

Debating the Role of *Helicobacter pylori* Infection

Based on a debate between Nimish B. Vakil, MD, and Mae F. Go, MD

Debate Summary

Discussion continues on the role of *Helicobacter pylori*. The following debate provides a venue to examine 2 sides of this complicated issue. Dr. Vakil presents evidence that the eradication of *H pylori* will improve patients' health, while Dr. Go introduces evidence that suggests the presence of *H pylori* can be beneficial in particular cases. These clinicians also discuss the issue of whether to test and treat for *H pylori* and the role of *H pylori* in patients with gastroesophageal reflux disease.

Dr. Vakil:

Helicobacter pylori infection has been shown to be an important cause of peptic ulcer disease and is causally linked to gastric mucosa-associated lymphoid tissue (MALT) lymphoma and distal gastric cancer.¹ MALT lymphoma, distal gastric cancers, gastric atrophy, and intestinal metaplasia may be linked to *H pylori*. This bacterial infection also may have a role in nonulcer dyspepsia and nonsteroidal anti-inflammatory drug (NSAID)-related processes.

Ulcers

Eradication of *H pylori* has been shown to eliminate duodenal ulcer recurrence.

Study results on duodenal ulcer patients in remission showed a

significant difference between ulcer recurrence rates in *H pylori*-positive versus *H pylori*-negative patients. After 24 months of remission, 25% of noninfected patients experienced ulcer recurrence compared with 92% of those testing positive for *H pylori*.¹⁻³ Randomized, controlled clinical trials have shown that rebleeding from peptic ulcer is prevented by eradication of *H pylori*.⁴

MALT Lymphoma

New data show that *H pylori* is associated with MALT lymphoma. In the most recent study, 34 patients with Stage 1 or 2 MALT lymphoma, including low-grade nodal involvement, received short-term (2- to 8-week) therapy for *H pylori* eradication. More than half (n = 28) of the patients experienced complete MALT lymphoma remission with *H pylori* eradication, 29% showed partial remission, and only 10% had no tumor response after treatment.⁵

Nonsteroidal Anti-inflammatory Drugs

Controversy surrounds the issue of the interaction between *H pylori* infection and NSAIDs in the genesis of ulcer disease. A study of 120 NSAID users randomized to prophylactic famotidine treatment to prevent NSAID-related ulcers or placebo found that ulcer formation was substantially higher in patients in

the placebo group with *H pylori* infection.⁶

One recent study assessed the risk of bleeding in patients who were taking NSAIDs and who also were infected with *H pylori*.⁷ In this study, 132 NSAID users hospitalized because of bleeding ulcer were compared with a control group of 136 NSAID users without gastrointestinal complications. Forty-four percent of patients had a bleeding gastric ulcer, 41% had a bleeding duodenal ulcer, 9% had both, and 6% were diagnosed with hemorrhagic gastritis. Overall, *H pylori* was present in 57% of these patients compared with only 43% of controls for an adjusted odds ratio of bleeding ulcer among NSAID users in the presence of *H pylori* of 1.81. This study found that NSAID users with *H pylori* infection have an increased risk of gastrointestinal bleeding.⁷

There is evidence that eliminating *H pylori* infection can help prevent

ulcer formation among NSAID users. A total of 92 *H pylori*-positive patients were randomized to receive either naproxen alone or naproxen plus bismuth-based triple therapy (bismuth subcitrate 120 mg, metronidazole 400 mg, tetracycline 500 mg). As expected, naproxen did not eradicate *H pylori*; however, 90% of patients receiving the additional triple therapy became *H pylori* negative. After 6 months, 25% of patients receiving naproxen alone developed ulcers compared with only 7% of those taking the triple therapy.⁸

Gastric Cancer

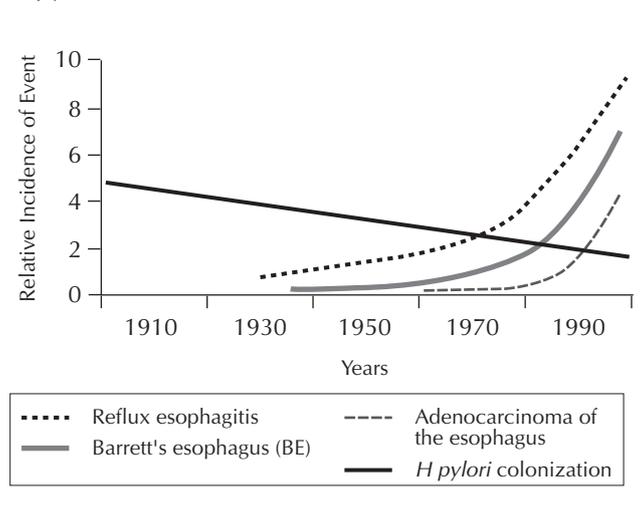
Atrophic gastritis is a precursor lesion to intestinal metaplasia and gastric cancer. Current data indicate that whether patients are treated with omeprazole or surgery, patients with *H pylori* infection have a significantly higher risk of developing atrophic gastritis than those not infected during a 3-year follow up.⁹ A recent study evaluated the effect of *H pylori* eradication therapy on atrophy. A group of 587 atrophic gastritis patients were randomized to receive triple therapy with omeprazole, amoxicillin, and clarithromycin or placebo. At 1 year, patients with documented *H pylori* eradication had significant histologic improvement of gastritis; no improvement was seen in the placebo group, which remained infected. In the *H pylori* eradication group, no significant improvement was observed in intestinal metaplasia.¹⁰

Dyspepsia

Whether *H pylori* eradication is beneficial in dyspepsia patients has been controversial and various studies have produced conflicting results.^{11,12} However, a recent meta-analysis shows a modest benefit with eradication therapy in nonulcer dyspepsia.¹³ Approximately 15 patients need to be treated to obtain 1 responder.

Recent data on uninvestigated dyspepsia in the primary care setting

Figure 1. Changing Incidence of GI Diseases and *H pylori* Infection



GI = gastrointestinal.
 Source: Blaser MJ. Hypothesis: The changing relationships of *Helicobacter pylori* and humans: Implications for health and disease. *J Infect Dis* 1999;179:1523-1530. Reprinted with permission.

also show benefit for eradication therapy. A group of 500 patients were randomized to *H pylori* testing and treatment or to early endoscopic management of dyspepsia. After 1 year, there was no difference between the groups in terms of number of days without dyspeptic symptoms, quality of life, or number of sick days. The test-and-treat group required 60% fewer endoscopy procedures and had no adverse outcomes.¹⁴

Dr. Go:

In some clinical settings, *H pylori* infection is detrimental to a patient's health, but in the majority of cases this is not observed. The steadily decreasing incidence of *H pylori* infection, peptic ulcer disease, and gastric cancer in contrast to the increasing prevalence of gastroesophageal reflux disease (GERD), reflux esophagitis, Barrett's esophagus (BE), and esophageal adenocarcinoma suggests *H pylori*'s role (**Figure 1**).¹⁵

CagA Gene

There is some evidence that *H pylori* strains without the *cagA* gene may confer a detrimental effect to patients with GERD. In 1 study, 153 patients with GERD, BE, or BE complicated by dysplasia or adenocarcinoma were compared with 57 controls who underwent endoscopy for reasons unrelated to GERD. The researchers found no significant difference in the prevalence of *H pylori* infection between the patients and controls (34% and 45.6%, respectively). However, the prevalence of *cagA*-positive strains of *H pylori* was significantly lower in patients with GERD and related complications compared with control patients, suggesting that the *cagA* strain may offer some protection against GERD-related disorders.¹⁶

Ulcers

A controversial study indicating potentially adverse outcomes after eradication of *H pylori* in patients with duodenal ulcer disease included 460 duodenal ulcer patients followed for approximately 3 years after treatment for *H pylori*. Life-table analysis suggested that endoscopically-proven reflux esophagitis occurred in 25.8% of those who were cured of *H pylori* infection compared with 12.9% of those remaining infected.¹⁷ In this case, retaining *H pylori* infection appeared to prevent development of reflux esophagitis.

Although data indicate that patients with true *H pylori*-related duodenal ulcers can benefit from *H pylori* eradication, the effect on NSAID-related ulcer disease is less clear. British researchers evaluated peptic ulcer patients taking NSAIDs and divided them into those presenting with duodenal versus gastric ulcers in terms of *H pylori* status. They found no difference in duodenal ulcer healing between *H pylori*-positive and *H pylori*-negative patients. In contrast, chronic NSAID users who developed gastric ulcers and remained *H pylori* positive showed improved and accelerated ulcer healing (**Figure 2**).¹⁸ These findings are important because the number of patients taking NSAIDs is increasing and more of them develop gastric ulcers than duodenal ulcers.

Dyspepsia

Patients with nonulcer dyspepsia represent a large proportion of those we see; these patients are often very difficult to manage in clinical practice. The question arises as to whether *H pylori* plays a positive or negative role in this patient population. There have been 4 studies to assess *H pylori* eradication in nonulcer dyspepsia to determine if there was a statistical benefit to this approach. Only 1 study showed a benefit in symptom reduction at 1 year follow up.¹² Three

other studies clearly showed no statistical advantage to eradicating *H pylori* infection in this group of patients. All 3 used omeprazole, amoxicillin, and clarithromycin combination therapy for *H pylori* infection and showed a 27% to 46% improvement in dyspeptic symptoms compared with a 21% to 50% improvement in control patients. Controls received omeprazole alone or placebo.^{11,19,20}

REBUTTAL

Dr. Vakil:

There have been several large studies evaluating the effect of *H pylori* eradication on GERD development. One well-designed study included 242 patients with endoscopically documented duodenal ulcer evaluated with rapid urease testing and histology before and after 6 months of therapy for *H pylori* eradication. At 6 months, only 1 patient had any evidence of esophagitis, suggesting that *H pylori*

treatment did not cause erosive esophagitis. In addition, the incidence of heartburn was similar among those who were *H pylori* positive and negative. Although a substantial number of patients in both groups reported new heartburn symptoms, the authors believe this was as a result of the discontinuation of chronic acid suppression therapy following the healing of the patient's duodenal ulcers, not because of the eradication of *H pylori*.²¹ The study by Labenz et al mentioned by Dr. Go did not use an appropriately matched control group.¹⁷

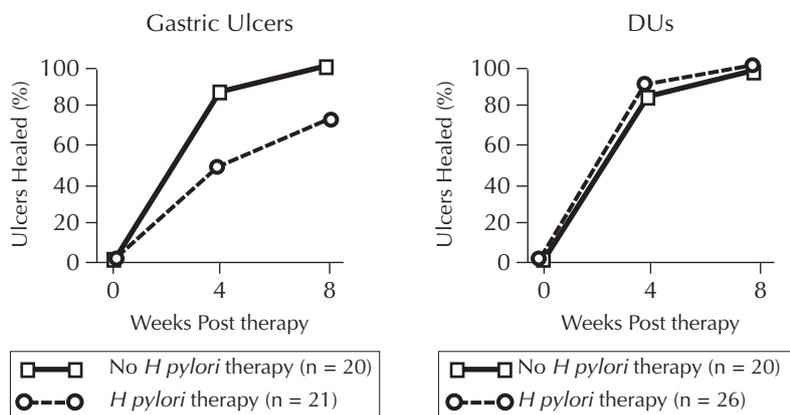
There has always been a question regarding the efficacy of proton pump inhibitors (PPIs) in the presence of *H pylori*. In a recently conducted study including approximately 3000 patients infected with *H pylori*, we found no difference in efficacy with omeprazole or esomeprazole in patients with erosive esophagitis who were infected with *H pylori*.²²

Dr. Go:

Additional data do examine the role of *H pylori* in reflux esophagitis. A study of 846 patients with grade II or III esophagitis given 40 mg of pantoprazole for 4 or 8 weeks showed that 87% of *H pylori*-positive patients had healing of their esophagitis at 4 weeks compared with only 76% of patients without *H pylori* infection.²³ Accelerated healing was also observed in the infected patients. These data were statistically significant between those with and without *H pylori* infection.

There is also evidence that *H pylori* can affect intragastric pH in patients taking a PPI. Nineteen *H pylori*-positive reflux patients were given 30 mg of

Figure 2. Healing of NSAID Ulcers in *H pylori* Positive Patients



DUs = duodenal ulcers; NSAID = nonsteroidal anti-inflammatory drug. Source: Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. *Helicobacter Eradication for Lesion Prevention*. *Lancet* 1998;352:1016-1021. Reprinted with permission.

lansoprazole once daily and then were randomized to receive either placebo or additional treatment to eradicate the infection. The median baseline intra-gastric pH upon 24-hour pH monitoring was similar in both groups. However, patients whose *H pylori* was treated and eradicated showed a decrease in intra-gastric pH to 3.5, indicating that in *H pylori*-negative settings, it may be more difficult to increase pH with a PPI.²⁴

Nocturnal acid breakthrough may be a very important factor in GERD management. Another study suggests that *H pylori* infection may prevent nocturnal acid breakthrough in patients taking a PPI. Twelve healthy volunteers with *H pylori* infection underwent 24-hour pH monitoring and were given a standard dose of rabeprazole; the results were compared with the pH monitoring results of uninfected patients. Prior to rabeprazole treatment the morning intra-gastric pH was about 1.7 in both groups regardless of *H pylori* status. However, nocturnal pH in infected patients was 4.9 among *H pylori* patients compared with only 1.5 in uninfected patients. After PPI therapy, *H pylori*-positive patients showed an approximately neutral nocturnal intra-gastric pH; *H pylori*-negative patients showed a pH that was much lower with treatment.²⁵

Debate Conclusion

In summary, *H pylori* infection is detrimental in a minority of situations and about 20% of infected patients will develop a significant related disorder.

There is consensus that patients with ulcer disease, those with MALT lymphoma and patients at risk for gastric cancer because of family history should undergo *H pylori* testing and treatment. Ethnicity is also important when deciding whether to test and treat. For example, the risk of *H pylori* complications is much smaller in the Caucasian patient

population than it is in the Japanese population although the reasons for this differing host susceptibility needs to be elucidated.

Despite all the data we have, current thinking is that there is no clear association between NSAID use and *H pylori* infection, and prophylactic infection treatment in NSAID users is not indicated. However, NSAID users who develop erosive gastritis or an ulcer should receive therapy to eradicate the infection in case the ulcer is *H pylori* related. There is general agreement that *H pylori* eradication will not produce long-term symptom relief in nonulcer dyspepsia. Although some benefit has been reported in these patients, it is marginal and treatment of *H pylori* is not routinely recommended.

The causal relationship between *H pylori* infection and esophageal disease has not been clearly established, and there is no indication for testing or treatment of *H pylori* in GERD patients. There is a negative association between gastritis related to *H pylori*, BE, and cancer in epidemiologic studies but this information is not solid enough at this time to suggest maintaining *H pylori* infection in order to prevent future cancer development.

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