

UDC: 578.891:616.36-002.1:616.34-008.87

CORRECTION OF LARGE INTESTINE DYSBIOSIS IN PATIENTS WITH ACUTE HEPATITIS B

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Introduction

Viral hepatitis is one of the global challenges for modern medicine. Among them, hepatitis B (GB) remains one of the most widespread viral diseases of the present day. According to the WHO estimates, more than 1/3 of the world's population (2 billion people) has serological evidence of current or transmitted HBV infection, of which 350 million are chronically infected. Annually 4 million new clinical cases of infection are registered [1, 2]. However, WHO states that official statistics are underestimated and do not reflect the current level of HBV infection. Patients and carriers of the GB virus have a high probability of developing severe complications, the main of which are cirrhosis of the liver and hepatocellular carcinoma [3].

Hepatitis B according to modern concepts should be considered as a disease of the immune response [4]. The existing link between microflora and immunity today is beyond doubt. It is proved that indigenous microorganisms form a special organ - the physiological microbial system, which provides the implementation of numerous biological functions, including contributing to the launch of a cascade of immune responses in response to the penetration of pathogens [5]. Separate studies have identified the state of the colon biocenosis in patients with acute hepatitis and found that dysbiotic lesions of varying degrees are found in patients with viral hepatitis in 73.3% - 96% of cases [6-8]. Disturbances of the quantitative and qualitative composition of the microflora reduce the detoxification function of the intestine and increase the toxic load on the liver, which, in turn, negatively affects the development of the basic pathological process.

The aim of the work was to determine the degree of dysbiotic changes in the microflora of the large intestine and to evaluate the effectiveness of their correction with a symbiotic drug in patients with acute hepatitis B.

Materials and methods

To perform the task, 108 patients with acute hepatitis B, aged 18-69 being on hospital treatment at Kharkiv Regional Clinical Hospital of Infectious Diseases, have been examined. Among the examined patients there have been 56 men and 52 women with an average age of 34 ± 1.9 years.

The diagnosis has been set on the basis of clinical anamnestic, epidemiological, laboratory and instrumental data. The etiological verification of the diagnosis has been performed by detecting specific serological markers of

hepatitis B (HBsAg, HBeAg, anti-HBc IgM, by the ELISA method). The diagnosis of GHB and its clinical and pathogenetic variants of the course, form and degree of severity have been determined according to the International Statistical Classification of Diseases and Related Security Problems Health (ICD-10, version 2006).

According to the purpose of study the patients have been divided into groups as follows:

- group A - the main one, where patients have additionally been taking symbiotic besides who the basic treatment;
- group B - patients to whom basic therapy has been applied.

Thus, 2 groups of 54 patients have been formed. The control group, which did not differ from the groups of patients by age and gender, has been made up of 17 clinically healthy persons.

Basic therapy included a restrictive regime, diet (table number 5a or 5), multivitamins. In patients with moderate severity, if necessary, detoxification agents (5% glucose solution, 0.9% NaCl solution, reosorbilact), riboxin, antispasmodics, sorbents and other drugs have been used, after the normalization of clinical and biochemical parameters and during the period of clinical supervision, hepatoprotectors have been prescribed.

For patients of group A patients we have been using symbiotic — Bifilact Extra, TM "Ariadna", Ukraine, certificate of registration No. 05.08.07 / 4089 of 02.10.2000 containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* and an additional complex of biological polymers: cellulose, hemicellulose, pectin and lignin. The prescription term of the symbiotic has been 14 days for patients with mild severity and 21 days for patients with moderate severity.

Determination of the qualitative and quantitative composition of microbiocenosis of the large intestine has been carried out in accordance with current normative documents as per generally accepted methods.

The degree of dysbiotic disturbances was determined by V.M. Bondarenko in 2007 [9]. According to the above criteria, the state of microbiocenosis of the large intestine has been divided into eubiosis, dysbiosis of the 1st degree, dysbiosis of the 2nd degree, dysbiosis of the 3rd degree and dysbiosis of the 4th degree.

Identification of isolated bacterial cultures has been carried out according to morphological, cultural, biochemical characteristics in accordance with Bergee's Manual of Determinative Bacteriology, identification of fungal strains – as per "The determinant of pathogenic and opportunistic fungi". The results of determination of the number of microorganisms (colony forming units) have been expressed in decimal logarithms per gram of clinical material - lg CFU / g.

Microbiological studies of the material have been conducted in dynamics before the treatment and 7 days after the end of the course of treatment with the symbiotic.

Statistical processing of the data was carried out using the Statistics-10 software package, Microsoft Office Excel 2003.

Results

In all patients, there was an acute cyclic course of HBV infection with clinically expressed jaundice in the background of cytotoxic syndrome. The period before jaundice proceeded with dyspeptic syndrome in 24,1% of patients, arthralgia in 19,4%, astenovegetative in 18,5% and mixed in 38%, which combined various syndromes. The period of breakthrough was characterized by an increase in the intensity of intoxication, which was accompanied by a

worsening of the condition in a separate part of the patients, determining the degree of severity of the disease.

By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96.3% of patients. It turned out that the degree of dysbiotic shifts did not depend on the severity of hepatitis. About half of patients had dysbiosis of grade III (Table 1).

Table 1. Characterization of the microbiocenosis state of the large intestine cavity in patients with AHB of varying severity in the icteric period

The severity of hepatitis	Specific gravity of patients with dysbiosis,%				
	eubiosis	I degree	II degree	III degree	IV degree
Mild severity (n=40)	5,0	20,0	15,0	55,0	5,0
Average severity (n=68)	2,9	2,9	47,1	44,2	2,9

Analyzing the species composition and population level of the microflora of the colon in patients with acute hepatitis B in the jaundice period, there was elimination or severe deficiency of bifidobacteria and lactobacilli and the vegetation of opportunistic bacteria of staphylococci (35,5%), *Klebsiella pneumonia* (16,1%), *Enterobacter spp* (19,4%), *Citrobacter spp* (16,1%), *Clostridium spp* (22,6%). But the most common cause of local microecology was *Candida spp*, it was determined in 30,8% of the total number of identified pathogenic microorganisms. In addition, the proportion of *Candida spp* in violation of the microecology of the large intestine increased in the dynamics of the disease to 42.3%, which was evidenced in the period of

reconvalescence. This was confirmed by studies of levels of immunoglobulins G to *Candida spp* in serum of patients with candidiasis dysbiosis, which showed an increase in titres in the dynamics of the disease from 1: 16/32 to 1: 256.

The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63,0% of patients compared to patients receiving baseline therapy. The acceptance of bifido and lactic symbiotic has a positive effect on the state of microbiocenosis of the large intestine compared with patients receiving only basic therapy, which is confirmed by the results of the dispersion analysis and the method of multiple comparisons (Sheffe test) (Table 2).

Table 2. Changes in degrees of dysbiosis of the large intestine in patients with acute hepatitis B depending on the prescribed therapy

Type of therapy	Specific gravity of patients with changes in the degree of dysbiosis,%		
	the degree of dysbiosis decreased	the degree of dysbiosis increased	remained unchanged
Basic therapy + symbiotic (n = 54)	63,0*	0	3,7*
Basic therapy (n = 54)	29,6	11,1	59,3

Notes: * - $p < 0,05$ between indicators.

The appointment of a symbiotic resulted in a reduction the length of stay of patients of mild severity and

patients of average severity in the hospital compared to patients receiving baseline therapy, $p < 0,05$ (Table 3).

Table 3. Days of stay in a hospital of patients with acute hepatitis B depending on the prescribed therapy

Type of therapy	Number of patients with hospitalization			
	according to standards		exceeding standards	
	mild severity (22 days)	average severity (30 days)	mild severity (> 22 days)	average severity (> 30 days)
Basic therapy (n=54)	2	4	18	30
Basic therapy + symbiotic (n=54)	8	14	12	20

Conclusions

1. By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96.3% of patients. About half of patients had dysbiosis of grade III.
2. The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63.0 % of patients compared to patients receiving baseline therapy.
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Statistical processing of the data was carried out using the Statistics-10 software package, Microsoft Office Excel 2003. **Results.** In all patients, there was an acute cyclic course of HBV infection with clinically expressed jaundice in the background of cytolysis syndrome. By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96.3% of patients. It turned out that the degree of dysbiotic shifts did not depend on the severity of hepatitis. About half of patients had dysbiosis of grade III. Analyzing the species composition and population level

of the microflora of the colon in patients with acute hepatitis B in the jaundice period, there was elimination or severe deficiency of bifidobacteria and lactobacilli and the vegetation of opportunistic bacteria. But the most common cause of local microecology was *Candida* spp, it was determined in 30,8 % of the total number of identified pathogenic microorganisms. In addition, the proportion of *Candida* spp in violation of the microecology of the large intestine increased in the dynamics of the disease to 42.3%, which was evidenced in the period of reconvalescence. The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63,0 % of patients compared to patients receiving baseline therapy. The appointment of a symbiotic resulted in a reduction the length of stay of patients of mild severity and patients of average severity in the hospital compared to patients receiving baseline therapy, $p < 0,05$.

Conclusions. By results of researches of the species composition of the microflora of the colon in jaundice period of AHB, a violation of the microecology of this biotope of different degrees was found in 96.3% of patients. About half of patients had dysbiosis of grade III. The appointment of a symbiotic resulted in a reduction in the clinical manifestations of dysbiosis in 63,0 % of patients compared to patients receiving baseline therapy. The appointment of a symbiotic resulted in a reduction the length of stay of patients of mild severity and patients of average severity in the hospital compared to patients receiving baseline therapy.

Keywords: acute hepatitis B, large intestine, microbiocenosis, complex treatment, symbiotic.