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FACTORS AFFECTING THE HELICOBACTER PYLORI BACTERIAL LOAD IN CHILDREN WITH UPPER GASTROINTESTINAL TRACT DISEASES

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Abstract. *Introduction.* Despite geographical differences, the Helicobacter pylori (HP) infection occurrence remains high worldwide [1]. As highlighted in a review conducted using systematic methodology, the worldwide rate of HP in adults decreased to 43% by 2020, with no trend toward a decline in the incidence of this infection among children. Currently, the level of HP infection across the world in children is 32.3% [2]. Given the influence of HP on the course of gastroduodenal diseases and the high risk of their chronicity, the issue of diagnosis and treatment of this infection in children remains relevant [3,4].

Purpose: To study the factors affecting the extent of bacterial load of *Helicobacter pylori* (*HP)* in pediatric patients with gastroduodenal diseases.

Methods. The study included 158 patients aged 4 to 17 years. Subgroup 1 included 65 children with a bacterial load of "1," while subgroup 2 included 73 children with a bacterial load of "2" or "3." Endoscopic, laboratory, and histological examinations were performed for diagnosis.

Results. Children in subgroup 2 were found to have a higher frequency of complaints related to upper gastrointestinal motility disorders compared to those in subgroup 1. Complaints of weakness and fatigue were more common in children in subgroup 1. A moderate positive correlation was established between hemoglobin levels and bacterial load. A strong positive relationship was also found between serum iron and bacterial load. Patients in subgroup 2 were characterized by *DGR*, a more pronounced density of lymphoplasmacytic infiltrate against the background of similar inflammatory activity. Metaplasia and atrophy of the mucosal epithelium were predominant in patients in subgroup 1.

Conclusions. The study found a direct correlation between the frequency of complaints and the level of *HP* bacterial load. Factors influencing the bacterial load include iron and hemoglobin levels, gastric pH, the presence of *DGR*, chronic inflammation, metaplasia, and atrophy of the gastric mucosa. It was concluded that microenvironmental conditions play a primary role in the fact and intensity of *HP* colonization.

Key words: Helicobacter pylori, gastroduodenal region, children, adolescent, diagnostics, endoscopy, peptic ulcer.

Фактори, що впливають на бактеріальне навантаження Helicobacter Pylori у дітей із захворюваннями верхніх відділів шлунково-кишкового тракту

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Резюме. *Вступ.* Попри географічні відмінності, поширеність H. pylori (HP) у світі залишається високою [1]. Згідно з систематичними оглядами, до 2020 року рівень інфікування серед дорослих знизився до 43%, тоді як серед дітей він становить 32,3% і не має тенденції до зниження [2]. З огляду на роль HP у хронізації гастродуоденальних захворювань, удосконалення діагностики та лікування цієї інфекції в педіатрії залишається актуальним [3,4].

Мета дослідження. Дослідити фактори, що впливають на ступінь бактеріального навантаження H. Pylori у дітей із захворюваннями верхніх відділів шлунково-кишкового тракту.

Матеріали та методи. У дослідження включено 158 пацієнтів віком від 4 до 17 років. До підгрупи 1 увійшли 65 дітей із бактеріальним навантаженням «1», до підгрупи 2 увійшли 73 дитини – бактеріальне навантаження оцінено як «2», «3». Для діагностики було проведено ендоскопічне дослідження, лабораторне та гістологічне дослідження.

Результати досліджень. Встановлено, що у дітей 2 підгрупи була більша частота скарг, пов'язаних із порушенням моторики верхніх відділів ШКТ, відносно 1 підгрупи. Скарги на слабкість і швидку втомлюваність частіше турбували дітей 1 підгрупи. Встановлено помірну позитивну кореляцію між рівнем гемоглобіну та бактеріальним навантаженням. Визначено наявність сильного позитивного взаємозв'язку між сироватковим залізом та бактеріальним навантаженням. Пацієнтам 2 підгрупи були

притаманні ДГР, явища більш вираженої щільності лімфоплазмацитарного інфільтрату на тлі однакової активності запального процесу. Метаплазія та атрофія епітелію слизової оболонки домінували у пацієнтів 1 підгрупи.

Висновки. За результатами проведеного дослідження встановлено пряму залежність частоти скарг від рівня бактеріального навантаження *Helicobacter pylori (HP)*. Факторами, що впливають на ступінь бактеріального навантаження, є рівень заліза та гемоглобіну, pH середовища шлунка, наявність ДГР, наявність хронічного запалення, метаплазії та атрофії слизової оболонки шлунка. Зроблено висновок про первинність умов мікросередовища у факті та інтенсивності колонізації *HP*.

Ключові слова: Helicobacter pylori, гастродуоденальна зона, діти, підлітки, діагностика, ендоскопія, пептична виразка.

Introduction

Despite geographical differences, the *Helicobacter pylori (HP)* infection occurrence remains high worldwide [1]. As highlighted in a review conducted using systematic methodology, the worldwide rate of *HP* in adults decreased to 43% by 2020, with no trend toward a decline in the incidence of this infection among children. Currently, the level of *HP* infection across the world in children is 32.3% [2]. Given the influence of *HP* on the course of gastroduodenal diseases and the high risk of their chronicity, the issue of diagnosis and treatment of this infection in children remains relevant [3,4].

Detecting *HP* using various diagnostic methods is not sufficient to analyze the bacteria's pathogenic effect on the host. Determining the bacterial load—the number of bacteria in each area of the mucosa—is also important [5], since it allows us to determine the links with clinical manifestations and morphological changes, as well as to investigate factors that potentially contribute to an increase in bacterial colonization with *HP*.

It is important to clarify the mechanisms that lead to an increase in the bacterial load of *HP*, since the intensity of *HP* colonies development is not random, but depends on the general condition of the human body and the stomach microenvironment, including the level of iron and hemoglobin, gastric pH, and impaired gastrointestinal motility [6,7,8].

Recently, studies have emerged that highlight the association of *HP* colonization intensity with the degree of morphological changes in the gastrointestinal mucosa, including chronic inflammation, activity, atrophy, and metaplasia [9]. At the same time, most authors limit themselves to a predominantly isolated study of laboratory, instrumental and histological parameters, ignoring clinical data and not conducting a systematic comparison of the results of the listed research methods.

Purpose

To study the factors affecting the extent of bacterial load of *HP* in pediatric patients with gastroduodenal diseases.

Study design and methods

We analyzed the outputs of examinations of 158 patients aged 4 to 17 years, 11 months, and 29 days (including 72 boys and 86 girls), with an average age of 14.6±2.6 years. All children underwent a clinical examination, fibroesophagogastroduodenoscopy (FEGDS), and histological examination of gastric and duodenal mucosal biopsies between 2019 and 2025.

Diagnostics and verification of the clinical diagnosis were carried out in accordance with the Standards of Medical Care "Peptic Ulcer of the Stomach and Duodenum in Adults and Children" (Order of the Ministry of Health of Ukraine No. 1514 dated August 25, 2023) [10].

Fibroesophagogastroduodenoscopy was performed using an MTW-Endoskopie W.Haag KG endoscope, with biopsy material obtained along both the lesser and greater curvatures of the antrum, body, and angle of the stomach. Measurements of pH were performed using an AGM-03 stationary acidogastrometer. Based on these data, the state of gastric secretion was determined: pH 5.0-2.1 (hypoacidity), pH 1.2-2.0 (normoacidity), and pH <1.2 (hyperacidity).

Diagnosis of *HP* infection was carried out using a rapid urease test - a commercial kit Ure Hp-test (Erba Lachema, Czech Republic) [11] and histological examination carried out on prepared preparations with a PAS reaction, stained with hematoxylin and eosin, Romanowsky stain [12].

The bacterial load of Helicobacter pylori was determined using the histological research method according to *the Updated Sydney System*, 1994, taking into account the degree of colonization density. Histological assessment of the chronic inflammatory process in the gastric mucosa was carried out in accordance with *the Updated Syd-*

ney System, 1994, by semi-quantitative analysis of the density of lymphoplasmacytic infiltrate, activity, atrophy, metaplasia [13].

The main group included 138 children with upper gastrointestinal tract *HP*- associated diseases. Children did not receive eradication therapy, treatment for gastritis, or iron supplements for at least 4 weeks prior to the endoscopic examination. Based on the data obtained from assessing the level of *HP* bacterial burden, the children were divided into 2 subgroups: subgroup 1 included 65 children (mean age 14.6±2.5 years) with a bacterial load of «1», subgroup 2 included 73 children (mean age 14.5±2.5 years) with a bacterial load of «2» and «3». The control group included 20 conditionally healthy children, representative in age and gender, who, according to the results of histological examination, did not have any pathological changes. Statistical data processing was performed on a personal computer using licensed software, including Statistica for Windows 13.0, serial number JPZ8041382130ARCN10-J, with the arithmetic mean (M), standard deviation (σ), and standard errors (m) determined for parameters whose distribution met the criteria. The Pearson χ^2 test was used to determine the relationship between categorical variables. Differences were considered significant at $p < 0.05$.

The survey protocol was obtained approval from the Bioethics Commission of the Zaporizhzhia State Medical and Pharmaceutical University. The protocol is based on the ethical principles outlined in the Belmond Report of April 18, 1979. The structure of the protocol meets the basic bioethical standards defined in the Declaration of Helsinki adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977), as well as the requirements of the World Health Organization, the International Council of Medical Scientific Societies, the International Code of Medical Ethics (1983) and the laws of Ukraine.

All procedures performed within the study complied with the ethical standards of the ethics committee and the provisions of the Declaration of Helsinki.

Results

During the first stage of the study, an analysis of complaints from patients in the main group was conducted. The data are presented in Table 1.

Table 1

Frequency of complaints in children with diseases of the upper gastrointestinal tract depending on the bacterial load of *Helicobacter pylori*

Compleints	Total n=138		Subgroup 1 n=65		Subgroup 2 n=73	
	n	%	n	%	n	%
Epigastric pain	86	62,3	38	58,5	48	65,8
Preprandial epigastric pain	10	7,2	5	7,7	5	6,8
Postprandial epigastric pain	47	34,1	26	40	21	28,8
Epigastric pain independent of meals	29	21	7	10,8	22	30,1*
Abdominal pain at night	19	13,8	7	10,8	12	16,4
Nausea	22	15,9	5	7,7	17	23,3*
Vomiting	14	10,1	1	1,5	13	17,8*
Bitter taste in the mouth	8	5,8	4	6,2	4	5,5
Heartburn	17	12,3	2	3,1	15	20,5*
A feeling of fullness in the stomach	12	8,7	3	4,6	9	12,3
Constipation	22	15,9	6	9,2	16	21,9*
Fatigue and weakness	25	18,1	17	26,2	8	11*
Dizziness	5	3,6	3	4,6	2	2,7

Note.

** – p<0,05 – compared with the values of subgroup 1.*

As shown in Table 1, children in subgroup 2 were 3 times more likely to complain of abdominal pain independent of meals, and nausea, and 7.5 times more likely to complain of heartburn. Constipation also significantly increased (2.6 times) and vomiting (10 times) in subgroup 2 (p<0.05). However, weakness and fatigue were 2 times more common in children in subgroup 1 (p<0.05).

It was found that the average duration of complaints in children of subgroup 1 was 378.8±50.2 days versus 875.5±80.7 days in children of subgroup 2, which exceeded the determinants of subgroup 1 by 2.3 times (p<0.05). A weak positive correlation was determined between the total duration of the disease and the bacterial load of *HP* (r=+0.2, p<0.05). The duration of the last exacerbation in children of subgroup 1 averaged 32.9±5.1 days, while in children of subgroup 2 it was 26.9±3.2 days, that is, no association was identified among the bacterial load and the duration of exacerbation (r=+0.04, p>0.05). We did not observe significant gender differences between the two groups. Among the children in subgroup 1, there were 39 (60%) girls and 26 (40%) boys; in group 2, there were 37 (50.7%) girls and 36 (49.3%) boys. No differences in the level of *HP* bacterial load were noted in association with gender (p>0.05).

We determined the average red blood cell count in both groups. According to the data obtained, the average red blood cell count in Group 1 was within the range 4,33±0,11*10^{12}/L and was statistically lower than in children in the reference group (4,73±0,12*10^{12}/L (p<0,05)). At that time, the studied indicator in children of the 2nd group was 4,5±0,09*10^{12}/L and did not differ in contrast to the reference group (p>0,05). The average hemoglobin level was within the age-appropriate range; however, there were differences in this indicator between the subgroups. Among children in subgroup 1, anemia was diagnosed in 24 cases (36.9%), while in subgroup 2, anemia was detected in 17 cases (23.3%). No anemia was detected in the control group. We observed the lowest hemoglobin levels in children of subgroup 1, differing from control levels by 21% (119,73±4,96 g/L, p<0,05), while in patients of subgroup 2 they were 12% lower (130±3,7 g/L, p<0,05). A moderate positive association was found between hemoglobin levels and bacterial load (r=+0,4, p<0,05). Against this background, the serum iron level in children of subgroup 2 and the control did not differ and amounted to 14.8±2.1 μmol/l and 18.1±1.2, respectively, while in children of subgroup 1 it was 2.9 times lower compared to the control and was estimated to 6.3±1.3 μmol (p<0,05). A strong positive relationship was found between serum iron and bacterial load (r=+0,7, p<0,05).

Subsequently we investigated the frequency of upper gastrointestinal motility disorders occur in children with established *HP* infection, taking into account the level of bacterial load (Table 2).

Table 2

Frequency of motility disorders in children with upper gastrointestinal tract diseases, taking into account the level of bacterial load

Upper gastrointestinal motility disorders	Study group n=138		Subgroup 1 n=65		Subgroup 2 n=73		Control group n=20	
	n	%	n	%	n	%	n	%
Gastroesophageal reflux	36	26,1	15	23,1	21	28,8	4	20
Duodenogastric reflux	50	36,2	13	20,0	37	50,7*	6	30

Note.

** – p<0,05 – compared with the values of subgroup 1.*

As can be seen from the data presented in Table 2, duodenogastric reflux (*DGR*) was more common in patients of group 2, that is, in the group of children with a high level of bacterial load (p<0.05). Among children in the control group, gastroesophageal reflux (GER) occurred in 4 patients (20%), *DGR* was established in 6 children (30%). The occurrence of motility disorders in children in the control group is due to the existence of functional gastrointestinal disorders. In the main group, the presence of *DGR* showed a significant association with the level of bacterial load (r=+0.4, p<0.05). We did not find a relationship between the incidence of epithelial barrier disorders (erosions and ulcers) and the level of *HP* bacterial load (Table 3).

Table 3

Frequency of mucosal defects in children with upper gastrointestinal tract diseases, depending on the bacterial load of *Helicobacter pylori*

Mucosal defects	Study group n=138		Subgroup 1 n=65		Subgroup 2 n=73	
	n	%	n	%	n	%
Gastric or duodenal ulcer	12	8,7	3	4,6	9	12,3
Gastric or duodenal erosion	34	24,6	15	23,1	19	26

Normoacidity was present in 70% of children, hypoacidity was present in 25%, and hyperacidity was diagnosed in only 5%. All cases of hypoacidity were detected only in children in subgroup 2. This finding was confirmed by comparing the bacterial load and gastric pH. (r=- 0,43, p<0,05).

The occurrence of inflammatory alterations of the gastric lining and duodenum and the association with *HP* was established using the histological diagnostic method in 138 children (62 boys and 76 girls), of which chronic mild gastritis occurred in 13 (9.4%) cases, chronic moderate gastritis in 71 (51.5%), severe chronic gastritis in 54 (39.1%). Mild bacterial load of *HP* was determined in 65 (47.1%) patients, moderate in 61 (44.2%) and severe in 12 (8.7%) patients.

As can be seen from Table 4, in children of subgroup 2 we reliably more often observed phenomena of a more pronounced density of lymphoplasmacytic infiltrate, characterizing chronic inflammation (p<0.05) against the background of the same activity of the inflammatory process.

A seemingly paradoxical observation was made: metaplasia and atrophy of the epithelium of the mucous membrane dominated in patients of group 1, and with low bacterial load (p<0.05).

Table 4

Morphological changes in the mucosa of the upper gastrointestinal tract, considering the levels of *Helicobacter pylori* bacterial load (M±m)

Parameter (scores)	Subgroup 1 n=65	Subgroup 2 n=73
Density of lymphoplasmacytic infiltrate	3,09 ± 0,09	3,4 ± 0,08*
Activity of the inflammatory process	2,1±0,1	1,8±0,1
Epithelial metaplasia	1,8±0,2	1,09±0,05*
Epithelial atrophy	1,73±0,1	1,23±0,09*

Note.
** – p<0,05 – compared with the values of subgroup 1.*

Additionally, moderate inverse relationships were found between the level of *HP* bacterial load and the presence of intestinal metaplasia (r=-0.42, p<0.05) and between the level of *HP* bacterial load and the level of atrophy (r=-0.33, p<0.05).

Discussion

The results of the comparisons indicated certain characteristics of the course of upper gastrointestinal diseases depending on the intensity of *HP* colonization. Bacterial load is a dynamic process, and the intensity of *HP* burden changes over time. This process is nonlinear, meaning that bacterial density does not always increase with the time span of the disease [14]. In some cases, a decrease in the bacterial load may occur with increasing disease duration. The lack of any association with the duration of the last exacerbation, on the contrary, indicated that the level of *HP* load was not determined according to the length of the inflammatory process; the bacteria did not exhibit increased proliferation during the exacerbation phase and likely was not the key initiator of active inflammation.

There are indications in modern literature that the intensity of *HP* colonization may be associated with increased irritability of the gastric mucosa [7, 8, 9], which was confirmed in our work, primarily due to the increase in complaints of abdominal pain that was not dependent on food intake (p<0.05).

To date, differences in gastric pH and changes in upper gastrointestinal motility when accompanied by *HP* have been described, which could also influence the presence and frequency of these complaints. Constipation could be a factor indirectly contributing to *HP* adherence and growth, especially when combined with other gastrointestinal motility disorders [9,15]. Chronic constipation was accompanied by a disruption in the movement of contents from the stomach to the intestine, which could lead to stagnation of gastric contents and local changes in pH and, therefore, act as a factor that promotes maintenance of bacteria.

The described complaints were possibly associated with emergence of gastroesophageal and duodenogastric reflux. Given the absence of notable variations in the frequency of motor disorders among the children in the study and control groups, *HP* can be considered not as a cause of motility disorders, but as a microorganism that colonizes the mucosa to a greater extent under conditions of hypoacidity and congestion. Further support for this opinion is the high incidence of *DGR* in children in subgroup 2, which may also indicate that the presence of *DGR* serves as a prerequisite for *HP* growth [8,16].

Additionally, a moderate inverse correlation was established between the bacterial load and the acidity of the gastric contents ($r=-0.43$, $p<0.05$), which is explained by the process of chronic inflammation, impaired regulation of hormones such as gastrin, somatostatin, and damage to parietal cells [16].

The increased frequency of complaints of weakness and fatigue in pediatric patients with gastrointestinal diseases can be explained, to some extent, by the onset of anemia due to chronic inflammation. According to literature, *HP* is linked to the appearance of anemia in children, and elevated iron levels in the stomach milieu create metabolically favorable conditions for its colonization and resistance to the host's immune response [17]. Iron is essential for the survival and growth of *HP* colonies, given that this pathogen is a microaerophilic gram-negative bacterium. We found a direct linear association in relation to hemoglobin levels and bacterial load ($r=+0.4$, $p<0.05$) and a positive correlation between serum iron and bacterial load ($r=+0.7$, $p<0.05$).

It was found that in pediatric patients with a higher bacterial load, chronic inflammation was, on average, more pronounced, which could reflect a dual effect: the involvement of *HP* in maintaining chronic inflammation and its increased colonization in response to the extent of the chronic inflammatory process [14]. At the same time, inflammatory activity is characterized by a rise in the quantity of neutrophils capable of synthesizing and releasing antimicrobial peptides that act specifically against the infectious pathogen, which in turn reduces the load of *HP* [18], so we also noted a tendency to decrease the activity of the inflammatory process with greater colonization of the bacteria ($p>0,05$).

It was established that atrophy and metaplasia were accompanied by a lower colonization of *HP*. When determining the relationship between the bacterial load of *HP* and the occurrence of intestinal metaplasia, a moderate negative relationship was established ($r=-0.42$, $p<0.05$). As a result of metaplasia, gastric epithelium is replaced by intestinal epithelium, which is cut off behind the receptor apparatus, which in turn reduces the capability of *HP* to adhere [9]. Altered mucus secretion in areas of metaplasia affects the ability of bacteria to persist [14]. It is possible to assume that intestinal metaplasia is not simply a consequence of chronic inflammation, but also a barrier to *HP* settlement, which explains the decrease in bacterial load with an increase in the degree of metaplasia.

Assessing the level of atrophic changes in children, it was found that in patients of subgroup 2 the degree of its severity was significantly lower. There was a moderate inverse association among the extent of atrophy severity and the bacterial load of *HP* ($r= -0,33$ ($p<0,05$)), since mucosal atrophy is characterized by a decrease in the number or complete loss of glandular structures, a decrease in the amount of mucin, and the density of epithelial cells, i.e. factors that maintain chronic inflammation and create conditions for better colonization by *HP* [9].

The Maastricht VI/Florence Consensus Report (2022) stated that although *HP* infection is considered to be the initial factor in morphological changes and contributes to the development of mucosal atrophy leading to gastric cancer, the development of severe clinical manifestations is observed only in a small proportion of infected individuals. This implied the significant influence of individual host characteristics and environmental factors in determining the progression of the disease [20].

According to the findings of the comparisons, we observed a seemingly paradoxical observation: more pronounced deficiencies and lesions

of the stomach lining were accompanied by less intensive colonization of *HP.* Conversely, with an increase in microbial density, the indicators did not become worse, and therefore it is more likely that the degree of contamination depended on the same factors that contributed to the formation of pathological changes. The data obtained require further study and clarification.

Conclusion

1. The frequency of complaints associated with upper gastrointestinal motility disorders directly depends on the level of bacterial load. Factors that potentially affect the density of *HP* presence include iron and hemoglobin levels, gastric pH, the manifestation of duodenogastric reflux, chronic inflammation, metaplasia and atrophy of the gastric mucosa.

2. Based on the data obtained from the comparisons, it is possible to speak about the primacy of microenvironmental conditions in the intensity of *HP* colonization, where it is realized as an opportunistic colonizer, and not the main factor in the initiation of pathological changes.

Conflict of interest: The authors report no conflict of interest.

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