Diseases of the Esophagus (2016) **29**, 1007–1012
DOI: 10.1111/dote.12429

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original article

Helicobacter pylori infection and gastroesophageal reflux in children

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SUMMARY. **Some studies suggest that *Helicobacter pylori* (*H. pylori*) infection would be a protective factor for the gastroesophageal reflux. The aim of this study was to explore this fact. A group of 72 children, admitted in a pediatric gastroenterology regional center in Northeast Romania, diagnosed with gastroesophageal reflux by 24-hour continuous esophageal pH monitoring (results were interpreted using the Boix-Ochoa score), underwent upper endoscopy with gastric biopsy to detect the presence of *H. pylori* by the rapid urease testing and for bacteriological and histologic examination. 19 children (26.39%) had *H. pylori* infection, while 53 (73.61%) did not. The grade of esophagitis was classified according to the Los Angeles classification system. Out of 47 children with esophagitis A, 16 (34.04%) had *H. pylori* infection, while out of the 25 children with esophagitis B, only 3 (12%) had *H. pylori* infection, with statistic significance ($\chi^2 = 54.69$, $P << 0.05$, 95% confidence interval [CI]). Regarding the value of the Boix-Ochoa score, it appears that the presence of the *H. pylori* determines lower pH-metry scores ($F = 8.13$, $P = 0.0015$, 95% CI). The presence of the *H. pylori* was not an important factor in the gastroesophageal reflux. On the other hand its relationship with esophagitis appears to be inverse ratio. The fact that the *H. pylori* presence is statistically greater in the grade A esophagitis could confirm the hypothesis that the bacteria would slow down the development of the esophagitis.**

KEY WORDS: **24-hour pH-metry, children, gastroesophageal reflux, *Helicobacter pylori*.**

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection plays a major role in the pathogenesis of many gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, gastric mucosa – associated lymphoid tissue lymphoma and the development of gastric cancer. However, its role in gastroesophageal reflux disease (GERD) without esophagitis and in reflux esophagitis is not fully understood.

There are many important issues to be elucidated regarding the effect of *H. pylori* eradication on reflux esophagitis or GERD. Several reports have shown beneficial effect of *H. pylori* on acid reflux by alkalinization of gastric secretions caused by the bacteria.[1,2] Contradictory results have been reported an association of *H. pylori* eradication with the development of GERD or reflux esophagitis symptoms.[3,4]

The American College of Gastroenterology guidelines define GERD as 'symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus'.[5]

Symptoms like heartburn, acid regurgitation, dysphagia in older children or agitation, and food refusal in toddler and infant are usually sufficient to confirm the diagnosis of GERD and start the treatment. The most common test used to confirm GERD is ambulatory 24-hour esophageal pH monitoring.

A satisfactory therapeutic response to proton pump inhibitors (PPI) in GERD induced us the idea to study whether GERD correlates with infectious etiology of some forms of gastritis, especially since there is an overlap of symptoms that raise issues of differential diagnosis. There is some evidence that the combination of *H. pylori* and chronic acid suppression can lead to atrophic gastritis, a precancerous condition in the stomach.[6] It has been demonstrated that interactions between bile acids, pH, and *H. pylori* it is associated with the occurrence of corpus-predominant gastritis after PPI therapy in *H. pylori*-positive patients with GERD.[7] It is

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Conflicts of interest: The authors declare that they have no competing interests.

recommended that patients being considered for long-term PPI therapy should be tested for *H. pylori* infection. If the infection is present, the bacteria should be eradicated.[8]

METHODS

A correlational study between GERD and gastritis with *H. pylori* was conducted on a group of 72 children, admitted in a pediatric gastroenterology regional center in Northeast Romania, diagnosed with gastroesophageal reflux by 24-hour continuous esophageal pH monitoring, which underwent upper endoscopy with gastric biopsy. Results were interpreted using the Boix-Ochoa score.

We used as control group 62 patients with suspicion of GERD, but who did not have gastroesophageal reflux proved by pH-metry.

Some exclusion criteria were applied: previous therapy to eradicate *H. pylori*, PPIs treatment in the last 3 months, concomitant consumption of aspirin and nonsteroidal antiinflammatory drugs, patients with endoscopic evidence of active gastrointestinal bleeding, presence of esophageal stricture or esophagitis secondary to systemic diseases or any past history of gastric or esophageal surgery.

Twenty-four-hour esophageal pH monitoring

To determine the pH, we used the Medtronic Digitrapper pH 100, SN 37660 with Polygram Net TM pH Testing Application and Zinetics 24 multiuse and ComforTec by Sandhill catheters. The sensor was positioned 5 cm above the lower esophageal sphincter. Continuous pH recording was performed for 24 hours. Meal periods were excluded.

Current consensuses show that the total percentage of time the pH is below 4 is the most useful single discriminator between physiologic and pathologic reflux.[9]

The Boix-Ochoa score was used to calculate the following distal pH variables: number of acid refluxes longer than 5 minutes, longest acid reflux, fraction of total time pH below 4, fraction of upright time pH below 4, fraction of supine time pH below 4 and fraction of prone time pH below 4. The Boix-Ochoa score is developed for infant/pediatric usage. A normal score is a score below 11.99.

During the study, the children took no medications that could interfere with the results and consumed an unrestricted diet.

Endoscopy

All study patients underwent upper gastrointestinal endoscopic examinations. Intravenous sedation was given and standard upper gastrointestinal endoscopy, using the Olympus and Pentax video pediatric gastroduodenoscopes was performed to identify evidence of macroscopic abnormalities. Endoscopy was performed under general anesthesia in children aged below 10 years.

The endoscopic findings of reflux esophagitis in the lower esophagus were classified according to the Los Angeles classification system. Esophagitis was graded by endoscopy: grade A, one (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds; grade B, one (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds; grade C, one (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference; grade D, one (or more) mucosal break which involves at least 75% of the esophageal circumference.[10]

Biopsies taken from the gastric antrum and corpus were used for rapid urease testing and for bacteriologic and histologic examination. For a conclusive bacteriologic examination of gastric biopsies, the sampling was made before any treatment with antibiotics, bismuth or PPI. Patients were considered *H. pylori* positive if, at least two of the four biopsy specimens had positive results. The same criteria for *H. pylori* diagnosis were used in each group.

One biopsy specimen from the antrum (2 cm from the pylorus) was used for the rapid urease test. The fragment of gastric mucosa is introduced into the environment, immediately after the biopsy. If gastric mucosa contains bacteria of the species *H. pylori*, the urease hydrolyzes urea to ammonia and carbon dioxide, the pH becomes alkaline, and the environment turns red. The results were interpreted after 24 hours. Any other biopsy from the corpus for the rapid urease test was not necessary because the sampling was made before any treatment with PPI.

One biopsy specimen from the antrum and one from the corpus were used for culture of *H. pylori*. Biopsy specimens were transported to the laboratory immediately after the endoscopy. *H. pylori* was cultured by rubbing gastric biopsy specimens into Columbia with agar supplemented with Skirrow's supplement (containing vancomycin, trimethoprim, and polymyxin B) and lysed horse blood. The plates were incubated under micro aerobic conditions at 35°C for 4 to 7 days.

A biopsy specimen from the antrum for histopathologic examinations was fixed in buffered 4% formalin overnight and was embedded in paraffin. Two sections were stained with hematoxylin-eosin and one section was stained by the modified Giemsa procedure and examined. The slides were microscopically examined for the bacterial density.

Table 1 The frequency of *Helicobacter pylori* in gastroesophageal reflux disease (GERD)

N = 72 esophagitis	Number of cases	%
With *H. pylori*	19	26.39
Without *H. pylori*	53	73.61
Total	72	

Table 2 The estimated parameters in the association gastroesophageal reflux disease with *Helicobacter pylori*

	χ^2	*P* 95% confidence interval
Pearson's χ^2	0.0658681	0.79745
Correlation coefficient (Spearman rank *R*)	0.016778	0.79850

Statistic analysis

Data management and statistic analyses were performed using the „STATISTICA' program.

RESULTS

In 19 of 72 patients (26.39%) *H. pylori* was present and in 53 patients the bacteria was not detected (Table 1).

Involvement of *H. pylori* in GERD

It was analyzed in comparison (making contingency table), the frequency of *H. pylori* in GERD in study group and in the control group. Thus, in the study group consisting of 72 patients with GERD were 19 positive results with a percentage of 26.39% and in control group composed of 62 children were 10 cases with *H. pylori* infection with a percentage of 16.13% (Fig. 1).

The presence of *H. pylori* was not found to be a causal factor in GERD, which is demonstrated by insignificant differences in the presence of *H. pylori* in children with GERD compared with the frequency of *H. pylori* in the control group ($\chi 2 = 0.065$, $P = 0.7974$, 95% confidence interval [CI]) (Table 2).

The calculation of chance or risk parameters did not bring additional items, the estimated value is insignificant (Table 3).

The involvement of *H. pylori* in GERD based on the grade of esophagitis

Trying an association between the presence of *H. pylori* and the grade of esophagitis it can be observed the existence of an inverse relationship. If the presence of *H. pylori* is lower, the grade of esophagitis is greater (34.04% for grade A vs. 12% for grade B of esophagitis) (Fig. 2).

The presence of *H. pylori* was found to be significantly associated with the presence of grade A esophagitis of GERD and not with grade B esophagitis ($\chi 2 = 54.69$, $P << 0.05$, 95% CI) (Table 4). It appears that the presence of bacteria would slow down the progression of esophagitis from grade A to B and then to more severe forms. The presence of *H. pylori* is beneficial and it does not aggravate the grade of esophagitis in GERD. The results seem to confirm the protective role of *H. pylori* in the evolution of GERD. However, further studies are needed to clarify this situation.

Table 3 Parameters estimation of chance and risk in the occurrence of gastroesophageal reflux disease versus *Helicobacter pylori*

	Estimated value	95% confidence interval	
		Minimum	Maximum
Parameters of chance			
Odds ratio	0.51	0.12	0.94
Parameters of risk			
Risk ratio	0.34	0.24	0.87

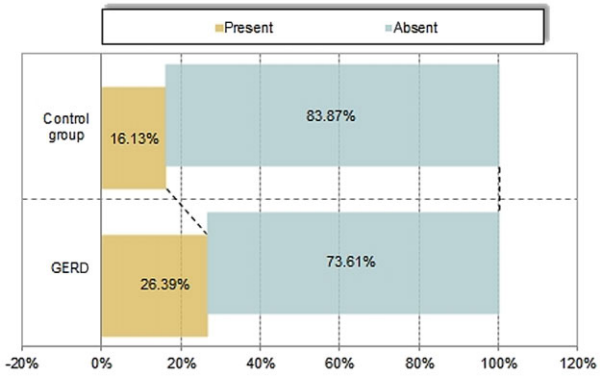

Fig. 1 The frequency of *Helicobacter pylori* in gastroesophageal reflux disease (GERD) and in the control group.

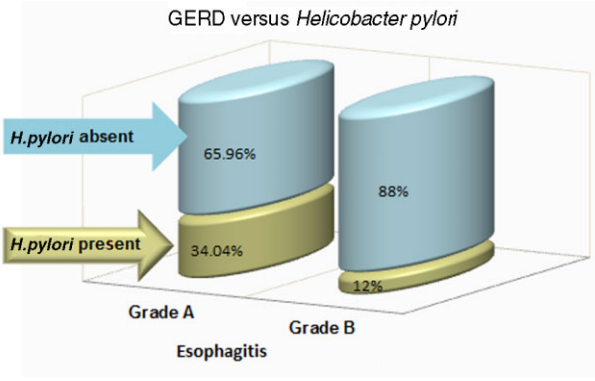

Fig. 2 The grade of esophagitis in gastroesophageal reflux disease (GERD) versus *Helicobacter pylori*.

Table 4 Estimated parameters in the association of *Helicobacter pylori* with esophagitis in gastroesophageal reflux disease

df = 1	χ^2	*P* 95% confidence interval
Pearson's χ^2	54.69916	0.00000
Correlation coefficient (Spearman rank *R*)	0.64294940	0.00000

df, degrees of freedom.

Table 6 Test for comparing average values of score Boix-Ochoa versus *Helicobacter pylori*

Boix-Ochoa score versus *H. pylori*	*F* (95% confidence interval)	*P*
Analysis of variance test	8.13	0.001535

Boix-Ochoa score vs. the presence of *H. pylori* in GERD

Analysis of Boix-Ochoa score according to the presence of *H. pylori* in patients with esophagitis clearly demonstrates that the presence of the bacteria in GERD determines a significantly lower Boix-Ochoa score than the values recorded in GERD when *H. pylori* is not present ($F = 8.13$, $P = 0.0015$, 95% CI) (Tables 5,6).

DISCUSSION

H. pylori has been shown to increase the risk of gastritis, peptic ulcer and precancerous lesions in the stomach. The role *H. pylori* infection plays in the esophagus remains doubtful. Epidemiologic studies have shown the incidence of *H. pylori* infection in patients with GERD from 30 to 90% and the average is approximately of 35% in most series.[11] Both conditions affect a large proportion of the population and they may occur either independently or concomitantly.[12]

It was suggested that *H. pylori* could contribute to GERD through different mechanisms: a decrease of lower esophageal sphincter pressure and impairment of gastric filling, the development of antral gastritis which increases acid production.[13]

Gastric acid secretion, therefore, is the key factor in the relationship between *H. pylori* and GERD. In patients who develop chronic atrophic gastritis as a consequence of *H. pylori* infection, gastric acid is suppressed and so acid would no longer appear to be produced in a critical amount for the induction of GERD.[14,15] A study in a large patient group suggests that, even a corpus-predominant gastritis would exert a protective effect against GERD development.[16] Studies from Japan in patients with atrophic gastritis reported increased acid production following *H. pylori* eradication and induction of GERD in a subset of patients.[17,18] The protective potential of *H. pylori* has been demonstrated in studies that discovered more virulent strains to be less prevalent or even absent in severe forms of GERD. Cag A carrying strains were suspected to protect from Barrett's adenocarcinoma.[19]

On the contrary, other studies found that *H. pylori* eradication did not lead to alterations in the gastroesophageal reflux pattern and the bacteria status in patients with GERD did not impact on the grade of esophageal acid exposure.[20,21]

The authors of a study found no influence of *H. pylori* infection either on pH-metry results or on endoscopic findings.[22] In a recent study, out of 184 GERD patients, 46% were *H. pylori*-infected while 54% were *H. pylori*-negative with no statistic difference regarding presence and severity of reflux esophagitis between patients with and without *H. pylori* infection.[23] In our trial consisting of 72 patients with GERD, 26.39% were positive and 73.61% were negative for *H. pylori* infection.

The authors of a study, report that the prevalence of reflux esophagitis, like a biomarker for GERD, among *H. pylori*-positive children regardless of their age and gender was twice as high as among *H. pylori*-negative patients: 81.3% vs. 38.1%; there was no difference in the apparent severity of reflux esophagitis between *H. pylori*-positive and -negative patients.[24] A study reported a correlation between *H. pylori* infection and a reduction in the severity of reflux esophagitis. These findings suggest an inverse correlation between *H. pylori* infection and the risk of esophagitis.[1] In our study, regarding the correlation between the presence of *H. pylori* and the grade of esophagitis we obtained the existence of an inverse relationship.

24-hour pH monitoring cannot be regarded as a definitive gold standard for GERD diagnosis. The main limitation of the 24-hour pH monitoring is its

Table 5 Statistic indicators of Boix-Ochoa score based on *Helicobacter pylori*

H. pylori	Mean Boix-Ochoa score	Mean –95%	Mean +95%	Standard deviation	Standard error	Min	Max	Q25	Median	Q75
Present	29.92	22.92	43.36	25.30	4.96	12.36	105.00	19.50	27.15	42.50
Absent	44.26	34.90	70.68	42.79	14.26	21.65	125.60	23.90	32.50	59.00

low tolerability.[25] Patients report that pH-metry frequently induces unpleasant side effects lasting for most of the day. North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines on pediatric GERD established that multichannel intraluminal impedance-pH monitoring detects acid, weakly acid and nonacid reflux episodes and it is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GERD.[26] This technique is limited by its high cost and the lack of normative data of multichannel intraluminal impedance-pH in the pediatric population.[27] However, as long as there is no effective medical therapy for weak acid and nonacid reflux, the clinical relevance of measuring these types of reflux remains debatable.[28]

When pH evaluation is performed over a prolonged period, it presents high sensitivity and specificity indices.[29] The Boix-Ochoa methodology is considered to be the most appropriate for application to the pediatric age group.[30]

The clinical reality is that there is a large population of children with *H. pylori* infection and concomitant GERD. There is inconclusive evidence that more severe forms of GERD have a lower prevalence of *H. pylori* infection or are infected with less virulent strains. From all current debates concerning the clinical management of *H. pylori* infection in patients with GERD, eradication treatment is recommended in those who require long-term PPI.[31]

The limitations of our study include the fact that the data reflect a single clinical center with a low prevalence of *H. pylori* in children with GERD.

Conclusions

The presence of the *H. pylori* is not an important factor in the gastroesophageal reflux. This is demonstrated by insignificant differences in the presence of *H. pylori* in children with GERD (26.39%) compared with the frequency of *H. pylori* in the control group (16.13%). On the other hand, its relationship with esophagitis appears to be inverse ratio. The fact that the *H. pylori* presence is statistically greater in the grade A esophagitis could confirm the hypothesis that the bacteria would slow down the development of the esophagitis. Also, the presence of *H. pylori* determines lower Boix-Ochoa score, so less acid reflux episodes.

Acknowledgments

The authors would like to thank the Endoscopy Department's staff, the Vth Pediatric Clinic's staff and the Pathology Department at 'St. Mary' Children's Emergency Hospital for their help.

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