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CLINICAL GUIDELINES
Ulcerative colitis (K51), adults

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LIST OF ABBREVIATIONS

ALT — alanine aminotransferase
AST — aspartate aminotransferase
5-ASA — 5-aminosalicylic acid
AZA — azathioprine
Anti-TNF — antibodies to tumor necrosis factor alpha
CD — Crohn's disease
BFB — biofeedback
IBD — inflammatory bowel diseases
gamma-GT — gamma-glutamyltranspeptidase
GEBD — genetically engineered biological drug
GCS — glucocorticosteroids
CI — coincidence interval
GIT — gastrointestinal tract
IPAA — ileal pouch anal anastomosis
BMI — body mass index
CT — computed tomography
LDH — lactate dehydrogenase
MMS — multimatrix shell
MP — mercaptopurin
MRI — magnetic resonance imaging
NSAIDs — nonsteroidal anti-inflammatory drugs
RCT — randomized controlled trial
ESR — erythrocyte sedimentation rate
CRP — C-reactive protein
TIS — targeted immunosuppressors
TNF-alpha — tumor necrosis factor-alpha
UC — ulcerative colitis

TERMS AND DEFINITIONS

Ulcerative colitis (UC) is a chronic colorectal characterized by immune inflammation of its mucosa.

Exacerbation (relapse, attack) of UC is the appearance of typical symptoms of the disease in patients with UC in the stage of clinical remission, spontaneous or medically supported.

In practice, signs of clinical exacerbation are an increase in the frequency of bowel movements with blood excretion and/or characteristic changes detected during colonoscopy.

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

UC remission, clinical — absence of blood admixture in the stools, absence of imperative/false urges at a frequency of defecation no more than 3 times per 24 hours.

UC remission, endoscopic — absence of visible macroscopic signs of inflammation during endoscopic examination of the large bowel.

UC remission, histological — absence of microscopic signs of inflammation.

Steroid resistance — in the case of a severe attack — the absence of positive changes on the part of clinical and laboratory indicators, despite the use of systemic GCS at a dose equivalent to 2 mg/kg of body weight of prednisolone ** per 24 hours, for more than 7 days;

In the case of a moderate attack, the activity of the disease is maintained with oral administration of GCS at a prednisolone ** dose equivalent to 1 mg/kg of body weight for 2 weeks [3,4].

Steroid addiction is an increase in the activity of the disease that occurred when the dose of GCS was reduced after the initial improvement

was achieved within 3 months from the start of treatment.
The relapse of the disease within 3 months after the end of treatment with GCS.
A bionaïve patient is a patient who has not previously received genetically engineered biological drugs (GEBD) or targeted immunosuppressors (TIS).
Colectomy is a surgery to remove caecum and the entire colon from ilecaecal valve to rectosigmoid.

1. BRIEF INFORMATION ON THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS)

1.1 Definition of the Disease or Condition (Group of Diseases or Conditions)

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucosa.
In UC, only the large intestine is affected (with the exception of retrograde ileitis), the rectum is necessarily involved in the process, inflammation is most often limited to the mucous layer (with the exception of acute severe colitis) and is diffuse.

1.2 Etiology and Pathogenesis of the Disease or Condition (Group of Diseases or Conditions)

The etiology of IBD, including UC, has not been clarified. The disease develops as a result of a combination of several factors, including genetic predisposition, defects in congenital and acquired immunity, intestinal microflora disorders and the influence of environmental factors. About 100 genetic polymorphisms associated with UC have been described. Genetic determinism leads to changes in the congenital immune response, autophagy, violation of the mechanisms of recognition of microbes, lesion of the epithelial barrier and, as a result, perversion of adaptive immunity. A key defect predisposing to the development of IBD is a violation of the recognition of bacterial molecular markers (patterns) by dendritic cells, which leads to hyperactivation of signaling proinflammatory pathways. Also, with 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*.
Against this background, the development of IBD occurs under the influence of triggering 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 *Clostridioides* difficile infection and cytomegalovirus infection.
The result of the mutual influence of genetic and predisposing factors is the activation of various subpopulations of T-lymphocytes: T-helper 1,2,17 types and regulatory T-lymphocytes at different stages of inflammation, which leads to over expression of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukins 1, 12, 23, 17 (IL1, IL12, IL23, IL17) and others and cell adhesion molecules.
As a result of these disorders, inflammatory lymphoplasmocytic infiltration and destruction of the colorectal mucosa with macroscopic changes characteristic of UC are formed.

1.3 Epidemiology of the Disease or Condition (Groups of Diseases or Conditions)

The maximum prevalence of UC in the world is currently 505/100,000 of the population (in Europe), and the incidence in different regions ranges from 0.6 to 24.3 per 100,000 population. The highest incidence of UC 24.3/100,000 was noted in Europe, 19.2/100,000 in North America [4–8].
Data on the prevalence of UC in Russia are limited [9,10]. The prevalence of UC is higher in northern latitudes and in western regions. The incidence and prevalence of UC in Asia is lower; however, it is currently increasing. Caucasians suffer from the disease more often than people of the Negroid and Mongoloid races. The peak of morbidity occurs in the age range of 20–30 years, in some countries the second peak of morbidity is observed at the age of 60–70 years. The incidence among males and females is approximately the same.

1.4 Features of Coding the Disease or Condition (Group of Diseases or Conditions) According to the International Statistical Classification of Diseases and Health-Related Problems

K51.0 — Ulcerative (chronic) enterocolitis
K51.1 — Ulcerative (chronic) ileocolitis
K51.2 — Ulcerative (chronic) proctitis
K51.3 — Ulcerative (chronic) rectosigmoiditis

Table 1. *Montreal classification of UC by lesion extent [12]*

The extent of inflammation	Designation according to the Montreal Classification	Characteristic
Proctitis	E1	Distal UC, limited to the rectum
Left-sided colitis	E2	Affected mucosa from the anal sphincter to the left flexure
Total colitis (pancolitis)	E3	The lesion spreads proximally to the left flexure, capturing the entire large intestine, sometimes in combination with retrograde ileitis (involvement of 10–15 cm of the ileum in the inflammatory process)

Table 2. *Severity of UC attack according to Truelove-Witts criteria [3,4]*

Indicator	Mild attack	Moderate attack	Severe attack
Frequency of stools with blood per 24 hours	< 4	⩾ 4, if:	⩾ 6 and:
FS per 1 minute	< 90 /min.	⩽ 90 /min.	> 90 /min. or
Temperature	< 37.5°C	⩽ 37.8°C	> 37.8°C or
Hemoglobin	> 115 g/l	⩾ 105 g/l	< 105 g/l or
ESR or CRP	⩽ 20 mm/h Norm	⩽ 30 мг/л	> 30 mm/h or > 30 mg/l

K51.4 — Pseudopolyposis of the colon
K51.5 — Mucosal proctocolitis
K51.8 — Other ulcerative colitis
K51.9 — Ulcerative colitis, unspecified

1.5 Classification of the disease or condition (groups of diseases or conditions)

The existing classification of UC by the extent of the lesion, the course, the severity of the attack and the presence of complications determines the choice of drug therapy, indications and the choice of the type of surgery, as well as the frequency of screening for colorectal cancer [11].

To describe the extent of the lesion, the Montreal Classification is used (Table 1), which estimates the extent of macroscopic changes during colonoscopy.

It should be particularly noted that proctosigmoiditis is included in the concept of left-sided UC, and total colitis also includes subtotal large intestine lesion proximal to the left flexure.

According to the course of the disease, there are:

1. Acute (less than 6 months from the onset of the disease);
2. Chronic continuous (duration of remission less than 6 months on the background of adequate therapy);
3. Chronic recurrent (duration of remission is more than 6 months).

For the correct formulation of the diagnosis and determination of treatment approach, the severity of the current attack should be assessed, for which simple Truelove-Witts criteria are used, usually used in common practice, and the UC activity index (Mayo index; DAI), usually used in clinical trials.

However, to assess the prognosis of the disease and determine the social status of the patient, including disability, preferential supply by medical agents, free rehabilitation and other social benefits, it is necessary to take into account the comprehensive severity of the disease, which 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 steroid addiction and resistance.

There are mild, moderate and severe attacks of UC (Tables 2, 3).

In clinical practice, the so-called “extremely severe or extremely severe attack” of UC is often found, characterized by diarrhea more than 10–15 times per 24 hours, a crucial drop of hemoglobin, fever above 38°C, severe hypoproteinemia and electrolyte downshifts, high levels of C-reactive protein (CRP) [13–15]. Approaches to the treatment of such colitis differ from the usual ones. In English-language literature, this condition is called “acute severe UC” [16].

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.

The classification of UC depending on the response to glucocorticosteroids (GCS) facilitates the

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

Index value (points)	0	1	2	3
Stools frequency	Usual	1–2 more per day than usual	3–4 more per day than usual	5 more per day than usual
Blood in the stools	No	Blood Streaks	Visible blood	Mostly blood
The condition of the mucous layer	Norm	Minimum activity (1 point according to Schroeder)	Moderate activity (2 points according to Schroeder)	Pronounced activity (3 points according to Schroeder)
General assessment of the condition by a doctor	Norm	Satisfactory condition	Condition of moderate severity	Severe condition
The severity of the UC attack is determined by the sum of the points of 4 parameters from the table: 0–2 points: remission (while the assessment of the parameters of rectal bleeding and the endoscopic state of the mucosa = 0 points); 3–5 points: mild UC attack; 6–9 points: moderate UC attack 10–12 points: severe UC attack				
Partial (incomplete) Mayo index without endoscopy data: 0–1 points: clinical remission (with the parameter “rectal bleeding” = 0 point) 1–2 points: mild attack 3–5 points: moderate attack ⩾ 6 points: severe attack				

Table 4. *Classification of UC depending on endoscopic activity (according to Schroeder) [17]*

0	1 (minimal activity)	2 (moderate activity)	3 (pronounced activity)
Norm or inactive disease	Slight hyperemia, blurred vascular pattern. Easy contact vulnerability	Pronounced hyperemia, absence of vascular pattern, moderate contact vulnerability, erosion)	Spontaneous vulnerability, ulceration

choice of rational therapeutic approach, since the goal of conservative treatment is to achieve stable remission with discontinuation of GCS therapy. For these purposes, [3,4] are distinguished as follows:

1. Steroid resistance:

a. In the case of a severe attack, there is no positive changes on the part of clinical and laboratory parameters, despite the use of systemic GCS at a prednisolone dose equivalent to 2 mg/kg of body weight per 24 hours for more than 7 days;

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

2. Steroid addiction:

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

b. The occurrence of a relapse of the disease within 3 months after the end of treatment with GCS.

When formulating a diagnosis, it is necessary to reflect the nature of the course of the disease, the extent of the lesion, the severity of the current attack or the presence of remission, the presence of steroid addiction or resistance, as well as the presence of extra-intestinal manifestations or intestinal complications of UC. Below are examples of formulations of the diagnosis:

1. “Ulcerative colitis, chronic recurrent course, proctitis, moderate attack”.
2. “Ulcerative colitis, chronic continuous course, left-sided lesion, moderate attack. Steroid addiction. Extra-intestinal manifestations (peripheral arthropathy)”.
3. “Ulcerative colitis, chronic recurrent course, total lesion, severe attack. Steroid resistance. Toxic megacolon”.

1.6 Clinical picture of the disease or condition (group of diseases or conditions)

The clinical picture of UC includes four clinical syndromes:

Intestinal syndrome. Typical intestinal symptoms include diarrhea, mainly at night (65% of cases), blood in the stools (95–100% of cases), tenesmus (more often with proctitis and proctosigmoiditis), sometimes tenesmus in combination with

Table 5. *The main extra-intestinal (systemic) manifestations of ulcerative colitis*

Autoimmune, associated with the activity of the disease	Autoimmune, non-activity-related diseases	Caused by prolonged inflammation and metabolic disorders
Arthropathies (arthralgia, arthritis) Skin lesion (erythema nodosum, gangrenous pyoderma) Mucosal lesion (aphthous stomatitis) Eye damage (uveitis, iritis, iridocyclitis, episcleritis) Liverdamage (autoimmunehepatitis)	Primarysclerosingcholangitis Ankylosing spondylitis (sacroiliitis) Osteoporosis, osteomalacia Psoriasis, psoriatic arthritis	Cholelithiasis Liver steatosis, steatohepatitis Peripheral vein throm BFB is, pulmonary embolism Amyloidosis

constipation with distal limited lesion. With proctitis and proctosigmoiditis, diarrhea may be absent, tenesmus predominate in the clinical picture. For UC, unlike CD, abdominal pain is not characteristic. There may be a moderately pronounced abdominal pain syndrome of a spastic nature, more often before the stools.

Endotoxemia is signs of systemic inflammation due to the high activity of the inflammatory process in the colon. Endotoxemia accompanies moderate and severe forms of UC to varying degrees. The main symptoms are general intoxication, fever, tachycardia, anemia, increased ESR, leukocytosis, thrombocytosis, increased levels of acute phase proteins: CRP, fibrinogen.

Metabolic disorders are the result of diarrhea, toxemia, excessive loss of protein with feces due to exudation and impaired absorption of water and electrolytes. Clinical symptoms are typical: weight loss (sometimes to the point of exhaustion), dehydration, hypoproteinemia, hypoalbuminemia with the development of edematous syndrome, hypokalemia and other electrolyte disorders, hypovitaminosis.

Extra-intestinal systemic manifestations (EISM) occur in 20–25% of cases of UC and usually accompany severe forms of the disease [18] (Table 5).

Autoimmune manifestations associated with the activity of the inflammatory process appear together with the main intestinal symptoms of exacerbation 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 (exacerbation or remission) and often determine a negative prognosis of the disease.

Intestinal complications of UC include intestinal bleeding, toxic dilation and perforation of the large intestine, as well as colorectal cancer. Since these complications require surgery, they are discussed in detail in Section 3.2 "Surgical treatment".

2. DIAGNOSIS OF THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS), MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF DIAGNOSTIC METHODS

Criteria for establishing a diagnosis/condition *based on pathognomonic data:*

1) anamnesis;
2) clinical examination;
3) laboratory tests;
4) instrumental tests.

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

2.1 Complaints and Anamnesis

• In all patients with suspected UC, it is **recommended** to collect anamnesis and complaints to verify the diagnosis [19–22].

Grade of recommendation — C (Level of evidence is 4)

• In particular, when collecting anamnesis, it is **recommended** to clarify the presence of the fact of smoking in order to narrow the circle of diagnostic search and verification of the diagnosis [23].

Grade of recommendations is C (Level of evidence is 5)

Comment. *It is necessary to pay attention to the frequency and structure of stools (liquid multiple stools, tenesmus), evaluate the 24-hour volume of stools, the duration of these symptoms, the presence of blood in the stools, the type of abdominal pain;*

trips to southern countries; medications taken (in particular, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)); smoking; the presence of inflammatory and malignant intestinal diseases in relatives [24,25].

2.2 Physical Examination

• Physical examination is **mandatory** for all patients with suspected UC in order to narrow the circle of diagnostic search and verification of the diagnosis: — inspection of the perianal area; — digital rectal examination [26].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Physical (clinical) examination may reveal various manifestations of UC, including fever, peripheral edema, nutritional deficiency, signs of perforation or toxic dilatation of the large bowel, as well as extra-intestinal manifestations.*

2.3 Laboratory Diagnostic Tests

• A detailed general (clinical) blood test is **recommended** for all patients with suspected UC to diagnose anemia, comorbidities, as well as to determine the degree of UC activity [27–32].

Grade of recommendations is C (Level of evidence is 4)

Comment. *During a clinical blood test, anemia (iron deficiency, anemia of chronic disease, B_{12}- or folic deficiency anemia), leukocytosis (against the background of chronic inflammation or against the background of steroid therapy), thrombocytosis, an increase in ESR can be diagnosed.*

• It is **recommended** for all patients with suspected UC to do biochemical blood analysis (total protein, albumin, glucose, ALT, AST, total bilirubin, gamma-GT, cholesterol, LDH, K+, Na+, Cl–, C-reactive protein, alkaline phosphatase, fibrinogen) for the diagnosis of comorbidities [29,32–36].

Grade of recommendations is C (Level of evidence is 4)

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

• It is **recommended** for patients with acute UC (the first attack of the disease) to differentiate diagnosis with acute intestinal infection [37].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with acute UC to check stools for toxins A and B *Cl. difficile* to exclude clostridial infection [38–41].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** to perform a laboratory test of the feces of toxigenic *Cl. difficile* by methods: enzyme immunoanalysis with the determination of toxins A and B and/or immunochemiluminescence analysis with the determination of toxins A and B and/or polymerase chain reaction.

Grade of recommendations is C (Level of evidence is 4)

• **B**iopsies and/or PCR in the biopsy material of the colorectal mucosa (from lesions) for the presence of cytomegalovirus (CMV) is **recommended** for all patients with suspected UC, moderate and severe UC attacks, with steroid resistance or resistance to biological therapy [42,43].

Grade of recommendations is C (Level of evidence is 4)

2.4 Instrumental Diagnostic Studies

• It is **recommended** that all patients with mild to moderate UC activity undergo ileocolonoscopy to verify the diagnosis. Sigmoidoscopy is **recommended** for patients with pronounced UC activity [25,44].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Colonoscopy is mandatory to establish the diagnosis of UC and assess the activity of UC, as well as to resolve the issue of colectomy. Colonoscopy is the main method of diagnosing UC, but there are no specific endoscopic signs. The most peculiaris diffuse inflammation, limited by the mucous layer, starting in the rectum and spreading proximally, with a clear border of inflammation. The endoscopic activity of the UC is best reflected by contact vulnerability (the release of blood in contact with the endoscope), the absence of a vascular pattern and the presence of erosions and ulcerations. Detection of persistent narrowing of the intestine against the background of UC requires mandatory exclusion of colorectal cancer.*

• Abdominal X-ray is **recommended** for patients with severe UC attack to exclude perforation of the large intestine [45].

Grade of recommendations is C (Level of evidence is 4)

•Abdominal X-ray is **recommended** that patients with severe UC attack have an to exclude toxic dilatation [25].

Grade of recommendations is C (Level of evidence is 5)

• For all patients with suspected UC at the initial diagnosis, in case of doubts about the correctness of the previously made diagnosis, it is **recommended** to perform a biopsy in order to verify the diagnosis [46,47].

Grade of recommendations is C (Level of evidence is 5)

Comment. *With a long history of UC (more than 7–10 years), chromoendoscopy with a targeted biopsy or a step biopsy (from each part of the large intestine) is advisable to exclude epithelial dysplasia.*

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

Microscopic signs of UC include crypt deformation (branching, multidirection, the appearance of crypts of different diameters, a decrease in crypt density, "shortening of crypts", crypts do not reach the underlying layer of the muscle plate of the mucosa), "uneven" mucosal surface in the biopsy of the mucous membrane, a decrease in the number of goblet cells, basal plasmocytosis, infiltration of its own plate of the mucosa mononuclear cells with an admixture of segmented leukocytes and eosinophils, the presence of crypt abscesses and basal lymphoid clusters. The degree of inflammatory infiltration usually decreases with distance from the rectum.

• It is **recommended** for all patients with suspected UC at the initial diagnosis, in case of doubts about the correctness of the previously made diagnosis, with a long history of UC, with suspected complications of UC, as well as to exclude pathology of other abdominal organs, to make abdominal ultrasound, ultrasound of retroperitoneal space and pelvis [48,49].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with suspected UC, as a screening diagnosis, as well as to evaluate the effectiveness of therapy, to conduct an ultrasound of the intestine to assess the extent and severity of colorectal lesions [50].

Grade of recommendations is B (Level of evidence is 2)

• It is **recommended** for all patients with suspected UC, if differential diagnosis is necessary or if it is impossible to perform aileocolonoscopy, one of the following imaging methods of examination:

– magnetic resonance imaging (MRI) of the large bowel with contrast [51];

Grade of recommendations is C (Level of evidence is 4)

– computed tomography (CT) with intestinal contrast (in case of unavailability of expert assessment or impossibility of performing MRI) [52,53].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients with suspected UC, if differential diagnosis is necessary or if it is impossible to perform a colonoscopy, MRI and CT, undergo double-contrast barium enema to assess the extent of colorectal lesions, clarify the presence of tumors, strictures, etc. [26,54,55].

Grade of recommendations is B (Level of evidence is 2)

Comment. *It is also possible for patients with suspected UC to perform additional studies, depending on the clinical situation.*

2.5 Other Diagnostics

Additional instrumental and laboratory studies are performed mainly 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 colorectal CD, acute intestinal infections (dysentery, salmonellosis, campylobacteriosis, yersiniosis, amoebiasis), parasitoses, intestinal lesions associated with Cl. difficile, including those caused by antibiotics [56], intestinal tuberculosis, systemic vasculitis, colorectal cancer, diverticulitis, microscopic colitis (collagen and lymphocytic) [56], radiation proctitis.

For the purpose of differential diagnosis and selection of therapy for extra-intestinal manifestations of UC and comorbidities, consultation may be required:

– *a psychotherapist or a medical psychologist (neurosis, planned surgery with the presence of a stoma, etc.);*
– *an endocrinologist (steroid diabetes mellitus, adrenal insufficiency in patients on long-term therapy of GCS);*
– *dermatovenerologist (differential diagnosis of erythema nodosum, pyoderma, etc.);*
– *rheumatologist (arthropathy, sacroiliitis, etc.);*
– *obstetrician-gynecologist (pregnancy).*

3. TREATMENT, INCLUDING DRUG AND NON-DRUG THERAPY, DIET THERAPY, ANESTHESIA, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF TREATMENT METHODS

3.1 Conservative Treatment

3.1.1 Goals and Principles of Therapy

Therapeutic measures for UC include prescribing medications, surgery treatment, psychosocial support and dietary recommendations.

Globally, the goals of UC treatment are currently defined by the "Treat-to-target (T2T)" strategy, which means "Treatment until the goal is achieved". This concept is aimed at achieving a long-term effect of treatment, prevention of complications, reducing the incidence of hospitalizations, reducing the risk of surgery and colorectal cancer, improving the quality of life and reducing the incidence of disability in patients with chronic diseases [57,58]. From the point of view of common practice, the goals of UC therapy are to achieve and maintain long-term steroidal clinical and endoscopic remission (discontinuation of GCS within 12 weeks after the start of therapy) [59].

In accordance with the "T2T" strategy for UC, the primary goal of therapy should be the complete relief of clinical symptoms (absence of blood in the stools and normalization of the stools), which are reported by the patient him/herself. It is mandatory to achieve endoscopic remission.

With the progression of the process and/or the development of life-threatening complications, the specific goal is timely surgical treatment.

As part of the "T2T" strategy, continuous monitoring of the effectiveness of treatment is provided through regular biological markers (CRP, FC) and endoscopy [58].

The choice of the type of conservative or surgical treatment is determined by the severity of the attack, the extent of the colorectal lesion, the presence of EIM (extra-intestinal manifestations), the duration of the anamnesis, the effectiveness and safety of previous therapy, as well as the risk of complications of UC [59,60] and the presence of risk factors for a negative prognosis of UC [61–64].

Risk Factors for a Negative Prognosis of the Course of UC

Predictors of Aggressive Course and Predictors of Colectomy Risk

- Age of diagnosis ⩽ 40 years (associated with a more severe disease, a short period of remission and a higher risk of colectomy);
- Age ⩾ 65 years at the time of diagnosis (associated with the risk of early colectomy);
- extensive lesion;
- high activity according to endoscopy (large and/or deep ulcers);
- presence of extra-intestinal manifestations;
- early need for systemic GCS (prescription at the onset of the disease) or the need for at least one course of GCS;
- severe attack according to Truelove-Witts (the number of criteria in addition to the frequency of stools with blood ⩾ 6 times/24 hours correlates with the prognosis: the incidence of colectomy in the outcome of the current attack) [65];
- Extremely severe attack of UC with diarrhea more than 10–15 times per 24 hours, progressive anemia, fever above 38°C, hypoalbuminemia ⩽ 27 g/l, high levels of CRP and deep extensive ulcers of the colorectal mucosa is associated with a high risk of colectomy in the first days of attack [13,15];
- Elevated levels of inflammatory markers;
- Non-smokers and former smokers tend to have a longer duration of inflammation and slower healing.

Smokers have more rare acute attacks and hospitalizations.

Since the complete cure of UC patients is achieved only by removal of large intestine (proctocolectomy), when remission is achieved, the non-operated patient must remain on constant maintenance (anti-relapse) therapy.

It should be particularly noted that GCS cannot be used as a maintenance therapy.

Below are 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 [26].

3.1.2 Proctitis. Mild and Moderate Attack

• Local treatment is **recommended** for this group of patients.

Grade of recommendations is A (Level of evidence is 1)

Comment. *In this situation, it is advisable to prescribe suppositories with mesalazine** (1 g/24-hr, if necessary, the dose can be increased to 2 g/24-hr) or rectal mesalazine foam (1 g 1 time/24-hr, if necessary, the dose can be increased to 2 times/24-hr) [26,66,67]. Evaluation of the therapeutic response is carried out after 2 weeks [66], with a positive response, treatment at these doses is prolonged to 6–8 weeks.*

• It is **recommended** for patients with ineffective treatment with rectal mesalazine to prescribe rectal forms of GCS.

Grade of recommendations is A (Level of evidence is 1)

Comment. *In this situation, it is advisable to prescribe rectal budesonide foam 2 mg per 24 hours, suppositories with prednisolone 10 mg (extempore) 2 times per 24 hours with an assessment of the response after 2 weeks to achieve remission [26,68,69].*

• When remission is achieved, maintenance therapy is **recommended** — rectal mesalazine (suppositories or rectal foam) 1 g 3 times a week in the form of monotherapy for at least 2 years to maintain remission [26,70].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended**, if local treatment is ineffective, to add oral forms of mesalazine (granules, tablets **, tablets in a multimatrix shell (MMX**) at a therapeutic dose according to the instructions for use to achieve remission [71].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is permissible to prescribe sulfasalazine** instead of mesalazine** [74,77].*

• It is **recommended** for patients in the absence of the effect of oral forms of mesalazine to prescribe GCS to achieve remission [26,69].

Grade of recommendations is C (Level of evidence is 5)

Comment. *In this clinical situation, GCS is prescribed in tablets at a dose equivalent to prednisolone 0.5–0.75 mg/kg of body weight per day to achieve remission.*

• It is **recommended** to combine GCS with azathioprine** (AZA) or mercaptopurine** (MP) in case of relapse requiring repeated administration of GCS to achieve remission [26,72].

Grade of recommendations is C (Level of evidence is 5)

Comment. *AZA is prescribed 2–2.5 mg/kg, and MP — 1.5 mg/kg. Local therapy (rectal budesonide foam 2 mg per 24 hours, suppositories with prednisolone 10 mg × 1–2 times per 24 hours) can be continued.*

• It is **recommended** to carry out maintenance therapy of AZA 2–2.5 mg/kg (or MP 1.5 mg/kg) for at least 2 years to maintain remission when GCS-induced remission is achieved [71,72].

Grade of recommendations is A (Level of evidence is 1)

• It is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa to be treated with ganciclovir** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days to eliminate the pathogen [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.3 Proctitis. Severe Course (Develops Extremely Rarely)

• It is **recommended** for patients with severe ulcerative proctitis intravenous administration of GCS at a dose equivalent to prednisolone ** 1–1.5 mg/kg of body weight per 24 hours in combination with local mesalazine therapy ** (suppositories, rectal foam) or in combination with GCS rectally (budesonide foam 2 mg per day, suppositories with prednisone 10 mg × 2 times per 24 hours) to achieve remission [26,69].

Grade of recommendations is C (Level of evidence is 5)

• In the case of the first attack of UC, when remission is achieved, to maintain it, patients are **recommended** to be treated with local forms of mesalazine preparations (suppositories, rectal foam) 1 g × 3 times a week in the form of

monotherapy or in combination with oral mesalazine (granules, tablets, MMX tablets) at a dose of 2–2.4 g — at least 2 years to maintain remission [26,67,70,71,74,75,76].

Grade of recommendations is A (Level of evidence is 1)

Comment. *It is permissible to prescribe sulfasalazine ** 2 g/24-hr instead of mesalazine ** [74,77].*

• It is **recommended** in case of relapse requiring repeated administration of GCS (systemic or topical), simultaneously with GCS, to prescribe AZA 2–2.5 mg/kg (or #MP 1.5 mg/kg) and then continue maintenance therapy with immunosuppressants (AZA or #MP) for at least 2 years to maintain remission [72].

Grade of recommendations is C (Level of evidence is 5)

• Ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days for the elimination of the pathogen is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.4 Left-sided and Total Ulcerative Colitis. Mild Attack

• It is **recommended** for patients with the first attack or relapse to administer mesalazine orally (granules, tablets, MMX tablets) in maximum therapeutic doses in accordance with the instructions for use in combination with mesalazine** in enemas of 4 g/24-hr to achieve remission [26,70,78,79].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The therapeutic response is evaluated after 2 weeks. With an improvement in the clinical picture and positive laboratory changes, therapy lasts up to 6–8 weeks.*

• It is **recommended** in the absence of the effect of combination therapy with mesalazine preparations** the administration of rectal forms of GCS [79,80].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is advisable to prescribe rectal budesonide foam 2 mg per 24 hours or a suspension of hydrocortisone acetate with lidocaine 125–250 mg once per 24 hours in the form of enemas or rectal drip to achieve remission.*

• It is **recommended** that patients, upon reaching remission, undergo maintenance therapy with oral mesalazine** (granules, tablets, MMX tablets) 2–2.4 g/24-hr to maintain remission [81].

Grade of recommendations is A (Level of evidence is 1)

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

• It is **recommended** for patients in the absence of a response to combined treatment with oral mesalazine preparations** in combination with any rectal drug, the administration of topical corticosteroids (budesonide MMX) or systemic corticosteroids (see section 3.1.4) to induce remission [82].

Grade of recommendations is B (Level of evidence is 3)

• Ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days for the elimination of the pathogen is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.5 Left-sided and Total Ulcerative Colitis. Moderate Attack

• It is **recommended** for patients with the first attack or relapse of UC to prescribe oral mesalazine (granules, tablets **, tablets ** MMX) at the maximum therapeutic dose (in accordance with the instructions for use) in combination with mesalazine ** in enemas of 4 g/24-hr to achieve remission [26,75,76].

Grade of recommendations is A (Level of evidence is 1)

Comment. *The therapeutic response is evaluated after 2 weeks. With an improvement in the clinical picture and positive laboratory dynamics, therapy lasts up to 6–8 weeks.*

• It is **recommended** that patients achieve remission with maintenance therapy with mesalazine** (granules, tablets, MMX tablets) 2.0–2.4 g/24-hr orally + mesalazine ** in enemas of 4 g × 2 times a week to maintain remission [26,75,76,79].

Grade of recommendations is A (Level of evidence is 1)

Comment. *It is permissible to prescribe sulfasalazine** 2 g/24-hr instead of mesalazine** [74,77].*

• It is **recommended** for patients without a response to mesalazine for 2 weeks, but in the absence of signs of systemic inflammation, the administration of topical GCS (budesonide MMX). Topical GCS is prescribed at a dose of 9 mg/24-hr. After 10 weeks of taking budesonide MMX, dose reduction is carried out every other day for 1–2 weeks until complete withdrawal [46,83,84,85].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with the ineffectiveness of mesalazine for 2 weeks and with signs of systemic inflammation, the administration of systemic GCS to achieve a therapeutic effect [46,82,86,87,88].

Grade of recommendations is A (Level of evidence is 1)

Comment. *Systemic GCS is prescribed at a dose equivalent to prednisolone * * 1 mg/kg body weight per24 hours until a clinical response is achieved, followed by a decrease of 5 mg in 5–7 days until complete withdrawal, for no more than 12 weeks.*

• It is **recommended** for patients, when reducing the dose of GCS to the equivalent of 35–45 mg of prednisolone **, to additionally prescribe mesalazine ** (granules, tablets, MMX tablets) at the maximum therapeutic dose in accordance with the instructions for the drugs to maintain the therapeutic effect (if the patient does not receive immunosuppressants and GEBD) [78].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Further reduction of GCS should be carried out against the background of mesalazine ** followed by the transition to maintenance therapy with mesalazine** (granules, tablets, MMX tablets) 2.0–2.4 g per24 hours.*

• It is **recommended** for patients in case of intolerance to mesalazine preparations ** or, if necessary, to re-prescribe GCS for a year or less, combine GCS with AZA** 2.0–2.5 mg/kg or MP 1.5 mg/kg to achieve a therapeutic effect [72,89].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** that patients, upon reaching remission, continue maintenance therapy with AZA 2.0–2.5 mg/kg/24-hr or MP 1.5 mg/kg for at least 2 years to maintain remission [72,89].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients in the absence of the effect of GCS for 2 weeks prescription of GEBD (infliximab **, adalimumab **, golimumab**, vedolizumab**, ustekinumab**) or TIS (tofacitinib**, upadacitinib** or ozanimod **) to achieve remission in the form of induction (initiating) course and maintenance therapy [90–96].

Grade of recommendations is A (Level of evidence is 2)

Regimens and doses of drugs for GEBD and TIS as part of the induction course and the maintenance therapy:

• for infliximab, the induction course provides for three intravenous injections at 0, 2 and 6 weeks at dose of 5 mg/kg of bode weight, then the same dose for maintenance therapy every 8 weeks.

• for adalimumab, the induction course consists of the first subcutaneous injection at dose of 160 mg, afterwards the second subcutaneous injection after 2 weeks at dose of 80 mg, then maintenance therapy at dose of 40 mg every 2 weeks.

• for golimumab, the induction course consists of the first subcutaneous injection of 200 mg, the second subcutaneous injection after 2 weeks at dose of 100 mg, then maintenance therapy is carried out at 100 mg subcutaneously every 4 weeks.

• for vedolizumab, the induction course provides for three-time administration at 0, 2 and 6 weeks intravenously at dose of 300 mg, then maintenance treatment of 300 mg intravenously every 8 weeks.

• for ustekinumab, the induction dose is administered intravenously on the first day at dose of 6 mg/kg of body weight, then after 8 weeks the first subcutaneous injection at dose of 90 mg and afterwards maintenance therapy at dose of 90 mg subcutaneously every 8 or 12 weeks (depending on the course of the disease).

• for tofacitinib, 8-week induction course at dose of 10 mg × 2 times a day, then 5 mg × 2 times a day as a maintenance therapy.
• for upadacitinib, 8-week induction course at dose of 45 mg in tablets once a day and then 30 mg or 15 mg in tablets once a day as a maintenance therapy.
• for ozanimod, the induction course is 7 days with a gradual increase in the dose orally according to the instructions for use, on the 8th day and further, the full dose is 0.92 mg once a day.

Grade of recommendations is A (Level of evidence is 2)

Comment. *In bio-naive patients, any of these drugs can be used as the first line of therapy [203].*
It should be borne in mind that vedolizumab is more effective than adalimumab in the first line of therapy [210].

• It is **recommended** that patients receiving infliximab** combine it with immunosuppressants (AZA** 2.0–2.5 mg/kg) to increase the effectiveness of treatment [72,97,98].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is permissible to use #MP 1.5 mg/kg instead of AZA due to the fact that MP is a metabolite of AZA. For other GEBD, the effectiveness of the combination with immunosuppressants has not been proven. The combined use of azathioprine and tofacitinib is contraindicated [99,100].*

• It is **recommended** for patients with the effectiveness of the induction course of GEBD and TIS to carry out anti-relapse therapy with the same drug for at least 2 years to maintain remission [91,92,93,101,102].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with primary ineffectiveness or loss of response to any of the anti-TNF drugs to change therapy to vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod** to achieve remission [93,95,96,103,104].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Any of these drugs can be prescribed as the 2nd and subsequent lines of therapy with or without GCS. When choosing vedolizumab after anti-TNF, it should be borne in mind that its effectiveness as a 2nd-line drug is lower than in the 1st line [211].*
The choice of ustekinumab as a second line of GEBD with the ineffectiveness of the first anti-TNF is associated with better results (achievement of clinical response and clinical remission) compared to switching to another anti-TNF or vedolizumab [225,226].

• It is **recommended** for patients with loss of response to anti-TNF drugs in the 1st line of therapy (recurrence of UC on the background of previously achieved remission) optimization of therapy in the form of increasing the dose of the drug (10 mg/kg of infliximab ** every 8 weeks, 100 mg of golimumab ** every 4 weeks, 80 mg of adalimumab every 2 weeks) or shortening the intervals between injections (infliximab ** up to 4–6 weeks, adalimumab **40 mg every week) or prescribing drugs of a different mechanism of action: vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod** to achieve a therapeutic effect [91,92,93,101,102,104,105].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Switching to another anti-TNF drug is possible, but its effectiveness is lower than when switching to drugs of other classes (vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod**).*

• It is **recommended** for patients with loss of response to vedolizumab** at a standard dose of 300 mg every 8 weeks to optimize therapy in the form of shortening the intervals between injections to 4 weeks or change to a biological drug of another class (anti-TNF, ustekinumab**, tofacitinib**, upadacitinib**, ozanimod**) [106,211].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The effectiveness of anti-TNF in the 2nd line of therapy after loss of response to vedolizumab does not decrease compared to their effectiveness in the 1st line, i.e. the use of vedolizumab does not affect the subsequent effectiveness of anti-TNF [211,212].*

• It is **recommended** for patients with loss of response to ustekinumab** in the standard mode of administration every 12 weeks, optimization of therapy in the form of shortening the intervals between injections to 8 weeks or changing to a drug of another class (GEBD or TIS) [104].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with loss of response to tofacitinib** at a standard dose of 10 mg per day to optimize therapy to 20 mg per day [107].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The evidence basis on the possibility of switching from tofacitinib to biological drugs is insufficient.*

The change of drugs is possible and remains at the discretion of the attending physician. When stable clinical and endoscopic steroidal remission is achieved, the duration of biological therapy is determined by the attending physician.

In most countries, treatment has been carried out for many years. Early withdrawal of drugs, as a rule, leads to a relapse of UC in a short time.

If prolonged use of GEBD and TIS is not possible, maintenance therapy is carried out only with immunosuppressants.

• It is **recommended** for patients with relapse that occurred against the background of maintenance therapy with thiopurines to prescribe GEBD (infliximab**, adalimumab**, golimumab**, vedolizumab ** or ustekinumab **) or TIS tofacitinib **, upadacitinib** or ozanimod ** (with the cancellation of thiopurines according to the instructions for medical use) [91,92,93,95,96,101].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Any of these drugs can be prescribed as a first-line therapy (see section 3.1.5).*

• It is **recommended** for patients who have cytomegalovirus DNA detected in the colorectal mucosa, ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days to eliminate the pathogen [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.6 Left-sided and Total Ulcerative Colitis. Severe Attack

• Intravenous administration of GCS is **recommended** for patients as the first line of therapy to achieve remission [26,108].

Grade of recommendations is A (Level of evidence is 1)

Comment. *The use of GCS is advisable at a dose equivalent to prednisolone ** 2 mg/kg of body weight intravenously (with a high body weight, 1.5 mg/kg may be prescribed) for 7 days or the use of hydrocortisone ** at an equivalent dose.*

The equivalence of doses and duration of action of GCS is shown in Table 6. The response is estimated in the range from 3 to 7 days. If the condition is stable for three days, then therapy is continued for up to 7 days. If the patient's condition worsens within three days, the question of "rescue therapy" or colectomy is raised.

If clinical improvement is noted after 7 days, then GCS therapy can be continued until stable improvement and then switch to oral medication and slowly reduce the dose of 5 mg every 5–7 days.

If there is no significant clinical improvement after 7 days, the condition is regarded as steroid resistance.

• It is **recommended** for patients to additionally prescribe local therapy with enemas with mesalazine ** 4 g per 24 hours or a suspension of hydrocortisone acetate with lidocaine 250 mg × 1 time per 24 hours in the form of enemas or rectal drip to achieve remission [79,80].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with metabolic disorders to carry out infusion therapy in order to rehydrate, correct protein-electrolyte disorders [59].

Grade of recommendations is C (Level of evidence is 5)

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

• It is **recommended** for patients with hemoglobin levels below 80 g/l to correct anemia in the form of hemotransfusion (erythromass), with hemoglobin levels from 80 to 100 g/l — parenteral iron therapy: sucrose hydroxide complex **, iron (III) dextran hydroxide, iron (III) hydroxide oligoisomaltosate, iron carboxymaltosate** [109].

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for patients to reduce the risk of thrombosis to carry out preventive therapy with low molecular weight heparins (ATC B01AB),

Table 6. *Comparative characteristics of GCS*

Drug	Duration of action ($t_{1/2}$)	Equivalent dose (mg)
Cortisol (hydrocortisone)	8–12 hours	20
Prednisone	12–36 hours	5
Prednisolone	12–36 hrs	5
Methylprednisolone	12–36 hrs	4

unfractionated heparin**, fondaparinux sodium** [204,205].

Grade of recommendations is B (Level of evidence is 2)

• It is **recommended** for patients with a body weight deficit (BMI less than 18) to prescribe additional enteral nutrition, including tube feeding, to improve the trophological status [110].

Grade of recommendations is C (Level of evidence is 2)

Comment. *Complete parenteral nutrition and/or temporary restriction of oral nutrition is impractical.*

• With the development of signs of systemic inflammation in patients, it is **recommended** to prescribe antibiotics to prevent septic complications:
1 line — #metronidazole** + fluoroquinolones (ciprofloxacin**, ofloxacin**) [111];
Line 2 — cephalosporins [112,113].

Grade of recommendations is A (Level of evidence is 1)

• It is **recommended** for patients with a clinical response to GCS after 7 days to change to oral prednisolone ** followed by a reduction to complete withdrawal of 5–10 mg of prednisolone ** in 5–7 days to maintain remission [59].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The scheme of transition from intravenous GCS to oral forms is considered individually by the attending physician, depending on the speed of achieving the effect and the severity of the therapeutic response.*

With the development of steroid resistance, if there is no immediate life-threatening or severe complications requiring immediate surgery, "rescue therapy" is indicated, against the background of continuing treatment of GCS, i.e. strengthening of conservative therapy, which is carried out with infliximab (at a dose of 5 mg/kg as part of an induction course at 0, 2 and 6 weeks) or cyclosporine A i/v (2–4 mg/kg for 7 days with monitoring of renal function and determination of the concentration of the drug in the blood) or tofacitinib (20 mg/24-hr as part of an induction course for 8 weeks) [103,206,207,208]. The clinical result of such therapy is evaluated after 7 days. Studies have shown that the effectiveness of both regimens (with infliximab and cyclosporine) on day 8 of treatment is identical, therefore, currently infliximab is mainly used in foreign practice, as drug is safer and does not require time-consuming and expensive concentration determination. If there is no effect after 7–8 days, surgical treatment options are considered. If it is impossible to prescribe infliximab, it is permissible to prescribe tofacitinib taking into account the speed of achieving the effect [207, 208] in accordance with the instructions for use.(see section 3.1.5).

• It is **recommended** that patients who achieve remission on infliximab** continue supportive anti-relapse therapy with the same drug according to the standard scheme in combination with AZA** 2–2.5 mg/kg (or #MP 1.5 mg/kg) or without it [98,102,114].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients with a positive response to i/v #cyclosporine ** after 7 days switch to oral administration of the drug at a dose of 2 mg/kg of body weight with the additional administration of AZA ** 2 mg/kg (against the background of a therapeutic dose of GCS) with the gradual abolition of GCS for 12 weeks until the therapeutic concentration is reached and the beginning of the action of AZA** to increase the duration of remission in the patient.

When remission is achieved, oral cyclosporine can be canceled, leaving the patient on the maintenance therapy of AZA** for at least 2 years [72,89,115,116].

Grade of recommendations is C (Level of evidence is 5)

Comment. *A significant drawback of such a treatment regimen is due to the simultaneous use of three immunosuppressive drugs at once with an increased risk of adverse events.*

3.1.7 Extremely severe Ulcerative Colitis of Any Extent

In this form, both the first attack of the UC and any of the subsequent acute attacks can occur (for a description, see the section "Classification of the UC"). The patient must be hospitalized in a multidisciplinary (specialized) hospital for conservative treatment, followed by mandatory supervision by a gastroenterologist and a coloproctologist (surgeon) to decide on the feasibility of performing surgery within 24 hours.

• It is **recommended** for patients with aextremely severe attack of UC to prescribe intravenous corticosteroids at a dose equivalent to prednisolone ** 2 mg/kg of body weight to achieve a therapeutic effect [117].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The effectiveness of conservative therapy in extremely severe UC attack does not exceed 50%. At the same time, the clinical picture and laboratory parameters are evaluated every 24 hours, and more often if necessary. With the worsening of the clinical picture and laboratory parameters, the only way to save a patient's life in anextremely severe attack of UC is colectomy. With significant positive changes on the part of the clinical picture and laboratory parameters, with a sufficient degree of caution, it is possible to continue intravenous therapy with GCS for up to 14 days. If there is no positive changes within 3 days, then this condition is regarded as steroid resistance.*

• In the case of steroid resistance, if there is no immediate threat to the patient's life or the development of severe complications requiring urgent surgery, for this group of patients it is **recommended** to prescribe "second-line" therapy (in the English literature, "rescue therapy"), which includes the following treatment options:
infliximab** 5 mg/kg (administered as part of an induction course at 0, 2 and 6 weeks) [118,119] or #cyclosporine** (preferably intravenous) 2–4 mg/kg for 7 days with monitoring of renal function [120,121] ortofacitinib 20 mg/24-hr as part of an induction course for 8 weeks [103,206,207,208].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Other biological drugs are not used as "rescue therapy". Surgery is indicated for this group of patients with negative shifts or in the absence of a response on day 7 of therapy with infliximab**, cyclosporine** or tofacitinib** [122].*

• It is **recommended** that patients who achieve remission on infliximab** continue supportive anti-relapse therapy with the same drug according to the standard scheme in combination with AZA** 2–2.5 mg/kg (or #MP 1.5 mg/kg) or without it [98,102,114].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients who achieve remission on tofacitinib ** continue maintenance therapy with the same drug 10 mg/24-hr. [103].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** that patients with a positive response to i/v #cyclosporine ** after 7 days switch to oral administration of the drug at a dose of 2 mg/kg of body weight with the additional administration of AZA ** 2 mg/kg (against the background of a therapeutic dose of steroids) with the gradual abolition of steroids for 12 weeks until the therapeutic concentration is reached and the beginning of the action of AZA** to increase the duration of remission in the patient.
When remission is achieved, oral cyclosporine can be canceled, leaving the patient on the maintenance therapy of AZA** for at least 2 years [72, 89,115,116].

Grade of recommendations is C (Level of evidence is 5)

3.1.8 Biosimilars (Bio-analogues)

Biosimilars are biological medicinal products containing a version of the active substance already approved by the original biological medicinal product (reference drug) [213]. Currently, the biosimilar market is constantly expanding. In relation to IBD, this still applies to biosimilars based on monoclonal antibodies to TNF-alpha. In Europe alone, 21 biosimilars have been registered in the last decade, of which 14 are based on adalimumab and 4 are based on infliximab [214]. Biosimilars of infliximab and adalimumab have also been registered in the Russia, analogues of tofacitinib have recently appeared. The use of biosimilars reduces the economic burden on the healthcare system and, thereby, significantly expands the

possibilities of using and accessibility of GEBD. Now there is a sufficient evidence for the effectiveness and safety of biosimilars, but among clinicians there remains a prejudice against them as drugs with lower efficacy [215].

The European Organization for the Study of IBD (ECCO) in 2017 declared a position on the use of biosimilars in IBD, which emphasizes that after registration, a biosimilar is considered to be as effective a drug as the original product, and large observational studies are required to assess its long-term effectiveness and safety [216]. It is from these positions that a systematic review of 90 studies in various immuno-inflammatory diseases in 2018 showed that in the vast majority of studies there were no differences in safety, efficacy or immunogenicity between biosimilars and the corresponding original drugs, which indicates the preservation of a good benefit-risk profile when switching from the original drug to a biosimilar [217]. Real clinical practice in European countries and the USA demonstrates similar efficacy, safety and immunogenicity when switching IBD patients from the original infliximab to its biosimilars [218–222]. Only in one study, in 9.9% of cases, the need for reverse switching from a biosimilar to a reference drug was recorded due to undesirable manifestations from the skin, gastrointestinal tract or due to loss of response to the drug. In the vast majority of patients, the response to treatment after the reverse switch restored [220]. Comparison of adalimumab and its two analogues in patients with IBD in Italy showed no significant difference in efficacy, safety and immunogenicity between the drugs after the induction course and after 6 months of maintenance treatment [223]. The results of long-term post-marketing monitoring of the efficacy and safety of biosimilars based on monoclonal antibodies for 7 years did not reveal any side effects specific to biosimilars [224]. The ECCO consensus emphasizes that the decision to switch from an original drug to a biosimilar for non-medical reasons should be carried out in accordance with national clinical guidelines and all information should be brought to the attention of the patient and explained to him [216]. Despite the clearly formulated statements about biosimilars, there are certain contradictions in this matter, according to which the adopted provisions are based on studies with different methodological approaches and an insufficient number of observations, which limits their reliability [227].

Russian publications indicate that frequency of secondary loss of response and adverse events in IBD patients when switching from the original infliximab to its biosimilar is about 30%, which is significantly higher than in patients who regularly receive the original drug. In addition, the frequency of adverse events is significantly higher in patients receiving the drug according to INN, which leads to unjustified and unregulated alternation of the original drug and bioanlogs compared with patients receiving drugs by trade name [228].

The provision on biosimilars is being introduced for the first time in the Russian clinical guidelines for UC. Because Russian biosimilars are not represented on the foreign market, international data on successful switching experience will have limited applicability for Russia. Therefore, it is necessary to extrapolate these data with caution to domestic clinical practice.

• It is **recommended** to use both the original drug and its biosimilars as equivalent medicines when indications for the administration of a GEBD class of TNF-alpha inhibitors (infliximab and adalimumab) [215,216].

Comment. *This provision applies equally to the primary administration of anti-TNF drugs in bio-naive patients, and switching from the original drug to a biosimilar for non-medical indications. However, it should be aware that frequent switching from the original drug to a biosimilar or different biosimilars and back according to INN can lead to a worsening of course of the disease, a rapid loss of response and adverse events [228].*

Switching from one anti-TNF drug to another within the same class with a loss of response to the first drug is not recommended either for original drugs or for biosimilars (see section 3.1.5). There is not yet a sufficient evidence basis for the use of biosimilars of drugs of other classes for the treatment of UC.

3.2 Surgical Treatment

3.2.1 Indications for Surgical Treatment of UC: Ineffectiveness or Impossibility to Continue Conservative Treatment

Indications for surgical treatment of UC are the ineffectiveness of conservative treatment (steroid

resistance, inefficiency of GEBD) or the impossibility of their continuation (steroid addiction, intolerance or contraindications for conservative treatment), intestinal complications of UC (toxic dilation, intestinal perforation, intestinal bleeding), as well as colorectal cancer or a high risk of its occurrence.

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

- Steroid resistance;
- Steroid addiction.

Steroid addiction can be effectively overcome with the help of GEBD and/or immunosuppressants (AZA**, MP**) in 40–55% of cases [78,116], and with steroid resistance, the administration of cyclosporine** or infliximab** allows to induce remission in 43–80% of cases [118,119,120].

However, in some patients with a high risk of complications and ineffectiveness of conservative therapy with the development of steroid resistance or addiction, surgical treatment is possible without attempting to use GEBD or immunosuppressants.

3.2.2 Indications for Surgical Treatment of UC: Intestinal Complications of UC

- Patients with complications of UC (intestinal bleeding, perforation of the large intestine, toxic dilation on the background of adequate infusion therapy) are **recommended** to undergo subtotal colectomy or total colectomy or proctocolectomy (with severe rectal activity) to increase the patient's life expectancy [123,124,125].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Toxic dilation of the colon (toxic megacolon) is an expansion of the colon 6 cm or more unrelated to obstruction with intoxication phenomena. Risk factors for toxic dilation include hypokalemia, hypomagnesemia, bowel cleansing for colonoscopy using osmotic laxatives and antidiarrheal medications. Indirectly, the development of toxic dilatation is indicated by a sudden decrease in the frequency of stools against the background of existing diarrhea, bloating, as well as a sudden decrease or disappearance of pain syndrome and an increase in symptoms of intoxication (an increase in tachycardia, a decrease in blood pressure). Perforation of the large intestine is the most dangerous complication of UC with almost 50% mortality.*

3.2.3 Indications for Surgical Treatment of UC: Colorectal Cancer

In patients with a long history of UC, the risk of colorectal cancer is significantly increased, which necessitates regular check-up to detect dysplasia in the epithelium of the colorectal mucosa. The probability of cancer is influenced by the following factors:

a) The duration of the history of UC: the risk of colorectal cancer is 2% at 10-year-old, 8% at 20-year-old and 18% at 30-year-old history [126];

b) The onset of the disease in childhood and adolescence, although this factor can only reflect the duration of the anamnesis and is not an independent predictor of colorectal cancer [127];

c) The extent of the lesion: the risk is most elevated in patients with total UC, while in patients with proctitis the risk does not differ from the average in the population;

d) The presence of primary sclerosing cholangitis [128];

e) Family history of colorectal cancer;

f) Severe attacks of UC in the anamnesis or continuous course of UC. The consequence of high UC activity may be inflammatory polyposis, which is also a risk factor for colorectal cancer [129].

A control colonoscopy should be performed in conditions of good preparation of the intestine and, preferably, during remission, since active inflammation makes it difficult to detect dysplasia.

Clarifying endoscopic techniques are used for screening neoplastic changes in the mucous membrane: video colonoscopy with chromoscopy in combination with dye or virtual (optical) chromoscopy with targeted biopsy [130, 131, 132]. When using clarifying endoscopic techniques, a search biopsy is not required.

The results of the screening biopsy affect the approach for further treatment and follow-up.

- Surgical treatment in the scope of total colectomy is **recommended** for patients with UC when a high degree of dysplasia is detected in the biopsy from a macroscopically unchanged mucosa [126].

Grade of recommendations is C (Level of evidence is 5)

Comment. *It is possible to perform a proctocolectomy with permanent terminal ileostomy or a proctocolectomy with the simultaneous ileal pouch with protective loop ileostomy.*

The presence of dysplasia in the epithelium of the colorectal mucosa should be confirmed by a second independent pathologist. The type of surgery is discussed together with the patient, thereby taking into account his/her desire for the preservation of anal defecation or the permanent ileostomy.

• It is **recommended**, when mild dysplasia is detected in the epithelium of a macroscopically unchanged mucosa, to discuss individually with the patient two options for surgical treatment — total colectomy (or proctocolectomy) with the permanent terminal ileostomy and proctocolectomy with the simultaneous formation of ileal pouch under the guise of a loop ileostomy to improve the patient's quality of life or continuation of regular endoscopic screening with a reduction in the interval between studies in the period from 6 to 12 months [126].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The type of surgery should be discussed with the patient, thereby taking into account his desire for the preservation of anal defecation or the formation of a permanent ileostomy.*

The patient has the right to refrain from surgical treatment, in which case endoscopic screening is offered.

• It is **recommended** for patients with UC remission, upon confirmation of the presence of an adenomatous polyp (endoscopically and according to the results of a pathomorphology), to perform a standard polypectomy for secondary cancer prevention [128].

Grade of recommendations is C (Level of evidence is 4)

Comment. *In patients with remission of UC in the presence of large neoplastic lesions of the large intestine and the absence of dysplasia in the epithelium of the mucosa outside of these lesions, it is possible to perform mucosectomy or dissection in the submucosal layer [133,134].*

• Colectomy is **not recommended** for patients with UC in the presence of an adenomatous polyp with severe dysplasia, if there is no dysplasia in the epithelium of the mucosa in other parts of the large intestine or corresponds to a mild degree [128].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with ulcerative colitis in the presence of a narrowing area in the large intestine to conduct an endoscopic examination with a biopsy from the narrowing area to exclude colorectal cancer [129].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Dysplasia in the epithelium of the mucous membrane should be confirmed by a second pathologist, and then the treatment program should be discussed by a multidisciplinary medical consultation.*

If the colonoscopy is not total due to the presence of narrowing, CT with intravenous and intraluminal contrast is necessary to assess the nature of changes in the large intestine wall proximal to the narrowing [135].

All patients with colorectal cancer on the background of ulcerative colitis, after an oncological consultation, are shown surgical treatment in the scope of total colectomy with abdominal-anal resection of the rectum to eliminate the risk of malignant transformation in the remaining parts of the large intestine.

3.2.4 Surgery Types

In most patients with UC, modern conservative treatment allows controlling the inflammatory process. However, in 10–30% of patients, due to the ineffectiveness of drug treatment, it is necessary to resort to surgery aimed at removing the large intestine [123,124]. Until the early 1980s, the standard of surgical treatment was proctocolectomy with terminal ileostomy, despite the episodic formation of ileorectal anastomosis.

Over the past 20 years, reconstructive surgery has become the new gold standard — total colectomy with pouch (proctocolectomy with IPAA) [136,137] (Table 7). In the absence of complications, this surgery provides the possibility of controlled defecation through the anus with a satisfactory quality of life [136]: the frequency of defecation after the formation of IPAA is 4–8 times per 24 hours [138–140], and the average 24-hour volume of semi-formed/liquid stools is about 700 ml per 24 hours (compared with 200 ml/24-hr in a healthy person).

All patients who are going to undergo surgery (total or subtotal colectomy or colectomy with intersphincter resection of the rectum) due to the

Table 7. *Methods of surgical treatment of UC*

With the formation of a permanent ileostomy	With the restoration of defecation through the anus		
Colectomy with abdominal-anal resection of the rectum and the formation of a permanent terminal ileostomy	With the formation of IPAA, in 2 stages:	With the formation of IPAA, in 3 stages:	Subtotal colorectal resection with ileorectal anastomosis (in exceptional cases)
	1. Colectomy with rectal resection, IPAA, loop ileostomy; 2. Closure of the loop ileostomy	1. Subtotal colorectal resection (subtotal colectomy), terminal ileostomy; 2. Proctectomy, IPAA formation, loop ileostomy; 3. Closure of the loop ileostomy	

ineffectiveness of conservative treatment, with the exception of intestinal complications, it is preferable to use laparoscopic technologies to reduce the rate of intraoperative and postoperative morbidity, faster recovery, reduce the risk of adhesions in the abdominal cavity, reducing the risk of fertility decline and improving the cosmetic result [141–146].

3.2.5 Choosing the Type of Surgery

Reconstructive surgery with IPAA, despite its obvious attractiveness to the patient, is not possible in all cases, since a number of factors worsen the functional outcome of the surgery and increase the risk of complications, leading to the need to remove the pouch in 3.5–10% of patients [147–149].

In patients of older age groups with UC, despite the higher incidence of concomitant diseases, the surgery itself with ileal pouch is safe [150]. The anal sphincter function, which plays a key role for the normal functioning of IPAA, as a rule, worsens in older age groups [151].

In addition, patients over 60 years old are more likely to develop complications, in particular, pouch and anastomotic stricture [152, 153]. At the same time, no specific age threshold for refusing to form IPAA has been determined.

The IPAA by 30–70% increases the risk of infertility in women of childbearing age with UC [154–158].

The risk of infertility is associated with the adhesive process involving the fallopian tubes. Planned pregnancy and the young age of a woman are not contraindications to the IPAA. However, the patient should be warned about the potential risk of infertility. In some cases, it is possible to consider the formation of an ileorectal anastomosis as an intermediate stage of surgical treatment (see below).

In all patients with UC, when indications for surgery arise, the use of laparoscopic technologies reduces the risk of infertility by 90% [158].

In approximately 10% of patients, even with a pathomorphological study of the surgical specimen after colectomy, it is not possible to make a differential diagnosis between CD and UC, and therefore they are diagnosed with unspecified colitis. The decision on the formation of IPAA in such cases is made individually, while the patient should be warned about the risks of ineffectiveness of reconstructive plastic surgery and other complications associated with CD.

In patients with UC in the presence of concomitant diseases such as rectal cancer and severe anal incontinence of the 2nd or 3rd degrees, the IPAA is impractical.

- It is **recommended** that patients with severe UC attack who did not respond to conservative treatment, as well as patients with UC who, by the time indications for surgery were established, had hormone therapy with prednisolone for more than 6 weeks** at a dose of at least 20 mg per 24 hours for more than 6 weeks, undergo three-stage surgical treatment (colectomy with ileostomy at the first stage, the ileal pouch and a loop ileostomy at the second stage, and the closure of a loop ileostomy at the third stage) to reduce the risk of postoperative complications [159–161].

Grade of recommendations is C (Level of evidence is 4)

Comment. *In all patients with severe or extremely severe attack of ulcerative colitis, if indications for surgery arise, surgical intervention should be at least colectomy with end ileostomy, which allows to improve the general condition of the patient, eliminate metabolic disorders, and pathomorphology of the removed specimen excludes CD. Colectomy is a relatively safe surgery even in patients in critical condition [159–161]. With sufficient qualification of the surgeon, it is safe to use laparoscopic technologies [162, 163].*

The ileorectal anastomosis does not lead to a cure of the patient and does not exclude the possibility of recurrence of inflammation in the rectum and the development of cancer [164–166]. This surgery in UC

can be performed only in exceptional cases in women planning pregnancy. A prerequisite is the presence of remission in the rectum and the patient's consent to a regular rectal examination with a mucosal biopsy [165, 167].

3.2.6 Surgery Features in the Formation of Ileal Pouch

In patients with UC who have undergone colectomy, reconstructive plastic surgery with IPAA is performed in specialized hospitals, since the morbidity rate and the functional outcome of such procedures significantly depends on the personal experience of the surgeon [165].

The Length of the Preserved Rectum and/or Sigmoid Colon

For patients with UC, when performing colectomy for urgent indications, which are planned for ileal pouch in the future, it is advisable to preserve the entire rectum and low mesenteric vessels to improve the quality of life. It is advisable to cross the rectum at the level of promontorium or additionally preserve the distal sigmoid colon (the decision is made by the operating surgeon). While maintaining the distal part of the sigmoid colon, it is displayed on the anterior abdominal wall in the form of aendsigmostomy. The latter option is the safest, since at the same time there is no stump of the intestine in the abdominal cavity. When crossing the rectum at the level of promontoriumfor several days, drainage of the stump through the anus is recommended to prevent the leakage due to the collection of mucus. In case of preservation of the diverted rectum or rectum and sigmoid colon, the development of secondary inflammatory changes of the mucosa (diversion colitis) is possible. Controlled trials of drugs in patients after colectomy have not been done yet. Empirical treatment consists in topical application of mesalazine [168], steroids, washing of the diverted rectum with antiseptic solutions.

The IPAA

For patients with UC who are planning surgical treatment with ileal pouch, in order to improve functional results, it is advisable to keep the distal rectum no longer than 2 cm above the dentate line. The preservation of an extended rectal stump (more than 2 cm above the dentate line) may cause chronic inflammation in it with pouch dysfunction, and also contributes to the preservation of the risk of dysplasia and (very rarely) cancer [164]. If it is impossible to form a pouch-rectal anastomosis using a stitching device, abdominal-anal resection of the rectum should be performed and a manual ileoanal anastomosis should be applied.

Morphological changes in the epithelium of the pouch usually develop 12–18 months after the closure of the ileostomy and are characterized by flattening and reduction of the number of villi, and are often accompanied by the development of colorectal metaplasia [169,170], which is potentially associated with the risk of malignant transformation of the mucosa of the pouch. In addition, when applying stapler IPAA, a small area of the rectal mucosa ("cuff") is preserved. The risk of developing pouch cancer is increased in patients operated for cancer or dysplasia against the background of UC (and when dysplasia is detected in removed specimen), as well as in patients with primary sclerosing cholangitis (PSC). Scientific substantiation of the frequency of control check-up of patients with IPAA has not been performed; however, in patients with the presence of the above risk factors, it is advisable to conduct control pouch endoscopy with a mucosal biopsy at least once every 2 years.

3.2.7 Medications during Surgical Treatment

The effect of drug therapy on the risk of operation.

- It is **recommended** to carry out drug therapy (hormonal, immunosuppressive, GEBT) with caution during surgical treatment to reduce the risk of postoperative complications [171–176].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Taking prednisolone** at a dose of more than 20 mg for more than 6 weeks increases the rate of postoperative complications [171, 172]. Preoperative administration of AZA and MP does not worsen the outcome of surgical treatment [173], while the administration of infliximab** and cyclosporine**# shortly before surgery may increase the frequency of postoperative complications [174, 175], although data on infliximab** remain contradictory [176]. Abrupt discontinuation of GCS therapy can cause withdrawal syndrome (acute adrenal insufficiency, the so-called Addison crisis), which necessitates the temporary continuation of hormone therapy after surgery until complete withdrawal. At the moment, there is no reliable scientific basis to substantiate any scheme for stopping hormone therapy after colectomy for UC. The dose of GCS for*

further oral administration during the withdrawal of hormone therapy is determined by the duration of previous therapy and the value of doses used.

*According to the recommendations of the European Society for the Study of UC and CD (ECCO) [26], if hormone therapy was carried out no more than a month before surgery, it is possible to stop taking GCS immediately after surgery.If the patient received GCS for more than a month before surgery, after surgery it is advisable to switch from the above-described high parenteral dose to oral administration of GCS at a dose not lower than the upper limit of the 24-hour stress production of cortisol, that is, not lower than 20 mg of prednisolone **.*

3.2.8 Pouchitis and Other Complications of Surgical Treatment in the Formation of a Small Intestine Pouch

Pouchitis is a nonspecific inflammation of the ileal pouch and the most common complication of IPAA.

Its incidence varies in a wide range from 15% to 50% within 10 years after the IPAA in large specialized centers [177–179]. Such differences may be due to a significantly higher risk of pouchitis in UC, exceeding the rate of this complication in IPAA for other diseases (in particular, familial adenomatous polyposis) [180–181].

In patients with picture of pouchitis, intestinoscopy (pouch endoscopy) should be performed to assess the degree of inflammatory changes in the pouch mucosa with biopsy.

Pouchitis is accompanied by abscesses, fistulas, stenosis of the IPAA and the risk of developing cancer in the pouch. The latter complication is extremely rare and almost always occurs when severe dysplasia or cancer is detected in the removed specimen after colectomy.

Differential diagnosis of suspected pouchitisis performed with irritable pouch syndrome (IPS), ischemic lesions, CD and other rare causes of pouch dysfunction, such as collagenose, cytomegalovirus and Clostridioides difficile-associated pouchitis. The possibility of the development of nonspecific ileitis caused by taking NSAIDs and the syndrome of excessive bacterial growth should be taken into account.

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

• For patients with pouchitis, first-line therapy, including a 14-day course of oral metronidazole** (15–20 mg/kg/24-hr) or ciprofloxacin** (1,000 mg/24-hr) is **recommended** to achieve a therapeutic effect [182].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Adverse events are much more common when taking metronidazole.*

In cases of antibiotic-resistant pouchitis, oral budesonide (9 mg) may be prescribed for 8 weeks.

• It is **recommended** for patients with pouchitis in the absence of an effect or with the development of dependence on taking these drugs, to prescribe reserve drugs — rifaximin (2,000 mg/24-hr) and tinidazole (1,000–1,500 mg/24-hr), including in combination with ciprofloxacin (1,000 mg/24-hr), rectal corticosteroids, rectal drugs mesalazine **, azathioprine** to achieve a therapeutic effect [182].

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for patients with chronic therapy-resistant pouchitis in case of ineffectiveness of first-line therapy and reserve medications, to prescribe #TNF-α blockers [183], #vedolizumab [184] or #ustekinumab [185] for induction and maintenance of remission.

Grade of recommendations is C (Level of evidence is 5)

Inflammation of the Mucosa of the Preserved Area of the Rectum

Another potential complication of IPAA is inflammation of the mucosa of the rectum, preserved during the application of a stapler anastomosis.

• It is **recommended** for patients with proctitis after ileal pouch, to conduct treatment with mesalazinesuppositories ** 500 mg 2 times per 24 hours and/or rectal corticosteroids to achieve a therapeutic effect [68].

Grade of recommendations is A (Level of evidence is 1)

3.2.9 Ileostomy Dysfunction after Surgical Treatment of UC

Ileostomy dysfunction refers to an increase in the volume of intestinal discharge through the ileostomy of more than 1,000 ml per 24 hours. This condition is also accompanied by rapidly progressing metabolic and water-electrolyte disorders [186, 187].

• It is **recommended** for patients with ileostomy dysfunction to use an algorithm for laboratory diagnosis of *Clostridioides difficile* –associated diarrhea, including molecular biological fecal test for the pathogen *Cl. difficile* or immunochromatographic rapid fecal test for toxins A, B and binary toxin *Cl. difficile* [186,188].

Grade of recommendations is C (Level of evidence is 5)

Comment. *In addition to abundant liquid discharge through the stoma, the clinical picture also shows an increase in body temperature to 39^{0}C, flatulence, rarely complaints of nausea, vomiting, abdominal spastic pain. In laboratory tests: anemia, hypoproteinemia, hypoalbuminemia, hypokalemia, an increase in the level of CRP, rarely an increase in creatinine concentration.*

• It is **recommended** for patients with mild ileostomy dysfunction to prescribe a diet therapy, antispasmodics and drugs that slow down the passage through the gastrointestinal tract to achieve a therapeutic effect and improve the patient's quality of life [186–188].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The mild form of the disease is characterized by an increase in the volume of intestinal discharge by ileostomy, without signs of systemic inflammation.*

• It is **recommended** for patients with a moderate form of ileostomy dysfunction, when confirming the diagnosis of clostridial infection, to prescribe metronidazole at a dose of 500 mg orally three times a day for 10 days. In the absence of a clinical effect from metronidazole ** after 5–7 days, the drug is changed to vancomycin ** at a dose of 1,000 mg per day *per os* for 10 days to achieve a therapeutic effect and improve the patient's quality of life [186,187,189,190].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The moderate form is characterized by an increase in the volume of intestinal discharge by ileostomy, an increase in body temperature and changes in laboratory parameters: with an increase in the level of leukocytes in the blood more than 15 × 10^9/l, serum creatinine above 115 mmol/l, a rise in body temperature above 38^{0}C and a decrease in albumin less than 25 g/l, patients should receive treatment in a 24h hospital. In case of confirmation of clostridial infection, the administration of vancomycin ** at a dose of 1,000 mg orally per day for 10 days is indicated.*

• It is **recommended** for patients with severe ileostomy dysfunction when confirming the diagnosis of clostridial infection, along with infusion therapy, to prescribe vancomycin 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 [187,191].

Grade of recommendations is C (Level of evidence is 5)

Comment. *A severe form of ileostomy dysfunction, in addition to an increase in the volume of intestinal discharge through the ileostomy, is manifested by abdominal pain of a spastic nature, the development of fever up to hectic values, leukocytosis, hypoalbuminemia. If it is impossible to administer the drug through the mouth, vancomycin ** is prescribed intramuscularly — while the drug at a dose of 500 mg is diluted in 500 ml of 0.9% sodium chloride solution and injected into the intestinal lumen four times a day. Deterioration of the patient's condition with the occurrence of hypotension, hyperthermia above 38.5° C, stools retention, pronounced bloating, change of consciousness, leukocytosis above 15 × 10^9 or leukopenia below 2 × 10^9, increased serum lactate levels above 2.2 mmol/L, the development of multiple organ failure syndrome requires his/her transfer to the intensive care unit for further treatment.*

4. MEDICAL REHABILITATION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF REHABILITATION METHODS

There are no specific rehabilitation measures for patients with UC.

Since in some cases UC therapy is associated with the use of immunosuppressants, the main method of rehabilitation of patients is the prevention of opportunistic infections described in section 5.

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

The 1st stage is early rehabilitation, carried out immediately after surgical treatment from the 2nd to the 14th day. The main task 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 assigned to the control of homeostasis, measures aimed at healing postoperative wounds, relief of postoperative pain syndrome, activation of the patient. During this period, laboratory parameters are monitored by prescribing a general blood test, a biochemical blood test, a blood coagulogram, and a general urine test.

The 2nd stage of rehabilitation begins after 15 days and continues as necessary in the future. It is aimed at the final healing of postoperative wounds with control over the activity of the gastrointestinal tract and other body systems. This stage can be carried out both on an outpatient basis and in a day- or 24h hospital.

The 3rd stage of rehabilitation is carried out in the late rehabilitation period in patients with both permanent ileostomy and before reconstructive and restorative surgery. The main task at this stage is to normalize the function of the gastrointestinal tract, measures aimed at identifying and correcting violations of the function of the rectal occlusion apparatus.

Anal Sphincter Incontinence

Rehabilitation is possible in stages 2 and 3. In a number of patients whose surgery for UC resulted in ileal pouch, there is a decrease in the anal function. In patients with UC with anal sphincter incontinence, before reconstructive and restorative treatment, it is advisable to study the function of the rectal occlusion apparatus (sphincterometry, profilometry, sacral nerve latency), followed by consultations with a physiotherapist for treatment aimed at improving the function of holding [192].

In patients with UC, when detecting anal sphincter incontinence of the 2nd-3rd degrees, it is advisable to conduct a 10-day cycle of electrostimulation, BFB therapy and tibial neuromodulation in a daytime or 24h hospital, aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of voluntary contraction [192,193].

BFB therapy is a non-invasive method involving 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. The method of tibial neuromodulation is also effective. Neuromodulation is a process in which an electric current through one nerve pathway modulates pre-existing activity in other nerve pathways or centers. Percutaneous electrical stimulation of the posterior tibial nerve is used in functional diseases of the pelvic organs, 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 disabled anal sphincter can respond to the right therapy, increasing both the tone and the strength of volitional contractions [192,193]. 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 stimulation sessions can be extended up to 1–3 months. The effectiveness of BFB therapy is monitored before and at the end of each course of procedures by a comprehensive physiological test of the function of the anal sphincter. With the improvement of the tone and contractility of the anal sphincters, it is possible to raise the question of performing reconstructive and restorative surgery aimed at resuming the natural passage through the gastrointestinal tract.

5. PREVENTION AND DISPENSARY SURVEILLANCE, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

*Ulcerative colitis is characterized by a chronic recurrent course. Dispensary surveillance for UC is carried out for life. The purpose of dispensary follow up is, first of all, 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 dispensary follow-up with colonoscopy may be different. The specifics of monitoring patients receiving immunosuppressants and/or biological drugs include the prevention of opportunistic infections. Risk factors for the development of opportunistic infections include: taking prednisolone ** 20 mg per 24 hours or more for 2 weeks, taking immunosuppressants (AZA**, MP**, MT**) and biological drugs, age over 50 years, concomitant*

diseases (chronic lung diseases, alcoholism, organic brain diseases, diabetes mellitus).

Patients should be explained the need for constant medication, since compliance with the prescriptions for therapy significantly (2–2.5 times) reduces the frequency of exacerbations, and the therapy itself is a method of chemoprophylaxis of colorectal cancer.

• Mandatory vaccination is **recommended** for all patients in accordance with the European Consensus on the Prevention, Diagnosis and Treatment of opportunistic infections in IBD for their prevention. The necessary minimum of vaccination is [194]:

• Recombinant vaccine against HBV;
• Polyvalent inactivated pneumococcal vaccine;
• Trivalent inactivated influenza virus vaccine;
• For women under 26 years old, if there is no virus at the time of screening, vaccination against human papillomavirus is recommended.

Grade of recommendations is C (Level of evidence is 5)

Comment. *Patients during the period of GCS therapy need to monitor the level of glycemia (study of blood glucose levels) to prevent the side effects of glucocorticoids.*

Patients also need monthly monitoring of leukocyte levels (general blood test) and liver enzymes (ALT, AST, bilirubin, alkaline phosphatase, GGT) at the beginning of treatment once every two weeks, then once a month during the first 6 months of therapy, then once every three months to prevent side effects from therapy.

• It is **recommended** for patients, before taking GEBD or TIS and further every 6 months, to consult a phthisiatrician and do screening for tuberculosis (quantiferon test, and if it is impossible, an intradermal test with a tuberculosis allergen — Mantoux test, diaskin test) for the diagnosis of tuberculosis [195].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Female patients with UC need an annual consultation with a gynecologist and screening of cervical cancer (Papanicolau cytology) to diagnose intraepithelial neoplasia of the cervix [209].*

• It is **recommended** that patients before the administration of immunosuppressive therapy, including GEBD or TIS, and against the background of treatment, make a screening for the diagnosis of comorbidities in accordance with professional clinical recommendations:

1) For the markers of viral hepatitis (Determination of antibodies to hepatitis C virus in the blood; Determination of antibodies to the surface antigen (HBsAg) of hepatitis B virus in the blood) [194].
2) For human immunodeficiency (Determination of antibodies of classes M, G (IgM, IgG) to the human immunodeficiency virus HIV-1 in the blood; Determination of antibodies of classes M, G (IgM, IgG) to the human immunodeficiency virus HIV-2 in the blood) [194].
3) For syphilis (Determination of antibodies to pale treponema in non-treponema tests (RPR, RMP) (qualitative and semi-quantitative study) in blood serum).

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for all patients to perform a stools test for calprotectin level and/or proctoscopy every 6 months in order to evaluate the effectiveness of the therapy [197–202].

Grade of recommendations is C (Level of evidence is 4)

Comment. *From the point of view of the long-term prognosis of the course of UC, it is advisable to regularly assess the presence of endoscopic remission (healing of the mucous membrane).*

6. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care within the framework of clinical testing, in accordance with Federal Law No. 323-FL of 21.11.2011 (ed. of 25.05.2019) "On the basics of protecting the health of citizens in the Russian Federation", Decree of the Government of the Russian Federation No. 1968 of 17.11.2021 "On approval of the rules for the phased transition of medical organizations to medical care based on clinical recommendations developed and approved in accordance with parts 3, 4, 6–9 and 11 of article 37 of the Federal Law "On the basics of protecting the health of citizens in the Russian Federation" is organized and provided:

1) In accordance with the regulations on the organization of medical care by type of medical

care, which is approved by the authorized federal executive authority;
2) In accordance with the procedures for providing assistance in the profiles "gastroenterology", "coloproctology", mandatory for execution on the territory of the Russian Federation by all medical organizations;
3) Based on the present clinical recommendations;
4) Taking into account the standards of medical care approved by the authorized federal executive authority.

Primary specialized medical and sanitary care for patients with UC is provided by a gastroenterologist, a coloproctologist and other specialist doctors in medical organizations licensed to provide appropriate types of medical activities.

In case of suspicion or detection of ulcerative colitis in a patient, internists, district internists, general practitioners (family doctors), specialist doctors, secondary medical workers, in accordance with the established procedure, refer the patient for consultation to a medical organization that has an office of a gastroenterologist, a coloproctologist, and/or an outpatient gastroenterology center (unit), and/or outpatient coloproctology center (unit), and/or center for the diagnosis and treatment of inflammatory bowel diseases (if present in the subject, organized on a functional basis) to provide him/her with primary specialized health care. Consultation in the specified structural divisions of the medical organization should be carried out no later than 15 working days from the date of issuance of the referral for consultation, and in cases of severe ulcerative colitis no later than 3 working days from the date of issuance of the referral for consultation.

A gastroenterologist, a coloproctologist of a medical organization that includes an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterology center (unit), an outpatient coloproctology center (unit), a center for the diagnosis and treatment of inflammatory bowel diseases, organizes timely qualified examination and treatment of the patient, including determining the severity of the inflammatory process, the extent of the lesion, the presence of intestinal and extra-intestinal manifestations, including the taking of biopsy material.

If treatment and in-depth examination in inpatient conditions are necessary, the patient is referred by the attending physician to the gastroenterology unit, coloproctology unit, the center for diagnosis and treatment of inflammatory bowel diseases or another medical organization that provides medical care in inpatient conditions to patients in the profile "gastroenterology", "coloproctology".

If ulcerative colitis is suspected and (or) detected in a patient during the provision of emergency medical care, such patients are transferred or referred to medical organizations providing medical care in the profile of "gastroenterology", "coloproctology" to determine the tactics of management and the need to additionally use other methods of specialized treatment, including targeted biological therapy.

A gastroenterologist, a coloproctologist of a medical organization that includes an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterology center (unit), an outpatient coloproctology center (unit), a center for the diagnosis and treatment of inflammatory bowel diseases directs the patient to medical organizations that have inpatient medical care in their as part of the gastroenterology unit and/or coloproctology unit, and/or a center for the diagnosis and treatment of inflammatory bowel diseases to clarify the diagnosis (in case it is impossible to establish a diagnosis in the provision of primary specialized medical care) and the provision of specialized, including high-tech, medical care.

The deadline for the start of specialized, with the exception of high-tech, medical care is determined by the decision of the commission for the selection of patients for hospitalization, depending on the severity of ulcerative colitis, the nature of the course, the prevalence of the inflammatory process, should not exceed 30 calendar days from the date of the referral for hospitalization.

Specialized, including high-tech, medical care for ulcerative colitis is provided by gastroenterologists, coloproctologists in medical organizations that have a gastroenterology unit and/or a coloproctology unit, and/or a center for the diagnosis and treatment of inflammatory bowel diseases, licensed, the necessary material and technical base, certified specialists, in inpatient and daytime

hospital conditions and includes prevention, diagnosis, treatment of ulcerative colitis, requiring the use of special methods and complex unique medical technologies, as well as medical rehabilitation.

Indications for hospitalization in a 24h or daytime hospital of a medical organization providing specialized, including high-tech medical care for ulcerative colitis are determined by a gastroenterologist and/or a coloproctologist with a multidisciplinary consultation, if necessary.

The indication for hospitalization to a medical organization in an emergency or urgent form is:

1) The presence of complications of ulcerative colitis that require specialized medical care in an emergency and urgent form;
2) The presence of complications of treatment (surgery, biological therapy, hormonal and cytostatic therapy, etc.) of ulcerative colitis.

The indication for elective hospitalization to a medical organization:

1) The need to perform complex interventional diagnostic medical interventions that require follow-up in a 24-hour or daytime hospital;
2) The presence of indications for specialized treatment of ulcerative colitis (surgery, hormonal and cytostatic therapy, biological and targeted therapy), requiring observation in a 24h or daytime hospital.

The indication for the patient's discharge from the medical organization is:

1) Completion of a course of treatment, or one of the stages of providing specialized, including high-tech medical care, in a 24h or daytime hospital, provided there are no complications of treatment requiring medical correction and/or medical interventions in a hospital setting;
2) Refusal of the patient or his/her legal representative from specialized, including high-tech medical care in a 24h or daytime hospital, established by the council of a medical organization providing treatment for ulcerative colitis, provided there are no complications of the underlying disease and/or treatment requiring medical correction and/or medical interventions in inpatient conditions;
3) The need to transfer the patient to another medical organization according to the appropriate profile of medical care. The conclusion on the expediency of transferring the patient to a specialized medical organization is carried out after a preliminary consultation on the provided medical documents and/or a preliminary examination of the patient by doctors-specialists of the medical organization to which the transfer is planned.

7. ADDITIONAL INFORMATION AFFECTING THE COURSE AND OUTCOME OF THE DISEASE

The risk of severe attack of UC during life is 15%, while the probability of a severe attack is higher in patients with total affected large intestine. If adequate anti-relapse therapy is carried out within 5 years, attacks can be avoided in half of patients, and within 10 years — in 20% of patients. During the first year after diagnosis, the probability of colectomy is 4–9% (with a severe attack — about 50%), in the future, 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 the lesion from distal (proctitis) to total, primary sclerosing cholangitis, as well as childhood and adolescence at the time of the onset of the disease. Pregnancy planning should be carried out during the period of IBD remission, which makes it possible to improve pregnancy outcomes. The use of most drugs for the treatment of IBD by pregnant women is associated with a low risk of adverse effects on the fetus, with the exception of methotrexate and 5-ASA preparations containing dibutyl phthalate. The abolition of anti-TNF or the transition to monotherapy is possible only in a limited number of patients with a low risk of IBD reactivation. Treatment with genetically engineered biological drugs that are not contraindicated during pregnancy (see the instructions for use) can be continued if the benefits to the mother exceed the potential risks to the fetus.

Reducing the risks associated with the administration of GCS is achieved by strict adherence to the principles of hormone therapy. GCS cannot be used as a maintenance therapy.

When prescribing hormone therapy, the following should be taken into account:

- Gradual reduction of the dose of steroids until complete withdrawal is strictly mandatory;
- The total duration of hormone therapy should not exceed 12 weeks;

• Concomitant intake of calcium and vitamin D preparations is mandatory;
• During the treatment period, regular monitoring of blood glucose levels is necessary.

Patients who have had an intestinal stoma formed as a result of surgical treatment may require consultation and supervision by a specialist in the rehabilitation of stomatized patients.

CRITERIA FOR ASSESSING THE QUALITY OF MEDICAL CARE

Criteria for assessing the quality of primary health care for adults with ulcerative colitis

№ п/п	Quality assessment criteria	Performance assessment
1.	An administration (examination, consultation) of a gastroenterologist and/or a coloproctologist with mandatory transrectal digital examination (at diagnosis) was performed	Yes/No
2.	Colonoscopy or rectosigmoidoscopy was performed (upon diagnosis)	Yes/No
3.	Ultrasound examination of abdominal organs (complex) was performed (at diagnosis)	Yes/No
4.	Fecal examination for the presence of the toxin *Clostridioides difficile* or immunochromatographic rapid examination of feces for toxins A and B of *Clostridioides difficile* or determination of the DNA of the pathogen *Clostridioides difficile* in fecal samples by PCR (in acute ulcerative colitis and/or suspected of this pathology) was performed	Yes/No
5.	Therapy with drugs of the aminosalicylic acid group and similar drugs or glucocorticosteroids for topical use has been prescribed	Yes/No

Criteria for assessing the quality of specialized medical care for adults with ulcerative colitis

№ п/п	Quality assessment criteria	Performance assessment
1.	An administration (examination, consultation) of a gastroenterologist and/or a coloproctologist with mandatory transrectal digital examination (at diagnosis) was performed	Yes/No
2.	Colonoscopy was performed (if it was not performed on an outpatient basis earlier during the previous 12 months)	Yes/No
3.	Ultrasound examination of the abdominal cavity organs (complex) was performed (at diagnosis, if it was not performed on an outpatient basis)	Yes/No
4.	A biopsy of the colorectal mucosa in the affected area was performed (upon diagnosis, if it was not performed on an outpatient basis or if the previously established diagnosis is doubtful, except for the stage of very high activity of the disease)	Yes/No
5.	Therapy was performed with drugs of the 5-aminosalicylic acid group and similar drugs and/ or systemic glucocorticosteroids and/or other immunosuppressants and/or inhibitors of tumor necrosis factor alpha (TNF-alpha) or ustekinumab or vedolizumab or tofacitinib or upadacitinib or ozanimodomi / or surgical intervention (depending on medical indications and in the absence of medical contraindications)	Yes/No

Clinical recommendations on the diagnosis and treatment of ulcerative colitis were discussed at a meeting of the profile commission on the specialty “Coloproctology” on October 8, 2022 within the framework of the All-Russian Scientific and Practical conference with international participation of “Congress of Coloproctologists of Russia”, at a meeting of the Commission in surgical sciences of the Scientific Council of the OMedS RAS on November 25, 2022 within the XVI All-Russian conference with international participation of “Levitan Readings”

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