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ORIGINAL ARTICLE

PREVALENCE, TREATMENT OUTCOMES, AND FACTORS ASSOCIATED WITH *HELICOBACTER PYLORI* INFECTION IN PATIENTS WITH DYSPEPSIA

UČESTALOST, ISHODI LEČENJA I FAKTORI POVEZANI SA INFEKCIJOM *HELICOBACTER PYLORI* U PACIJENATA SA DISPEPSIJOM

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Abstract

Introduction: *Helicobacter pylori* infection is among the most prevalent infectious diseases and a proven risk factor for gastric cancer. Alongside dyspepsia, it represents a rising global medical burden. Unsuccessful eradication of *H. pylori* infection imposed an imperative to determine risk factors and potential predictors that can be related to its prevalence and treatment outcome.

Aim: The study aimed to assess the prevalence of *H. pylori* infection in dyspeptic patients, identify related factors, and evaluate the effectiveness of commonly prescribed treatment regimens.

Material and methods: A retrospective study was conducted, including 324 patients with dyspeptic symptoms who presented to the gastroenterology outpatient unit at the University Clinical Center of Serbia. Diagnosis of *H. pylori* was made following upper endoscopy and histology. Socio-epidemiologic, clinical and laboratory data were analyzed.

Results: The overall prevalence of *H. pylori* infection in patients with dyspepsia was 19.7%. Hematological comorbidities were more common in *H. pylori*-positive patients than in the overall sample (15.6% vs 8.1%, $p = 0.012$). A significant negative correlation was found between *H. pylori* infection and TIBC levels ($p < 0.001$). Duodenitis (37.5% vs. 26%, $p < 0.01$), superficial chronic gastritis (71.9% vs. 25%, $p < 0.01$), and nonspecific inflammation (73.4% vs 58.9%, $p = 0.01$) were significant predictors of *H. pylori* infection. Overall *H. pylori* eradication rate was 88.4%. Most commonly prescribed regimen was quadruple clarithromycin / amoxicillin / metronidazole therapy (45%), while pantoprazole was the most prescribed proton pump inhibitor (PPIs).

Conclusion: A The prevalence of *H. pylori* infection was relatively low. Positive *H.pylori* status was more frequently observed in patients with hematological comorbidities, lower TIBC levels, duodenitis, chronic superficial gastritis, and nonspecific gastric mucosal inflammation. The overall eradication rate was satisfactory, with quadruple therapy being the most commonly prescribed regimen.

Keywords:
Helicobacter pylori,
dyspepsia,
infection treatment

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Sažetak

Uvod: *Helicobacter pylori* infekcija jedna je od najćešćih zaraznih bolesti i jedan od dokazanih faktora rizika za nastanak karcinoma želuca. Uz dispepsiju predstavlja jedan on rastućih globalnih zdravstvenih izazova. Nezadovoljavajući rezultati u eradikaciji *H. pylori* infekcije su glavni motiv za otkrivanje faktora rizika i potencijalnih uzroka koji mogu biti povezani sa prevalencijom infekcije i uspehom lečenja.

Cilj: Cilj ove studije je bio da se proceni učestalost *H. pylori* infekcije, ispitaju povezani faktori i efikasnost najčešće propisivanih terapijskih režima kod pacijenata sa dispepsijom.

Materijal i metode: Sproveli smo retrospektivnu studiju koja uključuje 324 bolesnika sa dispeptičnim tegobama koji su pregledani u gastroenterološkoj ambulanti Univerzitetskog kliničkog Centra Srbije. Dijagnoza *H. pylori* infekcije potvrđena je pomoću gornje endoskopije i histoloških metoda. Analizirani su socioepidemiološki, klinički i laboratorijski parametri.

Rezultati: Ukupna prevalencija *H. pylori* infekcije kod bolesnika sa dispeptičnim tegobama bila je 19,7%. Hematološki komorbiditeti bili su značajno češći kod *H. pylori* pozitivnih pacijenata u poređenju sa ukupnim uzorkom (15,6% naspram 8,1%, p = 0,012). Uočena je značajna negativna korelacija između *H. pylori* infekcije i vrednosti ukupnog kapaciteta vezivanja gvožđa (TIBC) (p < 0,001). Duodenitis (37,5% naspram 26%, p < 0,01), superficijalni hronični gastritis (71,9% naspram 25%, p < 0,01) i nespecifična inflamacija (73,4% naspram 58,9%, p = 0,01) bili su značajni prediktori *H. pylori* infekcije. Uspešnost eradikacije *H. pylori* infekcije iznosila je 88%. Najčešće propisivana je bila četvorostruka klaritromicin/amoksicilin/metronidazol antibiotska terapija (45%), dok je pantoprazol bio najčešće propisivan inhibitor protonske pumpe (80%).

Zaključak: Prevalencija *H. pylori* infekcije bila je relativno niska. Pozitivan *H. pylori* status je češće zabeležen kod pacijenata sa hematološkim komorbiditetima, nižim vrednostima TIBC, duodenitisom, hroničnim superficijalnim gastritisom i nespecifičnom inflamacijom želudačne sluznice. Uspešnost eradikacije bila je zadovoljavajuća sa četvorostrukom terapijom, koja je ujedno bila i najčešće propisivana.

Ključne reči:
Helicobacter pylori,
dispepsija,
terapija infekcije

Introduction

Helicobacter pylori is a spiral-shaped, microaerophilic, Gram-negative bacterium that has evolved to thrive in the acidic conditions of the stomach (1). Inflammation occurs in the gastric mucosa after colonization. Consequently, tissue damage occurs, and histological signs of active gastritis are evident (2). The *H. pylori* infection can lead to gastritis, peptic ulcer disease, MALT lymphoma, metaplasia, gastric atrophy, dysplasia, and gastric cancer. In *H. pylori*-positive patients, duodenal ulcer is present in 95% of cases, and gastric ulcer in 70%. In addition, *H. pylori* infection is frequently the root cause of dyspepsia, and studies have shown that eliminating the infection leads to symptom improvement in affected patients (3, 4). Of all patients with dyspepsia, in 20 - 25% of cases, the symptoms are the result of an organic cause that has been diagnosed, such as peptic ulcer disease, *H. pylori*-associated gastritis, gastroesophageal reflux disease (GERD), malignancy, gastroparesis, or pancreatitis (5). In the remaining 75 - 80% of patients, the cause is attributed to functional dyspepsia, which is characterized by the presence of dyspeptic symptoms lasting for at least 3 months, with symptoms beginning no more than 6 months ago (6). In 2015, the Kyoto Global Consensus defined *H. pylori*-related dyspepsia as the absence of symptoms for 6 - 12 months following the eradication of the infection, considering that 6 months is the period required for symptoms to reappear if eradication therapy was not carried out (7). It is estimated that nearly 50% of the global population is infected with *Helicobacter pylori*. In developing countries, the infection occurs more often at an earlier age (8). Recent epidemiological data from Serbia indicate a prevalence rate of 43% for *Helicobacter pylori* infection (9). A variety of tests, both non-invasive and invasive, are available for diagnosing *Helicobacter pylori* infection. Non-invasive tests are the urease breath test and the fecal antigen test. The sensitivity and specificity of the urease breath test are 88 - 95% (10, 11). In addition to diagnosing *H. pylori* infection, it is also used to assess eradication. Due to the presence of *H. pylori* in feces, enzyme immunoassay tests were made and are most often used for diagnosing infection. The stool test's sensitivity and specificity are 94%. These tests require preparation, which includes stopping antibiotic therapy, proton pump inhibitors (PPIs), and medications containing bismuth salts 14 - 28 days prior to testing (12-14). Apart from diagnostic purposes, it is also used to confirm the success of eradication (15). Esophagogastroduodenoscopy (EGDS) and tissue histological analysis are invasive tests. The test sample is taken from the biopsied tissue of the gastric antrum and corpus. After the biopsy, the tissue is subject to histological verification according to the Sydney classification (16). Histological examination is regarded as the gold standard for confirming *H. pylori* infection (13).

Material and methods

Study methodology, time period, and geographical area

A cross-sectional study was carried out that included patients in the period from August 2022 to August 2023. The study was conducted at the University Clinical Center of Serbia, Clinic for Gastroenterology and Hepatology, Upper Endoscopy unit.

Study participants

This study included patients who underwent EGDS with a biopsy from the region of the antrum and corpus according to the Houston modification of the Sydney protocol (16) to determine *H. pylori* infection; and whose referral diagnoses were: dyspepsia, gastric ulcer, duodenal ulcer, chronic gastritis, gastro-duodenitis, duodenitis, hiatal hernia, GERD, *H. pylori* infection and abdominal pain. All participants were ≥18 years old, had dyspeptic symptoms (e.g., epigastric discomfort, cramping, nausea, postprandial fullness, bloating, early satiety, belching), and provided informed consent. Patients with age <18, acute GI bleeding, malignancies, or without consent were excluded.

Data collection and diagnostic methods

Data on sex, age, lifestyle habits (smoking, alcohol use), comorbidities, dyspeptic symptoms, previous *H. pylori* infection, use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin (acetylsalicylic acid, ASA), oral anticoagulant therapy (OACs or DOACs), laboratory parameters, probiotic and PPI use, and the type of prescribed therapy regimen were obtained through retrospective review of medical records. Endoscopic findings were classified as GERD, gastritis, erosive gastritis, hiatal hernia, gastric ulcer, duodenal ulcer, and duodenitis. The endoscopic procedure was performed by a skilled and experienced specialist. An endoscopic tube was inserted after local anesthetic administration, and the biopsy was conducted by collecting samples from the antrum and corpus. Histopathology after upper endoscopy was used for diagnosing *H. pylori* infection. After the diagnosis of gastritis, the grading of gastritis in accordance with the Sydney classification included the assessment of the degree of colonization, inflammation, activity, and degree of mucosal atrophy (16).

Data analysis and interpretation

All processed variables in this research are presented in the form of absolute or relative numbers. Numerical data are expressed as the mean ± standard deviation. The normality of the data distribution was assessed using the Shapiro-Wilk test. For further analysis of the variables, descriptive statistical methods were used, as well as the Chi-squared test, Fisher's exact test, and Logistic regression. A p value <0.05 was taken as statistically significant. Statistical analysis of the data was performed using the licensed statistical package MedCalc ver. 20.218.

Ethical approval

Research was approved by the Ethical Committee of the University Clinical Centre of Serbia No 212//23.

Results

A total of 324 patients were included, of whom 64 (19.7%) tested positive for *H. pylori* and 260 (80.3%) tested negative. The mean age was 56.0 ± 16.3 years, with no statistically significant difference between *H. pylori* positive and negative patients (p = 0.076). No significant difference in infection prevalence was observed between sexes (p = 0.650). The prevalence of *H. pylori* infection was further examined in relation to lifestyle habits, medication use, and history of prior infection, and showed no significant differences based on prior infection status or the use of NSAIDs, ASA, OACs, or DOACs. The results are presented in **table 1**.

The status of *H. pylori*, along with the distribution of comorbidities and biochemical parameters, is presented in **table 2**. Hematological comorbidities were significantly more common among *H. pylori* positive patients (p = 0.012). A statistically significant negative correlation was found between *H. pylori* infection and TIBC values (p < 0.001).

The most common referral diagnoses were chronic gastritis (208 patients; 64.2%), hiatal hernia (167 patients; 51.5%), and gastroduodenitis (83 patients; 25.6%). Less frequent diagnoses included abdominal pain (71 patients; 21.9%), GERD (60 patients; 18.5%), stomach ulcer (22 patients; 6.8%), duodenal ulcer (13 patients; 4.0%), duodenitis (8 patients; 3.4%), dyspepsia (8 patients; 2.5%), and *H. pylori* infection (2 patients; 0.6%). There was no statistically significant difference in *H. pylori* infection rates across referral diagnoses (p = 0.12). Among *H. pylori*-positive patients, 12 (18.7%) had GERD, with no significant difference in GERD prevalence compared to *H. pylori* negative patients (p = 0.45). In addition, the degree of GERD did not differ significantly between the two groups (p = 0.98). **Table 3** presents the most common endoscopic findings. Duodenitis was more frequently observed in *H. pylori* positive patients than in the total sample (p < 0.01).

Table 4 shows the distribution of histological findings from gastric biopsies, categories of inflammation, and *H. pylori* status.

Data on the eradication therapy regimen and its outcome were obtained in 40 patients (62.5%). The remaining were lost to follow-up. Overall eradication rate was 88.4% (**figure 1**).

Out of 40, 18 patients (45%) received concomitant quadruple therapy without bismuth consisting of clarithromycin / amoxicillin / metronidazole plus PPI, with 15 patients being treatment naive, while 3 patients had at least one previous eradication attempt. Eradication results are shown in **figure 2**.

Types of PPIs and probiotics used are shown in **figures 3** and **4**, respectively.

Table 1. The difference in the prevalence of *H. pylori* infection in relation to lifestyle habits, medication use, and previous *H. pylori* infection

Variables	Total (N, %)	H. pylori infections		Chi squared test, Fisher's exact test p value
		Positive n = 64	Negative n = 260	
Smoking history				
Yes	45 (13.9)	11 (17.2)	34 (13.1)	0.411
No	279 (86.1)	53 (82.8)	226 (86.9)	
Alcohol history				
Yes	20 (6.3)	3 (4.7)	17 (6.5)	0.398
No	304 (93.7)	61 (95.3)	243 (93.5)	
NSAIDs				
Yes	50 (5.8)	5 (10)	45 (17.3)	0.086
No	274 (94.2)	53 (80.4)	215 (82.7)	
ASA				
Yes	56 (17.4)	11 (19.6)	45 (17.3)	1.00
No	268 (82.6)	53 (80.4)	215 (82.7)	
OACs/NOACs				
Yes	23 (7.1)	3 (13)	20 (7.7)	0.636
No	301 (92.9)	61 (87)	240 (92.3)	
Previous *H.pylori* infection				
Yes	50 (15.5	7 (10.9)	43 (16.5)	0.247
No	274 (84.5)	57 (89.1)	217 (83.5)	

N- number of patients, NSAID- non-steroid anti-inflammatory drugs, OACs/NOACs- direct/ novel oral anticoagulants.
Chi-squared test and Fisher's exact test were used; $p < 0.05$ was considered statistically significant

Table 2. H. pylori infection in relation to comorbidities and biochemical parameters

Comorbidities			
	Total (N, %)	*H.pylori* + (N, %)	Chi squared test, Fisher's exact test p value
None	115 (35.5)	22 (34.4)	0.721
Cardiovascular diseases	115 (35.5)	28 (43.7)	0.463
Endocrine diseases	100 (30.9)	21 (32.8)	0.718
Hematologic diseases	26 (8)	10 (15.6)	**0.012**
Respiratory diseases	18 (5.6)	3 (4.7)	1.00
Kidney and urotract diseases	14 (4.3)	2 (3.1)	1.00
Neurological diseases	10 (3.1)	1 (1.6)	0.695
CTD	8 (2.5)	1 (1.6)	1.00
GIT and liver diseases	4 (1.2)	0 (0)	0.924
Biochemical parameters			
Variables	Mean value	Logistic regression Odds ratio (OR); 95% Confidence interval (95% CI); p-value	
Hgb (g/l)	125.64 ± 31.00	OR = 1.00; 95% CI = 1.13-12.40; p = 0.821	
Hct	0.380 ± 0.088	OR = 1.10; 95% CI = 0.04-30.14; p = 0.957	
Serum iron	14.87 ± 8.99	OR = 0.976; 95% CI = 0.935-1.020; p = 0.280	
TIBC	53.85 ± 12.04	OR = 0.914; 95% CI = 0.875-0.953; **p < 0.001**	
Ferritin	176.04 ± 273.87	OR = 0.999; 95% CI = 0.997-1.000; p = 0.135	

Connected tissue diseases, GIT-Gastrointestinal tract, Hgb- Hemoglobin, Hct- Hematocrit, TIBC- Total iron binding capacity.
Chi-squared test, Fisher's exact test and Logistic regression were used; $p < 0.05$ was considered statistically significant

Table 3. Endoscopic results in relation to *H. pylori* infection

Endoscopic results	Total (N, %)	*H. pylori* + (N, %)	Chi squared test, Fisher's exact test p value
Gastritis	312 (96.3)	64 (100)	0.252
Hiatal hernia	241 (74.4)	50 (78.1)	0.441
Erosive gastritis	92 (28.4)	20 (31.2)	0.574
Duodenitis	85 (26.2)	24 (37.5)	**<0.010**
GERD	69 (21.3)	12 (18.7)	0.452
Gastric ulcer	21 (6.5)	4 (6.2)	0.935
Duodenal ulcer	16 (4.9)	5 (7.8)	0.237

GERD- Gastroesophageal reflux disease
Chi-squared test and Fisher's exact test were used; $p < 0.05$ was considered statistically significant

Table 4. Infection with *H. pylori* and histological parameters

Variables	Total (N, %)	*H.pylori* + (N, %)	Chi squared test, Fisher's exact test p value
Histological findings			
Atrophic gastritis	101 (31.2)	16 (25)	0.292
Superficial chronic gastritis	81 (25)	46 (71.9)	**<0.011**
Acute nonspecific inflammation	68 (21)	2 (3.1)	**<0.013**
Foveolar hyperplasia in the mucosa	56 (17.3)	0 (0)	**<0.010**
Normal gastric mucosa	18 (5.5)	0 (0)	**<0.014**
Histological assessment of the inflammation category			
Nonspecific inflammation	191 (58.9)	47 (73.4)	**0.010**
Atrophic gastric mucosa	101 (31.2)	17 (28.6)	0.456
Normal gastric mucosa	25 (7.7)	0 (0)	0.012
Reflux gastritis	7 (2.2)	0 (0)	0.353

Chi-squared test and Fisher's exact test were used; $p < 0.05$ was considered statistically significant

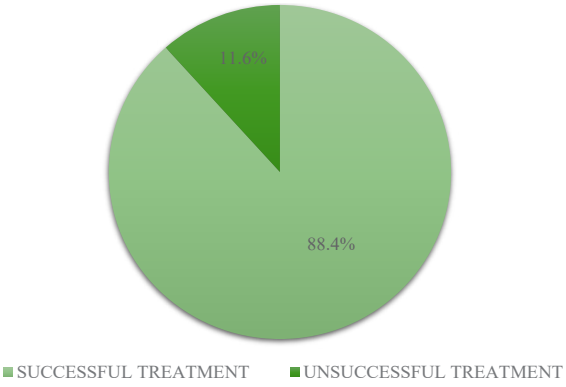

Figure 1. Success rate of eradication therapy

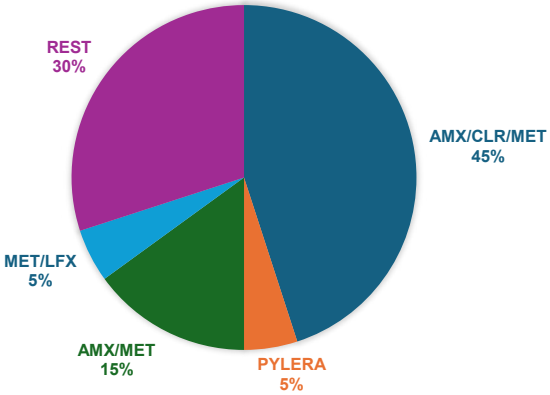

Figure 2. Eradication protocol of *H. pylori* infection.
AMX- Amoxicillin, MET- Metronidazole, CLR- Clarithromycin, LFX- Levofloxacin

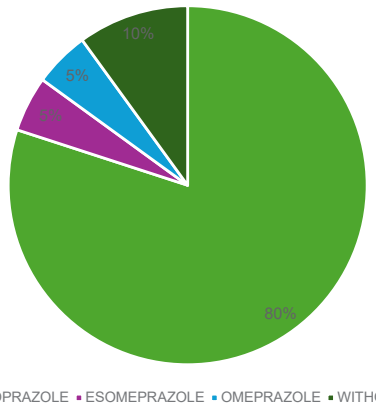

Figure 3. Proton pump inhibitor used in treatment of *H. pylori* infection

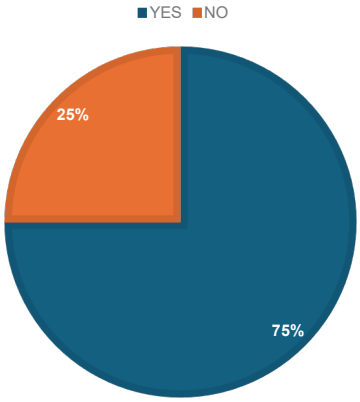

Figure 4. Rate of probiotics use in *H. pylori* treatment

Discussion

Based on the results of the study, the success rate of *H. pylori* eradication therapy was 88.4%, which is considered satisfactory and above the accepted threshold of 85% (17). The *H. pylori* infection continues to be a worldwide health issue. The prevalence of *H. pylori* infection among patients in our study was 19.7%. A prospective study from Serbia published in 2023 reported a prevalence of 43% (9). Higher prevalence rates have been reported in countries such as North India (85%) and Bangladesh (78%) (18, 19). Slightly higher rates have also been observed in developing countries, including Mongolia (80%), Cameroon (64.3%), Nigeria (64%), and Kenya (40.9%) (20–23). These differences in prevalence can be influenced by multiple factors, including socioeconomic status, living conditions, ethnicity, geographic location, variations in diagnostic methods, and prior antibiotic exposure (20, 24). The relatively lower rate in the study may be due to the sample size and the fact that prevalence was assessed only in patients undergoing EGDS, most of whom had no alarm symptoms. In this study, no statistically significant difference in *H. pylori* prevalence was found between sexes. In contrast, a large meta-analysis by Zamani et al. reported a higher prevalence in male patients (8). Among patients with *H. pylori* infection in our study, the most frequent endoscopic findings were gastritis (100%), hiatal hernia (78.1%), and duodenitis (37.5%). A study from Nepal reported different patterns, with duodenal ulcer (100%), gastritis (50.9%), and gastric ulcer (50%) being the most common (24). Similarly, a study from Saudi Arabia found duodenal ulcer (47.1%), gastric ulcer (45.2%), and gastritis (44%) to be the most frequent findings (25). Such differences may be related to ethnicity, geographic factors, and socioeconomic conditions (25). The findings did not reveal a statistically significant difference in *H. pylori* infection status in relation to smoking. Among infected patients, 17.8% were smokers, which is consistent with a Serbian study published in 2023 (9). Ogihara et al. found that non-smokers were 1.5 times more likely to be infected with *H. pylori* compared to smokers. They suggested that smoking may enhance gastric acid and pepsin production, potentially providing some protection against colonization (26). Conversely, another study reported higher infection rates among smokers (27). Alcohol consumption was less common among patients with *H. pylori* infection in the study. Some studies suggest that moderate alcohol intake may reduce infection prevalence and potentially support bacterial clearance (28, 29). Regarding medication use, no significant difference was observed between H. pylori-positive and negative patients in the use of NSAIDs and ASA, which is consistent with findings from the Serbian study (9). No notable variation in *H. pylori* status was found among patients using OACs or DOACs. A study by K. Issever et al. even reported a lower infection rate in patients using rivaroxaban compared to other oral anticoagulants (30). Various studies have explored potential links between *H. pylori* infection and conditions such as diabetes mellitus, anemia, hypertension, and other extraintestinal diseases (31–33). In this study, cardiovascular comorbidities were the most common, regardless of *H. pylori* status, followed by endocrine disorders. However, hematological comorbidities were more frequent among *H. pylori* positive patients (15.6%) compared to the overall sample (8%). Regarding biochemical data, there was a significant negative correlation between TIBC levels and *H. pylori* positive status. Similar results were reported in another study, which also found lower levels of hemoglobin, serum iron, and ferritin in *H. pylori* positive patients (9). In this research, the main referral diagnoses in patients who were referred to EGDS were chronic gastritis (64.2%), hiatal hernia (51.5%), and gastro-duodenitis (25.6%). The findings revealed that superficial chronic gastritis was the predominant histopathological diagnosis, with no observed differences in the prevalence of atrophic gastritis. Interestingly, a previous study conducted in Serbia reported a significantly higher prevalence of atrophic gastritis among *H. pylori* positive patients (9). According to the findings, a statistically significant difference was observed between the category of inflammation, the degree of inflammatory infiltrate, and the activity of inflammation, which is consistent with previous data (9). Regarding therapy regiments, concomitant quadruple therapy comprising a proton pump inhibitor (PPI), clarithromycin, amoxicillin, and metronidazole was administered to 45% of the patients. Most of them were treatment naive. The second most commonly prescribed regimen (15% of patients) was triple therapy of amoxicillin and metronidazole plus PPIs. Quadruple therapy containing bismuth in the form of a single capsule Pylera® was prescribed in only 5% of patients. The remaining 35% of patients were treated with different therapy regimens. The above data follow the national guidelines that suggest a transition from triple to quadruple therapy from 2016 and 2022 (34-36). According to the results of the study, the most common prescribed PPI was pantoprazole (80%), followed by esomeprazole (10%). Data suggest that the use of esomeprazole or rabeprazole increases the chance of successful therapy for *H. pylori* infection (37). Some clinical studies have indicated that incorporating probiotics into eradication therapy may enhance its effectiveness. However, most studies have focused on Asian populations, and more research is needed in North American and African-American populations to confirm these findings (38). Here, 75% of patients received probiotics alongside eradication therapy, and no significant difference in eradication success was observed between those who used probiotics and those who did not. However, the limitations of this study are reflected in the fact that in a certain number of patients who had *H. pylori* infection, the modality of eradication therapy was unknown, which rendered the sample rather small and possibly not sufficient to draw more relevant conclusions.

Conclusion

The prevalence of biopsy-proven *H. pylori* infection was relatively low among patients with non-alarming dyspeptic symptoms. Patients who were *H. pylori* positive more frequently presented with hematological comorbidities and lower TIBC levels. Endoscopy-proven duodenitis, superficial chronic gastritis, and increased gastric mucosal inflammation were also more commonly observed in this group. The majority of patients received a bismuth-free quadruple concomitant therapy consisting of amoxicillin, clarithromycin, and metronidazole. Pantoprazole was the most commonly prescribed PPI, and most patients used some form of probiotic during treatment.

Acknowledgment, conflict of interest

Nothing to disclose.

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