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CLINICAL GUIDELINES
Crohn's disease (K50), adults

Yuri A. Shelygin[1,10], Vladimir T. Ivashkin[2], Sergey I. Achkasov[1,10], Igor V. Reshetov[2], Igor V. Maev[3], Elena A. Belousova[4], Armen V. Vardanyan[1], Bella A. Nanaeva[1], Leila V. Adamyan[3,5], Oksana M. Drapkina[3,23], Leila S. Namazova-Baranova[6], Aleksandr Yu. Razumovsky[7], Amiran Sh. Revishvili[8,10], Igor E. Khatkov[9], Aleksey V. Shabunin[10], Maria A. Livzan[11], Aleksandr V. Sazhin[7], Vil M. Timerbulatov[12], Olga V. Khlynova[13], Diana I. Abdulganieva[14], Rustem A. Abdulkhakov[14], Timofey L. Aleksandrov[1], Olga P. Alekseeva[15], Sergey A. Alekseenko[16], Ivan S. Anosov[1], Igor G. Bakulin[17], Olga Yu. Barysheva[18], Kirill V. Bolikhov[7], Viktor V. Veselov[1,10], Oleg V. Golovenko[10], Irina V. Gubonina[19], Anastasia I. Dolgushina[20], Tatiana N. Zhigalova[21], Anna V. Kagramanova[9], Vladimir N. Kashnikov[1], Oleg V. Knyazev[9], Nikolay V. Kostenko[22], Aleksey A. Likutov[1], Ekaterina Y. Lomakina[4], Irina D. Loranskaya[10], Airat F. Mingazov[1], Aleksey I. Moskalev[1], Ilya V. Nazarov[1], Natalia V. Nikitina[4], Alfia H. Odintsova[24], Vitaly V. Omelyanovsky[10], Marina F. Osipenko[25], Andrey V. Oshchepkov[26], Vladimir V. Pavlenko[27], Elena A. Poluektova[2], Grigory V. Rodoman[7], Anastasia M. Segal[21], Stanislav I. Sitkin[17], Maria I. Skalinskaya[17], Andrey N. Surkov[6], Oleg I. Sushkov[1], Larisa V. Tarasova[28], Yulia B. Uspenskaya[29], Sergey A. Frolov[1], Elena Yu. Chashkova[30], Oleg S. Shifrin[2], Olga V. Shcherbakova[7], Oksana B. Shchukina[31], Tatiana V. Shkurko[1]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya st., 2, Moscow, 123423, Russia)
[2]I.M. Sechenov First Moscow State Medical University (Sechenov University) (Bolshaya Pirogovskaya st., 8, bld. 2, Moscow, 119991, Russia)
[3]Moscow State University of Medicine and Dentistry named after A.I. Evdokimov (Delegatskaya st., 20, bld. 1, Moscow, 127473, Russia)
[4]Moscow Regional Research and Clinical Institute, (Prospect Mira, 61/2, Moscow, 129090, Russia)
[5]Mational Medical Research Center of Obstetrics and Gynecology named after V.I. Kulakov (Akademika Oparina st., 4, Moscow, 117997, Russia)
[6]Reseach Instinute of Pediatrics and Child Health Protection of the Central Clinical Hospital of the Russian Academy of Sciences (Lomonosovsky Ave., 2, p.1, Moscow, 119991, Russia)
[7]Russian National Research Medical University named after N.I. Pirogov" (Ostrovityanova st., 1, Moscow, 117321, Russia)
[8]A.V. Vishnevsky National Medical Research Center of Surgery (Bolshaya Serpukhovskaya st., 27, Moscow, 115093, Russia)
[9]Moscow Clinical/research Center named after A.S. Loginov" of the Moscow Department of Health (Highway Enthusiasts, 86, Moscow, 111123, Russia)
[10]Russian Medical Academy of Continuous Professional Education (Barricadnaya st., 2/1, Moscow, 123995, Russia)
[11]Omsk State Medical University (Lenin st., 12, Omsk, 644099, Russia)
[12]Bashkir State Medical University (Lenin st., 3, Ufa, 450008, Russia)

[13]Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of Russia (Petropavlovsk st., 26, Perm, 614990, Russia)
[14]Kazan State Medical University (Butlerova st., 49, Kazan, 420012, Russia)
[15]Nizhny Novgorod Regional Clinical Hospital named after N.A. Semashko (Rodionova st., 190, Nizhny Novgorod, 603126, Russia)
[16]Far Eastern State Medical University (Muravyov-Amursky st., 35, Khabarovsk, 680000, Russia)
[17]I.I. Mechnikov Northwestern State Medical University of the Ministry of Health of Russia (Kirochnaya st., 41, St. Petersburg, 191015, Russia)
[18]Petrozavodsk State University of the Ministry of Education and Science of Russia (Lenin Ave., 33, Petrozavodsk, 185910, Russia)
[19]Clinic Scandinavia (Liteyny Ave., 55A, St. Petersburg, 191014, Russia)
[20]South Ural State Medical University (Vorovsky st., 64, Chelyabinsk, 454048, Russia)
[21]City Clinical Hospital No. 31 (Dynamo Ave., 3, St. Petersburg, 197110, Russia)
[22]Astrakhan State Medical University (Bakinskaya st., 121, Astrakhan, 414000, Russia)
[23]National Medical Research Center for Therapy and Preventive Medicine (Petroverigsky per., 10, bld. 3, Moscow, 101000, Russia)
[24]Clinical Hospital of the Ministry of Health of the Republic of Tatarstan (ul. Orenburg tract, 138, Kazan, 420064, Russia)
[25]Novosibirsk State Medical University (Krasny Ave., 52, Novosibirsk, 630091, Russia)
[26]Regional Clinical Hospital (Volgogradskaya st., 185, Yekaterinburg, 620102, Russia)
[27]Stavropol State Medical University of the Ministry of Health of Russia (Mira st., 310, Stavropol, 355017, Russia)
[28]I.N. Ulyanov Chuvash State University (Moskovsky Prospekt, 15, Cheboksary, 428015, Russia)
[29]Clinical Center "Clinic Dawn" (Stolyarny Lane, 3, bld. 2, Moscow, 123022, Russia)
[30]Irkutsk Scientific Center of Surgery and Traumatology (Bortsov Revolyutsii st., 1, Irkutsk, 664003, Russia)
[31]First St. Petersburg State Medical University named after Academician I.P. Pavlov (Lvatolstogo st., 6-8, St. Petersburg, 197022, Russia)

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LIST OF ABBREVIATIONS

ALT — alanine aminotransferase
AST — aspartate aminotransferase
5-ASA — 5-aminosalicylic acid
AZA — azathioprine
CD — Crohn's disease
BFB — biofeedback
IBD — inflammatory bowel diseases
VTEC — venous thromboembolic complications
Gamma-GT — gamma-glutamyltranspeptidase
GEBD — genetically engineered biological drug
GCS — glucocorticosteroids
CI — coincidenceinterval
GIT — gastrointestinal tract
CDAI — Crohn's disease activity index
IARA — ileoanal reservoir anastomosis
BMI — body mass index
CT — computed tomography
LDH — lactate dehydrogenase
MP — mercaptopurin
MT — methotrexate
MRI — magnetic resonance imaging
NSAIDs — nonsteroidal anti-inflammatory drugs
LMWH — low molecular weight heparin
UFH — unfractionated heparin
PCR — polymerase chain reaction
RCT — randomized controlled trial
ESR — erythrocyte sedimentation rate
CRP — C-reactive protein
TIS — targeted immunosuppressors
CMV — cytomegalovirus
FC — fecal calprotectin
TNF-alpha — Tumor necrosis factor-alpha
Ultrasound — ultrasound examination
TRUS — transrectal ultrasound examination
EndoUS — endosonography
UC — ulcerative colitis
SES-CD — Simple Endoscopic Score for Crohn's disease

TERMS AND DEFINITIONS

Crohn's disease (CD) is a chronic, recurrent disease of the gastrointestinal tract (GIT) of unclear etiology, characterized by transmural, segmental, granulomatous inflammation with risk of local and systemic complications [1].

CD recurrence is the resumption of typical manifestations of the disease in a patient with an established diagnosis of CD, in the stage of clinical remission, spontaneous or medically supported, or after surgical treatment confirmed by objective instrumental and laboratory tests [2].

Early recurrence of CD is the resumption of typical symptoms of the disease less than 3 months after achieving clinical remission on previous therapy.

The clinical response of CD is a decrease in the Harvey-Bradshaw index of 4 or less points, or the activity of CD (CDAI) by more than 100 points.

Clinical remission of CD- absence of symptoms of CD (corresponds to the value of the Harvey-Bradshaw index ⩽ 4 or the CD activity index (CDAI) < 150).

The endoscopic response of CD is a decrease in the endoscopic activity of the disease on the SES-CD scale by more than 50% from the initial one.

Endoscopic mucosal healing does not imply complete endoscopic remission, but the absence of mucosal ulcers by SES-CD in the affected area with the possible preservation of aphthae, hyperemia and other signs of inflammation.

Endoscopic remission of CD is a condition in which the inflammatory activity during endoscopy on the SES-CD scale is less than 4 points.

Transmural healing of CD — normalization (⩽ 3 mm) of the thickness of the intestinal wall (with radiation methods of investigation) [3].

Genetically engineered biological drugs (GEBD) are a group of drugs of biological origin, including monoclonal antibodies (chimeric, humanized, completely human) and recombinant proteins (usually include the Fc fragment of human IgG) obtained using genetic engineering methods that specifically suppress the immune-inflammatory process and slow down the progression of the disease [4].

Targeted immunosuppressors (TIS) are a group of synthetic anti inflammatory drugs of chemical origin, by the mechanism of action specifically blocking the functioning of intracellular signaling pathways of 'pro-inflammatory' and immunoregulatory cytokines [4].

A bio-naive patient is a patient who has not previously received genetically engineered biological drugs (GEBD) or targeted immunosuppressors (TIS).

Biosimilars are biological medicinal products containing a version of the active substance already approved by the original biological medicinal product (reference drug).

Steroid resistance

- In case of severe exacerbation of CD, there is no positive changes on the part of clinical and laboratory indicators, despite the use of systemic GCS at a dose of prednisone** equivalent to 2 mg/kg of body weight per day for more than 7 days
- In case of moderate exacerbation of CD — preservation of the activity of the disease with oral administration of GCS at a dose of prednisone ** equivalent to 1 mg/kg of body weight per day for 2 weeks

Steroid addiction

- Increased activity of the disease that occurred with a decrease in the dose of GCS after achieving initial improvement within 3 months from the start of treatment
- The occurrence of a recurrence of the disease within 3 months after the end of treatment with GCS [2]

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

1.1 Etiology and pathogenesis of a disease or condition (group of diseases or conditions)

The etiology of inflammatory bowel diseases (IBD), including CD, has not been established. The disease develops as a result of a combination of several factors, including genetic predisposition, defects of innate and acquired immunity, intestinal microflora disorders and the influence of environmental factors. About 100 genetic polymorphisms associated with CD have been described. Genetic determinism leads to changes in the innate immune response, autophagy, violation of the mechanisms of recognition of microorganisms, violation of the epithelial barrier and, as a result,

perversion of adaptive immunity. The key defect predisposing to the development of IBD is a violation of the mechanisms of recognition of bacterial molecular markers by dendritic cells, which leads to hyperactivation of signaling proinflammatory pathways. There is also a decrease in the diversity of intestinal microflora in IBD due to a decrease in the proportion of anaerobic bacteria, mainly *Bacteroidetes* and *Firmicutes* [5,6]. In the presence of these microbiological, immunological and genetic changes, IBD develops under the influence of triggering factors, which include smoking, nervous stress, vitamin D deficiency, a diet with a reduced 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 types 1, 2, 17 and regulatory T-lymphocytes at different stages of inflammation, which leads to over expression of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNFα), interlequins 1, 12, 23, 17 (IL1, IL12, IL23, IL17) and other cell adhesion molecules.

A cascade of humoral and cellular reactions in CD leads to transmural inflammation of the intestinal wall with the formation of sarcoid granulomas, consisting of epithelioid histiocytes without foci of necrosis and giant cells. With CD, any parts of the gastrointestinal tract can be affected — from the oral cavity to the anus. Nevertheless, in the vast majority of cases, CD affects the ileocecal department. CD, unlike UC, cannot be cured by either therapeutic or surgical methods [2].

1.2 Epidemiology of a disease or condition (groups of diseases or conditions)

The maximum prevalence of CD in the world is currently 322/100000 of the population (in Europe), and the incidence in different regions ranges from 0.3 to 20.2 per 100000 population [7–10]. Data on the prevalence and incidence of CD in the Russian Federation are extremely limited, presented by partial data from regional registers and differ significantly from each other [11–14]. The prevalence of CD is higher in northern latitudes and in the West, it is constantly increasing and currently reaches up to 1 per 200 people [9]. The incidence and prevalence of CD in Asia is lower, but is constantly increasing. Caucasians suffer from the disease more often than representatives of the Negroid and Mongoloid races. The peak of morbidity is observed between 20 and 30 years of life, and the second peak of morbidity in some countries is described at the age of 60–70 years. The incidence is approximately the same in men and women.

1.3 Features of coding a disease or condition (group of diseases or conditions) according to the International Statistical Classification of Diseases and Health-Related Problems

K50.0 — Crohn's disease of the small intestine
K50.1 — Crohn's disease of the large intestine
K50.8 — Other types of Crohn's disease
K50.9 — Crohn's disease, unspecified

1.4 Classification of a disease or condition (groups of diseases or conditions)

To classify CD, the Montreal classification is used, according to which CD is determined by several key categories: site of the inflammatory process, the nature of the course (phenotype of the disease) and the age of onset of the disease (Table 1). The need to isolate CD by age is due to the difference in clinical manifestations and different prognosis of the disease in different age groups [15].

According to the prevalence of the lesion, [10] **are distinguished:**

1. Localized CD:
- Lesion with a length of less than 30 cm. It is more common with an isolated lesion of the ileocecal zone;
- Isolated lesion of a small area of the large intestine is possible.

2. Extent CD:
- Lesion with a length of more than 100 cm (the sum of all affected areas).

According to the nature of the course, there are [16]:

1. Acute course (less than 6 months from the onset of the disease);
2. Chronic course (more than 6 months from the onset of the disease).

Assessment of the severity of CD

For the correct formulation of the diagnosis and determination of treatment approach, the

Table 1. *Montreal Classification of Crohn's disease [15]*

Classification category	Designation according to the Montreal Classification	Characteristic
Site of inflammation	**L1**	The focus of inflammation is limited to the terminal part of the ileum or the ileocecal region (with or without involvement in the process of the caecum)
	L2	Any site of an inflammatory focus in the large intestine between the caecum and the anal sphincter, without involving the small intestine or upper gastrointestinal tract
	L3	Terminal ileitis (with or without involvement of the cecum) in combination with one or more foci of inflammation between the cecum and the anal sphincter
	L4	Isolated lesion of the upper gastrointestinal tract (proximal to the terminal ileum (excluding the oral cavity). L4 can be combined with L1–L3 site
The phenotype of the disease (the nature of the course)	**B1**	Non-stricturing, non-penetrating (synonyms in Russian — lumen, inflammatory, uncomplicated, English — luminal) — the inflammatory nature of the course of the disease, which has never been complicated (at any time during the course of the disease)
	B2	Stricturing (stenosing) — narrowing of the intestinal lumen at any level (according to radiation and/or endoscopic methods or according to the results of surgery)
	B3	Penetrating (synonyms in Russian — fistula, English — fistulizing) — the formation of intraabdominal fistulas, and/or inflammatory abdominal mass with abscess at any time during the disease, excluding postoperative intraabdominal complications
	P	Perianal: the presence of perianal lesions (fistulas, anal fissures, perianal abscesses), which can be combined with any of these phenotypes or be an independent manifestation of perianal CD
Age of diagnosis	**A1**	Less than 16 years old
	A2	From 17 to 40 years old
	A3	More than 40 years old

severity of the current exacerbation (recurrence) should be assessed active CD with the release of mild, moderate and severe exacerbation. Various indices are used for this purpose, including the Harvey-Bradshaw index, the CD activity index (CDAI, synonym — the Best index) [17]. It should be noted at once that the CDAI (Table 2), as a rule, is used in clinical trials and is inconvenient for practical use due to the complexity of the calculation, and for clinical practice it is easier and more convenient to use the Harvey-Bradshaw index (Table 3) [18]. You can also use simple criteria developed by the Russian Society for the Study of IBD and the Russian Association of Coloproctology (Table 4) [19]. The use of a particular severity assessment system is determined by the routine practice of a particular medical institution.

However, it is necessary to assess not only the severity of the exacerbation, but also to take into account the severity of the disease as a whole, which is necessary to assess the prognosis of the disease and determine the social status of the patient, including disability, preferential medication, free treatment and other social benefits. The severity of the disease as a whole is determined not only by the severity of the current exacerbation, but also by the site and extent of inflammation, the presence of extra-intestinal manifestations and complications (abscesses, strictures, fistulas, etc.), refractory to treatment, in particular, the development of steroid addiction and resistance.

The classification of CD depending on the response to hormone therapy corresponds to that in UC. Highlight (see the section 'Terms and definitions'):

1. Steroid resistance:
2. Steroid addiction:

When formulating the diagnosis, it should reflect:

a) the site of the lesion with the enumeration of the affected segments of the gastrointestinal tract;

Table 2. *Harvey-Bradshaw Index [18]*

Assessment criteria	Severity of the symptom	Score in points
General health status the day before	Very good	0
	A little worse than usual	1
	Bad	
	Very bad	3
	Awful	4
Abdominal pain the day before	No	0
	Mild	1
	Moderate	2
	Severe	2
Frequency of liquid/soft stools/day (for example, the day before)		1 point for each defecation
Palpable formation in the abdominal cavity	No	0
	Doubtful	1
	Clearly defined	2
	Clearly defined, painfulon palpation	3
Complications (specify all that is applicable)	Arthralgia, uveitis, erythema nodosum, aphthous stomatitis, gangrenous pyoderma, anal fissure, fistula, abscess, other	1 point for each complication
Sum of points ⩽ 4 — remission, 5–7 points — mild exacerbation, 8–16 points — moderate exacerbation, ⩾ 16 points — severe exacerbation		

https://www.thecalculator.co/health/Harvey-Bradshaw-Index-For-Crohn%E2%80%99s-Disease-Calculator-1036.html (link to the Harvey-Bradshaw Index calculator)

Table 3. *Crohn's Disease Activity Index [17]*

Criteria. Score in points	Coefficient
1. The number of defecations with liquid or soft feces during the week (total for 7 days)	X 2
2. The intensity of abdominal pain (from 0 to 3 points) during the week (total for 7 days)	X 5
3. Health status during the week (from 0 to 4 points, total for 7 days)	X 7
4. The number of complications listed: arthralgia or arthritis; uveitis; erythema nodosum or gangrenous pyoderma or aphthous stomatitis; anal fissure, fistulas or abscesses; interstitial fistulas; fever during the last week	X 20
5. Taking opiates (0 points — no, 1 point — yes)	X 30
6. Abdominal inflammatory mass (0 points — absent, 2 points — doubtful, 5 points — determined)	X 6
7. Hematocrit less than 47% — for men or less than 42% for women (the difference between the normal and the actual value)	X 6
8. (1 — actual body weight) x 100 body mass index	X 1
	Total
The number of points below 150 indicates remission of the disease, 150–300 — for a mild form, 300–450 — for a moderate form, over 450 — for a severe form.	

b) phenotypic variant;
c) the severity of the current exacerbation or the presence of remission of the disease;
d) the nature of the course of the disease;
f) the presence of steroid addiction or resistance;
g) the presence of extra-intestinal and/or intestinal and perianal complications.

If a patient has fistulas and strictures at the same time or at different periods of the disease, the diagnosis of CD, according to the Montreal Classification, is formulated as 'penetrating', since this is a more severe complication, but stricture must also appear in the diagnosis as a complication.

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

The clinical picture of CD includes four clinical syndromes:

Intestinal syndrome. Typical intestinal symptoms include diarrhea (more than 6 weeks), in most cases without admixture of blood, abdominal pain.

Table 4. *Criteria for assessing the severity (clinical activity) of exacerbation of CD (Russian Society for the Study of IBD and the Russian Association of Coloproctology [19]*

Criteria	Mild CD	Moderate CD	Severe CD
Average stool frequency/day for the last 3 days	Less than 4	4–6	7 and more
Abdomen pain	Absent or insignificant	Moderate	Severe
Fever	Absent	< 38° C	> 38 °C
Tachycardia	Absent	< 90 в1′	> 90 в1'
Weightloss	Absent	Up to 5%	5% and more
Hemoglobin	> 100 g/l	90–100 g/l	< 90 g/l
ESR	Norm	< 30mm/hour	< 30 mm/hour
CRP	Norm	Up to 2 norms	> 2 norms
Hypoproteinemia (hypoalbuminemia)	Absent	Insignificant	Expressed
Extra-intestinal manifestations (any)	Absent	Present	Present
Intestinal complications (any)	Absent	Present	Present

Table 5. *The main extra-intestinal (systemic) manifestations of CD [14,20,21,22,23]*

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 lesion (uveitis, iritis, iridocyclitis, episcleritis) Liver lesion (autoimmunehepatitis)	Primarysclerosingcholangitis Ankylosing spondylitis (sacroiliitis) Osteoporosis, osteomalacia Psoriasis, psoriatic arthritis	Cholelithiasis Liver steatosis, steatohepatitis Peripheral vein thrombosis, pulmonary embolism Amyloidosis

Endotoxemia — signs of systemic inflammation due to the high activity of the inflammatory process in the intestine. Endotoxemia accompanies moderate and severe forms of CD 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 a consequence of 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), hypoproteinemia, hypoalbuminemia with the development of edematous syndrome, hypokalemia and other electrolyte disorders, hypovitaminosis.

Extra-intestinal systemic manifestations (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. The clinical picture of CD in the early stages does not always have clearly defined symptoms, which makes timely diagnosis difficult. In this regard, in a significant part of patients at the time of diagnosis, the disease already has a complicated course. In some cases, CD manifests complications, for example, a violation of intestinal patency, which appeared, as if, against the background of complete health. In this regard, when making a diagnosis, a significant part of patients shows symptoms associated with complications of CD.

Complications of CD:

1. Fistulas of various site:
- external (intestinal-skin)
- internal (inter-intestinal, intestinal-vesicular, rectovaginal)
2. Abdominal mass
3. Interstitial or intraabdominal abscesses
4. Gastrointestinal strictures (with and without intestinal obstruction)
5. Anal fissures, perineal abscess (with anorectal lesion)
6. Intestinal bleeding (rarely).

Table 6. *Simple endoscopic CD assessment scale (SES-CD) [27]*

	SES-CD (estimated in points for each of the 5 iliac-colonic segments			
	0	**1**	**2**	**3**
The presence and size of ulcers	Absent	Aphthae (d 0.1–0.5 cm)	Large ulcers (d 0.5–2 cm)	Very large ulcers (d > 2 cm)
Ulcerated surface	Absent	< 10%	10–30%	> 30%
Affected surface	Intact segment	< 50%	50–75%	> 75%
The presence of stenoses*	Absent	Single, passable	Multiple, passable	Impassable
The sum of points of all **SES-CD** criteria for 5 intestinal segments varies from 0 to 56 *The sum of points for the presence of narrowing (stenosis) varies from 0 to 11, because 3 means stenosis that is not passable for a colonoscope, i.e. it can be observed only once				

Table 7. *The scale of endoscopic assessment of the activity of postoperative recurrence of CD (Rutgeerts) [49].*

Endoscopic assessment	Definitions
i 0	no signs of inflammation
i 1	⩽ 5 aphthae
i 2	> 5 aphthae with normal mucosal layer between them or extended areas of healthy mucosal layer between more pronounced ulceration or lesions limited by ileocolic anastomosis
i 3	diffuse aphthous ileitis with diffusely inflamed mucosal layer
i 4	diffuse inflammation with large ulcers, 'cobblestone pavement' and/or narrowing of the lumen

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

There are no unambiguous diagnostic criteria for CD. The diagnosis is established based on a combination of history, clinical picture and typical endoscopic and histological changes [2,24,25].

The criteria for a reliable diagnosis of CD according to Lennard-Jones are generally accepted, including the definition of seven key signs of the disease [26]:

1. Location in any place of the gastrointestinal tract from the oral cavity to the anal canal; chronic granulomatous lesion of the mucosal layer of the lips or cheeks; pyloroduodenal lesion, small intestine lesion, chronic perianal lesion.

2. Intermittent nature of the lesion.

3. Transmural nature of the lesion: ulcers-fissures, abscesses, fistulas.

4. Fibrosis: strictures.

5. Lymphoid infiltration (histology): aphthoid ulcers or transmural focal lymphoid clusters.

6. Mucus (histology): normal mucus content (preservation of secretion) in the area of active inflammation of the large intestine mucosa.

7. The presence of epithelioid granuloma.

The diagnosis of CD is considered reliable in the presence of any 3 signs or when granuloma is detected in combination with any other sign.

The diagnosis must be confirmed by:

- *endoscopic and morphological method and/or endoscopic and radiation diagnostic method.*

Endoscopic criteria of CD:

- *Regional (intermittent) mucosal lesion;*
- *Symptom of 'cobblestone pavement' (combination of deep longitudinally and transversely oriented ulcers with bulging hyperplastic mucosa between them);*
- *Linear ulcers (ulcers-fissures);*
- *Aphthae;*
- *In some cases, strictures and mouths of fistulas.*

Endoscopic indices are used to objectify and quantify the endoscopic picture. The most convenient and easy to use SES-CD (Table 6) [27]. According to this scale, the endoscopic picture is necessarily evaluated in 5 intestinal segments: ileum, ascending colon, transverse colon, descending colon, sigmoid and rectum. In each segment, the presence and size of ulcers, the presence of aphthae, the surface area of ulceration, the surface area of lesions, the presence and severity of stenoses are determined. Each criterion is evaluated in points.

SES-CD allows not only to interpret the new objectives formulated in the STRIDE 2 concept [76], but also to monitor the changes of inflammation

activity and, accordingly, the effectiveness of treatment.

New objectives (see the terms section) include concepts such as:

- Endoscopic response — a decrease in the endoscopic activity of the disease on the SES-CD scale by more than 50% of the initial
- Mucosal healing — implies not a complete endoscopic remission, but the absence of mucosal ulcers in the affected area
- Endoscopic remission — interpreted as inflammatory activity ⩽ 4 points

To assess the activity of postoperative recurrence of CD, the Rutgeerts scale is used (Table 7) [49].

Radiological manifestations of CD:

- *Regional lesion;*
- *Intermittent lesion;*
- *Strictures;*
- *'Cobblestone pavement';*
- *Internal fistulas or intra-abdominal abscesses.*

Morphological signs of CD:

- *Deep slit-like ulcers penetrating into the submucosal base or muscle layer;*
- *Epithelioid granulomas (clusters of epithelioid histiocytes without foci of necrosis and giant cells), which are usually found in the wall of the resected area and only in 15–36% of cases — with a biopsy of the mucosal layer);*
- *Focal (discrete) lymphoplasmocytic infiltration of the own plate of the mucosal layer;*
- *Transmural inflammatory infiltration with lymphoid hyperplasia in all layers of the intestinal wall;*
- *Ileum lesion with structural changes of villi, mucoid or pseudopiloric crypt metaplasia and chronic active inflammation [28];*
- *Intermittent lesion — alternation of affected and healthy parts of the intestine (when examining the resected part of the intestine).*

Unlike UC, crypt abscesses in CD are rarely formed, and mucus secretion remains normal.

2.1 Complaints and anamnesis

When interviewing a patient, it is worth paying attention to the frequency and nature of the stool, the duration of these symptoms, the presence of blood admixture, the nature of abdominal pain, the presence of episodes of fever, anemia of unclear genesis, symptoms of intestinal obstruction, perianal complications (chronic anal fissures, recurrent after surgical treatment, paraproctitis, rectal fistulas), extra-intestinal manifestations of the disease [14,20,21,22,23].

When collecting history of the disease, it is necessary to clarify the presence of autoimmune manifestations associated and unrelated to the activity of the inflammatory process, as well as symptoms associated with complications of CD. In addition, it is necessary to clarify the nature of the onset of the disease, information about trips to southern countries, food intolerance, taking medications (including antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), smoking and family history.

2.2 Physical examination

- It is **recommended** to perform physical examination of all patients with suspected CD except for general methods (examination, auscultation, percussion and palpation of the abdomen) for the purpose of primary diagnosis:
- examination of the perianal area — digital rectal examination in order to identify perianal manifestations of CD [29].

Category of recommendations — C (Level of evidence — 5)

Comment: *physical examination may reveal various manifestations of CD, including fever, nutritional deficiency, the presence of infiltrate of the abdominal cavity, external intestinal fistulas, perianal manifestations (fissures, fistulas), as well as extra-intestinal manifestations.*

2.3 Laboratory diagnostic tests

- It is **recommended** for all patients to determine the degree of anemia, signs of systemic inflammation and metabolic disorders to determine the level of total hemoglobin, iron, transferrin and ferritin, hematocrit, the number of red blood cells, leukocytes, blood platelets and the rate of erythrocyte sedimentation (ESR) [24,29,30].

Category of recommendation — C (Level of evidence — 5)

- It is **recommended** to determine the level of C-reactive protein, total protein, albumins, glucose, ALT, AST, cholesterol, K + , Na + , Cl-, alkaline phosphatase, blood fibrinogen [24,31].

Category of recommendation — C (Level of evidence — 5)

Comment: *laboratory manifestations of CD are nonspecific in nature. During a clinical blood test, anemia (iron deficiency, anemia of chronic disease, B-12- or folate-deficient), leukocytosis (against the background of chronic inflammation, in the presence of an abscess or against the background of steroid therapy) can be diagnosed. Biochemical examination allows to identify electrolyte disorders, hypoproteinemia (in particular, hypoalbuminemia). If a differential diagnosis of anemia is necessary, it is advisable to examine the level of folic acid, vitamin B-12, serum iron, the total iron-binding capacity of serum, ferritin.*

• It is **recommended** for patients with CD, if necessary, to evaluate or monitor the activity of inflammation in the intestine, by fecal calprotectin (FC) rate [32–35].

Category of recommendation — A (Level of evidence — 2)

• It is **recommended** for patients with CD, with a recent course of antibiotic therapy or hospital stay to perform a coprology to exclude acute intestinal infection, to perform faecal examination for toxins A and B *Cl.difficile* to exclude clostridial infection [36–39].

Category of recommendation — C (Level of evidence — 4)

• It is **recommended** to perform a laboratory examination of feces for the identification of toxigenic *Cl.difficile* by enzyme immunoassay 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 (PCR).

Category of recommendation — C (Level of evidence — 4)

Comment: *at least 4 stool samples are required to detect infection in 90% of cases [38–40].*

Biopsies and/or PCR in the biopsy material of the large intestine mucosa (from lesions) for the presence of cytomegalovirus infection (CMV) is important in severe CD attack [41].

• For patients with suspected CD, it is **recommended** to perform a microscopy of feces for helminths using enrichment methods to exclude parasitic infection during the initial diagnosis [29,42].

Category of recommendation — C (Level of evidence — 5)

• It is **recommended** for patients with CD, before prescribing therapy, to check the level of bilirubin, creatinine, urea, glucose, K+, Na+, total calcium in the blood, determine the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, amylase in the blood and a general (clinical) urinalysis to assess the function of the liver, pancreas glands and kidneys [29].

Category of recommendation — C (Level of evidence — 5)

• It is **recommended** for patients with moderate or severe CD, with the presence of metabolic disorders to perform a general (clinical) and biochemical analysis of blood every 3–5 days [29].

Category of recommendation — C (Level of evidence — 5)

2.4 Instrumental diagnostics

• In patients with suspected CD it is **recommended** to perform a proctoscopy [29].

Category of recommendation — C (Level of evidence — 5)

• It is **recommended** that patients with symptoms of intestinal obstruction undergo abdominal X-ray [43, 44].

Category of recommendation — C (Level of evidence — 5)

• In order to determine the site, extent, and degree of activity of the inflammatory process, colonoscopy with examination of the terminal ileum and biopsy is **recommended** for patients with CD [45–48].

Category of recommendation — C (Level of evidence — 4)

• Esophagogastroduodenoscopy is **recommended** for patients with primary diagnosis of CD, suspected progression of the disease, signs of recurrence, as well as annual monitoring to exclude/confirm lesions of the upper gastrointestinal tract [50–52].

Category of recommendation — C (Level of evidence — 4)

• Magnetic resonance imaging (MRI) and/or computed tomography (CT) with intestinal contrast is **recommended** for patients with CD, if necessary, to determine the site, extent, degree of activity of the inflammatory process, as well as to detect abdominal masses, internal fistulas, perforations, strictures [53,54].

Category of recommendation — A (Level of evidence — 1)

• For patients with perianal manifestations of CD in the form of rectal fistulas or if they are suspected, it is **recommended** to make an MRI of the pelvis with intravenous contrast to confirm the diagnosis, determine the site, extent of the fistula and the presence/absence of complications [53,55,56].

Category of recommendation — A (Level of evidence — 1)

Comment: *the purpose of checking for perianal manifestations of CD is, first of all, the exclusion of an acute purulent process in the pararectal region that requires urgent surgical treatment. MRI is the main method of diagnosing the configuration of fistula tracts and cavities in the pelvic cavity.*

• For patients with perianal manifestations of CD or suspected of them, in the absence of cicatricial-inflammatory strictures of the anal canal and the low rectum it is **recommended** to perform a transrectal ultrasound (TRUS) both in B-mode and with three-dimensional image reconstruction [57].

Category of recommendation — A (Level of evidence — 2)

Comment: *TRUS (with a frequency of 5–16 MHz) allows to visualize in detail the fistula course and its location relative to muscle structures in 86–95% of cases, to identify internal fistula openings in 62–94% of cases. In the presence of external fistula openings, the injection of hydrogen peroxide into them significantly improves the visualization of the fistula tract. In the presence of an acute purulent-inflammatory process and with severe pain, it is advisable to use anesthesia. As an additional method, if it is impossible to insert the sensor into the lumen of the intestine, it is possible to use transperineal ultrasound, but its accuracy in diagnosing deeply located abscesses is quite low (47.1%) due to the limited field of vision [58, 59].*

• If CT or MRI are impossible for patients, after excluding intestinal obstruction disorders, it is **recommended** to make a contrast X-ray of the small intestine (with barium) to confirm the site and extent of the inflammatory process, internal fistulas and strictures [43].

Category of recommendation — C (Level of evidence — 5)

• Patients with acute CD attack are **recommended** to have a biopsy of the intestinal mucosa in the affected area to clarify the diagnosis [45,60,61].

Category of recommendation — C (Level of evidence — 4)

• All patients with CD are **recommended** to undergo abdominal ultrasound, retroperitoneal space, pelvis to exclude complications and comorbidities, as well as to assess the thickness of the intestinal wall, the presence of lesion in the affected area, to determine the degree of vascularization and other signs of inflammation.

During ultrasound, it is advisable to perform elastometry of the intestinal wall, especially in the narrowing zone to determine its nature by color mapping (fibrosis or inflammatory edema) [62–66].

Category of recommendation — B (Level of evidence — 2)

• For patients with suspected jejunum lesion (in the absence of areas of narrowing of the lumen of the gastrointestinal tract) and the lack of sufficient information about the presence of a focus of inflammation during MRI, CT and ultrasound or the impossibility of their implementation, it is **recommended** to make a videocapsular endoscopy to confirm the diagnosis, determine the site, the degree of activity of the inflammatory process [67].

Category of recommendation — B (Level of evidence — 1)

Comment: *it should be noted that capsule retention in the intestine occurred in 13% of patients [67].*

• For patients with CD, video capsule endoscopy is **recommended** in the absence of narrowing according to MRI or CT with intestinal contrast [68,69].

Category of recommendation — C (Level of evidence — 4)

• For patients with CD, with suspected small intestine lesion and the impossibility of reliable confirmation of the diagnosis according to colonoscopy (with examination of the terminal ileum), CT and MRI with intestinal contrast, the impossibility of carrying out a video capsule, two-balloon intestinoscopy is **recommended** to confirm the diagnosis, determine the site and degree of activity of the inflammatory process and biopsy [70].

Category of recommendation — C (Level of evidence — 4)

2.5 Other diagnostic tests

Additional instrumental and laboratory tests are performed mainly for the purpose of differential diagnosis with a number of diseases [71–73].

Differential diagnosis of CD is carried out with:

- ulcerative colitis
- acute bacterial infection colitis (dysentery, salmonellosis, campylobacteriosis, yersiniosis, amoebiasis)
- viral colitis (primarily cytomegalovirus)
- parasitosis
- helminthiasis
- intestinal lesions associated with *Cl.difficile*, including those caused by antibiotics
- tuberculosis of the intestine
- systemic vasculitis
- ischemic bowel disease (ischemic colitis, enteritis)
- colorectal cancer
- diverticulitis
- microscopic colitis (collagen lymphocytic)
- radiation colitis (usually proctitis)
- primary immunodeficiency conditions that mimic CD (general variable immunodeficiency, primary IgA deficiency)
- drug-induced intestinal lesions (NSAIDs).

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

Therapeutic measures for CD include drugs, surgical treatment, psychosocial support and dietary recommendations [74].

Globally, the objectives of CD 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 hospitalization rate, reducing the risk of surgery, improving the quality of life and reducing the disability rate in patients with chronic diseases [75,76].

From the point of view of routine clinical practice, the objectives of CD therapy are to achieve and maintain long-term clinical and endoscopic remission [2,24,77].

With the progression of the process and/or life-threatening complications, the specific objective is time of surgical treatment.

Within the framework of the 'T2T' strategy, continuous monitoring of the effectiveness of treatment is provided through regular check-up of biological markers (CRP, FC) and endoscopic and radiological tests [76,78].

Treatment options for patients with CD are determined based on the severity of the attack, the extent and site of inflammation in the gastrointestinal tract, the presence of extra-intestinal manifestations and intestinal complications (stricture, abscess, infiltration), the duration of the desease, the effectiveness and safety of previous therapy, as well as the risk of complications and the presence of risk factors for a negative prognosis of the CD.

Factors of negative prognosis and the risk of complications [79,80]:

- Age of the patient < 40 years at diagnosis (early onset of the disease, debut in childhood)
- Extent (> 100 cm in the sum of the affected segments) intestinal lesion
- The need for the administration of systemic GCS in the debut
- Presence of perianal lesions
- Deep ulcers of the mucosal layer by endoscopy
- Complicated phenotype of the disease. Stricturing or penetrating CD
- Involvement of the upper gastrointestinal tract
- Smoking (more aggressive course)
- The presence of concomitant autoimmune diseases or EIM
- Presence of granulomas.

Since surgical treatment does not lead to a complete cure of patients with CD even with radical removal of all affected segments of the intestine, it is necessary to use anti-recurrence therapy, which should be started no later than 2 weeks after surgery [81].

Medications prescribed to patients with CD are conditionally divided into:

1. Means for induction of remission: systemic GCS (prednisone** and methylprednisolone**) and topical (budesonide), in combination with thiopurines (azathioprine** (AZA), #mercaptopurine**

(MP)), #methotrexate**, GEBD: tumor necrosis factor inhibitors (infliximab**, adalimumab** and certolizumab pegol**), interleukin inhibitors 12/23 (ustekinumab**) and selective intestinal inhibitors of integrin α4β7 (vedolizumab**), TIS (upadacitinib**), as well as antibiotics.

2. Means to maintain remission (anti-recurrence drugs): thiopurines (AZA**, #MP**), #methotrexate**, GEBD (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab** and vedolizumab**) and TIS (upadacitinib**).

3. Auxiliary symptomatic agents: drugs for correction anemia, drugs for the correction of protein and electrolyte disorders, means for the prevention of osteoporosis (calcium and vitamin D preparations), etc.

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.

3.1.1 Mild CD of ileocecal site

• Budesonide** (intestinal-soluble capsules with prolonged release, intestinal-soluble granules in sachets) is **recommended** for this group of patients as first-line therapy [74,82,83].

Category of recommendation — B (Level of evidence — 1)

Comment: *when taking budesonide capsules, the daily dose is 9 mg/day. once or 3 mg 3 times a day for 8 weeks, followed by a decrease of 3 mg per week until complete effect.*

*When taking granules, the daily dose is 9 mg/day once for 8 weeks, followed by a decrease of 9 mg every other day for two weeks. The therapeutic effect of budesonide** should be evaluated after 2–4 weeks. In the absence of a therapeutic response to budesonide **, treatment is carried out as with a moderate attack of CD. Budesonide is not intended for maintenance therapy, but if necessary, the maximal duration of taking the drug can be 16 weeks [24].*

Oral administration of mesalazine has not shown efficacy in comparison with placebo for induction of remission and is **not recommended** for use with active CD *[24,61,84,85]*.

Category of recommendation — B (Level of evidence — 2)

• Early administration of thiopurines (AZA** 2–2.5 mg/kg per day or #MP** 1.5 mg/kg per day) is **recommended** for this group of patients as anti–recurrence therapy (simultaneously with budesonide**), and if they are intolerant or ineffective — # MT** (25 mg/week s/c or i/m).

The duration of anti-recurrence therapy with thiopurines (AZA **/ #MP**) is at least 2–4 years in therapeutic doses [24,61,86,87,88].

Category of recommendation — A (Level of evidence — 1)

Comment: *since AZA** begins to take effect after 12 weeks, an early administration is necessary in order for the beginning of its action to be realized by the time the GCS is canceled.*

• For this group of patients after the withdrawal of budesonide** it is **recommended** to carry out anti-recurrence therapy with thiopurines (AZA**/#MP**) for at least 2–4 years in therapeutic doses [88].

Category of recommendation — A (Level of evidence — 1)

3.1.2 CD of ileocecal site of moderate severity

• Topical GCS for oral administration (budesonide** capsules, intestinal-soluble with prolonged release, granules, intestinal-soluble in sachets), dosage regimen, and the timing of efficacy evaluation are **recommended** for this group of patients to induce remission. See section 3.1.1 'Mild CD of ileocecal site' [74,82,83].

Category of recommendation — A (Level of evidence — 1)

• For induction of CD remission in this group of patients, in the absence of budesonide effect, in the presence of infiltration, inflammatory narrowing and signs of systemic inflammation, GCS for systemic use (prednisone** or equivalent doses of other GCSs) are **recommended** [89] (Table 8).

Category of recommendation — A (Level of evidence — 1)

Comment: *the dose of prednisolone with this site and severity is 1 mg/kg of body weight per day 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. The effectiveness of GCS is evaluated after 2–4 weeks.*

• In this group of patients with signs of systemic inflammation and/or abdominal mass, it is **recommended** to combine systemic GCS in combination with antibiotics [24,90].

Table 8. *Duration of action and equivalent doses of glucocorticosteroids*

Drug	Duration of action ($t_{1/2}$)	Equivalent dose (mg)
Hydrocortisone**	8–12 hs	20
Prednisone**	12–36 hs	5
Methylprednisolone**	12–36 hs	4

Category of recommendation — B (Level of evidence — 3)

• Early administration of thiopurines (AZA** 2–2.5 mg/kg or #MP** 1.5 mg/kg) is **recommended** for this group of patients as anti–recurrence therapy, and if they are intolerant or ineffective, # MT** (25 mg/week s/c or i/m). The duration of anti-recurrence therapy with thiopurines (AZA **/ #MP**) is at least 2–4 years in therapeutic doses [24,61,86,87].

Category of recommendation — A (Level of evidence — 1)

• In this group of patients, when clinical remission is achieved, it is **recommended** to reduce the GCS by 5 mg in 5–7 days until complete withdrawal against the background of continued immunosuppressive therapy [91].

Category of recommendation — B (Level of evidence — 3)

Comment: *the total duration of GCS therapy should not exceed 12 weeks*.

For this group of patients after the withdrawal of GCS it is **recommended** to carry out maintenance therapy with immunosuppressants for a long time [24,61,85,92].

Category of recommendation — A (Level of evidence — 1)

• A group of patients with active CD with steroid resistance, steroid addiction, intolerance to GCS or with ineffectiveness/ intolerance of immunosuppressorsis **recommended** to undergotherapy with GEBD (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab**, vedolizumab**) or TIS (upadacitinib**) in the form of an induction (initiating) course followed by long-term supportive treatment [93,94,95,96].

Category of recommendation — A (Level of evidence — 1)

Regimens and doses of drugs for GEBD and TIS in the framework of the induction (initiating) course and maintenance therapy:

• for infliximab, the induction (initiating) course provides for three-fold administration at 0, 2nd and 6th weeks intravenously at a dose of 5 mg/kg of body weight, then the same dose for maintenance therapy once every 8 weeks;

• for adalimumab, the induction (initiating) course consists of the first subcutaneous injection at a dose of 160 mg, followed by a second subcutaneous injection after 2 weeks at a dose of 80 mg, followed by maintenance therapy at a dose of 40 mg every 2 weeks;

• for certolizumab pegol, the induction (initiating) course consists of the first subcutaneous injection of 400 mg, the second subcutaneous injection at a dose of 400 mg at week 2, the third subcutaneous injection of the drug at the same dosage at week 4 of treatment, then maintenance therapy is carried out at the same dosage, subcutaneously every 4 weeks;

• for vedolizumab, the induction (initiating) course provides for three-time administration at 0, 2nd and 6th weeks intravenously at a dose of 300 mg, then maintenance treatment of 300 mg intravenously every 8 weeks;

• for ustekinumab, an induction (initiating) dose is administered intravenously on the first day with the calculation of the dose according to the patient's body weight at the time of administration, then after 8 weeks — the first supportive subcutaneous injection at a dose of 90 mg and then — therapy at a dose of 90 mg subcutaneously every 8 or 12 weeks (depending on the nature of the course of the disease);

• for upadacitinib, a 12-week induction (initiating) course at a dose of 45 mg in tablets 1 time per day and then 30 mg or 15 mg (depending on the nature of the course of the disease) in tablets 1 time per day as maintenance therapy.

Comment: *all GEBD and TIS are approximately the same in effectiveness. Therefore, in bio-naive patients, any of these drugs can be used as the first line of therapy.*

However, the optimal sequence of administration of GEBD and TIS has not yet been established. To a large extent, the choice of the first drug depends on the individual characteristics of the patient and the presence of risk factors for a negative prognosis

of the disease. However, it should be borne in mind that all GEBDs are more effective in the first line in bio-naive patients. Each additional GEBD statistically significantly reduces the likelihood of achieving clinical, endoscopic and steroidal remission [97]. Some of GEBD and TIS remain effective in the 2nd and subsequent lines of therapy (ustekinumab, upadacitinib) [98–100].

In addition, when choosing different classes of drugs, it should be taken into account that ustekinumab and adalimumab demonstrated comparable efficacy in the 1st line therapy, but in the adalimumab group, the frequency of discontinuation of treatment due to adverse events was almost twice as high as in the ustekinumab group [101].

The absence of a primary response to therapy is determined after the induction course (depending on the drug). In the presence of negative changes, the effectiveness of the drug is evaluated earlier.

Patients who have achieved remission during treatment with any of the GEBD or TIS are **recommended** to undergo maintenance therapy with the same drug (with or without immunosuppressants) [24,61,85,102].

Category of recommendation — A (Level of evidence — 1)

Patients with active CD are **recommended** to combine the administration of infliximab** with thiopurines to increase the effectiveness of treatment [85,88,103].

Category of recommendation — A (Level of evidence — 1)

Comment: *for other GEBDs, the expediency of such a combination has not been proven. The administration of combination therapy remains at the discretion of the attending physician.*

- Patients with active CD with steroid addiction, thiopurine intolerance are **recommended** to use infliximab** in combination with #methotrexate** (#MT** 25 mg/week s/c or i/m) [61,85,104].
- Patients with primary ineffectiveness of any of the anti-TNF drugs are **recommended** to change therapy to vedolizumab**, ustekinumab**, upadacitinib** to achieve remission.

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 [105,106].*

- For patients with loss of response to anti-TNF drugs in the 1st line of therapy (recurrence of CD against the background of previously achieved remission) it is **recommended** to optimize therapy in the form of increasing the dose of the drug (10 mg /kg of infliximab ** every 8 weeks, 80 mg of adalimumab every 2 weeks) or reducing 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**, ustekinumab** upadacitinib** to achieve a therapeutic effect [107,108,109].

Category of recommendation — A (Level of evidence — 2)

Comment: *switching to another anti-TNF drug is acceptable, but its effectiveness is lower than when switching to drugs of other classes (vedolizumab**, ustekinumab**, upadacitinib**) [107, 111]. To increase the effectiveness of treatment when switching to another anti-TNF, a combination with immunosuppressants is possible [108, 109]. When choosing vedolizumab, it should be borne in mind that its effectiveness as a first-line drug is higher than in the second and subsequent lines [110].*

- For patients with loss of response to vedolizumab** at a standard dose of 300 mg every 8 weeks it is **recommended** to optimize therapy by reducing the intervals between injections to 4 weeks or changing to a biological drug of another class (anti-TNF, ustekinumab**, upadacitinib**) [105,110].

Category of recommendation — C (Level of evidence — 4)

Comment: *the effectiveness of anti-TNF in the 2nd line therapy after loss of response to vedolizumab does not decrease in comparison with their effectiveness in the 1st line, i.e. the use of vedolizumab does not affect the subsequent effectiveness of anti-TNF [110].*

- For patients with loss of response to ustekinumab** in the standard mode of administration every 12 weeks, it is **recommended** to optimize therapy in the form of reducing the intervals between injections to 8 weeks or changing to a drug of another class (anti-TNF, vedolizumab**, upadacitinib**) [85].

Category of recommendation — C (Level of evidence — 4)

• In case of primary inefficiency or loss of response to upadacitinib** it is **recommended** to optimize treatment with an increase in the maintenance dose from 15 mg to 30 mg or change to another class of drug.

Category of recommendation — C (Level of evidence — 4)

• Surgical treatment is **recommended** for patients with active CD with ineffectiveness of conservative therapy [61].

Category of recommendation — C (Level of evidence — 5)

3.1.3 CD of the large intestine of mild and moderate severity

For this group of patients, therapy with systemic GCS (prednisone** or equivalent doses of other GCSs) is **recommended** [89, 91].

Category of recommendation — A (Level of evidence — 1)

Comment: *the dose of prednisolone ** with this site and severity is 0.75–1 mg/kg of body weight per day until a clinical response is achieved, followed by a decrease of 5 mg every 5–7 days until complete withdrawal, for 12 weeks. The effectiveness of GCS is evaluated after 2–4 weeks.*

• Thiopurines (AZA** 2–2.5 mg/kg or MP#** 1.5 mg/kg) are **recommended** to be prescribed to this group of patients simultaneously with systemic GCS, and if they are intolerant or ineffective, MT # ** (25 mg/week s/c or i/m 1 time a week) [86,87,102].

Category of recommendation — A (Level of evidence — 1)

• In this group of patients, if there are signs of active systemic inflammation and/or infiltration, it is **recommended** to add antibiotics to the treatment regimen [61,85,90].

Category of recommendation — A (Level of evidence — 1)

Therapy with immunosuppressants, GEBD and TIS, see section 3.1.2 'CD of ileocecal site'.

• Surgical treatment is **recommended** for patients with active CD with ineffectiveness of conservative therapy [61].

Category of recommendation — C (Level of evidence — 5)

3.1.4 CD of the small intestine (except terminal ileitis)

• Oral administration of mesalazine has not shown efficacy compared to placebo for induction of remission and is **not recommended** for use with active CD [24,61,79,84,85].

Category of recommendation — B (Level of evidence — 2)

• Systemic GCS (prednisone** or equivalent doses of other GCSs) are **recommended** for this group of patients [24,85,89,91].

Category of recommendation — A (Level of evidence — 1)

Comment: *the dose of prednisolone ** with this site and severity is 1 mg/kg of body weight per day until a clinical response is achieved, followed by a decrease of 5 mg every 5–7 days until complete withdrawal, for no more than 12 weeks. The effectiveness of GCS is evaluated after 2–4 weeks.*

• For this group of patients, it is **recommended** to prescribe thiopurines simultaneously with systemic GCS (AZA** 2–2.5 mg/kg or MP #** 1.5 mg/kg), and if they are intolerant or ineffective, MT #** (25 mg /week s/c or i/m 1 time a week).

The duration of anti-recurrence therapy with thiopurines (AZA **/ MP #**) is at least 2–4 years in therapeutic doses [24,61,86,87].

Category of recommendation — A (Level of evidence — 1)

• In this group of patients, in the presence of signs of systemic inflammation and/or the presence of infiltration, antibacterial therapy is **recommended**: metronidazole 1g/day + fluoroquinolones 1 g/day parenterally for 10–14 days [24, 61, 90].

Category of recommendation — A (Level of evidence — 1)

Therapy with immunosuppressors, GEBD and TIS, see section 3.1.2 'CD of ileocecal site'

• Surgical treatment is **recommended** for patients with active CD with ineffectiveness of conservative therapy [61].

Category of recommendation — C (Level of evidence — 5)

3.1.5 Severe course of active CD of any site

The severe course of CD is assessed by the Harvey-Bradshaw index (Table 2) (see Section 1.5 'Classification of a disease or condition (groups of diseases or conditions)') more than 16 points.

Patients with severe CD are **recommended** to start treatment with systemic corticosteroids

(prednisone ** or equivalent doses of other corticosteroids) intravenously or orally. The equivalence of doses and duration of action of GCS is given in Table 8 (see Section 3.1.2 'CD of ileocecal site of moderate severity') [89,91].

Category of recommendation — A (Level of evidence — 1)

Comment: *the dose of prednisolone ** with this site and severity is 1.5–2 mg/kg of body weight per day until a clinical response is achieved, followed by a decrease of 5 mg every 5–7 days until complete withdrawal, for no more than 12 weeks.*

The effectiveness of GCS is evaluated after 2–4 weeks.

• For this group of patients, it is **recommended** to prescribe thiopurines simultaneously with systemic GCS (AZA** 2–2.5 mg/kg or MP #** 1.5 mg/kg), and if they are intolerant or ineffective, MT #** (25 mg /week s/c or i/m 1 time a week).

The duration of anti-recurrence therapy with thiopurines (AZA **/ MP #**) is at least 2–4 years in therapeutic doses [24,61,86,87].

Category of recommendation — A (Level of evidence — 1)

• In this group of patients, in the presence of signs of systemic inflammation and/or the presence of infiltration, antibacterial therapy is **recommended**: metronidazole 1g/day + fluoroquinolones 1 g/day parenterally for 10–14 days [24,61,90,112].

Category of recommendation — A (Level of evidence — 1)

• In this group of patients with an early recurrence of the disease less than 3 months after achieving clinical remission, it is **recommended** to start immediately with GEBD or TIS without re-prescribing systemic GCS [24,74].

Category of recommendation — C (Level of evidence — 5)

Comment: *repeated courses of GCS are highly undesirable. GCS is permissible to use only if it is impossible to use GEBD or TIS.*

Therapy with immunosuppressors, GEBD and TIS, see section 3.1.2 'CD of ileocecal site'

• Surgical treatment is **recommended** for patients with active CD with ineffectiveness of conservative therapy [61].

Category of recommendation — C (Level of evidence — 4)

3.1.6 CD with perianal lesions

Perianal lesions in CD often require surgical treatment, which is discussed in Section 3.2.6 'Surgical treatment of perianal CD'.

• In all patients with perianal CD lesion, in the absence of indications for surgical treatment or after it, the administration of immunosuppressants (AZA**, #MP **, #MT **) and/or GEBD (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab**, vedolizumab**) or TIS (upadacitinib **) in the form of an induction (initiating) course followed by long-term supportive treatment [58, 113, 114, 115] is **recommended**.

Category of recommendation — C (Level of evidence — 5)

• Metronidazole** 0.75 g /day and/or ciprofloxacin** 1 g/day are **recommended** for patients with perianal CD lesions for the treatment of purulent-inflammatory process [24, 116].

Category of recommendation — B (Level of evidence — 2)

Comment: *antibiotics are prescribed for a long time (up to 6 months. or before the appearance of side effects). Combination therapy of anti-TNF (infliximab, adalimumab) with antibacterial drugs increases their effectiveness [116–120].*

• In patients with perianal manifestations of CD, addition to metronidazole therapy** in the form of suppository and ointments is **recommended** [116, 117].

Category of recommendation — B (Level of evidence — 2)

• In patients with perianal manifestations of CD, in the presence of anal canal fissures, surgery is **not recommended**, but preference is given to the above-described local conservative treatment [24, 58, 116].

Category of recommendation — B (Level of evidence — 2)

3.1.7 Monitoring the effectiveness and side effects of drug therapy

During the period of GCS therapy, patients need to monitor their blood glucose levels.

During immunosuppressant therapy, control general blood tests and biochemical blood tests are required, taking into account the level of leukocytes and liver enzymes (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).

In addition, before carrying out GEBT and TIS and further every 6 months, according to the order of the Ministry of Health of the Russian Federation (No. 124n of 21.03.2017 'On approval of the procedures and timing of preventive medical examinations of citizens in order to detect tuberculosis'), consultation of a phthisiatrician and screening for tuberculosis (quantiferon test, and if it is impossible to conduct an intradermal test with tuberculosis allergen: Mantoux test, diaskin test).

• For patients before the administration of treatment with immunosuppressors, GEBD and TIS against the background of treatment, it is **recommended** to determine the antigen (HBsAg) of Hepatitis B virus in the blood, determination of Hepatitis C virus antibodies in the blood; determination of antibodies to Treponema pallidum in non-treponema tests (RPR, RMP) (qualitative and semi-quantitative study) in blood serum; determination of antibodies of classes M, G (IgM, IgG) to Human immunodeficiency virus HIV-1 in blood; determination of antibodies of classes M, G (IgM, IgG) to Human immunodeficiency virus HIV-2 in blood [121].

Category of recommendation — C (Level of evidence — 5)

• Strict adherence to the doses and schedule of administration of GEBD and TIS is **recommended**. Irregular administration of GEBD and TIS increases the risk of allergic reactions and ineffectiveness of treatment [24,61,122].

Category of recommendation — B (Level of evidence — 2)

• It is **recommended** for patients with hemoglobin levels below 80 g/l correction of anemia in the form of hemotransfusion (erythromass), with hemoglobin levels from 80 to 100 g/l — therapy with parenteral iron preparations (iron (III) hydroxide sucrose complex**, iron (III) dextran hydroxide, iron (III) hydroxide oligoisomaltosate, iron carboxymaltosate**) [30].

Category of recommendation — C (Level of evidence — 5)

3.1.8 Biosimilars

Biosimilars are biological medicinal products containing a version of the active substance already approved by the original biological medicinal product (reference drug) [123]. Currently, the biosimilar use 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, 14 of them based on adalimumab and 4 based on infliximab [124]. Infliximab and adalimumab biosimilars are also registered in the Russian Federation. 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 base on the effectiveness and safety of biosimilars, but among clinicians there remains a prejudice against them as drugs with lower efficacy [125]. In 2017, the European Organization for the Study of IBD (ECCO) 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 [126]. 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 [127]. 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 [128–132]. 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 was restored [130]. 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 [133]. 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 [134]. 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 [126].

Despite the rather clearly formulated statements regarding 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 [232].

Russian publications indicate that the frequency of secondary loss of response and adverse events in IBD patients when transferring from the original infliximab to its biosimilar is about 30%, which is significantly higher than in those who constantly receive the original drug. In addition, the frequency of adverse events is significantly higher in patients receiving the drug under the international nonproprietary name (INN), which leads to unjustified and unregulated alternation of the original drug and biosimilars compared with patients receiving drugs under the trade name [233].

The provision on biosimilars is being introduced for the first time in the Russian clinical guidelines for BC.

Since 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.

The provision on biosimilars is being introduced for the first time in the Russian clinical guidelines for CD.

- It is **recommended** to use both the original drug and its biosimilars as equivalent agents if there are indications for the administration of GEBD of TNF-alpha inhibitors (infliximab and adalimumab) [125,126].

Comment: *this provision applies equally to the primary administration of anti-TNF drugs in bio-naive patients, and when switching from the original drug to a biosimilar and back for non-medical indications. However, it should be borne in mind that uncontrolled switching from the original to a biosimilar or different biosimilars and back according to INN can lead to a worsening of the course of the disease, rapid loss of response and undesirable phenomena. 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. There is no sufficient evidence base for the use of biosimilars of drugs of other classes for the treatment of CD yet.*

3.2 Surgical treatment of CD

Most patients with CD undergo at least one surgery on the gastrointestinal tract during their lifetime.

The inability to radically cure patients with CD often leads to repeated resections, increasing the risk of short bowel syndrome. Modern tactics of surgical treatment of CD are aimed at performing limited resections, and, if possible, organ–preserving surgeries (stricturoplasty, dilation of strictures) [135].

Preoperative administration of steroids at a dose of more than 20 mg per day is associated with an increase in postoperative septic complications [136].

In patients with CD who underwent surgical treatment, the use of biological therapy (anti-TNF drugs, vedolizumab or ustekinumab) in the history is not associated with an increase in postoperative septic complications [137–142].

Discontinuation of these medications before surgery is not mandatory.

Taking immunomodulators before surgery is not associated with an increase in postoperative septic complications [143,144].

3.2.1 Indications for surgical treatment of CD

Indications for surgery in CD are acute and chronic complications, as well as ineffectiveness of conservative therapy and delayed physical development [135].

Acute complications of CD

Acute complications of CD include intestinal bleeding, intestinal perforation and toxic dilation of the colon.

- In case of intestinal bleeding, emergency surgery is **recommended** if it is impossible to stabilize the hemodynamics, despite transfusion of blood and intensive hemostatic therapy [145,146].

Category of recommendation — C (Level of evidence — 4)

Comment: *intestinal bleeding is detected with a loss of more than 100 ml of blood per day according to objective laboratory tests (scintigraphy,*

examination of feces for latent blood, rapid test of feces for latent blood by immunochromatographic method) or with a volume of feces with a visually detectable blood admixture of more than 800 ml/day. In such cases, resection of the affected part of the intestine is performed (with or without anastomosis, as well as with the possible stoma) with mandatory intraoperative enteroscopy or colonoscopy [147].

• In patients with a complicated form of CD, in case of perforation of the small or large intestine into the free abdominal cavity with peritonitis, emergency surgery with resection of the affected part of the intestine and, preferably, with intestinal stoma is **recommended** [148,149].

Category of recommendation — C (Level of evidence — 4)

Comment: *the formation of an intestinal stoma, as an alternative to primary anastomosis, with complicated CD and contamination of the abdominal cavity, due to perforation into the free abdominal cavity, reduces the risks of septic complications and recurrence of CD. In patients with CD site in the small intestine, its perforation into the free abdominal cavity is a fairly rare complication and usually occurs either distal or proximal to the intestinal area with the presence of stricture. In case of an emergency surgery, it is recommended to avoid the formation of a primary anastomosis without protection using a loop ileostomy [150].*

• In patients with CD site in the large intestine, with the development of toxic dilation, subtotal colectomy with end ileostomy is **recommended** as the method of choice [150].

Category of recommendation — C (Level of evidence — 4)

Comment: *toxic dilation of the colon is a rare complication in CD and is an expansion of the colon up to 6.0 cm or more unrelated to obstruction with intoxication phenomena. Risk factors for toxic dilation include hypokalemia, hypomagnesemia, preparation of the intestine for colonoscopy using osmotic laxatives and taking antidiarrheal medications. The toxic dilatation is indicated by a sudden decrease in the frequency of stool 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). With the perforation of the large intestine in patients with a complicated course of CD, in a serious condition and with metabolic disorders, exteriorization of the affected area is better.*

Chronic complications of CD

Chronic complications include strictures, abdominal masses, internal or external intestinal fistulas and the presence of neoplasia [151].

Also, chronic complications should include a delay in physical development, due to inadequate drug therapy, which most often occurs when the upper gastrointestinal tract is affected.

3.2.2 Surgical treatment of terminal ileitis or ileocolitis

• For a patient with a clinical picture of acute appendicitis, upon revision of the abdominal cavity and detection of a macroscopically unchanged appendix and terminal ileitis, it is **recommended** to refrain from appendectomy, as well as intestinal resection or ileocecal resection of the intestine [149,152].

Category of recommendation — C (Level of evidence — 4)

Comment: *sometimes the onset of Crohn's disease in the form of terminal ileitis can occur under the guise of acute appendicitis, which leads to hospitalization of the patient in a general surgical hospital and often to appendectomy and unjustified resection of the affected ileum [153,154]. In the clinical recommendations of the Russian Society of Surgeons in 2020, this situation is described as 'secondary appendicitis'. In this case, it is strongly recommended to refrain from appendectomy in the absence of macroscopic signs of secondary inflammation in the appendix. There are no prospective studies on this issue. In 2021, a systematic review by Quaresma A.B. was published, based on the data from 6 retrospective studies, most of which are descriptions of clinical cases. As a result of the review, the authors do not recommend appendectomy and primary resection of the ileum in uncomplicated CD [155]. It is important to note that this recommendation is consistent with the consensus position of the panel of experts of the European Organization for the Study of UC and CD (ECCO) and the European Association of Coloproctologists (ESCP) [152,156].*

• In patients with a penetrating form of CD with abdominal abscess, it is **recommended** to drain it under the control of ultrasound or CT with subsequent conservative treatment (antibacterial,

steroid therapy and GEBT) as an alternative to surgical treatment by resection [149,152,157].

Category of recommendation — B (Level of evidence — 3)

Comment: *drainage of the abdominal abscess and subsequent conservative treatment serve as a bridge to resection methods of treatment, allowing to reduce the surgery extent due to the reduction in the size of inflammatory changes.*

It is also important to note that the conservative approach after drainage reduces the likelihood of anastomosis leakage, the formation of external intestinal fistulas and the need for intestinal stoma after elective intestinal resection [158,159,160]. In particular, in the meta-analysis by He X., et al. a significant decrease in the probability of postoperative complications was revealed (OR = 0.44; 95% CI 0.23–0.83; p = 0.03) [161].

In the case of primary resection of the intestine in conditions of abdominal mass and abscess in CD, the surgery volume increases, which can subsequently lead to short bowel syndrome [162]. It is important to emphasize that according to a systematic review by Clancy, S., et al., abscess drainage in combination with conservative therapy allowed to avoid surgical treatment by resection in more than 30% of patients [157].

• In patients of this group, when ileocecal stricture or ileocecal valve is formed, ileocecal resection with ileo-ascendoanastomosis or stoma is **recommended** as the method of choice [163,166].

Category of recommendation — C (Level of evidence — 4)

Comment: *approximately $^{1}/_{3}$ of all patients with CD have a similar site, which is often complicated by stricture of the ileum or ileocecal valve. At the same time, the decisive factor for refusing to perform primary anastomosis is intestinal obstruction.*

• In patients of this group, if stricture is detected after the first course of conservative treatment (i.e., the use of corticosteroids), resection of the affected area of the intestine is **recommended** as the first stage of treatment, rather than a repeated course of conservative (steroid) therapy [165].

Category of recommendation — C (Level of evidence — 5)

• In patients with active CD with abdominal abscess, antibiotics are **recommended**, as well as abscess drainage or resection of the affected area [157,161].

Category of recommendation — B (Level of evidence — 3)

Comment: *drainage can be performed surgically or, in specialized centers and with sufficient qualifications, by percutaneous drainage. The latter option can be used only in the absence of stricture of the affected part of the intestine, which determines the need for resection of the affected part.*

In patients with a complicated form of CD, in the presence of loose strictures of the jejunum or ileum, including anastomosis strictures after previous resection, dissection of cicatricial strictures of the small intestine (stricturoplasty) is **recommended** as an alternative to resection, which avoids extensive resections of the small intestine [149,166].

Category of recommendation — B (Level of evidence — 3)

Comment: *this surgery is possible with a stricture length of no more than 10 cm. Contraindications to stricturoplasty are the presence of infiltrate, abscess, malignant formations in the intestinal wall or active bleeding and pronounced inflammation of the affected area.*

• In the presence of short stricture (less than 4 cm) of the jejunum or ileum, including anastomotic strictures after previous resection without infiltration, purulent cavities, internal fistulas without acute intestinal obstruction, balloon dilation of the narrowing zone can be an alternative to resection and stricturoplasty when located in an area accessible to an endoscope [167].

Category of recommendation — C (Level of evidence — 2)

Comment: *performing endoscopic balloon dilation avoids surgery by resection method. Balloon dilation is more effective and safe in the diagnosis of no more than 4 strictures located in close proximity to each other than in cases of multiple strictures. Balloon dilation is* ***not recommended*** *in the presence of an extended stricture (more than 4 cm), interstitial fistulas, purulent cavities, deep ulceration in the stricture area, as well as prestenotic expansion.*

• In patients of this group, in the absence of abdominal mass and abscess, surgery on the small

intestine and ileocecal zone by laparoscopic method is **recommended** [168–171].

Category of recommendation — A (Level of evidence — 2)

Comment: *simultaneous formation of more than one anastomosis does not lead to an increase in the rate of postoperative complications and the frequency of disease recurrence [172]. The preferred method for anastomosis on the small intestine is the imposition of a stapled anastomosis of the 'side-to-side' type, which reduces the likelihood of its failure [173] and the subsequent stricture.*

3.2.3 Surgical treatment of the large intestine CD

- In patients of this group, with limited lesion in the large intestine, resection of the affected segment with the formation of intestinal anastomosis within healthy tissues is **recommended** [174,175].

Category of recommendation — B (Level of evidence — 3)

Comment: *patients with a limited large intestine lesion (less than a third of the large intestine), with the development of CD complications, do not need to undergo a colectomy. In the presence of a lesion in the ascending colon, due to anatomical features, a right-sided hemicolectomy is indicated (with the preservation of the terminal ileum). If the splenicflexure and/or descending colon are/is affected, a left-sided hemicolectomy is performed with the formation of a transversosigmoid anastomosis or stoma. When CD is located in the sigmoid colon, resection of the affected area is performed.*

- In patients with advanced large intestine CD with severe clinical manifestations, subtotal colectomy with single-stem ileostomy is **recommended** as the surgery of choice [74,176].

Category of recommendation — B (Level of evidence — 3)

Comment: *it is possible not to resect the distal part of the large intestine, provided there is no pronounced inflammation in it, and to bring it to the anterior abdominal wall as end sigmostoma, or to make the stump of the rectum close to stoma.*

- In patients with lesions of the entire large intestine, as well as the presence of pronounced rectal inflammation and severe perianal lesions, proctocolectomy resection of the rectum and the end ileostomy is **recommended** as an alternative [74,149].

Category of recommendation — C (Level of evidence — 5)

Comment: *this approach is recommended only in patients with pronounced activity of the inflammatory process in the rectum or severe perianal manifestations, since it makes it impossible to restore anal defecation in future.*

- Abdominal-perineal excision (APE) is **not recommended** in patients with severe perianal lesions [149].

Category of recommendation — C (Level of evidence — 4)

Comment: *APE is impractical due to extremely low wound healing, which invalidates patients and limits their social activity.*

- In the surgical treatment of large intestine CD with purulent-septic process in the perianal region and perineum, rectal resection is **recommended** to be performed as total mesorectumectomy [149,177].

Category of recommendation — C (Level of evidence — 3)

Comment: *in CD the mesentery of the intestine plays a key role in the pathogenesis of the inflammatory process in the intestinal wall. Thus, according to de Groof et al., mesorectum contains an increased activated CD14+ macrophages producing anti — TNF-α, as well as a reduced concentration of the wound healing marker CD206 compared to similar tissue in UC.*

These fundamental data are also of practical importance, since the performance of total mesorectumectomy, in comparison with the resection of the rectum along the wall with the retention of fat in the pelvic cavity, is accompanied by a lower rate of postoperative complications in the perineum, including recurrence of CD: 17.6% and 59.5%, p = 0.007 [177]. It is important to note that we mean CD with pronounced perianal manifestations, purulent-septic process in the perineum. The decision on the need to perform mesorectumectomy in other situations remains at the choice of the operating surgeon.

- In patients with total large intestine lesion, in the absence of severe clinical manifestations and minimal activity of inflammatory changes in the rectum, adequate anal continence and absence of perianal lesions, colectomy with ileo-rectal anastomosis is **recommended** as the method of choice [149].

Category of recommendation — C (Level of evidence — 5)

Comment: *the possibility of pouch (ileoanal pouch anastomosis (IAPA)) with CD of the large intestine, it is controversial due to the high rate of complications and the frequent indications for the removal of the pouch. At the same time, the average life expectancy of patients after IAPA without permanent ileostomy reaches 10 years, which is important for young patients [172,164]. The main problems threatening a patient with IAPA on the background of CD are the development of perianal lesions and the development of CD in the small intestine pouch.*

• In patients with CD site in the large intestine, the ileostomy (diverting loop stoma) in order to stop the transit of intestinal contents through the large intestine is **recommended** only in extremely weak patients and pregnant women [168].

Category of recommendation — B (Level of evidence — 3)

Comment: *this type of surgical treatment is temporary. Considering that in CD, diverting the passage through the large intestine is not always effective, in the future it is necessary to re-discuss this issue.*

All of these surgical procedures can be safely performed using laparoscopic technologies [170,171,174,180].

• In patients with CD site in the large intestine, balloon dilation of large intestine stenoses (endoscopically) is **recommended** when detecting a not extended stricture [167,182,183].

Category of recommendation — B (Level of evidence — 3)

Comment: *this manipulation is associated with a higher risk of recurrence of the disease compared to resection of the affected area of the intestine.*

• In patients with CD site in the large intestine, dissection of cicatricial strictures (stricturoplasty) is **not recommended** [166,184,185].

Category of recommendation — B (Level of evidence — 2)

3.2.4 Surgical treatment of CD with lesions of the upper gastrointestinal tract

• In patients of this group, in the presence of single or multiple short strictures, various options for dissection of cicatricial strictures of the small intestine (stricturoplasty) are **recommended** as the surgeries of choice [64,149,184,185,186].

Category of recommendation — B (Level of evidence — 2)

Comment: *involvement of the intestinal tract proximal to the terminal part of the ileum in the inflammatory process often leads to multiple strictures and internal fistulas, which causes an unfavorable prognosis of CD and requires surgical treatment. In patients of this group, it is recommended to resort to the formation of a bypass anastomosis only in exceptional cases, since the risk of a syndrome of excessive bacterial growth in the disconnected part of the small intestine is high, and cancer may also develop. At the same time, extensive resections cause the development of short bowel syndrome [149].*

• In patients of this group, when identifying the stricture of the gastroduodenal zone (usually the duodenum), endoscopic balloon dilation or dissection of the cicatricial stricture (stricturoplasty) is **recommended** [186].

Category of recommendation — C (Level of evidence — 4)

3.2.5 Treatment of CD with perianal manifestations (perianal CD)

The approach to surgery on the perianal area should be individual for each patient [187,188].

• In patients with perianal manifestations of CD, in the presence of simple external perianal fistulas, it is **recommended** to treat the fistula by excision (fistulotomy) [189] or its adequate drainage in the presence of abscesses by use of setons in combination with drug treatment [191,192].

Category of recommendation — C (Level of evidence — 4)

Comment: *simple fistulas, clinically insufficient, do not require surgery.*

Follow-up against the background of the above-described conservative therapy is recommended. Indications for seton in most cases are trans- and extrasphincteric fistulas. In the absence of an inflammatory process in the rectal mucosal layer, it is possible to use rectal advancement flap for closure of internal fistula opening [190,193].

• In patients with perianal manifestations of CD, in the treatment of complex fistulas, their drainage (latex drainage setons) in combination with biological therapy is **recommended** [58,191,192].

Category of recommendation — C (Level of evidence — 2)

Comment: *the draining latex seton is used as an adjunct to the drug treatment of CD as a means of ensuring adequate drainage of the fistula to prevent the re-formation of abscesses and eliminate the local inflammatory reaction in the surrounding tissues. Often, the installation of a drainage ligature is a preliminary stage for radical surgery to eliminate the fistula.*

*The advantages of this method are: low cost, the possibility of preventing the new fistula tracts and cavities, reducing the need for temporary or permanent intestinal stoma, as well as a low rate of re-operations (from 10% to 20%). Given the high efficiency of biological therapy with proper drainage of complex anal fistulas, its early administration is justified (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab**, vedolizumab). Nevertheless, complex fistulas with pronounced purulent inflammation are often an indication for diverting stoma [190].*

• In patients with perianal manifestations of CD, with rectovaginal fistula, its excision with vagine repair rectal advancement flap is **recommended** [58].

Category of recommendation — C (Level of evidence — 5)

Comment: *rectovaginal fistulas in most cases require surgery.*

At the same time, surgical treatment is indicated under protective ileostomy. Only in some situations, in the presence of a low fistula between the rectum and the vestibule of the vagina, only conservative treatment is recommended. In the presence of an active lesion of the rectum, adequate anti-inflammatory therapy before surgery increases the effectiveness of the surgery [58].

• For patients with perianal manifestations of CD, accompanied by evacuatory disorders and anal incontinence, leading to a significant decrease in the quality of life, it is **recommended** to perform proctectomy [58,149].

Category of recommendation — C (Level of evidence — 4)

Comment: *the most unfavorable factor that increases the likelihood of permanent ileostomy or colostomy is the presence of stricture of the low rectum or anal canal stenosis.*

In some situations, in the absence of active inflammation in the other parts of the intestine, it is possible to dilate stricture [58].

• Multistage surgical treatment is **recommended** for patients with complex fistulas. As the first stage, it is recommended to open and drain abscesses.

Category of recommendation — C (Level of evidence — 5)

Comment: *adequate opening of the purulent cavity allows to start immunosuppressive therapy for CD without the risk of abscess in the perianal region or generalization of infection.*

Drainage is also possible with the use of a draining latex seton, if the internal fistula opening is clearly visualized.

• It is recommended for patients with complex fistulas as a second stage to make fistulectomy with closure of internal opening by rectal advancement flap if there is no additional abscesses, no proctitis and severe scars in anal canal or low rectum [193]

Category of recommendation — C (level of evidence — 2).

Comment: *the advancement flap can be mucosal-submucosal or mucosal-muscular. The procedure is safe for anal sphincters. Wound healing is above 60% with 10% risk of incontinence. It is possible to use VAAFT or LIFT as well in selected patients if there is no additional abscesses, no proctitis and severe scars in anal canal or low rectum [194,195].*

3.2.6 Anti-recurrence therapy after surgical treatment of CD

Even with the complete removal of all macroscopically altered parts of the intestine, surgery does not lead to complete recovery: within 5 years, a clinically significant recurrence is observed in 28–45% of patients, and within 10 years — in 36–61%, which dictates the need to prescribe or continue anti-recurrence therapy after surgeries for CD [196,197].

Factors that significantly increase the risk of postoperative recurrence include: smoking, two or more intestinal resections in the history, extended resections of the small intestine in the anamnesis (> 50 cm), perianal lesions, penetrating phenotype [198].

Depending on the combination of risk factors, as well as on the effectiveness of previously performed anti-recurrence treatment, patients after surgery should be stratified into groups with different risks of postoperative recurrence.

A high risk of postoperative recurrence includes the presence of 2 or more risk factors:

– *smoking;*
– *perianal lesions;*
– *penetrating CD;*
– *extended resection (more than 50 cm) of the intestine;*
– *previous surgery;*
– *early onset of the disease.*

• Thiopurine therapy is **recommended** for patients from the low-risk group in order to prevent recurrence(AZA** 2.0–2.5 mg/kg/day or #MP** 1.5 mg/kg/day) [199].

Category of recommendation — B (Level of evidence — 1)

• For patients with a high risk of exacerbation of CD before a control endoscopy to prevent recurrence, therapy with GEBD (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab**, vedolizumab**) or TIS (upadacitinib**) is **recommended** [61, 85, 200, 201, 202, 203].

Category of recommendation — C (Level of evidence — 3)

Comment: *data on the use of ustekinumab**, vedolizumab** and upadacitinib are currently insufficient to reliably assess their effectiveness as postoperative anti-recurrence therapy.*

• Patients with CD are **recommended** to start anti-recurrence therapy within 4 weeks after surgery in the absence of postoperative complications [204].

Category of recommendation — C (Level of evidence — 5)

• 6–12 months after surgery, patients with CD are **recommended** to undergo a control endoscopy, and if necessary, MRI and/or CT with intestinal contrast [200,205,206,207].

Category of recommendation — C (Level of evidence — 3)

• For operated patients with CD, if it is impossible to visualize the anastomosis zone, it is **recommended** to state the presence or absence of a recurrence, based on a combination of CT and/or MRI with intestinal contrast and biomarkers of inflammation — CRP, FC, etc. [200,206,207,208].

Category of recommendation — C (Level of evidence — 3)

Comment: *when resecting the terminal ileum or ileocecal segment, it is advisable to use the Rutgeerts scale of endoscopic activity of postoperative recurrence of CD (see Section 2.4 'Instrumental diagnostics', Table 7) [49, 209].*

• In patients with CD, in the absence of signs of inflammation or the detection of minimal (i1 on the Rutgeerts scale) inflammatory changes, it is **recommended** to continue therapy [209].

Category of recommendation — C (Level of evidence — 5)

• In the presence of more pronounced inflammatory changes (i2-i4), it is **recommended** to strengthen therapy: the inclusion of immunosuppressants in patients who have not previously received them, or the implementation of GEBD or TIS, who are on maintenance therapy with thiopurines (AZA**/MP#**) or if it is impossible to prescribe them [210,211].

Category of recommendation — C (Level of evidence — 5)

Comment: *the presence of more pronounced inflammatory changes (i2-i4) indicates the ineffectiveness of the therapy.*

• In the future, in patients with CD, regardless of the nature of the course of the disease and the clinical manifestation of CD, it is **recommended** to perform a control endoscopy at least once every 1–3 years [212].

Category of recommendation — C (Level of evidence — 4)

3.2.7 Ileostomy dysfunction after surgical treatment of CD

Ileostomy dysfunction refers to an increase in the volume of intestinal discharge through the ileostoma of more than 1,000 ml per day. The management of patients with this condition is described in the clinical guidelines 'Ulcerative colitis' [213].

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

Medical rehabilitation measures are aimed at preventing complications of conservative therapy and undesirable consequences of surgical treatment. Mild and moderate degree of dysfunction requires treatment on an outpatient basis. A severe degree of dysfunction, or its absolute impossibility, requires hospitalization in a round-the-clock hospital.

In patients who required surgical treatment of CD complications, 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, a general blood test, a biochemical blood test, a blood coagulogram, and a general urine test are monitored. 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 round-the-clock hospital.

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

Anal sphincter incontinence (ASI) — rehabilitation is possible at stages 2 and 3. In patients after surgery for CD with the formation of a stoma, there is a decrease in the retension function.

• For patients with anal sphincter incontinence before reconstructive treatment it is **recommended** to study the function of the rectal sphincter (occlusion) apparatus of the rectum with the further consultations with a physiotherapist [214].

Category of recommendation — C (Level of evidence — 5)

• Patients with the 2–3-degree anal sphincter incontinence are **recommended** to undergo rehabilitation treatment, including a 10-day cycle of BFB therapy and tibial neuromodulation in a day or round-the-clock hospital [214].

Category of recommendation — C (Level of evidence — 4)

Comment: *in the rehabilitation of patients with anal sphincter incontinence, according to the literature, the method of biofeedback therapy is widely used, aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of arbitrary compression [214,215]. This non-invasive method involves the body's own resources in the rehabilitation process with the development of the right skills at the level of creating new conditioned reflex connections. 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 (n.tibialis) is used for 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 occlusion apparatus can respond to BFB therapy and the conduct of tibial neuromodulation, increasing both the tone and the strength of volitional contractions [214,215]. 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 study of the function of the rectal occlusion apparatus. With the improvement of the tone and contractility of the anal sphincters, it is possible to raise the question of performing reconstructive surgery aimed at resuming the natural passage through the gastrointestinal tract.*

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

CD is characterized by progressive intestinal lesion. At the time of diagnosis, complications (strictures, fistulas) are found in 10–20% of patients,

while within 10 years such complications develop in more than 90% of cases. Within 10 years, surgeries due to complications and/or ineffectiveness of conservative therapy are performed in half of patients with CD, and 35–60% develop a recurrence of the disease within 10 years after surgery. Hormonal addiction in CD for 10 years is detected at least once in 30% of cases [216].

Due to the progressive nature of the disease, patients suffering from CD should receive constant (lifelong therapy) and undergo regular (lifelong) monitoring of disease activity. Monitoring the activity of the disease allows not only instrumental research methods, but also the determination of markers of inflammation, primarily the level of FC, the concentration of which in the stool correlates with the degree of ulcerative lesions of the gastrointestinal tract.

The frequency and volume of dispensary follow-up is determined individually, but in most patients, it is advisable to adhere to the following: — On average, every 6 months — a consultation with a gastroenterologist, every 12 months an examination by a coloproctologist with a mandatory transrectal digital examination to exclude perianal manifestations of CD, external intestinal fistulas, fistulas with hollow organs, interstitial fistulas, intestinal stricture.

Every 6 months:

– a general (clinical) detailed blood test, a study of the level of CRP, determination of the level of FC;
– routine (annual) endoscopic examination in the absence of clinical indications (doubts about the diagnosis, the need to exclude concomitant conditions, an increase in clinical manifestations, suspected complications, the need for monitoring after surgical treatment) is not carried out in most cases;
– if the condition worsens, the level of inflammatory markers (C-reactive protein, fecal calprotectin) increases, a colonoscopy should be performed to assess the activity of the disease, then an examination by a gastroenterologist and/or a coloproctologist with a complete objective examination.

If it is necessary to determine the site, extent, degree of activity of the inflammatory process, to exclude complications of the underlying disease in the form of infiltrates of the abdominal cavity, interstitial, inter-organ fistulas, perforations, strictures (in the absence of medical contraindications to the introduction of contrast agents), magnetic resonance imaging and/or computed tomography of the abdominal cavity and pelvic organs should be performed with intravenous contrast.

• The frequency and volume of dispensary follow-up is determined individually, but in most patients, it is **recommended** to perform a study of the level of C-reactive protein in blood serum, as well as a study of the level of calprotectin in feces every 3 months [74].

Category of recommendation — C (Level of evidence — 5)

• In patients receiving immunosuppressants it is **recommended** to perform a monthly study of the level of erythrocytes, leukocytes, blood platelets, free and bound bilirubin, creatinine, urea, determination of the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, amylase in the blood to assess liver function [74].

Category of recommendation — C (Level of evidence — 5)

• Patients are **recommended** to undergo an annual X-ray or MR examination of the intestine to exclude the formation of strictures and the development of other complications [74].

Category of recommendation — C (Level of evidence — 5)

Patients are **recommended** to annually undergo a local examination of the perianal area and a digital examination of the rectum to exclude perianal complications, as well as, if necessary, EUS [29, 59].

Category of recommendation — C (Level of evidence — 5)

• Patients with a dynamic increase in the level of inflammatory markers (CRP, FC) are **recommended** to undergo (ileo) colonoscopy to assess the activity of the disease [208].

Category of recommendation — B (Level of evidence — 3)

Comment: *routine (annual) endoscopic examination in the absence of clinical indications (doubts about the diagnosis, the need to exclude concomitant conditions, an increase in clinical manifestations, suspected complications) is not required in*

most cases. In the absence of indications related to CD, the frequency of ileocolonoscopy is determined by clinical recommendations for the early detection of malignant neoplasms of the large intestine.

6. SPECIAL SITUATIONS

6.1 Prevention of venous thrombosis

In patients with CD during hospitalization, as well as at the outpatient stage during exacerbation, in the presence of other known risk factors for venous thrombosis, prevention of venous thromboembolic complications (VTEC) is **recommended** [217].

Category of recommendation — B (Level of evidence — 2)

Comment. *CD patients have a two- or more-fold increased risk of venous thrombosis [218]. The risk of venous thrombosis increases during the period of disease activity and during hospitalization for any reason. Thromboprophylaxis after discharge from the hospital should be considered only in patients with high risk factors for VTEC [217]. To assess the likelihood of their development in hospitalized non-surgical patients, it is recommended to use the Padua [219] and IMPROVEVTE scales, in surgical patients — the Caprini scale [220]. For thromboprevention in patients with CD, it is recommended to use unfractionated heparin (UFH), low molecular weight heparin (LMWH), in preventive doses. In the presence of contraindications to the use of UFH, LMWH and a high risk of hemorrhagic complications according to the HAS-BLED, RIETE scales, the use of mechanical methods of prevention is recommended.*

6.2 Vaccination

Timely diagnosis of infections and their specific prevention, primarily in the form of vaccination, are recognized as strategies for leveling the risks of attachment and/or reactivation of various infections for a patient with CD [221,222,223].

For all patients with CD it is recommended to perform an assessment of the vaccination status at the stage of diagnosis, followed by regular monitoring during further counseling. Documented vaccination replaces serological screening of the intensity of the immune response, which is carried out in the absence of documents confirming the immunization [222]. Vaccines (inactivated) are used in patients with CD regardless of the treatment used [223]. Planning of immunization with live vaccines should be carried out before the administration of immunosuppressive therapy, if the start of treatment can be safely delayed, or vaccines should be administered during the minimum dose of a drug with an immunosuppressive effect [222]. With a high risk of infection with a vaccine-preventable infection and the development of a severe course, both potential threats to the life and health of the patient should be weighed and the possibility of vaccination (including live vaccines) should be provided against the background of ongoing CD therapy [224]. In addition, relatives and friends who are in close contact with CD patients should be vaccinated, which is an important strategy for protecting patients with IBD from severe vaccine-preventable infections. This approach is called 'cocoon vaccination' [222].

Patients with CD have the highest risk of severe infections caused by pneumococcus, influenza viruses, hepatitis B, measles, rubella, mumps, chickenpox, which requires priority vaccination against these pathogens.

It is **recommended** in patients with CD, when diagnosing the disease, to evaluate the vaccination status, the risk of infection and the consequences of the infection in order to determine the need and type of vaccination [221].

Category of recommendation — C (Level of evidence — 5)

Comments: *it should also be clarified whether the patient had previously vaccine-preventable infections (for example, measles, rubella, chickenpox, mumps, etc.). In the future, during observation and treatment, the vaccination status of the patient should be regularly monitored (at least once a year).*

- It is **recommended** that patients with CD be vaccinated in accordance with the national calendar of preventive vaccinations in order to prevent/reduce the likelihood of severe (complicated) course of infections, taking into account the period of the disease and the therapy received [221,222,223,225].

Category of recommendation — C (Level of evidence — 5)

Comment: *patients who are not receiving immunosuppressive therapy can use any vaccines in accordance with the instructions (inactivated and live).*

Inactivated vaccines are prescribed to patients receiving immunosuppressive therapy without restrictions, live vaccines are prescribed with restrictions. Currently, there is no unambiguous data on the optimal interval between the possible use of live vaccines after the completion of immunosuppressive therapy. The dose of GCS that causes immunosuppression is 2 mg/kg/day for prednisone, taken for 14 days or more; the introduction of live vaccines to these patients is allowed 1 month or more after the end of therapy [Guidelines MU 3.3.1.1095—02. 'Medical contraindications to preventive vaccinations with preparations of the national vaccination calendar']. The use of such a dose for less than 2 weeks or smaller doses for a longer period does not lead to the development of pronounced immunosuppression. At the same time, other guidelines recommend longer intervals between the administration of live vaccines after the completion of immunosuppressive therapy — no earlier than 1–3 months, and in the case of high doses of glucocorticoids, the interval after the end of treatment can be up to 6 months and depends on how it is fixed in the instructions for use of the drug [221, 222].

*The necessary immunization with the use of vaccines (including live ones) should, if possible, be carried out before the start of immunosuppressive therapy. Otherwise, immunization can be continued with the establishment of control over the disease, if necessary, its maintenance — against the background of the administration of basic therapy, strict adherence to dietary and other recommendations of a gastroenterologist. At the same time, immunosuppressive treatment can be initiated no earlier than 3–4 weeks after the introduction of live vaccines, without an interval — after the introduction of inanimate vaccines [221,222]. In a number of patients with CD, the risk of insufficient immune response remains after the standard vaccination regimen, and therefore it is possible to consider conducting selective control of immunity intensity no earlier than 1 month after the completed vaccination (for example, after the vaccine for the prevention of viral hepatitis B ** — Determination of antibodies to surface antigen (anti-HBs) Hepatitis B virus in the blood, quantitative study), followed by the introduction of a booster dose of the vaccine in the absence of protective antibody titers [221,226].*

6.2.1 Vaccination against priority infections

• Vaccination **against pneumococcal infection** in patients with CD for prevention purposes is recommended to be carried out sequentially, starting with a single dose of a conjugated vaccine for the prevention of pneumococcal infections** (PCV13 or another vaccine of the widest valence), followed by the introduction of a polysaccharide vaccine for the prevention of pneumococcal infections** (for example, PPV23) with a minimum interval of 8 weeks. Repeated vaccination is also provided with the use of pneumococcal polysaccharide vaccine (PPV23) after 5 years [222].

Category of recommendation — C (Level of evidence — 5)

• It is recommended for patients with CD to carry out **annual vaccination against influenza** in preparation for the flu season with the use of quadrivalent vaccines (inactivated) for preventive purposes [221,222,227].

Category of recommendation — C (Level of evidence — 5)

• It is **recommended** for patients with CD to carry out appropriate vaccination before the administration of immunosuppressive therapy in the absence of confirmation of the infection or vaccination **against hepatitis B, chickenpox, measles, rubella and mumps** [221, 222].

Category of recommendation — C (Level of evidence — 5)

Comments: *vaccination is carried out in accordance with the instructions.*

For patients with IBD for the prevention of a new coronavirus infection COVID-19** vaccination with a combined vector vaccine is recommended with caution in order to prevent/reduce the likelihood of a severe (complicated) course of infection, taking into account the activity and type of therapy of the underlying disease [228].

Category of recommendation — C (Level of evidence — 5)

Comment: *the frequency of vaccination is determined by the regulatory documents of the Ministry of Health of Russia.*

***There is no data on the deterioration of the course of the underlying disease against the background of vaccination** [229,230,231].*

It should be noted that the issues of vaccination against SARS-CoV-2 currently need to be addressed individually and with caution, taking into

account the benefit/risk indicator. This is due to a change in the nature of the course of infection, rapid mutation of the virus and the absence of modified vaccines, since the existing vaccines in the Russian Federation were developed for the original strains of the virus. It is recommended to **vaccinate patients with CD in preparation for pregnancy, as well as during pregnancy** in accordance with the national calendar of preventive vaccinations in order to prevent/reduce the likelihood of severe (complicated) course of any infections, taking into account the period of the disease and the therapy received [221, 222, 223, 225]. **Category of recommendation — C (Level of evidence — 5)**

7. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care within the framework of clinical testing, is organized and provided according to:

- Federal Law No. 323-FL of 21.11.2011 (as amended on 13.06.2023) 'On the Basics of Public Health Care in the Russian Federation';
- Resolution of the Government of the Russian Federation of 17.11.2021 No. 1968 'On Approval of the Rules for the Gradual 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 Public Health Care in the Russian Federation';
- Decree of the Government of the Russian Federation No. 2497 dated 29.12.2022 'On the Program of State guarantees of free medical care for citizens for 2023 and for the planning period of 2024 and 2025';
- Order of the Ministry of Health of the Russian Federation No. 206n dated 02.04.2010 (ed. dated 21.02.2020) 'On approval of the procedure for providing medical care to the population with coloproctological diseases of the large intestine, anal canal and perineum';
- Order of the Ministry of Health of the Russian Federation No. 906n dated 12.11.2012 'On approval of the Procedure for providing medical care to the population in the 'Gastroenterology' profile';
- Order of the Ministry of Health of the Russian Federation No. 76n dated 14.02.2022 'On approval of the standard of medical care for adults with Crohn's disease (diagnosis and treatment)';
- Order of the Ministry of Health of the Russian Federation No. 168n dated 15.03.2022 'On approval of the procedure for dispensary supervision of adults';
- Order of the Ministry of Health of the Russian Federation No. 1363n dated 23.12.2020 'On Approval of the Procedure for Sending Insured Persons to Medical Organizations, the Functions and Powers of the Founders in Respect of which are carried out by the Government of the Russian Federation or Federal Executive Authorities, to provide medical care in accordance with the Uniform requirements of the basic program of compulsory medical insurance';
- Order of the Ministry of Health of the Russian Federation No. 203n dated 10.05.2017 'On approval of criteria for assessing the quality of medical care':

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 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 CD 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, an outpatient gastroenterological center (unit), outpatient coloproctology center (unit), the center

for the diagnosis and treatment of inflammatory bowel diseases (if available in the individual, it is possible to organize on a functional basis) to provide him/her with primary specialized medical care. Consultation in the specified structural divisions of the medical organization must be carried out no later than 14 working days from the date of issuance of the referral for consultation, and in cases of severe forms of CD 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 organize the performance of diagnostic studies necessary to establish a diagnosis, 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 it is impossible to perform diagnostic tests necessary to establish a diagnosis, including determining the severity of the inflammatory process, the extent of the lesion, the presence of intestinal and extra-intestinal manifestations, including taking biopsy material, as well as if there are indications for medical care in hospital, the patient is referred by the attending physician to the gastroenterology unit, coloproctology unit, center for diagnosis and treatment of inflammatory bowel diseases or other medical organization, providing medical care in inpatient conditions to patients in the profile of 'gastroenterology', 'coloproctology'.

In case of suspicion and (or) detection of CD 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 structure 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 CD, the nature of the course, the prevalence of the inflammatory process.

The period should not exceed 30 calendar days from the date of issuance of the referral for hospitalization. Specialized, including high-tech, medical care for CD 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 conditions and conditions of a day hospital and includes prevention, diagnosis, treatment of CD, requiring the use of special methods and complex unique medical technologies, as well as medical rehabilitation.

If it is necessary to use treatment methods that are not performed in medical organizations operating in the field of compulsory medical insurance within the framework of the territorial compulsory medical insurance program, the need for additional examination in diagnostically difficult cases and (or) in cases of complex preoperative preparation in patients with complicated forms of the disease and (or) comorbid diseases for subsequent treatment, as well as the need for re-hospitalization on the recommendation of a federal medical organization, the patient is sent to a federal medical organization providing medical care in inpatient conditions to patients in the profile of 'gastroenterology', 'coloproctology' to provide high-tech medical care in accordance with the procedure for organizing the provision of high-tech medical

care using a unified state information system in the field of healthcare.

Indications for hospitalization in a round-the-clock or day hospital of a medical organization providing specialized, including high-tech medical care for CD are determined by a consultation of gastroenterologists and coloproctologists, with the involvement of other specialist doctors, if necessary.

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

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

The indication for hospitalization in a medical organization in a planned form is:

1) The need to perform complex interventional diagnostic medical interventions that require follow-up in a 24-hour or day hospital;
2) The presence of indications for specialized treatment of CD (surgery, hormonal and cytostatic therapy, biological and targeted therapy), requiring observation in a round-the-clock or day 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 round-the-clock or day 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 legal representative from specialized, including high-tech medical care in a round-the-clock or day hospital, established by the consultation of the medical organization providing CD treatment, provided there are no complications of the underlying disease and/or from 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 doctor- specialists of the medical organization to which the transfer is planned.

8. ADDITIONAL INFORMATION (INCLUDING FACTORS AFFECTING THE OUTCOME OF THE DISEASE OR CONDITION)

Prognostically unfavorable factors in CD are smoking, the onset of the disease in childhood, perianal lesions, a penetrating phenotype of the disease and a widespread lesion of the small intestine. A conversation about the need to stop smoking must be conducted with a smoker patient.

Pregnancy planning should be carried out during the period of IBD remission, which allows improving 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 #MT** and mesalazine** in tablets with a shell containing dibutyl phtholate. The cancellation of anti-TNF is possible only in a limited number of patients with a low risk of CD reactivation. Treatment with GEBD, not contraindicated during pregnancy (see instructions for the use of the drug), can be continued if the benefits to the mother exceed the potential risks to the fetus.

Clinical recommendations for the diagnosis and treatment of Crohn's disease (K 50, adults) were discussed on March 31, 2023 at a joint meeting of the Commissions on Surgical and Therapeutic Sciences of the Scientific Council of the Medical Academy of Sciences of the Russian Academy of Sciences, as well as at open meetings of the Board of the All-Russian Public Organization 'Association of Coloproctologists of Russia', a meeting of the profile commission on the specialty 'Coloproctology', and also on the Portal of public discussion of draft clinical recommendations.

CRITERIA FOR ASSESSING THE QUALITY OF MEDICAL CARE

Criteria for assessing the quality of primary health care for adults with Crohn's disease

№	Quality assessment criteria	Performance assessment
1	An appointment (examination, consultation) by a gastroenterologist and/or a coloproctologist was performed with a mandatory transrectal digital examination (in the presence of fistulas and/or perianal manifestations of Crohn's disease, external intestinal fistulas, fistulas with hollow organs, interstitial fistulas, intestinal stricture)	Yes/No
2	Colonoscopy was performed with examination of the terminal part of the ileum (at diagnosis)	Yes/No
3	A biopsy of the intestinal mucosal layer was performed (upon diagnosis)	Yes/No
4	Magnetic resonance imaging and/or computed tomography of the abdominal and pelvic organs with intravenous contrast was performed (if necessary, to determine the site, extent, degree of activity of the inflammatory process, to exclude complications of the underlying disease in the form of infiltrates of the abdominal cavity, interstitial, inter-organ fistulas, perforations, strictures in the absence of medical contraindications to the introduction of contrast agents)	Yes/No
5	The administration of systemic antibacterial drugs was performed (in case of detection of inflammatory infiltration of the abdominal cavity or extra-intestinal manifestations of the disease)	Yes/No

Criteria for assessing the quality of specialized medical care for adults with Crohn's disease

№	Quality assessment criteria	Performance assessment
1	An appointment (examination, consultation) by a coloproctologist and/or a gastroenterologist with mandatory transrectal digital examination (in the presence of fistulas and/or perianal manifestations of Crohn's disease, external intestinal fistulas, fistulas with hollow organs, interstitial fistulas, intestinal stricture) was performed	Yes/No
2	Colonoscopy was performed with examination of the terminal part of the ileum (if not performed within 6 months prior to hospitalization)	Yes/No
3	A biopsy of the intestinal mucosal layer was performed (at diagnosis, if it was not performed on an outpatient basis)	Yes/No
4	An overview X-ray of the abdominal cavity organs was performed within 2 hours from the moment of hospitalization or computed tomography of the abdominal cavity and retroperitoneal space (in the presence of clinical signs of intestinal obstruction)	Yes/No
5	Magnetic resonance imaging and/or computed tomography of the abdominal and pelvic organs with intravenous contrast was performed (if necessary, to determine the site, extent, degree of activity of the inflammatory process, to exclude complications of the underlying disease in the form of infiltrates of the abdominal cavity, interstitial, inter-organ fistulas, perforations, strictures, in the absence of medical contraindications to the introduction of contrast agents)	Yes/No
6	Therapy with systemic corticosteroids or tumor necrosis factor alpha (TNF-alpha) inhibitors or ustekinumab or vedolizumab or upadacitinib or azathioprine or mercaptopurine was performed	Yes/No
7	Therapy with systemic antibacterial drugs was carried out (in case of detection of inflammatory infiltration of the abdominal cavity or extra-intestinal manifestations of the disease)	Yes/No
8	Anti-recurrence therapy has been prescribed: azathioprine or mercaptopurine or infliximab or adalimumab or certolizumab pegol or ustekinumab or vedolizumab or upadacitinib (after surgery or after achieving drug remission)	Yes/No
9	Examination/consultation by a coloproctologist or a surgeon is recommended (for external intestinal fistulas, fistulas with hollow organs, interstitial fistulas, intestinal strictures, perianal manifestations, bleeding)	Yes/No

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