

**CORRECTION OF INTESTINAL DISBIOSIS IN PATIENTS WITH CHRONIC HEPATITIS C AGAINST THE BACKGROUND OF NON-ALCOHOLIC FATTY LIVER DISEASE**

Uzhhorod National University (Uzhhorod, Ukraine)

morika1415@gmail.com

*Liver pathologies such as non-alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma are associated with changes in the composition of the microbiome in the intestine. There is strong evidence that bowel dysbiosis is associated with the progression and complication of these pathologies.*

*The purpose of the work was to study the effectiveness of treating intestinal dysbiosis in patients with chronic hepatitis C against the background of non-alcoholic fatty liver disease using a probiotic containing *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis subsp. lactis* BB-12 and a combination of ursodeoxycholic acid.*

*84 patients with CHC participated in the study. In all patients, determination of hepatitis B and C markers was carried out by ELISA, followed by determination of HCV RNA, genotype and virus quantity by PCR. The degree of liver fibrosis and steatosis was determined using a non-invasive diagnostic method – FibroMax (BioPredictive, Paris) and an indirect liver elastometry method using a diagnostic device manufactured by France – Fibroscan 502 F01261 sensor M 7 7012. The condition of gut microbiocenosis was determined by microbiological examination of stool.*

*Two groups were formed depending on the prescribed treatment: 1 gr (n = 40) – patients who received – LA-5 and BB-12 1 gtt. x TID and 2 g (n = 44) received LA-5 and BB-12 + UDCA 500 mg qhs for 1 month.*

*As a result of the study, it was established that patients with CHC against the background of NAFLD as part of the therapy, for correction of the intestinal microbiocenosis disorders in addition to probiotics, the additional prescription of UDCA is indicated, which helps to restore the colon microbiocenosis, improves the course of CHC and NAFLD, regulates dysfunction of the cytokine link of the immune system, and improves the quality of life of patients.*

**Key words:** colon dysbiosis, hepatitis C, non-alcoholic fatty liver disease, probiotic, UDCA.

**Connection of publication with planned research work.** The scientific research was carried out within the framework of the initiative theme of the Department of Faculty Therapy of the State University “UzhNU”: «Combined pathology and correction of disorders of homeostasis of residents of the Carpathian region, taking into account the effect of adverse factors», state registration number 0121U110808.

**Introduction.** Chronic hepatitis C (CHC) remains one of the most important problems of modern medicine, which is due to its significant spread, a progressive increase in morbidity, a high level of chronization, the risk of developing cirrhosis of the liver and hepatocellular carcinoma [1]. According to WHO expert estimates, the number of people infected with the hepatitis C virus is 325 million, and the number of patients dying annually as a result of this pathology reaches 1.4 million people (WHO, 2019) [2, 3].

Along with CHC among liver diseases, non-alcoholic fatty liver disease (NAFLD) occupies a valid place, which in developed countries occurs in 20-30% of the adult population, and non-alcoholic steatohepatitis (NASH) is registered in 2-3% of the general population [4]. According to a number of authors, during the initial examination in 30-40% of patients with NASH, liver fibrosis is detected, which within 5-10 years in 20-25% of cases progresses to cirrhosis of the liver, and 30-40% of these patients die from complications [5]. NASH is currently considered one of the most common causes of increased liver tests without the presence of clinical symptoms [6].

According to various studies, almost 50% of patients with CHC have different degrees of NAFLD, which contributes to the onset and further progression of fibrosis from the initial stages to cirrhosis of the liver within a short time [7-11].

In the pathogenesis of NAFLD, a significant role is assigned by a violation of the functional state of the colon and, as a result – the accumulation of waste products of microorganisms, endotoxins (ET) [12]. A decrease in the detoxification function of the microflora in dysbiosis increases the load on the enzymatic systems of the liver and contributes to the development of non-alcoholic steatosis, steatohepatitis, intrahepatic cholestasis [13]. In addition, dysbiotic disorders in the intestine are accompanied by active deconjugation of bile acids, excessive formation of their toxic salts and increased reabsorption in the lumen of the colon occur [14, 15]. As a result, bile acid synthesis decreases, and liver metabolism switches to cholesterol synthesis (CS), which leads to the development of dyslipoproteidemia [16, 17].

The correction of intestinal dysbiosis is more often carried out by prescribing probiotics that inhibit the reproduction of pathogenic strains of bacteria, improve the condition of the mucin barrier of the intestine, reduce endotoxemia and intestinal permeability, and also have a positive effect on the immune system. One of this is a probiotic whose capsule contains at least  $1 \times 10^9$  CFU *Lactobacillus acidophilus* (LA-5),  $1 \times 10^9$  CFU *Bifidobacterium animalis subsp. lactis* BB-12. Both bacteria are components of normal human intestinal microflora, resistant to hydrochloric acid and bile, which increases the percentage of their survival when passing through the stomach and duodenum and have GRAS status (generally recognized as safe) [18].

Recently, ursodeoxycholic acid (UDCA) drugs are increasingly used to treat various liver diseases, especially those accompanied by cholestatic and cytolytic syndrome [19-21]. UDCA has a unique ability to settle in the phospholipid bilayer membrane of hepatocytes, stabilizing its structure and protecting the liver cell from

damaging factors. Many randomized studies have proven the multifactorial effect of UDCA [22, 23].

**Purpose.** To determine the effectiveness of treating intestinal dysbiosis in patients with chronic hepatitis C against the background of non-alcoholic fatty liver disease using a probiotic containing *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis* subsp. *lactis* BB-12 and a combination with ursodeoxycholic acid.

**Object and research methods.** 84 patients with CHC were examined. There were 41.7% of men (35), 58.3% of women (49). The average age of patients was 56,7±1,3 years. The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the ethics commission of the Uzhhorod National University (Protocol No. 7/1 of 12.09.2021). All patients gave signed consent to the collection of personal data into the database and for the use of blood and feces samples for research purposes and for participation in the study.

The classification of chronic hepatitis proposed at the International Gastroenterological Congress (Los Angeles, 1994) was used to establish the diagnosis of CHC. Determination of hepatitis B and C markers was carried out by ELISA, followed by determination of RNA VCS, genotype and virus quantity by PCR. The degree of liver fibrosis and steatosis was determined using a non-invasive diagnostic method – FibroMax (BioPredictive, Paris) and an indirect liver elastometry method using a diagnostic device manufactured by France – Fibrosan 502 F01261 sensor M 7 7012. The degree of liver fibrosis and steatosis was determined using a non-invasive diagnostic method – FibroMax (BioPredictive, Paris) and an indirect liver elastometry method using a diagnostic device manufactured by France – Fibrosan 502 F01261 sensor M 7 7012 (regional clinical infectious disease hospital, Uzhhorod).

The condition of gut microbiocenosis was determined by microbiological examination of stool. To detect dysbiosis of the large intestine, a quantitative accounting of microorganisms that grew on a nutrient medium of Agar, Saburo, Endo and 5% blood agar calculated per 1 g of feces was carried out, taking into account the dose of inoculated material and the degree of its dilution. Culture identification was carried out on the basis of biochemical tests and the ‘Enterotest’ system. During material taking, all patients did not have acute infectious diseases, did not receive antibacterial, pre- or probiotic therapy. According to the unified working classification of dysbiosis (I.B. Kuvaieva, K.S. Ladodo, 1991), 4 degrees of dysbiotic disorders of the intestine were distinguished. The levels of cytokine profile indicators were determined for all patients and assessed psychological status and the quality of life. When planning therapeutic measures for intestinal dysbiosis in patients with CHC, we took into account the presence of metabolic factors and the main clinical and laboratory syndromes and prescribed hepatoprotective therapy (UDCA) in addition to probiotics.

Two groups were formed depending on the prescribed treatment: 1 gr (n = 40) – patients who received – LA-5 and BB-12 1 gtt. x TID and 2 g (n = 44) received LA-5 and BB-12 + UDCA 500 mg qhs for 1 month.

The two-sided Fisher’s exact test was used in the work using Statistica 8.0 for Windows. The difference was considered probable at  $p < 0.05$ .

**Research results and their discussion.** Among the complaints noted by patients, constipation was leading – 69% (58 out of 84) and diarrhea – 31% (26 out of 84) of patients. The study of clinical manifestations in patients with CHC revealed their connection with the degree of DB. It was established that 28 patients had DB of the I-st degree, DB of the II-nd degree -41, DB of the III-rd degree -15 patients, and DB of the IV-th stage – was not detected in any patient. In patients with CHC with DB of the III-rd degree, 33.3% (5 out of 15) were significantly more likely to record periodic discomfort with lower abdominal location compared to 14.3% (4 out of 28) and 20.0% (3 out of 15) patients with I-st and II-nd degree of DB, respectively. The presence of this localization of discomfort in patients with CHC is obviously explained by the strengthening of dysbiotic processes and impaired intestinal function. This was confirmed by the presence of a reliable connection of the feeling of discomfort in the lower abdomen with dyspeptic manifestations, such as nausea ( $p = 0.007$ ), flatulence ( $p = 0.02$ ), decreased appetite ( $p = 0.003$ ). The next most frequent complaint was flatulence which was observed in 32 (38.1%) patients with DB. The frequency of flatulence increased against the background of the progression of DB and was one of the persistent dyspeptic complaints that are difficult to correct with medication in patients with CHC. Flatulence was constantly present in 100% of patients with the III-rd degree of DB, in persons with the II-nd degree of DB it bothered less often 41.5% (17 out of 41), and was not recorded at all at the I-st degree of DB. The patients also had other complaints (hepatobiliary): pain, heaviness in the right hypochondrium 32.1% (27 out of 84), weakness and rapid fatigue 85.7% (72 out of 84).

After the treatment, all patients showed an improvement in well-being. Thus, in the first group in 62.5% (25 out of 40) of patients disappeared clinical and laboratory signs of colon DB by the end of the treatment, in contrast to patients of the second group, where taking LA-5 and BB-12 in combination with UDCA contributed to the normalization of the microbial component of the colon in 93.2% (41 out of 44) of patients. In this group, only 2 patients had the 2-nd degree of DB and 1 had DB of the 1-st degree (**table 1**).

As a result of simultaneous administration of LA-5 and BB-12 and UDCA in the above-mentioned doses, in 93.2% of patients with CHC ( $p < 0.01$ ) an increase in the number of bifido- and lactobacteria, *Escherichia* with normal activity and a decrease in the number of hemolytic microorganisms, proteus, staphylococci and yeast-like fungi were found, which was accompanied by

**Table 1 – Dynamics of the degree of DB of the large intestine in the examined patients**

Degree of dysbiosis	Groups of patients			
	1 gr (n=40)		2 gr (n=44)	
	a	б	a	б
0	0	25 (62,5%)	0	41 (93,2%)
I	14 (35,0%)	8 (20,0%)	14 (31,8%)	1 (2,3%)*
II	19 (47,5%)	5 (12,5%)	22 (50,0%)	2 (4,6%)*
III	7 (17,5%)	2 (5,0%)	8 (18,2%)	0

Notes: a – before treatment; b – after treatment; \* – the difference between the indicators before and after treatment is statistically significant ( $p < 0.05$ ).

**Table 2 – Dynamics of the main complaints under the influence of treatment**

Complaints	Groups			
	1 gr (n=40)		2 gr (n=44)	
	b	a	a	b
Constipation	27(67,5%)	11(27,5%)	31(70,45%)	2(4,5%)*
Diarrhea	12(30%)	4(10%)	14(31,8%)	1(2,27%)
Flatulence	15(37,5%)	6(15%)	17(38,6%)	1(2,27%)*
Itchy skin	12(30%)	9(22,5%)	14(31,8%)	4(9,1%)*
Pain in the right hypochondrium	11(27,5%)	8(20%)	14(31,8%)	3(6,8%)*
Dyspeptic syndrome	25(62,5%)	18(45,0%)	27(61,3%)	7(15,9%)*
Asthenovegetative syndrome	34(85%)	23(57,5%)	38(86,3%)	10(22,7%)*

**Notes:** a – before treatment; b – after treatment; \* – the difference between the indicators before and after treatment is statistically significant ( $p < 0.05$ ).

the normalization of the act of defecation and the disappearance of symptoms of intestinal dysbiosis. In patients taking only LA-5 and BB-12, the above-mentioned positive changes were observed in 62.5% ( $p < 0,05$ ). The elimination of DB symptoms, in particular constipation and flatulence, contributed to the positive dynamics of the clinical course of CHC. Thus, the number of patients who complained of pain, heaviness in the right hypochondrium, flatulence, weakness and rapid fatigue decreased with a significant predominance of those in the second group (table 2).

After the treatment, a decrease in the activity of pro-inflammatory cytokines and a slight increase in the level of anti-inflammatory cytokines were noted. The most significant was the decrease of *fetoplacental insufficiency* –  $\alpha$  and neopterin, almost in 4 times ( $r \leq 0,01$ ) and IL-6 in 3.5 times ( $r \leq 0,05$ ) in patients of the 2-nd group who additionally received a probiotic and UDCA. The dynamics of anti-inflammatory cytokines in this group of patients also turned out to be positive, namely an increase of IL-4 in 2.7 times ( $r \leq 0,05$ ) and IL-10 in 3.2 times ( $r \leq 0,01$ ).

Within the framework of the study, a high sensitivity of IL-6 was established under the influence of the proposed therapy schemes and the normalization of the microbial landscape of the colon. There is an assumption

that the level of concentration of this cytokine depends on the degree of bacterial aggression [24, 25], which was confirmed in our research. Therefore, the obtained significant decrease of IL-6 concentration after the complex therapy is a sign of a decrease in bacterial aggression and elimination of manifestations of systemic inflammation. The most significant decrease in the level of IL-6 was observed in patients receiving a probiotic and UDCA.

Since part of neopterin is catabolized by the symbiotic microflora of the colon [26], a decrease in its concentration in the blood serum of patients after complex treatment confirms the positive effect of the proposed therapy on the composition of the microflora of the colon.

Assessing the psychological status of patients as a result of the treatment, it should be noted that the tendency towards improvement was observed in all patients, however, a decrease in the level of anxiety and depression was observed only in patients of the second group. Namely, the severity of depression in patients of the 2nd group decreased in  $1,7 \pm 0,2$  ( $p < 0.05$ ) points and anxiety in  $2,5 \pm 0,8$  ( $p < 0.05$ ), while in other patients these indicators remained unchanged.

**Conclusions.** For patients with CHC against the background of NAFLD as part of the therapy in order to correct disorders of intestinal microbiocenosis, an additional prescription of UDCA is indicated. Its use positively affects not only the microbiocenosis of the colon, but also the course of CHC and NAFLD, contributes to the regulation of the cytokine link of the immune system and improving the state of psychological status.

**The prospect of further research** is to study the impact of the proposed therapy on the lipid profile indicators in patients with CHC against the background of NAFLD.

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### КОРЕКЦІЯ КИШКОВОГО ДИСБІОЗУ У ХВОРИХ НА ХРОНІЧНИЙ ГЕПАТИТ С НА ТЛІ НЕАЛКОГОЛЬНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ

Дербак М. А., Воробець В. В., Грига В. І.

**Резюме.** Хронічний гепатит С (ХГС) залишається однією з найважливіших проблем сучасної медицини, що зумовлено його значним поширенням, прогресивним зростанням захворюваності, високим рівнем хронізації, ризиком розвитку цирозу печінки та гепатоцелюлярної карциноми. За даними різних досліджень, майже у 50% хворих на ХГС спостерігається різного ступеня НАЖХП, що сприяє виникненню та подальшому прогресуванню фіброзу від початкових стадій до цирозу печінки протягом короткого часу.

**Мета:** визначити ефективність лікування кишкового дисбіозу у хворих на хронічний гепатит С на тлі неалкогольної жирової хвороби печінки із застосуванням пробіотика, що містить *Lactobacillus acidophilus* (LA-5) і *Bifidobacterium animalis subsp. lactis* BB-12 у поєднанні із урсодезоксихолевою кислотою.

**Об'єкт і методи дослідження.** Обстежено 84 хворих на ХГС. Усім хворим проведено мікробіологічне дослідження випорожнень, визначено рівні показників цитокінового профілю та оцінено психологічний статус і якість життя. Сформовано дві групи в залежності від призначеного лікування: 1 гр (n=40) – хворі, які отримували – LA-5 і BB-12 по 1 кап. x 3 рази на добу і 2 гр (n=44) – отримували LA-5 і BB-12 + УДХК по 500 мг на ніч протягом 1 місяця.

**Результати дослідження та їх обговорення.** У результаті одночасного прийому LA-5 і BB-12 і УДХК у вищевказаних дозах у 93,2% хворих на ХГС встановлено збільшення кількості біфідо- і лактобактерій, ешерихій із нормальною активністю та зниження кількості гемолітичних мікроорганізмів, протея, стафілококів та дріжджеподібних грибів, нормалізація акту дефекації та зникнення симптомів кишкового дисбіозу. У хворих, що приймали тільки LA-5 і BB-12, вказані вище позитивні зміни спостерігались у 62,5% осіб. Розроблена комплексна терапія зменшує прозапальний компонент (достовірно знизилися рівні ФНП-α і неоптерину, ІЛ-6) та активує протизапальний компонент системи цитокінів (рівень ІЛ 10 достовірно зростав) та покращує психологічний статус і якість життя пацієнтів.

**Висновки.** Встановлено, що додаткове призначення УДХК у поєднанні із пробіотиком сприяє не тільки відновленню мікробіоценозу товстої кишки, а і покращує перебіг ХГС та НАЖХП, регулює дисфункцію цитокінової ланки імунної системи та підвищує якість життя пацієнтів.

**Ключові слова:** дисбіоз товстого кишечника, гепатит С, неалкогольна жирова хвороба печінки, пробіотик, УДХК.

### CORRECTION OF INTESTINAL DYSBIOSIS IN PATIENTS WITH CHRONIC HEPATITIS C AGAINST THE BACKGROUND OF NON-ALCOHOLIC FATTY LIVER DISEASE

Derbak M. A., Vorobets V. V., Griga V. I.

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**Object and methods.** 84 patients with CHC were examined. All patients underwent a microbiological study of stool, the levels of cytokine profile indicators were determined and the psychological status and the quality of life

were assessed. Two groups were formed depending on the prescribed treatment: 1 gr (n=40) – patients who received – LA-5 and BB-12 1 gtt. x TID and 2 g (n=44) received LA-5 and BB-12 + UDCA 500 mg qhs for 1 month.

**Results and their discussion.** As a result of simultaneous administration of LA-5 and BB-12 and UDCA in the above-mentioned doses, in 93.2% of patients with CHC an increase in the number of bifido- and lactobacteria, Escherichia with normal activity and a decrease in the number of hemolytic microorganisms, proteus, staphylococci and yeast-like fungi, normalization of the act of defecation and the disappearance of symptoms of intestinal dysbiosis were found. In patients taking only LA-5 and BB-12, the above-mentioned positive changes were observed in 62.5%. The developed complex therapy reduces the pro-inflammatory component (the levels of fetoplacental insufficiency –  $\alpha$  and neopterin, IL-6 decreased significantly) and activates the anti-inflammatory component of the cytokine system (IL-10 level increased significantly), improves the psychological status and the quality of life of patients.

**Conclusions.** It was found that the additional prescription of UDCA in combination with a probiotic not only contributes to the restoration of colon microbiocenosis, but also improves the course of CHC and NAFLD, regulates the dysfunction of the cytokine link of the immune system and increases the quality of life of patients.

**Key words:** colon dysbiosis, hepatitis C, non-alcoholic fatty liver disease, probiotic, UDCA.

**ORCID and contributionship:**

Derbak M. A.: 0000-0003-4791-4080 <sup>A EF</sup>

Vorobets V. V.: 0000-0002-3115-9327 <sup>BD</sup>

Griga V. I.: 0000-0003-3666-8910 <sup>C</sup>

Conflict of interest:

The authors of the paper confirm the absence of conflict of interest.

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Corresponding author

Derbak Mariya Antonivna

Uzhhorod National University

Ukraine, 88000, Uzhhorod, 20 Hryboiedova str.

Tel: +380506275075

E-mail: morika1415@gmail.com

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<sup>1</sup>Dubivska S. S., <sup>2</sup>Viedienieva R. Y., <sup>1</sup>Hryhorov Yu. B.

**DIRECTIONS FOR RECOVERY OF COGNITIVE FUNCTION IN SURGICAL PATIENTS AFTER GENERAL ANESTHESIA**

<sup>1</sup>Kharkiv National Medical University (Kharkiv, Ukraine)

<sup>2</sup>Kharkiv National Air Force University named after Ivan Kozhedub (Kharkiv, Ukraine)

Dubovskaya@ukr.net

*Purpose of the study: to develop directions for correcting changes in cognitive functions in patients after general anesthesia in the early postoperative period against the background of neuroprotective therapy based on the results of a survey of 126 patients using neuropsychological testing. The follow-up was carried out by us based on the KNP "Kharkiv City Clinical Hospital for Emergency and Emergency Care named after Professor O.I. Meshchaninov" XMR, which is the clinical base of the department. Patients were divided into 3 groups. 1st group – young patients (18-43 years); 2nd group – middle-aged patients (44-59 years); 3rd group – elderly patients (60-80 years). The obtained changes in cognitive functions against the background of neuroprotective therapy according to the test results may be due to the age-related plasticity of cognitive functions and the depletion of compensatory capabilities. Recovery of results was determined in the immediate follow-up period: in young patients it was gradual than in other age groups, with complete recovery to the level of cognitive impairment in this test at the level before surgery in middle-aged patients. Thus, the obtained results unequivocally recommend the appointment of neuroprotective therapy in the standard postoperative management of surgical patients operated under anesthesia to prevent the onset or deterioration of cognitive functions, which further improves the quality of life.*

**Key words:** general anesthesia, neuroprotective therapy, cognitive function, surgery.

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