The Association and Clinical Implications of Gastroesophageal Reflux Disease and *H. pylori*

The relationship between GERD and *H. pylori* is complex and negatively associated with important implications for both individual patients and the nations of the world. Whereas the incidence of GERD and its complications, including Barrett’s esophagus and adenocarcinoma of the esophagus and gastric cardia have increased, the incidence of *H. pylori* related gastroduodenal peptic ulcer disease and distal gastric adenocarcinoma has decreased in Western Europe and the United States. This suggests an inverse, negative, relationship between the two. *H. pylori* infection eradication does not cause GERD, but there is possibly a protective and negative effect of *H. pylori* in patients with GERD which is related to the virulence of the infecting strain and the distribution and severity of gastritis. It remains controversial whether or not to test and treat for the infection of *H. pylori* with respect to the direct management of GERD, because of its potentially protective effect. However, in patients who require long term therapy with PPI agents, a test and treat strategy may be appropriate, since PPI therapy might increase the risk of atrophic gastritis and its potential for B₁₂ malabsorption and gastric cancer in *H. pylori* infected individuals. If the prevalence of *H. pylori* decreases in the developing countries of the world, one may anticipate that there will be a decrease in incidence of cancer of the gastric body and antrum and an increase in the prevalence of GERD and incidence of adenocarcinoma of the esophagus and gastric cardia over the next few decades. This is an evolving area with important implications for individual patients as well as for the nations of the world.
INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal problem seen in clinical practice. It is estimated that 10%–20% of adults have symptoms at least once weekly and 15%–40% have symptoms at least once monthly (1). Complications of GERD vary from esophagitis and esophageal stricture to Barrett’s esophagus and esophageal cancer. In contrast, *H. pylori* infection is the most common acquired factor in the etiology of gastritis and ulcers of the stomach and duodenum and in adenocarcinoma of the body and antrum of the stomach (2). Remarkably, as the prevalence of *H. pylori* and its complications has declined in the industrialized nations of the world, the incidence of GERD and its complications have increased, suggesting a negative association between the two disease states. *H. pylori* does not predispose to GERD. In fact, evidence indicates a possible protective role. But, there is a higher incidence of atrophic gastritis in patients taking proton pump inhibitor (PPI) agents with *H. pylori* infection. Therefore, the relationship between GERD and *H. pylori* is complex and may have important implications for the individual patient as well as for the nations of the world.

PATHOPHYSIOLOGY OF GERD AND *H. PYLORI*

GERD is predominantly a motility disorder. The abnormalities that appear to play a pathogenic role in GERD are a defective antireflux barrier, abnormal esophageal clearance, reduced salivary production, altered esophageal mucosal resistance, and delayed gastric emptying. Injury to the esophagus is due primarily to reflux of gastric acid and pepsin. In some cases, duodenogastric reflux of bile may cause the injury (3). Nocturnal gastroesophageal reflux is associated with more severe manifestations and esophageal and extraesophageal complications of GERD (4–6). The lower esophageal sphincter (LES) is the antireflux barrier. Abnormalities that make it dysfunctional promote acid reflux and the constellation of GERD problems. The most common cause of reflux episodes is transient LES relaxations, the drop in LES pressure not accompanied by swallowing. Multiple medications, such as nitrates, calcium channel blockers, benzodiazepines, anticholinergics, and antidepressants decrease LES pressure. The presence of a hiatal hernia impairs the function of the LES and may impair the clearance of refluxed acid from the distal esophagus (7). Reduction in esophageal acid clearance impaired by disturbances of esophageal motility and saliva production, delayed gastric emptying and duodenogastric reflux are also important factors. Although all ages are affected, the elderly tend to have more severe complications of GERD (8). GERD is also associated with the development of adenocarcinoma of the distal esophagus and gastric cardia. The pre-malignant lesion for the development of these cancers is Barrett’s esophagus.

*H. pylori* is highly associated with gastritis and gastroduodenal peptic ulcer disease. However, its effect on gastric acid depends upon the severity and distribution of gastritis within the stomach, with either increased, decreased, or unchanged gastric acid secretion. In *H. pylori* infection that is antrum predominant, there is hypergastrinemia, gastric hypersecretion and the propensity to gastroduodenal ulcer. All of the abnormalities resolve completely after eradication of the *H. pylori* organism except for the increased maximal acid output in response to gastrin which remains unchanged in these patients (9). In contrast, patients with corpus predominant infection tend to decreased gastric acid secretion which returns to normal with eradication of *H. pylori*. Basal gastric acid secretion is increased in subjects whose infection was eradicated, but not in those with persistent infection. However, basal and meal stimulated gastric acid secretion does not change after *H. pylori* eradication (10). Therefore, most studies suggest that patients with antrum predominant gastritis have increased gastric acid secretion that returns to normal after *H. pylori* eradication and patients with corpus predominant gastritis have reduced gastric acid secretion that returns to normal after eradication (11). Additionally, *H. pylori* may influence the gastric acid content of the gastric refluxate and affect patterns of gastritis and gastric acid secretion by release of ammonia by *H. pylori*, which may partially neutralize gastric acid (12). The amount of gastritis in the body of the stomach associated with lower gastric acidity returns to normal when *H. pylori* is eradicated. Also, the hypergastrinemia noted in these patients may lead to lower esophageal sphincter pressure (13). *H. pylori*, is associated with the development of atrophic gastritis and ade-
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nocarcinoma of the body and antrum of the stomach. Atrophic gastritis is associated with B₁₂ malabsorption and is a pre-malignant lesion for the development of gastric cancer (2). Virulent strains of *H. pylori*, such as the cag A+ strain are associated with increased development of atrophic gastritis and gastric cancer (14,15).

No causal relationship between *H. pylori* infection and gastroesophageal reflux disease has been demonstrated (16,17). However, *H. pylori* eradication may have a possible negative effect upon GERD. *H. pylori* eradication effects on the development of GERD would largely depend upon the patterns of gastritis and the disturbance of gastric acid secretion induced by the infection and could vary from individual to individual (18). For example, in patient’s with *H. pylori* antrum predominant infection, which is associated with increased acid secretion, eradication of the infection will lower acid secretion and may improve the GERD. On the contrary, if the infection is corpus predominant, which is associated with reduced acid secretion, treatment of the infection will result in increased acid secretion which may induce or aggravate GERD. If *H. pylori* infection produces no overall disturbance of acid secretion, then treatment of the infection is unlikely to have an effect on GERD (19).

Also, by treating *H. pylori* infection in a given population, the development or aggravation of GERD in that population will depend upon the pattern of *H. pylori* infection prevalent in that population. For example, studies from Asia, where *H. pylori* tends to be corpus predominant and associated with lower gastric acid secretion, show aggravation of esophagitis after *H. pylori* treatment (19,20). However, studies from Western Europe and the United States, where there is no regional preponderance of *H. pylori* infection, show conflicting results after *H. pylori* eradication (21,22).

THE NEGATIVE RELATIONSHIP BETWEEN GERD AND *H. PYLORI*

There is a substantial body of epidemiologic evidence that shows an inverse or negative association between the incidence of gastroesophageal reflux disease and *H. pylori* infection. The incidence of GERD in the industrialized countries of the Western world is quite high. For example, approximately 15%–40% of the adult U.S. population has heartburn symptoms. (1) Also, the incidence of GERD complications, especially adenocarcinoma of the esophagus, is rising. In contrast the prevalence of *H. pylori* along with its complication of gastric adenocarcinoma is steadily decreasing in these nations. This is probably due to improvements in hygiene and socioeconomic factors and the treatment of *H. pylori* (23). Labenz, in a study of 6,125 patients with GERD, evaluated independent predictors of erosive disease, including male gender, increased body mass, regular alcohol intake and duration of disease. He showed that *H. pylori* had a protective effect in the subgroup analysis of patients with more severe Los Angeles C and D grade of esophagitis (24). Some studies have found that this negative association between *H. pylori* and GERD is more marked with more virulent cagA+ strains of the infection. In another study, however, Kuipers did not observe a significant change in inflammation in patients with and without eradication of *H. pylori* in GERD patients, although there was a trend towards reduced control in the eradicated group (25).

*H. pylori* may have a possible protective effect, especially the cagA+ strain, for the development of the complications of GERD, including Barrett’s esophagus and adenocarcinoma of the esophagus and gastric cardia. It is well known that complications of GERD are significantly more frequent in Caucasian rather than in African American or Asian populations, which is inversely proportional to the frequency of *H. pylori* infection. Several studies have reported a negative association between the prevalence of *H. pylori*, especially the cagA+ strain, and the severe GERD complications of Barrett’s esophagus and esophageal adenocarcinoma, which suggests a protective effect (26). A study from China revealed a stepwise relationship found between the increasing grade of esophagitis and decreasing prevalence of *H. pylori* (27). A Swedish study showed that *H. pylori* was associated with a significantly decreased risk of adenocarcinoma of the esophagus (27). A subgroup analysis showed that the negative association was only apparent for the cagA+ strains of *H. pylori* (28).

PROTON PUMP INHIBITORS AND *H. PYLORI*

The most common and effective way of treating patients with GERD is by suppressing gastric acid
secretion with proton pump inhibitor (PPI) agents. The degree of inhibition of gastric acid secretion and elevation of gastric pH that are achieved by PPI agents are substantially greater in the \( \text{H. pylori} \) infected than uninfected patients and in \( \text{H. pylori} \) eradicated patients. For example, in \( \text{H. pylori} \) infected patients, Omeprazole at 20 mg per day produced a median gastric pH of 5.5. After eradication of \( \text{H. pylori} \), the pH fell to 3.0 (29). Wu demonstrated that \( \text{H. pylori} \) eradication was the only predictor of treatment failure in patients after adjustments for age, sex, erosive esophagitis and hiatal hernia (30). Holtzman found that both the rate of healing of endoscopically proven esophagitis and the rate of resolution of symptoms was more rapid in the \( \text{H. pylori} \) infected patients treated with PPI agents, as compared to \( \text{H. pylori} \) uninfected patients (31).

Two mechanisms are likely to contribute to the enhanced potency of PPI agents in the presence of \( \text{H. pylori} \). PPI agents appear to transform the pattern of \( \text{H. pylori} \) gastritis into a corpus predominant pattern of gastritis, producing a marked increase in the inflammation in the acid secretion regions of the stomach which inhibits parietal cell function and gastric acid secretion. (32,33) This reduction of gastric acid supplementation the pharmacological affect of PPI agents. In addition, ammonia produced by the \( \text{H. pylori} \) urease helps neutralize acid and thus contribute to the elevation of intragastric pH. Although both effects are probably minor, the increased efficacy of PPI agents may be associated with improved symptom control and more rapid healing of esophagitis.

\( \text{H. pylori} \) infection has also been shown to affect the level of gastric acid secretion after discontinuing PPI therapy. For example, discontinuation of PPI therapy in some patients results in rebound hypersecretion of gastric acid which continues for several months in \( \text{H. pylori} \) eradicated patients. This may be the result of a trophic affect of the elevated gastrin level during \( \text{H. pylori} \) infection that exerts a prolonged effect upon the parietal cell mass. In contrast, some patients with \( \text{H. pylori} \) infection did not show a significant rebound hypersecretion. This protective effect may be explained by a corpus predominant pattern of gastritis induced by PPI agents in \( \text{H. pylori} \) infected subjects that produces a persistent inhibition of gastric acid secretion after stopping the drug and prevents rebound acid hypersecretion (34).

As PPI agents change the \( \text{H. pylori} \) distribution to a corpus predominant pattern, it has been postulated that they may accelerate the development of atrophic gastritis and potentially increase the risk of gastric cancer as compared to uninfected patients. Virulent strains of \( \text{H. pylori} \), such as cagA+, have been reported to cause a greater risk of developing atrophic gastritis and gastric adenocarcinoma. Because of this potential threat of increased gastric cancer in these patients, a test and treat strategy has been proposed by the Maastricht Consensus Conference as well as by other investigators (35). However, PPI agents do not promote intestinal metaplasia (36). Thus, it remains unclear if long term use of PPI agents in \( \text{H. pylori} \) infected patients poses a significant risk for the development of gastric cancer in later life.

**CONCLUSION**

The relationship between GERD and \( \text{H. pylori} \) is complex and negatively associated with important implications for the individual and the populations of the world. The incidence of GERD and its complications, including adenocarcinoma of the esophagus, has increased in recent years, whereas the incidence of \( \text{H. pylori} \) related gastroduodenal peptic ulcer disease and distal gastric adenocarcinoma has decreased in the industrialized nations of the Western world, suggesting an inverse relationship between the two. Current data demonstrate that \( \text{H. pylori} \) infection eradication does not cause gastroesophageal reflux disease. However, there is possibly a protective and negative association between \( \text{H. pylori} \) infection, especially the more virulent cagA+ strain, and the development of GERD and its complications of Barrett’s esophagus and esophageal cancer that appears to depend upon the distribution and severity of the \( \text{H. pylori} \) gastritis. It remains controversial whether or not to treat for the infection of \( \text{H. pylori} \) with respect to the direct management of GERD, because of its potentially protective effect. However, in patients who require long term therapy with PPI agents, a test and treat strategy may be appropriate, since PPI therapy might increase the risk of atrophic gastritis with its potential for B12 malabsorption and gastric cancer in \( \text{H. pylori} \) infected individuals. This may be more important in patients from non-industialized countries and Asia where there

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is a higher incidence of corpus predominant type of *H. pylori* infection. If this were to be the case, then one may anticipate an increased prevalence of GERD and its complications of Barrett’s esophagus and adenocarcinoma of the esophagus and gastric cardia in the developing countries of the world during the next few decades associated with a decreased prevalence of *H. pylori* infection and incidence of gastric cancer of the body and antrum. This is an evolving area with important implications for both individual patients as well as for the nations of the world.

References
