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Prevention of Recurrence of Crohn's Disease

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Abstract: The use of the developed treatment and diagnostic algorithm for the prevention of relapse of Crohn's disease made it possible to reduce the frequency of its development in mild form from 31% to 27.5%, in moderate form from 21.4% to 12.5% and completely avoid its severe forms.

Keywords: Crohn's disease, generalization of infection, prognosis, prevention

Relevance. Less than 100 years have passed since the first report of Crohn's disease (CD), which was presented in 1932 by the American gastroenterologist B.B. Crohn under the term "terminal ileitis." More in-depth research in this area led to the recognition of CD as an independent nosological entity in which the entire intestine is affected (1,3,9). However, the ileal region of the small intestine remains the predominant site of damage in CD.

The prevalence of CD in Europe ranges from less than 10 to approximately 150 cases per 100,000 inhabitants (2,4,10). An adjusted prevalence of 133 cases of CD per 100,000 population was found in California, USA, at the beginning of this century (8). One study conducted in South Korea showed a prevalence of 112 cases of CD per 100,000 population (5.7,11). A recent study of the prevalence of Crohn's disease in Uzbekistan, conducted by the Republican Center for Proctology of the Ministry of Health of the Republic of Uzbekistan, revealed a rate of 80 cases per 100,000 population (2.4). Based on the available data, it can be concluded that Crohn's disease is a very common disease today.

Treatment of Crohn's disease is multidisciplinary (10). While drug therapy for Crohn's disease is aimed at healing the mucosa and reducing symptoms, surgical intervention plays a key role in the treatment of complications such as stenosis, perforation, intestinal fistulas, and abscesses of the abdominal cavity and cellular spaces (1,3,7).

Recurrence of Crohn's disease in the postoperative period develops in more than 80% of patients who underwent surgery (1,2,4).

Numerous studies in this area have allowed the development of various surgical strategies aimed at improving treatment outcomes and reducing the incidence of Crohn's disease recurrence in the postoperative period (6,12).

Some improvement in surgical outcomes for Crohn's disease was achieved after the introduction of laparoscopic technology. However, even this technology failed to reduce the incidence of Crohn's disease recurrence in the postoperative period (8,10). All of this has led to the development of a specific concept regarding the purpose of Crohn's surgery as a means of delaying the onset of recurrence, which is considered inevitable in the long term.

The aim of the study is to improve treatment outcomes for patients with Crohn's disease by developing pathogenetically substantiated clinical and immunological criteria for predicting and preventing recurrence of this disease.

Material and methods. The results of a comprehensive examination and treatment of 82 patients with Crohn's disease (CD) are analyzed. Patients were divided into two study groups: a control group (42 patients) and a study group (40 patients). A distinctive feature of the study groups was the use of different approaches to predicting and preventing CD recurrence. Twenty healthy individuals, deemed practically healthy by a medical commission, were examined as reference values. Males predominated in the control and study groups (59% and 55%, respectively), and the average age ranged between young and middle-aged (according to the WHO classification).

CD predominantly affected the terminal ileum (61%). Combined lesions of the terminal ileum and colon were diagnosed in 24.4% of patients. Isolated colonic lesions were diagnosed in 14.6% of patients. In each study group, patients with lesions of the terminal ileum predominated. Perianal lesions were predominantly characterized by the presence of rectal fistulas (75%), anal fissures (37.5%), stenosis of the lower ampullary rectum (8.3%), anal strictures (4.2%), and non-healing wounds (4.2%).

The chronology of the disease course depended on the affected part of the intestine in CD. Thus, the shortest time was required for damage to the terminal ileum (89.7 ± 13.4 months). For CD to develop with damage to the large intestine, the disease course averaged 121.3 ± 33 months. Patients with a CD chronology of 179.8 ± 43.8 months were diagnosed with combined lesions of the terminal ileum and large intestine.

Among the surgical operations undergone in the anamnesis, appendectomy should be highlighted, which was performed in 9 patients (21.4%) of the control group and in 15 patients (37.6%) of the main group. Operations aimed at opening acute paraproctitis were performed significantly more often (in 35.7% of cases in the control group and 40% of cases in the main group of patients, respectively). Also, the list of operations undergone included excision of pararectal fistulas (in 16.7% of cases in the control group and 22.5% of cases in the main group of patients, respectively), excision of anal fissures (in 11.9% of cases in the control group and 15% of cases in the main group of patients, respectively), diagnostic laparotomy (in the control group 7.1% of cases and 15% of cases in the main group of patients, respectively) and laparoscopy (in the control group 14.3% of cases and 20% of cases in the main group of patients, respectively). In 54.9% of cases, patients had previously received hormonal therapy, with steroid resistance diagnosed in 53.7%.

Results and discussion. The obtained results on the frequency and nature of Crohn's disease recurrence in the postoperative period, on the one hand, and the characteristics of changes in cellular-humoral immunity indicators over the course of the study, on the other, created the conditions for developing a picture of these relationships. This will allow us to identify criteria for predicting the development of Crohn's disease recurrence and options for preventing it.

The causes of Crohn's disease recurrence and the criteria (markers) for predicting them were identified through direct and cross-correlation analysis of the obtained data, dividing them into the early and late postoperative periods.

The overall dynamics of the postoperative period in Crohn's disease were characterized by high correlations between CD16+/CD3+ cells (R=0.905) and CD3+/CD4+ cells (R=0.781).

We also found a high inverse correlation between the level of change in CD3+/CD8+ cells (R=-0.745), CD25+/CD83+ cells (R=-0.762), CD16+/CD25+ cells (R=-0.737), and CD3+/CD25+ cells (R=-0.699).

In the remaining cases, the correlation was moderate (CD4+/CD8+ cells, R=-0.576; CD8+/CD83+ cells, R=-0.530 and CD3+/CD83+ cells, R=0.595) or low (CD3+/CD16+ cells, R=0.450; CD4+/CD16+ cells, R=-0.174; CD8+/CD16+ cells, R=-0.341; CD4+/CD25+ cells, R=-0.290; CD8+/CD25+ cells, R=0.208; CD4+/CD83+ cells, R=0.023).

Overall, of the 15 indicators, the presence of a low correlation was noted in the majority (40%).

The correlation between the dynamics of CD3+ and CD4+ cell counts in the blood of patients with Crohn's disease in the postoperative period, both in the remission and relapse phases, showed no significant differences, other than a decrease or increase in the ratio. This pattern of changes was apparently associated with the early response of the body's immune system in differentiating naive T lymphocytes from T helper cells when macrophages present primary antigens.

The cross-correlation of the overall dynamics of CD8+ cell counts showed a high direct correlation (R = 0.877) between patients with different phases of Crohn's disease. In other words, relapse and remission of Crohn's disease share the same mechanism of cytotoxic cell activation in both the first

and second stages of the immune response and in the perception of antigen presentation by macrophages. Our findings are supported by changes in the CD8+ correlation coefficient in the early postoperative period (R = 1.000). The pattern of changes was so similar that it likely determined the minimal rate of Crohn's disease recurrence during this observation period.

In the late postoperative period, the correlation coefficient for changes in CD8+ cells in the blood was also positive (R = 0.979), which likely determined the role of cytostatic T cells in the cellular immune system and its relationship with Th1 T helper cells.

The overall dynamics of CD16+ cells in the postoperative period in patients in the study and comparison groups were characterized by a high direct correlation (R = 0.782). A separate analysis by postoperative period revealed that, in the early stages, the correlation between Crohn's disease remission and relapse was identical, differentiated only by the level of values. In the late postoperative period, the correlation became inverse between patients with different stages of Crohn's disease (R = -0.243).

Thus, the involvement of T-suppressors in the development of Crohn's disease relapse was minimal, and its contribution to the immune response was characterized by the overall course of the postoperative period. Meanwhile, natural killer cell activity was more significant in the late postoperative period, during which we observed a high proportion of Crohn's disease relapses. These changes were likely associated with the active recruitment of CD16+ cells into the immune response specifically in patients with Crohn's disease relapse in the late postoperative period.

The correlation between the overall dynamics of CD25+ and CD83+ cell changes between patients at different stages of Crohn's disease was characterized by low positive values (R = 0.479 and R = 0.202, respectively), which was apparently due to the different directions of their expression both at different stages of the disease and at different periods of the postoperative course of the disease.

We identified different directions of expression of T-regulatory cells (CD25+ cells) and dendritic cells (CD83+ cells) among patients with Crohn's disease, regardless of the disease stage. The role and significance of these lymphocytes in the timing of Crohn's disease relapse also varied. Thus, in the early postoperative period, a high correlation was found between patients at different stages of Crohn's disease for the dynamics of CD83+ cell changes, which was inverse (R = -0.905). In contrast, the dynamics of CD25+ cell changes were more dependent in the late postoperative period, with a high direct correlation (R=0.801).

Analysis of the dynamics of blood cytokine changes based on the correlation coefficient of 15 indicators revealed a high direct correlation in the overall dynamics of the postoperative period in 10 cases (66.7%). In the remaining 5 cases, the correlation was inverse and related to the dynamics of transforming growth factor. The greatest difference was observed between the dynamics of TGF-β and IL-4 (R=-0.562), followed in descending order by TNF-α (R=-0.415), IL-21 (R=-0.402), INF-γ (R=-0.396), and IL-17 (R=-0.304).

It is noteworthy that we observed a stronger correlation value for tissue growth factor in the early postoperative period than in the late postoperative period, indicating the potential use of this marker in predicting Crohn's disease recurrence (Table 1).

Presentation of antigens by dendritic cells leads to the differentiation of Th17 and T-regulatory cells. In this case, everything depends on adequate TGF-β levels, low levels of which stimulate Th17 cell expression and the synthesis of IL-17, which was elevated in patients with relapsed Crohn's disease. The subsequent reaction leads to increased production of IL-21, which induces the recruitment of immune cells to peripheral tissues and simultaneously activates natural killer cells (NF-κB), promoting apoptosis and the release of TNF-α. Overall, it can be noted that Th17 cells and their derived cytokines play an important role in the early diagnosis and prognosis of Crohn's disease relapse.

Th17 cells and T-regulatory lymphocytes exist in a dynamic equilibrium under normal conditions. This balance is disrupted by an excessive increase in Th17 cells, excessive immunogenicity, and decreased or impaired T-regulatory lymphocyte function, leading to relapse of Crohn's disease.

Primary T cells differentiate into Th17 cells at low TGF-β concentrations. However, our studies have shown that Th17 cell production is inhibited at high TGF-β concentrations. It is the sufficient production of T-regulatory lymphocytes under the influence of TGF-β that leads to suppression of the immune response and, consequently, remission of Crohn's disease. Thus, regulating the balance between Th17/T-regulatory cells may offer a new method for the prevention and treatment of Crohn's disease.

Thus, in Crohn's disease, an imbalance occurs between Th1/Th2 cells and Th17/T-regulatory cells, the intensity of which determines the outcome of the disease (remission or relapse). Immunological disturbances in Crohn's disease relapse are based on mechanisms that generate an autoimmune response due to increased cell apoptosis, accompanied by the expression of proinflammatory cytokines TNF-α, IL-17, and IL-21, through the induction of natural killer cells against a background of low TGF-β concentrations. Relatively high stimulation of TGF-β production by naive T-helper cells stimulates T-regulatory lymphocytes, enhancing their role in tissue regeneration and, accordingly, creating favorable conditions for the onset of remission in Crohn's disease.

When developing a treatment and diagnostic algorithm for preventing Crohn's disease relapse, the clinical manifestations of the disease should be considered alongside the results of immunological studies. These clinical manifestations, based on immediate treatment results, can determine the likelihood of unsatisfactory outcomes.

Certain difficulties in choosing drug therapy for Crohn's disease include the limited use of hormonal therapy due to the development of resistance to this type of treatment. Hormonal dependence also creates side effects of the treatment.

An attempt to analyze the pathogenesis of immunological disturbances during the development and recurrence of Crohn's disease revealed the significance of changes in cellular immunity in terms of altered mutual regulation, resulting in an imbalance in the blood cytokine profile, specifically high levels of TNF-α, IL-17, and IL-21 and low levels of TGF-β.

As demonstrated by our studies in the control group of patients, stool frequency, body temperature, heart rate, and the presence of a history of early postoperative complications according to the Clavien-Dindo classification can be identified as clinical parameters predicting the likelihood of Crohn's disease recurrence after surgery. Body temperature and daily stool volume were more significant than heart rate and the presence of postoperative complications. However, the latter criterion was only slightly more significant than the former. In this case, a detailed breakdown of complications revealed the significance of grade III complications, which are most likely to cause Crohn's disease recurrence (grade IIIa complications accounted for 37.9%, while grade IIIb complications accounted for 63.1%). The number of stools per day also varied significantly, ranging from 4.6±0.5 times per day.

The regression differences in the significance of the main immunological criteria for predicting Crohn's disease recurrence in the postoperative period were not unambiguous (Table 3). This was apparently due to the different levels of dispersion of values in the postoperative period and the differences in the manifestation of Crohn's disease.

Distribution parameters revealed high sensitivity to TGF-β, moderate sensitivity to TNF-α and IL-21, and relatively low sensitivity to IL-17. Moreover, the confidence interval for the selected values was significant in all cases ($p < 0.001$).

This allowed us to grade these indicators as criteria for the probability of Crohn's disease recurrence in the postoperative period according to the following parameters, which must be assessed dynamically (dynamic prognosis).

The prognostic probability of Crohn's disease recurrence will be low with a stool frequency of up to 2 times per day; normal body temperature and heart rate; The absence of postoperative complications or their presence only at level I of the Clavien-Dindo classification; deviations in the blood level of no more than one of the following parameters TGF-β, TNF-α, IL-71 and IL-21 by more than 10% from the reference value.

The prognostic probability of Crohn's disease recurrence is high with a stool frequency of 3 or more times per day; the presence of persistent subfebrile body temperature; the presence of tachycardia; the presence of postoperative complications at level II or higher of the Clavien-Dindo classification; deviations in the blood level of two or more of the following parameters TGF-β, TNF-α, IL-71 and IL-21 by more than 10% from the reference value.

Prophylactic measures for Crohn's disease recurrence were initiated during surgery by intramesenteric administration of Infliximab (Adalimumab) diluted in saline at a dose of 5 mg per 1 kg of the patient's weight. Intramesenteric administration of this drug was technically performed in the affected intestinal area after resection. If the patient had multiple intestinal lesions, the dose was divided evenly by the number of lesions.

This drug is known to have affinity for TNF-α and, accordingly, rapidly binds to this proinflammatory cytokine, reducing its functional activity.

Postoperatively, this drug is administered intravenously at a rate of no more than 2 ml per minute. The total infusion time should not be less than 2 hours. A system with a pyrogen-free filter and low protein-binding activity was used for intravenous infusion.

For patients with a high risk of Crohn's disease recurrence, Infliximab (Adalimumab) was administered every 5 days at a dose of 10 mg per kg of body weight until prognostic parameters decreased. Entyvio® (vedolizumab) was administered intravenously at a dose of 300 mg every 7 days. If the risk of Crohn's disease recurrence was low, infliximab (adalimumab) was administered every 10 days at a dose of 5 mg per 1 kg of body weight until normal prognostic parameters were achieved. Entyvio® (vedolizumab) was administered intravenously at a dose of 300 mg every 14 days.

In the absence of a risk of Crohn's disease recurrence, conservative therapy was continued with prednisolone at a dose of 1 mg/kg per day (as tapered before discontinuation) and azathioprine at a dose of 3 mg per day in tablet form. Patients remained under dynamic monitoring.

This treatment regimen was also acceptable for active forms of Crohn's disease, if detected subsequently.

The treatment and diagnostic algorithm we developed not only allows us to predict and prevent recurrence of Crohn's disease but also to determine the timing of reconstructive surgeries, which have a greater chance of achieving effective results.

We applied the methods we developed for predicting and preventing recurrence of Crohn's disease to patients in the study group, whose baseline clinical and pathognomonic features did not differ from those in the control group.

At the time of presentation to the clinic, abdominal pain was 9.4% more common in patients than in the control group. Nausea, reported in 30% (12 patients) of cases, was also 3.8% more common than among patients in the control group. Flatulence was also more common among patients in the study group (4.3% higher). Patients in the study group had 2.1 times more abdominal wall fistulas than among patients in the control group, and 1.5 times more frequent bowel movements during the day.

There were relatively fewer patients with anal pain (1.5% less), fecal incontinence (1.9 times less), and blood in the stool (1.3 times less).

Overall, the number of complaints among patients in the study group (an average of 2.1 complaints per patient) was consistent with the frequency of complaints in the control group (an average of 2 complaints per patient).

During the examination of patients, Crohn's disease was localized in the terminal ileum in 55% of cases (22 patients), and in another 11 patients (27.5%), this lesion was combined with colonic pathology. Only 7 patients (17.5%) had Crohn's disease manifesting itself as colonic lesions, a 5.6% higher rate than among patients in the control group.

Among patients with ileocolitis, jejunal lesions were observed in 81.8% of cases, while among patients with terminal ileitis, combined jejunal lesions were observed in 36.4% of cases. Overall, 17 patients in the study group had jejunal lesions, representing a 42.5% rate and 1.5 times higher than among patients in the control group.

Perianal lesions were observed in 24 patients (60%) in the study group.

Overall, 17% more ileal resections and subtotal colon resections with ileosigmoid anastomosis were performed among patients in the study group. Segmental jejunal resections were also performed 1.5 times more often.

Abdominal infiltrates were detected during surgery in 62.5% of patients. In addition, 17 (42.5%) patients were also diagnosed with interintestinal fistulas, which were predominantly between the affected segment of the ileum and the sigmoid colon.

In 12 (30%) patients, the interintestinal fistulas were sutured after their separation, and only 5 (12.5%) patients in the study group underwent resection of the affected section of the intestine with the formation of a colorectal anastomosis.

Intra-abdominal abscesses were diagnosed in 5 (12.5%) patients in the study group.

Single-barrel ileostomy was used in 11 (27.5%) patients, which was half the rate in the control group. In the remaining cases, bowel resection with anastomosis was performed without a preventive stoma.

Thus, the nature of Crohn's disease, the extent of intestinal damage, and the nature of complications among patients in the study group did not significantly differ from those in the control group overall.

During the first stage of Crohn's disease recurrence prevention at the completion of surgery, patients in the study group received intramesenteric administration of Infliximab at a dose of 5 mg/kg of body weight. This stage of the surgery affected the humoral immunity parameters we studied.

The use of anti-TNF-α therapy disrupts the vicious cycle of autoimmune processes, creating conditions for immunosuppression and thereby increasing the likelihood of Crohn's disease recurrence. Furthermore, as can be seen from the changes in the nomogram curves, baseline cytokine levels in the blood were more significantly altered among patients in the study group, which ultimately did not prevent them from normalizing their change dynamics.

Postoperative complications were observed in 13 (32.5%) patients in the study group, which was 1.8 times lower than among patients in the control group.

According to the Clavien-Dindo classification, postoperative complications were predominantly grade I (20%), with fewer grades II (7.5%) and IIIa (5%).

Parastomal complications were observed in 5 patients (12.5%), and wound infection and abdominal infiltrate occurred in 4 cases each (10%), which did not require repeat surgery.

Overall, in the study group, immediate treatment outcomes were rated as good in 47.5% of cases, which was 1.7 times higher than among patients in the control group.

The proportion of satisfactory immediate outcomes also exceeded the incidence in the control group, reaching 42.5%.

Unsatisfactory treatment outcomes were observed in 4 patients (10%), which was 3.1 times lower than in the control group.

Targeted anti-cytokine and immunosuppressive therapy during surgery and in the early postoperative period allowed us to improve treatment outcomes and reduce the average length of hospital stay from 26.9 ± 7.5 bed days to 13.6 ± 2.1 bed days, which was almost half that of patients in the control group.

The use of methods for predicting and preventing autoimmune manifestations of postoperative Crohn's disease allowed us to reduce the recurrence rate in the study group from 59.5% to 40%.

Furthermore, the proportion of moderate Crohn's disease relapses was reduced by 1.7 times, completely preventing severe relapses.

The use of the preventive measures we developed also allowed us to delay the development of Crohn's disease relapse. In the study group of patients, the use of our developed treatment and diagnostic algorithm for predicting and preventing Crohn's disease recurrence prevented its development within 1 month after surgery and reduced its incidence by an average of 1.3 times by 90-180 days after surgery.

The results of applying the clinical criteria for predicting Crohn's disease recurrence were, on average, 10.5±5.9% true-positive results, 33.3±2.9% true-negative results, 25.7±5.1% false-positive results, and 30.5±4.4% false-negative results. Overall, the use of clinical criteria for predicting Crohn's disease recurrence increased diagnostic sensitivity from 6.67% on day 14 postoperatively to 33.3% on day 180 postoperatively, and specificity from 46.15% on day 14 postoperatively to 57.14% on day 180 postoperatively. The prognostic value of clinical criteria at 14 days postoperatively was 6.3%, at 30 days postoperatively – 14.3%, at 90 days postoperatively – 30.8%, and at 180 days postoperatively – 42.9%. On average, the diagnostic value was 28.9±14.4%.

The use of prognostic criteria with the inclusion of humoral immunity indicators generally increased the diagnostic sensitivity of the method by 3.5 times, diagnostic specificity by 1.9 times, and the prognostic value of the criteria for predicting Crohn's disease relapse by 3.3 times.

The use of the developed treatment and diagnostic algorithm for the prevention of relapse of Crohn's disease made it possible to reduce the frequency of its development in a mild form from 31% to 27.5%, in a moderate form from 21.4% to 12.5% and completely avoid its severe forms under the influence of pathogenetically substantiated differentiated and targeted anti-cytokine, hormonal and immunosuppressive therapy.

CONCLUSIONS:

1. Traditional approaches to treating Crohn's disease are associated with postoperative complications in 57.1% of cases, with parastomal complications (33.3%) and wound infection (25%) predominating, leading to a high rate (31%) of unsatisfactory immediate treatment outcomes. Crohn's disease recurrence with traditional approaches to treatment occurs in 59.5% of cases, predominantly mild to moderate (88%). The chronology of the increasing incidence of Crohn's disease recurrence is directly proportional to the increasing duration of the postoperative period.
2. The basis of the treatment and diagnostic algorithm for predicting and preventing recurrence of CD is the dynamic monitoring of the level of cytokines (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as clinical signs of the postoperative course (frequency of stool per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien-Dindo classification), which make it possible to determine the level (low or high) of the likelihood of an attack, on the one hand, and to apply differentiated approaches to the regimen of anti-cytokine (Infliximab and Vedolizumab), hormonal (Prednisolone) and immunosuppressive (Azathioprine) therapy, on the other.
3. The effectiveness of the developed method for predicting CD recurrence in the postoperative period, due to the significant inclusion of immunological criteria, allows for a 3.5-fold increase in test sensitivity, a 1.9-fold increase in specificity, and a 3.3-fold increase in prognostic value. Application of the developed treatment and diagnostic algorithm for preventing CD recurrence has reduced the incidence of mild CD from 31% to 27.5%, moderate CD from 21.4% to 12.5%, and

completely prevented its severe forms through the use of pathogenetically justified differentiated and targeted anti-cytokine, hormonal, and immunosuppressive therapy.

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