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CLINICAL GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF CROHN'S DISEASE IN ADULTS (PROJECT)

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[Key words: Crohn's disease, inflammatory bowel diseases, conservative treatment, surgery, immunosuppressors, steroids, biological therapy, anti-recurrence therapy]

LIST OF ABBREVIATIONS

AZA-azathioprine
CD-Crohn's disease
IBD-inflammatory bowel diseases
GCS-glucocorticosteroids
CI-coincidence interval
GIT – gastrointestinal tract
CDAI-Crohn's disease activity index
IPA – ileoanal pouch anastomosis
CT-computed tomography
MMS-multimatrix shell
MP-mercaptopurin
MRI-magnetic resonance imaging
MT-methotrexate
NSAIDs – nonsteroidal anti-inflammatory drugs
RCT-randomized controlled trial
US – ultrasound examination
TNFA-tumor necrosis factor alpha
UC-ulcerative colitis

TERMS AND DEFINITIONS

Crohn's disease (CD) is a chronic, recurrent disease of the gastrointestinal tract of unclear etiology, characterized by transmural, segmental, granulomatous inflammation with the development of local and systemic complications [1].
Exacerbation of CD is the appearance of typical symptoms of the disease in patients with CD in the stage of clinical remission, spontaneous or medically supported [1].
Remission of CD is the disappearance of typical manifestations of the disease [1].
Remission of CD, clinical – there are no symptoms of CD (corresponds to the value of the activity Index of CD (CDAI) <150) [2].
Remission of CD, endoscopic - [2]. Compliance with the value of the simplified endoscopic CD severity index (SES CD) ≤ 3.

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

1.1 Definition of the disease or condition (group of diseases or conditions)

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

1.2 Etiology and pathogenesis of the disease or condition (group of diseases or conditions)

Table 1. Montreal Classification for Crohn's Disease (lesion site)

L1 Terminal ileitis: the disease is limited to the terminal ileum or ileocecal region (with or without involvement in the caecum)
L2 Colitis: 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 Ileocolitis: terminal ileitis (with or without involvement of the caecum) in combination with one or more foci of inflammation between the caecum and the anal sphincter
L4 Upper gastrointestinal tract: lesion proximal to the terminal part (excluding the oral cavity)

According to the prevalence of the lesion, there are:

1. Localized CD:
* The lesion is less than 30 cm long. It is more often used to describe an isolated lesion of the ileocecal zone;
* There may be an isolated lesion of a small area of the colon.
2. Extended CD:
* A lesion extending more than 100 cm (the sum of all affected areas).

According to the nature of the disease course there are [9]:

1. Acute (less than 6 months from the disease debut);
2. Chronic (over 6 months from the disease debut).

The etiology of IBD, including CD, has not been established: the disease develops as a result of a combination of several factors, including genetic predisposition, defects in congenital and acquired immunity, intestinal microflora and various environmental factors.

About100 single-nucleotide polymorphisms associated with CD have been described. This genetic background leads to changes in the congenital immune response, autophagy, mechanisms for recognizing microorganisms, endoplasmic reticular stress, epithelial barrier functions, and adaptive immune response.

The key immune defect predisposing to IBD development is a violation of recognition of bacterial molecular markers (patterns) by dendritic cells, which leads to hyperactivity of signaling proinflammatory pathways [3,4].

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.

In the presence of these microbiological and immunological changes, IBD develops under the influence of trigger factors, which include smoking, nervous stress, vitamin D deficiency, nutrition with a low content of dietary fiber and an increased content of animal protein, intestinal infections, especially infections associated with C. difficile.

The result of the mutual influence of these risk factors is the activation of Th1-and Th17-cells, hyperexpression of proinflammatory cytokines, primarily tumor necrosis factor-alpha (TNF-alpha), interleukins 12 and 23, and 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 peculiar for CD, but not for ulcerative colitis (UC), consisting of epithelial histiocytes without foci of necrosis and giant cells.

With CD, any parts of the gastrointestinal tract can be affected – from the mouth to the anus. However, in the vast majority of cases, CD affects the ileocecal part. CD, unlike UC, cannot be cured by either therapeutic or surgical methods [5].

1.3 Epidemiology of the disease or condition (group of diseases or conditions)

According to the foreign data, the incidence of CD is from 0.3 to 20.2 per 100,000 people, the prevalencereaches 322 per 100,000 people [6].

Data on the CD prevalence in the Russian Federation is limited. The CD prevalence is higher in northern latitudes and in the West. The incidence and prevalence of CD in Asia is lower, but is increasing. Caucasians suffer from the disease more often than representatives of the Negroid and Mongoloid races. The peak incidence is observed between 20 and 30 years of life [7]. The incidence is approximately the same in men and women.

1.4 Features of coding the disease or condition (group of diseases or conditions) according to the International statistical classification of diseases and health-related problems

C50.0 - Crohn's Disease of the small intestine
C50.1 - Crohn's Disease of the colon
C50.8 - Other forms of Crohn's disease
C50.9 - unspecified Crohn's Disease

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

The Montreal classification (Table 1) is used to classify the CD by lesion site [8].

Table 2. ExtrabowelCrohn'sDiseaseManifestations

Autoimmune, activity-relateddiseases:	Autoimmune, non-activity-related diseases:	Caused by long-term inflammation and metabolic disorders:
Arthropathies (arthralgias, arthritis) Skin lesions (nodular erythema, gangrenous pyoderma) Mucosal lesions (aphthous stomatitis) Eye lesions (uveitis, iritis, iridocyclitis, episcleritis)	Ankylosingspondylitis (sacroileitis) Primary sclerosing cholangitis (rare) Osteoporosis, osteomalacia Psoriasis Psoriaticarthritis	Cholelithiasis Liver steatosis, steatohepatitis Peripheral veinthrombosis, Pulmonary embolism Amyloidosis

The severity of the disease, in general, is determined by: the severity of the current exacerbation, the presence of extra-intestinal manifestations and complications, the extent of the lesion, the resistance to treatment, in particular, the development of steroid dependence and steroid resistance.

However, to formulate a diagnosis and determine treatment approach, the severity of the current exacerbation should be determined, using simple criteria developed by the Russian Society for the study of IBD [10], the Harvey-Bradshaw index [11].

There is also the CDAI (CD activity index – Best index [12]), usually used in clinical trials due to the complexity of its calculation, according to which there are mild, moderate and severe active CDs (Appendices G1-3).

The use of a particular severity assessment system is determined by the routine practice of a particular medical institution.

The CD is classified according to the phenotypic variant of the disease:

1. Non-stricturating, non-penetrating (the synonyms in the Russian literature – intraluminal, infiltrative-inflammatory, uncomplicated, in the English literature –luminal) is the inflammatory nature of the disease, which has never been complicated (at any time during the disease course).
2. Stricturating (stenosing) – narrowing of the intestine lumen (according to radiology and/or endoscopy or the surgical results).
3. Penetrating (the synonyms: fistulising) occurrence of intraabdominal fistulas, and / or inflammatory infiltrate with an abscess at any time during the disease, excluding postoperative intraabdominal complications.
4. Perianal (in the presence of perianal lesions: fistulas, anal fissures, perianal abscesses) can be combined with any of the specified forms, as well as be an independent manifestation of perianal CD.

The classification of CD depending on the response to steroid therapy corresponds to that for UC:

1. Hormonal resistance:

1.1 In the case of a severe attack, there is no positive changes of clinical and laboratory tests, despite the systemic administration of glucocorticosteroids (GCS) at a dose equivalent to 2 mg/kg of prednisolone body weight for more than 7 days;

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

2. Hormone dependence:

2.1 Increase in disease activity when reducing the dose of GCS after achieving initial improvement within 3 months from the start of treatment;

2.2 Occurrence of the disease relapse within 3 months after the end of treatment with GCS.

When making a diagnosis, you should reflect:

a) lesion site with a list of the affected GIT segments;
b) phenotypic variant;
c) the severity of the current exacerbation or the presence of the disease remission;
d) the nature of the disease course;
e) the presence of hormone dependence or resistance;
f) the presence of extra-intestinal 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 the diagnosis must also include the stricture as a complication.

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

The most common clinical symptoms of CD include chronic diarrhea (more than 6 weeks), in most cases, without blood admixture, abdominal pain, fever and anemia of unknown origin, symptoms of intestinal obstruction, as well as perianal complications (chronic anal fissures that recur after surgical treatment, paraproctitis, rectal fistulas).

In patients with CD with a lesion of the upper GIT, other gastroenterological complaints may be observed. Thus, when the esophagus is affected, there are complaints of chest pain, heartburn and belching (similar to those in gastroesophageal reflux disease), in more severe cases - dysphagia and odynophagia, vomiting and body weight loss. In CD with lesions of the stomach and duodenum, patients may complain of pain, heaviness and overflow in the epigastric region, nausea, and decreased appetite [13].

A significant part of patients may have extraintestinal manifestations of the disease [14] (Table 2).

They may have autoimmune manifestations associated with the activity of the inflammatory process, which appear together with the main intestinal symptoms of inflammation and disappear with them during treatment. The autoimmune manifestations that are not associated with the process activity tend to progress regardless of the phase of the underlying disease (exacerbation or remission) and often determine the negative prognosis of the disease.

The clinical picture in the early stages of the disease may not be expressed, which slows down the diagnosis.

In this regard, when making a diagnosis, a significant number of patients show symptoms associated with complications of CD. The complications of CD include: external fistulas (intestinocutaneos), internal fistulas (inter-intestinal, intestino-vesical, recto-vaginal), abdominal mass, inter-intestinal or intraabdominal abscesses, gastrointestinal strictures (with or without intestinal obstruction), anal fissures, perianal abscess (with anorectal lesion), intestinal bleeding (rarely).

Perianal manifestations develop in 26-54% of patients suffering from CD [15-17], and are more common in colorectal lesions.

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

There are no unambiguous diagnostic criteria for CD, and the diagnosis is based on a combination of the disease history, clinical picture, and typical endoscopic and histological changes [18-20].

The diagnosis must be confirmed by:

endoscopic and morphological methods and / or endoscopic and radiological methods of diagnosis.

Endoscopic criteria for the diagnosis of CD are segmental (intermittent) lesions of the mucosa, the symptom of the "cobblestone pavement" (a combination of deep longitudinally oriented ulcers and transversely directed ulcers with islands of edematous hyperemic mucosa), linear ulcers (ulcer fissure), aphthae, and in some cases - strictures and the internal opening of fistula.

Radiological signs of CD include regional, intermittent lesions, strictures,

"cobblestone pavement", fistulas and inter-intestinal or intra-abdominal abscesses.

The morphological features of CD are:

** Deep slit ulcers that penetrate the submucosal or muscular layer;*

** Epithelioid granulomas (clusters of epithelial 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 - during a mucosal biopsy);
** Focal (discrete) lymphoplasmacytic infiltration of the lamina propria of the mucosa;*
** Transmural inflammatory infiltration with lymphoid hyperplasia in all layers of the intestinal wall;*
** Intermittent lesion-alternation of affected and healthy parts of the intestine (when examining the resected part of the intestine).*

In contrast to UC, crypt abscesses in CD are rarely formed, and mucus secretion remains normal. The diagnosis must be confirmed by: endoscopic and morphological methods and / or endoscopic and radiological methods of diagnosis.

2.1 Complaints and disease history

When interviewing a patient, you should pay attention to the frequency and nature of stool, the duration of these symptoms, the presence of blood, the nature of abdominal pain, episodes of fever, anemia, symptoms of intestinal obstruction, perianal complications (chronic anal fissures that recur after surgical treatment, perianal abscess and fistula), and extraintestinal manifestations of the disease [14] (Table 2).
When clear up the disease history, you should pay attention to the presence of autoimmune manifestations associated and unrelated to the activity of the inflammatory process, and to complications of CD.
In addition, it is necessary to clarify the nature of the disease debut, information about travel to southern countries, food intolerance, medication (including antibiotics and NSAIDs), smoking and family anamnesis.

2.2 Physical examination

Physical examination of all patients except for general methods (examination, auscultation, percussion and palpation of the abdomen) should include:
* inspection of the perianal area;
* transrectal digital examination to detect perianal manifestations of CD [11,21].
Grade C (level of evidence – 5).
Comment. *Physical examination may reveal various manifestations of CD, including fever, nutritional deficiencies, abdominal infiltrate, external intestinal fistulas, perianal manifestations (fissures, fistulas), and extra - intestinal manifestations.*

2.3 Laboratory diagnostic tests

* It is **recommended** that all patients with CD undergo a comprehensive blood test to diagnose anemia, comorbidities, and determine the level of CD activity [22-24].
Grade C (level of evidence – 4).
Comment*. Laboratory manifestations of CD are non-specific. In clinical blood analysis, anemia (iron deficiency, anemia of chronic disease, B-12or folate-deficient), leukocytosis (on the background of chronic inflammation, in the presence of an abscess or on the background of steroid therapy), and thrombocytosis can be diagnosed.*
If the differential diagnosis of anemia is necessary, it is advisable to examine the level of folic acid, vitamin B12, serum iron, total iron-binding capacity of serum, ferritin.
* It is **recommended** for all patients with CD to do biochemical blood tests (total protein, albumin, ALT, ACT, total bilirubin, GGT, LDH, K+, Na+, Cl-, C-reactive protein, ALP, and fibrinogen) for the diagnosis of comorbidities [23,25-28].
Grade C (level of evidence – 4).
Comment*. The biochemical blood test allows to identify electrolyte disorders, hypo-proteinemia (in particular, hypoalbuminemia), as well as an increase in ALP, which is a possible manifestation of primary sclerosing cholangitis associated with CD.*
For patients who need assessing or monitoring the activity of the intestine inflammation,it is ***recommended*** *to perform a fecal calprotectin test [29].*
Grade A (level of evidence – 2).
For patients with a recent course of antibiotic therapy or hospital stay, it is **recommended** to perform fecal analysis to exclude acute intestinal infection, study of clostridial toxins A and B to exclude

clostridial infection [30-35].
Grade C (level of evidence – 4).
Comment. *A minimum of 4 stool samples are required to detect infection in 90% of cases. It is important to determine CMV infection in the blood and/or intestinal mucosa by PCR in case of a severe CD attack.*
* It is **recommended** that patients with an exacerbation of CD (or the first attack of the disease) undergo differential diagnostics with acute intestinal infection [36-37].
Grade C (level of evidence – 5).

2.4 Other diagnostic tests
Patients are **recommended** to undergo proctoscopy during the initial examination [11,21].
Grade C (level of evidence – 5).
Patients with suspected intestinal obstruction or intestinal perforation are **recommended** to undergo abdominal X-ray to confirm this condition [38,39].
Grade C (level of evidence – 5).
For patients who need determining the site, extent and degree of activity of the inflammatory process,it is **recommended** to perform ileocolonoscopy [40,41].
Grade C (level of evidence – 4).
In patients with primary diagnosis, suspected disease progression, or with signs of relapse, it is **recommended**to perform esophagogastroduodenoscopy to exclude / confirm the lesion of the upper GIT [13,42,43].
Grade C (level of evidence – 4).
If it is necessary to determine the site, extent, degree of activity of the inflammatory process, as well as to exclude complications of CD (abdominal masses, fistulas, perforations, strictures), it is **recommended** to conduct MRI and/or computed tomography (CT) with intestinal contrast [18,44,45].
Grade A (level of evidence – 1).
Patients with perianal manifestations of CD in the form of rectal fistulas or if they are suspected of them are **recommended** to undergo pelvic MRI with intravenous contrast to confirm the diagnosis, determine the site, and extent of the fistula [18,46,47].
Grade A (level of evidence – 1).
Comment. *If it is impossible to perform MRI, such patients are* ***recommended*** *to undergo a transrectal US and/or fistulography.*
However, the sensitivity and specificity of these methods are currently inferior to MRI.
The purpose of the examination for perianal manifestations of CD is, first of all, to exclude an acute purulent process in the pararectal area that requires emergent surgical procedure.
Patients who cannot undergo CT or MRI, after excluding intestinal obstruction, are **recommended** to undergobarium enemato confirm the site and extent of the inflammatory process, fistulas, strictures [38,48-50].
Grade C (level of evidence – 5).
In patients with acute attack or at the first treatment, it is **recommended** to conduct a biopsy of the intestinal mucosa in the affected area for pathologic examination of the biopsy material [40,51].
Grade C (level of evidence – 2).
All patients are **recommended** to undergoabdominal US, US of retroperitoneal area and pelvis to exclude complications of the underlying disease and concomitant pathology [52-54].
Grade B (level of evidence – 2).
Patients with suspected lesions of the upper GIT (in the absence of areas of narrowing of the GIT) and no signs of inflammation during MRI, CT and US, or the inability to perform them, are **recommended** to undergo a video capsule endoscopy to confirm the diagnosis, determine the site and the degree of activity of the inflammatory process [55].
Grade B (level of evidence – 1).
Comment. *It should be remembered that capsule retention in the intestine is observed in 13% of patients [55].*
Patients with CD who require capsule endoscopy prior to this study are **recommended** to undergoradiology (CT-enterography or MR-enterography) to detect small bowel strictures [56,57].
Grade C (level of evidence – 4).

Patients with CD with suspected small bowel lesion and the inability to reliably confirm the diagnosis according to ileocolonoscopy, CT and MRI, the inability to conduct a video capsule test, are **recommended** to have a double - balloon enteroscopy to confirm the diagnosis, determine the site and degree of activity of the inflammatory process [58].
Grade B (level of evidence – 2).

2.5 Other diagnostics

Additional instrumental and laboratory tests are performed primarily for the purpose of differential diagnosis with a number of diseases [59].
These are infectious, vascular, medication induced, toxic and radiative lesions, as well as diverticulitis, etc.
At the next stage of differential diagnosis, verification of clinical diagnoses of UC and CD belonging to the IBD group is performed.
Thus, the differential diagnosis of CD is performed with UC, acute intestinal infections (dysenteria, salmonellosis, campylobacteriosis, yersiniosis, amoebiasis, parasitosis), antibiotic-associated intestinal lesions (including infection associated with C. difficile) [36,37,60], NSAIDs-associated enteropathies, intestinal tuberculosis, systemic vasculitis, colorectal and small intestine tumors, diverticulitis, appendicitis, endometriosis, solitary rectal ulcer, ischemic colitis, actinomycosis, radiation lesions and irritable bowel syndrome.
For the purpose of differential diagnosis and choosing therapy for extraintestinal manifestations of CD and accompanying conditions, may be required the consultation by:
– a psychotherapist or medical psychologist (neurosis, planned surgery with the stoma presence, etc.);
– endocrinologist (steroid sugar diabetes, adrenal insufficiency in patients on long-term hormone therapy);
– dermatovenerologist (differential diagnosis of nodular erythema, pyoderma, etc.);
- rheumatologist (arthropathy, sacroiliitis, etc.);
-obstetrician-gynecologist (pregnancy).

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

3.1 Conservative treatment

Principles of treatment

Treatment for CD include the use of medications, surgery, and diet [11].
*For all patients with CD it is **recommended** to determine the type of conservative or surgical treatment based on the severity of the attack, the extent and site of inflammation in the GIT, the presence of extra-intestinal phenomena and intestinal complications (stricture, abscess, infiltration), the duration of the anamnesis, the effectiveness and safety of previously performed therapy, as well as the risk of developing complications of CD [11,66]. When choosing therapy, it is necessary to pay attention to the presence of factors of an unfavorable prognosis of the disease at the time of diagnosis (the patient's age <40 years, extended (>100 cm) small intestine lesion, early need for systemic steroids, the presence of perianal Crohn's disease, as well as the penetrative form, involvement of the upper GIT, lack of healing of the mucosa when reaching clinical remission, the status of the smoker, the presence of epithelial granulomas, the presence of concomitant autoimmune diseases.*
Therapy aim corresponds to the "Treat to target" strategy.
The CD therapy objectives are to induce remission and maintain it without GCS, prevent complications, prevent surgery, and in case of the progression and development of life-threatening complications, to make surgery in time.
Since surgery 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 conduct anti-inflammatory therapy, which should be started not later than 2 weeks after the surgery [62].
Agents prescribed to patients with CD are conditionally divided into:
*1. Remedies for inducing remission: systemic GCS (prednisone** and methylprednisolone**) and topical*

*(budesonide**), in combination with immunosuppressants (azathioprine** (AZA), #mercaptopurine** (MP), #methotrexate** (MT)), biological genetic engineering drugs: monoclonal antibodies to TNF - alpha (infliximab**, adalimumab** and cert - tolizumab pegol**), monoclonal antibodies to Il - 12/23 (ustekinumab**) and monoclonal antibodies to integrin alpha4-beta7, selectively acting only in the GIT (vedolizumab**), as well as antibiotics.*
*2. Remedies for maintaining remission (anti-recurrent remedies): immunosuppressors (AZA**, #MP**), biologics (infliximab**, adalimumab**, certolizumab pegol** ustekinumab** and vedolizumab**).*
3. Auxiliary symptomatic remedies: drugs for the anemia correction, drugs for the protein-electrolyte disorders correction, drugs for the osteoporosis prevention (calcium drugs), etc.
It should be particularly noted that systemic GCS cannot be used as a maintenance therapy, nor can they be prescribed for more than 12 weeks [63].

3.1.1 CD in the form of terminal ileitis, mild severity

Budesonide is **recommended** for this group of patients as first-line therapy** in capsules or granules in the form of sachets (when taking capsules, the daily dose is 9 mg / day once or 3 mg 3 times a day for 10 weeks, followed by a reduction of 3 mg per week until complete withdrawal.
When taking sachet, the daily dose is 9 mg / day once for 16 weeks, followed by a reduction of 9 mg every other day for two weeks) [11,64-66].
Grade B (level of evidence – 1).
Comment. *The effect of budesonide** should be evaluated after 2-4 weeks. In the absence of a response to budesonide**, treatment is performed as in a moderate attack of CD.*
In this group of patients,early (simultaneous with budesonide**) administration of immunosuppressants (AZA** 2-2.5 mg/kg per day or #MP** 1.5 mg/kg per day) is **recommended** as anti-inflammatory therapy, and if they are intolerant or ineffective – #MT** (25 mg / week per cutaneous or intramuscular) [67-69].
Grade A (level of evidence – 1).
Comment.*Since AZA * * begins to effect after 12 weeks, an early administration is necessary to enable AZA** to take effect by the time the GCS is canceled.*
*For this group of patients after budesonide** with drawal, it is **recommended** to have anti-recurrent therapy with thiopurines (AZA**/#MP**) for at least 4 years at the therapeutic doses [11,70-72].*
Grade C (level of evidence – 5).

Table 3. *Comparative Characteristics of Glucocorticoids*

Drug	Duration of action (t1/2)	Equivalent dose (mg)
Hydrocortisone	8-12 hs	20
Prednisolone	12-36 hs	5
Methylprednisolone	12-36 hs	4

3.1.2 CD of ileocecal site of moderate severity

Topical steroids (budesonide** 9 mg/day) are **recommended** for the induction of remission in this group of patients.
The dosage regime, the timing of evaluating the effectiveness are the same as in mild CD of a similar site [66].
Grade A (level of evidence – 1).
In this group of patients, it is **recommended** to use systemic corticosteroids (prednisone** or equivalent doses of other GCS (Table 3) [73-75] to induce the CD remission when topical steroids (budesonide**) are ineffective or if there is abdominal mass, intestinal stenosis, and/or signs of systemic inflammation.
Grade A (level of evidence – 1).
Comment. *The dose of prednisone for this site and severity is 1 mg/kg of body weight.*
The GCS effectiveness is evaluated after 2-4 weeks with a further reduction in the GCS dose by 5 mg in 5-7 days before complete withdrawal against the background of continued therapy with immunosuppressants. The total duration of GCS therapy should not exceed 12 weeks.
In this group of patients with signs of active systemic inflammation and/or the presence of infiltration and/or purulent complications, it is **recommended** to add antibiotics [76-79].

Grade B (level of evidence – 3).

Comment. *It is* ***recommended*** *to use metronidazole 1 g/day + fluoroquinolones 1 g/day for 10-14 days orally or parenterally.*

A long-term transition to long- erm (up to 3 months) oral medication is possible.

This group of patients is **recommended** to take early (simultaneously with GCS) immunosuppressors (AZA** 2-2.5 mg/kg or #MP** 1.5 mg/kg) as an anti-inflammatory therapy,and if they are intolerable or ineffective - #MT**(25 mg/week per cutaneous or intramuscular) [67-69].

Grade A (level of evidence – 1).

This group of patients is **recommended** to takesupportive therapy with thiopurines (AZA**/#MP**) for at least 4 years after the GCS cancellation [11,70-72].

Grade A (level of evidence – 1).

For the group of patients with active CD with steroid resistance, steroid dependence, intolerance to GCS, or if immunosuppressors are ineffective or intolerable, the biological therapy in the form of an induction course (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab** or vedolizumab**) is **recommended** [80-83].

Grade C (level of evidence – 3).

Comment. *Doses of biological drugs are prescribed in accordance with the instructions for use.*

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

All biologics are approximately the same in effectiveness, so they are equally likely to be prescribed as first-line therapy.

Patients who have reached remission with any biologics are **recommended** to changefor long-term supportive therapy with the same drug (with or without immunosuppressors) [87-90].

Grade A (level of evidence – 1).

Comment. *Doses and schemes of administration of biological drugs for supportive therapy are prescribed in accordance with the instructions for use.*

For patients with active CD when infliximab is prescribed**, it is **recommended** to combine it with thiopurines to increase the treatment effectiveness [87-90].

Grade A (level of evidence – 1).

Comment. *For other biological drugs, the feasibility of such a combination is not proven.*

The administration of combination therapy remains at the discretion of the attending physician.

* It is **recommended** that patients with primary ineffectiveness of any biological drugs change therapy for a drug of another class to achieve remission [91-93].

Grade A (level of evidence – 1).

Comment. *Changefor a drug of the same class is possible, but its effectiveness is lower than change for another class of drugs.*

* It is **recommended** for patients with loss of response to treatment with any biological drugs (CD relapse on a background of the previously achieved remission) to conduct thetherapy optimization with the interval reduction ofinjections or the dose increase of the same drug, according to the usage instructions, or the therapy change for another drug [80-82,92,94-96].

Grade A (level of evidence – 1).

Surgery is **recommended** for patients with active CD when conservative therapy is ineffective [97-98].

Grade A (level of evidence – 1).

3.1.3 The colorectal CD of any site

Patients with mild and moderate exacerbation are**recommended** to be treated with systemic GCS (prednisone** or equivalent doses of other GCSs) orally [73-75].

Grade A (level of evidence – 1).

Comment. *The dose of prednisone for this site and severity is 1 mg/kg of body weight.*

The therapeutic effect is evaluated after 2-4 weeks with a further reduction in the GCS dose by 5 mg in 5-7 days before complete withdrawal against the background of continued immunosuppressant therapy.

The total duration of GCS therapy should not exceed 12 weeks.

Patients with severe exacerbation are **recommended** to be treated with systemic GCS (prednisone** or

equivalent doses of other GCSs) orally or intravenously [73-75].

Grade A (level of evidence – 1).

Comment. *The dose of prednisone for this site and severity is 2 mg/kg of body weight.*

The therapeutic effect is evaluated after 2-4 weeks with a further reduction in the GCS dose by 5 mg in 5-7 days before complete withdrawal against the background of continued immunosuppressant therapy.

The total duration of GCS therapy should not exceed 12 weeks.

In this group of patients, it is **recommended** to prescribe immunosuppressants simultaneously with GCS: AZA** (2-2.5 mg/kg) or #MP** (1.5 mg/kg), and if thiopurines are intolerable, #MT** (25 mg/weekper cutaneous or intramuscular 1 time a week) [67-69].

Grade A (level of evidence – 1).

In this group of patients with signs of active systemic inflammation, the threat of sepsis and/or the presence of infiltrate and/or purulent complications, it is **recommended** to add antibiotics [76-79].

Grade B (level of evidence – 3).

This group of patients receiving supportive therapy with immunosuppressors is **recommended** to continue it for at least 4 years to maintain stable remission [11,70-72].

Grade C (level of evidence – 5).

In patients with active CD with steroid resistance, steroid dependence, intolerance to GCS or with non-effectiveness of/intolerance to immunosuppressors, is **recommended** to take the biological therapy in the form of an induction course (infliximab**, adalimumab**, certolizumab pegol**, ustikinumab** or vedolizumab**) [80-83].

Grade C (level of evidence – 4).

Comment. *Doses and administration schemes of biological drugs are prescribed in accordance with the instructions for use.*

The absence of a primary response to biological 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.

All biological drugs are approximately the same in effectiveness, so they can be prescribed as first-line therapy with the same probability.

Patients who have reached remission with any biological drugs are **recommended** to change for supportive therapy with the same drug (with or without immunosuppressors) [84-86].

Grade A (level of evidence – 1).

Comment. *Doses of biological drugs for supportive therapy are prescribed in accordance with the instructions for use.*

For patients with active CD, when infliximab is prescribed**, it is **recommended** to combine it with thiopurines to increase the treatment effectiveness [87-89].

Grade A (level of evidence – 1).

Comment*. For other biological remedies, the feasibility of such a combination is not proven. The administration of combination therapy remains at the discretion of the attending physician.*

It is **recommended** that patients with primary ineffectiveness of any biological drugs change therapy for a drug of another class to achieve remission [91-93].

Grade A (level of evidence – 1).

Comment.*Change for a drug of the same class is possible, but its effectiveness is lower than changing for another class of drugs.*

It is **recommended** for patients with loss of response to treatment with any biological drugs (CD relapse on the background of the previously achieved remission) to conduct therapy optimization withthe interval reduction of injection or the dose increase of the same drug according to the usage instructions or the therapy change for another drug [80-82,92,94-96].

Grade A (level of evidence – 1).

Surgery is **recommended** for patients with active CD when conservative therapy is ineffective [97-98].

Grade A (level of evidence – 1a).

3.1.4 CD of the small intestine (except terminal ileitis)

Patients with mild CD with limited lesions are **recommended**to take mesalazine therapy with preferential release in the small intestine at a dose of 4 g orally [99,100].

Grade C (level of evidence – 5).

Comment.*The therapeutic effect is evaluated after 2-4 weeks.*

Patients who have reached remission during themesalazine therapy with preferential release in the small intestine are **recommended** to take supportive therapy at a dose of 4g orally [99,100].

Grade C (level of evidence – 5).

Patients with ineffective mesalazin therapy are **recommended** to be treated with systemic GCSs (prednisolone** or equivalent doses of other GCSs) orally [73-75].

Grade A (level of evidence – 1).

Comment. *The dose of prednisone for this site and severity is 1mg/kg of body weight.*

The therapeutic effect is evaluated after 2-4 weeks.

Patients with moderate CD are commended to be treated with systemic GCSs (prednisone** or equivalent doses of other GCSs) or ally [73-75].

Grade A (level of evidence – 1).

Comment.*The dose of prednisone for this site and severity is 1mg/kg of body weight.*

The therapeutic effect is evaluated after 2-4 weeks.

Patients with severe CD are **recommended** to be treated with systemic GCSs (prednisone** or equivalent doses of other GCSs) intravenously or orally [73-75].

Grade A (level of evidence – 1).

Comment.*The dose of prednisone for this site and severity is 2mg/kg of body weight. The therapeutic effect is evaluated after 2-4 weeks.*

This group of patients is **recommended** to take immunosuppressants simultaneously with GCS: AZA** (2-2.5 mg/kg) or #MP** (1.5 mg/kg), and if thiopurines are intolerable - #MT** (25 mg/week p/c or i/m 1 time a week) [67-69].

Grade A (level of evidence – 1).

This group of patients with signs of systemic inflammation, the threat of sepsis and/or the presence of abdominal mass and/or purulent complications is **recommended** to add antibiotics [76-79].

Grade B (level of evidence – 3).

Comment. *Is* ***recommended****the administration of metronidazole 1g/day + fluoroquinolones 1 g/day for 10-14 days orally or parenterally. The further transition to long-term (up to 3 months) oral medication is possible.*

This group of patients receiving anti-recurrent therapy with immunosuppressors is **recommended** to continue it for at least 4 years to maintain stable remission [11,70-72].

Grade A (level of evidence – 1).

A group of the active CD patients with steroid resistance, steroid dependence, intolerance to GCS, or with ineffectiveness (relapse 3-6 months after the GCS cancellation on the background of AZA**/#MP**) or intolerance to immunosuppressors, is **recommended**to have the biological therapy in the form of an induction course (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab** or vedolizumab**) with subsequent transition to long - term (multi - year) supportive treatment [80-83].

Grade C (level of evidence – 3).

Comment*. Doses and administration schemes of biological drugs are prescribed in accordance with the instructions for use. The absence of a primary response to the biological 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. All biological drugs are approximately the same in effectiveness, so they can be prescribed as first-line therapy with the same probability.*

Patients who have reached remission with any biological drugs are **recommended** to change for supportive therapy with the same drug (with or without immunosuppressors) [84-86].

Grade A (level of evidence – 1).

Comment*. Doses of biological drugs for supportive therapy are prescribed in accordance with the instructions for use.*

For patients with active CD when infliximab is prescribed**, it is **recommended** to combine it with thiopurines to increase the treatment effectiveness [87-90].

Grade A (level of evidence – 1).

Comment*. For other biological drugs the feasibility of such a combination is not proven. The administration of combination therapy remains at the discretion of the attending physician.*

*It is **recommended** that patients with primary ineffectiveness of anybiological drugs change therapy for a drug of another class to achieve remission [91-93].

Grade A (level of evidence – 1).

***Comment**. Change for a drug of the same class is possible, but its effectiveness is lower than changing for another class of drugs.*

*It is **recommended** for patients with loss of response to treatment with any biological drugs (CD relapse on the background of the previously achieved remission) to have the therapy optimization with the interval reduction or the dose increase of taking the same drug, according to the usage instructions, or to change therapy for another drug [80-82,92,94-96].

Grade A (level of evidence – 1).

Surgery is **recommended** for patients with active CD when conservative therapy is ineffective [97,98].

Grade A (level of evidence – 1).

3.1.5. CD with esophagus, stomach and duodenum lesions

For patients with an active CD with a lesion ofesophagus, stomach and duodenum, in order to achieve remission, the initial therapy with systemic GCS in combination with proton pump inhibitors is **recommended** [13].

Grade C (level of evidence – 5).

***Comment**.There are currently no controlled studies on the effectiveness of medication remedies for the CD treatment with upper GIT lesions.*

In the case of refractory course, a good effect of biological therapy was observed [13].

*This group of patients simultaneously with GCS is **recommended** to take immunosuppressors: AZA** (2-2.5 mg / kg) or #MP** (1.5 mg/kg), and if thiopurines are intolerable - #MT** (25 mg/weekpercutaneous or intramuscular1 time a week) [67-69].

Grade A (level of evidence – 1).

*This group of patients receiving antirecurrent therapy with immunosuppressors is **recommended** to continue it for at least 4 years to maintain stable remission [11,70-72].

Grade A (level of evidence – 1).

*A group of patients with active CD with steroid resistance, steroid dependence, intolerance to GCS, or if immunosuppressors are ineffective/intolerable, the biological therapy similar to situations with other CD sites is **recommended** [80-90].

Grade C (level of evidence – 3).

*Patients with active CD with inefficient conservative treatment are **recommended**to have surgery [97-98].

Grade A (level of evidence – 1).

3.1.6 Severe course of active CD of any site

Patients with severe CD are **recommended** to be treated with systemic GCSs (prednisone** or equivalent doses of other GCSs) intravenously or orally [73,74].

Grade A (level of evidence – 1).

***Comment**. The dose of prednisone for this site and severity is 1-2 mg/kg of body weight.*

The therapeutic effect is evaluated in 2-4 weeks.

In this group of patients, it is **recommended** to prescribe immunosuppressants simultaneously with GCS: AZA** (2-2.5 mg/kg) or #MP** (1.5 mg/kg), and if thiopurines are intolerable, #MT** (25 mg/week p/c or i/m 1 time a week) [67-69].

Grade A (level of evidence – 1).

This group of patients with signs of systemic inflammation, the threat of sepsis and/or the presence of infiltrate, and/or purulent complications is **recommended** to add antibiotics [76-79].

Grade B (level of evidence – 3).

***Comment**. It is **recommended** to use metronidazole 1g/day + fluoroquinolones 1 g/day for 10-14 days orally or parenterally. The further change for long-term (up to 3 months) oral medication is possible.*

This group of patients receiving anti-inflammatory therapy with immunosuppressors is **recommended** to continue it for at least 4 years to maintain stable remission [11,70-72].

Grade C (level of evidence – 5).

The group of patients with active CDwith steroid resistance, steroid dependence, intolerance to GIS, or inefficiency (relapse after 3-6 months after the GCS withdrawal on the background of ASA**/#MP**), or intolerance to immunosuppressive drugs, is **recommended** to take biological treatment in the form of an induction course (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab** or vedolizumab**) [80-83].

Grade C (level of evidence – 3).

Comment*. Doses and schemes of administration of biological drugs are prescribed in accordance with the instructions for use. The absence of a primary response to biological therapy is determined after the induction course (depending on the drug). In the presence of negative dynamics, the effectiveness of the drug is evaluated earlier. All biological drugs are approximately the same in effectiveness, so they can be prescribed as first-line therapy with the same probability.*

In this group of patients with an early relapse of the disease within 6 months, treatment is **recommended** to start immediately with biological drugs in combination with systemic corticosteroids in combination with or without immunosuppressants [11].

Grade C (level of evidence – 5).

Comment*. Repeated courses of GCS can be prescribed only if it is impossible to use biological drugs.*

Patients who have reached remission with any biological drugs are **recommended** to change for supportive therapy with the same drug (with or without immunosuppressors) [84-86].

Grade A (level of evidence – 1).

Comment*. Doses of biological drugs for supportive therapy are prescribed in accordance with the instructions for use.*

For patients with active CD when infliximab is prescribed**, it is **recommended** to combine it with thiopurines to increase the treatment effectiveness [87-90].

Grade A (level of evidence – 1).

Comment*. For other biological drugs, the feasibility of such a combination is not proven. The administration of combination therapy remains at the discretion of the attending physician.*

*It is **recommended** that patients with primary ineffectiveness of any biological drugs change therapy for a drug of another class to achieve remission [91-93].

Grade A (level of evidence – 1).

Comment*.Change for a drug of the same class is possible, but its effectiveness is lower than changing for another class of drugs.*

*It is **recommended** that patients who have lost their response to therapy with any biologics (relapsing CD against the background of the previously achieved remission) have the therapy optimization by reducing the intervals or increasing the dose of injection of the same drug according to the usage instructions,or change therapy for another drug [80-82,92, 94-96].

Grade A (level of evidence – 1).

Surgical treatment is **recommended** for patients with active CD when conservative therapy is ineffective [97,98].

Grade A (level of evidence – 1).

3.1.7 CD with perianal lesions

Perianal lesions in CD often require surgical treatment, which is discussed in Section 3.2.5 "Treatment of CD with perianal lesions".

In all patients with perianal CD lesions, if there is no indication for surgical treatment or after it, it is **recommended** to prescribe immunosuppressors (AZA**, #MP**, #MT**) and/or biological drugs (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab** or vedolizumab) in standard doses [16,101,102].

Grade C (level of evidence – 5).

Patients with perianal CD lesions are **recommended** to take metronidazole 1g/day and/or ciprofloxacin 1g/day [16,17,102,103].

Grade B (level of evidence – 2).

Comment*. Antibiotics are prescribed for a long time (up to 6 months or until side effects appear).*

In patients with perianal manifestations of CD, it is **recommended** to add to the therapy metronidazole in the form of candles and ointments [16,102,104].

Grade B (level of evidence – 2).
In patients with perianal manifestations of CD, in the presence of anal fissures, surgical intervention is not **recommended**, and preference is given to the above described local conservative therapy [16,102,104].
Grade B (level of evidence – 2).

3.1.8 Monitoring the effectiveness and side effects of medication therapy

*For all patients it is **recommended** to examine calprotectin in the feces [105-108] to monitor thetreatment effectiveness with any drugs.
Grade B (level of evidence – 2).
Comment.*The frequency of monitoring of 1 time in 3 months allows you to timely (before the onset of the disease symptoms) detect reactivation of the intestine inflammation.*
*In order to monitor the treatment effectiveness with any medications, the endoscopy is **recommended** for all patients 6-9 months after the therapy administration [109].
Grade B (level of evidence – 3).
*In order to monitor the treatment effectiveness with any medications, all patientsare **recommended** to undergo visualizing methods (CT or MRI of the intestines) once a year [110].
Grade B (level of evidence – 3).
*Patients are **recommended** to annually undergo local examination of the perianal area and finger examination of the rectum to exclude perianal complications, as well as, if necessary, transrectal US (if an expert assessment is available) [11,111].
Grade C (level of evidence – 5).
*Patients with a dynamic increase in the level of inflammation markers (C-reactive protein, fecal calprotectin) are **recommended** to under go (ileo) colonoscopy to have the disease activity assessed [112].
Grade A (level of evidence – 1).
Comment*. Routine (annual) endoscopy in the absence of clinical indications (doubts about the diagnosis, the need to exclude concomitant conditions, increasing clinical manifestations, suspected complications) is not required in most cases. If there are no indications associated with CD, the frequency of (ileo) colonoscopy is determined by clinical recommendations for early detection of malignant neoplasms of the colon.*
*Patients receiving immunosuppressants are **recommended** to have a monthly test of the level of red blood cells, white blood cells, blood platelets, free and bound bilirubin, creatinine, urea, determining the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and amylase in the blood to assess liver function [11].
Grade C (level of evidence – 5).
*Patients prior prescribing biological therapy and further every 6 months are **recommended** to consult with a phthisiatrician and to have screening for tuberculosis (a quantiferon test, and if it is impossible, an intradermal test with a tuberculosis allergen – the Mantoux test, thediaskin test) for the diagnosis of tuberculosis [113].
Grade C (level of evidence – 5).
Patients prior to prescribing immunosuppressive therapy, including biological agents, and during treatment, are **recommended** to screen for the presence of viral hepatitis markers B (HBsAg, anti-HBc, DNA by qualitative method), C (anti-HCV) and human immunodeficiency (anti-HIV), as well as syphilis for the diagnosis of associated diseases in accordance with professional clinical recommendations [114].
Grade C (level of evidence – 5).
Strict compliance with the doses and schedule of administration of biological drugs is **recommended**. Irregular administration of biologics increases the risk of allergic reactions and treatment inefficiency [115].
Grade B (level of evidence – 2).
Comment*. Interruptions in treatment without medical indications are unacceptable.*

3.2 Surgery for CD

Most patients with CD have at least one surgical intervention on the GIT during their lifetime. Failure 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, performing organ – preserving procedures (stricturoplasty, stricture dilation) [97-87].
In patients with a complicated CD who have undergone surgical treatment, the use of biological therapy in the history is associated with an increase in postoperative septic complications.
In this regard, it is **recommended** to use caution when prescribing biological therapy in patients who are scheduled for surgical treatment.
At the same time, the safe period of time for withdrawal of the biological drug before surgery is unknown [116-119].
Grade A (level of evidence – 2).
Comment*. Recent results of studies and meta-analyses have shown an increased risk of postoperative complications, such as failure of the anastomosis, occurrence of intra-abdominal abscesses, and poor wound healing in patients who received biological treatment before surgery [116-119]*.

3.2.1 Indications for surgery in CD patients

Indications for surgical procedure in CD are acute and chronic complications, as well as ineffectiveness of conservative therapy and a delay in physical development [97,98].
Acute complications of CD
These include intestinal bleeding, intestinal perforation and toxic dilation of the colon. For intestinal bleeding, emergency surgery is **recommended** if it is impossible to stabilize the patient's hemodynamics, despite transfusions of red blood cells and intensive hemostatic therapy [120,121].
Grade C (level of evidence – 5).
Comment*. Intestinal bleeding is detected when more than 100 ml of blood per day is lost according to objective laboratory methods (scintigraphy, determination of hemoglobin in fecal masses by the hemoglobin cyanide method), or when the volume of fecal masses with a visually determined blood mass is over 800 ml per 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 formation) with mandatory intraoperative entero - or colonoscopy [121]*.
In patients with a complicated form of CD, if threatening symptoms are detected (peritoneal symptoms, free gas in the abdominal cavity according to the data of the abdominal X-ray), emergency surgery is **recommended**, which in such a situation may be limited to resection of the lesion section with the formation of an anastomosis or stoma [122,123].
Grade C (level of evidence – 5).
Comment*. In patients with CD of the small intestine, its perforation into the abdominal cavity is a fairly rare complication and usually occurs either distal or proximal to the section of the intestine with the presence of strictures. In case of emergency surgery, it is* ***recommended*** *to avoid the formation of a primary anastomosis without protection using a double-barrelled ileostomy [123]*.
In patients with CD, in the case of colorectal perforation, subtotal colectomy with end ileostomy is **recommended** as the surgery of choice [123].
Grade C (level of evidence – 4).
In patients with the colorectal CD, complicated by toxic dilatation, subtotal colectomy with end ileostomy is **recommended** for the surgery of choice [123].
Grade C (level of evidence – 4).
Comment*. Toxic dilatation of the colon is a rare complication in CD and is a non-obstructive dilation of the colon up to 6.0 cm or more with intoxication symptoms. Risk factors for toxic dilation include hypokalemia, hypomagnesemia, bowel cleansing for colonoscopy using osmotic laxatives, and taking antidiarrhoeal medications. The development of 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 (increased tachycardia, decreased blood pressure).*
Chronic complications of CD
Chronic complications include strictures, abdominal mass, internal or external intestinal fistulas, and the presence of neoplasia [124].
Ineffectiveness of conservative therapy and delay in physical development
The ineffectiveness of conservative therapy is evidenced by the presence of hormone dependence and

resistance (see Section 1.5Classification of CD).
The manifestation of inadequate drug therapy is also a delay in physical development, most often occurring when the upper GIT is affected.

3.2.2 Surgical treatment of CD in the form of thermal ileitis or ileocolitis

In patients of this group, when ileocecal stricture or ileocecal valve is formed, ileocecal resection with ileo-ascendoanastomosis or stoma (if there is a bowel obstruction) is **recommended** as the surgery of choice [125,126].

Grade C (level of evidence – 4).

Comment*. Approximately 1/3 of all patients with CD have a similar site, which is often complicated by the formation of stricture of ileum or ileocecal valve. In this case, the decisive factor for refusing to perform primary anastomosis is the presence of a bowel obstruction.*

In patients of this group, if strictures are detected after the first course of conservative treatment (i.e., the use of GCS), resection of the affected area of the intestine is **recommended** as the first stage of treatment, rather than a repeat course of conservative (hormonal) therapy [127].

Grade C (level of evidence – 5).

In patients with active CD with abdominal abscess formation, it is **recommended** to prescribe antibiotics, as well as drainage of the abscess or resection of the affected area [127].

Grade C (level of evidence – 5).

Comment*. Drainage can be performed surgically or in specialized units and, if a surgeon is qualified enough, by percutaneous drainage. The latter option can be used only in the absence of stricture of the affected area of the intestine, which determines the need for resection of the affected section.*

In patients with a complicated form of CD, with the presence of short strictures of the jejunum or ileum, including anastomosis strictures after previous resection, an alternative to resection is **recommended** to perform dissection of scarred small intestine strictures (stricturoplasty), which allows avoiding extensive resections of the small intestine [98].

Grade C (level of evidence – 5).

Comment*.This surgery can be performed if the length of the stricture is 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 patients of this group, in the absence of infiltrate and abscess, it is preferable to perform surgery on the small intestine and ileocecal zone by laparoscopic approach [128,129].

Grade C (level of evidence – 5).

Comment*. Simultaneous formation of two anastomoses does not lead to an increase in the rate of postoperative morbidity and the frequency of disease recurrence [130]. The preferred method of forming an anastomosis on the small intestine is the stapler "side-to-side" type, which reduces the probability of its failure [131] and subsequent development of stricture.*

3.2.3 Surgical treatment of colorectal CD

In patients of this group, when the colorectal lesion is limited, resection of the affected segment with the formation of intestinal anastomosis within healthy tissues is **recommended** [132,133].

Grade B (level of evidence – 2).

Comment*. Patients with limited colon lesion (less than a third of the large intestine) do not need a colectomy if they develop CD complications.*

If there is a lesion in the ascending part of the colon, due to anatomical features, right - sided hemicolectomy is indicated (with the preservation of the terminal part of the ileum). If the left flexure and/or descending colon is affected, a left-sided hemicolectomy is performed with the transversosigmoid anastomosis or stoma. When CD is localized in the sigmoid colon, the affected area is resected.

In patients with prevailing CD in the colon with severe clinical manifestations, subtotal colectomy with an end ileostomy is **recommended** as the surgery of choice [98].

Grade C (level of evidence – 5).

Comment*.It is possible not to resect the distal part of the large intestine if there is no pronounced inflammation in it and bring it to the anterior abdominal wall as end sigmostomy, or to suture the stump of the rectum.*

In patients with lesions of the entire large intestine, as well as the presence of severe inflammation in the rectum and severe perianal lesions, colectomy with intersphincteric resection of the rectum with anend ileostomy is **recommended** as an alternative surgery [98].

Grade C (level of evidence – 5).

Comment*. This surgery is performed only in patients with a pronounced inflammatory process in the rectum or severe perianal manifestations, since it makes it impossible to restore anal defecation further.*

In patients with severe perianal lesions, abdominoperineal excision is not **recommended** if possible [98].

Grade C (level of evidence – 5).

Comment*. The abdomino-perineal excision is not appropriate due to extremely low reparative capabilities and the risk of formation of extensive perineal wounds, which later heal for along time, which invalidizes patients and restricts their social activity.*

In patients with total colorectal lesion, in the absence of severe clinical manifestations and minimal activity of inflammatory changes in the rectum, adequate function of intestinal contents retention and the absence of perianal lesions, colectomy with the formation of ileo-rectal anastomosis is **recommended** as the surgery of choice [132].

Grade C (level of evidence – 5).

Comment*.The possibility of forming an intestinal pouch (IPA) in colorectal CD is controversial due to the high rate of complications and the high occurrence of indications for removal of the pouch. At the same time, the average life expectancy of patients after IPA without permanent ileostomy reaches 10 years, which is important for young patients [133]. The main problems that threaten patients with IPA on the background of CD are the development of perianal lesions and CD of the pouch.*

In patients with colorectal CD, loop ileostomy, in order to stop the transit of intestinal contents through the colon, is **recommended** only in extremely emaciated patients and in pregnant women [128].

Grade C (level of evidence – 5).

Comment*. This type of surgery is temporary. Taking into account that the passage through the colon is not always effective in CD, it is necessary to re-discuss the issue of the volume of surgical procedure after conducting an accurate differential diagnosis between the colorectal CD and the UC.*

All these surgeries can be safely performed using laparoscopic approach [134,135].

In patients with colorectal CD, balloon dilatation of colon stenoses (by endoscopic method) is **recommended** for detection of non-stretched stricture [136].

Grade C (level of evidence – 5).

Comment*.This procedure is associated with a higher risk of relapse compared to resection of the affected area of the intestine.*

In patients with colorectal CD, incision of scar strictures (stricturoplasty) is not **recommended** [127,137,138].

Grade B (level of evidence – 2).

3.2.4 Surgery for CD of the upper GIT

In patients of this group, when detecting strictures, infiltrates and interintestinal fistulas in the proximal parts of the small intestine, the formation of bypass anastomoses, dissection of scar strictures (stricturoplasty) or resection of the affected area is **recommended** [98,137,138].

Grade B (level of evidence – 2).

Comment*. Involvement in the inflammatory process of the intestinal area proximal to the terminal ileum often leads to the formation of multiple strictures and fistulas, which causes a poor prognosis of CD and requires surgery.*

In patients of this group, it is **recommended** to make bypass anastomosis only in exceptional cases, since there is a high risk of developing a syndrome of excessive bacterial growth in the disconnected part of the small intestine, as well as the development of cancer. However, extensive resections cause the development of short bowel syndrome [139].

Grade C (level of evidence – 5).

In patients of this group, in the presence of single or multiple short strictures, the surgery of choice may be different options for dissecting scarring strictures of the small intestine (stricturoplasty) [140].

Grade C (level of evidence – 4).

In patients of this group, endoscopic balloon dilation or incision of the scar stricture (stricturoplasty) is

recommended when a gastroduodenal stricture is detected (as a rule in duodenum) [140].
Grade C (level of evidence – 4).

3.2.5 Treatment of CD with perianal lesions (perianal CD)

The surgical approach to should be individual for each patient [101,141].
In patients with perianal manifestations of CD, in the presence of external perianal fistulas, it is **recommended** to eliminate the fistula by excision (using fistulotomy) [142] or its adequate drainage in the presence of abscesses (using the installation of latex drainage setons) [143].
Grade C (level of evidence – 4).
Comment*. Simple fistulas that are not accompanied by any symptoms do not require surgical intervention. Dynamic monitoring against the background of the above described conservative therapy is* ***recommended****. In most cases the indication for the seton installation istrans-and extrasphincter fistulas. In the absence of an inflammatory process in the rectal mucosa, it is possible to perform a reduction of the rectal mucosal flap with plastic surgery of the internal fistula hole [143].*
In patients with perianal manifestations of CD, in the treatment of complex fistulas, their drainage (installation of latex drainage setons) in combination with aggressive medication therapy is **recommended** [16].
Grade C (level of evidence –5).
Comment*. Given the high effectiveness of the biological therapy with proper drainage of complex rectal fistulas, its early administration is justified (infliximab, adalimumab, certolizumab pegol, ustekinumab, vedolizumab). However, complex fistulas with additional cavities and pronounced purulent inflammation are often an indication for diverting ileostoma.*
In patients with perianal manifestations of CD, rectovaginal fistula excision with suturing of the vaginal defect and rectal advancement flapis **recommended** [16].
Grade C (level of evidence –5).
Comment*. Rectovaginal fistulas in most cases require surgery. At the same time, surgical procedure is indicated under the protective ileostomy. Only in certain situations, if there is 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 operation [16].*
In patients with perianal manifestations of CD, in the presence of stricture of the low rectum or anal stenosis, proctosigmoidectomy (or proctectomy) or intrashincteric resection of the rectum is **recommended** [16].
Grade C (level of evidence –5).
Comment*. The most unfavorable factor that increases the likelihood of permanent ileostomy or colostomy is the presence of a stricture of the lowrectum or anal stenosis. In some situations, if there is no active inflammation in the overlying parts of the intestine, it is possible to dilatestricture [16].*

3.2.6 Anti-recurrent therapy after surgical treatment of CD

Even with complete removal of all macroscopically altered parts of the intestine, surgical intervention does not lead to complete recovery: within 5 years, a clinically significant relapse is observed in 28-45% of patients, and within 10 years - in 36-61%, which dictates the need to prescribe or continue anti-recurrent therapy after surgeries for CD [144,145].
Factors that significantly increase the risk of postoperative relapse include: smoking, two or more intestinal resections in the history, extended resections of the small intestine in the history (>50 cm), perianal lesions, and a penetrating phenotype [146].
Depending on the combination of risk factors, as well as on the effectiveness of previous anti-recurrent therapy, patients after surgery should be stratified into groups with different risks of postoperative relapse.
The presence of 2 or more risk factors is associated with a high risk of postoperative relapse:
- smoking;
- perianal lesions of CD;
- penetrating CD;
- extended intestinal resection (over 50 cm);

– previous surgeries;
- early debut of the disease.
Patients from the low-risk group are **recommended** to undergo AZA therapy** (2.0-2.5 mg/kg/day) or #MP** (1.5 mg/kg/day) [147].
Grade B (level of evidence – 2).

Table 4. *Postoperative Crohn's Disease Recurrence Scale by Rutgeerts [149] after terminal ileum resection or ileocaecal resection*

Assessment	Definition
i0	No signs of inflammation
i1	≤5 aphthous ulcers
i2	>5 aphthous ulcers with a normal mucosa between them or extended areas of healthy mucosa between more pronounced ulcers or lesions limited to ileo-colonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, “cobblestone pavement” and/or narrowing of the lumen

Patients with a high risk of relapse are **recommended** to start a course of biological therapy (infliximab**, adalimumab**, certolizumab pegol**, ustekinumab**, vedolizumab**) before conducting a control endoscopic study [148-153].
Grade C (level of evidence – 3).
Comment. *Data on the use of ustekinumab and vedolizumab are not sufficient to assess their effectiveness as a postoperative anti-recurrent therapy.*
Patients with CD are **recommended** to start anti-recurrent therapy 4 weeks after surgery in the absence of postoperative complications [154].
Grade C (level of evidence – 3).
After 6-12 months, all operated patients with CD were **recommended** to undergo a control endoscopy, and if necessary, MRI, CT (Table 4) [155-157].
Grade C (level of evidence – 3).
In operated patients with CD, if it is impossible to visualize the anastomosis zone, it is **recommended** to state the presence or absence of a relapse, based on a combination of radiological data (CT or MRI) and non-invasive markers of inflammation - C-reactive protein, fecal calprotectin, etc. [18,107,108,112,155-157].
Grade C (level of evidence –3).
In patients with CD, if there are no signs of inflammation or inflammatory changes are detected minimal (i1 as per the Rutgeerts scale) (Table 4), the current therapy is **recommended** to continue [149].
Grade C (level of evidence – 5).
In patients with CD in the presence of more pronounced inflammatory changes (i2 - i4), it is **recommended** to strengthen therapy: it is **recommended** to add immunosuppressors in patients who have not previously received them or to conduct biological therapy (adalimumab**, infliximab**, certolizumab pegol**, ustekinumab**, vedolizumab**) in patients who are undergoing supportive therapy with AZA**/#MP** or if it is impossible to prescribe them [147-153].
Grade C (level of evidence – 5).
Comment. *The presence of more pronounced inflammatory changes (i2 - i4) indicates that the therapy is ineffective.*
In the future, in patients with CD, regardless of the nature of the disease course and the clinical manifestation of CD, it is **recommended** to perform a control endoscopy at least once every 1-3 years, following the same algorithm for choosing an anti-recurrent treatment [158].
Grade C (level of evidence – 4).

3.2.7 Ileostomy dysfunction after surgery for CD

Ileostomy dysfunction refers to an increase in the volume of ileostomy discharge of over 1,000 ml per day. Administration of patients with this condition is described in the clinical guidelines “Ulcerative colitis”.

4. MEDICAL REHABILITATION, MEDICAL INDICATIONS AND CONTRAINDICATIONS

TO THE USE OF REHABILITATION METHODS

Medical rehabilitation measures are aimed at preventing complications of conservative treatment and undesirable consequences of surgery.
Mild and moderate functional disorders require treatment on an outpatient basis.
A severe degree of functional impairment, or its absolute failure requires hospitalization in a 24-hour hospital.
In patients who required surgical treatment of complications of CD, rehabilitation is possible in three stages.
The 1st stage – an early rehabilitation is carried out directly after surgerywithin the period from the 2ndto the 14thday. The main task of stage1of rehabilitation is to restore normal functioning of the GIT after surgery.
It is at this stage that urinary disorders are most often detected and should be corrected.
An important role is also assigned to homeostasis control, measures aimed at healing postoperative wounds, relief of postoperative pain, and patient activation.
During this period, general blood test, biochemical blood test, blood coagulogram, and general urine test are monitored.
The 2nd stage of rehabilitation begins after 15 days and continues as long as necessary furthermore.
It is aimed at the final healing of postoperative wounds with control over the activity of the GIT and the other body systems. This stage can be performed as an outpatient, or in a day-time or 24-hourhospital stay.
The 3rd stage of rehabilitation is performed in the late rehabilitation period in patients with both permanent ileostoma and before reconstructive surgery.
The main task at this stage is to compensate for the GIT function, measures aimed at identifying and correcting the anal sphincter function.
As for the anal incontinence, itsreabilitation is possible at stages 2 and 3. In patients after surgery for CD with stoma, there is a decrease in the retention function.
Patients with anal sphincter incontinence, before reconstructive treatment, are **recommended** to undergo pathophysiological test (sphincterometry, pro-filometry, pudendal nerve conduction test) [159].
Grade C (level of evidence – 5).
Patients with the 2nd or 3rd degree anal incontinenceare **recommended** to have reabilitationtreatment, which includes a 10-day cycle of biofeedback therapy and tibial neuromodulation in a day time or 24-hour hospital stay [159,160].
Grade C (level of evidence –4).
Comment. *In the rehabilitation of patients with anal incontinence, according to the literature, the method of biofeedback treatment is widely used.*
It is aimed at improving the contractile ability of the external sphincter and pelvic floor muscles by increasing both the strength and duration of voluntary contraction [159,160].
This non-invasive method involves the body's own resources in the rehabilitation process with the development of correct skills at the level of the formation of new conditioned reflex connections.
The method of tibial neuromodulation is also quite effective.
Neuromodulation is a process in which an electric current along one neural path way modulates pre-existing activity in other neural pathways or centers.
Percutaneous electrical stimulation of the posterior tibial nerve (nervus tibialis) is used for functional diseases of the pelvic organs, since the posterior tibial nerve contains fibers from the II and III sacral segments of the spinal cord, which play a significant role in the innervation of the rectum, bladder and their sphincters.
It is proved that the muscle structures of the divertedanal canal can respond to biofeedback therapy and the conduct of tibial neuromodulation, increasing both the tone and the strength of voluntary contractions [159,160].
Stimulation of the tibial nerve is performed using a skin stimulating electrode, which allows the patient to continue the course of treatment independently at home after a course of preliminary training.
In this case, the course of treatment with daily sessions of stimulation can be extended up to 1-3 months.
The effectiveness of BFB-therapy is monitored before and after each course of procedures by means of a

complex physiological test of the function of the anal sphincter (sphincterometry + physiological test of the reservoir function of the rectum).
When improving the indicators of tone and contractility of the anal sphincters, it is possible to raise the question of stoma reversal.

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

CD is characterized by progressive intestinal lesion. At the time of diagnosis, complications (strictures, fistulas) are detected only in 10-20% of patients, while within 10 years, such complications develop in >90% of patients. Within 10 years, surgical procedure due to complications and/or ineffectiveness of conservative therapy is performed in half of the total number of patients with CD, and 35-60% develop a relapse within 10 years after the surgery. Steroid dependence in CD has been detected at least once in 30% of patients for 10 years [161].
Due to the progressive nature of the disease, patients suffering from CD should receive permanent (lifetime therapy) and undergo regular (lifetime) monitoring of disease activity.
Monitoring of the disease activity is possible not only by instrumental examination methods, but also by laboratory tests (the inflammation markers), primarily the level of fecal calprotectin, the concentration of which in the stool correlates with the degree of ulcerative lesion of the GIT.
The frequency and volume of dispensary surveillance is determined individually, but in most patients, it is **recommended**, with the availability of expert test, to perform abdominal US every 6 months [11,162-165].
Grade C (level of evidence – 5).
Patients are **recommended** to undergo an annual radiology (CT or MR) of the intestines to exclude strictures or other complications [11,110].
Grade C (level of evidence – 5).
Patients are **recommended** to undergo an annual local examination of the perianal area and finger examination of the rectum to exclude perianal complications, as well as, if necessary, transrectal US (if an expert assessment is available) [11,111].
Grade C (level of evidence – 5).
Patients receiving immunosuppressors and/or biologics are **recommended** to be vaccinated as a prevention of opportunistic infections and other complications: recombinant HBV vaccine, polyvalent inactivated pneumococcal vaccine, trivalent inactivated influenza virus vaccine and for women under 26 years of age, in the absence of the virus at the time of screening, vaccination against human papillomavirus is **recommended** [114].
Grade C (level of evidence – 5).
Comment. *Risk factors for opportunistic infections include: taking prednisolone* * 20 mg per day or more for 2 weeks, taking immunosuppressants (AZA**, #MP**, #MT**) and biological drugs, age over 50 years, concomitant diseases (chronic lung diseases, alcoholism, organic brain diseases, diabetes mellitus).*
All patients receiving biological therapy are not **recommended** to change the original drug for a biosimilar, or vice versa, more than once [166].
Grade C (level of evidence – 5).
Comment. *Currently, biosimilars of anti - TNF drugs that are similar to the original biological drugs in terms of efficacy and safety have been registered, but their interchangeability with the original drugs has not been proven at present.*
Given the absence of clinical trials in patients with IBD that have proven the safety and effectiveness of alternating or completely changing from the original drug to bio-analogues and vice versa, such a therapeutic approach is not ***recommended*** *[11].*

6. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care in the framework of clinical testing, in accordance with Federal law No. 323-FZ of 21.11.2011 (ed. from 47 of 25.05.2019) “On the basics of public health

protection in the Russian Federation", is organized and provided:
1) in accordance with the regulations on the organization of medical care by type of medical care, which is approved by the authorized federal executive body;
2) in accordance with the procedures for providing assistance in the profiles"gastroenterology", "coloproctology", mandatory for all medical organizations in the territory of the Russian Federation;
3) based on these clinical recommendations;
4) taking into account the standards of medical care approved by the authorized federal executive body.

Primary specialized medical care is provided by a gastroenterologist, a coloproctologist, and other specialist doctors in medical organizations licensed to provide the appropriate types of medical services.
If a patient is suspected or diagnosed with CD, general practitioners, district therapists, general practitioners (family doctors), specialist doctors, and mid-level medical professionals refer the patient to a medical organization that has an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterology center (unit), an outpatient coloproctology center (unit), and a center for the diagnosis and treatment of inflammatory bowel diseases (if available in the subject, is organized on a functional basis) to provide it with primary specialized health care.
Consultation in these structural units of healthcare organizations must be held no later than 15 work days from the date of issue of referral, and in cases of severe CD forms - no later than 3 work days from the date of referral for consultation.
Gastroenterologist, coloproctologist of a medical organization, which has got an office of the gastroenterologist, ofcoloproctologist, outpatient gastroenterology center (unit),outpatientcoloproctology center (unit), center for diagnosis and treatment of inflammatory bowel diseases, organize the implementation of diagnostic tests required for diagnosis, including determining the extent of pronounced inflammatory process, extent of lesion, the presence of intestinal and extraintestinal manifestations, including taking a biopsy.
In case of failure to perform diagnostic tests required for diagnosis, including determining the extent of pronounced inflammatory process, extent of lesion, the presence of intestinal and extraintestinal manifestations, including taking a biopsy, as well as with the indications for medical care in day hospital conditions, the patient is referred by the attending physician to the gastroenterology unit, coloproctology unit,centre for diagnostics and treatment of inflammatory bowel diseases or other medical organization which provides medical care in day hospital conditions to patients in the profile of "gastroenterology", "coloproctology".
If a patient is suspected and/or diagnosed with CD in the course of emergency medical care, sucha patient is transferred or referred to medical organizations that provide medical care in the "gastroenterology", "coloproctology" profile to determine the treatment modalities and the need to apply additional methods of specialized treatment, including targeted biological therapy.
A gastroenterologist, a coloproctologist of a medical organization that has got an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterological center (unit), an outpatient coloproctological center (unit), a center for the diagnosis and treatment of inflammatory bowel diseases refers the patient to medical organizations that have a gastroenterological unit and/or coloproctological unit, and/or a center for diagnosis and treatment of inflammatory bowel diseases in order to specify the diagnosis (if it is impossible to diagnosein the primary specialized health care) and to provide specialized, including high-tech, medical care.
The start date for specialized medical care, with the exception of high-tech medical care, is determined by the decision of the commission for selecting patients for hospitalization, depending on the severity of CD, the nature of the course, and the prevalence of the inflammatory process.
The period shall 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 gastroenterological unit and/or coloproctology unit, and/or a center for the diagnosis and treatment of inflammatory bowel diseases, licensed, having the required material technical base, employing certified specialists, working in a24-hour and day hospital. It provides prevention, diagnosis, treatment of CD that require the use of special methods and complex unique medical technologies, as well as medical rehabilitation.
Indications for hospitalization in a 24-hour or day hospital of a medical organization that provides

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 the emergency and urgent form;
2) the presence of complications of CD treatment (surgery, biological therapy, hormonal and cytostatic therapy, etc.).

The indication for hospitalization to a medical organization in a planned form is:
1) the need to perform complex 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), which requires surveillance in a round-the-clock or day hospital.

An indication for the patient's discharge from a 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 24-hour or day hospital, provided that there are no treatment complications that require 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 council of the medical organization that provides treatment for Crohn's disease, provided that there are no complications of the underlying disease and/or treatment that requires medical correction and/or medical interventions in hospital conditions;
3) the need to transfer the patient to another medical organization in the appropriate field of medical care.

The conclusion on the feasibility of transferring a patient to a specialized medical organization is made after a preliminary consultation on the provided medical documents and/or a preliminary examination of the patient by medical specialists of the medical organization to which the transfer is planned.

7. ADDITIONAL INFORMATION (INCLUDING FACTORS THAT AFFECTON THE OUTCOME OF A DISEASE OR CONDITION)

Prognostically unfavorable factors in CD are smoking, the debut of the disease in childhood, perianal lesions, the penetrating phenotype of the disease, and common small bowel disease. The patient-smoker must necessarily be interviewed about the need to stop smoking.
Pregnancy planning should be carried out during the period of IBD remission, which can improve pregnancy outcomes. The use of most IBD medications 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 phto-lat. Cancellation of anti-TNF is possible only in a limited number of patients with a low risk of IBD reactivation. Treatment with genetically engineered biological drugs that are not contraindicated in pregnancy (see instructions for use of the drug), may be continued if the benefit to the mother exceeds the potential risks to the fetus.

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