone 10 mg x 1-2 times per day) [56,59].

Category of recommendation - D (level of evidence - 5).

Comment. *It is possible to prescribe topical steroids - budesonide MMS at a dose of 9 mg per day, in combination with local therapy with mesalazine or GCS.*

- In this group of patients in the case of the first attack, maintenance therapy in achieving remission is done with the local mesalazine forms (suppositories, rectal foam) 1-2 g x 3 times a week as monotherapy (regular use, therapy on demand or "weekend therapy") or in combination with oral mesalazine (granules, tablets, pills MMS) in a dose of 2-2.4 g for at least 2 years [57].

Category of recommendation - A (level of evidence - 1).

- For this group of patients with relapse requiring repeated administration of GCS (systemic or topical), it is recommended to simultaneously administer AZA 2-2.5 mg / kg (or MP 1.5 mg/kg) and continue maintenance therapy with immunosuppressors (AZA or MP) for at least 2 years [59].

Category of recommendation - D (level of evidence - 5).

- In case of detection of cytomegalovirus DNA by polymerase chain reaction in the biopsy from the affected area of the colon mucosa, the patient is indicated for ganciclovir therapy at a dose of 5mg / kg 2 times a day for 14-21 days [20,60].

Category of recommendation - C (level of evidence - 4).

3.1.4 Left-sided and total ulcerative colitis. Mild attack.

- For this group of patients with the first or recurrent attack, it is recommended to prescribe mesalazine in oral forms (granules, tablets, MMS tablets) 2.4-3 g/day (or sulfasalazine 3g/day.) in combination with mesalazine in enemas 2-4 g/day (depending on endoscopic activity) [61-66].

Category of recommendation - A (level of evidence - 1).

Comment. *The therapeutic response is assessed after 2 weeks. If the response is positive, the treatment will last up to 6-8 weeks.*

- For this group of patients in the absence of the effect of combination therapy with 5-aminosalicylic acid (5-ASA), is recommended the appointment of rectal forms of GCS: rectal foam budesonide 2 mg per day or suspension of hydrocortisone acetate with lidocaine 125-250 mg 1 time per day in the form of enemas or rectal drip [67].

Category of recommendation - C (level of evidence - 4).

- For this group of patients, when remission is achieved, it is recommended to carry out maintenance therapy with oral mesalazine (in granules, tablets, MMS tablets) 2-2.4 g/day [68].

Category of recommendation - A (level of evidence-1).

Comment. *Additional administration of mesalazine in enemas of 2 g x 2 times a week ("weekend therapy") increases the likelihood of long-term remission. Permissible appointment of sulfasalazine (2 g) instead of mesalazine*.

- Topical GCS (budesonide MMS) or systemic GCS (see section 3.1.4) are generally recommended in this group of patients in the absence of a response to oral 5-ASA therapy in combination with any local treatment option [69].

Category of recommendation - B (level of evidence - 2).

• In case of detection of cytomegalovirus DNA by polymerase chain reaction in the biopsy from the affected area of the colon mucosa, the patient is indicated for ganciclovir therapy at a dose of 5mg / kg 2 times a day for 14-21 days [20,60].

Category of recommendation – C (level of evidence - 4).

3.1.5 Left-sided and total ulcerative colitis. Moderate attack

- For this group of patients with the first attack or relapse, it is recommended to prescribe oral mesalazine (in granules, tablets, MMS tablets) 3.0-4.8 g / day in combination with mesalazine in enemas 2-4 g/day. (depending on endoscopic activity) [63,70].

Category of recommendation - A (level of evidence - 1).

Comment. *The therapeutic response is evaluated after 2 weeks. With improvement of clinical symptoms and positive laboratory dynamics, therapy lasts up to 6-8 weeks.*

- When remission is achieved, maintenance therapy with mesalazine (taken in granules, tablets, MMS tablets) 2-2.4 g/day and mesalazine enemas of 2 g x 2 times a week (as a "weekend" therapy) is recommended for this group of patients [66,71].

Category of recommendation - A (level of evidence - 1).

Comment. *It is permissible to prescribe sulfasalazine 2 g/day instead of mesalazine* [70].

- This group of patients in the absence of the effect of 5-ASA and the absence of systemic signs of inflammation is prescribed to take topical GCS (budesonide MMS) [69,72-74].

Category of recommendation - B (level of evidence - 2).

This group of patients in the absence of the effect of 5-ASA and the presence of systemic inflammation is prescribed to take systemic GCS [69,72-74].

Comment. *Systemic GCS are prescribed at a dose equivalent to prednisolone 0.75-1 mg/kg body weight, tropical (budesonide MMS) at a dose of 9 mg/day. Reducing the dose of systemic GCS is by 5 mg for 5-7 days before complete withdrawal. After 10 weeks of taking budesonide MMS, dose reduction is carried out every other day for 1-2 weeks until complete withdrawal.*

• This group of patients with repeated administration of GCS for a year or less or in the case of intolerance to 5-ASA drugs, a combination of GCS with AZA 2-2.5 mg/kg or MP 1.5 mg/kg is recommended [75,76].

Category of recommendation - A (Category of evidence - 1).

• This group of patients with remission is recommended to continue maintenance therapy AZA 2-2. 5 mg / kg / day or MP 1.5 mg / kg for at least 2 years [75,76].

Category of recommendation- A (Category of evidence - 1).

- Biological therapy (infliximab, adalimumab, golimumab, vedolizumab or tofacitinib) is indicated in this group of patients in the absence of the effect of GCS for 2 weeks, starting from the induction course, at doses corresponding to the instructions for use [77-81].

Category of recommendation - A (level of evidence - 1).

- For patients receiving infliximab, to increase its effectiveness, it is recommended to combine it with immunosuppressants (AZA 2-2.5 mg / kg or MP 1.5 mg/kg [82,83].

Category of recommendation -A (level of evidence - 1).

Comment. *For other biological preparations, such a combination may not be carried out [84,85]*.

- In this group of patients, with the effectiveness of the induction course of biological drugs, maintenance therapy is carried out with them in accordance with the instructions for use for at least 2 years [86-90].

Category of recommendation - A (level of evidence - 1).

- For this group of patients in the absence of a primary response to anti-TNF drugs, it is recommended to change therapy to tofacitinib [91].

Category of recommendation - A (level of evidence - 1).

Comment. *Tofacitinib can be assigned as the 1stand 2ndtherapy line in combination with GCS. Changing anti-TNF to vedolizumab is possible, but its effectiveness is lower.*

- Optimization of therapy in the form of increasing the dose of the drug (10 mg/kg infliximab every 8 weeks, 100 mg golimumab every 4 weeks) or reducing the intervals between injections (infliximab every 4 weeks, adalimumab every week) or changing therapy to vedolizumab or tofacitinib is recommended for this group of patients with recurrent UC against the background of previously achieved remission (loss of response) to anti-TNF therapy [86-90].

Category of recommendation - B (level of evidence - 2).

Comment. *Changing to another anti-TNF drug is possible, but its effectiveness is lower than when switching to tofacitinib.*

- For this group of patients with loss of response to vedolizumab at a standard dose of 300 mg every 8 weeks, it is recommended to optimize therapy in the form of reducing the intervals between injections to 4 weeks or change to a biological drug of another class [92].

Category of recommendation - C (level of evidence - 4).

- For this group of patients with loss of response to tofacitinib at a standard dose of 10 mg per day, it is recommended to optimize therapy to 20 mg per day or change to a biological drug of another class [93].

Category of recommendation - A (level of evidence - 1).

Comment. *The duration of biological therapy is determined by the attending physician. In most countries, treatment is carried out for many years. Early withdrawal of drugs usually leads to a recurrence of UC in a short time. In case of impossibility of prolonged use of biological drugs, maintenance therapy is carried out only with thiopurines. In case of intolerance to thiopurines - monotherapy with biological drugs.*

Currently, biosimilars (analogues) of anti-TNF drugs similar to the original biological drugs in efficiency and safety are registered, but their interchangeability with the original drugs is not currently proven.

Given the lack of clinical trials in patients with IBD that have proven the safety and effectiveness of alternating or complete switching from the original drug to biosimilars and vice versa, such a therapeutic approach is not recommended.

- For this group of patients with a reduced dose of GCS equivalent to 35-45 mg of prednisolone, if the patient does not receive immunosuppressors and biological therapy, it is additionally recommended to connect mesalazin (in granules, tablets, MMS tablets) at a dose of 4-4.8 g [66].

Category of recommendation - A (level of evidence - 1b).

Comment. *Further reduction of GCS should be carried out on the background of mesalazine, followed by the transition to supportive therapy with mesalazine (in granules, tablets, MMS tablets) 2-2.4 g per day. Prescribing sulfasalazine 2 gin stead of mesalazineis acceptable.*

- For this group of patients with relapse of severe UC, which occurred on the background of maintenance therapy with mesalazine, it is recommended toimmediately prescribe GCS in combination with ASA / MP [94].

Category of recommendation - C (level of evidence - 4).

Comment. *Further tactics are similar to treatment at the first attack.*

- For this group of patients with relapse, which occurred on the background of maintenance therapy with thiopurines, it is recommended to prescribe biological drugs (infliximab, adalimumab, golimumab, vedolizumab or tofacitinib) [86-90].

Category of recommendation - A (level of evidence - 1).

• In case of detection of cytomegalovirus DNA by polymerase chain reaction in the biopsy from the affected area of the colon mucosa, the patient is indicated for ganciclovir therapy at a dose of 5mg / kg 2 times a day for 14-21 days [20,60].

Category of recommendation – D (level of evidence - 5).

3.1.6 Left-sided and total ulcerative colitis. Severe attack.

- This group of patients is recommended intravenous therapy with GCS at a dose equivalent to prednisone 1-2 mg/kg body weight for 7 days or intravenous administration of hydrocortisone at a dose of 300 mg per day [95].

Category of recommendation - A (level of evidence - 1).

Comment. *The equivalence of doses and duration of action of GCS is given in table 7.*

- This group of patients is additionally recommended to prescribe local therapy with enemas with mesalazine 2-4gr. per day or a suspension of hydrocortisone acetate with lidocaine 125-250 mg x 1 time per day in the form of enemas or rectal drip [67].

Category of recommendation - C (level of evidence - 3).

- This group of patients in the presence of metabolic disorders is recommended infusion therapy for rehydration, correction of protein-electrolyte disorders [54].

Category of recommendation - C (level of evidence - 4).

Comment. *Hypokalemia and hypomagnesemia increase the risk of toxic dilatation of the colon.*

- This group of patients with hemoglobin levels below 80 g/l is recommended correction of anemia in the form of hemotransfusion (erythromass), from 80 to 100 g / l-therapy with iron parenterally (iron (III) hydroxide sucrose complex, iron (III) dextran hydroxide, iron carboxymaltosate) [96].

Category of recommendation - A (level of evidence - 1).

- For patients with body mass deficit (BMI less than 18) it is recommended to connect additional enteral (probe) nutrition [97];

Category of recommendation - D (level of evidence - 5).

Comment. *Fully parenteral nutrition and/or a temporary restriction of food intake to the inside is impractical*

- In the presence of symptoms of intoxication, antibiotics are recommended:

o 1 line-metronidazole 1 g / day i/v + fluoroquinolones (ciprofloxacin, ofloxacin) i/v for 10-14 days; [95,98].

o line 2 - cephalosporins 1-2 g per day i/v for 7-10 days [99,100].

Category of recommendation - C (level of evidence – 4).

Table 7. *Comparative characteristics of GCS*

Drug	Durationofaction ($t_{1/2}$)	Equivalentdose (mg)
Cortisol (hydrocortisone)	8-12 hs	20
Prednisone	12-36 hs	5
Prednisolone	12-36 hs	5
Methylprednisolone	12-36 hs	4

• This group of patients with a clinical response to GCS after 7 days is prescribed to change to oral prednisolone with subsequent reduction by 5-10 mg for 5-7 days to complete withdrawal of prednisolone [54].

Category of recommendation - B (level of evidence - 3).

Therapeutic tactics in the absence of effect from GCS therapy under severe attack is described in item 3.1.7.

3.1.7 Super severe ulcerative colitis of any extent.

In this form, both the first attack of the UC and any of the subsequent flare-up can occur (see the section "classification of the UC" for a description). The patient should be hospitalized in a multidisciplinary (specialized) hospital followed by mandatory supervision by a specialist gastroenterologist and a specialist coloproctologist (surgeon).

- Patients with super severe attack of UC are recommended to have GCS i/v at a dose equivalent to prednisolone 2 mg / kg body weight.

Comment. *The effect is evaluated no later than 7 days after the start of therapy with mandatory examination by a specialist gastroenterologist and specialist coloproctologist and evaluation of laboratory parameters on the 3rd and 5th days.*

The transition from intravenous to oral administration of GCS is carried out in the same way as in a severe attack, if necessary, intravenous hormone therapy can be prolonged until a stable positive shift is achieved, but not more than 14 days.

You can add topical administration of hormones (hydrocortisone acetate with lidocaine prednisolone in microclyster).

- For this group of patients in the presence of hormonal resistance, continuation of hormonal monotherapy or an increase in the dose of GCS is not recommended [69].

Category of recommendation - B (level of evidence - 2).

• If there is no immediate threat to the patient's life or the development of severe complications requiring immediate surgical intervention, this group of patients is recommended to prescribe "second line" therapy (in the English literature as "rescue therapy"), which includes the following treatment options:

- Infliximab 5 mg/kg (administered as part of the induction course at the $0.2^{nd}$and 6^{th}week) [101,102].

Category of recommendation - A (level of evidence - 1).

- cyclosporine A (preferably intravenous) 2-4 mg/kg for 7 days with monitoring of renal function [103,104].

Category of recommendation - A (level of evidence - 1).

Comment. *Other anti-TNF drugs and vedolizumab as "rescue therapy" are not used. The use of tofacitinib is possible, but at the moment the data are limited.*

- For this group of patients, with the absence of response to the 2nd infusion of infliximab or 7-day therapy with cyclosporine A, it is recommended to consider options for surgical treatment [105].

Category of recommendation - 4 (level of evidence - C).

• In this group of patients, in response to an induction course of infliximab, further maintenance therapy is performed every 8 weeks for at least 2 years in combination with or without AZA 2 mg/kg (or MP 1.5 mg/kg) [83,106,107].

Category of recommendation - A (level of evidence-1).

• In this group of patients, with impossibility of long-term administration of infliximab, maintenance therapy is recommended to conduct AZA at a dose of 2 mg / kg for at least 2 years. System GCS are cancelled according to the scheme of decrease [75,76].

Category of recommendation - C (level of evidence - 4).

• This group of patients, with a positive response to cyclosporine A i/v after 7 days, is recommended to change to oral drug in a dose of 2 mg / kg of body weight with additional administration of AZA 2 mg/kg (to the background therapeutic doses of steroids) with gradual withdrawal of steroids within 12 weeks to reach therapeutic concentration and onset of AZA action.

When remission is achieved, oral cyclosporine can be canceled, leaving the patient on maintenance therapy of AZA for at least 2 years [108,75,76,109].

Category of recommendation - B (level of evidence - 2).

• In case of detection of cytomegalovirus DNA by polymerase chain reaction in the biopsy from the affected area of the colon mucosa, the patient is indicated for ganciclovir therapy at a dose of 5 mg/kg 2 times a day for 14-21 days [20,60].

Category of recommendation - C (level of evidence - 4).

3.1.8 Predicting the effectiveness of conservative therapy in supersevere attack of UC

Joint observation of the patient by a gastroenterologist and a coloproctologist is necessary for optimal control of the course of the disease. Although drug therapy is effective in many cases, there is evidence indicating that the delay in carrying out the necessary surgical treatment adversely affects the outcome of treatment of the patient, in particular, increasing the risk of surgical complications [110].

Most studies of predictors of colectomy conducted before the widespread use of biological therapy and cyclosporine and predict the ineffectiveness of GCS, rather than infliximab and immunosuppressors:

- *Defecation frequency >12 times / day on the 2nd day of i/v hormone therapy increases the risk of colectomy by up to 55% [111];*
- *If on the 3rd day of hormonal therapy the defecation frequency exceeds 8 times / day or is from 3 to 8 times/day and the level of CRP exceeds 45 mg / l, the probability of colectomy is 85% (the so-called "Oxford index") [112];*
- *On the 3rd day, you can also determine the "Swedish index" by the formula: defecation frequency ×0.14 ×CRP level. Its value of 8 or more increases the probability of colectomy up to 75% [113];*
- *The risk of colectomy is also increased by 5-9 times in the presence of hypoalbuminemia and fever on admission, as well as in the absence of more than 40% reduction in the defecation frequency for 5 days of intravenous hormone therapy [114];*
- *The presence of deep ulceration of the large intestine (against which the residual mucous layer is detected only in the form of "islands") increases the risk of colectomy to 86-93% [115,116].*

The effectiveness of infliximab in hormonal resistance according to different data ranges from 25% to 80%, which can be explained by differences in the effectiveness of the drug in individual patients. Research on predicting the effectiveness of biological therapy remains limited; however, it has been found that:

- *The effectiveness of infliximab in hormone-resistant severe UC attack decreases with age [117], in the presence of total large intestine lesion[118], as well as in severe hypoalbuminemia [119], hemoglobin level less than 95 g / l and CRP level more than 10 mg/l at the time of the first administration of infliximab [120].*

- *The effectiveness of infliximab is significantly lower in patients whose indications for anti-cytokine therapy arose already at the first attack of UC.*
- *The presence of extensive ulcerative defects of the mucous layer ("islands of the mucous layer") of the large intestine during colonoscopy before the start of infliximab therapy with 80% accuracy predicts its further inefficiency [105], increasing the risk of colectomy by 2.38-5.13 times [121,122].*

In patients with high risk of colectomy, an individual decision should be made on the "second-line" therapy with cyclosporine or infliximab or on surgical treatment immediately after an ineffective course of intravenous GCS.

3.2 Surgical treatment

3.2.1 Indications for surgical treatment of UC: Inefficiency or inability to continue conservative therapy

Indications for surgical treatment of UC are inefficiency of conservative therapy (hormonal resistance, inefficiency of biological therapy) or impossibility of its continuation (hormonal dependence, intolerance or contraindications for conservative therapy), intestinal complications of UC (toxic dilation, perforation of the intestine, intestinal bleeding), as well as colon cancer or a high risk of its occurrence.

The ineffectiveness of conservative therapy is evidenced by(see section 1.5):

- *hormoneresistance;*
- *hormonedependence.*

Hormonal dependence can be effectively overcome with the help of biological drugs and / or immunosuppressors (AZA, MP) in 40-55% of cases [65,109], and with hormonal resistance, cyclosporine A or biological therapy can induce remission in 43-80% of cases [123].

However, some patients with a high risk of complications and inefficiency of conservative therapy in the development of hormonal resistance or dependence may undergo surgical treatment without attempting to use biological drugs or immunosuppressants.

3.2.2 Indications for surgical treatment of UC: Intestinal complications of UC

- In all patients with UC complication in the form of intestinal bleeding, emergency surgery in the volume of subtotal colectomy or total colectomy (colproctectomy - with pronounced rectal activity) is indicated [112].

Category of recommendation - C (level of evidence – 4).

- In all patients with UC complication in the form of toxic dilatation on the background of adequate intensive therapy, emergency surgery in the volume of subtotal colectomy or total colectomy (colproctectomy - with pronounced rectal activity) is indicated [111,124].

Category of recommendation - C (level of evidence – 4).

Comment. *Toxic dilatation of the colon (toxic megacolon), which is not associated with obstruction of the expansion of the colon to 6 cm or more with the intoxication. Risk factors for toxic dilatation include hypokalemia, hypomagnesemia, bowel cleansing for colonoscopy using osmotic laxatives and taking antidiarrheal drugs. Indirectly, the development of toxic dilatation is evidenced by a sudden reduction in stool frequency against the background of diarrhea, bloating, as well as a sudden decrease or disappearance of pain and the increase in signs of intoxication (increase in tachycardia, decrease in blood pressure).*

- Subtotal colectomy or total colectomy (colproctectomy – with pronounced rectal activity) is indicated in all patients with UC complication in the form of perforation of the colon when revealing threatening symptoms (peritoneal symptoms, free gas in the abdominal cavity according to the X-ray examination) [111].

Category of recommendation - C (level of evidence – 4).

Comment. *Large intestine perforation, the most dangerous complication of UC with almost 50% mortality.*

3.2.3 Indications for surgical treatment of UC: Colorectal cancer. Screening recommendations.

In patients with a long history of UC the risk of colorectal cancer is significantly increased, which necessitates regular examination to detect dysplasia of the large intestine epithelium. The following factors affect the likelihood of developing cancer:
a) duration of UC history: the risk of colorectal cancer is 2% in 10-years' time, 8% in20-years' time and 18% in 30-years' time [125];
b) debut of disease in childhood and adolescence, although this factor may only reflect the duration of history and is not an independent predictor of colorectal cancer [126];
c) extent of disease: the risk is highest in patients with total UC, while in patients with proctitis the risk is not different from the average in the population;
(d) the presence of primary sclerosing cholangitis [127];
(e) family history of colorectal cancer;
f) severe recurrent attacks of UC in history or continuous course of UC. The consequence of high activity of UC may be inflammatory polyposis, which is also a risk factor for colorectal cancer [128].
Control colonoscopy should be carried out in conditions of good bowel cleansing and, preferably, in remission, since active inflammation makes it difficult to detect dysplasia.
Two modalities are used to screen for neoplastic mucosal changes:
1. Chromo endoscopy with targeted biopsy of areas suspected of neoplasia.
2. Biopsy of the mucous layer of 4 fragments of every 10 cm of the colon and rectum (with endoscopy in white light). This approach does not exclude mandatory biopsy of all suspicious formations.
The results of the screening biopsy influence the modality of further treatment and follow-up.
• All patients with UC with high degree dysplasia detected by biopsy in the intact mucosa (i.e., not in the raised formations) are recommended for surgery, in the volume of total colectomy (proctocolectomy with the end permanent stoma) or the ileal pouch (proctocolectomy with ileal pouch with the protective ileostomy) [125].
Category of recommendation - B (level of evidence - 2).
Comment. *The presence of dysplasia should be confirmed by a second independent pathologist. The volume of surgical treatment is discussed together with the patient, thus taking into account the patient's desire for the preservation of anal defecation or the formation of a permanent stoma.*
• In all patients with UCandmild dysplasia detected in intact mucosa (not in the raised formations), the decision should be taken individually with the patient: it is necessary to discuss the two options – total colectomy (proctocolectomy with the formation of a permanent stoma) and the ileal pouch creation(proctocolectomy with simultaneous ileal pouch with protective ileostomy); however, continued regular endoscopic screening with reduced interval between the examinations up to 3 months can be acceptable[125].
Category of recommendation - B (level of evidence - 2).
Comment. *The volume of surgical procedure is discussed together with the patient, thus taking into account the patient's desire for the preservation of anal defecation or the formation of a permanent stoma.*
The patient has the right to refrain from surgery, in this case, endoscopic screening is offered.
- For all patients with remission of UC, when confirming the presence of adenomatous polyp (endoscopic and pathomorphological examination), it is recommended to perform a standard polypectomy [127].

Category of recommendation - B (level of evidence - 2).

- For all patients with UC in the presence of a polyp with dysplasia in the large intestine affected by UC, colectomy is not recommended if the histological structure of the polyp is an adenoma and no dysplasia in the surrounding unchanged mucosa or anywhere in the intestine, as well as in the edges of the removed polyp [127].

Category of recommendation - B (level of evidence - 2).

3.2.4 Types of surgical procedures

In the majority of patients with UC, modern conservative therapy allows controlling the course of the inflammatory process, but in 10-30% of patients, due to the ineffectiveness of medical treatment, it is necessary to resort to surgical procedure aimed at removing the large intestine [112].

Until the early 1980s, the standard of surgical treatment was colproctectomy with ileostomy, despite the occasional use of ileorectal anastomosis.
Over the past 20 years, the new gold standard has been total colectomy with ileal pouch (colproctectomy with ileoanal reservoir anastomosis (IARA)) [129,130] (Table 8).
If successful, this surgery provides the possibility of controlled anal defecation with a satisfactory quality of life [131]: the average frequency of defecation after the formation of IARA is from 4 to 8 times a day [132-134], and the daily volume of semi-formed / liquid feces is about 700 ml per day (compared to 200 ml/day in a healthy person).

Table 8. *Surgical procedures for UC*

With the permanent end ileostomy	**With the restoration of anal defecation**		
1.Proctocolectomy with permanent end ileostomy	With ileal pouch in 2 stages:	With ileal pouch in 3 stages:	
	• Restorative proctocolectomy, ileal pouch, loop ileostomy • Closure of ileostomy	1.Subtotal colectomy, end ileostomy; 2.Restorative proctectomy, ileal pouch, loop ileostomy 3.Closure of ileostomy	* Subtotal colectomy with ileorectal anastomosis (in exceptional cases)

3.2.5 Choice of surgical treatment
Reconstructive surgery with the ileal pouch, despite the obvious attractiveness for the patient, is not possible in all cases, since a number of factors worsen the functional outcome of the operation and increase the risk of complications, leading to the need to remove the pouch in 3.5-10% of patients [135-137].
In patients with UC, despite the higher incidence of co morbidities after 65 years, the surgical procedure with the ileal pouch in older persons is safe and effective [138].
The anal continence, which plays a key role for the normal functioning of the ileal pouch, obviously deteriorates in older age [139]. In addition, elderly patients are more likely to develop complications, in particular pouchit is and strictures of anastomosis [140,141]. At the same time, any certain age threshold for refusal of formation of ileal pouch is not defined.
In all UC patients, the formation of an ileal pouch by 30-70% [142-146] increases the risk of infertility in women of childbearing age with UC.
The risk of infertility is associated with pelvic adhesions involving the fallopian tubes. Planned pregnancy and the young age of the woman are not contraindications to the ileal pouch; however, the patient should be warned about the potential risk of infertility. In some cases, it is possible to consider the formation of ileorectal anastomosis as an intermediate stage of surgical treatment (see below).
In all female patients with UC, when there are indications for surgery, the use of laparoscopic technologies reduces the risk of infertility by 90% [142-146].
In approximately 10% of patients with colitis, even when examining the removed specimen, it is not possible to make a differential diagnosis between Crohn's disease (CD) and UC, in connection with which they are diagnosed with unspecified ulcerative colitis. The decision on the formation of ileal pouch in such cases is taken individually, and the patient should be warned about the risks of inefficiency of reconstructive surgery and other complications associated with CD.
• All patients with UC in the presence of comorbidities such as rectal cancer and severe anal sphincter incontinence (grade 2 or 3) are not recommended to ileal pouch [147].
Category of recommendation - B (level of evidence - 3).
• In patients with a severe attack of UC who did not respond to conservative treatment, a three-stage surgical treatment is recommended (with colectomy, end ileostomy as the first stage, proctectomy, ileal

pouch and loop ileostomy as the second stage and closure of the loop ileostomy as the third stage) [148-150].

Category of recommendation - C (level of evidence - 4).

• In patients with UC, in whom hormone therapy with prednisone at a dose of at least 20 mg per day for more than 6 weeks was performed at the time of setting the indications for surgery, a three-stage surgical treatment is recommended (with colectomy as the first stage, proctectomy with ileal pouch and loop ileostomy as the second stage and ileostomy closure as the third stage) [148-150].

Category of recommendation - C (level of evidence - 4).

Comment. *A colectomy with an end ileostomy stops the intoxication caused by colitis, which improves the general condition of the patient, restores metabolism, and the morphological study of the removed specimen also allows you to clarify the diagnosis and exclude CD.*

Colectomy is a relatively safe procedure, even in patients in bad condition [148-150], while minimally invasive or laparoscopic surgery is safe if the surgeon is qualified [151,152].

Ileorectal anastomosis [153-155].

The formation of an ileorectal anastomosis does not lead to the healing of the patient and does not exclude the possibility of recurrence of inflammation in the rectum and the development of cancer. This surgery in UC can be performed only in exceptional cases in women planning a pregnancy.

A prerequisite is the presence of remission in the rectum and the patient's consent to a regular examination of the rectum with a biopsy of the mucous layer [156,147].

3.2.6 Features of surgical procedure with ileal pouch.

• In patients with UC, who have undergone colectomy, reconstructive surgery with the creation of ileal pouch is recommended to be performed in specialized units, since the frequency of complications and the functional outcome of such surgeries significantly depend on the skill of the surgeon (in particular, on the number of similar surgeries performed) [147].

Category of recommendation - C (level of evidence - 4).

The length of the preserved rectum and / or sigmoid colon.

• All patients with UC, who underwent colectomy for urgent indications of ulcerative colitis and planning surgery for ileal pouch in the future, are recommended to preserve the entire rectum and lower mesenteric vessels [147].

Category of recommendation - C (level of evidence - 4).

Comment. *It is advisable to cut the rectum at the level of the promontorium (i.e., at the level of "rectosigmoid transition") or additionally maintain the distal part of the sigmoid colon (the decision is made by the operating surgeon).*

While maintaining the distal sigmoid colon, it is displayed on the anterior abdominal wall as sigmostomy.

The latter option is the safest, since there is no bowel stump in the abdominal cavity.

When cutting the rectum at the promontorium level, it is recommended that the stump be drained through the anus for several days to prevent suture leak due to the accumulation of mucus in the stump.

In case of preservation of the diversed rectum or rectum and sigmoid colon, the development of secondary inflammatory changes in the mucosa as diversion colitis is possible. Controlled drug trials in patients after colectomy have not been conducted.

Empirical treatment involves the use of local mesalazine [157], prednisolone, and washing the diversed rectum with antiseptic solutions.

The creation of an anastomosis during ileal pouch

• In all cases of the ileal pouch, it is recommended to preserve no more than 2 cm between the dentate line and the anastomosis [158].

Category of recommendation - C (level of evidence - 4).

Comment. *Preservation of an extended part of the rectum (more than 2 cm above the dentate line) when using a stapler to form an anastomosis can cause chronic inflammation in it with pouch dysfunction, and also contributes to maintaining the risk of dysplasia and (very rarely) cancer [158].*

If it is not possible to make anastomosis using a stapler, an abdominal-anal resection of the rectum and manual ileoanal anastomosis should be performed.

In UC patients, who underwent surgery with ileal pouch, despite the fact that when using a stapler, a small fragment of the mucous layer is preserved, the risk of cancer is low and corresponds to that in the formation of manual anastomosis [158].

• In all patients with UC, the ileal pouch should be performed under the guise of a loop ileostomy [158].

Category of recommendation - C (level evidence - 4).

Observation of patients with ileal pouch

Morphological changes in the epithelial layer of the pouch usually develop in 12-18 months after the closure of the ileostomy and are characterized by flattening and a reduction in the number of villi leading to their atrophy ("colonic metaplasia") [159,160], which makes it potentially associated with the risk of malignant transformation of the reservoir mucosa.

In addition, when applying a stapler pouch, a small area of the rectal mucosa is preserved ("cuff"). The risk of developing cancer of the pouch is increased in patients operated on for cancer or dysplasia on the background of UC (and if dysplasia is found in the removed specimen), and in patients with primary sclerosing cholangitis (PSC).

Scientific prove of the frequency of control examinations of patients with ileal pouch was not performed; however, in patients with the above risk factors, it is advisable to conduct control endoscopic examinations (reservoiroscopy) with a biopsy of the mucous layer at least once every 2 years.

3.2.7 Drug therapy during surgical treatment

The effect of drug therapy on the risk of surgery.

Taking prednisolone at a dose of more than 20 mg for more than 6 weeks increases the risk of surgical complications [161,162]. Preoperative administration of AZA and MP does not worsen the outcome of surgical treatment [163], while administration of infliximab and cyclosporinan long before surgery may increase the incidence of postoperative complications [164,165], although data on infliximab remain inconsistent [166].

Hormone therapy before surgery and in the early postoperative period.

Sudden stop of GCS therapy can cause withdrawal syndrome (acute insufficiency of the adrenal cortex, the so-called Addison crisis), which makes it necessary to temporarily continue hormone therapy after surgery until it is completely canceled.

At present, there is no reliable scientific basis for substantiating any scheme for discontinuing hormonal therapy after colectomy for UC.

The dose of GCS for further oral administration during the period of discontinuation of hormonal therapy is determined by the duration of the previous therapy and the doses used.

According to the recommendations of the European Society for the Study of UC and CD (ECCO) [20], if hormone therapy was carried out before the surgery for no more than a month, immediately after the operation it is possible to stop taking GCS.

If the patient received GCS for more than a month before the operation, after surgery, it is advisable to switch from the above high parenteral dose of GCS to oral administration of GCS at a dose not lower than the upper threshold of the daily stress production of cortisol, that is, not lower than 20 mg of prednisolone. Further dose reduction and cancellation of GCS is carried out under the supervision of an endocrinologist.

3.2.8 Pouchitis and other pouch complications.

The pouchitis is a non-specific inflammation of the ileal pouch and the most common complication.

Its incidence varies in a wide range from 15 to 50% within 10 years after the surgery in high volume units [167-169].

Such differences may be due to a significantly greater risk of the pouchitis in UC patients, exceeding the morbidity rate of the pouch complications in other diseases (in particular, familial adenomatosis) [170,171].

Complications of the ileal pouch include abscesses, fistulas, stenosis of the pouch-anal anastomosis, and adenocarcinoma of the pouch. The last complication is extremely rare and almost always - with a revealed dysplasia or cancer in the removed specimen obtained during colectomy.

A suspected pouchitis differential diagnosis is made with irritable pouch syndrome (IPS), ischemic lesions, Crohn's disease (CD), and other rare causes of pouch dysfunction, such as collagenous, cytomegalovirus, and Clostridium difficile-associated pouchitis.

It should be borne in mind the possibility of developing non-specific ileitis caused by NSAIDs and bacterial overgrowth syndrome.

Treatment of the pouchitis and maintenance of remission.

The main drugs used to treat the pouchitis remain antibiotics, which makes it possible to classify the pouchitis as antibiotic-sensitive, antibiotic-dependent and antibiotic-resistant.

• In all patients with a pouchitis, the first line of therapy includes a 14-day course of oral metronidazole (15-20 mg / kg / day) or ciprofloxacin (1,000 mg / day) [172].

Category of recommendation - C (level of evidence - 3).

Comment. *Adverse events are much more common when taking metronidazole. In cases of an AB-resistant pouchitis, oral budesonide (9 mg) may be given for 8 weeks.*

• In patients with a pouchitis, in the absence of effect or in the development of dependence on the use of these drugs, the use of reserve drugs is recommended - rifaximin (2,000 mg / day), tinidazole, rectal glucocorticosteroids, rectal mesalazine, azathioprine [172].

Category of recommendation - C (level of evidence - 3).

Inflammation of the mucous layer of the preserved portion of the rectum and irritable pouch syndrome.

Another potential complication of ileal pouch is inflammation of the rectal mucosa, which is preserved when creating stapler anastomosis.

• In patients with ileal pouch and proctitis, treatment is performed with 500 mg mesalazine suppositories 2 times a day and / or rectal GCS [172].

Category of recommendation - C (level of evidence- 3).

Irritable pouch syndrome [173] is a functional disorder whose symptoms coincide with manifestations of the pouchitis.

Irritable pouch syndrome is more common in patients taking anxiolytics or antidepressants before colectomy, which indirectly indicates the manifestations of irritable bowel syndrome before surgery.

The treatment for these two functional disorders is the same and include psychotherapeutic help and the prescribing of antidepressants, the prescribing of dietary fiber, antidiarrheal drugs, antispasmodics, as well as non-absorbable antibiotics to correct the syndrome of excessive bacterial growth.

3.2.9. Ileostoma dysfunction after surgery for UC

Ileostomy dysfunction refers to an increase in the volume of intestinal discharge through the ileostoma of more than 1,000 ml per day.

This condition is also accompanied by rapidly progressing metabolic and water-electrolyte disturbances [174].

It is necessary to conduct a general physical examination of the patient with an assessment of the general condition, monitoring of a general blood test, biochemical blood test, hemocoagulogram, general urinalysis, assessment of local status. The nature of digestive dysfunction is determined.

• In patients with ileostoma dysfunction initially at the outpatient stage, it is recommended to exclude enteritis caused by *Clostridium difficile* [174].

Category of recommendation- B (level of evidence - 3).

Comment. *In addition to abundant fluid discharge through the stoma, the clinical picture also shows an increase in body temperature to 39°C, flatulence, rarely complaints of nausea, vomiting, spastic abdominal pain.*

In laboratory tests: anemia, hypoproteinemia, hypoalbuminemia, hypokalemia, increased levels of CRP, rarely an increase in creatinine concentration.

• In patients with ileostoma dysfunction, for the rapid diagnosis of enteritis caused by *Clostridium difficile* in the microbiological laboratory, are recommended [174,175]:

1. Detection of glutamate dehydrogenase (GDH) and toxins A and B in luminal feces: immunochromatographic analysis method (ICA);
2. Diagnostic test kits for detection of *C.dificile* antigens: GDH, toxins A and B. ELISA method–the ELISA method;
3. Diagnostic test kits for detection of *C.dificile* antigens: GDH, toxins A and B. - immunochemiluminescent analysis;
4. Tests for the detection of GDH, toxins A and B, binary toxin - PCR, including multiplex.

Category of recommendation - A (level of evidence - 1b).

• Patients with a mild form of the disease are recommended diet therapy, antispasmodics and drugs that slow down the passage of the gastrointestinal tract [175]

Category of recommendation - B (level of evidence - 2).

• Patients with a moderate form of the disease are prescribed metronidazole at a dose of 500 mg orally three times a day for 10 days [176].

Category of recommendation - B (level of evidence - 2).

• In patients with moderate disease in the absence of a clinical effect of metronidazole, after 5-7 days, the drug is changed to vancomycin at a dose of 125 mg 4 times a day *per os* for 10 days [177].

Category of recommendation n- A (level of evidence - 1).

Comment. *If in the laboratory indicators there is an increase in the level of leukocytes in the blood over 15 × 10^9 cells / l, creatinine in the blood serum above 115 μmol / l, a rise in body temperature above 38.8^{0}C and a decrease in the level of albumin below 25 g / l, patients should receive treatment in a 24-hour unit. These patients were initially prescribed to take vancomycin at a dose of 125 mg orally 4 times a day for 10 days.*

• Patients with worsening condition and hypotension, defecation retention, severe bloating, altered consciousness, increased serum lactate levels above 2.2 mmol /l, and the development of multiple organ failure syndrome are recommended to be transferred to the intensive care unit for further treatment [178].

Category of recommendation- B (level of evidence is 2).

Comment. *Along with infusion therapy, vancomycin is prescribed orally at a dose of 500 mg 4 times a day in combination with metronidazole at a dose of 500 mg 3 times a day intravenously. If it is impossible to administer the drug by mouth, vancomycin is administered rectally. In this case, the drug in a dose of 500 mg is diluted in 500 ml of a 0.9% sodium chloride solution and is administered as enemas four times a day.*

4. REHABILITATION

There are no specific rehabilitation measures for patients with UC. Medical rehabilitation measures are aimed at preventing complications of conservative treatment and prevention of colorectal cancer.

Since in some cases UC therapy is associated with the use of immunosuppressants, the main way to rehabilitate patients is the prevention of opportunistic infections, described in Section 5.

In patients who require surgical treatment of ulcerative colitis, rehabilitation is possible in three stages.

Stage 1 - early rehabilitation, carried out immediately after surgical treatment from the 2nd to the 14th days. The main objective of the 1st stage of rehabilitation is to restore the normal functioning of the gastrointestinal tract after surgery. It is at this stage that urination disorders are most often detected and should be corrected. An important role is also given to the control of homeostasis, measures aimed at healing postoperative wounds, relief of postoperative pain syndrome, activation of the patient.

During this period, a general blood test, a biochemical blood test, a blood coagulogram, and a general urinalysis are monitored.

The 2nd stage of rehabilitation begins after 15 days and continues as necessary afterwards. It is aimed at the final healing of postoperative wounds with control over the activity of the gastrointestinal tract and other body systems.

The 3rd stage of rehabilitation is carried out in the late rehabilitation period in patients with a permanent ileostomy, and before reconstructive surgery. The main task at this stage is the compensation of the function of the gastrointestinal tract, measures aimed at identifying and correcting the anal continence.

Deficiency of the anal sphincter - rehabilitation is possible at stages 2 and 3.

In a number of patients in whom surgery for UC resulted in the formation of a small intestinal reservoir, a decrease in retention function is noted.

• Patients with UC with anal sphincter insufficiency before reconstructive treatment are recommended to perform a pathophysiological study (sphincterometry, profilometry, examination of the congestion on the shameless nerve) with subsequent consultation of a physiotherapist [179].

Category of recommendation - B (level of evidence is 2).

• In patients with UC, when detecting insufficiency of the anal sphincter of degree 2–3, it is necessary to carry out rehabilitation treatment, including a 10-day cycle of therapy with biological feedback and tibial neuromodulation in a day or around-the-clock hospital [179,180].

Category of recommendation - B (level of evidence is 2).

Comment. *According to the literature, the method of treatment with biological feedback is widely used in the rehabilitation of patients with anal sphincter insufficiency, aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of voluntary compression [179,180].*

This non-invasive method involves the body's own resources in the rehabilitation process with the development of the right skills at the level of creating new conditioned reflex connections. Tibial neuromodulation is also effective.

Neuromodulation is a process in which an electric current along one nerve pathway modulates preexisting activity in other nerve pathways or centers.

Percutaneous electrical stimulation of the posterior tibial nerve - n.tibialis - is used for functional diseases of the pelvis, since fibers from the II and III sacral segments of the spinal cord pass through the posterior tibial nerve, which play a significant role in the innervation of the rectum, bladder and their sphincters.

It has been proved that the muscle structures of the diversed anal sphicter can respond to biofeedback therapy and tibial neuromodulation, increasing both the tone and strength of volitional contractions [179,180].

The stimulation of the tibial nerve is carried out using a cutaneous stimulating electrode, which allows the patient to continue the course of treatment independently at home after a course of preliminary training. In this case, the course of treatment with daily sessions of stimulation can be extended up to 1-3 months.

The effectiveness of biofeedback therapy is monitored before and at the end of each course of procedures through a comprehensive physiological study of the anal sphincter function (sphincterometry + physiological study of the reservoir function of the pouch).

With an improvement in the tone and contractility of the anal sphincters, one can raise the question of performing reconstructive surgery.

5. PREVENTION AND DISPENSARY SURVEILLANCE

Ulcerative colitis is characterized by a chronic recurrent course. Clinical observation in UC is carried out for life and can be interrupted only when the large intestine is removed.

The purpose of the follow-up is primarily the prevention of colorectal cancer.

In most patients in clinical remission, colonoscopy should be performed at least every 3 years. In some patients, the frequency of follow-up with colonoscopy may be different.

The features of monitoring patients receiving immunosuppressive drugs and / or biological drugs include the prevention of opportunistic infections.

Risk factors for the development of opportunistic infections include: taking prednisolone 20 mg per day or more for 2 weeks, taking immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate) and biologicals, patient’s age over 50 years old, comorbidities (chronic lung diseases, alcoholism, organic diseases of the brain, diabetes).

In accordance with the European Consensus on the Prevention, Diagnosis and Treatment of Opportunistic Infections in IBD, such patients are subject to mandatory vaccination prophylaxis.

The necessary minimum of vaccination is:

• Recombinant HBV vaccine;

• Polyvalent inactivated pneumococcal vaccine;

• Trivalent inactivated influenza virus vaccine.

For women aged under 26 years old, in the absence of the virus at the time of screening, vaccination against human papillomavirus is recommended.

• During the GCS treatment, glycemia monitoring is recommended.

Category of recommendation - B (level of evidence - 3).

• During the period of immunosuppressive therapy, monthly monitoring of the level of leukocytes and liver enzymes is recommended (at the beginning of treatment once every two weeks, then once a month for the first 6 months of therapy, then once every three months).

Category of recommendation - C (level of evidence - 3).

• For patients before biological therapy and every 6 months thereafter, according to the order of the Ministry of Healthcare of Russia, it is recommended to consult a TB doctor and screening for tuberculosis (quantiferon test, and if it is not possible to carry out the Mantoux test, diaskin test) [181].

Category of recommendation - A (level of evidence - 1b).

• Patients prior to prescribing immunosuppressive therapy and during treatment, are recommended to screen for the presence of markers of viral hepatitis B (HBsAg, anti-HBC, DNA with a qualitative method), C (anti-HCV) and human immunodeficiency (anti-HIV), and also syphilis.

Category of recommendations is D (level of evidence - 5).

• Recommended strict adherence to doses and schedule for the introduction of biological agents. Irregular administration of biological drugs increases the risk of allergic reactions and treatment failure [20].

Category of recommendation - B (level of evidence - 1b).

Comment. *Treatment interruptions without medical indications are unacceptable.*

• All patients receiving biological therapy are not recommended to change the original drug to a bio-analogue or vice versa more than once.

Category of recommendation - D (level of evidence - 5).

Comment. *At present, biosimilars (bio-analogues) of anti-TNF drugs that are similar to the original biological drugs in terms of effectiveness and safety have been registered, but their interchangeability with the original drugs has not yet been proven.*

Given the lack of clinical trials in patients with IBD who have proven the safety and effectiveness of alternating or completely switching from the original drug to bio-analogues and vice versa, such a therapeutic approach is not recommended [57].

The patient should be explained the need for constant medication, since compliance with the prescription for therapy significantly (by 2-2.5 times) reduces the frequency of recurrence, and the therapy itself is a method of chemoprophylaxis of colorectal cancer.

From the point of view of a long-term prognosis of UC, it is advisable to regularly assess the presence of endoscopic remission (healing of the mucous layer). For these purposes, it is recommended that every 6 months a fecal examination be performed on the level of fecal calprotectin and / or sigmoidoscopy.

6. ADDITIONAL INFORMATION INFLUENCING THE COURSE AND OUTCOME OF THE DISEASE

The risk of severe flare-up of UC during life is 15%, while the likelihood of a severe attack is higher in patients with total damage to the colon. With adequate anti-relapse therapy for 5 years, recurrent attacks can be avoided in half of the patients, and within 10 years in 20% of patients.

In the first year after diagnosis, the probability of colectomy is 4–9% (with a severe attack - about 50%), then, with each year of the disease, the risk of colectomy increases by 1%.

Risk factors for the aggressive course of UC are the progression of damage from distal (proctitis) to total, primary sclerosing cholangitis, as well as childhood and adolescence at the onset of the disease.

Pregnancy planning should be carried out during the period of remission of IBD, which allows improving pregnancy outcomes. The use by pregnant women of most drugs for the treatment of IBD is associated with a low risk of adverse effects on the fetus, with the exception of methotrexate and mesalazine with dibutyl phthalate in shell.

The abolition of anti-TNF or the transition to monotherapy is possible only in a limited number of patients with a low risk of reactivation of IBD. Treatment with biological agents that are not contraindicated during pregnancy (see instructions for use) can be continued if the benefits to the mother outweigh the potential risks to the fetus.

Reducing *the risks associated with the prescribing of GCS* is achieved by strict adherence to the principles of hormonal therapy. GCS cannot be used as maintenance therapy.

When prescribing hormone therapy, the following should be considered:

• A gradual reduction in the dose of steroids until complete withdrawal is strictly necessary;

• The total duration of hormone therapy should not exceed 12 weeks;
• Concomitant use of calcium, vitamin D preparations is mandatory;
• During treatment, regular monitoring of blood glucose levels is necessary.
Patients who have developed an intestinal stoma as a result of surgical treatment may need to be consulted and monitored by a rehabilitation specialist for ostomy patients.

6.1. Scope of recommendations
Clinical recommendations are intended for general practitioners, family doctors, gastroenterologists, coloproctologists, surgeons, endoscopists, healthcare organizers, nurses, medical experts of medical insurance organizations, including during medical and economic examinations.
Conservative treatment can be carried out on an outpatient basis with the participation of a gastroenterologist and / or coloproctologist.
Observation and treatment of diagnostically complicated cases should be carried out in specialized centers for the diagnosis and treatment of inflammatory intestine diseases.
Inpatient treatment is carried out in specialized gastroenterological and coloproctological departments (in exceptional cases, in therapeutic departments with specialized gastroenterological beds and a specialist who has professional retraining in the specialty "gastroenterology", and, accordingly, in surgical departments with specialized coloproctological beds and a specialist who has professional retraining in the specialty "coloproctology").
Initiation of biological therapy, can be carried out in a day hospital, in such cases, clinical statistical group ds 36.004 “Treatment with the use of genetic engineering biological agents”, or a 24-hour hospital as part of the provision of high-tech medical care in profile “Gastroenterology”, included in the list of types of high-tech medical care, the basic program of compulsory medical insurance, the financial support of which is provided by subventions from the budget of the Federal Mandatory Medical Insurance Fund budgets of territorial compulsory health insurance funds.
In stationary conditions, when providing specialized medical care, it is necessary to use clinical statistical group st 36.003 “Treatment with the use of genetically engineered biological preparations in the absence of the effectiveness of basic therapy”.
Given the peculiarities of the frequency of administration of biological drugs, when conducting a medical and economic examination and examination of the quality of medical care, the criterion for deviation from the standard of treatment (case for 100% examination) “Repeated hospitalization for one disease within 90 days after completion of the first case of treatment (according to the registers of one medical organization)”**is not applicable.**
The frequency of hospitalization is determined by the regimen of administration of a particular biological preparation and varies from 1 time in 2 weeks to 1 time in 8 weeks. The number of hospitalizations of more than 1 within 90 days after the completion of the first case of treatment (according to the registers of one medical organization) during genetic engineering therapy cannot be a reason to establish a defect in the provision of medical care and be subject to penalties.
During surgical treatment in a round-the-clock hospital, clinical statistical group st 14.003 is used - surgeries on the intestines and anal area (level 3), or, depending on the treatment method and the nature of the course of the disease, provides high-tech medical care in the "Abdominal Surgery" profile, included in the list of high-tech types medical care of the basic program of compulsory medical insurance, the financial support of which is provided through a subvention from the budget of the Federal Fund for Compulsory Medicine insurance to the budgets of territorial compulsory health insurance funds.

6.2. Limitation of the application of recommendations
Clinical recommendations reflect expert opinion on key issues. In clinical practice, situations may arise that go beyond the recommendations presented, therefore, the final decision on the management tactics of each patient should be made by the attending physician, who is responsible for his treatment.

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