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Gastric Microbiota in Patients with Dyspepsia: Metatranscriptomic Analysis

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Aim: to assess the composition of the microbiota of the mucous membrane of the body and the antrum of the stomach.
Materials and methods. Sixty patients with dyspeptic symptoms were included into the study. Two biopsy samples of the gastric mucosa (from the body of the stomach and the antrum) were obtained from each patient. The presence of *H. pylori* infection was confirmed by PCR; RNA was isolated and then libraries were prepared for metatranscriptomic analysis of the *16S rRNA* gene. Sequencing was performed on MiSeq (Illumina, USA) using MiSeq Reagent Kit v3 (600-cycle) (Illumina, USA).
Results. The bacterial diversity decreases with the predominance of *Helicobacter pylori* species in *H. pylori*-positive patients. These results were confirmed by the Shannon index, the average value of which was 3.6 in the *H. pylori*-positive group and 5.4 in the *H. pylori*-negative group. In *H. pylori*-negative patients an increase in the representation of *Streptococcus, Prevotella* and *Alloprevotella* genera was observed. The level of *H. pylori* contamination of the gastric mucosa varies in the antrum and body of the stomach, in some cases reaching a 3.5-fold difference. Representation of other bacteria in the body and antrum of the stomach does not differ significantly.
Conclusion. The bacterial composition of the stomach is dependent on the presence of *H. pylori*. *H. pylori* leads to the decrease of the bacterial diversity with the predominance of *H. pylori* in gastric microbiome.
Keywords: *H. pylori,* dyspepsia, gastric microbiota, metatranscriptome, *16S rRNA* sequencing
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Микробиота желудка у пациентов с диспепсией: метатранскриптомный анализ

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Цель исследования: оценить состав микробиоты слизистой оболочки тела и антрального отдела желудка.
Материалы и методы. В исследование были включены 60 пациентов с симптомами диспепсии. Проанализировано по два образца слизистой оболочки желудка каждого пациента — из тела и антрального отдела. В полученных биоптатах определяли наличие инфекции *H. pylori* методом ПЦР, проводили выделение РНК и подготовку библиотек для метатранскриптомного анализа гена *16S рРНК*. Секвенирование осуществляли на приборе MiSeq (Illumina, США) с использованием набора реагентов MiSeq Reagent Kit v3 (600-cycle) (Illumina, США).
Результаты. В группе *H. pylori*-положительных пациентов выявлено снижение видового разнообразия на фоне преобладания бактерий вида *Helicobacter pylori*, что было подтверждено с помощью индекса Шеннона, среднее значение которого составило 3,6 в группе *H. pylori*-положительных и 5,4 в группе *H. pylori*-отрицательных пациентов. В случае отсутствия *H. pylori* наблюдали увеличение представленности бактерий родов *Streptococcus, Prevotella* и *Alloprevotella*. Уровень обсемененности *H. pylori* слизистой оболочки

желудка варьирует в антральном отделе и теле желудка, в отдельных случаях достигая разницы в 3,5 раза. При сравнении представленности других бактерий в теле и антральном отделе желудка статистически значимых различий выявлено не было.
Выводы. Состав микробиоты желудка существенно отличается в зависимости от наличия или отсутствия инфекции *H. pylori*. Наличие *H. pylori* сопровождается снижением видового разнообразия бактерий с преобладанием в составе желудочного микробиома *H. pylori*.
Ключевые слова: *H. pylori,* диспепсия, микробиота желудка, метатранскриптом, секвенирование *16S рРНК*
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Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

The human gastrointestinal tract contains about 10^{14} microbial cells [1]. Microorganisms are presented unevenly: their number and diversity increase from the proximal to the distal parts of the gastrointestinal tract, where their content is maximum [2].

For a long time, it was believed that the stomach was a sterile organ, and the gastric mucosa was considered uninhabitable. The discovery of *Helicobacter pylori* (*H. pylori*) in 1982 and further research using modern methods of molecular biology refuted previous ideas about the sterility of the stomach and confirmed that *H. pylori* species are not the only one capable to survive in the acidic environment of the stomach. Certain anatomical features of stomach form a unique bacterial composition in it, which is different from other parts of the digestive tract [3].

It has now been proven that *H. pylori* infection can lead to chronic inflammation of the gastric mucosa, and subsequently to the development of precancerous changes in the mucosa: atrophy, intestinal metaplasia and intraepithelial neoplasia (dysplasia), known as the "Correa's cascade" [4]. In this regard, back in 1994, *H. pylori* was classified by the International Agency for Research on Cancer (IACR) of the World Health Organization as a Group 1 carcinogen [5].

However, today it is known that other types of bacteria, in addition to *H. pylori,* can provoke the development of chronic inflammatory changes in the gastric mucosa, and even contribute to the development of gastric cancer [6]. However, the mutual influence of *H. pylori* and other representatives of the gastric microbiota remains poorly understood. Presumably, these relationships within the microbial community of the stomach can determine the development of pathological changes in the mucous membrane and, possibly, contribute to the progression of existing diseases of stomach. Considering the morphological and functional characteristics of different parts of stomach, including those caused by the production of hydrochloric acid, it is obvious that the microbial composition in different parts of stomach may differ. This, in turn, explains the need to take biopsy samples from the antrum and body of the stomach when diagnosing *H. pylori* infection using a rapid urease test.

Thus, the **aim of this study** was to assess the composition of the microbiota of the mucous membrane of the body and the antrum of the stomach.

Materials and methods

Biological samples

The study included patients who were admitted with dyspeptic complaints to a primary care physician and/or gastroenterologist of the Medical and Sanitary Unit of the Kazan (Volga Region) Federal University and underwent upper gastrointestinal endoscopy. Patients were selected for the study in accordance with the inclusion/exclusion criteria.

Inclusion criteria were the following: age 18 years or older; presence of dyspeptic symptoms; no history of *H. pylori* eradication therapy; voluntary consent of the patient to participate in the study, confirmed by signing the informed consent form. *Exclusion criteria:* polyps or gastric malignancy revealed by endoscopy; a history of concomitant conditions and diseases that can lead to pronounced changes in the composition of the gastrointestinal microbiota: inflammatory bowel diseases; malabsorption syndrome; obesity, etc.; patients' taking certain medications (immunosuppressive drugs, cytostatics, glucocorticosteroids, antibiotics, prebiotics, probiotics, regular use of

proton pump inhibitors, bismuth tripotassium dicitrate, non-steroidal anti-inflammatory drugs) for three months before inclusion in the study.

During endoscopy, all patients underwent collection of at least two biopsies from the antrum and body of the stomach.

A total of 60 patients (49 women and 21 men, aged 24 to 67 years) were included in the study; respectively, 120 biopsies of the gastric mucosa of the antrum and body of the stomach were obtained. All samples were stored in RNA later solution at –80 °C.

The study was approved by the Local Ethics Committee of the Kazan (Volga Region) Federal University (protocol No. 20 dated December 27, 2019).

RNA isolation

Biopsies of the gastric mucosa, stored in RNA later solution, were thawed at room temperature. The tissue pieces were then transferred into tubes containing a mixture of 790 μL of TRIzol reagent (Thermo Fisher, USA) and 10 μL of glycogen, 300 mg of 0.1 mm glass beads and one 6.35 mm ceramic bead, and homogenized on a FastPrep 24 instrument (MP Biomedicals, USA) until a homogeneous solution was obtained. Further isolation was carried out according to the protocol recommended by the manufacturer, with minor modifications. 160 μL of chloroform was added, mixed thoroughly and incubated for 3 min at room temperature. Then the mixture was centrifuged for 15 min at a speed of 12,000 g and a temperature of 4 °C. The upper aqueous phase was transferred to a clean tube, 400 μL of isopropyl alcohol was added, mixed and left for incubation at –20 °C for an hour. Then the samples were centrifuged for 10 min at a speed of 12,000 g at 4 °C, the supernatant was collected, and the resulting sediment was washed three times with 800 μL of 75 % ethanol, centrifuging for 5 min at 7500 g. The remaining ethanol was removed, the precipitate was dried for 5 min, and was dissolved in 50 μL of water afterwards. The isolated RNA was stored at –80 °C. Nucleic acid concentrations were measured on a Qubit 2.0 fluorimeter (Thermo Fisher Scientific, USA) using Qubit RNA HS Assay Kits.

Sequencing

The isolated RNA was reverse transcribed using RNAscribe reverse transcriptase (Biolabmix, Russia) to obtain cDNA. This step was necessary to characterize only the metabolically active part of the microbiota. To prepare libraries with the resulting cDNA, PCR was performed with *16S rRNA* gene primers (V3–V4 variable region). Sequencing was carried out on a MiSeq instrument (Illumina, USA) using the MiSeq Reagent Kit v3 (600-cycle) (Illumina, USA).

Data analysis

As a result of sequencing, sequences of the V3–V4 region of *16S rRNA* were obtained in fastq format for each sample. After preliminary filtering of reads by quality, trimming of service sequences, and removal of chimeric sequences, the reads were analyzed using the QIIME metagenomic pipeline (v. 2). The taxonomic composition of the microbial community was assessed by assigning operational taxonomy units (OTU) to reads. The GreenGenes2 reference sequence database was used for these purposes. The Shannon index was calculated to assess metagenomic diversity. Statistical processing of the research material was carried out using the Microsoft Excel 2021 software package (Microsoft Corp., USA).

Results

A total of 120 paired biopsies of the gastric mucosa of the antrum and body of the stomach, obtained from 60 patients, were included in the study. However, 28 samples from 14 patients were excluded from further analysis due to the small amount of material insufficient for sequencing.

Based on endoscopic data, 65 % of the patients included in the analysis had endoscopic signs of chronic non-atrophic gastritis, a minority (33 %) were patients with the signs of acute erosive gastritis, one patient had endoscopic signs of gastric ulcer exacerbation.

General bacterial composition of the gastric mucosa

The data obtained during sequencing were analyzed in the QIIME2 software and the Greengenes2 database. Taxonomic analysis of the identified OTUs shows that the dominating classes in the gastric mucosa of the patients included in the study are *Campylobacteria, Bacilli, Bacteroidia* and *Gammaproteobacteria* – 20.4 %, 20.3 %, 15 % and 11.2 %, respectively (Fig. 1). The remaining classes of bacteria, representing 3 % or less of gastric microbiota of studied samples, were *Clostridia*, *Alphaproteobacteria*, *Fusobacteria*, *Negativicutes*. About 17 % of the total metatranscriptomic data included underrepresented (< 1 %) and unidentified bacterial classes.

A more detailed analysis of cDNA samples subjected to sequencing made it possible to determine the bacterial composition of gastric biopsies down to the genus and, in some cases, species of bacteria (Figs. 2, 3). In general, when comparing two mucosal biopsy sites (body and antrum), the dominant part of the bacterial community remains unchanged: representatives of *Helicobacter, Streptococcus, Prevotella* and *Alloprevotella* genera are prevailing. In addition to the dominant

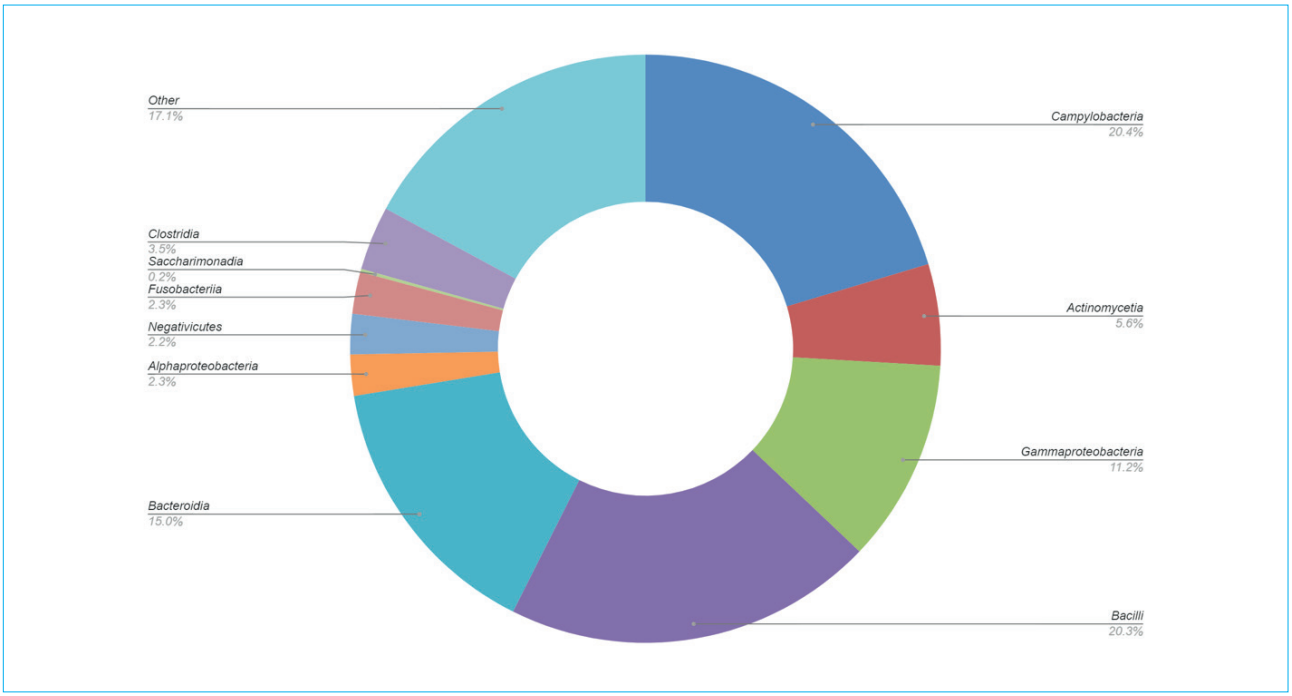

Figure 1. Representation of the main classes of bacteria in biopsy samples of the mucous membrane of the body and antrum of the stomach

Рисунок 1. Представленность основных классов бактерий в биоптатах слизистой оболочки тела и антрального отдела желудка

representatives, the gastric microbiota includes bacteria of the *Veillonella, Gemella, Haemophilus, Staphylococcus, Sphingomonas* and *Lawsonella* genera.

Bacterial composition of the microbiota of the gastric mucosa in *H. pylori*-positive and *H. pylori*-negative patients

Based on sequencing results, the *H. pylori*-positive group included all patients whose biosamples (at least one of the compartments — body or antrum) contained > 2 % of the *H. pylori* in the gastric microbiome. Thus, biosamples of 20 out of 46 patients (43.47 %) were considered as *H. pylori*-positive.

In majority of *H. pylori*-positive patients, a significant (up to 90 %) dominance of bacteria of the *Helicobacter* genus was found (Fig. 4). Bacteria of the *Streptococcus* genus, in particular *Streptococcus vestibularis* species, as well as *Prevotella* and *Alloprevotella* genera, were represented to a lesser extent. In *H. pylori*-negative samples (Fig. 5) an increase in the representation of *Streptococcus* (40.1 % vs. 15.2 %), *Prevotella* (3.8 % vs. 1.7 %) and *Alloprevotella* (6 % vs. 1.9 %) genera was found, as well as the greater abundance of *Gemella, Haemophilus, Staphylococcus, Sphingomonas* genera, which, according to the literature data, can be considered as normal gastric microbiota representatives [8].

The decrease in species (taxonomic) diversity in the group of *H. pylori*-positive patients was also confirmed using the Shannon index, the average value of which was 3.6 in *H. pylori*-positive group and 5.4 in *H. pylori*-negative group (Fig. 6). There is a relationship between a decrease in biodiversity and a significant predominance of *H. pylori* in gastric microbiota of *H. pylori*-positive patients.

***H. pylori* prevalence in the gastric mucosa of different parts of stomach (body and antrum)**

H. pylori diagnosing guidelines suggest the need to take biopsies from both the antrum and the body of the stomach [9]. This is explained by the possibility of colonization of the body and the absence (or detection in smaller quantities) of *H. pylori* in the antrum in some cases, for example, in severe atrophy of the antral mucosa. The level of *H. pylori* contamination of the gastric mucosa in the antrum and body of the stomach differs in the same patient, in some cases reaching a significant difference (Fig. 7). For example, in case of samples 3-20, 5-20 and 8-20, the percentages of contamination of the antrum and body are 25 and 87, 33 and 81, 32 and 69 %, respectively.

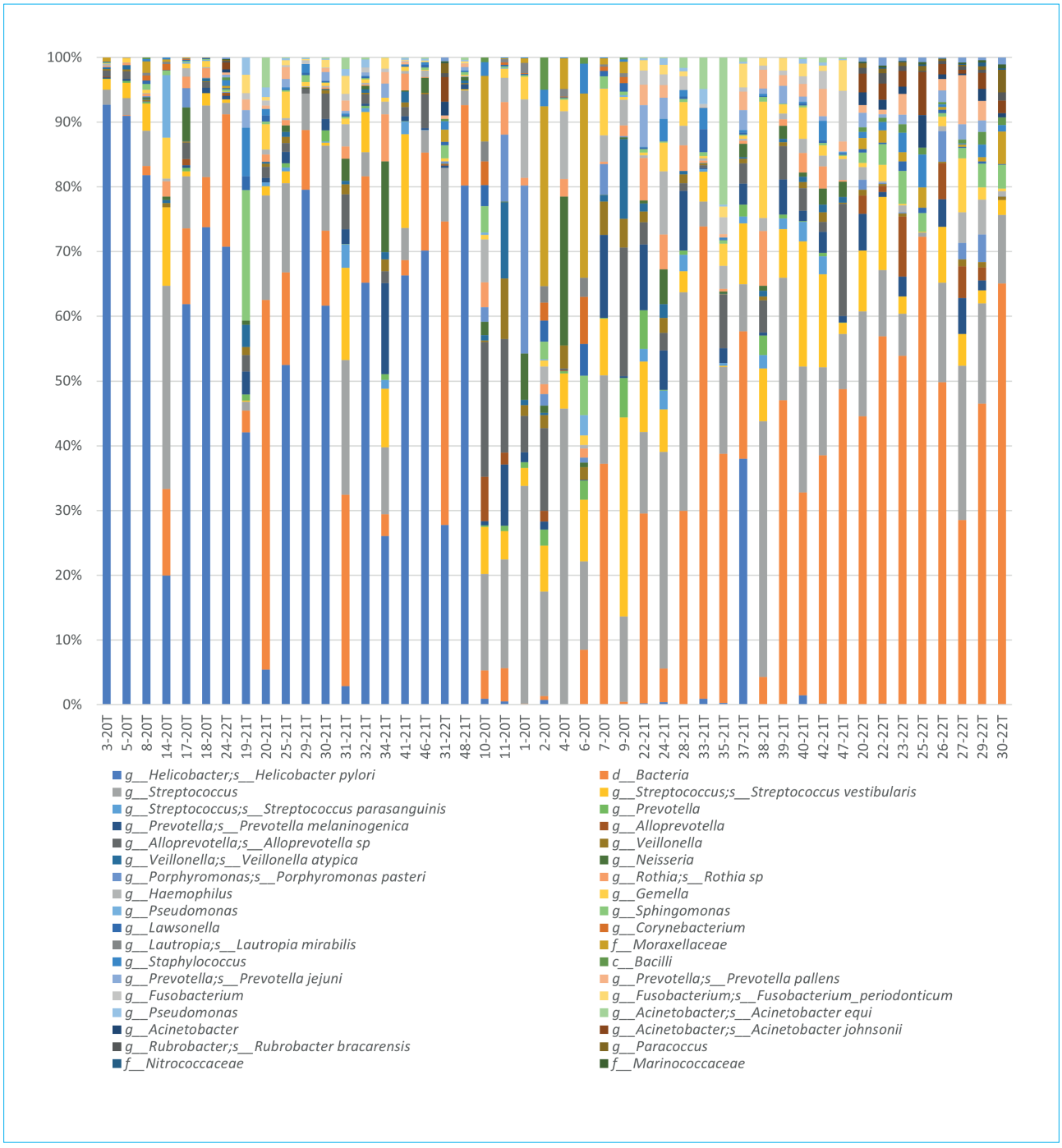

Figure 2. Representation of the main genera and species of bacteria in biopsy samples of the mucous membrane of the body of the stomach (samples from 3-20T to 31-22T — *H. pylori*-positive, from 10-20T to 30-22T — *H. pylori*-negative)

Рисунок 2. Представленность основных родов и видов бактерий в биоптатах слизистой оболочки тела желудка (образцы с 3-20T по 31-22T — *H. pylori*-положительные, с 10-20T по 30-22T — *H. pylori*-отрицательные)

Such variations can lead to false-negative results when testing biopsies of the gastric antrum for *H. pylori* infection and support the need to obtain biopsies from two different parts: the body and the antrum.

When comparing the representation of other bacteria in the body and antrum of the stomach, no statistically significant differences were found in either *H. pylori*-positive or *H. pylori*-negative patients.

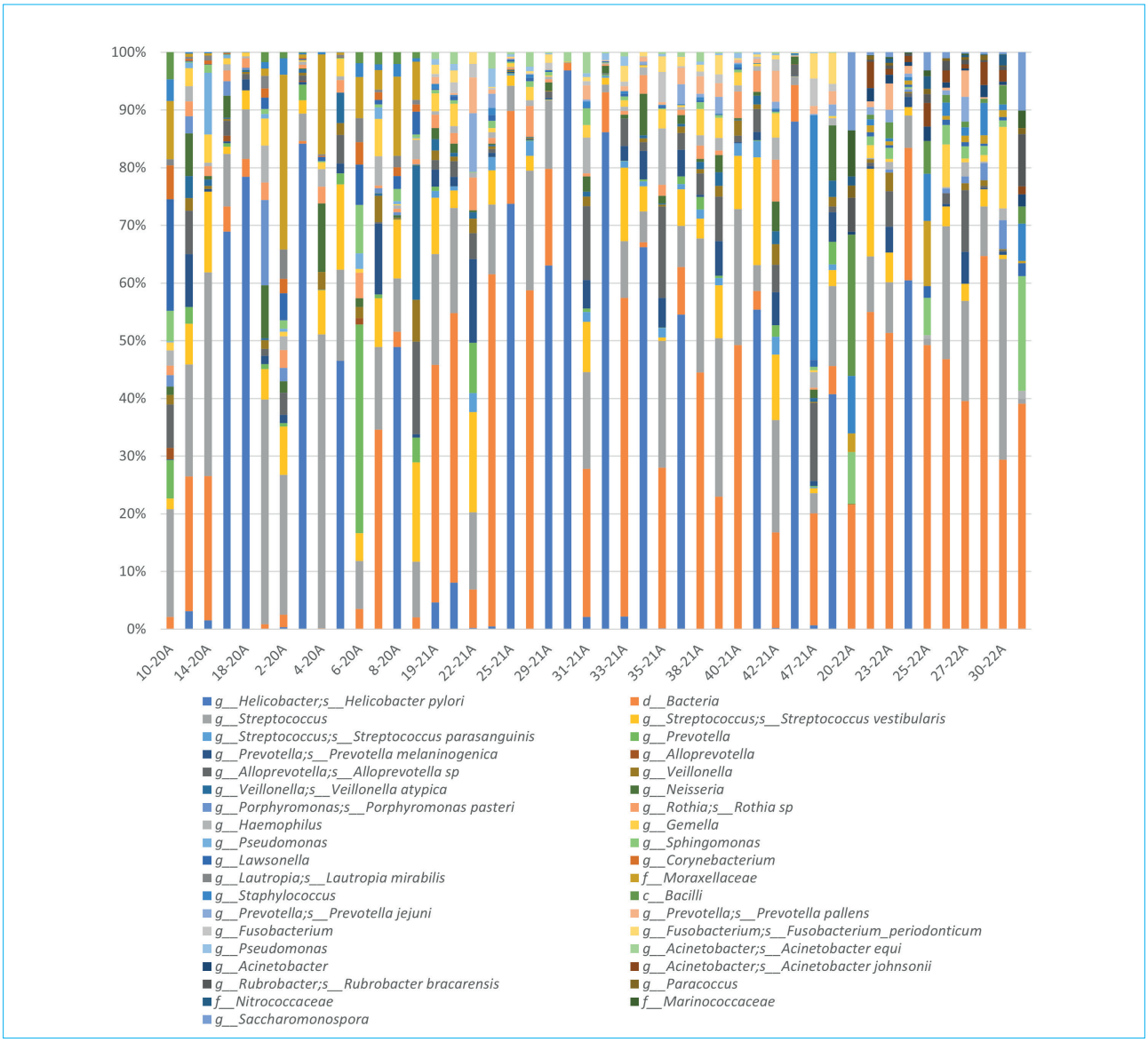

Figure 3. Representation of the main genera and species of bacteria in biopsy samples of the mucous membrane of the antrum of the stomach (samples from 3-20A to 31-22A — *H. pylori*-positive, from 10-20A to 30-22A — *H. pylori*-negative)

Рисунок 3. Представленность основных родов и видов бактерий в биоптатах слизистой оболочки антрального отдела желудка (образцы с 3-20А по 31-22А — *H. pylori*-положительные, с 10-20А по 30-22А — *H. pylori*-отрицательные)

Discussion

The present study examined the composition of the gastric microbiota in patients with symptoms of dyspepsia and different *H. pylori* status.

A distinctive feature of this study is that the presence of *H. pylori* was confirmed by analyzing isolated RNA using the reverse transcription method. This method makes it possible to characterize the metabolically active part of the microbiota. In this study, it was revealed that representatives of four classes of bacteria were predominant in gastric biopsies — *Campylobacteria, Bacilli, Bacteroidia* and *Gammaproteobacteria*. According to the literature, these bacteria are the most common inhabitants of the human stomach [10]. The results of this study are generally consistent with the results of similar studies on the composition of the gastric microbiota presented in the literature, including data from domestic studies [6, 11–14]. However, it should be noted that in the listed studies, slightly different methods were used to study the composition of the gastric microbiota: most often, the microbiome was studied at the

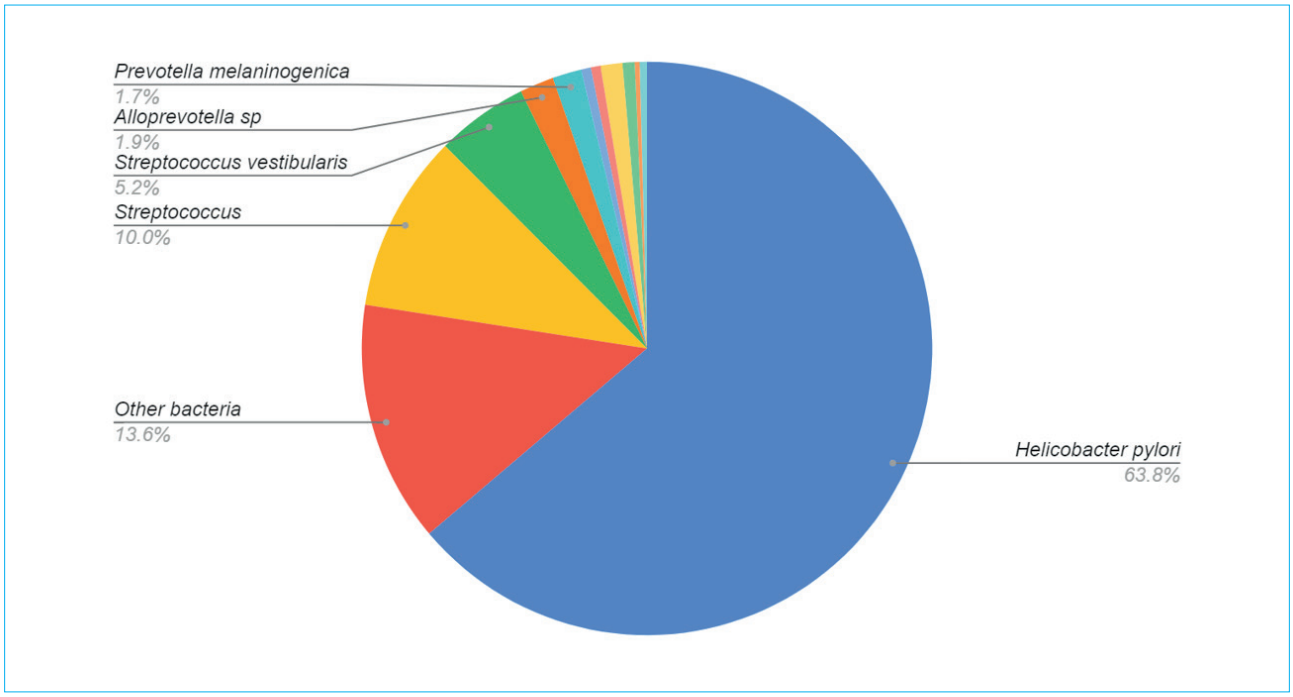

Figure 4. Representation of various genera and species of bacteria in the gastric microbiota of *H. pylori*-positive patients

Рисунок 4. Представленность различных родов и видов бактерий в микробиоте желудка *H. pylori*-положительных пациентов

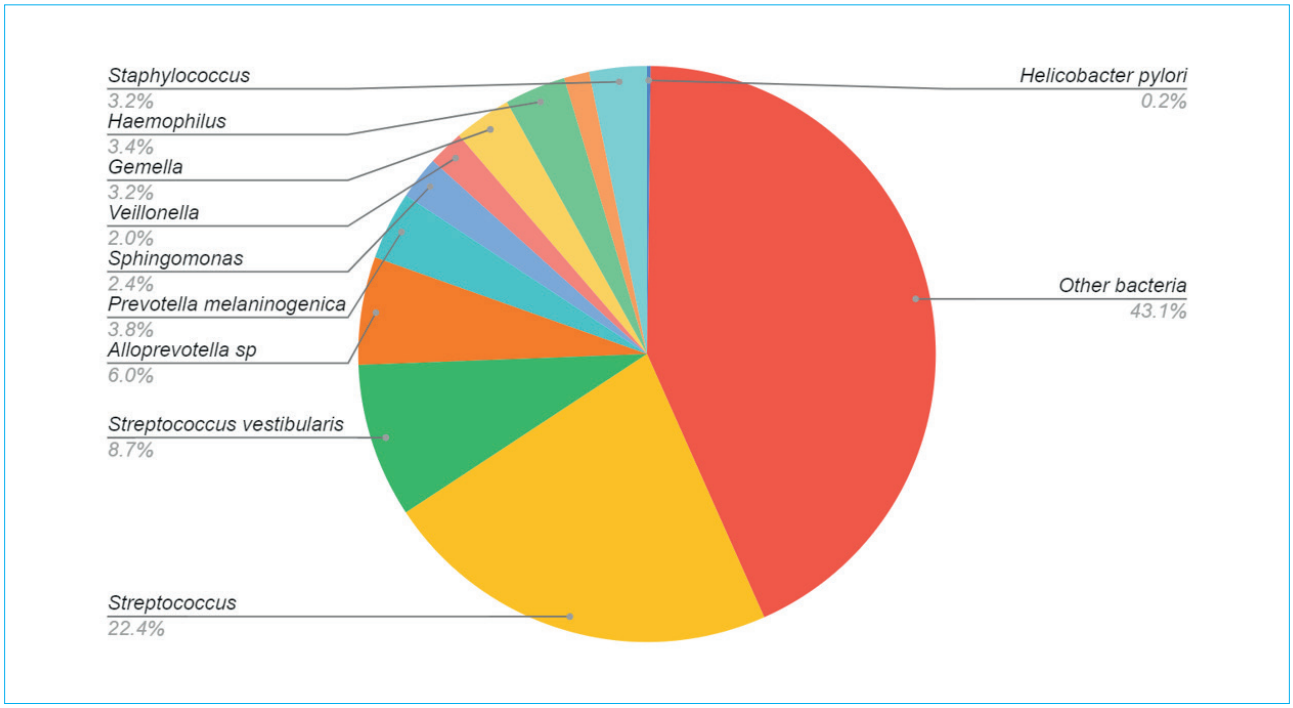

Figure 5. Representation of various genera and species of bacteria in the gastric microbiota of *H. pylori*-negative patients

Рисунок 5. Представленность различных родов и видов бактерий в микробиоте желудка *H. pylori*-отрицательных пациентов

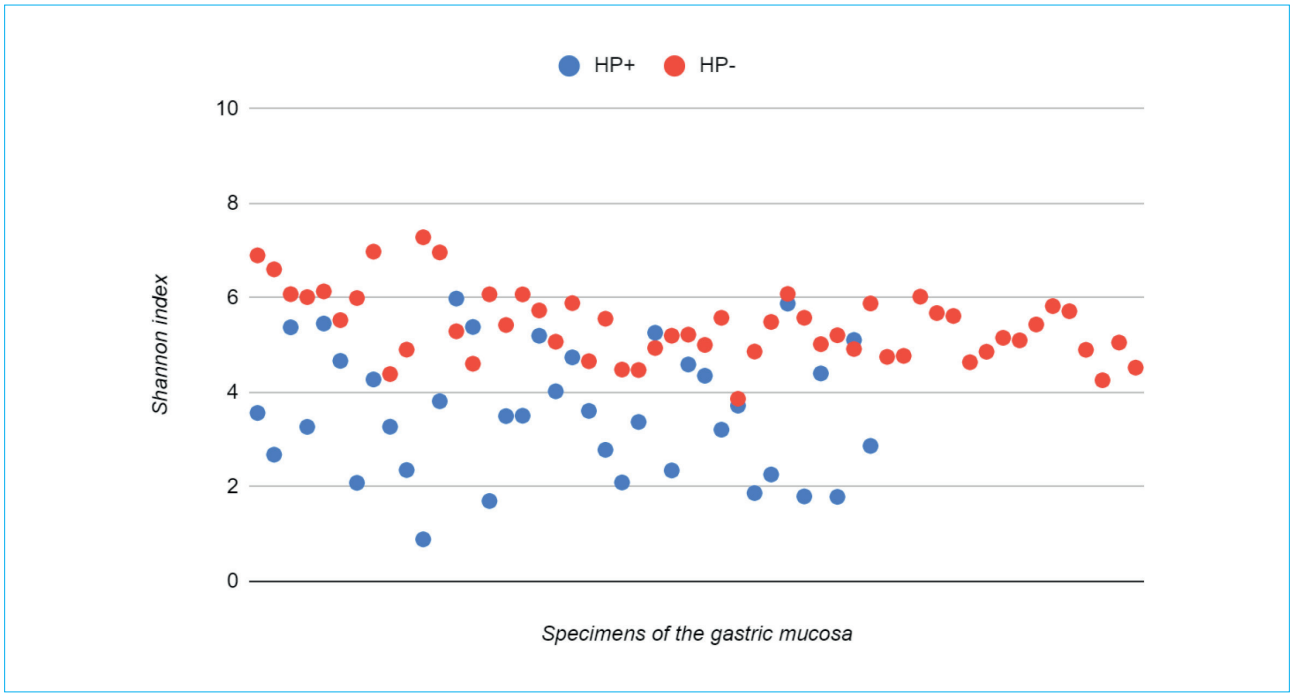

Figure 6. Species diversity of the gastric microbiota (Shannon index) in the groups of *H. pylori*-positive (HP^+) and *H. pylori*-negative (HP^-) patients

Рисунок 6. Видовое разнообразие микробиоты желудка (индекс Шеннона) в группах *H. pylori*-положительных (HP^+) и *H. pylori*-отрицательных (HP^-) пациентов

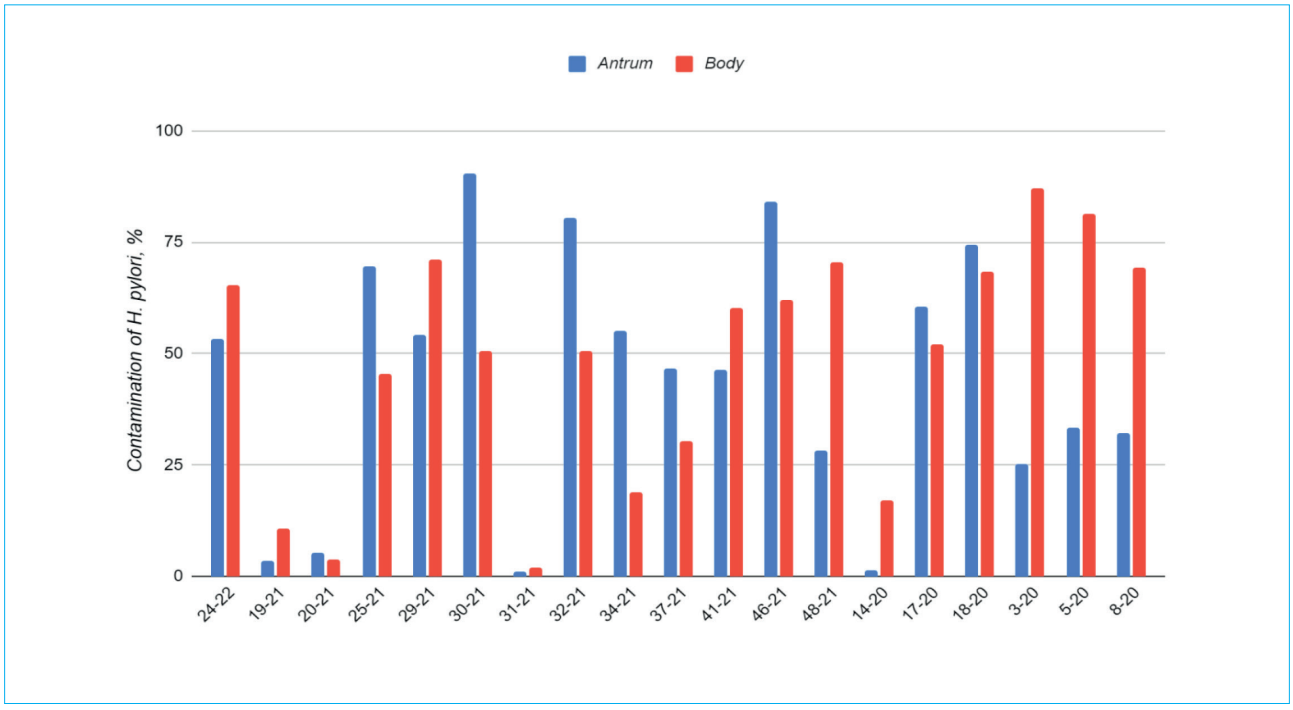

Figure 7. *H. pylori* contamination of the mucous membrane of the body and antrum of the stomach

Рисунок 7. Обсемененность *H. pylori* слизистой оболочки тела и антрального отдела желудка

level of bacterial DNA using *16S rRNA* gene sequencing. Thus, the bacterial composition of the stomach at the bacterial class level is similar for the vast majority of people, and differences may be more pronounced at the family and genus level. It was revealed that the qualitative composition of the gastric microbiota of both *H. pylori*-negative and *H. pylori*-positive patients is comparable. However, there are significant differences in the quantitative ratio of representatives of the gastric microbiota in the compared groups of patients, which confirms the results described previously by other researchers [15–17].

In the absence of *H. pylori* infection, an increase in the representation of bacteria of the *Streptococcus, Prevotella* and *Alloprevotella* genera was shown. Previous studies examining the composition of the gastric microbiota in patients with chronic gastritis showed that there was a significant negative correlation between the presence of *H. pylori* and the abundance of bacteria of the *Streptococcus* genus: the presence of *H. pylori* inhibited the growth of *Streptococcus*, and in *H. pylori*-negative patients their number increased [18]. It has also been established that there is an increase in the number and predominance of *Streptococcus* genus in gastric mucosa in case of stomach cancer [19, 20], which differs significantly from the composition of bacteria in healthy humans or patients with chronic gastritis [21]. In this regard, *Streptococcus* is considered as a potential marker for predicting the development of gastric cancer [22], but this issue needs further research.

In the group of *H. pylori*-positive patients there is a predominance of bacteria of the *Helicobacter* genus (up to 90 %), which is accompanied by a significant decrease in the species diversity of the microbial community. As known, biodiversity is one of the most important characteristics of the microbiota: the greater the species diversity of the microbial community is, the more "reliable" and the more "stable" is the composition of the microbial community. Similar changes in the bacterial composition of the gastric microbiota in a group of *H. pylori*-positive patients are widely described in the literature [23–25]. Most authors agree that a decrease in the species diversity of the gastric microbiota and the predominance of *Helicobacter* genus can be considered as an additional "aggressive" factor contributing to the development and progression of gastric diseases.

It is encouraging that the described changes in the composition of the gastric microbiota due to *H. pylori* infection are potentially reversible, and *H. pylori* eradication can help restore and increase the biodiversity of the gastric microbial community [26, 27].

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