

Does *Helicobacter pylori* Infection Contribute to Gastroesophageal Reflux Disease?

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Helicobacter pylori organisms that infect the stomach conceivably could contribute to esophageal inflammation in patients with gastroesophageal reflux disease (GERD) through any of at least three potential mechanisms: 1) by causing an increase in gastric acid secretion; 2) by spreading to infect the gastric-type columnar epithelium that occasionally can line the distal esophagus; and/or 3) by secreting noxious bacterial products into the gastric juice. Studies regarding these potential mechanisms are discussed in this report. Most investigations have found no apparent association between *H. pylori* infection and reflux esophagitis. Presently, infection with *H. pylori* does not appear to play an important role in the pathogenesis of GERD.

INTRODUCTION

The clinical approach to peptic ulcer disease has changed dramatically over the past decade as evidence has accumulated to support a pivotal role for *Helicobacter pylori* infection in the pathogenesis of most peptic ulcerations in the stomach and duodenum [1]. Reflux esophagitis is also a common "peptic" disorder of the upper gastrointestinal tract [2], and some studies have found an association between duodenal ulcer disease (a disorder that almost always is associated with *H. pylori* infection) and gastroesophageal reflux disease (GERD)^b [3]. On the basis of these observations, investigators have hypothesized that *H. pylori* might play a pathogenetic role in GERD, and some have sought an association between *H. pylori* infection and reflux esophagitis. However, a number of studies on this issue have found no apparent association between the two disorders [4-7]. In a recent prospective study of 93 adult patients with GERD who had endoscopic examinations, for example, no significant association was found between *H. pylori* status and the endoscopic grade of reflux esophagitis [4]. Two other recent endoscopic investigations, one involving elderly patients [5] and one involving children [6], found no significant differences in the frequency of *H. pylori* infection among groups of patients with and those without reflux esophagitis. Interestingly, one recent prospective study of consecutive patients in a general endoscopy unit found that *H. pylori* infection was significantly less common in patients with reflux esophagitis than in control patients without GERD, an observation raising the intriguing (but unlikely) possibility that gastric infection with *H. pylori* might even protect against the development of reflux esophagitis [7]. Despite the results of these studies, it is conceivable that *H. pylori* could contribute to esophagitis in GERD through any of at least three potential mechanisms: 1) *H. pylori* infection might predispose to GERD by increasing gastric acid secretion; 2) *H. pylori* might cause esophageal damage directly by infecting the gastric-type columnar epithelium that can line the distal esophagus normally or as part of Barrett's esophagus; or 3) *H. pylori* might

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^bAbbreviations: GERD, gastroesophageal reflux disease; GRP, gastrin releasing peptide.

cause esophageal damage indirectly through the action of noxious substances that are secreted by the organism into the refluxed gastric juice. Studies regarding these potential mechanisms are discussed below.

H. PYLORI INFECTION AND GASTRIC ACID SECRETION

A number of abnormalities in gastrin homeostasis have been described in individuals who are infected with *H. pylori*. Compared to uninfected control subjects, for example, fasting serum gastrin levels are approximately 40 percent higher in normal individuals who have *H. pylori* infection [8]. Also, some *H. pylori*-positive individuals exhibit exaggerated gastrin release both in response to meals and to infusion of gastrin releasing peptide (GRP) [9, 10]. As a result of the latter abnormalities, postprandial and GRP-stimulated gastric acid output may be enhanced in *H. pylori*-positive individuals. The importance of these abnormalities is not clear, however, because both basal and maximally-stimulated gastric acid outputs appear to be unaffected by *H. pylori* infection in otherwise healthy subjects [8]. Furthermore, no significant differences in gastric acidity have been found during 24-hour gastric pH monitoring studies in groups of normal individuals with and without *H. pylori* infection [11]. In normal individuals, therefore, it seems unlikely that *H. pylori* infection contributes importantly to GERD through the organism's effects on gastric acid secretion.

For decades, it has been known that patients who have duodenal ulcers are hypersecretors of gastric acid. Some of the observed abnormalities in gastric acid secretion, such as elevated basal and GRP-stimulated acid outputs, can be reversed by eradication of the *H. pylori* infection that accompanies most duodenal ulcers [10]. However, it is not clear that *H. pylori*'s effects on gastric acid secretion plays a role in the reflux esophagitis that can be associated with duodenal ulcer disease. Indeed, it seems unlikely that *H. pylori*-induced elevations of gastric acid secretion contribute importantly to GERD in this setting, because it has been found that treatment of the infection actually may precipitate reflux esophagitis. In one recent study, for example, 17 (nine percent) of 190 patients with duodenal ulcer disease developed reflux esophagitis within one to four years after their *H. pylori* infection was eradicated with antibiotics [12]. The authors speculated that the development of reflux esophagitis might have been due to the withdrawal of antisecretory medications that were no longer necessary after cure of the peptic ulcer disease, or to the weight gain that some patients experienced after eradication of *H. pylori* infection.

Several years ago, investigators who knew of the phenomenon of acid hypersecretion in duodenal ulcer disease were surprised to find that the proton pump inhibitor omeprazole was more effective in controlling gastric acidity for patients with duodenal ulcers than for healthy control subjects [13]. Given the same dose of omeprazole, duodenal ulcer patients (most of whom were infected with *H. pylori*) developed higher median gastric pH values than healthy controls. Other investigators found that omeprazole was also more effective at raising the gastric pH in healthy subjects (without peptic ulcer disease) who were infected with *H. pylori* than in their uninfected counterparts [14]. These observations suggested that *H. pylori* infection might somehow augment the acid inhibitory effects of the proton pump inhibitor. In a recent study of patients with duodenal ulcer disease, gastric acidity was measured by 24-hour pH monitoring both before and six weeks after antibiotic therapy for *H. pylori* [15]. Eradication of *H. pylori* had no significant effect on the 24-hour gastric pH values for patients who were not taking omeprazole. In contrast, treatment of the infection caused a dramatic decrease in the efficacy of omeprazole for controlling gastric acidity. Before *H. pylori* eradication, the median 24-hour gastric pH value during omeprazole treatment in 17 patients was 5.5. After antibiotic therapy, the

median 24-hour gastric pH value for the same patients taking the same dose of omeprazole was 3.0. In terms of H⁺ ion concentration, the difference between a pH value of 5.5 and one of 3.0 is more than 100-fold. This study shows that for some patients with duodenal ulcers, the eradication of *H. pylori* infection renders proton pump inhibitor therapy less effective in elevating the gastric pH. Similar results on proton pump inhibitor efficacy have been observed after the eradication of *H. pylori* infection in subjects without peptic ulcer disease [16]. Consequently, higher doses of proton pump inhibitors may be required to control gastric acid secretion after antibiotic therapy aimed at *H. pylori*. For patients with GERD who are treated chronically with proton pump inhibitors, these observations suggest that eradication of *H. pylori* has the potential to cause an exacerbation of reflux esophagitis by decreasing the efficacy of the antisecretory drug. Presently, few published data are available on this subject.

H. PYLORI INFECTION OF COLUMNAR EPITHELIUM IN THE ESOPHAGUS

To infect the stomach, *H. pylori* organisms first must adhere to gastric epithelial cells [17]. Initially, this adherence is effected by specific *H. pylori* surface proteins (adhesins) that bind glycoprotein, glycolipid and phospholipid receptors on the gastric cell membranes [17,18]. *H. pylori* appears to be capable of infecting only columnar epithelia of the gastric type [17]. Outside of the stomach, the organisms have been observed in islands of gastric-type epithelia (heterotopic or metaplastic) that occasionally can be found in the duodenum, the ileum, the rectum and the esophagus [19]. In addition to these isolated islands of gastric-type epithelia, the mucosa of the gastric cardia normally can extend as far as 2 cm above the esophagogastric junction to line the distal esophagus [20]. In this situation, *H. pylori* infecting the cardia of the stomach can spread directly into the columnar lining of the distal esophagus. The organisms cannot infect squamous cells, however, and it seems unlikely that *H. pylori* in the cardiac epithelium contribute importantly to inflammation in the squamous lining of the esophagus for patients with GERD. As noted above, no significant association has been found between *H. pylori* infection of the stomach and reflux esophagitis [4-7].

In some patients with GERD, the chronically inflamed squamous epithelium of the esophagus is replaced by a metaplastic columnar lining that can have features of both gastric and intestinal mucosae [21]. This condition is called Barrett's esophagus. The reported frequency of *H. pylori* infection of the stomach in patients with Barrett's esophagus ranges from 32 percent to 62 percent [22-28]. Among patients who have both Barrett's esophagus and gastric infection with *H. pylori*, the organisms can be found frequently in the metaplastic gastric-type epithelium that lines the distal esophagus [22-27]. However, no study has reported results that suggest an important role for *H. pylori* infection in the pathogenesis of Barrett's esophagus. Two studies have shown that gastric infection with *H. pylori* is no more frequent in patients with Barrett's esophagus than in control patients

Table 1. Frequency of *H. pylori* infection in patients with Barrett's esophagus and in age- and sex-matched control patients without Barrett's esophagus.

Study [Ref.]	Frequency of <i>H. pylori</i> in patients with Barrett's	Frequency of <i>H. pylori</i> in control patients without Barrett's
Paull [22]	10/26 (38%)	11/26 (42%)
Blaser [28]	27/58 (47%)	26/58 (45%)

(without Barrett's esophagus) who were matched for age and gender (Table 1). Furthermore, *H. pylori* infection in patients with Barrett's esophagus does not appear to correlate with the degree of esophageal inflammation as assessed by histologic or endoscopic examination [23, 25, 27].

By far the most common and important type of columnar lining found in Barrett's esophagus is an aberrant intestinal-type of epithelium known as specialized intestinal metaplasia [21]. This distinctive epithelium can be found in more than 90 percent of patients who have long segments of columnar mucosa that extend to the mid- and proximal esophagus [29]. Furthermore, 10 percent to 20 percent of white patients without endoscopic evidence of Barrett's esophagus can be found to have short segments of specialized intestinal metaplasia in biopsy specimens obtained at the esophagogastric junction [30, 31]. The latter condition has been called "shortsegment Barrett's esophagus" by some authors. The precise pathogenetic factors that result in the development of specialized intestinal metaplasia are not known. In the antrum and body of the stomach, intestinal metaplasia is judged to be the result of chronic inflammation with gastric atrophy, and a pathogenetic role for *H. pylori* infection has been proposed but not proved [32, 33]. *H. pylori* infect only gastric-type epithelia, and so the organisms are not found in the specialized intestinal metaplasia that characterizes Barrett's esophagus. As noted above, there is no apparent association between Barrett's esophagus and *H. pylori* infection. Therefore, it seems unlikely that the organisms contribute importantly to the development of specialized intestinal metaplasia in the esophagus. Few published data are available on the role of *H. pylori* in the development of specialized intestinal metaplasia at the esophagogastric junction (short segment Barrett's esophagus), but at least one preliminary report has concluded that *H. pylori* infection is not a risk factor for intestinal metaplasia in this location [34].

NOXIOUS SUBSTANCES PRODUCED BY *H. PYLORI*

Table 2 lists some of the noxious substances produced by *H. pylori*. If these substances are secreted by the organisms into the gastric juice, they might be carried into the esophagus during episodes of gastroesophageal reflux. It is conceivable that these agents might injure the esophageal epithelium through a variety of mechanisms. Toxic ammonia is generated through the action of a urease enzyme that *H. pylori* produces in large quantities [19]. The organism also produces a protease that can degrade protective mucous [35], as well as lipase and phospholipase A that can attack mucosal lipids [36]. Furthermore, some strains of *H. pylori* produce cytotoxins that can cause intracellular vacuolization in cultured cells [37]. In one recent study of 11 patients with GERD who were infected with *H. pylori*, only five of the 11 patients had organisms that produced vacuolating cytotoxin [37]. However, four of the five patients whose *H. pylori* produced the cytotoxin had esophageal ulcerations, an observation suggesting that cytotoxin production could be a virulence factor for *H. pylori*. Further studies are needed to establish a role for

Table 2. Noxious substances produced by *H. pylori*.

Amonia
Protease
Lipase
Phospholipase A
Cytotoxins

the reflux of noxious *H. pylori* products in the pathogenesis of GERD. However, the lack of any apparent association between reflux esophagitis and *H. pylori* infection argues against an important pathogenetic role for the bacteria in GERD.

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