Helicobacter pylori Is Not Associated With the Manifestations of Gastroesophageal Reflux Disease

Stefan Oberg, MD; Jeffrey H. Peters, MD; John J. Nigro, MD; Jörg Theisen, MD; Jeffrey A. Hagen, MD; Steven R. DeMeester, MD; Cedric G. Bremner, MD; Tom R. DeMeester, MD

Hypothesis: Helicobacter pylori is not associated with gastroesophageal reflux disease and its complications, including adenocarcinoma of the esophagus and the gastroesophageal junction (GEJ).

Design: Retrospective analysis.

Setting: University tertiary referral center.

Patients: Two hundred twenty-nine patients with symptoms suggestive of foregut disease underwent esophageal manometry, 24-hour pH monitoring, and upper gastrointestinal tract endoscopy, with biopsy specimens obtained from the gastric antrum, the GEJ, and the distal esophagus. In these and in an additional 114 patients with adenocarcinoma of the esophagus and the GEJ, the presence of Helicobacter pylori was determined by Giemsa stain. The presence of gastroesophageal reflux disease, defined by abnormal esophageal acid exposure, and its manifestations (carditis, erosive esophagitis, intestinal metaplasia limited to the GEJ, Barrett esophagus, and adenocarcinoma of the esophagus and GEJ) were correlated with the presence of H pylori.

Results: Helicobacter pylori was found on the biopsy specimens of the gastric antrum in 14.0% (32/229) of the patients with benign disease. It was not related to the features of gastroesophageal reflux disease, including abnormal esophageal acid exposure, erosive esophagitis, or Barrett esophagus. The presence of inflamed cardiac mucosa at the GEJ or carditis was inversely related to H pylori infection and strongly associated with increased esophageal acid exposure. There was no association between the presence of intestinal metaplasia and H pylori infection. Helicobacter pylori was found in 22 (19.3%) of the 114 patients with esophageal adenocarcinoma, which was not different from the prevalence of H pylori in patients with benign disease.

Conclusion: Helicobacter pylori plays no role in the pathogenesis of gastroesophageal reflux disease or its complications.


THE ISOLATION of Helicobacter pylori from gastric mucosa by Marshall and Warren in 1983 dramatically altered our understanding of the pathophysiological characteristics of acid peptic disease. Helicobacter pylori is accepted as an important factor in the development of duodenal ulcer and distal gastric cancer. It is also true that, in most developed countries, the prevalence of these disorders has dropped dramatically during the past several decades. It is likely that the decreasing incidence of these disorders is the result of improvements in sanitation and public health, which has resulted in a lower prevalence of H pylori infection in the general population.

On the contrary, the prevalence of gastroesophageal reflux disease (GERD) and its complications, erosive esophagitis, Barrett esophagus, and adenocarcinoma of the esophagus and the gastroesophageal junction (GEJ), have increased dramatically during the same period. The role of H pylori in the pathogenesis of GERD and its complications has not been fully evaluated. Reports to date have been conflicting, with some authors arguing an important role for H pylori in GERD and others arguing that it does not play a role. Recent data suggest that H pylori may actually protect against the development of erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma. Furthermore, it has been suggested that eradication of H pylori may precipitate reflux esophagitis in patients with duodenal ulcers.

To evaluate the role of H pylori in the pathogenesis of GERD, its presence in a large group of patients representing the full spectrum of GERD was studied.
PATIENTS AND METHODS

PATIENT POPULATION

Between April 1993 and June 1998, 229 consecutive patients (122 men and 107 women; median age, 31 years; age range, 16-85 years) with symptoms of foregut disease and no history of gastric or esophageal surgery were examined. Patients with a named motility disorder and those in whom the histological evaluation of the biopsy specimens did not include a staining specific for H pylori (Giemsa) were excluded. The foregut symptoms consisted of heartburn, regurgitation, dysphagia, chest pain, epigastric pain, or symptoms suggestive of aspiration, such as recurrent pneumonia, wheezing, and cough. All patients underwent upper endoscopy with biopsy, standard esophageal manometry to evaluate the lower esophageal sphincter, and 24-hour esophageal pH monitoring to quantify esophageal exposure to gastric juice.

An additional 114 patients (96 men and 18 women; median age, 68 years; age range, 28-82 years) with adenocarcinoma of the esophagus or GEJ and with biopsy specimens obtained from the gastric antrum were studied.

ENDOSCOPIC DATA

All patients underwent a systematic endoscopic examination of the duodenum, pylorus, stomach, and esophagus. The GEJ was defined as the place where the gastric rugal folds ended and the tubular esophagus began. A columnar-lined esophagus was identified when the squamocolumnar junction or any part of its circumference extended above the GEJ. In patients with an irregular squamocolumnar junction, biopsy specimens were obtained from the tongues of the glandular mucosa extending into the esophagus. In patients whose squamocolumnar junction was above the GEJ, 4 quadrant biopsy specimens were obtained every 2 cm of the columnar-lined segment. Multiple biopsy specimens were also obtained immediately below the squamocolumnar junction and from the gastric antrum in all patients.

Patients were identified as having Barrett esophagus by the presence of intestinal metaplasia in a columnar-lined esophagus.

HISTOLOGICAL FEATURES

The biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and mounted on slides by means of standard technique. Slides were stained with hematoxylin-eosin and analyzed for the type and the condition of the epithelium. The biopsy specimens were evaluated for the presence of H pylori infection using a Giemsa stain.

Gastric fundic mucosa was characterized by glands that contain parietal and chief cells but are devoid of mucous cells except those lining the surface and foveolar region. Glands composed entirely of mucous cells without any parietal or chief cells characterized cardiac mucosa. Inflammation of cardiac mucosa or carditis was identified by the presence of eosinophil or plasma cell infiltration of the lamina propria and hyperplasia of the mucous cells in the foveolar region of the cardiac mucosa. Specialized intestinal metaplasia in cardiac mucosa was identified by the presence of a columnar epithelium with a villiform surface, mucous glands, and well-defined goblet cells. The presence of goblet cells was confirmed by positive staining with Alcian blue at pH 2.5.

RESULTS

The overall prevalence of H pylori in patients with foregut symptoms and benign disease was 14.0% (32/229). Table 1 shows demographic data and the distribution of H pylori infection in these patients. In addition to antral infection, 24 patients also had evidence of H pylori on biopsy specimens just below the squamocolumnar junction, indicating a generalized infection. When found just below the squamocolumnar junction, H pylori infection was always present in the antrum.

Table 2 shows the relationship between H pylori infection and the features of GERD in the total study population. There was no difference in the prevalence of abnormal esophageal acid exposure, erosive esophagitis, and Barrett esophagus in patients with and without H pylori infection. The prevalence of erosive esophagitis in the subset of patients with abnormal esophageal acid exposure was not different when stratified according to the presence or absence of H pylori infection (25.0% vs 31.1%; P = .54). Similarly, the prevalence of Barrett esophagus in patients with abnormal esophageal acid exposure was
not different in patients with and without *H pylori* infection (15.6% vs 17.8%; *P* = 1.00). In the presence of Barrett esophagus, *H pylori* was never found in an unindented mucosa that was intestinalized, although it was seen in biopsy specimens of cardiac mucosa from the lower esophagus in 2 patients with Barrett esophagus. Five of the 40 patients with Barrett esophagus had low-grade dysplasia, none of whom had histological evidence of *H pylori* infection.

Inflamed cardiac mucosa at the GEJ or carditis was found in 61.2% (113/188) of patients with a normal GEJ. The presence of carditis was inversely related to *H pylori* infection and significantly associated with greater esophageal acid exposure (Table 3). In contrast, when fundic mucosa was found on biopsy specimens of the GEJ, inflammation was weakly associated with the presence of *H pylori* but not with higher esophageal acid exposure (Table 4). Eleven (5.8%) of the 188 patients with an endoscopically normal GEJ had cardiac mucosa harboring intestinal metaplasia found at the GEJ. One (9.1%) of these patients had evidence of *H pylori* infection that was not different from those without intestinal metaplasia (26 [14.6%] of 178, *P* = .52).

**Table 1. Demographic Data of the Patients Without Adenocarcinoma Grouped According to the Presence and Distribution of Helicobacter pylori Infection**

<table>
<thead>
<tr>
<th>Feature of Gastroesophageal Reflux Disease</th>
<th>H pylori Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 197)</td>
<td>Yes (n = 32)</td>
</tr>
<tr>
<td>Esophageal pH &lt; 4.0*</td>
<td>5.5 (2.3-10.4)</td>
</tr>
<tr>
<td>Abnormal acid exposure†</td>
<td>110 (55.8)</td>
</tr>
<tr>
<td>Erosive esophagitis†</td>
<td>61 (30.9)</td>
</tr>
<tr>
<td>Barrett esophagus†</td>
<td>35 (17.7)</td>
</tr>
</tbody>
</table>

*Values are given as median (interquartile range) percentage of time.
†Values are given as median (interquartile range) percentage of time.

**Table 2. Relationship Between Helicobacter pylori Infection and the Features of Gastroesophageal Reflux Disease**

<table>
<thead>
<tr>
<th>Feature of Gastroesophageal Reflux Disease</th>
<th>H pylori Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 197)</td>
<td>Yes (n = 32)</td>
</tr>
<tr>
<td>Esophageal pH &lt; 4.0*</td>
<td>5.5 (2.3-10.4)</td>
</tr>
<tr>
<td>Abnormal acid exposure†</td>
<td>110 (55.8)</td>
</tr>
<tr>
<td>Erosive esophagitis†</td>
<td>61 (30.9)</td>
</tr>
<tr>
<td>Barrett esophagus†</td>
<td>35 (17.7)</td>
</tr>
</tbody>
</table>

*Values are given as median (interquartile range) percentage of time.
†Values are given as number (percentage) of patients.

**Table 3. Prevalence of Helicobacter pylori in Patients With and Without Carditis and No Evidence of Barrett Esophagus**

<table>
<thead>
<tr>
<th>Carditis</th>
<th>No (n = 73)</th>
<th>Yes (n = 115)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>50 (16-80)</td>
<td>51 (23-85)</td>
<td>.13</td>
</tr>
<tr>
<td>Esophageal pH &lt; 4.0*</td>
<td>2.9 (0.7-6.8)</td>
<td>4.9 (3.9-9.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Abnormal acid exposure†</td>
<td>28 (38.4)</td>
<td>64 (55.7)</td>
<td>.02</td>
</tr>
<tr>
<td><em>H pylori</em> infection†</td>
<td>16 (21.9)</td>
<td>11 (9.6)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Values are given as median (interquartile range) percentage of time.
†Values are given as number (percentage) of patients.

**Table 4. Prevalence of Helicobacter pylori in Patients With and Without Inflamed Fundic Epithelium at the Gastroesophageal Junction and No Evidence of Barrett Esophagus**

<table>
<thead>
<tr>
<th>Fundic Mucosa</th>
<th>No (n = 141)</th>
<th>Yes (n = 41)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Median age (range), y</td>
<td>51 (16-85)</td>
<td>48 (27-80)</td>
</tr>
<tr>
<td>Inflamed</td>
<td>Esophageal pH &lt; 4.0*</td>
<td>3.8 (1.5-7.6)</td>
<td>3.6 (1.0-7.8)</td>
</tr>
<tr>
<td>Abnormal acid exposure†</td>
<td>73 (51.8)</td>
<td>22 (53.7)</td>
<td>.86</td>
</tr>
<tr>
<td><em>H pylori</em> infection†</td>
<td>4 (2.8)</td>
<td>27 (65.9)</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Values are given as median (interquartile range) percentage of time.
†Values are given as number (percentage) of patients.

Twenty-two (19.3%) of the 114 patients with adenocarcinoma of the esophagus and GEJ had *H pylori* infection. There was no difference in the prevalence of *H pylori* between patients with benign (32 [14.0%] of 229) and malignant disease regardless of the location or between patients with tumors of the esophagus (5 [13.5%] of 37) and the GEJ (17 [22.1%] of 77).

**COMMENT**

This study demonstrates that *H pylori* plays no role in the pathogenesis of GERD or its complications. We found no difference in the median time of esophageal acid exposure or the prevalence of abnormal esophageal acid exposure, erosive esophagitis, and Barrett esophagus in patients with and without *H pylori*.

In the present study, the prevalence of *H pylori* was similar in patients with and without erosive esophagitis. Furthermore, there was no difference in the prevalence of esophagitis in patients with pH-positive GERD when grouped according to the presence or absence of *H pylori* infection. Although our data suggest that *H pylori* plays no role in the development of erosive esophagitis, there are studies suggesting that it may have a protective effect. Labenz et al have shown that patients with duodenal ulcer and successful eradication of *H pylori* developed esophagitis significantly more frequently during the ensuing 3 years than those who remained positive for *H pylori*. The investigators suggested that the increased frequency of esophagitis may result from increased gastric acid secretion following eradication therapy. Others have suggested, however, that gastric acid secretion may decrease following *H pylori* eradication and have questioned the association between eradication therapy and GERD with and without erosive esophagitis.

Recent investigations have focused on the role of subpopulations of *H pylori*, including cagA+ strains, in the development of GERD and its complications. Vicari et al demonstrated that in patients with *H pylori* infection the prevalence of cagA+ strains progressively decreased with the severity of GERD, including Barrett esophagus and esophageal adenocarcinoma. Chow et al confirmed an inverse relationship between the presence of cagA+ and adenocarcinoma of the esophagus and the GEJ. Both groups postulated that cagA+ strains may protect from the development of adenocarcinoma by induc-
ing more severe mucosal inflammation and atrophic gastritis, thereby decreasing acid reflux. Present data regarding gastric acid secretion are conflicting, however, and further studies are required to test if this hypothesis is true.20-22

We have shown that carditis represents one of the earliest histological changes of GERD,23 while others24-28 have suggested that carditis and intestinal metaplasia of the cardia are caused by *H pylori*. We found no association between the presence of cardiac mucosa or carditis, with or without intestinal metaplasia to *H pylori* infection. In fact, carditis was inversely related to the presence of *H pylori*, and patients with carditis had significantly greater esophageal acid exposure than patients without carditis. Inflammation in fundic epithelium found on biopsy specimens obtained from the area just below the squamocolumnar junction, however, was strongly associated with *H pylori* infection. The controversy about the role of *H pylori* in the pathogenesis of carditis exists in part because most researchers26,28-30 do not relate the location of the biopsy specimens to the underlying type of mucosa in which inflammation and intestinal metaplasia occurs. Carditis in these reports is defined by the location of the biopsy specimens, ie, the anatomic gastric cardia, which infrequently harbors cardiac mucosa.31 Inflammation and intestinal metaplasia arising in fundic or antral mucosa have been associated with *H pylori* infection.36-38 In contrast, intestinal metaplasia in cardiac mucosa is not associated with the presence of *H pylori* or other gastric pathological features; rather, it is associated with gastroesophageal reflux.7,32,33

The incidence of adenocarcinoma of the esophagus and GEJ has risen more rapidly during the past decade than any other solid tumor.5,6,34 Most of these cancers arise in patients with Barrett esophagus. The reason for its progression to cancer in a few patients is unknown. Helicobacter pylori is likely important in the pathogenesis of chronic atrophic gastritis and cancer of the gastric antrum and body.35-38 The result of the present study confirms the results of other reports,7,8 and finds no association with the presence of *H pylori*, indicating that it has no role in the pathogenesis of adenocarcinoma of the esophagus and GEJ.

Helicobacter pylori has no role in the pathogenesis of GERD or its manifestations. Whether specific strains of *H pylori* protect against the complications of GERD needs further investigation.

Presented at the 106th Scientific Session of the Western Surgical Association, Indianapolis, Ind, November 17, 1998.

Reprints: Jeffrey H. Peters, MD, Department of Surgery, University of Southern California, School of Medicine, 1510 San Pablo St, Suite 514, Los Angeles, CA 90033-4612 (e-mail: jhpeters@hsc.usc.edu).

REFERENCES


James R. DeBord, MD, Peoria, Ill: These authors have presented a defining paper that clearly and scientifically confirms the absence of any role of Helicobacter pylori in the pathogenesis of reflux disease or adenocarcinoma of the esophagus. Bacterial infections have plagued surgeons for centuries. However, bacterial vectors for surgical disease is a relatively new concept that has impacted surgeons in the treatment of peptic ulcer disease, inflammatory bowel disease, mucosal-associated lymphoma of the stomach, and probably other entities yet to be discovered. This paper confirms that gastro-esophageal reflux disease, a common surgical disease with effective surgical treatment, will not likely be removed from our therapeutic arena by antibiotics. The authors’ study was well designed and thoroughly carried out. I believe the results speak for themselves. Did any of the patients with benign or malignant disease harboring H pylori infection have active peptic ulcer disease? Since 16% of your total patient population were H pylori positive, should surgeons be routinely screening for this infection and treating it proactively? Might this not reduce stress ulcerations and postoperative GI [gastrointestinal] bleeding?

Dr Peters: Twenty years ago at this meeting, we probably would have had 6 or 7 papers on peptic ulcer disease, rather than the 6 or 7 on reflux that we heard today. I wonder if that is not because of this bug. The title here says that there is no association with gastroesophageal reflux disease. As our data suggest, it is not involved in the pathogenesis. It may be, however, that there is an inverse relationship between Helicobacter and reflux disease. I suspect this will become clear in the years to come.

To answer the questions, there was not any peptic ulcer disease in the population of patients that were included in this study. It is actually fairly uncommon for us to see concomitant reflux disease and ulcer disease these days.

Second, we do perform routine biopsies, and if H pylori is identified, it is my practice to treat it. Routine treatment of H pylori is a controversial topic that is much debated. Largely because of its association with gastric cancer, many feel that it is reasonable to do so, and we do.

ARCHIVES OF INTERNAL MEDICINE
Quality of Survival After Cardiopulmonary Resuscitation
Rien de Vos, RN; Hanneke C. J. M. de Haes, MS, PhD; Rudolph W. Koster, MD, PhD; Rob J. de Haan, RN, PhD

Background: Outcome of cardiopulmonary resuscitation (CPR) can be poor, in terms of life expectancy and quality of life. Objective: To determine the impact of patient characteristics before, during, and after CPR on these outcomes, and to compare results of the quality-of-life assessment with published studies.

Methods: In a cohort study, we assessed by formal instruments the quality of life, cognitive functioning, depression, and level of dependence of survivors after in-hospital CPR. Follow-up was at least 3 months after discharge from the hospital (tertiary care center).

Results: Of 827 resuscitated patients, 12% (n = 101) survived to follow-up. Of the survivors, 89% participated in the study. Most survivors were independent in daily life (75%), 17% were cognitively impaired, and 16% had depressive symptoms. Multivariate regression analysis showed that quality of life and cognitive function were determined by 2 factors known before CPR—the reason for admission and age. Factors during and after resuscitation, such as prolonged cardiac arrest and coma, did not significantly determine the quality of life or cognitive functioning of survivors. The quality of life of our CPR survivors was worse compared with a reference group of elderly individuals, but better than that of a reference group of patients with stroke. The quality of life did not importantly differ between the compared studies of CPR survivors.

Conclusions: Cardiopulmonary resuscitation is frequently unsuccessful, but if survival is achieved, a relatively good quality of life can be expected. Quality of life after CPR is mostly determined by factors known before CPR. These findings may be helpful in informing patients about the outcomes of CPR. (1999;159:249-254)

Reprints: Rien de Vos, RN, Academic Medical Center, University of Amsterdam, Division Operation Center H1-212, Meibergdreef 9, PO Box 22700, 1100 DE Amsterdam, the Netherlands (e-mail: r.vos@amc.uva.nl).