ЛЕЧЕНИЕ ХЕЛИКОБАКТЕРИОЗА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА В СОЧЕТАНИИ С ХРОНИЧЕСКОЙ ГАСТРОДУОДЕНАЛЬНОЙ ПАТОЛОГИЕЙ

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ОБОСНОВАНИЕ. Лечение инфекции *Helicobacter pylori (HP)* у больных сахарным диабетом 2 типа (СД2) с хроническими гастродуоденальными заболеваниями (ГДЗ) остается актуальной задачей, учитывая высокую степень инфицированности данных пациентов: от 70 до 90%.

ЦЕЛЬ. Состояла в изучении эффективности и последствий тройной и оптимизированной последовательной схем антихеликобактерной терапии больных СД2 в сочетании с ГДЗ.

МАТЕРИАЛЫ И МЕТОДЫ. Обследовано 54 больных СД2 и 64 пациента без СД2, последние в качестве группы сравнения, в возрасте от 30 до 60 лет. Проведена гастродуоденоскопия для подтверждения ГДЗ, хеликобактерную инфекцию определяли уреазным методом и исследованием антигена бактерии в кале. Оценивали динамику клинической картины по балльной шкале GSRS, эндоскопическую ремиссию, эффективность эрадикации HP. Изучали влияние схем антихеликобактерной терапии на синдром избыточного бактериального роста в тонком кишечнике (СИБР) у данных больных. СИБР определяли дыхательным водородным тестом. Сформированы 4 группы обследованных: 1-я группа без СД2 и 2-я – с СД2 получали тройную антихеликобактерную терапию 10 дней; 3-я группа без СД2 и 4-я группа с СД2 – оптимизированную последовательную терапию 14 дней.

РЕЗУЛЬТАТЫ. Установлено, что оптимизированная последовательная схема лечения привела к эрадикации *HP* у больных без СД2 в 90% случаев, а у пациентов с СД2 – в 85,7% случаев, что достоверно больше, чем при тройной схеме – 67,6% и 65,3% соответственно. Кроме того, клиническая эффективность и эндоскопическая ремиссия также были выше при использовании последовательной схемы лечения. Интерес представляют данные по влиянию эрадикационной терапии на СИБР в тонком кишечнике, который исходно имел место у 44–46% больных ГДЗ без СД2 (в зависимости от группы) и у 69–78% больных СД2. Только оптимизированная последовательная схема терапии позволила достоверно уменьшить число больных с СИБР в обеих группах.

ЗАКЛЮЧЕНИЕ. Использование в качестве антихеликобактерной терапии больных СД2 с ГДЗ оптимизированной последовательной схемы повышает клиническую эффективность лечения, степень эрадикации возбудителя по сравнению со стандартной тройной терапией.

КЛЮЧЕВЫЕ СЛОВА: хеликобактерная инфекция; сахарный диабет; гастродуоденальные заболевания

TREATMENT OF HELICOBACTER PYLORI CONTAMINATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH GASTRODUODENAL DISORDERS

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BACKGROUND: The treatment of *Helicobacter* pylori (HP) infection in patients with diabetes mellitus with chronic gastroduodenal disorders is a substantial problem because of its high incidence.

AIMS: To compare between the effectiveness of triple and optimised consecutive regimens in anti-HP treatment in patients with type 2 diabetes mellitus with gastroduodenal disorders.

MATERIALS AND METHODS: The study included 54 patients with diabetes mellitus and 64 healthy individuals (the control group) aged 30–60 years. Gastroduodenal pathology was confirmed by gastroduodenoscopy; HP contamination was confirming using Marshall's urease method or by finding bacterial antigen in excrements. We studied the dynamics of clinical manifestations using the GSRS scale and showed remission via endoscopy and the effectiveness of HP eradication. We also analysed the effects of anti-HP therapy regimens on the presence of small intestinal bacterial overgrowth syndrome (SIBOS) in patients with diabetes mellitus. SIBOS was diagnosed via the respiratory hydrogen method.

RESULTS: The use of an optimised consecutive regimen resulted in HP eradication in 85.7% of patients with diabetes mellitus compared with a 65.3% eradication in patients on the triple therapy. Moreover, clinical improvement and endoscopy-con-

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firmed remission were more frequently observed in patients on the optimised consecutive regimen. A statistically significant decrease in the number of patients with SIBOS was found only in patients who underwent the optimised consecutive therapy regimen.

CONCLUSIONS: This study showed that the optimised consecutive therapy regimen was more effective than the triple therapy in HP eradication.

KEYWORDS: Helicobacterpylory; diabetes mellitus; gastroduodenal diseases

The main postulate of treating the pathology associated with *Helicobacter pylori* (*HP*) infection is the pathogen eradication principle. In accordance with the international consensus of Maastricht V (2015), the Kyoto consensus (2015) and the recommendations of the Russian Gastroenterological Association for the Diagnosis and Treatment of *HP* in Adults (2012), the standards of anti-*Helicobacter* therapy are regulated [1,2]. However, as evidenced by numerous Russian and foreign studies, during the last decade, the efficacy of classical schemes of the first and second eradication lines has decreased [3]. This is due to a number of problems, the main of which are an increase in *HP* resistance to metronidazole and clarithromycin, side effects of proton pump inhibitors (PPIs) and antibacterial drugs [4].

One new eradication therapy consists of a sequential scheme (5 days of PPI + amoxicillin and then 5 days PPI + clarithromycin + tinidazole/metronidazole). This is currently one of the most studied schemes of eradication in the world, as shown by the high figures of efficacy of such therapy [5]. In the framework of the Maastricht V consensus, this eradication protocol is regulated as an alternative to the first-line scheme [2]. This consensus also recommends prolonging treatment with first-line schemes for up to 14 days to optimise treatment and increase eradication efficiency.

For patients with type 2 diabetes mellitus (DM2) with chronic gastroduodenal disorders (GDDs), the issue of *HP* eradication is also topical, as there is a high degree of infection in these patients, from 70% to 90% [6]. However, studies in which *HP* eradication schemes were evaluated in patients with DM and GDD occasionally have been performed in our country and abroad [7,8]. However, we have not found in the available literature any study on the use of a sequential scheme in these patients.

The actual problem is the tolerance achieved by patients for eradication therapy, as well as its influence, positive or negative, on the quality of life of patients and on the state of the intestinal microbiota. This is especially important in view of the modification of eradication schemes, with increases in the duration of treatment and number of antibacterial drugs used in these schemes.

We analysed the efficacy and consequences of the triple and optimised sequential schemes of anti-*Helicobacter* therapy in patients with DM2 plus GDD.

METHODS

Study Design

The open-label comparative controlled randomised study included 118 patients suffering from various GDDs and *HP* infection, 54 of whom had reliably diagnosed DM2 in the compensation stage. A total of 64 patients with GDD who did not have DM2 constituted the control group. GDDs were diagnosed according to existing standards of examination using special methods, such as oesophagogastroduodenoscopy (EGD) and biopsy of stomach and duodenal mucosa with histological examination. *HP* infection was determined with a urease test (in biopsy material from at least two places—the body and antrum of the stomach) and by the enzyme-linked immunoassay (ELISA) method with monoclonal antibodies to identify the pathogen antigens in the faeces. The latter method was mandatory for monitoring eradication, which was performed 1 month after the end of treatment.

All patients were divided into four groups: groups 1 and 2 included patients without and with DM2, respectively, who received a standard triple scheme of *HP* eradication, and groups 3 and 4 included patients without and with DM2, respectively, who underwent an optimised sequential eradication scheme. Groups 1 and 3 were regarded as controls with respect to DM2 groups 2 and 4. Table 1 shows the comparative characteristics of all four groups according to the results of randomisation.

As shown in Table 1, patients in the four groups did not differ significantly in age, sex distribution, body mass index, duration of the disease, distribution according to the frequency of GDD and assessment methods, which made them as homogeneous as possible excluding absence or presence of DM2. The only difference between the control and DM2 groups was in the frequency of cardiac pathology, which was more prevalent in the DM2 groups, but this could not affect the further course of the study.

The tasks of the study included determining the clinical endoscopic and laboratory effectiveness of eradication schemes. To evaluate clinical efficacy, the Gastrointestinal Symptom Rating Scale (GSRS) technique developed by Wiklund was used [9]. The Russian-language version of the GSRS questionnaire was created by researchers from the Interethnic Center for the Study of the Quality of Life (St. Petersburg, Russia) [10]. The essence of the technique consisted of polling patients on five scales: diarrhoea (DS), dyspeptic (IS), constipation (CS), abdominal pain (AP) and reflux (RS) syndromes. A maximum of 14 to 28 points could be obtained for each syndrome, depending on the frequency of symptoms. For a general assessment of complaints, scores of different scales were summarised.

One task of our study was to analyse the effect of eradication schemes on the microbiota of the small intestine and on the bacterial overgrowth syndrome (BOGS) in the small intestine. The latter occurs quite often in patients with DM2 [7]. To determine the BOGS, the results of the hydrogen test with lactulose, which was performed initially and 1 month after the end of treatment, were used. The hydrogen test is considered the most informative for assessing the presence of BOGS in the intestine. The 'Gastrolizer' (Bedfont

Table 1. Initial characteristics of DM and control groups that received triple and sequential anti-Helicobacter therapy

Sign	Triple therapy		Sequential therapy		P 1-2	P 3-4	P 1-3	P 2-4
	Group 1, control, n = 34	Group 2, DM2, n = 26	Group 3, control, n = 30	Group 4, DM2, n = 28				
Age, years	52.4±6.3	54.6±4.2	47.3±5.2	52.3±4.1	0.458	0.438	0.265	0.722
Sex, n, %								
men	14 (41.2)	10 (38.5)	8 (26.7)	11 (39.3)	0.376	0.321	0.244	0.558
women	20 (58.8)	16 (61.5)	22 (73.3)	17 (60.7)	0.621	0.458	0.332	0.416
BMI, kg/m^2	27.5±3.2	29.5±2.8	26.4±2.1	30.2±3.1	0.578	0.345	0.389	0.421
Diseases, n,%								
NEr gastritis	11 (32.4)	8 (30.8)	13 (43.3)	9 (32.1)	0.434	0.465	0.433	0.211
Er. gastritis	16 (47.1)	12 (46.1)	13 (43.3)	13 (46.4)	0.786	0.278	0.465	0.390
UD	7 (20.6)	6 (23.1)	4 (13.4)	6 (21.4)	0.146	0.277	0.132	0.178
Average duration of the disease, years	16.4±4.2	14.2±3.6	14.2±3.6	15.8±4.2	0.389	0.567	0.234	0.543
Concomitant diseases, n, %								
GERD	14 (41.2)	13 (59.1)	11 (36.7)	10 (55.5)	0.089	0.078	0.099	0.121
PBD	16 (47.1)	12 (54.5)	11 (36.7)	8 (44.4)	0.768	0.422	0.322	0.237
IHD	8 (23.5)	10 (45.5)	5 (16.7)	12 (66.7)	0.034	0.021	0.235	0.267
hypertensive disease	15 (44.1)	20 (90.9)	10 (33.3)	23 (82.1)	0.007	0.012	0.562	0.711
Initial estimate of HP, n, %								
Urease test	27 (79.4)	18 (69.2)	23 (76.7)	18 (64.3)	0.534	0.347	0.356	0.558
ELISA in faeces	7 (20.6)	8 (30.8)	7 (23.3)	10 (35.7)	0.711	0.544	0.566	0.497

Notes: BMI, body mass index; GERD, gastroesophageal reflux disease; NEr, nonerosive; Er, erosive; UD, ulcer disease; PBD, pancreatobiliary diseases.

Scientific Ltd, Maidstone, UK) device was used to perform the hydrogen test, and the method itself did not differ from the standard one [11].

Inclusion criteria

The examination excluded persons suffering from severe decompensated diseases of the heart, lungs, liver, pancreas and intestines. All patients signed written consent for examination and treatment, according to the order of the Ministry of Health of the Russian Federation No. 173/1 of 25 July 2012, 'Concerning Informed Voluntary Consent to Medical Assistance'.

Study protocol

All patients were residents of the city of Khabarovsk, observed by gastroenterologists in the State Budgetary Healthcare Institution City Clinical Hospital No. 16 and by the endocrinologist at the Endocrinological Health Center in Khabarovsk. On the basis of these institutions, the patients were examined and treated.

Duration of the Study

The study was conducted for 2 years. Each patient examined before the beginning of the study did not take PPIs within 2 weeks and antibiotics for at least 6 months. After diagnosing GDD and detecting infection, one anti-*Helicobacter* therapy scheme was prescribed to patients according to the study design. To determine the endoscopic efficacy of the treatment, EGD was performed at the end of treatment to evaluate the gastric and duodenal mucosa. It should be noted that patients, in addition to eradication therapy, received antacid and antisecretory therapy (only the PPI that was prescribed initially) for up to 1 month. The hydrogen test with the BOGS determination was performed initially and 1 month after the end of anti-*Helicobacter* therapy.

Description of Medical Intervention

The standard triple scheme of anti-*Helicobacter* therapy included omeprazole 40 mg/day + clarithromycin 1 g/day + amoxicillin 2 g/day for 10 days. The sequential scheme of eradication was presented above, and the dosages of the preparations were the same as in the triple scheme + metronidazole 1 g/day. Optimisation of this scheme consisted of increasing the duration of treatment: PPI + amoxicillin for 7 days, then PPI + clarithromycin + metronidazole for 7 more days. In addition, instead of omeprazole, rabeprazole was used in this scheme, because, according to provision 10 of Maastricht V working group 3, this PPI is recognised to be the least susceptible to the CYP2C19 genotype and metabolised primarily as a result of a nonenzymatic process [2].

Primary Study Outcome

The laboratory efficacy of eradication schemes was considered to be negative ELISA results for antigens of in the faeces 1 month after the end of treatment.

Additional Study Outcomes

Clinical efficacy of treatment was assessed by a reliable decrease in GSRS relative to baseline 1 month after the onset

Table 2. Results of treatment with triple anti-Helicobacter scheme of in DM2 group 1 and control group 2.

Sign	Control (group 1) n = 34		DM2 patients (group 2) n = 26	
	baseline	After treatment	baseline	After treatment
Patients with HP, n (%)	34 (100)	11 (32.4)*	26 (100)	9 (34.6)*
Patients with remission according to data of EGD, n (%)	-	24 (70.6)	-	16 (61.5)
Total GSRS, score	56.7±4.3	38.1±2.3*	79.6±4.1	54.6±3.2*
Syndromes of GSRS, score				
DS (diarrhoea)	14.4±2.4	10.4±1.1	7.9±1.2	14.3±1.1*
IS (dyspeptic)	17.6±2.1	10.7±1.3*	26.6±2.1	11.6±2.1*
CS (constipation)	8.2±1.8	14.8±1.8*	13.1±1.3	12.2±2.4
AP (abdominal pain)	6.8±1.1	3.1±0.4*	13.2±1.6	4.2±1.1*
RS (reflux)	14.2±1.3	4.1±1.1*	20.8±1.6	8.3±1.4*
BOGS,n, %	15 (44.1)	10 (29.4)	18 (69.2)	13 (50)

Notes: reliability of differences in baseline values between groups, P < 0.05. *Reliability of differences with baseline values in each group, P < 0.05.

of GDD therapy. Endoscopic efficacy was determined by the disappearance of endoscopic signs of the disease according to EGD data also 1 month after the onset of treatment.

Ethical Review

The conclusion of the expert commission on the issues of medical ethics of the Federal State Budgetary Educational Institution of Higher Education Far East State Medical University (regulations on the ethical committee at the scientific and planning commission of the Far East State Medical University dated 8 January 2014, approved by the rector V.P. Molochny) was obtained for the submitted study. The scientific research performed corresponded to the generally accepted norms of morality and observance of the rights, interests and personal dignity of the persons participating in the study.

Statistical Analysis

The results of the study were processed using the 'Statistica 10' 'Excel 2014' application software package (Microsoft Corp., Natick, WA, USA). Absolute values were compared with calculation of mean values, error of means, using Student's t-test. For relative values, the exact Fisher test was used. Differences were considered statistically significant with

RESULTS

The results of the triple scheme of anti-*Helicobacter* therapy of DM2 group 2 and control group 1 are presented in Table 2.

It should be noted that initially the total GSRS score was significantly higher in group 2 than in group 1, which gave a more pronounced clinical picture of GDD. IS, RS and AP were clinically significantly more frequent in group 2 than in group 1. In turn, DS was significantly more frequent in group 1. CS was observed with approximately the same frequency in both groups.

After 1 month of treatment, including anti-*Helicobacter* treatment, in group 1, the manifestations of IS, RS and AP decreased significantly compared with initially, but CS began to be observed more often. There were no significant changes in DS. In general, the overall average GSRS score became significantly lower. In group 2, a significant decrease in the manifestations of IS and RS also occurred with the use of therapy, but DS became more frequent in patients. The total GSRS score decreased significantly from 79.6 to 54.6 (P < 0.05).

When EGD was performed after completion of treatment, 70.6% of group 1 and 61.5% of group 2 patients had positive dynamics in the form of healing of ulcers and erosions, with improvement of the histological picture of the mucosa of the stomach and duodenum. The effectiveness of eradication with triple anti-*Helicobacter* therapy was established: 67.6% and 65.3% in groups 1 and 2, respectively (P > 0.05).

The study revealed that initially BOGS was significantly more frequent in group 2 with DM2 than in control group 1. In this case, the triple therapy scheme reduced the number of patients with BOGS in both groups, but this decrease was not significant.

As can be seen from Table 3, the initial clinical picture, according to the overall average GSRS score, was significantly more pronounced in group 4 with DM2, compared with control group 3. IS, AB, RS and, more rarely, DS were significantly more frequent in group 4. When a sequential scheme was used, the manifestations of DS, IS, AP and RS significantly decreased in group 3. Similar positive changes occurred in group 4, which also were significant.

In the course of the treatment, endoscopic remission was achieved in 93.3% of patients in group 3 and 82.1% in group 4. Effective eradication of against an optimised sequential scheme occurred in 90% of patients in group 3 and in 85.7% of patients in group 4.

Initially, BOGS in the small intestine, like in the case of the triple scheme of treatment, was observed significantly more often in group 4 than in group 3. However, unlike the results of treatment with triple therapy, under this scheme in groups 3 and 4 there was a significant decrease in the number of patients with BOGS at the end of therapy.

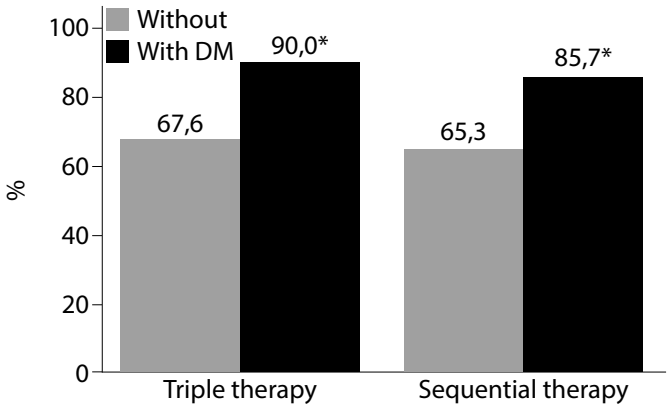
DISCUSSION

Thus, our results enabled us to compare the effectiveness of the triple and optimised sequential schemes of anti-*Helicobacter* therapy in patients with GDD with and without DM2. It should be noted that, according to recommendations

Table 3. Results of treatment with optimised sequential anti-Helicobacter therapy scheme of DM2 group 3 and control group 4.

Sign	Control (group 3) n = 30		Patients with DM (group 4) n = 28	
	baseline	After treatment	baseline	After treatment
Patients with HP, n (%)	30 (100)	3 (10)*	18 (100)	4 (14.2)*
Patients with remission according to data of EGD, n (%)	-	28 (93.3)	-	23 (82.1)
Total GSRS, score	57.2±3.8	30.2±2.4*	76.4±2.5	38.6±2.4*
Syndromes of GSRS, score				
DS (diarrhoea)	13.6±1.4	4.4±1.1*	9.4±1.2	3.1±1.1*
IS (dyspeptic)	18.2±1.2	7.8±1.4*	25.2±2.6	11.1±1.3*
CS (constipation)	7.8±1.3	6.3±1.2	10.8±2.2	7.9±2.1
AP (abdominal pain)	7.2±1.4	3.1±0.6*	12.8±1.3	5.2±1.3*
RS (reflux)	9.8±1.2	3.6±1.2*	18.2±1.8	8.4±1.4*
BOGS,n, %	14 (46.7)	6 (20)*	22 (78.5)	6 (21.4)*

Notes: reliability of differences in baseline values between groups, P < 0.05. *Reliability of differences with baseline values in each group, P < 0.05.



* – Significance of differences, P < 0.05

Fig. 1. Comparison of the effectiveness of HP with the triple and the optimised sequential therapy schemes.

on the problem of helicobacteriosis, the goal of treatment is more than 80% eradication of the pathogen, whereas the optimal goal is considered to be 85% to 90% eradication [1]. However, as evidenced by numerous Russian and foreign studies, over the past decade the effectiveness of the classical first- and second-line treatment schemes has decreased and rarely exceeds the required percentage [3]. As our studies showed (Fig. 1), in the triple therapy group, in patients with and without DM2, the percentage of eradication did not reach 70%.

For patients with DM2, the percentage of eradication was lower than that in the control group, although not significantly. In patients receiving optimised sequential therapy, a greater effect of eradication was obtained, namely, 90% versus 85.7% in patients without and with DM2, respectively. Differences with the triple treatment scheme were significant (P = 0.035 and P = 0.044 for patients without and with DM2, respectively).

Both treatment schemes in all groups led to a reduction in the clinical picture of GDD, but this was observed to a greater extent in the groups with optimised sequential therapy. For patients with DM2, the ΔGSRS (decrease in the total score) with triple therapy was 25.1 ± 3.2 points (P < 0.05), whereas ΔGSRS with successive therapy was 38.4 ± 2.5 points (P < 0.05).

Endoscopic remission was also found in a greater percentage of cases in all sequential therapy groups with respect to triple therapy.

The consistent scheme effectiveness can be judged by a series of clinical studies conducted in different countries around the world. Thus, in Italy and Spain, studies were performed from 2003 to 2007 involving more than 100 people each, and the level of eradication of reached 91% to 95% [12]. In the study of Kim et al. (2011) conducted in South Korea, the efficacy of the 10 day sequential scheme was 92.6% compared with 85% for the 14 day triple scheme with the same adverse events [13]. A meta-analysis including 36 randomised controlled studies demonstrated the advantages of a sequential scheme, with a higher efficacy (84.1%) compared with that of the classical triple therapy protocol (75.1%) [14]. However, it should be noted that none of the studies listed concerned patients with DM2.

According to recommendations of the Russian Gastroenterological Association (2012), the sequential scheme is approved as an alternative and highly effective treatment, the effect of which depends little on the resistance to clarithromycin. So it can be used in areas where this resistance is high or where it is not investigated. In these recommendations, a sequential scheme of treatment was noted to be promising, and with respect to Russia, Russia requires its own studies to clarify its place in the therapy of infection [1].

The data on the effect of eradication therapy on BOGS in the small intestine are of interest. Initially, eradication occurred in 44% to 46% of GDD patients without DM2 (depending on the group) and in 69% to 78% of those with DM2. In our study, only an optimised sequential therapy scheme significantly reduced the number of patients with BOGS in both groups.

On the basis of analysis of the results obtained in our study, we concluded that use of an optimised sequential treatment scheme for patients with helicobacteriosis and GDD has significant advantages over classical triple therapy. This is subject to patients without and with concomitant DM2. For the latter group, these results are particularly significant, because previously such studies have not been conducted to our knowledge. As part of the Maastricht V consensus, the

sequential scheme protocol is regulated as first-line therapy, especially in regions with high resistance to clarithromycin [2]. However, because in the Khabarovsk Territory no studies to analyse this resistance were performed, the sequential scheme becomes particularly relevant.

CONCLUSIONS

Use of an optimised sequential scheme in patients with DM2 and GDD as an anti-*Helicobacter* therapy enabled an increased effectiveness of eradication compared with the triple scheme of therapy from 65.3% to 85.7%. Use of an optimised sequential eradication scheme in patients with DM and GDD has advantages over the triple scheme in terms of the degree of reduction in the clinical picture and achievement of endoscopic remission in patients. The prescription of an optimised sequential therapy scheme for patients with DM and GDD, in contrast to the triple scheme of therapy, enables significant reduction in the number of patients with concomitant BOGS in the intestine.

ADDITIONAL INFORMATION

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Participation of authors. Fedorchenko Yu.L.—conception, study design, data analysis and writing the article; Martyniuk M.V.—collection of material, processing, data analysis and writing the article.

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