RESEARCH ARTICLE

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Histopathological Evaluation of *Helicobacter pylori* Infection in Children

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Objective: *Helicobacter pylori* infection, which is among the most common childhood infections, is frequently seen around the world, especially in developing countries. *H. pylori* can cause infection, gastritis, ulcers and gastric cancer in infected individuals. Morbidity and mortality can be prevented with early diagnosis and treatment. This study aimed to histopathologically evaluate the frequency of *H. pylori* in the pediatric age group (3-18 years old) in Malatya province and examine the accompanying pathologies.

Materials and Methods: In the study, the tissues of 187 pediatric patients who applied to Malatya Training and Research Hospital Pediatric Gastroenterology clinic between January 2017 and December 2022 and underwent upper gastrointestinal system endoscopy for any reason between the ages of 3-18 were retrospectively examined. The presence and severity of *H. pylori*, chronic inflammation, activity, atrophy, intestinal metaplasia and lymphoid follicles were evaluated histopathologically in the cases. Bacterial density was evaluated and reported as absent (-), low (+), medium (++) and high (+++) according to the Sydney classification.

Results: A total of 187 biopsy samples, 103 from girls and 84 from boys, were included in the study. Among 187 patients, the number of *H. pylori* positive patients was 95 (50.8%), 48 of which were girls and 47 were boys. The frequency of *H. pylori* in the 3-10, 11-15, 16-18 age ranges was determined as 55.0%, 46.9%, 48.0%, respectively. A statistically significant relationship was found between the presence of *H. pylori* and activity, inflammation and lymphoid follicle ($p<0.01$).

Conclusion: *H. pylori* infection continues to be an important health problem in children, especially in developing countries.

Key Words: *H. pylori*, childhood, histopathology, intestinal metaplasia, lymphoid follicle

Çocuklarda Histopatolojik Olarak *Helicobacter pylori* Enfeksiyonunun Değerlendirilmesi

Amaç: En yaygın çocukluk çağı enfeksiyonları arasında yer alan *Helicobacter pylori* enfeksiyonu, dünya genelinde özellikle gelişmekte olan ülkelerde sıklıkla görülmektedir. *H. pylori* enfekte bireylerde enfeksiyon, gastrit, ülser ve gastrik kansere neden olabilmektedir. Erken tanı ve tedavi ile morbidite ve mortalite önlenebilir. Bu çalışmada Malatya ilinde pediatrik yaş grubunda (3-18 yaş) *H. pylori* sıklığının histopatolojik olarak değerlendirilmesi ve eşlik eden patolojilerin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada, Ocak 2017-Aralık 2022 tarihleri arasında Malatya Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Kliniği'ne başvurmuş, 3-18 yaş aralığında herhangi bir nedenle üst gastrointestinal sistem endoskopisi yapılmış 187 çocuk hastaya ait dokular retrospektif olarak incelendi. Olgularda *H. pylori* varlığı ve şiddeti, kronik inflamasyon, aktivite, atrofi, intestinal metaplazi ve lenfoid folikül varlığı histopatolojik olarak değerlendirildi. Bakteri yoğunluğu Sydney sınıflamasına göre yok (-), hafif (+), orta (++) ve yüksek (+++) olacak şekilde değerlendirilerek raporlandı.

Bulgular: 103'ü kız, 84'ü erkek çocuğa ait olmak üzere toplam 187 biyopsi örneği çalışmaya dahil edilmiştir. 187 hasta içinde *H. pylori* pozitif hasta sayısı 95 (%50.8) olup bunlardan 48'i kız, 47'si erkek çocuk hastalara aitti. 3-10, 11-15, 16-18 yaş aralıklarında *H. pylori* sıklığı ise sırasıyla %55.0, %46.9, %48.0 olarak belirlenmiştir. *H. pylori* varlığı ile aktivite, inflamasyon ve lenfoid folikül arasında istatistiksel olarak anlamlı ilişki saptanmıştır ($p<0.01$).

Sonuç: *H. pylori* enfeksiyonu çocuklar açısından özellikle gelişmekte olan ülkelerde önemli bir sağlık problemi olmaya devam etmektedir.

Anahtar Kelimeler*: H. pylori*, çocukluk çağı, histopatoloji, intestinal metaplazi, lenfoid folikül

Introduction

Helicobacter pylori infection is one of the most common chronic bacterial infections in humans. Reports of infection prevalence rates vary widely between geographical regions, with levels reaching high levels in developing countries. High *H. pylori* prevalence generally depends on multiple factors, including age, ethnicity, geographic and socioeconomic status, bacterial virulence, host characteristics, and environmental factors (especially hygienic conditions). After colonization of the gastric mucosa, *H. pylori* can cause chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (1, 2).

The Gram-negative rod, first isolated by Marshall and Warren in 1982, is classified as a class 1 carcinogen by the International Agency for Research on Cancer. *H. pylori* infection is an important cause of diseases such as peptic ulcer, anemia, thrombocytopenic purpura, developmental delay and gastric malignancies. Infection is most often acquired during infancy or childhood. Intrafamilial transmission is the main route, with potential routes of transmission including oral-oral, fecal-oral and gastro-oral routes (3-5).

Diagnostic methods for *H. pylori* infection, in which at least 50% of people are infected, are categorized as invasive and non-invasive tests. Non-invasive diagnostic tests are urea breath test, stool antigen examination, serological and molecular tests. Invasive tests include endoscopy, biopsy, rapid urease test, culture and molecular tests. Endoscopy to evaluate *H. pylori* associated lesions is also used for advanced testing such as rapid urease tests, histopathological examinations, culture, and molecular methods. The use of endoscopy is a prerequisite for all invasive methods, and it poses difficulties in children because it is a laborious procedure and requires patient cooperation. For this reason, non-invasive tests are widely used in children, although invasive tests may be preferred to confirm the diagnosis when necessary. Biopsy is preferably performed from the gastric antrum. Histological examination is the gold standard for diagnosing *H. pylori* infection. Collected biopsy tissues are stained with Hematoxylin Eosin (H&E) to determine the presence and severity of inflammation of the gastric mucosa, atrophy, and intestinal metaplasia based on the updated Sydney classification of histopathology of gastritis. Most *H. pylori* are found in high density in the antrum. Special stains such as Warthin-Starry silver stain, Giemsa stain, Genta stain and immunohistochemistry also help in the diagnosis of *H. pylori* infection (6-8).

Since infection occurs in childhood in regions where prevalence is high, there is a need to investigate especially pediatric patients. Eradication of *H. pylori* can effectively prevent infection-related diseases. In our country, there are insufficient studies on the histopathological prevalence of *H. pylori* in the pediatric age group. In this study, it was aimed to histopathologically evaluate the frequency of *H. pylori* in gastric endoscopic biopsies obtained and examined retrospectively from the Malatya Training and Research Hospital Pathology Laboratory archive in the childhood age group and to compare it with the criteria of the Sydney classification.

Materials and Methods

Research and Publication Ethics: This study was conducted in accordance with the Principles of the Declaration of Helsinki. Ethical approval of the study was obtained from Malatya Turgut Ozal University Non-Interventional Clinical Research Ethics Committee (Date: 15/11/2022, Protocol code: 2022/187).

Study Population: In the study of Deveci and Acar (9) in which they examined children aged 0-18 who underwent upper gastrointestinal system (GIS) endoscopy for any reason in Şanlıurfa province, the frequency of *H. pylori* was found to be 67.1%. In the study, the frequency was found to be 67.1%, the two-tailed test, type 1 error level was 0.05, and the sample size to be reached was 161, taking the power as 80% (10). A total of 187 files were retrospectively included in the study through archive scanning.

Gastric antrum and corpus biopsy samples of 187 cases, taken from patients aged between 3 and 18 years who applied to the Malatya Training and Research Hospital Pediatric Gastroenterology clinic with dyspeptic complaints between January 2017 and December 2022, were retrospectively examined. Cases for which sufficient clinical and pathological data could not be obtained were not included in the study.

Demographic and Clinical Data: Parameters of the cases, such as age and gender, were obtained from the hospital computer record system. The cases were divided into 3 groups: 3-10 years old, 11-15 years old and 16-18 years old.

H&E stained sections were removed from the archive and biopsy samples of each case were re-examined. PAS-AB and modified Giemsa stain were used histochemically for *H. pylori* evaluation. The presence of *H. pylori,* its severity, atrophy, activity, chronic inflammation, lymphoid follicles and intestinal metaplasia were examined histopathologically in the cases. Bacterial density was evaluated and reported according to the Sydney classification as none (-), mild (+), medium (++) and high (+++). In the study, biopsy preparations of the patients were stained with H&E and modified Giemsa dyes and examined under a light microscope (Nikon Eclipse Ci-L) by an experienced pathologist and histologist.

Statistical Analysis: IBM SPSS Statistics Version 25.0 (IBM, Armonk, NY, USA) program was used to analyze the data. In the analysis of descriptive data, frequency distributions were expressed as percentages. Chi-Square and Fisher Exact tests were used to analyze categorical data. A value of $p<0.05$ was considered statistically significant.

Results

A total of 187 patient biopsies, 84 boys and 103 girls, who met the criteria were included in this study. Among 187 patients, the number of *H. pylori* positive patients was found to be 95 (50.8%). The age distribution of the patients was between 3-18 years in *H. pylori* positive patients and 4-18 years in *H. pylori* negative patients. There was no significant difference between *H. pylori* positive and negative patients in terms of age and gender. Distributions by gender and age are given in Table 1.

Table 1. Distribution of *H. pylori* positive and negative patients according to gender and age range

		H. pylori		**p**
		Positive	**Negative**	
Sex [n (%)] **	Male	47 (44.0)	37 (56.0)	0.203*
	Female	48 (46.6)	55 (53.4)	
Age [n (%)]**	3-10	22 (55.0)	18 (45.0)	0.705*
	11-15	23 (46.9)	26 (53.1)	
	16 and over	47 (48.0)	51 (52.0)	

*Ki-Kare Test, **Row

The degree of *H. pylori* in *H. pylori* positive patients was compared in terms of gender and no significant difference was found between them. When age ranges were categorized as 3-10, 11-15 and 16-18, mild (+) patients aged 16 and over were significantly lower than the other two groups. Moderate (++) severity was significantly higher in patients aged 16 and over compared to the 11-15 age group. In terms of its severity, *H. pylori* was at a mild (+) level in patients aged 3-10 and 11-15, and it showed a distribution in three levels in patients aged 16 and over (Table 2). Microscopic appearances of cases in which *H. pylori* was detected at different severities in gastric corpus biopsy samples are shown in Figures 1-4. Two different stains were used for biopsy samples: Hematoxylin Eosin (Figure 1) and Modified Giemsa (Figure 2-4).

Table 2. Distribution of *H. pylori* severity by gender and age range

		***H. pylori* severity**			**p**
		(+)	**(++)**	**(+++)**	
Sex [n (%)] **	Male	39 (83.0)	4 (8.5)	4 (8.5)	.694*
	Female	42 (87.5)	4 (8.3)	2 (4.2)	
Age [n (%)] **	3-10	18 (100.0)	0 (0)	0 (0)	.032*
	11-15	25 (96.1)	0 (0)	1 (3.9)	
	16 and over	38 (74.5)	8 (15.7)	5 (9.8)	

Ki-Kare Test, **Row

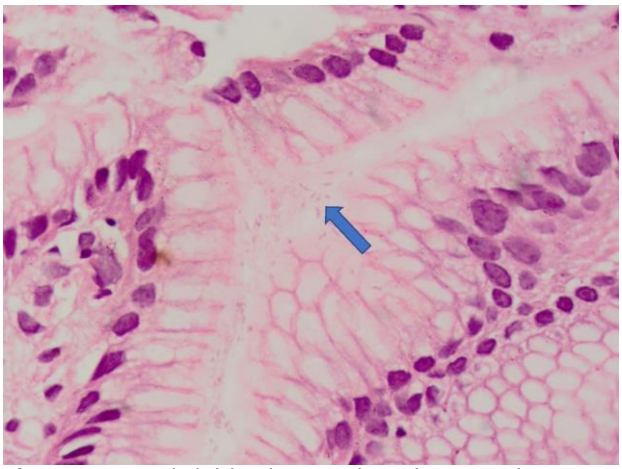

Figure 1. *H. pylori* (+) microorganisms in a gastric corpus biopsy sample (blue arrow) (Hematoxylin Eosin 100x)

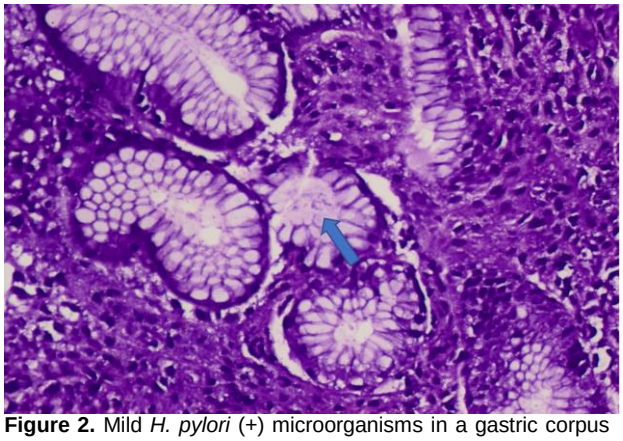

Figure 2. Mild *H. pylori* (+) microorganisms in a gastric corpus biopsy sample (blue arrow) (Modified Giemsa 100x)

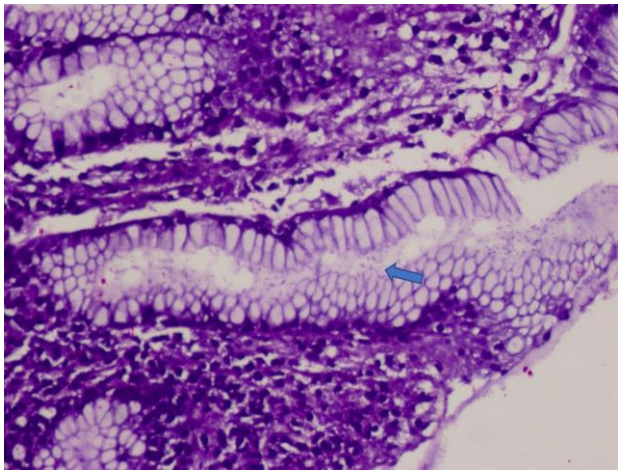

Figure 3. Moderate *H. pylori* (++) microorganisms in a gastric corpus biopsy sample (blue arrow) (Modified Giemsa 40x)

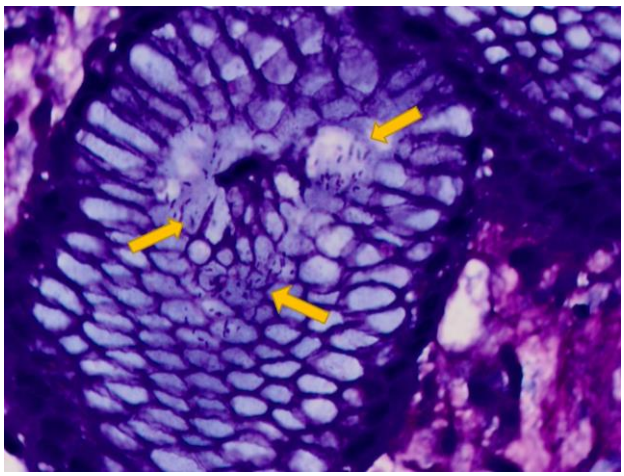

Figure 4. Severe *H. pylori* (+++) microorganisms in a gastric corpus biopsy sample (yellow arrow) (Modified Giemsa 40x)

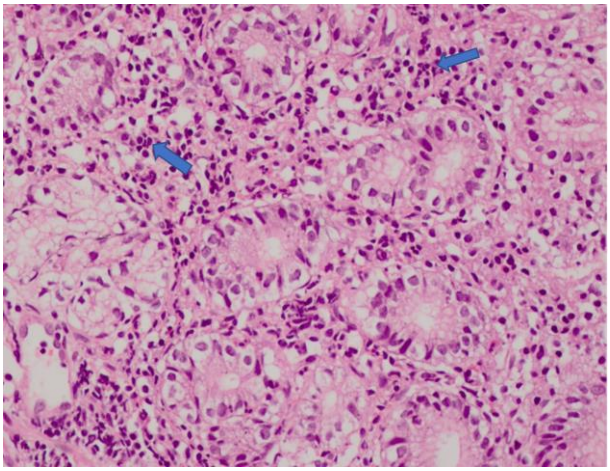

Figure 5. Inflammatory cells in a gastric antrum biopsy sample (blue arrow) (Hematoxylin Eosin 40x)

Data were evaluated in Table 3 in terms of *H. pylori* severity and activity and inflammation levels. The relationship between *H. pylori* severity and activity and inflammation levels was statistically significant (p<.001). As *H. pylori* severity increased, activity and inflammation levels increased significantly (p<.001). Figure 5 shows the microscopic image of inflammatory cells consisting of neutrophils and lymphocytes in the gastric antrum biopsy sample.

Activity, inflammation, atrophy, metaplasia, and the presence of lymphoid follicles in the patients were compared with gender, age, and the presence of *H. pylori*. In the non-inflammation group, the number of girls was significantly higher than that of boys. In the *H. pylori* positive group, activity, inflammation and the presence of lymphoid follicles were found to be significantly higher (p<.001). There was no significant difference between the groups in terms of other characteristics (p>0.001) (Table 4).

Table 3. Distribution of *H. pylori* severity by activity and inflammation degree

		***H. pylori* severity**		**p***
		(+)	(++) ve üstü	
Activity degree [n (%)]**	1+	77 (97.5)	4 (25.0)	<.001
	2+	2 (2.5)	12 (75.0)	
Inflammation degree [n (%)]**	1+	67 (82.7)	0 (0,0)	<.001
	2+ and over	14 (17.3)	14 (100.0)	

*Ki-Kare ya da Fisher's Exact Test, **Row

Table 4. Comparison of histopathological findings observed in the gastric mucosa with the presence of *H. pylori*

		Sex (%)[a]			**Age**		***H. pylori* (%)[a]**		
		Male	**Female**	**p***	**Median (IQR)**	**p****	**Yes**	**No**	**p***
Activity	Yes	68 (81.0)	72 (69.9)	0.118	16 (5)	.168	95 (100.0)	45 (51.1)	<0.001
	No	16 (19.0)	31 (30.1)		17 (5)		0 (0.0)	47 (48.9)	
Inflammation	Yes	84 (100.0)	93 (90.3)	0.002	16 (6)	.170	95 (100.0)	82 (89.1)	0.001
	No	0 (0.0)	10 (9.7)		14 (10)		0 (0.0)	10 (10.9)	
Atrophy	Yes	0 (0.0)	2 (1.9)	0.503	12 (0)	.254	2 (2.1)	0 (0.0)	0.497
	No	84 (100.0)	101 (98.1)		16 (6)		93 (97.9)	92 (100.0)	
Metaplasia	Yes	6 (7.1)	2 (1.9)	0.143	13 (8)	.544	6 (6.3)	2 (2.2)	0.279
	No	78 (92.9)	93 (90.3)		16 (5)		89 (93.7)	90 (97.8)	
Lymphoid Follicle	Yes	4 (4.8)	4 (3.9)	>0.999	13.5 (8)	.422	8 (8.4)	0 (0.0)	0.007
	No	80 (95.2)	99 (96.1)		16 (5)		87 (91.6)	92 (100.0)	

*Chi-Square or Fisher Exact Test, **Mann-Whitney U Test, [a] column

Discussion

While the prevalence of *H. pylori* colonizing the human stomach varies between 1.8-65% in developed countries, it is generally higher in developing countries and reaches up to 90% in some countries. The pathophysiology of *H. pylori* infection depends on complex bacterial virulence mechanisms and their interaction with the host immune system and environmental factors. Unlike adults, the rate of serious disease associated with *H. pylori* is low in children and gastric malignancies are almost absent, the infection is usually asymptomatic. Both invasive and non-invasive methods can be used in diagnosis in pediatrics. To detect *H. pylori* infection in children, especially in the first decade of life, initial diagnosis is made including endoscopy and histological evaluation. Identification of histological samples is accomplished by the widely used updated Sydney classification (11-13).

A meta-analysis covering 60 countries showed that the overall prevalence of *H. pylori* infection in children worldwide was 32.3%, and this rate varied according to the diagnostic tests applied. In particular, the prevalence of *H. pylori* infection in children in low- and middle-income countries (43.2%) is almost twice that in high-income countries (21.7%). Studies have shown a significant decrease in the prevalence of *H. pylori* infection in children in recent years, especially in western industrialized countries. However, prevalence has remained stable at a high level in developing and newly industrialized countries. The infection rate in China decreased from 58.3% to 40.0% in the last decade, and in Taiwan from 63.8% to 28.2% (12). In a study conducted in Jordan in 2020 with 98 children with an average age of 11.7±4.7 years who underwent endoscopy, *H. pylori* was detected in the stomach biopsy of 53 (54%) patients (11). In a study conducted in Morocco with 213 patients aged 1-17 years who underwent upper GI endoscopy in a two-year period between January 2019 and January 2021, they determined that 95 (45%) children were infected with *H. pylori* (14). In Romania, the presence of *H. pylori* was detected in 82 (33.06%) of 248 pediatric patients aged 0-18 who underwent upper gastrointestinal endoscopy (4).

In the study conducted by Yıldırım (15) in Antalya, 195 (47.8%) of the cases were boys and 213 (52.2%) were girls, and *H. pylori* was observed at various severities in 158 cases (38.7%). In the distribution of cases by age, it was determined that the frequency of *H. pylori* increased with age in the 0-6 year old, 7-12 year old, 13-18 year old groups (20.7%, 28.9% and 47% respectively). In their study, they found a significant relationship between the presence of *H. pylori* and chronic inflammation and activity. Similarly, in our study, as *H. pylori* severity increases, activity and inflammation severity increase significantly.

Deveci and Acar (9) in their study conducted in Şanlıurfa by evaluating the endoscopy and pathology reports of 428 patients aged 1-18 years, reported the presence of *H. pylori* in 67.1% of the cases, with the average age of the patients being 9.8±4.6. According to the study, it was observed that the frequency of *H. pylori* increased with age. In our study, the presence of *H. pylori* at various severities was detected in 50.8% of our patients. In this study, no difference was found between genders in terms of *H. pylori* positivity, consistent with studies conducted in the world and in our country.

Kara et al. (16), in their study between 2004 and 2008 in Istanbul with 358 pediatric patients with an average age of 10.8±3.26, detected *H. pylori* in 214 patients (59.8%). Özbey et al. (17), in their study conducted with 101 child patients aged between 4 and 18 in Elazığ between March 2011 and September 2012, found that the prevalence of *H. pylori* infection was high (75.8%) in children between the ages of 13 and 18, and in children between the ages of 4 and 6. (40%) showed that the prevalence was lower. In this study, the prevalence of *H. pylori* was found to be higher in the 11-15 age groups (53.1%) compared to other age groups.

In their study, which included 1612 patients whose stomach biopsies were taken after upper GI endoscopy was performed in Konya between 2010 and 2018, Bayramoğlu and colleagues (18) recorded the frequency of mononuclear cell infiltration as 79.9%, the frequency of neutrophil infiltration as 50.2%, and the frequency of *H. pylori* as 25%. They observed that the presence and severity of *H. pylori* increased with age. In our study, no statistically significant relationship was found between the presence and severity of *H. pylori* and age.

Erdoğan Durmuş et al. (19), in their study conducted in the province of Erzurum between July 2014 and May 2015 with 59 cases between the ages of 1-18, found that 35.6% of the cases were boys, 64.4% were girls, the average age was 11.84±4.88, and 61.01% of the patients had various severities. *H. pylori* has been detected. They determined the frequency of *H. pylori* in the 1-5 year old, 6-10 year old, 11-18 year old groups as 57.14%, 56.25%, 63.88%, respectively. In our study, the frequency of *H. pylori* in the 3-10, 11-15, 16-18 age ranges was determined as 55.0%, 46.9%, 48.0%, respectively. Among 187 patients, the number of *H. pylori* positive patients was found to be 95 (50.8%).

There are some limitations in our research. The limitation of the study is that it is single-centered and there are no clinical findings from the pediatric patients included in the study.

The gold standard in the diagnosis of *H. pylori* continues to be upper GI endoscopy and histopathological examination. Histopathological evaluation of the biopsy taken by endoscopy is very important as it provides information about other accompanying pathologies and shows the presence and severity of *H. pylori*. When the data obtained in this study were compared with previous studies, we determined that the presence of *H. pylori* was generally lower in our study. Despite a recent decline in the overall prevalence of infection, morbidity and mortality rates due to gastric cancer remain high (20). The results we recorded in our study are an indication that the prevalence of *H. pylori* is on a downward trend in our country, as well as all over the world. It is known that the

presence and severity of *H. pylori* is directly related to factors such as socioeconomic level and hygiene habits. Although the results are promising, the rates are still quite high compared to studies conducted in Western countries and the western part of our country.

In conclusion, early diagnosis of *H. pylori*, which causes many problems in the GI tract and can lead to serious diseases such as stomach cancer, is very important. Indications for endoscopy in children are limited. Although invasive diagnostic methods are more risky, they are more reliable than noninvasive methods. There are few studies conducted with children on this subject in our country. More comprehensive, multicenter studies are needed to fill the gap in this area.

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