

## USE OF THE DRUG “ENTEROL” IN THE COMPREHENSIVE TREATMENT OF CHRONIC VIRAL HEPATITIS

**Gulrukh Y. Sultonova<sup>2</sup>., Ikrom A Artikov<sup>3</sup>.**

**Fazliddin I Kamalov<sup>4</sup>., Nilufar F Chulieva<sup>5</sup>.**

<sup>1</sup>Doctor of Medical Sciences of the Department of

Infectious and children’s Infectious Diseases,

Tashkent State Medical University, Tashkent, Uzbekistan

<sup>2</sup>PhD, Senior Lecturer of the Department of

Infectious and children’s Infectious Diseases,

Tashkent State Medical University, Tashkent, Uzbekistan

<sup>3</sup>Assistant Lecturer at the Department of Infectious Diseases,

Urgench Medical Institute.

<sup>4</sup>Head of Department, Koson District Infectious Diseases Hospital,

Kashkadarya Region, Republic of Uzbekistan

<sup>5</sup>Infection doctor at the Tashkent Regional Infectious Diseases Hospital.

**Abstract.** Background: Disturbances of the intestinal microbiota are increasingly recognized as an important factor in the persistence of inflammation and progression of chronic viral hepatitis. Modulation of gut microbiota may represent a promising pathogenetic approach. Objective: To assess alterations of the intestinal microbiota in patients with chronic hepatitis B and C and to evaluate the clinical and laboratory effects of probiotic therapy containing *Saccharomyces boulardii* as an adjunct to standard treatment. Methods: A total of 70 patients with chronic viral hepatitis (40 with hepatitis B and 30 with hepatitis C) were enrolled. Patients were divided into two groups: a probiotic

group (n=40), receiving standard therapy plus a probiotic containing *Saccharomyces boulardii*, and a control group (n=30), receiving standard therapy alone. Clinical symptoms, laboratory parameters, and bacteriological stool analyses were evaluated before and after treatment. Results: Intestinal dysbiosis was identified in all patients and was significantly associated with disease duration and severity of clinical manifestations. Patients receiving probiotic therapy demonstrated a marked improvement in intestinal microbiota composition, characterized by increased levels of beneficial bacteria and reduced opportunistic microorganisms, compared with the control group. Probiotic supplementation was associated with faster regression of gastrointestinal and systemic symptoms and a reduction in dysbiosis severity. The therapy was well tolerated, with no adverse events reported. Conclusions: Intestinal dysbiosis is a common finding in chronic viral hepatitis and correlates with disease duration and clinical severity. Adjunctive probiotic therapy containing *Saccharomyces boulardii* improves gut microbiota balance and clinical outcomes and may serve as an effective component of pathogenetic treatment in patients with chronic hepatitis B and C.

**Keywords** Chronic viral hepatitis; gut microbiota; intestinal dysbiosis; probiotics; *Saccharomyces boulardii*; hepatitis B; hepatitis C

## 1. Introduction.

In recent years, considerable attention has been focused on the study of risk factors for the progression and destabilization of chronic viral hepatitis, as well as on the development of new approaches to its pathogenetic therapy. The pathogenesis of the development and progression of chronic viral hepatitis involves a complex interplay of interrelated mechanisms, among which hepatocyte necrosis and progressive liver fibrosis are considered the leading processes [2,4]. According to both domestic and international studies, intestinal dysbiosis (dysbacteriosis) represents one of the significant contributing factors. It is assumed that alterations in the intestinal microbiota play an important role in maintaining hepatic inflammation and in the development of complications associated with chronic viral hepatitis [2].

The normal intestinal microbiota constitutes a complex and functionally significant ecological system that provides metabolic, immune, and barrier functions of the host organism. Under the influence of various endogenous and exogenous factors, quantitative and qualitative disturbances of the intestinal microbiocenosis may occur [1,5].

Disruption of the intestinal barrier facilitates the translocation of bacteria and their toxins from the intestinal lumen, leading to the activation of inflammatory responses, the development of infectious complications, and the involvement of both portal and systemic circulation. A consequence of dysbiotic changes is the excessive growth of opportunistic microorganisms [6,7]. An increased abundance of opportunistic microflora in patients with chronic viral hepatitis is associated with enhanced inflammatory–necrotic activity, hepatocellular damage, and progression of liver fibrosis [1,6,7].

Colonic dysbiosis in patients with chronic viral hepatitis is regarded as one of the factors contributing to the development of minimal hepatic encephalopathy, which negatively affects patients' quality of life by reducing social functioning and the physical component of health.

It has been established that bacterial translocation, predominantly involving Gram-negative microorganisms, plays an important role in the development of endotoxemia and in the maintenance of a systemic inflammatory response in chronic liver diseases.

The relevance of chronic viral hepatitis as a public health problem in the Republic of Uzbekistan is обусловлена its high prevalence and the heterogeneous circulation of hepatotropic viruses across different regions, which is associated with medico-social conditions and lifestyle characteristics of the population. Despite the introduction of modern antiviral agents, the possibilities of etiological therapy remain limited due to the high cost of treatment, the presence of contraindications, and the development of adverse effects.

In this regard, the importance of pathogenetic therapy for chronic viral hepatitis aimed at reducing inflammatory activity, protecting hepatocytes, and correcting disturbances of the intestinal microbiota is increasing. In this context, the inclusion of probiotic preparations in the comprehensive management of patients appears promising. Probiotics

containing live microorganisms and their metabolites contribute to the restoration of intestinal microbiocenosis, reduction of bacterial translocation, and attenuation of inflammatory responses, which may exert a beneficial effect on the course of chronic viral hepatitis.

**The aim of the study** was to investigate disturbances of the intestinal microbiota in patients with chronic viral hepatitis and to evaluate the clinical and laboratory efficacy of the drug *Enterol* as part of comprehensive therapy, taking into account the severity of the disease course.

**Materials and Methods.** The diagnosis of chronic viral hepatitis was established on the basis of medical history, clinical examination, laboratory parameters (total protein, total bilirubin levels, ALT and AST activity, creatinine, urea, and prothrombin index), as well as enzyme-linked immunosorbent assay (ELISA) results with determination of viral hepatitis markers (HBsAg, anti-HBs, anti-HCV) using certified test systems manufactured by *Diagnostic Systems*, in accordance with the current regulatory documents of the Ministry of Health of the Republic of Uzbekistan.

Molecular genetic testing was performed using polymerase chain reaction (PCR) to detect HBV DNA and HCV RNA in blood samples, employing the Rotor-Gene Q amplifier (QIAGEN, Germany). Instrumental investigations included abdominal ultrasound examination and non-invasive assessment of liver fibrosis using elastometry with the FibroScan device.

In the analysis of patient complaints and physical examination findings, in addition to syndromes characteristic of chronic liver disease, particular attention was paid to clinical manifestations associated with gastrointestinal dysfunction. To assess qualitative and quantitative changes in the intestinal microbiocenosis and the balance among major groups of microorganisms, bacteriological stool examination for dysbiosis was performed in accordance with approved laboratory diagnostic standards.

The study included 70 (100%) patients with chronic viral hepatitis. The mean age of the examined patients was  $38 \pm 9.7$  years. Depending on the administered therapy, patients were divided into two groups. The main group consisted of 40 patients who, in addition to

basic therapy, received the probiotic drug *Enterol*. The control group included 30 patients who received standard symptomatic and pathogenetic therapy without probiotic supplementation.

Treatment efficacy was evaluated based on the dynamics of clinical and laboratory parameters, the state of the intestinal microbiota, and the clinical course of the disease during the follow-up period.

**Results.** The study included 70 patients with chronic viral hepatitis, among whom 40 (57.1%) were diagnosed with chronic hepatitis B (CHB) and 30 (42.9%) with chronic hepatitis C (CHC).

At the first stage of the study, the state of the intestinal microbiota was assessed in patients of both groups. Disturbances of intestinal microbiocenosis were detected in all examined patients regardless of the etiology of viral hepatitis; however, the nature and severity of dysbiotic changes varied considerably.

Bacteriological examination of stool samples demonstrated that the majority of patients with CHB and CHC exhibited a reduction in the levels of normal intestinal microflora, particularly bifidobacteria, lactobacilli, and *Escherichia coli* with normal enzymatic activity.

An increased growth of opportunistic microflora was identified in 20 patients (28.6%), predominantly due to various strains of *Escherichia coli*, *Proteus* spp., and *Klebsiella* spp. The growth of *Staphylococcus aureus* and streptococcal flora was detected in 4 cases each. An elevated content of fungi of the genus *Candida* was found in 41 fecal samples (60%), with no statistically significant differences between patients with CHB and CHC.

According to the severity of dysbiotic changes, grade I intestinal dysbiosis was diagnosed in 24 patients (34.2%), grade II in 34 patients (48.5%), and grade III in 14 patients (20.0%). The distribution of dysbiosis grades did not differ significantly between the CHB and CHC groups ( $p > 0.05$ ).

The next stage of the study involved an analysis of the intestinal microbiocenosis depending on the duration of chronic viral hepatitis. In 16 patients (22.8%), disease

duration exceeded 10 years, with a mean duration of  $13.1 \pm 0.5$  years; in 30 patients (42.8%), disease duration ranged from 6 to 10 years (mean  $8.13 \pm 0.4$  years); and in 24 patients (34.2%), the diagnosis had been established within the last 5 years (mean  $3.6 \pm 0.4$  years).

It was established that the severity of intestinal dysbiosis directly correlated with the duration of the chronic inflammatory process in the liver, regardless of viral hepatitis etiology. Among patients with disease duration exceeding 10 years, grade III dysbiosis was detected in 10 of 16 patients ( $62.5 \pm 18.2\%$ ), and grade II in 6 patients ( $37.5 \pm 18.2\%$ ). In patients with disease duration of 6 to 10 years, grade II dysbiosis was diagnosed in  $60.0 \pm 13.5\%$  of cases (18 patients), grade I in  $33.3 \pm 12.6\%$  (10 patients), and grade III in  $6.7 \pm 6.7\%$  (2 patients).

In patients with a disease duration of less than 5 years, grade I intestinal dysbiosis was significantly more frequently detected ( $58.3 \pm 14.8\%$ ) compared with patients with a longer disease course ( $p < 0.05$ ), while grade II dysbiosis was diagnosed in  $41.7 \pm 14.8\%$  of patients.

At the subsequent stage of the study, the frequency of clinical symptoms of chronic viral hepatitis was analyzed depending on the severity of intestinal dysbiosis in patients with CHB and CHC. It was found that, with increasing severity of dysbiotic changes, the frequency of the main clinical manifestations of the disease also increased (Table 1).

**Table 1**

**Frequency of selected clinical symptoms in the compared patient groups (M±m)**

Symptoms	Grade I dysbiosis n=22		Grade II dysbiosis n=26		Grade III dysbiosis n=22		P
	abs	%	abs	%	abs	%	

Weakness	22	100,0±0, 0	26	100,0±0, 0	22	100,0±0, 0	>0,05
Fatigue	12	54,5±15, 7	16	61,5±14, 0	18	81,8±12, 2	>0,05
Loss of appetite	22	100,0±0, 0	26	100,0±0, 0	22	100,0±0, 0	>0,05
Nausea	18	81,8±12, 2	24	92,3±7,7	22	100,0±0, 0	>0,05
Vomiting	8	36,4±15, 2	12	46,2±14, 4	16	72,7±14, 1	>0,05
Headache	6	27,3±14, 1	14	53,8±14, 4	16	72,7±14, 1	>0,05* >0,05** <0,01** *
Pain in the right hypochondrium	6	27,3±14, 1	14	53,8±14, 4	18	81,8±12, 2	>0,05* >0,05** <0,01** *
Sleep disturbances	4	18,2±12, 2	12	46,2±14, 4	16	72,7±14, 1	>0,05* >0,05** <0,01** *

*Note: P – statistical significance of differences between groups; P\* – statistical significance of differences between Grade I and Grade II dysbiosis; P\*\* – statistical significance of differences between Grade II and Grade III dysbiosis; P\*\*\* – statistical significance of differences between Grade I and Grade III dysbiosis.*

The symptom of general weakness was observed in 54.5% of patients with Grade I dysbiosis, 61.5% of patients with Grade II, and 81.8% of patients with Grade III dysbiosis; however, these differences did not reach statistical significance ( $p > 0.05$ ), indicating the absence of a direct relationship between this symptom and the severity of intestinal dysbiosis.

At the same time, the frequency of symptoms such as headache, right hypochondrial pain, and sleep disturbances was significantly higher in patients with Grade III dysbiosis ( $72.7 \pm 14.1\%$ ) compared to those with Grade I dysbiosis ( $27.3 \pm 14.1\%$ ) ( $p < 0.01$ ), regardless of the viral etiology of hepatitis.

The occurrence of nausea and vomiting also increased with the severity of dysbiotic changes; however, the differences between groups were not statistically significant ( $p > 0.05$ ).

The prolonged course of chronic viral hepatitis, accompanied by reduced work capacity and diminished quality of life, is often complicated by limited possibilities of etiological therapy, high costs of antiviral drugs, and the development of adverse effects. Therefore, the development of pathogenetic treatment regimens that meet the requirements of accessibility, ease of use, good tolerability, and optimal cost-effectiveness is highly relevant.

In the complex therapy of patients with chronic viral hepatitis, the domestic probiotic preparation *Enterol* was used, which possesses a broad spectrum of biological activity and is aimed at correcting intestinal microbiota disorders.

The study included 70 patients with chronic viral hepatitis, of whom 40 (57.1%) had chronic hepatitis B (CHB) and 30 (42.9%) had chronic hepatitis C (CHC). All patients received standard baseline therapy, including protective regimen, diet therapy (Diet No.

5), symptomatic treatment, infusion therapy, vitamin supplementation, as well as pathogenetic agents (hepatoprotectors and metabolic modulators).

The main group consisted of 40 patients who, in addition to baseline therapy, received the probiotic *Enterol* at a dose of 250 mg, 1 capsule twice daily for 30 days. The comparison group included 30 patients who received similar baseline therapy without probiotics. The efficacy of treatment was evaluated based on the dynamics of clinical manifestations, laboratory parameters, and results of bacteriological assessment of intestinal microbiota.

*Enterol* contains live lyophilized yeast microorganisms (*Saccharomyces boulardii*), which are highly resistant to gastric juice and antibiotics. In the intestine, the preparation exerts an antagonistic effect against pathogenic and conditionally pathogenic microbiota, reduces bacterial translocation, promotes restoration of the intestinal barrier function, and modulates the immune response.

According to repeated bacteriological analysis of stool in patients of the main group, a significant improvement in the qualitative and quantitative composition of the intestinal microbiota was observed: an increase in bifidobacteria by an average of 2 log, normalization of lactobacilli levels, and a reduction in colonization by *Candida* species. The response of *Escherichia coli* with normal enzymatic activity was less pronounced. *Enterol* was well tolerated; no adverse effects were registered during the treatment.

It was established that even after a short course of therapy (30 days), most patients in the main group demonstrated a marked positive dynamic in intestinal microbiota status, manifested as a reduction in the severity of dysbiosis or a tendency toward its regression. The duration of certain clinical symptoms in patients receiving the probiotic was shorter compared to the comparison group. For specific symptoms (vomiting, general fatigue, sleep disturbances), statistically significant differences were observed.

Before therapy, in the main group, Grade I dysbiosis was diagnosed in 12 (30.0%) patients, Grade II in 16 (40.0%), and Grade III in 14 (35.0%). In the comparison group, the corresponding values were 10 (33.3%), 10 (33.3%), and 8 (26.7%) cases, respectively ( $p > 0.05$ ).

According to repeated bacteriological stool analysis in patients receiving *Enterol*, improvement in both qualitative and quantitative composition of intestinal microbiota was confirmed: increased bifidobacteria (by an average of 2 log), normalization of lactobacilli, and decreased *Candida* colonization. The response of *E. coli* with normal enzymatic activity was less pronounced.

As a result of treatment, the number of patients with severe forms of dysbiosis in the main group significantly decreased. At the end of the therapy course, Grade III dysbiosis was found in only 2 (5.0%) patients, Grade II in 6 (15.0%), and Grade I in 2 (5.0%). In the comparison group, these indicators remained significantly higher, amounting to 8 (26.6%), 10 (33.3%), and 8 (26.7%) cases, respectively.

Thus, the inclusion of the probiotic *Enterol* in the complex therapy of chronic viral hepatitis contributes to the normalization of intestinal microbiota and a reduction in the severity of clinical symptoms. The preparation was well tolerated, and no adverse effects were observed during the treatment.

**Discussion.** The obtained results confirm the significant role of intestinal microbiota disturbances in the pathogenesis of chronic viral hepatitis. The observed relationship between disease duration and the degree of dysbiosis indicates the involvement of the “gut-liver axis” in the processes of chronic inflammation.

The inclusion of *Enterol* in the complex therapy of CHB and CHC promotes a more pronounced positive dynamic in clinical manifestations and normalization of intestinal microbiota. The mechanism of action of the preparation, based on the activity of *Saccharomyces boulardii*, makes it a promising agent for the pathogenetic treatment of chronic viral hepatitis.

Analysis of clinical symptoms revealed that, at more severe degrees of intestinal dysbiosis, symptoms such as headache, right hypochondrial pain, and sleep disturbances were significantly more frequent. These findings indicate the clinical relevance of dysbiotic changes and their contribution to the development of intoxication symptoms and the deterioration of quality of life in patients with chronic viral hepatitis.

Thus, correction of intestinal dysbiosis using probiotics can be considered an important adjunct to baseline therapy for chronic viral hepatitis, aimed at reducing inflammatory activity and improving the clinical course of the disease.

## Conclusions

1. All patients with chronic hepatitis B and C exhibited intestinal microbiota disturbances of varying severity.
2. The severity of intestinal dysbiosis is directly associated with the duration of chronic viral hepatitis.
3. Severe forms of dysbiosis are linked to an intensification of clinical manifestations and a reduction in patients' quality of life.
4. The inclusion of *Enterol* in complex therapy contributes to significant normalization of intestinal microbiota and a reduction in dysbiosis severity.
5. *Enterol* is well tolerated and may be recommended as an effective component of pathogenetic therapy in patients with CHB and CHC.

## References

1. Uspensky Y.P., Baryshnikova N.V., Balukova E.V. Intestinal Microflora and Liver Pathology. *Journal of Infectious Diseases and Gastroenterology*. 2017; 1(24): 66–74.
2. Zhdanov K.V., Gusev D.A., Zakharenko S.M., et al. Intestinal Dysbiosis in Liver Cirrhosis. *Experimental and Clinical Gastroenterology*. 2011; 6: 38–44.
3. Tashpolotova A.Sh., Suranbayeva G.S. The Role of Viral Hepatitis in the Development of Liver Cirrhosis. *International Journal of Applied and Fundamental Research*. 2019; 7: 68–72.
4. Gromova N.I. The Role of Chronic Viral Hepatitis in the Development of Liver Cirrhosis and Hepatocellular Carcinoma. *Journal of Infectology*. 2012; 1: 37–44.

5. Teterina L.A., Chikhacheva E.A., Seliverstov P.V., et al. The Role of Colonic Microflora in the Development of Minimal Hepatic Encephalopathy. Journal “Treating Physician”. 2012; 9: 1–6. Available at: [www.lvrach.ru](http://www.lvrach.ru)
6. Anikina E.V., Kovtun A.V., Yakovenko A.V. Disturbances of Intestinal Biocenosis in the Pathogenesis of Liver Cirrhosis and Complications of Portal Hypertension. Experimental and Clinical Gastroenterology. Issue 112, No. 12, 2014.
7. Zhdanov K.V., Gusev D.A., Zakharenko S.M. Intestinal Dysbiosis in Liver Cirrhosis. Experimental and Clinical Gastroenterology. 2011; 6.
8. Bilalova A.R., Makashova V.V., Shipulin G.A. Clinical and Biochemical Features of Liver Cirrhosis of Different Etiologies. Archive of Internal Medicine. 2016; 3(29).
9. Kovtun A.V., Anikina E.V., Yakovenko A.V. Gastrointestinal Microflora in the Pathogenesis of Liver Cirrhosis and Complications of Portal Hypertension. Bulletin of the National Medical and Surgical Center named after N.I. Pirogov. 2014; 9(4).
10. W. Reiner., G. Melissa., Markus. Pathological bacterial translocation in liver cirrhosis//Journal of Hepatology. -2014 -vol. 60 Pp. 197–209.