

Helicobacter pylori Infection at Crossroads between Specialties

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Rezumat

Infecția cu Helicobacter pylori la intersecția dintre specialități

Introducere: Infecția cu *Helicobacter pylori* (*H. pylori*) reprezintă una dintre marile probleme de sănătate publică actuale, având incidență ridicată la nivel global. Această afecțiune se asociază cu alte patologii precum ulcerul peptic sau cancerul gastric, determinând o reală provocare pentru specialitățile din domeniul medical.

Metode: Am realizat un studiu retrospectiv ce include o cohortă 275 de pacienți care au efectuat endoscopie digestivă superioară și au fost testați pentru prezența infecției cu *H. pylori* prin testul antigenului din scaun, în perioada Iulie 2022 – Decembrie 2023.

Rezultate: Vârsta medie a întregului lot a fost de 62.79 ± 13.8 ani, având o predominanță a sexului masculin cu 156 pacienți (56.7%), cea mai frecventă patologie fiind aceea de gastrită antrală (149 cazuri, 54.2%). Ulcerul gastric are o incidență dublă în cazul celor cu infecție *H. pylori* comparativ cu cei la care aceasta nu este prezentă (19.7% vs. 9.2%, $p=0.012$).

Concluzii: Infecția cu *H. pylori* rămâne o afecțiune ce se poate complica prin diferite condiții patologice ce pot să evolueze de la o ușoară eroziune a mucoasei gastrice la neoplazii digestive ce necesită abordare multidisciplinară, motiv pentru care este esențială înțelegerea mecanismelor acestei boli și aplicarea de resurse terapeutice cât mai rapid.

Cuvinte cheie: *Helicobacter pylori*, gastrită, cancer gastric, ulcer peptic, antibiotic, chirurgie.

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is one of the major current public health problems, its incidence being high worldwide. This condition is associated with other pathologies such as peptic ulcer or gastric cancer, causing a real challenge for specialists in the medical field.

Methods: We conducted a retrospective study that includes a cohort of 275 patients who performed EGD and were tested for the presence of *H. pylori* by the stool antigen test, between July 2022 and December 2023.

Results: The cohort had an average age of 62.79 ± 13.8 years old, with a male predominance 156 patients (56.7%) and the most frequent lesion is antral gastritis (149 cases, 54.2%). Gastric ulcer in those with positive tests in *H. pylori* had a double incidence compared to those in which the infection is not present (19.7% vs. 9.2%, $p=0.012$).

Conclusions: *H. pylori* infection still remains a condition that can be complicated by various pathological conditions that can evolve from a slight erosion of the gastric mucosa to digestive neoplasia that require complex multidisciplinary treatments, which is why understanding the mechanisms and applying therapeutic resources as soon as possible is essential.

Key words: *Helicobacter pylori*, gastritis, gastric cancer, peptic ulcer disease, antibiotics, surgery

Introduction

Helicobacter pylori (*H. pylori*) is a flagellated bacterium with a helical shape, part of the gram-negative category and found in approximately half of the world's population (1). It was discovered in 1983 by Australian doctors Barry Marshall and Robin Warren, at a time when it was considered by the scientific community that bacteria could not colonize the acidic environment of the stomach (2). Nowadays, being infected with *H. pylori* represents a big public health problem, associating large costs both with the treatment against the infection, and also with the pathologies associated with it, such as peptic ulcer disease (PUD) or gastric cancer (GC). A great challenge is the diagnosis, being known that the infection caused by *H. pylori* does not trigger a specific symptomatology, and patients are often diagnosed at the time of complications.

Currently, screening programs have indications for *H. pylori* testing, such as the following: active peptic ulcer disease, low grade gastric MALT lymphoma, dyspepsia for patients < 45 years old, history of endoscopic mucosal resection for early gastric cancer (3).

The investigations used for the diagnosis of *H. pylori* infection are varied and come with different levels of sensitivity or specificity. These are divided into invasive or non-invasive tests, the differences between them being the costs, the time required to perform them, etc. The first category of tests includes the esophagogastroduodenoscopy (EGD) with biopsy, at least 5 samples and then histologic examination. The second category is represented by the urea breath test, stool antigen test or serology, these tests being used frequently in the screening programs (4).

Epidemiology and Transmission Routes

The incidence varies depending on the type of population, race or geographical location, depending on certain factors. Among the most important aspects that must be taken into account is the socioeconomic status, for example developing countries have an increased incidence of *H. pylori* infection, including pediatric population. Also, the access to basic resources, such as drinking water, antibiotics are important factors that must be taken into account.

The highest prevalence is found in Africa,

70.1%, being also the area with the greatest economic difficulties. Also, in the country ranking, Nigeria has a prevalence of 87.7%, while Switzerland is at the opposite pole with 18.9%. Currently, it is considered that *Helicobacter pylori* infection is found in over 4.4 billion people (5).

The transmission routes of this bacteria are not fully elucidated, but from what is known up to this moment, the stomach is the place where the germ is hosted and the spread of the infection is a direct consequence of human contact or through the environment (6). It is important to mention the fact that there are 2 ways of inter-human transmission, vertical in case it is transmitted to descendants, respectively horizontal in the case of contact with people in the environment and those who are not from that family (7). Regarding interpersonal transmission, it is considered that horizontal transmission from mother to children is more common in western countries with low prevalence, while in developing countries, transmission is more common in the community.

Oral-oral transmission is generally from mother to child, as it has been proven that *H. pylori* can be found in the oral cavity, respectively in the salivary fluid, and there is even a risk of recurrence of the infection in the case of patients with bacteria in the oral cavity (8-10). Also, another way of transmission that should be mentioned is the gastro-oral one, through vomiting, externalizing important amounts of hydrochloric acid that also contain *H. pylori* (11). The fecal-oral route is one of the most common and was among the first known regarding the transmission of the bacterium, especially in conditions of poor hygiene (12).

Environmental contamination is extremely important, especially in countries with a low socioeconomic status, with little access to drinking water sources, most of the time having contact with contaminated water or foods such as meat, vegetables or milk that represents important sources of infection (13,14).

Pathogenesis

Although initially it was considered that the gastric acidic environment could not be colonized by bacteria, self-ingestion experiments had shown that an impairment of the gastric mucosa can develop, with the appearance of inflammation and subsequent gastritis due to *H. pylori* (15).

A first mechanism of the pathogenesis is represented by the flagellar motility that allows the bacteria to perform movements in the gastric contents and penetrate up to the gastric wall structures, despite the presence of acidic gastric juice (16). The pathogenesis of this bacterium in terms of colonization of the gastric environment and motility depends a lot on chemoreceptors, such an action carried out by various molecules such as CheA kinase or T1pA, B, C, and D (17).

Also, the most important enzymes produced by bacteria are those of urease and hydrogenase, they are deeply involved in the pathogenic mechanisms that allow the neutralization of gastric acidity and the development of the energetic metabolism of the *H. pylori* microorganism (18).

The continuation of the pathogenesis process is carried out by the adhesion molecules, which ensure the interaction between the microorganism and the host, the most important ones being antigen binding adhesin A (BabA), respectively Hp HopQ. The first was studied in the pathogenesis of gastric cancer and in the development of duodenal ulcer (19), while the second is involved in the mechanism of inflammation realised through CagA translocation (20).

CagA is the most representative protein involved in pathogenesis, being responsible for the increase of the cell proliferation while reducing the apoptosis. The mechanism of phosphorylation of this protein produces morphological changes in the epithelial cells of the gastric mucosa, thus determining the onset of gastritis or, in more advanced cases, gastric adenocarcinoma (21).

H. pylori represents a bacteria with an elaborate complexity regarding pathogenic

mechanisms, which has been extensively studied in the last decades, and the pathological conditions determined by them can vary from simple erosions of the mucosa to poorly differentiated neoplastic transformation.

Peptic Ulcer Disease

Peptic ulcer disease (PUD) is the most common pathology associated with *H. pylori* infection, being diagnosed in over 8 million cases globally. The outcome of this pathology can be favorable, provided that it is treated from the early stages, or it can evolve into aggravated forms accompanied by complications, in the case of late stages (22).

Although it represents an important cause of morbidity, this pathology does not manifest itself as it advances through specific symptoms, usually initially appearing diffuse abdominal pain, feeling of early satiety, dyspeptic syndrome (23). The most common forms of peptic ulcer are gastric ulcer and duodenal ulcer. It is also worth mentioning that, apart from the association with *H. pylori* infection, these pathologies are also associated with the consumption of NSAIDs (24).

According to literature, the persistence of *H. pylori* at the gastric and duodenal level leads to successive erosions of the mucosa, with the subsequent appearance of gastritis and ulcer disease. If the infection is not treated, the evolution will be towards chronic gastritis (25).

Ulcer perforation is one of the most serious complications of PUD, generating the need for immediate therapeutic resources, including emergency surgery. Currently, the prevalence among patients with PUD has reached approximately 5% (26). Despite the fact that the number of PUD cases with *H. pylori* infection varies depending on several cases, such as access to drinking water, developed health system, socioeconomic level, studies in the literature have shown that *H. pylori* infection can be associated with perforated duodenal ulcer up to approximately 80% of cases (27).

Bleeding is another complication of the peptic ulcer disease caused by *Hp*, this being present in a proportion of 15-20% (28). Also, this pathological condition represents approximately half of the causes for upper digestive hemorrhage (29). The treatment in these cases varies depending on the severity of the bleeding, starting from electrolytic rebalancing fluids, intravenous administration of PPIs to endoscopic hemostasis, and in the case of repeated bleeding, emergency surgery is necessary (30).

Gastric Cancer

Gastric cancer (GC) is the fourth most common cancer in the world, with approximately 1 million new cases diagnosed each year. The incidence varies depending on the geographical regions, Japan being the country with the highest incidence rate. The biggest problem related to this pathology is the lack of symptoms, due to the fact that it can only be diagnosed in the early stages under the conditions of a very well-designed screening program, which is lacking in most countries on the world map (31).

The connection between *H. pylori* infection and the development of gastric cancer was a widely debated topic, but after the appearance of some studies from Japan that demonstrated this connection, showing that approximately 3% of *H. pylori* infected patients will develop gastric cancer, things were unanimously accepted (32). One of the most important proteins from the structure of *H. pylori* involved in the process of neoplastic transformation of the cells is CagA, this being responsible for increasing the proliferation of the cells while also inhibit the cell apoptosis.

Also, in the case of rapid treatment of the infection, the risk of developing premalignant lesions or gastric cancer decreases greatly over time, these facts being demonstrated by large cohort trials (33,34).

The purpose of this study was to evaluate the frequency and characteristics of positive *H. pylori* patients which underwent EGD.

Materials and Methods

We performed a retrospective study carried out in an emergency hospital in Romania, which included a group of 275 patients that had upper GI symptoms and performed an EGD.

The period in which patients were recruited was July 2022 to December 2023 and the inclusion criteria are represented: age over 18 years old, patients who have performed EGD for upper GI symptoms.

The exclusion criteria are represented by: age under 18 years, contraindications to performing an EGD.

In total, 275 patients were included in the study, grouped into 2 subgroups, depending on the presence of *H. pylori* infection detected by stool antigen test. Data was gathered using hospital records. Continuous data was reported as mean and standard deviation (SD), and dichotomous data was reported as number and percentage, respectively. The analysis was performed using SPSS v.20, and the comparison was made using chi-square test and student t-test.

Results

As we mentioned before, the number of patients included in the study was 275, with an average age of 62.79 ± 13.8 years old. The gender distribution shows a predominance of the male sex, being included 156 (56.7%) men, respectively 119 (43.3%) women. Also, most of the patients come from rural areas (67 cases, 60.7%), and approximately half of them are smokers (122 cases, 44.4%), respectively alcohol consumers (129 cases, 46.9%). Among the associated pathologies, it is important to mention that gastric diseases are the most frequent, antral gastritis being the most common (149 cases, 54.2%), respectively ulcers, such as gastric ulcer (38 cases, 13.8%), duodenal ulcer (28, 10.2%), while cancers are a smaller number, gastric cancer (16 cases, 5.8%) and colon cancer (9 cases, 3.3%) (*Table 1*).

In the case of patients tested positive for

Table 1. Patients characteristics

Characteristics	Total N=275
Age (years) mean \pm SD	62.79 \pm 13.8
Male n,%	156, 56.7%
Rural environment n,%	67, 60.7%
Smoker n,%	122, 44.4%
Alcohol consumption n,%	129, 46.9%
Gastric Ulcer n,%	38, 13.8%
Duodenal Ulcer n,%	28, 10.2%
Antral Gastritis n,%	149, 54.2%
Gastric Cancer n,%	16, 5.8%
Portal Hypertension n,%	10, 3.6%
Upper Gastrointestinal Bleeding (UGIB) n,%	70, 25.5%
Hipoanabolic Syndrome n,%	94, 34.2%
Hiatal Hernia n,%	123, 44.7%
Colon Cancer n,%	9, 3.3%
Obesity n,%	12, 4.4%
GERD n,%	17, 6.2%
Hepatic Steatosis n,%	39, 14.2%
Diverticulosis n,%	21, 7.6%
Hemorrhoids n,%	46, 16.7%
Cirrhosis n,%	20, 7.3%
Diabetes mellitus n,%	32, 11.6%
Anemia n,%	106, 38.5%
Gastric Polyps n,%	10, 3.6%
Colon Polyps n,%	36, 13.1%

H. pylori, the average age is 64.84 ± 12.0 years, and the male gender predominates in this case as well, with 73 cases, respectively 59.8%. Also, the environment of rural origin is predominant in this group (72 cases, 59.0%). Gastric lesions among patients with *H. pylori* infection is already a known fact, antral gastritis being observed in more than half of the cases (69 cases, 56.6%), while gastric ulcer (24 cases, 19.7%) and duodenal ulcer (16 cases, 13.1%) also comprise a significant number of patients. The development of neoplasia in the cases associated with *H. pylori* is present both on stomach in 10 cases (8.2%) and at the colonic level in 6 cases (4.9%).

The average age of *H. pylori* positive patients was 64.84 ± 12.0 years old, which was higher than the average age of the entire cohort (62.79 ± 13.8), unlike those with negative *H. pylori*, which was 61.14 years old. Regarding the male sex, there were in a higher proportion those with *H. pylori* than those who did not present the infection. (59.8% vs. 54.2%) From

the point of view of the environment of origin, the rural environment predominates in the case of patients with positive *H. pylori*. (59.0%). Regarding smoking, it is found in 42.5% of uninfected cases, compared to 46.7% in those tested positive for *H. pylori*. Also, alcohol consumption is also higher in the category of patients with the present infection, compared to those who do not have *H. pylori*. (50.8% vs. 43.8%) (Table 2).

Another interesting aspect is the gastric ulcer, it is important to mention that there was significant statistical differences between the 2 subgroups, the percentage being almost double in the case of those with *H. pylori* infection present (19.7% vs. 9.2%, $p=0.012$).

Also, for all other diseases located at the gastric level, patients with positive *H. pylori* show higher percentages, for example in antral gastritis (56.6% vs. 52.3%). At the same time, in duodenal ulcer the differences are maintained. (13.1 % vs. 7.8%)

If we take into account the neoplasms with which it is associated, patients with positive

H. pylori show a higher number of cases in both gastric cancer (10 vs. 6 cases) and colorectal cancer (6 vs. 3 cases), but the differences are not statistically significant ($p=0.132$, $p=0.191$). Also, the cases of colonic polyps are more numerous in *H. pylori* positive patients, while, on the other hand, the results regarding gastric polyps look different, the presence being higher in cases not infected with *H. pylori*, the difference being almost double (4.6 % vs. 2.5 %, respectively 7 vs. 3 cases).

Another important difference is represented by upper gastrointestinal bleeding, there were 70 patients who had this pathology and performed an EGD, an aspect in which the patients with positive *H. pylori* are more numerous both in percentage and numerically compared to those in whom the infection was not detected. (29.5% vs. 22.2%, 36 vs. 34 cases, $p=0.168$). Also, other associated pathology, anemia was present in 106 cases (38.5%), being present to a greater degree in patients positive for *H. pylori* (41.8% vs 35.9%).

Characteristics	HP negativ N= 153	HP pozitiv N= 122	p
Age (years) mean \pm SD	61.14 \pm 14.9	64.84 \pm 12.0	0.024
Male n,%	83, 54.2%	73, 59.8%	0.353
Rural environment n,%	95, 62.1%	72, 59.0%	0.604
Smoker n,%	65, 42.5%	57, 46.7%	0.482
Alcohol consumption n,%	67, 43.8%	62, 50.8%	0.246
Gastric Ulcer n,%	14, 9.2%	24, 19.7%	0.012
Duodenal Ulcer n,%	12, 7.8%	16, 13.1%	0.151
Antral Gastritis n,%	80, 52.3%	69, 56.6%	0.480
Gastric Cancer n,%	6, 3.9%	10, 8.2%	0.132
Portal Hypertension n,%	6, 3.9%	4, 3.3%	1.000
Upper Gastrointestinal Bleeding (UGIB) n,%	34, 22.2%	36, 29.5%	0.168
Hipoanabolic Syndrome n,%	50, 32.7%	44, 36.1%	0.556
Hiata Hernia n,%	76, 49.7%	47, 38.5%	0.065
Colon Cancer n,%	3, 2.0%	6, 4.9%	0.191
Obesity n,%	8, 5.2%	4, 3.3%	0.558
GERD n,%	9, 5.9%	8, 6.6%	0.817
Hepatic Steatosis n,%	26, 17.0%	13, 10.7%	0.134
Diverticulosis n,%	14, 9.2%	7, 5.7%	0.290
Hemorrhoids n,%	27, 17.6%	19, 15.6%	0.647
Cirrhosis n,%	13, 8.5%	7, 5.7%	0.381
Diabetes mellitus n,%	14, 9.2%	18, 14.8%	0.150
Anemia n,%	55, 35.9%	51, 41.8%	0.322
Gastric Polyps n,%	7, 4.6%	3, 2.5%	0.352
Colon Polyps n,%	18, 11.8%	18, 14.8%	0.869

Table 2. Patients distribution Hp+/Hp-

Despite the fact that obesity was found 2 times more often in cases without infection (8 vs. 4 cases, 5.2% vs 3.3%, $p=0.558$), the number of GERD cases was almost equal between patients with negative *H. pylori* and those with positive *H. pylori* (9 vs. 8 cases, 5.9% vs. 6.6%, $p=0.817$) (Table 2).

Discussion

The current study presents a group of patients hospitalized in an emergency hospital, totaling a number of 275 patients who underwent EGD and were tested for *H. pylori* infection. The frequency of *H. pylori* positive patients was 44.4 %, confirming a study from the literature, which was conducted on a cohort of 200 patients (35). However, another study conducted in Nepal shows a significantly lower prevalence, with an infection rate of 23.9% (36). An aspect taken into account was the environment from which these patients come, rural or urban, the result being that of the predominance of the rural environment in patients with positive *H. pylori*. These data confirm the specialty literature, where a review of several studies from China shows that 66% of *H. pylori* cases are found in rural areas (37). At the same time, another study carried out in South America highlights a higher rate in the population from the rural environment compared to the urban one (38).

The predominance of the male sex in our study, 56.7% of cases, is also found by another work conducted in Beijing, which highlighted that 51.8% of the patients tested positive for *H. pylori* were men, confirming the result from the study we are presenting. Another relevant characteristic from this study was represented by the higher percentage of smokers who have the infection, compared to those who do not have this habit, this difference being statistically significant (54.2% vs. 45.1%, $p=0.033$) (39), this result confirming what we found in the study (46.7% vs.42.5%).

Related to the occurrence of upper gastrointestinal bleeding (UGIB), another study carried out in Romania points out that infection with *H. pylori* is more often associated

with this pathology than those who are negative for *H. pylori*. The results of our study, 70 patients were diagnosed with UGIB, and 51.4% of them were *H. pylori* positive), similar results with a study, *H. pylori* positivity being 56.8% (40). At the same time, another paper highlights the fact that in NSAID users, the presence of *H. pylori* is an independent risk factor for the occurrence of UGIB (41).

The association of *H. pylori* bacteria with neoplasia is another aspect that has been studied in the literature and that was also emphasized in our study. A review of the literature shows that *H. pylori* was responsible for 36.3% of gastric cancers in a single year, with the predominant male sex being affected, being more frequent in the better developed regions (42). Also, a meta-analysis should be mentioned that showed a value of the prevalence of gastric cancer among patients infected with *H. pylori* in Europe, this being 16.26% ($p<0.001$), this result being higher than the 8.2% obtained in the framework of our study (43).

Conclusion

H. pylori infection still remains an extremely important public health problem, which can cause or associate important pathologies that must be treated at an early stage, especially since ulcerative lesions can lead to extremely serious complications. In the long term, the process of carcinogenesis must also be taken into account, especially if we refer to gastric cancer, characterized by high mortality, that is treated by a complex multidisciplinary team.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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