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Application of N-Acetyl-Glucosaminil-N-Acetyl-Muramyl Dipeptide during Triple Component Anti-*Helicobacter Pylori* Therapy in the Period of Coronavirus Infection COVID-19

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Aim: evaluation of the incidence of COVID-19 infection after three-component *H. pylori* eradication therapy while taking N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide (GMDP).
Materials and methods. A prospective randomized comparative clinical study was carried out. The study included 208 patients (147 men, 61 women; mean age — 48.1 ± 14.5 years) with duodenal ulcer associated with *Helicobacter pylori* (*H. pylori*) who underwent eradication therapy. *H. pylori* in the gastric mucosa was detected by a morphological method and a rapid urease test before treatment and 6–8 weeks after the end of treatment and the withdrawal of all drugs. Patients were divided into three groups according to treatment protocols: omeprazole 0.04 g/day, clarithromycin 1 g/day, amoxicillin 2 g/day (OCA; n = 103); omeprazole 0.04 g/day, clarithromycin 1 g/day, amoxicillin 2 g/day + GMDP 0.001 g/day (OCAL1; n = 61) or 0.01 g/day (OCAL10; n = 44) for 10 days. Detection of SARS-CoV-2 RNA by PCR was carried out from April 2020 to April 2022. Tracking completeness was 96.6 %.
Results. The frequency of *H. pylori* eradication depending on "intention to treat" (ITT) and "per protocol" (PP): OCA — 79 % (95 % CI: 71–87) and 83 % (95 % CI: 75–91); OCAL1 — 95 % (95 % CI: 88–100) and 97 % (95 % CI: 92–100); OCAL10 — 96 % (95 % CI: 89–100) and 98 % (95 % CI: 93–100) respectively. The frequency of adverse reactions depending on ITT and PP: OCA — 24 % (95 % CI: 16–33) and 26 % (95 % CI: 17–35); OCAL1 — 2 % (95 % CI: 0.01–8) and 2 % (95 % CI: 0.01–8); OCAL10 — 2 % (95 % CI: 0.01–7) and 2 % (95 % CI: 0.01–7). The incidence of COVID-19 infection depending on ITT and PP: OCA — 9 % (95 % CI: 3–14) and 9 % (95 % CI: 3–15); OCAL1 + OCAL10 — 1 % (95 % CI: 0.003–1.9) and 1 % (95 % CI: 0.001–2.9), respectively.
Conclusions. In *H. pylori*-infected patients, GMDP (an immunomodulator based on *L. bulgaricus*) at a dose of 1–10 mg/day, during a 10-day triple eradication therapy, allows a significant ($p < 0.05$) increase in the frequency of *H. pylori* eradication and reduce the incidence of adverse reactions compared with a 10-day protocol without adjuvant therapy with GMDP. There was a significant ($p < 0.05$) decrease in the incidence of COVID-19 infection after *H. pylori* eradication therapy with GMDP.
Keywords: *Helicobacter pylori*, duodenal ulcer, triple eradication therapy, N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide, COVID-19
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Применение N-ацетилглюкозаминил-N-ацетилмурамил-дипептида при проведении трехкомпонентной антихеликобактерной терапии в период коронавирусной инфекции COVID-19

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Цель исследования: оценка заболеваемости инфекцией COVID-19 после проведения трехкомпонентной эрадикационной терапии *H. pylori* на фоне приема N-ацетил-глюкозаминил-N-ацетилмурамилдипептида (ГМДП).

Материалы и методы исследования. Проведено проспективное рандомизированное сравнительное клиническое исследование. Эрадикационную терапию прошли 208 пациентов (147 мужчин, 61 женщина; средний возраст — 48,1 ± 14,5 года) с язвенной болезнью двенадцатиперстной кишки, ассоциированной с *Helicobacter pylori* (*H. pylori*). Диагностика *H. pylori* в слизистой оболочке желудка осуществлялась морфологическим методом и быстрым уреазным тестом до лечения и через 6–8 недель после окончания лечения и отмены всех лекарственных средств. Пациентов разделили на три группы согласно протоколам лечения: омепразол 0,04 г/сут, кларитромицин 1 г/сут, амоксициллин 2 г/сут (ОКА; *n* = 103); омепразол 0,04 г/сут, кларитромицин 1 г/сут, амоксициллин 2 г/сут + ГМДП 0,001 г/сут (ОКАЛ1; *n* = 61) или 0,01 г/сутки (ОКАЛ10; *n* = 44) в течение 10 дней. Обнаружение РНК SARS-CoV-2 методом ПЦР осуществлялось с апреля 2020 по апрель 2022 г. Полнота отслеживания составила 96,6 %.
Результаты. Частота эрадикации *H. pylori* в зависимости от назначенного лечения (ITT) и фактически полученного лечения (PP): ОКА — 79 % (95 % ДИ: 71–87) и 83 % (95 % ДИ: 75–91), ОКАЛ1 — 95 % (95 % ДИ: 88–100) и 97 % (95 % ДИ: 92–100), ОКАЛ10 — 96 % (95 % ДИ: 89–100) и 98 % (95 % ДИ: 93–100) соответственно. Частота нежелательных реакций в зависимости от ITT и PP: ОКА — 24 % (95 % ДИ: 16–33) и 26 % (95 % ДИ: 17–35); ОКАЛ1 — 2 % (95 % ДИ: 0,01–8) и 2 % (95 % ДИ: 0,01–8); ОКАЛ10 — 2 % (95 % ДИ: 0,01–7) и 2 % (95 % ДИ: 0,01–7). Заболеваемость инфекцией COVID-19 в зависимости от ITT и PP: ОКА — 9 % (95 % ДИ: 3–14) и 9 % (95 % ДИ: 3–15); ОКАЛ1 + ОКАЛ10 — 1 % (95 % ДИ: 0,003–1,9) и 1 % (95 % ДИ: 0,001–2,9) соответственно.
Выводы. У инфицированных *H. pylori* пациентов ГМДП (иммуномодулятор на основе *L. bulgaricus*) в дозе 1–10 мг/сут при проведении 10-дневной тройной эрадикационной терапии позволяет достоверно ($p < 0,05$) увеличить частоту эрадикации *H. pylori* и уменьшить частоту нежелательных реакций по сравнению с 10-дневным протоколом без адъювантной терапии ГМДП. Отмечено достоверное ($p < 0,05$) снижение заболеваемости инфекцией COVID-19 после проведения эрадикационной терапии *H. pylori* с приемом ГМДП.
Ключевые слова: *Helicobacter pylori*, язва, двенадцатиперстная кишка, тройная эрадикационная терапия, N-ацетилглюкозаминил-N-ацетилмурамилдипептид, COVID-19
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Introduction

Having first isolated *Helicobacter pylori* (*H. pylori*) in 1982, B.J. Marshall and J.R. Warren [1] opened a new era in the microbiology of the upper gastrointestinal tract. Despite the fact that spiral microorganisms were observed in the gastric mucus layer repeatedly by various researchers in the 19th and 20th centuries, the isolation of *H. pylori*, combined with increased interest in the pathogenesis of gastroduodenal diseases, as well as the availability of studying clinical specimens using endoscopic biopsy led to important breakthroughs in medicine. Unfortunately, over the past 40 years since the identification of the bacterium, *H. pylori* remains one of the most common chronic bacterial infections in humans, retaining colonization on the mucosa with gastric epithelium in half of the world's population [2–4]. *H. pylori* infection is associated with a variety of upper gastrointestinal pathologies ranging from *H. pylori*-induced gastroduodenitis and *H. pylori*-associated dyspepsia to gastroduodenal ulcer, MALT lymphoma, and gastric cancer. Appropriate anti-*Helicobacter* therapy is required for the prevention and treatment of this pathology [3, 5]. Bacterial eradication is also required to control complications and reduce the number of recurrences of gastroduodenal ulcer associated with *H. pylori* infection [6]. The presence of natural resistance to some antibiotics in bacteria, as well as the emergence of primary and secondary resistance to antibacterial drugs, complicates the eradication of *H. pylori* and leads to the search for new methods of therapy. This is reflected in the latest International Guidelines for the Eradication of *H. pylori*, which present not only first-line treatment regimens, but also various other treatment regimens, considering clarithromycin-resistant *H. pylori* strains in the regions [3, 7, 8].

Measures to improve the effectiveness of standard triple therapy, considering the growth of *H. pylori* resistance to antibacterial drugs, are reflected in the Recommendations of the Russian Gastroenterological Association of 2018. It is recommended to add probiotic strains of *Bifidobacterium* and *Lactobacillus* to the standard triple therapy [9].

Thus, various approaches are being explored to optimize standard triple therapy, including the use of probiotics [3, 10, 11], which is reflected in the Provisions of the Maastricht Consensus VI. Specific strains should only be selected based on proven clinical efficacy [8]. Some probiotics can have a beneficial effect on the eradication of *H. pylori*, in particular, probiotic strains of *Lactobacillus*, reduce the activity of bacterial urease, *H. pylori* mobility and adhesion of *H. pylori* to gastric epithelial cells [9].

The idea has been formulated that the immunomodulatory effect plays a significant role in the mechanism of the antimicrobial action of probiotics [12]. The main questions are the origin of the immunomodulator and its effect on the mucous membrane [13, 14]. It is known that glucosaminyl muramyl dipeptide (GMDP isolated from the cell wall of *L. bulgaricus*) modulates the immune response through NOD2 receptors and the YB1 protein [15, 16] and is effective in the treatment of allergies [17, 18] and microbiocenosis [19]. The positive effect of glucosaminyl muramyl dipeptide 10 mg on the elimination of *H. pylori*, previously studied [20, 21], correlates with another dosage of this drug — 1 mg. This fact can be explained by the compensatory effect of GMDP on the missing signal to innate immunity receptors, associated with the loss of commensal microorganisms, when using antibacterial drugs, which ensures an adequate immune response.

Purpose of the study was to evaluate the efficacy and safety of *H. pylori* eradication during standard 10-day triple therapy while taking N-acetylglucosaminyl-N-acetyl-muramyl dipeptide at a dose of 1 mg and 10 mg per day, with a prospective assessment of the incidence of COVID-19 infection.

Materials and research methods

The study was carried out in accordance with the WMA Declaration of Helsinki. All stages of the study were carried out in accordance with the law. This study was approved by the Ethics Committee of the Vitebsk State Medical University (Vitebsk, Belarus) and was conducted during 2020–2022. Prior to the start of the study, informed consent was obtained from all patients to participate in the study and to process personal data. A prospective randomized comparative clinical study was carried out. Inclusion criteria: the presence of duodenal ulcer associated with *H. pylori*. Exclusion criteria: using antibacterial drugs less than a month before the start of eradication therapy or conducting fiberoptic esophagogastroduodenoscopy. At the time of the examination, all patients had no history of COVID-19 infection. Eradication therapy was administered to 208 patients (147 males, 61 females, mean age — 48.1 ± 14.5 years (mean ± SD; 18–65 years) with *H. pylori*-associated duodenal ulcer (Table 1). Patients were divided by randomized method (drum lottery) into three groups according to treatment protocols: group 1 — omeprazole 0.04 g/day, clarithromycin 1 g/day, amoxicillin 2 g/day, duration of treatment — 10 days (OCA; n = 103); group 2 — omeprazole 0.04 g/day, clarithromycin 1 g/day, amoxicillin 2 g/day, GMDP 0.001 g/day, duration of treatment — 10 days (OCAL1; n = 61); group 3 — omeprazole 0.04 g/day, clarithromycin 1 g/day, amoxicillin 2 g/day, GMDP 0.01 g/day, duration of treatment — 10 days (OCAL10; n = 44).

The study was completed by 201 patients. Due to the lack of data on the diagnosis of *H. pylori* or drug discontinuation seven people (3.4 %) were excluded: 5 people — from the OCA group, 1 person — from the OCAL1 group, and 1 person — from the OCAL10 group. Tracking completeness was 96.6 %.

The study of the mucous membrane of the stomach and duodenum was carried out according to standard systematizations and methods [22, 23]. To identify areas of gastric metaplasia of the duodenum, additional staining of histological sections of the duodenal mucosa was used with PAS-alcian blue (Serva) pH 1.0 and 2.5 [24].

Intestinal metaplasia and all cellular and tissue morphological characteristics were assessed on a visual analogue scale [25–27] according to the histological section of the Houston modification of the Sydney classification.

Histological examination of the duodenal mucosa considered standard parameters [24, 28]. *H. pylori* was diagnosed by a morphological method (Romanovsky — Giemsa stain; assessment by a standard visual analogue scale [29]) and a rapid urease test (standard test systems Jatrox®-H.p.-Test (Rohm Pharma, Germany); HELPIL® and AMA RUT Pro® (AMA, Russia)) [30] before treatment and 6–8 weeks after the end of treatment and the withdrawal of all drugs. Detection of SARS-CoV-2 RNA by PCR was carried out from April 2020 to April 2022.

For statistical processing, the certified program STATISTICA 10.0 (StatSoft Inc., USA) and the t-test with a normal distribution of the variable were used. If the distribution of the variable was not normal, Shapiro — Wilk test was used. Mann — Whitney U-test was used to assess the differences between two independent small samples in terms of the level of a quantitatively measured trait. Patient age was presented as mean ± standard deviation (SD). P-levels < 0.05 were considered significant [31].

Results of the study and discussion

Histological characteristics of the mucous membrane of the stomach and duodenum of patients with duodenal ulcer are presented in Table 2.

Lymphatic follicles of the gastric fundic mucosa were found in 28 patients (13.5 %; 95 % CI: 8.9–18.1), intestinal metaplasia of the mucous membrane — in 17 (8.2 %; 95 % CI: 4.5–11.9) of the examined: mild degree — in 5 (2.4 %; 95 % CI: 0.3–4.5), moderate — in 4 (1.9 %; 95 % CI: 0.1–3.8) and severe — in 8 patients (3.9 %; 95 % CI: 1.2–6.4 %).

Lymphatic follicles of the gastric antrum mucosa were found in 35 patients (16.8 %; 95 % CI: 11.7–21.9), intestinal metaplasia of the mucosa — in 20 (9.6 %; 95 % CI: 5.6–13.6) of those examined: mild degree — in 7 (3.4 %; 95 % CI: 0.9–5.9),

Table 1. Patients' characteristics
Таблица 1. Характеристика пациентов

Treatment protocols Протоколы лечения	Number of patient Количество пациентов	Gender Пол		Age, years Возраст, лет	Duration of illness, years Длительность заболевания, лет
		муж. Male	жен. Female		
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут	103	73	30	46.1 ± 14.8	8.3 ± 3.9
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day GMDP 0.001 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут ГМДП 0,001 г/сут	61	43	18	47.2 ± 14.3	8.4 ± 3.6
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day GMDP 0.01 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут ГМДП 0,01 г/сут	44	31	13	55.2 ± 12.1	8.6 ± 2.7
Total Всего	208	147	61	48.1 ± 14.5	8.5 ± 3.7

moderate — in 4 (1.9 %; 95 % CI: 0.1–3.8) and severe — in 9 patients (4.3 %; 95 % CI: 1.5–7.1).

Gastric metaplasia of the duodenal mucosa was detected in 116 patients (55.8 %; 95 % CI: 49.1–62.5): gastric metaplasia occupied less than 5 % of the area of the duodenal mucosa in the microscope field in 88 cases (42.3 %; 95 % CI: 35.6–49.0), 5–25 % — in 25 (12.0 %; 95 % CI: 7.6–16.4) and 25–50 % — in 3 patients (1.5 %; 95 % CI: 0.01–3.2).

The results of a prospective randomized comparative clinical trial are presented in Table 3.

The frequency of *H. pylori* eradication depending on "intention to treat" (ITT) and "per protocol" (PP): OCA — 78.6 % (95 % CI: 70.4–86.8) and 82.7 % (95 % CI: 75.1–90.5); OCAL1 — 95.1 % (95 % CI: 87.5–100) and 96.7 % (95 % CI: 91.7–100); OCAL10 — 95.5 % (95 % CI: 89.0–100) and 97.7 % (95 % CI: 93.0–100), respectively. The frequency of adverse reactions depending on the prescribed treatment and the actual treatment received: OCA — 24.3 % (95 % CI: 15.9–33.1) and 25.5 % (95 % CI: 16.8–34.8); nausea, $n = 25$), discontinued treatment — 4.9 % (95 % CI: 0.7–9.5) and 5.1 % (95 % CI: 0.8–10.0; diarrhea, $n = 5$); OCAL1 — 1.6 % (95 % CI: 0.01–7.7) and 1.7 % (95 % CI: 0.01–7.8; nausea, $n = 1$), discontinued treatment — 0 %; OCAL10 — 2.3 % (95 % CI: 0.01–6.8) and 2.3 % (95 % CI: 0.01–6.9; nausea, $n = 1$), discontinued treatment — 0 %.

The cost of treatment regimens: OCA — 3875 rubles, OCAL1 — 4120 rubles, OCAL10 — 5765 rubles. Effectiveness of "per protocol" regimens (PP): OCA — 82.7 %; OCAL1 — 96.7 %; OCAL10 — 97.7 %. Cost-effectiveness ratio (CER): OCA — 46.9 rubles, OCAL1 — 42.6 rubles, OCAL10 — 59.0 rubles. According to the cost-effectiveness ratio (CER), the OCAL1 regimen is more effective and the least expensive compared to other eradication regimens (OCA and OCAL10).

The results of the incidence of COVID-19 infection after eradication therapy, depending on "intention to treat" and "per protocol", are presented in Table 4.

The incidence of COVID-19 infection depending on "intention to treat" and "per protocol": OCA — 8.74 % (95 % CI: 3.23–14.25) and 9.18 % (95 % CI: 3.4–14.96; $n = 9$); OCAL1 + OCAL10 — 0.95 % (95 % CI: 0.003–1.90) and 0.97 % (95 % CI: 0.001–2.90; $n = 1$) respectively.

Taking GMDP 1 mg per day during a 10-day three-component anti-Helicobacter treatment significantly increased *H. pylori* eradication by 16.5 % (according to ITT) and 14.0 % (according to PP; $\chi^2 = 5.41$; $p = 0.0200$ and $\chi^2 = 4.27$; $p = 0.0387$ respectively), with a significant decrease in the

Table 2. Histological characteristics of the mucous membrane of the stomach and duodenum in patients with duodenal ulcer (n = 208)

Таблица 2. Гистологическая характеристика слизистой оболочки желудка и ДПК пациентов с язвенной болезнью ДПК (n = 208)

Morphological changes in mucous membrane Морфологические изменения слизистой оболочки	Fundal department Фундальный отдел			Antrum Антральный отдел			Bulb of duodenum Луковица ДПК		
	n абс.	%	95 % CI 95 % ДИ	*n* абс.	%	95 % CI 95 % ДИ	*n* абс.	%	95 % CI 95 % ДИ
Atrophy Атрофия	126	60.6	54.0–67.2	146	70.2	64.0–76.4	109	52.4	45.6–59.2
Inflammation Воспаление	208	100.0	–	208	100.0	–	208	100.0	–
Activity Активность	161	77.4	71.7–83.1	173	83.2	78.1–88.3	164	78.8	73.3–84.3

Table 3. Results of a prospective randomized comparative clinical study of frequency of *H. pylori* eradication and adverse reactions depending on "intention to treat" and "per protocol"

Таблица 3. Результаты проспективного рандомизированного сравнительного клинического исследования частоты эрадикации *H. pylori* и нежелательных реакций в зависимости от назначенного лечения и фактически полученного лечения

Treatment protocols Протоколы лечения	*n*	Eradication % (95 % CI) Эрадикация % (95 % ДИ)	Adverse reactions % (95 % CI) Побочные реакции % (95 % ДИ)
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут	ITT – 103 PP – 98	ITT – 78.6 (70.4–86.8) PP – 82.7 (75.1–90.5)	ITT – 24.3 (15.9–33.1) PP – 25.5 (16.8–34.8) discontinued treatment: ITT – 4.9 (0.7–9.5) PP – 5.1 (0.8–10.0) ITT – 24.3 (15.9–33.1) PP – 25.5 (16.8–34.8) прекратили лечение: ITT – 4.9 (0.7–9.5) PP – 5.1 (0.8–10.0)
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day GMDP 0.001 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут ГМДП 0,001 г/сут	ITT – 61 PP – 60	ITT – 95.1 (87.5–100) PP – 96.7 (91.7–100)	ITT – 1.6 (0.01–7.7) PP – 1.7 (0.01–7.8) discontinued treatment – 0 ITT – 1.6 (0.01–7.7) PP – 1.7 (0.01–7.8) прекратили лечение – 0
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day GMDP 0.01 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут ГМДП 0,01 г/сут	ITT – 44 PP – 43	ITT – 95.5 (89.0–100) PP – 97.7 (93.0–100)	ITT – 2.3 (0.01–6.8) PP – 2.3 (0.01–6.9) discontinued treatment – 0 ITT – 2.3 (0.01–6.8) PP – 2.3 (0.01–6.9) прекратили лечение – 0

Notes: n – number of patients; ITT – "intention to treat"; PP – "per protocol"; CI – confidence interval.

Примечание: ITT – назначенное лечение; PP – фактическое полученное лечение.

incidence of adverse reactions by 22.7 % (according to ITT) and 23.8 % (according to PP; χ^2 = 14.71; p = 0.0001 and χ^2 = 15.39; p = 0.0001 respectively), and full completion of the course of anti-*Helicobacter* therapy in all patients.

Taking GMDP 10 mg per day during a 10-day three-component anti-Helicobacter treatment significantly increased *H. pylori* eradication by 16.9 % (according to ITT) and 15.0 % (according to PP; χ^2 = 4.39; p = 0.0363 and χ^2 = 4.00; p = 0.0455 respectively), with a significant decrease in the

Table 4. Detection of COVID-19 infection after eradication therapy while taking N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide

Таблица 4. Выявление инфекции COVID-19 после проведения эрадикационной терапии на фоне приема N-ацетилглюкозаминил-N-ацетилмурамилдипептида

Treatment protocols **Протоколы лечения**	***n***	**COVID-19 (RNA SARS-CoV-2+)** **% (95 % CI)** **COVID-19 (РНК SARS-CoV-2+)** **% (95 % ДИ)**
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут	ITT — 103 PP — 98	ITT — 8.74 (3.23–14.25) PP — 9.18 (3.40–14.96)
Omeprazole 0.04 g/day Clarithromycin 1 g/day Amoxicillin 2 g/day GMDP 0.001 or 0.01 g/day Омепразол 0,04 г/сут Кларитромицин 1 г/сут Амоксициллин 2 г/сут ГМДП 0,001 или 0,01 г/сут	ITT — 105 PP — 103	ITT — 0.95 (0.003–1.90) PP — 0.97 (0.001–2.90)

Notes: *n* — number of patients; ITT — "intention to treat"; PP — "per protocol"; CI — confidence interval.
Примечание: ITT — назначенное лечение; PP — фактическое полученное лечение.

frequency of adverse reactions by 22.0 % (according to ITT) and 23.2 % (according to PP; $\chi^2 = 10.25$; $p = 0.0014$ and $\chi^2 = 10.68$; $p = 0.0011$ respectively) and full completion of the course of anti-*Helicobacter* therapy in all patients.

Taking GMDP 1 mg or 10 mg per day for a 10-day three-component anti-Helicobacter treatment significantly reduced the incidence of COVID-19 infection by 7.79 % (according to ITT) and 8.21 % (according to PP; $\chi^2 = 6.89$; $p = 0.0087$ and $\chi^2 = 7.16$; $p = 0.0074$ respectively).

The choice of patients with an ulcer localized in the duodenal bulb (duodenal ulcer) as participants in this clinical study was based on the fact that in duodenal ulcer of the bulbous localization, the maximum degree of *H. pylori* colonization of the mucous membrane in the stomach (99.0 %) [32] and areas of gastric metaplasia of the duodenal bulb mucosa (87.8 %) [33] are noted.

The choice of standard triple therapy as first-line therapy is based on monitoring data on antimicrobial resistance of respiratory pathogens (*Streptococcus*) to clarithromycin in a multidisciplinary medical hospital with more than 500 beds (Vitebsk Regional Clinical Hospital, Belarus), according to the provisions of the Maastricht Consensus VI [8]. Resistance of respiratory pathogens (*Streptococcus*) to clarithromycin for 2020–2022 was equal to 12.3 % (low (< 15 %) resistance to clarithromycin).

The choice of a ten-day regimen versus a fourteen-day regimen is due to a 2–3-fold increase in the number of adverse reactions of the two-week regimen compared to the 7–10-day regimens based on the results of previous studies [21]. The effectiveness of ten-day standard triple therapy for *H. pylori* in the Republic of Belarus, according to other authors [34], was 90 %.

The choice of GMDP as an immunomodulator during a 10-day three-component *H. pylori* eradication therapy corresponded to the idea of an "ideal" immunomodulator and was based on three main criteria, according to modern scientific studies [35].

The first criterion includes the presence of N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide. One of the reasons for the ineffectiveness of eradication therapy is the transition of *H. pylori* to metabolically inactive forms (coccoid and *U*-form), resistant to antibiotics. Previously, it was shown that glucosaminyl muramyl dipeptide promotes the release of Mycobacterium tuberculosis from the dormant form, which, apparently, determines the effectiveness of GMDP therapy [36]. Similarly, activation of NOD1 and NOD2 receptors has previously been shown to promote elimination of *H. pylori* [37, 38]. The active substance N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide (glucosaminyl muramyl dipeptide, GMDP) is the main complete repetitive structurally unchanged fragment of the cell wall of almost all known bacteria, the ligand of the NOD2 receptors of the innate immune system. According to the second criterion of an "ideal" immunomodulator, it is necessary to activate the immune system through type 1 T-helpers. It has been shown that activation of the immune response through T-helper

type 1 is necessary for successful eradication of *H. pylori* [39–42]. GMDP fully complies with the second criterion — its influence on the shift of the type 1 T-helper / type 2 T-helper ratio towards type 1 T-helpers has been proven [17, 18, 43]. According to the third criterion, the "ideal" immunomodulator has a bacterial, probiotic origin. In accordance with the Maastricht Consensus VI Statements [8] and based on 14 meta-analyses of RCTs (2007–2019) [44–57], which pooled 259 RCTs involving 41,727 patients, the addition of *Lactobacillus* strains optimizes therapy and reduces the incidence of adverse reactions.

These meta-analyses showed that certain strains of *Lactobacillus* or several probiotic strains increased *H. pylori* eradication by 8.1 % and reduced the number of adverse reactions when using a probiotic within 14 days before eradication therapy or during eradication therapy. At the same time, *Bifidobacterium* and *Saccharomyces boulardii* did not significantly affect the level of eradication during anti-*Helicobacter* therapy [53, 57]. The use of specific strains of probiotics (*Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus casei DN-114001*, *Lactobacillus gasseri*, *Lactobacillus* reuteri, *Lactobacillus rhamnosus GG, Bifidobacterium infantis 2036* and *Saccharomyces boulardii*) during eradication therapy can be considered as an option to increase eradication level *H. pylori*, especially in the absence of the effectiveness of antibiotics [51, 58, 59]. The effect of probiotics on the reduction of adverse reactions during eradication therapy has been proven [57]. A significant increase in *H. pylori* eradication by 17 % was found using predominantly specific strains of *Lactobacillus*. When multicomponent probiotics were used as adjuvant therapy, eradication increased by only 2.8 % [49]. Monotherapy with probiotics using specific strains of *Lactobacillus* led to a significant ($p < 0.001$) compared with placebo eradication of *H. pylori* in 16.0 % of patients, with the use of multicomponent probiotics (which included *Lactobacillus* strains) — in 14.0 % of patients [58].

It should be noted that GMDP was first identified as a fragment of the cell wall of *Lactobacillus bulgaricus* [60], and thus its positive effect in *H. pylori* therapy is consistent with the data of the above studies [46].

An interesting detail of this study was the fact that after eradication therapy while taking N-acetyl-glucosaminyl-N-acetyl-muramyl dipeptide at doses of 1 mg and 10 mg, during the COVID-19 pandemic, a significant decrease by 8.0 % in the incidence COVID-19 infection was noted, which is associated to a greater extent with the activation of the innate immune system.

The use of 2–3 antibacterial drugs in *H. pylori* eradication therapy regimens destroys not only pathogenic, but also commensal microorganisms, whose metabolic products are vital and maintain immune homeostasis [61], including through NOD2 receptors of innate immunity. The success of complex eradication therapy for *H. pylori* infection can be explained by the compensatory effect of GMDP on the signal to innate immunity receptors, which is missing due to the absence of commensals, providing an adequate immune response.

Based on the data obtained, it can be concluded that therapy with the immunomodulator glucosaminyl muramyl dipeptide 1 mg and 10 mg per day in a 10-day *H. pylori* eradication regimen showed an encouraging result in increasing *H. pylori* eradication and reducing the number of adverse reactions. Therapy with the immunomodulator glucosaminyl muramyl dipeptide 1 mg and 10 mg per day in a 10-day *H. pylori* eradication regimen during the period of coronavirus infection COVID-19 significantly reduced the incidence of COVID-19 infection.

Conclusions

1. Admission of glucosaminyl muramyl dipeptide 1 mg per day during a 10-day three-component anti-*Helicobacter* therapy significantly increased the eradication of *H. pylori* by 16.5 % (according to ITT) and 14.0 % (according to PP; $\chi^2 = 5.41$; $p = 0.0200$ and $\chi^2 = 4.27$; $p = 0.0387$ respectively), with a significant decrease in the frequency of adverse reactions by 22.7 % (according to ITT) and 23.8 % (according to PP; $\chi^2 = 14.71$; $p = 0.0001$ and $\chi^2 = 15.39$; $p = 0.0001$ respectively) with complete completion of the course of anti-Helicobacter therapy in all patients. This regimen is more effective and the least expensive compared to other eradication regimens studied (cost-effectiveness ratio (CER) — 42.6 rubles).

2. Admission of glucosaminyl muramyl dipeptide 10 mg per day during a 10-day three-component anti-*Helicobacter* treatment significantly increased the eradication of *H. pylori* by 16.9 % (according to ITT) and 15.0 % (according to PP; $\chi^2 = 4.39$; $p = 0.0363$ and $\chi^2 = 4.00$; $p = 0.0455$ respectively), with a significant decrease in the frequency of adverse reactions by 22.0 % (according to ITT) and 23.2 % (according to PP; $\chi^2 = 10.25$; $p = 0.0014$ and $\chi^2 = 10.68$; $p = 0.0011$ respectively) with complete completion of the course of anti-*Helicobacter* therapy in all patients. Cost-effectiveness ratio (CER) — 59.0 rubles.

3. Taking glucosaminyl muramyl dipeptide at a dose of 1 mg or 10 mg per day for a 10-day three-component anti-*Helicobacter* treatment significantly reduced the incidence of COVID-19 infection by 7.8 % (according to ITT) and 8.2 % (according to PP; $\chi^2 = 6.89$; $p = 0.0087$ and $\chi^2 = 7.16$; $p = 0.0074$ respectively).

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