8. Dignass A. et al.*Second European evidence-based consensus on the diagnosis and management of ulcerative colitis. Part 2: Current management*. In: J. Crohn's Colitis, 2012, nr. 6(10), p. 991-1030.
9. Sandborn W. *State-of-the-art: immunosuppression and biologic therapy*. In: Dig. Dis., 2010; nr. 28, p. 536-542.
10. Travis S., Stange E., Lemann M. et al. *European evidence-based Consensus on the management of ulcerative colitis: Current management*. In: J. Crohn's Colitis, 2008; nr. 2, p. 24-62.
11. Oren R., Arber N., Odes S. et al. *Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial.* In: Gastroenterology, 1996; nr. 110, p. 1416-1421.
12. Sharkey L., Bredin F., Nightingale A. et al. *The use of Cyclosporin A in acute steroid-refracory ulcerative colitis: long term outcomes.* In: J. Crohn's Colitis, 2011; nr. 5(2), p. 91-94.
13. Hanauer S.B., Rutgeerts P., Clark M. et al. *AGA institute consensus development conference on the use of biologics in the treatment of inflammatory bowel disease.* In: Gastroenterology, 2007; nr. 133, p. 312-339.
14. Lawson M.M., Thomas A.G., Akobeng A.K. *Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis.* In: Cochrane Database Syst. Rev., 2006; nr. 3, p. CD005112.
15. Hanauer S. *The role of biologics in ulcerative colitis*. In: Dig. Dis., 2010; nr. 28, p. 497-500.
16. Hotineanu V., Timiş T., Bendelic V., Palii L. *Patologia chirurgicală a colonului*. În: Hotineanu V. Chirurgie: curs selectiv. Ch.: CEP Medicina, 2008, p. 606-668.
17. Summers R.W., Elliott D.E., Urban J.F. et al. *Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial.* In: Gastroenterol., 2005; nr. 128, p. 825-832.
18. Sandborn W.J. *Preliminary data on the use of apheresis in inflammatory bowel disease*. In: Inflamm. Bowel Dis., 2006; nr. 12 (Suppl. 1), p. S15-21.
19. Regueiro M., Loftus Jr. E.V., Steinhart A.H., Cohen R.D. *Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials*. In: Inflamm. Bowel Dis., 2006; nr. 12, p. 979-994.
20. Marteau P., Probert C.S., Lindgren S. et al. *Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study.* In: Gut, 2005; nr. 54, p. 960-965.
21. Su C., Lewis J.D., Goldberg B., Brensinger C., Lichtenstein G.R. *A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis.* In: Gastroenterology, 2007; nr. 132, p. 516-526.
22. Higgins P.D.R. *New keys to maintenance treatment in ulcerative colitis.* In: Dig. Dis., 2010; nr. 28, p. 483-489.

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SECONDARY INTESTINAL INFECTION AND ANTIBACTERIAL TREATMENT IN ULCERATIVE COLITIS

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Summary

Secondary intestinal infection and antibacterial treatment in ulcerative colitis

The aim of the study was to evaluate the role of the short-term treatment with ciprofloxacin and metronidazole in the remission induction and maintenance in moderate and severe ulcerative colitis complicated with secondary intestinal infection. In the prospective study 156 patients with moderate and severe ulcerative colitis were included. The signs of the secondary intestinal infection were observed in 47 patients (30.1%). These patients were randomized in two groups. Ciprofloxacin (1000 mg/day, 10 days) and metronidazole (1500 mg/day, 10 days) were administered to a treatment group (25 patients). Introduction of ciprofloxacin and metronidazole in the standard treatment schemes in patients with signs of a secondary intestinal infection resulted in a relative decrease of relapse risk on 72%. Ten-day antibacterial therapy with ciprofloxacin and metronidazole is an effective and safe method of treatment of the secondary intestinal infection in patients with ulcerative colitis.

Keywords: *ulcerative colitis, complications, secondary infection, treatment, antibiotics.*

Резюме

Антибиотерапия неспецифического язвенного колита у больных с признаками вторичной кишечной инфекции

Целью настоящего исследования было изучение эффективности короткого курса комбинированной антибиотикотерапии ципрофлоксацином и метронидазолом при среднетяжелом и тяжелом обострении неспецифического язвенного колита (НЯК) у больных с признаками вторичной кишечной инфекции.

Исследование являлось открытым проспективным рандомизированным неконтролируемым и включало 156 больных НЯК в стадии обострения среднетяжелой и тяжелой степени. 47 больных (30,1%) с признаками вторичной кишечной инфекции были рандомизированы в две группы. Группа лечения (25 больных), наряду с базисной терапией, получала ципрофлоксацин (1000 мг/день) и метронидазол (1500 мг/день) в течение 10 дней. Введение ципрофлоксацина и метронидазола в стандартные схемы лечения среднетяжелого и тяжелого обострения НЯК у больных с признаками вторичной кишечной инфекции приводит к относительному сни-

жению риска обострений на 72%. Десятидневный курс комбинированной антибактериальной терапии ципрофлоксацином и метронидазолом является эффективным и безопасным методом лечения вторичной кишечной инфекции при неспецифическом язвенном колите.

Ключевые слова: *язвенный колит, осложнения, вторичная инфекция, лечение, антибиотики.*

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology with predomination of genetically determined autoimmune mechanisms in pathogenesis. Pathogenetic role of obligate and / or opportunistic intestinal microorganisms, which can be triggers of the disease appearance and exacerbation, is actively discussed in recent years [1, 2, 7, 8].

Information about the role and importance of antibiotic therapy in ulcerative colitis is rather contradictory. Antibacterial drugs are not included in the standard schemes for remission induction and maintenance UC, recommended by European and American guidelines [11, 14]. However, physician often prescribe a short course of antibiotics for severe and moderate exacerbations of the disease. The aim of this treatment is the suppression of the opportunistic intestinal pathogens and the prevention of possible infection. Standardized approach to such treatment does not exist.

The aim of the study was to evaluate the effectiveness of the short-term treatment with ciprofloxacin and metronidazole in the remission induction and maintenance in moderate and severe ulcerative colitis complicated with secondary intestinal infection.

Material and methods

In the prospective comparative clinical trial were included 156 patients with UC: 63 men (40.4%) and 93 women (59.6%), aged between 16 and 77 years, the average age – 40.91 ± 12.48 years.

Detection in fecal mass of pathogens (*Staphylococcus aureus, Clostridium* etc.) or opportunistic flora in high titers (more than 10^5–10^7) was considered as a sign of secondary intestinal infection (SII). Patients diagnosed with secondary infection and / or with overgrowth of opportunistic flora were randomized into two groups. The first group was treated with mesalazine, prednisolone, ciprofloxacin and metronidazole (treatment group – TG). The second group received standard treatment with prednisolone and mesalazine (control group – CG). Ciprofloxacin was administered at a dose of 500 mg twice daily and metronidazole – 500 mg three times a day for 10 days.

All patients in this study were treated with prednisone at a dose of 40-60 mg in the first ten days, 30-40 mg in the next 2 weeks with a further gradual reduction of the dose of 5 mg per week and complete withdrawal of the drug after 9-12 weeks of treatment. Mesalazine was administered at a dose of 3-4 grams per day and, in the case of distal lesions, was recommended combined treatment: 2-3 g *per os* and 1 g *per rectum*. After achieving of clinical remission, usually in 4-8 weeks, patients passed to maintenance therapy of mesalazine, 2 g.

The disease activity was determined at the 1-st, 10-th and 30-th days. The disease evolution, number of exacerbations and complications were followed for 12 months.

Statistical analysis was performed using the χ^2 or Fisher's exact test, depending on the number of patients in groups. The absolute and relative risk reduction as the difference of the events between the treatment and control groups was calculated. T-test was used to compare continuous variables in the study groups, the Pearson correlation coefficient - for the analysis of relationships between the different indicators. Statistical significance was calculated for all the results and the level of *p* less than 0.05 was considered significant.

Results

SII symptoms were detected in 47 patients (30.1%). More extent intestinal lesions were characteristic for patients with SII signs. For example, the frequency of subtotal and total colitis was 34.04% and 19.26%, respectively, but this trend is not significant ($p = 0.071$). The mean Truelove & Witts activity indices were significantly higher in patients with SII ($p < 0{,}001$).

The most important laboratory parameters of SII, according to our study, were leukocytosis with a left shift and increased ESR. Increasing of ESR, in general, correlated with the Truelove & Witts activity index ($r = 0.59$; $p < 0{,}001$). At the same time, the level of leukocytes and neutrophils has no clear dependence on the degree of disease activity: the Pearson correlation coefficients between the Truelove & Witts activity index and the level of leukocyte / neutrophil were 0.2 / 0.22. Additionally, the number of patients with leukocytosis and / or with a left shift of leukocytes formula was significantly higher in the patients with SII, $p < 0.001$. Probably, leukocytosis, neutrocytosis, increased number of immature leucocytes in the peripheral blood reflects not so much the level of activity of ulcerative colitis as the presence of SII caused by pathogenic and / or opportunistic flora.

Other indicators of the general inflammatory syndrome (platelet count, the level of α2-, γ-globulin and C-reactive protein) were not significantly different in the comparison groups.

Combination antibiotic therapy was performed in 25 patients (TG) from the 47 patients with SII, and 22 patients constituted a control group (CG). The treatment and control groups did not differ by sex, age, disease duration, localization and activity. The groups did not differ initially on the basic parameters of the clinical and biochemical blood tests, also.

Patient's status improved significantly in both TG and CG groups as a result of the treatment (*table 1*).

Table 1

Ulcerative colitis activity and some laboratory parameters in the treatment and control groups after 10 and 30 days of observation

Characteristics	10 days			30 days		
	Treatment group (n=25)	Control group (n=22)	p	Treatment group (n=24)	Control group (n=22)	p
Truelove & Witts activity index	3,56 ± 1,92	5,09 ± 3,21	= 0,05[1]	2,38 ± 1,25	4,73 ± 2,41	= 0,000[1]
Number of patients with Truelove & Witts activity index:						
≥ 11 (severe activity)	0	1 (4,5%)	n[2]	0	0	= 0,000[2]
6-10 (moderate activity)	2 (8,0%)	5 (22,7%)		0	6 (27,3%)	
3-5 (mild activity)	12 (48,0%)	10 (45,5%)		5 (20,8%)	12 (54,5%)	
≤ 2 (remission)	11 (44,0%)	6 (27,3%)		19 (79,2%)	4 (18,2%)	
Number of patients with:						
leukocytosis (>9×10^9/mm^3)	8 (32,0%)	9 (40,9%)	n[2]	0	6 (27,3%)	= 0,008[3]
left shift of leukocytes formula (>6%)	8 (32,0%)	11 (50,0%)	n[2]	0	12 (54,5%)	= 0,000[3]
thrombocytosis (>320×10^3/mm^3)	8 (32,0%)	3 (13,6%)	n[3]	3 (12,5%)	5 (22,7%)	n[3]
ESR >10 men and >15 women	14 (56,0%)	9 (40,9%)	n[2]	0	6 (27,3%)	= 0,008[3]

n = not significant; [1] = T-test; [2] = χ^2 test; [3] = Fisher's exact test

More significant results were achieved in the TG: modified Truelove & Witts activity index decreased to 3.56 ± 1.92 in the TG and to 5.09 ± 3.21 – in the CG after 10 days of treatment (p = 0.05). There were no patients with severe activity, there were 2 patients (8.0%) with moderate activity, and 11 patients (44.0%) were in clinical remission after 10 days of treatment in the TG. At the same time, the CG had six patients (27.2%) with severe and moderate disease activity, and clinical remission was achieved in 6 patients only (27.3%). In this period of time there were no significant differences in the TG and CG by the number of blood leukocytes and by the number of patients with leukocytosis, thrombocytosis and increased ESR. Probably laboratory parameters normalized slower in comparison with clinical characteristics.

More significant differences were achieved after 30 days of treatment in the groups of comparison (*table 2*).

Table 2

12 months evolution of ulcerative colitis in the groups of comparison

	6 months			12 months		
	Treatment group (n=24)	Control group (n=22)	p	Treatment group (n=24)	Control group (n=22)	p
Remission	20 (83,3%)	9 (40,9%)	= 0,008[1]	13 (54,2%)	0	= 0,000[2]
1 exacerbation	4 (16,7%)	4 (18,2%)	n[2]	9 (37,5%)	4 (18,2%)	n[2]
2 and more exacerbations	0	9 (40,9%)	= 0,000[2]	2 (8,3%)	18 (81,8%)	= 0,000[2]
Colectomy	0	0	n[2]	0	2 (9,1%)	n[2]

n = not significant ; [1] = χ^2 test; [2] = Fisher's exact test

Modified Truelove & Witts activity index fell to 2.38 ± 1.25 in the TG and to 4.73 ± 2.41 – in the CG (p <0.001). Severe or moderate degree of disease activity was not diagnosed in the TG, 19 patients (79.2%) achieved clinical remission. At the same time in the CG, a moderate level of UC activity persisted in 6 patients (27.3%) and clinical remission was achieved in 4 patients only (18.2%) (p < 0.001). Patients with leukocytosis, leukocyte left shift or increased sedimentation rate were not in the TG at 30 days, whereas, in the CG, such patients constituted > 25% of cases, and leukocyte left shift was observed in 54.5% of patients. The average number of leukocytes in the treatment group was 6.15 ± 3.93 x 10^9 / l, and in the control group – 9.43 ± 4.53 x 10^9 / l (p <0.01).

Thus, remission was achieved faster and in a larger number of patients in the TG in comparison with CG. Six patients (27.3%) from the CG were transferred to other treatment schemes in the absence of an adequate response after 30 days of observation.

The disease evolution over the next 12 months is presented in *table 2*. Further observation showed that 20 patients (83.3%) from the TG and only 9 (40.9%) from the

CG were in remission after 6 months of monitoring (p <0.005). During the first 6 months of observation, no patient in the TG had more than one exacerbation, and no patient changed treatment regimen. At the same time, 9 patients in the CG had more than 1 exacerbation or have not achieved complete disease remission, which required the transfer to other treatment regimens (including the addition of antibiotics and parenteral corticosteroids).

Analysis of the results after 12 months of observation showed that in the TG remission persisted in 13 patients (54.2%), while in CG no one of patients was able to maintain remission for 12 months (p <0.001). Most of the patients in the CG (81.8%) had 2 or more relapses, including 17 patients (77.3%) were transferred to other treatments. Only 2 patients with more than one exacerbation were in the treatment group during this observation period.

Thus, a much more favorable evolution of the disease is noted in the treatment group in comparison with the control group. Introduction of ciprofloxacin and metronidazole into standard treatment regimens of moderate and severe ulcerative colitis in patients with secondary intestinal infection leads to a relative risk reduction of exacerbations by 72% (*table 3*), and the relative risk of two or more exacerbations reduced by 89.9%.

Table 3

The absolute and relative exacerbations risk reduction in the treatment and control groups

	Absolute risk reduction	Relative risk reduction
Risk reduction of:		
1 exacerbation	42,4	72
2 and more exacerbations	73,5	89,9

Discussion

Modern literature data about the feasibility of antibiotics in UC treatment is rather contradictory. Antibiotics were used in the combined treatment of severe acute ulcerative colitis since the 70-80 years of the last century [5, 12]. However, further controlled studies have shown no additional effect from the introduction of a seven-day course of vancomycin in treatment regimen, a five-day course of metronidazole, a ten-day course of ciprofloxacin, [4, 6, 9]. This led to the fact that antibiotic therapy is not included in modern guidelines on the management of ulcerative colitis [11, 14]. "The consensus on the management of inflammatory bowel disease for the Asia-Pacific region" refers to the necessity of introducing antibiotics in case of infectious complications [10]. Should be noted, that in the named studies, the antibacterial therapy was introduced in all cases of severe UC, regardless of the presence or absence of SII. This fact has not yielded significant positive results, although in all these works there is a trend to a more favorable outcome in the case of antibiotic therapy introduction.

According to the literature data [3, 8] and the results of the present study, not all patients with moderate or severe exacerbation of ulcerative colitis have symptoms of SII (30.1%). Respectively, only this group of patients needs antibiotics. Severity of exacerbation in most patients, probably due to other causes, including autoimmune aggression and additional antibiotics is not effective in such cases.

Interesting study, carried out in the Nordic countries by Turunen U. et al [13], showed the effectiveness of a long six-month course of oral ciprofloxacin for the remission induction and maintenance in ulcerative colitis. More significant results were obtained after 3 months of treatment, and then the differences between the treatment and placebo groups decreased significantly. Perhaps the long-term treatment with antibiotics leads to permanent intestinal dysbiosis, which affects the future evolution of the disease.

Conclusions

1. Symptoms of secondary intestinal infection are quite common in moderate and severe ulcerative colitis (30.1%).

2. The typical laboratory sings of secondary intestinal infections are leukocytosis with a left shift and a significant increase of ESR.

3. Ten-day course of combined antibiotic therapy with ciprofloxacin and metronidazole is an effective and safe treatment for secondary intestinal infection, which allows to achieve remission in less time and to reduce significantly the risk of exacerbations.

Bibliography

1. Asakura H., Suzuki K., Kitahora T., Morizane T. *Is there a link between food and intestinal microbes and the occurrence of crohn's disease and ulcerative colitis?* In: Journal of Gastroenterology and Hepatology, 2008, nr. 23, p. 1794-1801.
2. Cucchiara S., Iebba V., Conte M., Schippa S. *The microbiota in inflammatory bowel disease in different age groups*. In: Dig. Dis., 2009, nr. 27, p. 252-258.
3. D'Haens G., Sandborn W.J., Feagan B.G. et al. *Clinical trials of medical therapy in adults with ulcerative colitis*. In: Gastroenterology, 2007, nr. 132, p. 763–786.
4. Dickinson R.J., O'Connor H.J., Pinder I. et al. *Double blind controlled trial of oral vancomycin as adjunctive treatment in acute exacerbations of ulcerative colitis*. In: Gut, 1985, nr. 26, p. 1380-1384.
5. Jarnerot G., Rolny P., Saulbergh-Gertzen H. *Intensive intravenous treatment of ulcerative colitis*. In: Gastroenterology, 1985, nr. 89, p. 1005-1013.

6. Mantzaris G.J., Petraki E., Archavlis E. et al. *A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis*. In: Scandinavian Journal of Gastroenterology, 2001, nr. 36, p. 971-974.
7. Marteau P., Chaput U. *Bacteria as trigger for chronic gastrointestinal disorders*. In: Dig. Dis., 2011, nr. 29, p. 166-171.
8. Ng S.C., Hart A.L., Kamm M.A. et al. *Mechanisms of action of probiotics: recent advances*. In: Inflammatory Bowel Disease, 2009, nr. 15, p. 300-310.
9. Ohkusa T., Nomura T., Terai T. et al. *Effectiveness of antibiotic combination therapy in patients with active ulcerative colitis: a randomized, controlled pilot trial with long-term follow-up*. In: Scand. J. Gastroenterol., 2005, nr. 40, p. 1334-1342.
10. Qin Ouyang, Rakesh Tandon, K.L. Goh et al. *Management consensus of inflammatory bowel disease for the Asia-Pacific region*. In: J. Gastroenterol. and Hepatol., 2006, nr. 21, p. 1772-1782.
11. Travis S., Stange E., Lemann M. et al. *European evidence-based Consensus on the management of ulcerative colitis: Current management*. In: J. Crohn's Colitis, 2008, nr. 2, p. 24-62.
12. Truelove S., Jewell D. *Intensive intravenous regimen for severe attacks of ulcerative colitis*. In: Lancet, 1974; nr. 1, p.1067-1070.
13. Turunen U.M., Farkkila M., Hakala K. et al. *Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study*. In: Gastroenterology, 1998, nr. 115, p. 1072-1078.
14. *World Gastroenterology Organization Global Guideline: inflammatory bowel disease: a global perspective*. Munich (Germany): World Gastroenterology Organization, 2009, 23 p.

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РОЛЬ ПРО- И ПРЕБИОТИЧЕСКИХ ПРЕПАРАТОВ В КОМПЛЕКСНОЙ РЕАБИЛИТАЦИИ БОЛЬНЫХ ХРОНИЧЕСКИМ ПАНКРЕАТИТОМ

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Summary

Role of pro- and prebiotic drugs in complex rehabilitation patients with chronic pancreatitis

In this work is proved the expediency of including the drugs of synbiotyc composition, especially a synbiotic Lactiale, in the complex scheme of treatment of chronic pancreatitis. The use of a complex program of correction with inclusion of synbiotic Lactiale significantly has improved the condition of the patients with chronic pancreatitis according to the indicators of clinical symptoms by 47,4%, normalized microflora of the colon and increased the quality of life of patients by 60.1%.

Keywords*: chronic pancreatitis, bowel dysbiosis, synbiotic.*

Резюме

В работе доказана целесообразность включения в комплексную схему лечения хронического панкреатита препаратов синбиотического состава, в частности синбиотика Лактиале, поскольку такая схема улучшала клиническую симптоматику на 47,4%, нормализировала микрофлору толстой кишки и повышала качество жизни больных на 60,1%.

Ключевые слова: *хронический панкреатит, дисбиоз толстой кишки, синбиотик.*

Введение

Согласно Международной Марсельско-Римской классификации (1989 г.) хронический панкреатит (ХП) – это хроническое воспалительное повреждение ткани поджелудочной железы с деструкцией экзокринной паренхимы, ее атрофией, фиброзом и, по крайней мере, на поздних стадиях, деструкцией эндокринной паренхимы. Заболевание имеет фазно-прогрессирующее течение с периодическими приступами острого панкреатита, ответственного за рецидивирующую боль, которая нередко является единственным клиническим синдромом [3, 5].

ХП – одно из самых распространенных гастроэнтерологических заболеваний. Заболеваемость ХП в разных странах Европы составляет от 4 до 8 случаев на 100 тыс. населения в год, а распространенность – 250–500 больных на 100 тыс. населения. Через 10 лет после постанов-