

NEITHER GENOTYPE NOR THE GASTRIC COLONIZATION SITE OF *Helicobacter pylori* ARE PREDICTIVE FACTORS FOR THE DEVELOPMENT OF EROSIIVE ESOPHAGITIS IN PATIENTS WITH PEPTIC ULCER DISEASE, 1 YEAR AFTER ERADICATION

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ABSTRACT – *Context* - Whether *Helicobacter pylori* infection is a protective or predisposing factor for the development of gastroesophageal reflux disease remains controversial. The most virulent strains, such as those expressing the cytotoxin-associated gene A (*CagA*), and the site of gastric colonization have been correlated with the prevention or development of esophagitis. *Aim* - To determine the incidence of erosive esophagitis following eradication of *H. pylori* in patients with peptic ulcer disease and to evaluate the association of erosive esophagitis with virulent strains of *H. pylori* and the site of gastric colonization. *Methods* - Triple therapy with lansoprazole, amoxicillin and clarithromycin was administered to 159 patients with peptic ulcer disease. Endoscopy, histopathology, urease and carbon-14 urea breath tests were performed prior to treatment, at 3 months and 1 year following treatment. Genotyping of *H. pylori* strains using polymerase chain reaction was performed separately on samples from the corpus and antrum. *Results* - One year after treatment, 148 successfully treated patients were reevaluated. Twenty-eight patients (19%) had erosive esophagitis, classified as Los Angeles grade A in 24 and B in 4. The samples taken from the corpus were *CagA*-positive in 18 patients (64%), while the samples taken from the antrum were *CagA*-positive in 21 patients (75%). *Conclusions* - The incidence of erosive esophagitis in peptic ulcer patients who had their *H. pylori* eradicated was 19%. No correlation was found between the gastric site colonized by *H. pylori* or strains expressing *CagA* and the prevention or development of erosive esophagitis in patients with peptic ulcer disease, 1 year after infection eradication.

HEADINGS - *Helicobacter pylori*. Peptic ulcer. Esophagitis.

INTRODUCTION

Helicobacter pylori infection is highly prevalent worldwide; its incidence rate varies in accordance with the geographical region studied and the age and socioeconomic conditions of infected individuals^(21,33,40). Around 50% of the population worldwide is estimated to be infected⁽⁶⁾; however, only a small percentage of colonized individuals will develop a pathology related to the infection; for example, only 10%-20% will develop a gastric and/or duodenal ulcer⁽¹⁵⁾.

H. pylori is known to alter gastric acid secretion, consequently affecting the physiopathology of gastroduodenal ulcer disease⁽¹¹⁾ and gastroesophageal

reflux disease (GERD)⁽⁷⁾. The relationship between peptic ulcers and *H. pylori* has been well-established in the literature⁽³⁰⁾. The same cannot be said with respect to its effect on the pathogenesis of GERD, although it has been proposed a complex interaction between them; however, data remain sparse and further studies must be carried out before this hypothesis can be confirmed^(25,29). The different ways in which *H. pylori* infection evolves may be explained by the response of the host and the different strains of the bacterium. The most aggressive strains, for example those expressing the cytotoxin-associated gene A (*CagA*), have been more frequently linked to the pathologies associated with this bacterium⁽²⁾.

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Studies investigating the participation of *H. pylori* in the physiopathology of GERD in patients with peptic ulcers were initiated following the pioneering work of LABENZ et al.⁽¹⁷⁾, who studied *H. pylori*-positive duodenal ulcers patients. The authors reported a higher rate of esophagitis in patients who had their *H. pylori* eradicated compared to the group in which the infection had continued. Following this first study, other trials were carried out, either confirming LABENZ' work^(8, 9, 14) or reporting contradictory results^(1, 24, 36, 38, 41, 42, 44).

Another focus of investigation has been the relation between the severity of GERD and *H. pylori* infection. Some investigators have suggested that *H. pylori*-positive patients have a lower incidence of GERD and less severe esophagitis when compared to uninfected patients⁽³⁵⁾. A relevant study published by VICARI et al.⁽³⁹⁾ showed that the more aggressive the strains of *H. pylori* (*CagA*-positive), the less intense were the esophagitis and vice-versa.

In many studies, *H. pylori* strains were isolated in the antral region of the stomach. Recently paper reported the infection with the *CagA*-positive strains of the bacterium promoted epithelial proliferation⁽³⁾ that was directly and significantly correlated with inflammation in the colonized area of the stomach.

A meta-analysis summarizing the results of 14 case-control studies and 10 clinical trials confirmed that *H. pylori*-negative status is associated with a significant increased risk of GERD⁽⁵⁾. This finding may also be explained by the fact that individuals with a predominantly antral infection are expected to have greater gastric acid secretion and are, therefore, more likely to develop a duodenal ulcer and/or GERD. On the other hand, gastric acid secretion would be lower in individuals in whom the infection is predominantly in the gastric corpus, which may reduce the risk of GERD.

Studies on the pathogenesis of *H. pylori* are of interest in Brazil, where prevalence of the infection is high⁽⁴³⁾, a common characteristic in developing countries, although the prevalence of GERD is similar to that found in the first world⁽²⁷⁾.

Objective

The objective of this study was to evaluate the incidence of erosive esophagitis in patients with peptic ulcers, 1 year after eradication of *H. pylori*, taking into consideration the effect of strains expressing *CagA* and the gastric site of colonization: the gastric antrum or corpus.

METHODS

Population

One hundred and fifty nine patients receiving care at the Gastroenterology Outpatient Department of the University of São Paulo, "Hospital das Clínicas", São Paulo, SP, Brazil, with a peptic ulcer diagnosed at upper digestive endoscopy and *H. pylori* status confirmed by at least two of three tests (urease, histopathology and carbon-14 urea breath test) were included in this study.

Exclusion criteria consisted of: patients who had been in use of nonsteroidal anti-inflammatory drugs (NSAIDs) or

antibiotics, either chronically or in the 4 weeks that preceded inclusion in the study; patients with complicated peptic ulcers, erosive esophagitis, Barrett's esophagus, cancer of the digestive tract, pregnant or breast-feeding women, patients with a history of surgery of the esophagus, stomach, duodenum or gall bladder; those who had undergone previous treatment for *H. pylori* and patients with chronic diseases such as diabetes, neuropathies, hypo- or hyperthyroidism, kidney failure and collagenosis.

All patients recruited to the study gave their written, informed consent. The study protocol was approved by the Internal Review Board of the institution.

Endoscopy and biopsies

Upper digestive tract endoscopy was performed to confirm diagnosis of a peptic ulcer and to collect samples for confirmation of *H. pylori* colonization. Four fragments of gastric mucosa were collected, two from the antrum and two from the corpus, one sample from each site for histopathological investigation and the other for urease test. The fragments used in the urease test were sent for genotyping whenever the presence of *H. pylori* was detected. Endoscopic diagnosis and grading of reflux esophagitis were based on the Los Angeles classification⁽²⁰⁾.

Genotyping

DNA was extracted from gastric biopsy samples with positive rapid urease tests using a salting out procedure⁽²⁶⁾. Polymerase chain reaction (PCR) was performed according to a previously reported method⁽²³⁾ using a thermal cycler (2400 Gene Amp PCR system, PerkinElmer, Branchburg, NJ, USA). PCR conditions for *CagA* amplification consisted of initial denaturation at 94°C for 5 minutes followed by 27 cycles of denaturation at 94°C for 30 seconds, annealing at 53°C for 30 seconds and extension at 72°C for 30 seconds⁽⁴⁾. The final extension at 72°C was performed for 7 minutes. One set of primers (P1 and P2) that amplifies the 26 kDa antigen gene present in all strains of *H. pylori* was then used according to the following conditions: initial denaturation at 94°C for 5 minutes followed by 40 cycles of denaturation at 93°C for 1 minute, annealing at 57°C for 2 minutes and extension at 70°C for 2 minutes⁽¹⁰⁾.

Urea breath test

Carbon-14 (14C) urea breath test was carried out to diagnose *H. pylori* and to evaluate its eradication, according to a previously described technique⁽²²⁾.

Treatment and follow-up

All patients received a 7-day therapeutic regimen consisted of 30 mg lansoprazole, 500 mg clarithromycin and 1 g amoxicillin, BID. After treatment, neither proton-pump inhibitors nor H₂-receptor antagonists were permitted; however, patients were allowed to take antacids and/or prokinetics during the entire study period.

The patients were reevaluated 3 months after the eradication treatment, when a second upper digestive endoscopy was performed; two samples were collected from the gastric

antrum and the corpus for urease test and histopathology. Additionally, the patients were submitted to a urea breath test. They were considered cured of the infection when all tests were negative. One year after treatment, the remaining patients were reevaluated by undergoing another upper endoscopy during which the presence of *H. pylori* was investigated.

Statistical analysis

Quantitative variables were described as means and standard deviations, range, and absolute and relative frequencies. Comparison between the groups of interest with respect to the qualitative variables was carried out using the chi-square test. Significance level was established as $P < 0.05$.

RESULTS

Of the 159 patients admitted to the study, the *H. pylori* eradication failed in 11, which resulted in an eradication rate of 93% (per protocol). One year after treatment 148 patients were available for analysis. The mean age of these patients was 46.5 years with median 46 years (range 18-82 years), 96 (64.9%) were female. At baseline upper endoscopy, 106 patients (71.6%) had duodenal and 26 (17.6%) had gastric ulcers (Table 1). The gastric corpus samples were *H. pylori* *CagA*-positive in 91 patients (61.5%), while the samples taken from the antrum were *H. pylori* *CagA*-positive in 103 patients (69.6%) (Table 2).

TABLE 1. Demographic and type of ulcer data of the sample of patients that concluded the study (148 patients)

Age	Mean	46.5 years
	Median	46 years
	Range	18-82 years
Gender	Female	96 (64.9%)
Type of ulcer	Gastric	26 (17.6%)
	Duodenal	106 (71.6%)
	Gastric + duodenal	16 (10.8%)

TABLE 2. *CagA* status according to gastric site

Gastric site	<i>CagA</i> -positive	<i>CagA</i> -negative
Corpus	91 (61.5%)	57 (39%)
Antrum	103 (69.6%)	45 (30%)

$P = 0.14$

Upper endoscopy carried out 1 year after *H. pylori* eradication revealed erosive esophagitis in 28 patients (19%). In these patients, gastric mucosal samples taken from the corpus were *H. pylori* *CagA*-positive in 18 patients (64%) and *CagA*-negative in 10 (36%) (Table 3).

TABLE 3. *CagA* status and intensity of erosive esophagitis 1 year after eradication

Intensity of erosive esophagitis	<i>CagA</i> -positive	<i>CagA</i> -negative	Total
Grade A*	15	9	24 (86%)
Grade B*	3	1	4 (14%)
Total	18 (64%)	10 (36%)	28/148 (19%)

* Los Angeles classification $P = 0.63$

Fifteen patients had erosive esophagitis grade A (Los Angeles classification⁽²⁰⁾) and were *CagA*-positive, while nine patients were *CagA*-negative. Of the remaining four patients with grade B erosive esophagitis, three were *CagA*-positive, while one was *CagA*-negative. Statistical analysis showed no significant correlation between *CagA*-positive strains and the grade of esophagitis (Table 4). No statistically significant correlations were found between the groups of patients with and without erosive esophagitis and *CagA*-positive status either in the gastric corpus or antrum (Table 5).

TABLE 4. *CagA* status according to gastric site of colonization in patients with erosive esophagitis

Gastric site	<i>CagA</i> -positive	<i>CagA</i> -negative
Corpus	18 (64%)	10 (36%)
Antrum	21 (75%)	7 (25%)

$P = 0.38$

TABLE 5. *CagA*-positive and erosive esophagitis status in gastric sites

Gastric site	With erosive esophagitis	Without erosive esophagitis	Total
Corpus	18/28	73/120	91/148
Antrum	21/28	82/120	103/148

$P = 0.91$

DISCUSSION

The first authors who described the influence of *H. pylori* in the pathophysiology of GERD in patients with peptic ulcer were LABENZ et al.⁽¹⁷⁾. This study had great impact in medical literature, being the first to show a greater incidence of erosive esophagitis in duodenal ulcer patients who had their *H. pylori* eradicated (25.8%), compared to the group that remained *H. pylori* positive (12.9%). After that, a new study that analyzed eight double-blind prospective trials comprising 1,165 patients with duodenal ulcer disease (940 active, 225 past history) added further support to the theory that eradication of *H. pylori* in duodenal ulcer patients does not lead to reflux disease. It was verified the development of erosive esophagitis in 24 (4%) of 621 healed patients versus 14 (3%) of 544 with persistent *H. pylori*⁽¹⁹⁾. In this study, final endoscopies were done 4-30 weeks after therapy completion, differently from our patients who passed through endoscopies 3 months and 1 year after eradication.

KUPCINSKAS et al.⁽¹⁶⁾ also followed patients with duodenal ulcer for 1 year after *H. pylori* eradication and have not observed any increase in reflux esophagitis incidence, either. Other studies, obtained similar data in patients with gastric ulcers⁽¹²⁾.

The present study included patients predominantly with duodenal ulcers (71.6%). We verified the development of erosive esophagitis in 19% of them after *H. pylori* eradication, similarly to RAGHUNATH et al.⁽³⁴⁾ systematic review publication.

A previous reflux disease hidden by peptic ulcer disease⁽²⁸⁾, population differences⁽⁹⁾ and methodological differences can justify these conflicting results.

The most aggressive strains, for example those expressing the cytotoxin-associated gene A (*CagA*), have been more frequently linked to pathologies associated with this bacterium (peptic ulcer disease, MALT gastric lymphoma, gastric adenocarcinoma).

In our study, the analysis of *H. pylori*-infected gastric mucosal samples taken from the corpus and antrum revealed no statistically significant difference in the predominance of the *CagA* gene among patients who developed erosive esophagitis, suggesting that despite the high predominance of this gene in both groups. This was expected since it is already known the association of peptic ulcer disease and *CagA* strains.

Several studies made evident that the virulence of the *CagA*-positive *H. pylori* strains can determine a protector effect against the development of reflux esophagitis, especially that more severe^(18, 39), including Barrett's esophagus⁽³⁷⁾.

In Brazil, PEREIRA-LIMA et al.⁽³¹⁾ concluded that *H. pylori* gastric infection and especially *H. pylori CagA*-positive may play a protective role against the development of the most severe forms of GERD. On the other hand in this study, the patients had dyspepsia, peptic ulcer and erosive gastritis, differently that our study, in which all patients homogeneously

had peptic ulcer disease. However, KILTZ et al.⁽¹³⁾ did not observe the development of reflux esophagitis for those cured of the *H. pylori* infection, even if infected by *CagA*-positive strains. Another Brazilian study, by QUEIROZ et al.⁽³²⁾ has provided evidence supporting the independent protective roles of *CagA*-positive *H. pylori* strains and the degree of corpus gastritis against GERD. When the *CagA* genotypes were analyzed, no statistically significant differences were found among the samples collected from the corpus and those from the antrum.

The present study was the first to analyze whether *H. pylori* genotype and its site in the stomach affect progression to erosive esophagitis 1 year after eradication of the infection in patients with peptic ulcer.

CONCLUSION

One year after eradication of *Helicobacter pylori* in patients with peptic ulcers, erosive esophagitis developed in almost one-fifth of the patients. The cytotoxin-associated gene A (*CagA*) carried by some *H. pylori* strains had no effect on whether the patient developed esophagitis or not, irrespective of the site of infection in the stomach.

Batista CAG, Silva FM, Barbutti RC, Eisig JN, Mattar R, Navarro-Rodriguez T. O genótipo e o local no estômago de isolamento do *Helicobacter pylori* em pacientes com úlcera péptica não são fatores preditivos para o desenvolvimento de esofagite erosiva 1 ano após a erradicação da bactéria. *Arq Gastroenterol.* 2009;46(3):204-8.

RESUMO – *Contexto* - É controverso se a infecção pelo *Helicobacter pylori* é um fator de proteção ou de predisposição para o desenvolvimento da doença de refluxo gastroesofágico. Cepas mais virulentas tais como as que expressam a citotoxina *CagA* e o local no estômago de infecção pela bactéria, podem estar correlacionados com a prevenção ou desenvolvimento de esofagite. *Objetivos* - Determinar a incidência de esofagite erosiva após a erradicação do *H. pylori* em pacientes com úlcera péptica e a sua associação com a virulência das cepas da bactéria e o local no estômago de seu isolamento. *Métodos* - Um tratamento triplice com lansoprazol, amoxicilina e claritromicina foi administrado a 159 pacientes com úlcera péptica. Endoscopia digestiva alta, exame histológico, teste rápido da urease e o teste respiratório de uréia com carbono-14 foram realizados antes, 3 meses e 1 ano após o tratamento. A genotipagem das cepas do *H. pylori* por meio de PCR foi realizada separadamente em amostras obtidas da mucosa do corpo e do antro gástricos. *Resultados* - Um ano após o tratamento, 148 pacientes curados da infecção foram avaliados: 28 (19%) apresentavam esofagite erosiva, 24 com grau A da classificação de Los Angeles e 4 com grau B. Nas amostras obtidas da mucosa do corpo gástrico, a citotoxina *CagA* foi positiva em 18 (64%) pacientes com esofagite erosiva, enquanto que nas amostras obtidas do antro gástrico, a citotoxina *CagA* foi positiva em 21 (75%). *Conclusões* - A incidência de esofagite erosiva em pacientes com doença péptico-ulcerosa foi de 19%. Não houve correlação entre o local de isolamento no estômago ou as cepas *CagA*-positivas do *H. pylori* e a proteção ou o desenvolvimento de esofagite erosiva, em pacientes com úlcera péptica, 1 ano depois da erradicação da bactéria.

DESCRIPTORIOS - *Helicobacter pylori*. Úlcera péptica. Esofagite.

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