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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

OPTIMIZATION OF ERADICATION TREATMENT OF PATIENTS WITH GASTRODUODENAL DISEASES ASSOCIATED WITH HELICOBACTER PYLORI

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GENERAL DESCRIPTION OF THE WORK

The relevance of the work. Today, Helicobacter pylori is one of the most common human bacterial infections, according to epidemiological data, about three billion people are infected with this microorganism[1].

It is proved that H. pylori, by colonizing the gastric mucosa, leads to its damage and the development of serious diseases such as peptic and duodenal ulcer, gastric adenocarcinoma and MALT lymphoma (extranodal marginal zone B-cell lymphoma associated with mucous membranes)[2].

To support interdisciplinary research aimed at the study of H. pylori-associated diseases, the European H. pylori – European Helicobacter Pylori Study Group (EHSG). Recent updates to recommendations for anti-Helicobacter therapy are due to new clinical studies on eradication and the emergence of such key international documents as the Kyoto Consensus and Maastricht V (2015) of the European Helicobacter pylori and Microbiota Study Group (EHMSG)[3,4].

Chronic gastritis, peptic ulcer, MALT lymphoma and adenocarcinoma of the stomach are a direct indication for eradication therapy (ET) since the etiopathogenetic role of H. pylori infection in their development has been established for more than a quarter-century. The eradication efficiency should be at least 80%, however, limited choice of the proposed antibiotics in treatment regimens, a steady increase in the level of resistance of H.pylori to them, side effects of anti-Helicobacter therapy, low patient adherence to

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[1] Mitchell, H, Katelaris, P. Epidemiology, clinical impacts and current clinical management of Helicobacter pylori infection // Med J Aust., -2016. v.204. No 10, - p.376–380.

[2]Ford, A. Helicobacter pylori eradication for the prevention of gastric neoplasia / A.Ford, Y.Yuan, D.Forman [et al.] // Cochrane Database Syst Rev. -July 6, 2020. URL: https://doi.org/10.1002/14651858.CD005583.pub3.

[3] Kuipers E.J, Sugano K., et al., Kyoto global consensus report on Helicobacter pylori gastritis / Gut, -2015. v. 64. No 9, -p.1353-1367.

[4] Malfertheiner P., et al., Management of Helicobacter pylori infection- the Maastricht V/Florenence Consensus Report/ Gut, -2017. v. 66, - p.6-30.

treatment reduce the effectiveness[5]. For increasing of the efficiency the ET in modern clinical practice, the following is used: the use of high doses of proton pimp inhibitors (PPI), the modernization of anti-Helicobacter pylori regimens through the use of more modern antibiotics, adding probiotics and the drugs containing bismuth tripotassium dicitrate (BTD) to them, lengthening duration of ET [6].

Unfortunately, in the context of increasing resistance of H. pylori in many traditionally used antibiotics in the first-line regimens, the eradication efficiency decreases from 80 - 90 to 30 - 60% and even to 12.5 - 18.3% [7].

According to the 19th position of the Kyoto Consensus, eradication schemes should be based on the most effective local scheme, preferably taking into account individual or antibiotic sensitivity in this population (Level of recommendation: strong. Level of evidence: high. Level agreed to awn: 100%)[3].

In recent years, data published in the literature indicates that the decline in the effectiveness of triple first-line therapy is mainly associated with an increase in resistance to macrolides[8]. H.pylori infection is characterized by cross-resistance to existing macrolides, but replacing them in eradication schemes with more modern representatives of this group has several advantages. Such drugs include josamycin, which, in contrast to clarithromycin, has a more complex spatial and chemical structure, due to which the drug's fast translocation from the bacterial cell to the outside is delayed, as a result of

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[5] Yamaoka, Y., Tshibangu-Kabamba, E. Helicobacter pylori infection and antibiotic resistance - from biology to clinical implications // Nature Reviews Gastroenterology &Hepatology, - 2021, v.18, - p. 613–629.

[6] Маев И.В. и др., Возможности оптимизации эрадикационной терапии инфекции *H.pylori* в современной клинической практики /Тер.архив, -Москва: -2017. №2, -с. 84-90.

[7] Thung I., et al., Review article: the global emergence of Helicobacter pylori antibiotic resistance // Aliment Pharmacol. Ther., -2016. v.43, - p. 514-533.

[8] Megraud, F. Helicobacter pylori resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community / F. Megraud, R. Bruyndonckx, S. Coenen [et al.] // Gut. BMJ - April 9, 2021, v.70, s.10. URL: http://dx.doi.org/10.1136/gutjnl-2021-324032.

which it is possible to contact the bacterial cell ribosome[9]. Thus, resistance to josamycin does not appear, which is associated with the expression of efflux pumps characteristic of other representatives of the macrolide group[9].

In the course of antibiotic therapy of patients experience the development of adverse reactions, which as a rule often leads to the patient's refusal of treatment and, as a result, the effectiveness of eradication of this infection again decreases. One of the promising ways to prevent the development of antibiotic-associated changes in the intestinal environment and improve patient's compliance with anti-Helicobacter pylori therapy is to add probiotics to eradication schemes, which is confirmed by the recommendations of the Maastricht Consensus V (2015) EHMSG[4]. Today, several meta-analyses immediately demonstrate that the addition of probiotics based on Saccharomyces boulardii, Bifidobacterium lactis, Lactobacillus rhamnosus to standard ET regimens increases the frequency of eradication by 8.1-14.1%, and also reduces the frequency of side effects associated with ET, especially diarrhea and taste disturbances[10].

The choice of the latest generation of PPIs as the base drug in anti-Helicobacter pylori regimens is one of the options for increasing the effectiveness of H. pylori eradication therapy. The effectiveness of PPI depends on its metabolic rate, which is due to the polymorphism of the gene encoding the isoform of the cytochrome P450-CYP2C19 system and depending on the types of CYP2C19 mutations, the population is divided into the following phenotypic groups: “fast”, “ultrafast”, “intermediate”, “slow” metabolizers 10. Rabeprazole, metabolized non-enzymatically, has a more stable pharmacokinetic profile, which makes it minimally dependent on CYP2C19 polymorphisms[6]. According to one of the provisions of Maastricht V (2015), preference is given to using rabeprazole in Europe and North America is due to the high prevalence of the

[9] Моисеев С. В., Джозамицин: отличительные особенности и перспективы применения // Клин. фармакол. и тер., - Москва: - 2005, № 4, - с.66-70.

[10] Zhou X. Lv.Z., Wang B., Et al. Efficacy and safety of probiotics as adjuvant for Helicobacter pylori infection: a meta-analysis // Exp Ther Med, 2015. v. 9, - p.707-716.

phenotype of “fast” metabolizers 4. In addition, rabeprazole makes it possible to accumulate rather quickly in a large number of parietal cells, while binding the proton pump, thereby leading to a rapid and pronounced inhibition of the production of hydrochloric acid, which from the first day of administration enhances the activity of antibiotics during H. pylori eradication[6]. It should also be noted that the importance of using rabeprazole in H.pylori eradication therapy regimens is also explained by the fact that it has its own anti-Helicobacter pylori activity, which is achieved by stimulating mucin-mediated antibacterial defense mechanisms of the mucous membrane[6].

In the absence of new drugs used in the treatment of H. pylori infection, the optimization of the proposed standard regimens of anti-Helicobacter therapy, which today is considered an important clinical task[6]. Nowadays it can be argued that the inclusion of drugs containing bismuth tripotassium dicitrate (BTD) in the composition of the Helicobacter therapy (HT) regimens is also one of the most successful ways to optimize the treatment of H.pylori infection[11]. The use of BTD is effective not only in classical quadrotherapy schemes but also in its use as the fourth component in standard triple first-line HT schemes increases the eradication efficiency[12]. Thus, it can be said that the use of BTD helps to overcome the resistance of H.pylori to clarithromycin, thereby increasing the effectiveness of anti-Helicobacter pylori treatment. It should also be remembered that the essence of treatment optimization is not only to increase the effectiveness of the applied schemes, but also the safety of their use[4]. A meta-analysis of 35 randomized controlled trials involving 4763 patients showed the safety of bismuth tripotassium dicitrate and good tolerance of such treatment to patients[11].

All the facts described above indicate the urgent need to conduct our own research in Azerbaijan which would clarify the level of resistance to the main antibacterial drugs used in the proposed

[11] Dore M.P., Graham D.Y. Role of bismuth in improving Helicobacter pylori eradication with triple therapy // Gut, 2016. v. 65. No5, -p. 870-878.

[12] McNicholl A. Combination of bismuth and standard triple therapy eradicates Helicobacter pylori infection in more than 90% of patients / D.Bordin, A.Lucendo, M.Fernandez [et al.] // ClinGastroenterolHepatol., -2020, v.18. No 1, -p. 89–98.

standard schemes of the Maastricht recommendations and, depending on the results of these studies, offer adapted schemes of the HT. Thereby optimizing eradication therapy. A correct prognosis of the effectiveness of the HT will help to improve the quality and life expectancy of patients, which is an urgent problem of modern medicine.

Object and subject of the work: Educational and Therapeutic Clinic of the AMU, patients with gastric and duodenal ulcer associated with H. pylori infection.

Purpose of the work: to optimize and increase the effectiveness of the anti-Helicobacter pylori therapy by modifying the standard three-component scheme.

Research Objectives:

1. Bacteriological examination of H. pylori strains and determination of sensitivity to antibacterial drugs proposed in international recommendations.

2. A comparative assessment of the effectiveness of classical triple therapy and modified treatment regimens.

3. Analysis of the clinical, endoscopic and morphological components of gastroduodenal diseases associated with H. pylori infection and the effect of tested H. pylori eradication patterns on their dynamics.

4. Assessment of the dynamics of quality of life indicators in patients using the studied treatment regimens.

Methods of the work: Clinical diagnostic, therapeutic, sociological (questionnaire), statistical.

The main provisions of the dissertation submitted to the defense:

- The improvement of the clinical and endoscopic picture of the disease is much less observed with the use of classical triple therapy compared with the modified regimens of anti-Helicobacter therapy.

- Adding a probiotic to the studied regimens leads not only to a decrease in side effects during their application but also to an improvement in eradication parameters.

- The inclusion of bismuth tripotassium dicitrate in one standard scheme and the replacement of clarithromycin with josamycin

in another scheme in the standard triple therapy of bismuth has certain advantages over classical triple therapy, which is confirmed by the pronounced positive dynamics of diseases in the study of clinical, laboratory, endoscopic and morphological results.

- The rapid relief of the main symptoms of gastric ulcer and duodenal ulcer associated with H. pylori leads to an increase in the quality of life of patients.

Putting research results into practice:

The results of the studies have been introduced into the clinical practice of the Department of Rheumatology-Gastroenterology of the Educational Therapeutic Clinic of the Azerbaijan Medical University. The data obtained as a result of the study are included in the materials of lectures and practical classes of the Department of the Internal Medicine III AMU.

The scientific novelty of the work:

- Based on the study of the effectiveness of the applied modified regimens, the most optimal regimens of eradication therapy were selected taking into account the regional resistance of H. pylori strains to antibacterial drugs.

- A comparative analysis of the morphological picture before and after treatment with modified regimens of gastric and duodenal ulcer associated with H. pylori infection.

- The benefits of using modified anti-Helicobacter treatment regimens have been comprehensively studied: with the addition of a probiotic (lactobacillus rhamnosus GG-6milliard, saccharomyces boulardii-2,5milyard, bifidobacterium lactis Bb-12), the bismuth tripotassium dicitrate, with the replacement of clarithromycin with josamycin.

- The questionnaire method according to the SF-36 survey assessed the quality of life in the examined patients with peptic ulcer and duodenal ulcer associated with H. pylori infection as a result of the use of eradication therapy.

The theoretical and practical significance of the work:

The theoretical significance of this study lies in the fact that in conditions of growing resistance of H. pylori to the proposed antibacterial drugs, based on the data obtained during the study, by

means of a comparative analysis, modified schemes of eradication treatment have been developed and proposed. And in practical terms the use of the proposed modified regimens of the anti-Helicobacter therapy with the replacement of clarithromycin with josamycin in one and with the inclusion of bismuth tripotassiumdicitrate in another in practical terms leads to a higher level of eradication, a significant improvement in the clinical endoscopic and morphological picture. Due to the use of a probiotic in these regimens, adverse reactions from antibiotics are practically minimized, the tolerance of therapy is improved, the compliance of patients and the efficacy of tested anti-Helicobacter regimens are increased.

Personal contribution of the author. The author carried out an analytical review of the literature (100%); collection and processing of primary material (the share of participation is more than 95%), the goal and objectives of the study are set, the stages and the program of the study are determined (98%), the statistical processing of the results of the study is carried out (95%). The analysis of the research results (100%), the development of conclusions and practical recommendations (85.0%). The share of the author's participation in the preparation of publications is over 90%.

Approbation of work.

On Nowember 29, 2018 the initial discussion of the dissertation was held at a joint meeting of the Departments of the Internal Medicine I, II, III of the Azerbaijan Medical University. The work was tested on June 14, 2021 at the scientific seminar of the Approval Commission of the Dissertation Council ED.2.27 at the Azerbaijan Medical University. The results of the research were introduced into the clinical practice of the Department of Rheumatology-Gastroenterology of the Educational Therapeutic Clinic of the Azerbaijan Medical University. The data obtained as a result of the research are included in the materials of lectures and practical classes of the Department of the Internal Medicine III of the AMU.

Place of research: Educational and Therapeutic Clinic of the Azerbaijan Medical University, histomorphological laboratory of the National Cancer Center.

The structure and scope of the dissertation. The dissertation is presented on 168 pages of computer text: introduction - 9 pages (16579), 1 chapter (literature review - 26 pages (51384), 2 chapter (materials and research methods) - 30 pages (50175), 3 chapter (results (1415), practical recommendations - 1 page (840), 158 works reflecting the list of used literature - 17 pages, 6 tables and 22 figures. The work without illustrations and bibliography is 235491 characters.

Publications:

On the topic of the dissertation 12 printed works (7 articles and 5 thesis) were published. Four out of them (2 articles and 2 thesis) were published abroad.

MATERIALS AND METHODS OF RESEARCH

The work was carried out on the basis of the Training Therapeutic Clinic of the Azerbaijan Medical University from January 2014 to 2016. To solve the tasks, 300 patients were included into the study, who were selected according to the inclusion criteria in the study, i.e. male and female patients aged 18 to 65 years with uncomplicated gastric and duodenal ulcer associated with H. pylori infection; patients who have not previously received antibiotic therapy for H. pylori eradication; lack of acceptance by patients in the last 4 weeks before diagnostic tests of proton pump inhibitors, bismuth preparations and antibiotic therapy. In order to compare the effecttiveness of the applied anti-Helicobacter regimens, patients using random selection with almost the same complaints were divided into five groups of 60 patients each. For each group, appropriate drug combinations were used. The first group consisted of patients taking standard three-component therapy - rabeprazole 20 mg twice a day + clarithromycin 500 mg twice a day + amoxicillin 1000 mg twice a day. In patients of the second group, in the standard three-component therapy, clarithromycin was replaced with josamycin - rabeprazole 20 mg twice a day + josamycin 500 mg twice a day + amoxicillin 1000 mg twice a day. A probiotic (lactobacillus rhamnosus GG-6milyard, saccharomyces boulardii-2.5 milyard, bifidobacterium lactis Bb-12) was added 1 capsule once a day to all three other groups.

Thus, patients of the third group took rabeprazole 20 mg twice a day + clarithromycin 500 mg twice a day + amoxicillin 1000 mg twice a day + probiotic 1 capsule per day, and along with the addition of a probiotic, clarithromycin was replaced with josamycin in the same dosage as in the second group. In patients of the fifth group, BTD 120 mg 1 tablet four times a day was also added to the standard three-component therapy in parallel with the probiotic. After completing a 14-day course of antibiotic therapy, patients continued taking rabeprazole for the next two weeks, and patients of the fifth group took BTD along with rabeprazole.

All patients included in the study underwent a comprehensive examination, consisting of clinical, instrumental and laboratory examination methods. The initial detection of H.pylori was carried out by the following diagnostic methods: a quick urease CLO test, blood serum samples for H. pylori infection using the enzyme-linked immunosorbent assay on a StatFax 303 Plus semiautomatic analyzer using the "RioCheck, Inc 837 test system CowanRdBurlingame, CA 94010", as well as a urease breath test (Headway HUBT-20 apparatus) with urea labeled with the stable thirteenth carbon isotope (13C). After four weeks after completion of treatment, the effectiveness of the eradication therapy urea breath test was carried out, and the determination in the stool H.pylori antigens.

In our study, we also used the bacteriological method for determining H. pylori infection in order to determine the sensitivity of this microorganism to the antibiotics used, since antibacterial drugs are a determining factor in the effectiveness of the proposed eradication therapy regimens of the Maastricht accords. For bacteriological research during fibrogastroduodenoscopy (FGDS), biopsy specimens were collected from the antrum for large and small curvature, the area of the angle of the stomach, body for large and small curvature. Two methods were used to isolate H.pylori: classical cultivation and microcapillary method. The sensitivity study of H. pylori was carried out in accordance with the recommendations of the Institute for Clinical and Laboratory Standards of the USA (CLSI) by the disk diffusion method (Kirby-Bauer) in cation-balanced Muller – Hinton agar (BBL, USA) enriched with 5% horse blood.

Of the instrumental examination methods, FGDS, ultrasound examination of the abdominal cavity were used. Before treatment, the presence of an inflammatory process (hyperemia, swelling), erosive - ulcerative defects of the mucous membrane of the stomach and duodenum, as well as the localization, size, shape, and nature of these defects were determined during FGDS. Eight weeks after eradication therapy, a control FGDS was performed to assess the dynamics of the endoscopic picture.

In order to conduct a comparative assessment of the state of the mucosa of the gastroduodenal zone when applying schemes No.4 (rabeprazole + josamycin + amoxicillin + probiotic) and No.5 (rabeprazole + clarithromycin + amoxicillin + BTD + probiotic) relative to scheme No.3 (rabeprazole + clarithromycin + amoxicillin probiotic) studied the morphological picture before and after treatment in the third, fourth and fifth groups (40 patients from each group). In 120 patients included into a histological examination, FGDS was combined with an aim biopsy from 5 points of the mucous membrane (antrum in the greater and lesser curvature, from the region of the angle of the stomach, from the body in the greater and lesser curvature) for subsequent histological examination to determine the severity of inflammatory and dystrophic changes.

All gastrobiopsy samples taken from patients were examined in the histomorphological laboratory of the National Cancer Center. A morphological assessment of the state of the mucous membrane of the gastroduodenal zone was carried out in accordance with the visual-analog scale according to the modified Sydney system (1996), taking into account the following indicators: activity, inflammation, atrophy, intestinal metaplasia.

The quality of life of patients included in the study was also evaluated. Assessment of quality of life (QOL) in patients with various diseases is very relevant today. Thanks to this assessment, it is possible to determine the patient's tolerance of the disease, to solve some issues that arise during treatment. The analysis of the quality of life can also be used as an additional criterion in the selection of a particular treatment regimen to compare the effectiveness of the applied regimen, especially when modifying them using new drugs.

To study the quality of life in the patients of our study, the Russian version of the international questionnaire SF-36 (MOS-SF – Item Short Health Survey) was used twice, i.e. before and after treatment. This questionnaire contains thirty-six items grouped into eight scales. Thanks to these questions, the quality of various spheres of human life was assessed, such as physical functioning, role-playing activities, bodily pain, general health, vitality, social functioning, emotional and mental health. Data was processed using a special computer program for Windows XP. The data obtained were subjectted to statistical processing with the calculation of the significance of differrences. Instructions for processing data obtained using the SF-36 questionnaire were prepared by Evidence Clinical and Pharmacological Research.The results of the study were analyzed by methods of variation statistics for groups that differ in qualitative characteristics, absolute numbers, their percentage shares, and its average error were determined. Fisher's exact test was used to assess differences between groups. And to characterize groups of homogeneous units, their arithmetic mean values (M) and its standard error (m) were determined. In order to compare the quantitative data in the observation groups, a parametric method for assessing differences in indicators was used - Student t-test. A statistical difference between the groups was considered significant at a value of $p<0.05$.

Statistical processing was performed using Microsoft Office Excel and the MedCalc application software package on a personal computer.

RESEARCH RESULTS AND DISCUSSION

Basically, the complaints consisted of pain, dyspeptic symptoms, and general weakness. So, when analyzing subjective symptoms, it was revealed that in all five groups, the pain was the dominant complaint.

Comparing the nature of the pain syndrome in patients of each of the five groups with gastroduodenal diseases, we can say that there was no reliable significant difference between the groups of examined patients ($p> 0.05$).

Of dyspeptic symptoms, patients complained of heartburn, belching with air or the remnants of eaten food, nausea, vomiting, a

feeling of fullness in the epigastrium after eating or fast satiety, regardless of the amount of food taken. Patients noted flatulence and bloating difficult gas discharge, unstable stools very often.

An objective examination attracted attention to pain in the epigastrium during palpation and percussion of the anterior abdominal wall, the presence of limited muscle tension over the projection of the affected organs. Conducting an analysis of an objective examination of the organs of the gastrointestinal tract of patients in our study, there were no significant differences between the comparison groups.

Analyzing the results of an objective study of patients with gastroduodenal pathology associated with H.pylori, we can say that the identified signs were characteristic of the classical clinic of these diseases.

An endoscopic examination at the time of an exacerbation of gastroduodenal disease on the gastric mucosa and duodenum revealed signs of nonspecific inflammation in the form of edema and hyperemia, thinned or atrophied folds of the mucosa, single or multiple erosions, ulcerative defects of oval and round shape, with hematin or fibrin film at the bottom concomitant inflammatory infiltration. Peptic ulcer was detected in 155 patients (51.7% of the total number of patients), and the mucosal defect was localized mainly in the antrum. Duodenal ulcer was recorded in 145 patients (48.3% of the total number of patients), while the ulcer defect was oftener located on the front wall of the duodenal bulb.

The results of endoscopic examination before treatment are presented in table 1.

Table 1

Endoscopic picture in patients with erosive - ulcerative lesions of the gastric and duodenum associated with H.pylori

Indicator	Scheme No1 n=60		Scheme No2 n=60		Scheme No3 n=60		Scheme No4 n=60		Scheme No5 n=60	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Hypere-mia and edema	32	53,3	35	58,3	34	56,7	38	63,3	36	60,0
Erosive-ulcerative defects	53	88,3	49	81,7	45	75,0	48	80,0	44	73,3

In general, when analyzing the localization, shape and size of erosive-ulcerative defects, no statistically significant differences between the groups were obtained ($p > 0.05$).

Before treatment, morphologically, according to the presence of inflammation and activity in the gastroduodenal zone, no significant differences were observed between the comparison groups. In all patients of the third, fourth and fifth groups of 40 people each included in the morphological study, inflammation was recorded both in the fundus and antrum of the stomach. In 30 (75.0%) patients of the third group, in 26 (65.0%) patients of the fourth group, and in 28 (70.0%) patients of the fifth group, gastritis activity was mainly more pronounced in the antrum compared with the fundus. So, in the fundus of the stomach in 10 (25.0%) of the third, in 14 (35.0%) of the patients of the fourth group and in 12 (30.0%) of the fifth group of patients, process activity was noted. In all three comparison groups, the activity of inflammation was mainly strong and moderate. The atrophic process was mainly recorded in the antrum of the stomach - in the third group in 32 (26.7%) people, in the fourth group in 30 (25.0%) people, and in the fifth group in 33 (27.5%) patients. At fundus, atrophy was observed in 8 (6.7%) patients of the third group, in 5 (4.2%) of the fourth group and in 7 (5.8%) people of the fifth group. In a certain number of patients with an atrophic process, intestinal metaplasia was also recorded. In metaplasia of the large intestine and small intestine type, no significant statistical differences were observed ($p > 0.05$). Thus, in the antrum, intestinal metaplasia was observed in the third group in 10 (31.3%) of 32 people, in the fourth in 7 (23.3%) of 30 people, and in the fifth in 9 (27.3%) from 33 patients. And in the fundus, intestinal metaplasia was observed in 3 (37.5%) of 8 patients of the third group, in 2 (40.0%) of the fourth group and 5 (3, 42.9%) of 7 people of the fifth group.

In all groups during ultrasound, signs of diffuse changes in the pancreatic parenchyma were often observed. The size of the pancreas was within normal limits. With this instrumental study of the liver, 35% of patients showed signs of non-alcoholic steatohepatosis.

To study the primary antibiotic resistance of H.pylori strains isolated from the studied patients by the bacteriological method,

gastrobioptates of 103 patients aged 18 to 65 years were used. The bacteriological method identified the microorganism in 52 patients, which amounted to 50.5%. The sensitivity of H. pylori to antimicrobial agents was determined in 41 strains isolated by the microcapillary method, due to the failure of the classical cultivation method. Among the analyzed H. pylori isolates, strains of 23 (56.1%) were resistant to metronidazole, 6 (14.6%) to clarithromycin, 1 (2.4%) to tetracycline, 10 (24.4%) to levofloxacin. In addition, 1 (2.4%) strain resistant to amoxicillin was identified. In cases of detection of resistance to two or more groups of antimicrobial agents, the helicobacter strain was classified as multiresistant. During the study, 5 (12.2%) microorganism strains were multiresistant. Double resistance to clarithromycin and metronidazole was found in 1 (2.4%) isolate, metronidazole and levofloxacin - in 4 (9.8%) microorganisms.

Gastroduodenal diseases have a negative effect on all aspects of the life of patients: emotional, physical and psychological. A survey using the SF-36 questionnaire was conducted in each group in 20 people before and after treatment. When questioning patients, a decrease was observed mainly for all items. But as the survey showed before treatment, the emotional side was mainly affected, that is, the psychological component of the patient's health, given the pronounced clinical symptoms, and mainly this abdominal pain was detected at a low level. The results of the survey before treatment are presented in table 2.

Table 2

QL indicators according to the survey test SF-36 before treatment

Groups	Physical component of health, PH				Psychological component of health, MH			
	Phys. function PF	Role play in function RP	Intensity of the pain BP	Gene-ral health GH	Life activi-ty VT	Social function SF	Role function RE	Psych. health MH
Group 1	59,5± 5,04	43,8± 10,08	39,6± 5,16	44,3± 3,31	39,0± 3,47	41,3± 5,67	46,7± 8,85	45,2± 3,15
Group 2	56,7± 5,21	47,0± 5,46	43,2± 5,32	42,2± 1,23	37,1± 3,23	36,3± 5,34	49,9± 7,35	39,4± 7,34
Group 3	52,3± 5,25	52,5± 11,17	35,3± 4,95	46,8± 2,52	38,0± 3,90	38,1± 6,12	53,3± 10,65	43,2± 3,57
Group 4	52,8± 5,87	42,8± 10,37	39,2± 4,26	37,2± 2,38	31,3± 2,69	42,7± 4,59	63,5± 14,85	33,8± 3,12
Group 5	54,3± 5,85	28,8± 8,94	38,5± 4,84	34,5± 3,34	34,0± 2,89	43,1± 4,30	26,7± 8,24	35,6± 2,49

Next, a comparative analysis of the dynamics of the clinical picture, and laboratory and instrumental studies as a result of the application of tested schemes in the corresponding groups was carried out. When evaluating the effectiveness of the treatment, the following indicators were taken into account: dynamics of pain and dyspeptic syndromes; the effectiveness of eradication therapy according to the urease breath test and determination of H.pylori antigen in feces; dynamics of endoscopic and morphological patterns; assessment of quality of life according to the SF-36 survey.

The number of PP-patients (per-protocol, fully treated according to the study protocol) varied depending on the combination of drugs used according to the treatment regimen. So, during eradication according to the scheme No.1 (rabeprazole + clarithromycin + amoxicillin) n = 39 (65.0%), scheme No.2 (rabeprazole + josamycin + amoxicillin) n = 45 (75.0%), scheme

No.3 (rabeprazole + clarithromycin + amoxicillin + probiotic) n = 52 (86.7%), and in the case of schemes No.4 (rabeprazole + josamycin + amoxicillin + probiotic) and No.5 (rabeprazole + clarithromycin + amoxicillin + BTD + probiotic), respectively, n = 57 (95.0%) and n = 58 (96.7%).

Monitoring the effectiveness of the eradication therapy according to laboratory parameters was carried out 4 weeks after the end of the course of eradication therapy with a urease breath test or determination of H. pylori antigen in feces. Given that the eradication efficiency should be at least 80%, a replacement of clarithromycin with josamycin in the classical three-component eradication therapy of the first line was made. This increased the effectiveness of scheme No.2 relative to scheme No. 1 (51.3%, 20 of 39 PP-patients of the first group) to 75.6% (34 of 45 PP-patients), which was significantly more effective than classical triple therapy with OR 2, 94 (95% CI 1.164-7.409; p1 = 0.0225). However, at the same time, it was not possible to overcome the line of eighty percent effectiveness. In this regard, a probiotic (lactobacillus rhamnosus GG-6milyard, saccharomyces boulardii-2.5 milliard, bifidobacterium lactis Bb-12) was added to the

remaining three regimens, resulting in a decrease in the severity of side effects from the antibiotics used and increasing the number of PP-patients significantly improved eradication rates. So in patients of the third group who received a combination of drugs according to scheme No.3, the treatment efficiency relative to scheme No.1 was respectively 80.8% (OR 3.99; 95% CI 1.570 - 10.140; p1 = 0.0036) in 42 of 52 PP - patients. And the eradication efficiency in the fourth group, who received scheme No. 4 with josamycin instead of clarithromycin, was even higher relative to the third and first schemes and amounted to 89.5% (OR 8.07; 95% CI 2.816-23.156; p1 = 0.0001 and OR 2.02; 95% CI 0.679-6.028; p3 = 0.2055) in 51 of 57 PP patients. When using classical triple therapy with BTD, the level of eradication of H.pylori infection in the fifth group increased to 96.6% (OR 26.60; 95% CI 5.680-124.565; p1 = 0.0001 and OR 6.67; 95% CI 1.387-32.046; p3=0.0179) in 56 of 58 PP patients. When analyzing side effects from the used eradication therapy regimens, it was noted that when applying regimens 1 and 2, where there was no probiotic, the incidence of side effects (nausea, bloating, discomfort in the abdomen, defecation more than 3 times a day with watery stools) was enough high and amounted to 51.3% (in 20 of 39 PP-patients) and 51.1% (in 23 of 45 PP-patients), respecttively, while the OR was only 1.00. The OR of the formation of at least one side effect in patients receiving treatment regimens No.3, No.4, No.5 with the addition of a probiotic compared to the first two schemes was 8.07 - 6 (11.5%) out of 52 PP-patients (95% CI 2.803-23.232; p = 0.0001), 18.95-3 (5.3%) of 57 PP patients (95% CI 5.055-71.023; p = 0.0001) and 29.47-2 (3,4%) of 58 PP patients (95% CI 6.294-138.022; p = 0.0001), respectively. Statistical analysis revealed no significant differences in safety between groups.

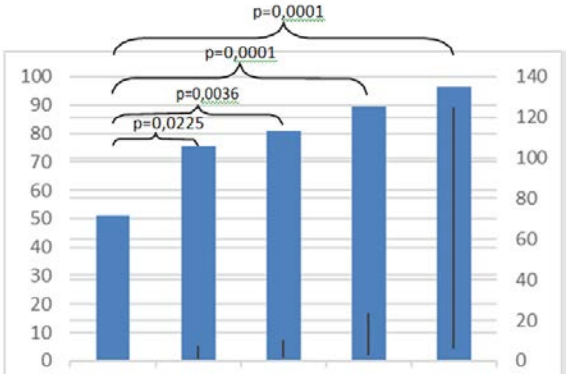

Fig. 1 Treatment efficacy

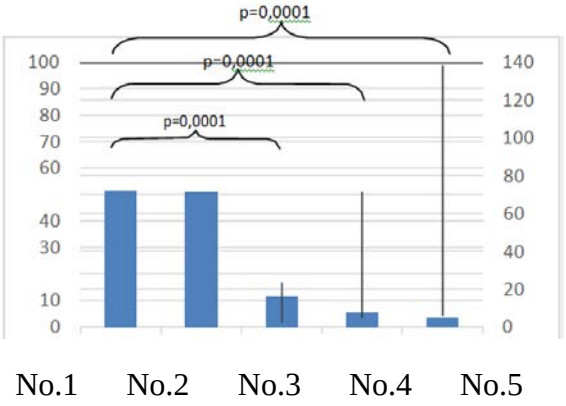

Fig. 2 Side effects

When studying the dynamics of the intensity of the pain syndrome, it was revealed that against the background of the therapy in the fourth and fifth groups, the pain had completely passed on the sixth and fifth day of treatment, respectively. In the remaining three groups, pain syndrome significantly decreased only on the tenth day of treatment. In parallel with the pain syndrome, an assessment was given of the change in pain in the epigastric and pyloroduodenal

areas during palpation, the absence of muscle tension. As it turned out, these symptoms stopped at the same time as the pains in groups 4 and 5, and in groups 1, 2 and 3, they decreased three to five days after the pain was stopped. In the study of gastric dyspepsia syndrome in dynamics, it was noted that the complete relief of dyspepsia syndrome, i.e. 100% of patients of groups 1,2 and 3 occurred by the fourth week from the start of treatment, and on the tenth day, 100% of patients of groups 4 and 5 had practically no complaints of dyspepsia. Analysis of changes in symptoms of intestinal dyspepsia showed that basically stools returned to normal on the eighth day of therapy in groups 4 and 5, and in groups 1,2,3 in 100% of patients on the tenth day.

To study the effectiveness of the tested regimens, a control fibro gastro duodenoscopy was carried out by the eight week of treatment, which revealed that in all groups receiving modified regimens of eradication treatment, more pronounced positive dynamics compared with the first group treated with classical triple therapy (scheme No1). So, if in the antrum the decrease or disappearance of hyperemia and edema in the patients of the first group was 48.7% (Scheme No1), then in the other groups the following was noted in comparison with it: the second (Scheme No. 2) - 71.1% (OR 2.59; CI 1,054-6,372; p1 = 0,0381) and in the third (scheme No. 3) - 80.0% (OR 4.21; CI 1.607-11.032; p1 = 0.0034). Scheme No. 4 and No. 5 also proved to be significantly more effective than scheme No. 1, i.e. 84.2% (OR 5.61; CI 2.173-14.506; p1 = 0.0004) and 89.1% (OR 8.63; CI 2.814-26.477; p1 = 0.0002), respectively. However, statistically, these schemes in terms of efficiency did not exceed scheme No3, i.e. scheme No4 was 84.2% (OR 1.33; CI 0.481-3.698; p3 = 0.5804), and scheme No. 5 - 89.1% (OR 2.05; CI 0.629-6.680; p3 = 0, 2337). As can be seen from the diagram, the positive dynamics of the endoscopic picture is also observed in all groups and in the fundus. In this case, a decrease or disappearance of hyperemia and edema in the first group (scheme No.1) was observed in 46.2% of patients, in the second group (scheme No. 2) in 68.9% (OR 2.58; CI 1,059-6,300; p1 = 0.0369), in the third group (scheme No. 3), 73.1% had (OR 3.17; CI 1.315-7.623; p1 = 0.0101), while in the fourth

group (scheme No. 4) - 86.0% (OR 7.15; DI 2.689-18.987; p1 = 0.0001; OR 2.26; CI 0.858-5.932; p3 = 0.0988) and in the fifth group (Scheme No. 5) - 90.2 % (OR 10.73; CI 3.512-32.805; p1 = 0.0001; OR 3.39; CI 1.119-10.263; p3 = 0.0308). As for the dynamics in the bulb, 12 p.p., then in the first group (scheme No. 1) in 48.7% of patients, in the second group (scheme No. 2) in 73.3% (OR 2.89; CI 1.163-7.202; p1 = 0.0223), in the third group (scheme No. 3), 61.1% (OR 1.65; CI 0.660-4.144; p1 = 0.2827), and in the fourth (scheme No. 4) group 82, 5% (OR 4.95; CI 1.957-12.507; p1 = 0.0007; OR 2.99; CI 1.149) and in the fifth (chart No. 5) group, 86.1% (OR 6.52; CI 2.099- 20.289; p1 = 0.0012; OR 3.95; CI 1.239) there was a decrease or disappearance of hyperemia of edema. In the post bulbar department, the effectiveness of treatment according to the endoscopic picture was as follows: In the first group of patients receiving treatment according to scheme No. 1, it was 46.2%, in the second group with scheme No. 2 it was 68.9% (OR 2.58; CI 1.059- 6.300; p1 = 0.0369), in the third group with the scheme No. 3 was observed in 63.5% of patients (OR 2.03; CI 0.870-4.720; p1 = 0.1016), while the positive dynamics compared with the first and second groups was more pronounced among patients of the fourth group (scheme No. 4) - 86.0% (OR 7.15; CI 2.689-18.987; p1 = 0.0001; OS 3, 52; CI 1.388-8.997; p3 = 0.0084) and the fifth group with scheme No. 5 - 87.9% (OR 8.50; CI 3.095-23.342; p1 = 0.0001; OR 4.19; CI 1.589-11.076; p3 = 0.0038). Judging by the dynamics of the endoscopic picture, epithelization of erosive-ulcerative defects in the gastroduodenal zone was observed in 15 (38.5%) of 39 patients of the first group (Scheme No. 1), in the second group (Scheme No. 2) in 29 (64.4%, OS 2.90; CI 1.193-7.050; p1 = 0.0188) out of 45 patients, in the third group (Scheme No. 3) in 19 - (55.9%, OS 2.03; CI 0.796-5.163; p1 = 0 , 1387) out of 34 patients, in the fourth group (Scheme No. 4) in 50 (87.7%, OR 11.43; CI 4.118-31.715; p1 = 0.0001; OR 5.64; CI 1.991-15.972; p3 = 0.0011) out of 57 patients and in the fifth group (Scheme No. 5) - in 32 (94.1% OR 25.60; CI 5.339-122.742; p1 = 0.0001; OR 12.63; CI 2.599-61.379 ; p3 = 0.0017) out of 34 patients. All of the above is clearly illustrated in Fig.3.

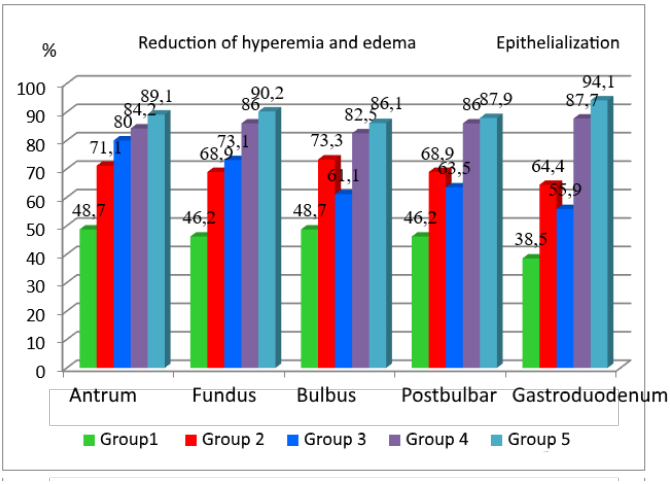

Fig. 3. Endoscopic view after treatment

Histological examination of biopsy samples showed that when using scheme No. 3, a decrease in inflammation was observed - in 25 (62.5%) patients in the fundus of the stomach, a decrease in the degree of activity of 23 (57.5%)) patients in antrum, 24 (60.0%) patients in the fundus of the stomach. Morphological study showed when using scheme No. 4, positive dynamics was more pronounced relative to scheme No. 3. Thus, in the antrum, a decrease in inflamemation was observed in 34 (85.0%, OR 3.40; CI 1.156-9.996; p = 0.0261), in 37 (92.5%, OR 6.64; CI 1.732-25.466; p = 0.0058) in the fundus of the stomach, a decrease in the degree of activity –34 (85.0%, OR 7.38; CI 2.201-31.883; p = 0.0018) in antrum, 30 (75.0%, OR 2.00; CI 0.769-5.198; p = 0.1549) - in the fundus of the stomach. And when applying scheme No.5, a decrease in inflamemation was observed - in 35 (87.5%, OS 4.20; CI 1.350-13.065; p = 0.0132) patients in the antrum, in 38 (95.0%, OS 10.23); CI 2.143-48.849; p = 0.0036) patients in the fundus of the stomach, a decrease in the degree of activity - 36 (90.0%, OR 6.65; CI 1.987-22.271; p = 0.0021) in antrum, in 31 (77.5%, OR 2.29; CI 0.866-6.089; p = 0.0948) - in the fundus of the stomach. The decrease in the degree of atrophy in patients using scheme No. 3 was as follows - in the antrum of 32 patients only 15 (46.9%), and in fundus of 8 in 3 (37.5%)

patients. The tendency of a more pronounced decrease in atrophy in relation to scheme No.3 was observed in patients who took scheme No. 4 and No. 5. So when using scheme No. 5 with BTD from 33 patients in 26 (78.8%, OR 4.21; CI 1.421-12.466; p = 0.0095) in antrum, from 7 patients in 6 (85.7%, OR 10.00; CI 0.776-128.781; p = 0.0774) in fundus, a decrease in atrophy was observed, and when applying scheme No.4 of 30 patients in 24 (80.0%, OR 4.53; CI 1.481-14.068; p = 0.0089) in antrum and out of 5 patients in 3 (60.0%, OR 2.50; CI 0.253-24.720; p = 0.4332) in fundus, a decrease in atrophy was also noted.

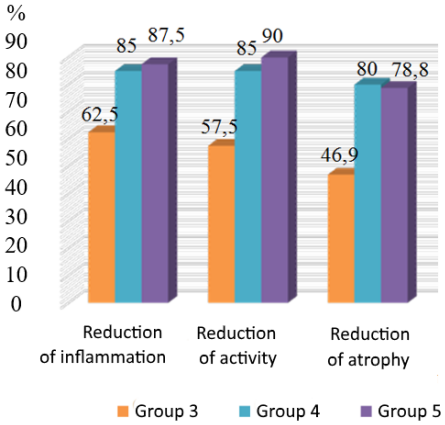

Fig.4. Histological picture after treatment in antrum

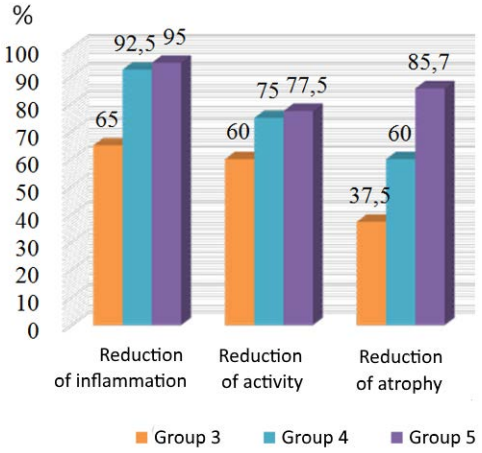

Fig.5 Histological picture after treatment in the fundus

In all groups, at the end of the study, the physical and mental components of health were compared before and after treatment. By the sixth week from the start of therapy, patients in the fourth and fifth groups observed an improvement in physical health and, accordingly, the rate was 54.2 ± 1.55 ($p < 0.001$) and 53.0 ± 1.50 ($p < 0.001$) relative to 20 people 36, 3 ± 2.06 and 38.1 ± 1.83 at the beginning of therapy. In the second and third groups, an increase in the level of the physical side of the quality of life was also noted, which prevailed to 49.2 ± 1.50 ($p < 0.001$) and 48.3 ± 1.51 ($p < 0.001$), respectively, compared to 37, 2 ± 1.75 and 36.0 ± 1.09 before treatment. At the sixth week of therapy, the indicators of physical health of the first group were 44.6 ± 1.20 ($p < 0.001$) relative to 37.9 ± 1.35 at the beginning of treatment.

When analyzing the dynamics of mental health, the fact that in the fourth and fifth groups there was a significant jump in this indicator compared with that before the start of therapy, i.e. 53.8 ± 1.72 ($p < 0.001$) and 53.5 ± 2.16 ($p < 0.001$) with respect to 20 people 34.7 ± 2.54 and 30.7 ± 1.46. The second group also noted an improvement in mental health, so the rate was 50.1 ± 1.65 ($p<0.001$) relative to the results of 38.1 ± 1.32 before treatment. And in the first and third groups, the indicators were lower, respectively 45.5 ± 1.71 ($p < 0.001$) and 48.7 ± 1.48 ($p < 0.001$) relative to 35.6 ± 2.16 and 36.5 ± 2, 64.

As can be seen from the above, the improvement in the quality of life indicators in patients of the first group in dynamics turned out to be significantly lower compared with the fourth and fifth groups ($p < 0.01$).

The results of bacteriological studies revealed a high level of resistance to metronidazole (56.1%). The frequency of occurrence of H. pylori strains resistant to levofloxacin and clarithromycin was 24.4% and 14.6%, respectively. At the same time, a low level of H. pylori resistance to amoxicillin and tetracycline was recorded, which amounted to 2.4%. Thus, according to the study, H. pylori was resistant to the three antibacterial drugs currently used in the regimens. The high activity of amoxicillin and tetracycline against H. pylori has been found. According to the provisions of the Maastricht Consensus

V (2015), in regions where H.pylori resistance to clarithromycin is more than 15%, the use of this drug in eradication regimens is not recommended. In our study, clarithromycin resistance is in the borderline zone, and therefore the standard three-component and sequential eradication scheme in Azerbaijan cannot be recommended. The revealed high resistance of H.pylori to metronidazole limits its use in sequential and hybrid regimens, as well as in quadrotherapy without bismuth. The presence of resistance to two components (metronidazole and clarithromycin) can lead to a significant decrease in the effectiveness of all eradication regimens with these drugs (standard three-component, hybrid).The study has shown high resistance of H.pylori to levofloxacin, which explains the inappropriateness of fluoroquinolones for eradication under local conditions. Analysis of the efficiency of the standard three-component scheme has found that it is low and amounts to 51.3%. The replacement of clarithromycin with josamycin has increased the eradication efficiency to 75.6%, but also has not met the requirements (according to the Maastricht III recommendations, eradication therapy should be ≥80%). In order to increase the eradication efficiency, the standard three-component regimen has been modified in the case of counting the introduction of a probiotic into it, and in the other by adding both a probiotic and an application containing BTD. The scheme, in which clarithromycin has been replaced by josamycin, has been enhanced only with a probiotic. It should be noted that an important role of probiotics in ET. Maastricht Consensus IV and V. Maastricht recommend the use of probiotics, containing *Saccharomyces boulardii, Bifidobacterium lactis, Lactobacillus rhamnosus* to increase the eradication efficiency and side effects. Currently, another way to increase the effectiveness of eradication therapy is to supplement anti-helicobacter regimens with drugs containing bismuth tripotassium dicitrate, the use of which is effective not only in classical quadrotherapy regimens, but also as a fourth component in standard triple therapy regimens.The analysis of the effectiveness after the added ones presented that in all three cited data it has appeared, respectively, 80.3%, 89.5%, 96.6%. It should also be emphasized that the choice of PPI, which is one of the basic drugs of anti-Helicobacter pylori

regimens, is important to increase the effectiveness of eradication. According to modern concepts, the effectiveness of PPI depends on the rate of its metabolism, which is due to the polymorphism of the gene encoding the isoform of the cytochrome P450-CYP2C19 system. So, use rabeprazole in our study, having a more stable pharmacokinetics profile, minimally dependent on gene polymorphism. And also, having a pronounced acid-suppressive effect, from the first day of administration, it enhances the activity of antibiotics during the eradication of H.pylori.

Thus, despite the high resistance of H.pylori to clarithromycin, the addition of only the combined probiotic to the classical eradication regimen has already increased its effectiveness. And substitution in the standard three-way regimen with josamycin and the same time addition of the probiotic has led to an increase in efficacy of up to 89.5%. It has also been noted that the best result has been obtained when using a modified scheme in which probiotic and BTD (96.6%) have been added, i.e. managed to improve the quality of life due to more rapid relief of pain and dyspeptic syndromes, high-quality healing of erosive and ulcerative defects of the gastric mucosa and duodenum without the formation of deformations and scars.It should also be noted that our proposed modified eradication regimens have been well tolerated by side patients, with this prognosis being observed less frequently than with standard triple therapy. Therefore, in conditions of increasing resistance of H.pylori to antibacterial drugs, these eradication regimens can be an alternative to the widely used anti-Helicobacter treatment regimens.

CONCLUSIONS:

1. The study revealed a high level of resistance of H.pylori to metronidazole 56.1%, levofloxacin 24.4%. The primary H.pylori resistance to clarithromycin was 14.6%. Tetracycline and amoxicillin with a low level of resistance of 2.4% can be used in eradication therapy regimens [10].
2. The effectiveness of the classic triple therapy regimen No.1 was low, 51.3%, but the replacement of clarithromycin with josamycin in it increased the eradication level of scheme No.2 to

75.6% (p1<0.05). Adding a probiotic to the standard eradication regimen increases the efficacy of regimen No. 3 to 80.8% (p1<0.01), and to the modified josamycin regimen No.4 to 89.5% (p1<0.001). The most effective was the triple scheme No.5 with the addition of probiotic and bismuth tripotassiumdicitrate -96.6% (p1<0.001) [7,9,5,4].

3. The use of the proposed three modified regimens of anti-Helicobacter therapy with the addition of a probiotic to all three, with the replacement of clarithromycin with josamycin in one and with the inclusion of bismuth tripotassium dicitrate in the other, led to a significant improvement in the clinical endoscopic and morphological picture [9,5,4].
4. Evaluation of the dynamics of quality of life in patients receiving modified treatment regimens (regimen No.4, regimen No.5) showed a significant improvement in the indicators of physical and mental components relative to classical triple therapy — regimen No. 1 (p <0.01) [12].

PRACTICAL RECOMMENDATIONS

1. to level side effects from the use of antibiotics and increase the effectiveness of AHT in the applied treatment regimens, it is possible to use a probiotic including lactobacillus rhamnosus GG-6milyard, saccharomyces boulardii-2,5 milliard, bifidobacterium lactis Bb-12;
2. to increase the effectiveness of standard triple therapy, josamycin with the addition of a probiotic (rabeprazole + amoxicillin + josamycin + probiotic) may be proposed as an alternative to clarithromycin;
3. in order to overcome possible resistance to clarithromycin, improve the regeneration processes in the damaged gastric mucosa and prevent the formation of deforming scar tissue, the addition of the BTD drug (rabeprazole + amoxicillin + clarithromycin + BTD + probiotic) could be recommended in standard triple therapy.

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LIST OF CONDITIONAL ABSTRACTS

ET	- eradicasion therapy
PPİ	- proton pump inhibitors
BTD	- bismuth tripotassium dicitrate
HT	- Helicobacter therapy
FGDS	- fibrogastroduodenoscopy
QOL	- assessment of quality of life
OR	- odds ratio
CI	- confidence interval

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