REVIEW

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Helicobacter pylori: Why it still matters in 2005

Helicobacter pylori still matters clinically in 2005. Although *H pylori* infection rates are falling in the developed world and its associated diseases are decreasing in prevalence, *H pylori* is still widespread in many populations, especially within the United States, and still causes significant morbidity. Fortunately, treatment regimens combining antibiotic and antisecretory agents can be effective in eradicating *H pylori* and improving outcomes in most of the conditions in which the organism has been clearly implicated.

This article briefly reviews the clinical relevance of *H pylori* infection today, with a focus on its evolving epidemiology and the state of the evidence on the organism's role in various conditions in which it has been clearly or theoretically implicated.

WHO IS INFECTED WITH *H PYLORI*?

H pylori is an extremely common bacterium in humans, infecting an estimated one half of the world's population. Its primary reservoir is the stomach, and person-to-person contact is believed to be its principal mode of transmission. Infection is often associated with poor sanitation, crowded living conditions, and poor water supplies. For this reason, the prevalence of *H pylori* is much higher in less developed countries than in developed countries (Figure 1), although there are subgroups within many developed nations in which the prevalence is considerably higher than in the general population. Prevalence varies by geographic location (Table 1),[1] ethnic background, socioeconomic status, and age. Recent studies indicate that *H pylori* prevalence is declining in developed countries and in those with rapid socioeconomic improvement.[2,3]

DISCLOSURE: Dr. Fennerty has served as a consultant to AstraZeneca Pharmaceuticals, Eisai, Meridian Bioscience, Santarus, and TAP Pharmaceutical Products.

Differing epidemiologies in the United States

The prevalence of *H pylori* infection in the United States was estimated at 30% to 40% in the 1990s.[4] Since most people acquire the organism during childhood and since *H pylori* infection rates during childhood are falling,[2,3,5] it is believed that the US prevalence is currently somewhat lower than this and will continue to decline in the coming years.

Nevertheless, given the racial and ethnic diversity of the United States and its large numbers of recent immigrants from the developing world, it is important to recognize that there are differences in the epidemiology of *H pylori* within the United States. Graphical plotting of *H pylori* prevalence data in the United States (Figure 2) shows that the African American and Hispanic subpopulations have curves similar to that of a developing country, whereas the white subpopulation demonstrates the cohort effect curve of a developed country (see Figure 1). In light of the higher *H pylori* prevalence rates in their countries of origin, immigrants from Asia, Eastern Europe, and Africa have rates of *H pylori* infection that are more like those of US African Americans and Hispanics than of US whites. Native Americans from Alaska are another population at elevated risk of *H pylori* infection.[6,7]

The epidemiology of *H pylori* in the United States varies profoundly among different racial and ethnic groups

Clinicians should recognize this variable epidemiology of *H pylori* infection within the United States and be prepared to stratify their patients for *H pylori* risk accordingly.

WHAT ARE THE EFFECTS OF *H PYLORI* INFECTION?

H pylori causes histologic gastritis in all those infected with it. It is the most common cause of chronic gastritis, but most infected individuals have no reportable symptoms.[8] The organism can directly damage epithelial cells in the gastric mucosa as well as induce an inflammatory response in the host. Both host factors and organism factors determine the phenotypic expression of the infection over time. It is in this

FIGURE 1. Typical prevalence curves for *Helicobacter pylori* infection in less economically developed and more economically developed nations. The steep curve for the developing world reflects rapid and widespread acquisition in childhood. The curve for the developed world reflects a cohort effect, with a low incidence of new infections in young people and a "carrier state" from pre-1945 childhood infection in older people. Adapted from *Am J Gastroenterol*, Vol. 89 (8 Suppl), Marshall BJ, "*Helicobacter pylori*," pages S116–S128, copyright 1994, with permission from the American College of Gastroenterology.

TABLE 1

Worldwide prevalence of *H pylori* infection in the mid-1990s*

United States and Canada	30%–40%
Mexico and Central/South America	70%–90%
Western Europe	30%–50%
Eastern Europe	70%
Africa	70%–90%
Asia	70%–80%
Australia	20%

*Data are from reference 1.

phenotypic expression that the significance of *H pylori* lies, and the rest of this review will summarize our current understanding of established, controversial, and theoretical phenotypic manifestations of *H pylori* infection.

DISEASES IN WHICH *H PYLORI* HAS AN ESTABLISHED ROLE

Peptic ulcer disease

H pylori is the major cause of peptic ulcer disease, and peptic ulcer disease remains the chief driver of interest in the organism in the United States. *H pylori* has been found in up to 95% of patients with duodenal ulcers and 80% of patients with gastric ulcers in some regions of the world.[9] In the United States, the percentage is closer to 75%,[10,11] which likely reflects a larger role for ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs). Rates vary somewhat among different regions of the United States.

The causative role of *H pylori* in peptic ulcer disease has been confirmed by studies showing that *H pylori* eradication markedly reduces peptic ulcer recurrence. A meta-analysis of *H pylori* treatment trials demonstrated an odds ratio of 0.20 (95% confidence interval [CI], 0.13 to 0.31) for ulcer recurrence at 6 months in patients in whom *H pylori* had been eradicated.[11]

However, clinicians must recognize that *H pylori* eradication does not necessarily mean that a patient's ulcer symptoms will disappear. Indeed, the above meta-analysis showed a pooled ulcer recurrence rate of 20% at 6 months even in patients with successful *H pylori* eradication.[11] This recurrence of ulcer symptoms may be attributable to NSAID-induced ulcers, idiopathic ulcers, or other causes; regardless, the much higher likelihood of symptom resolution, together with other reasons for *H pylori* eradication (discussed below), clearly justifies testing for and treatment of *H pylori* in patients with peptic ulcer disease. Patients should be warned, however, that *H pylori* eradication will not always make their ulcer symptoms go away.

Gastric cancer

A series of epidemiologic and case-control studies[12–14] support an association between *H pylori* infection and gastric adenocarcinoma, an association that is also supported by animal studies. One of the epidemiologic studies, conducted in Japan, found *H pylori* to be associated with a twofold- to threefold-higher risk of gastric cancer among men but with no increased risk among women.[12]

Despite this epidemiologic evidence of a connection between *H pylori* and gastric can-

cer, it is not clear whether *H pylori* eradication, at least in adults, reduces the risk of gastric cancer development. There are currently no randomized trials showing a reduction in gastric cancer incidence in individuals who received treatment for *H pylori* eradication. Uemura et al[15] conducted a nonrandomized comparison of *H pylori* eradication vs no eradication following endoscopic resection of early gastric cancer in *H pylori*–positive patients. After 3 years of follow-up, the incidence of gastric cancer recurrence was 0% in the eradication group vs 9% in the control group, but the design of this observational study was poor and its findings require confirmation in a randomized trial. A South American study assessing *H pylori* eradication in patients with precursor lesions for gastric cancer suggested that eradication was associated with regression only at more advanced stages of disease (multifocal atrophic gastritis and intestinal metaplasia).[16] Wong et al[17] recently reported no reduction in gastric cancer incidence with *H pylori* eradication in high-risk Chinese patients, although a subgroup analysis (not prespecified) revealed a significant reduction among patients with no precancerous lesions at presentation.

The bottom line is that while *H pylori* is likely an important factor in gastric carcinogenesis, eradication of the organism after many decades of infection and promotion of carcinogenesis is not likely to prevent most cases of gastric cancer.

MALT lymphoma

A connection between *H pylori* and mucosa-associated lymphoid tissue (MALT) lymphoma is well established, as *H pylori* infection has been documented in up to 90% of patients with low-grade MALT lymphoma.[18–20] In contrast to gastric adenocarcinoma, clinical trials have more clearly indicated an interventional role for *H pylori* eradication in MALT lymphoma, with as many as three quarters of patients with low-grade MALT lymphoma experiencing complete or partial tumor remission following *H pylori* eradication.[21–24] The completeness and durability of this treatment effect remain unknown, however.

Uninvestigated dyspepsia

There are many mechanisms by which *H pylori* may produce dyspeptic symptoms (eg, upper abdominal pain or discomfort, bloating, nausea, early satiety). These include the effect of *H pylori*–related inflammation on receptors, perturbations of motility, and acid sensitivity. Epidemiologic studies have suggested a higher prevalence of *H pylori* in dyspeptic patients, but confirmatory randomized controlled interventional trials are lacking.

Because of this lack of data from interventional studies, decision analytic models have been developed to investigate the value of a "test-and-treat" strategy for *H pylori* in patients with *uninvestigated* dyspepsia (ie, dyspepsia not evaluated via endoscopy or imaging of the upper gastrointestinal tract).[25–29] The *H pylori* test-and-treat strategy was dominant over strategies involving early endoscopy in each of these economic models, showing similar outcomes at lower cost.

Thus, despite a lack of randomized trial data supporting a test-and-treat strategy for *H pylori*, this strategy has increasingly been adopted for appropriate patients with uninvestigated dyspepsia—ie, those younger than 50 years of age with no "alarm features" (weight loss, evidence of bleeding, vomiting, dysphagia, anemia, or family history of gastric malignancy). A test-and-treat strategy for *H pylori* in such patients has been endorsed by the United Kingdom's

Diverse epidemiologies of *H pylori* infection within the United States

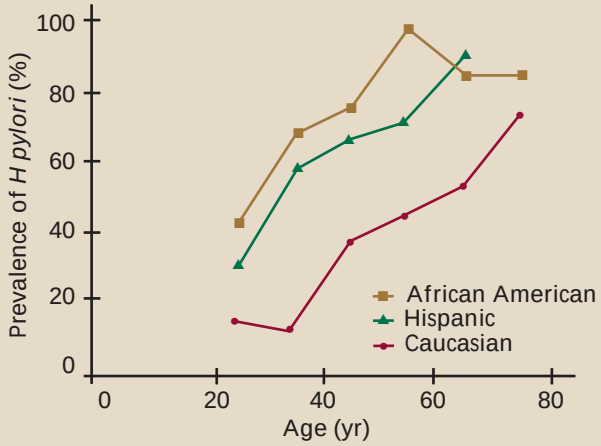

FIGURE 2. The prevalence of *Helicobacter pylori* infection within the United States differs dramatically by race, with racial and ethnic minorities showing prevalence curves more typical of developing nations (see Figure 1). Adapted from *H pylori and Peptic Ulcer*, NIH Publication 97-4225. Bethesda, MD: National Digestive Diseases Information Clearinghouse; 1997.

Clinicians should stratify patients for *H pylori* risk according to the variable epidemiology of the infection

National Institute for Clinical Excellence[30] and will soon be recommended in upcoming guidelines on dyspepsia from the American Gastroenterological Association and the American College of Gastroenterology.[31]

CONDITIONS IN WHICH A ROLE FOR *H PYLORI* IS UNCERTAIN OR UNLIKELY

Nonulcer dyspepsia

In contrast to uninvestigated dyspepsia, *nonulcer* dyspepsia refers to dyspepsia in which the patient has undergone upper gastrointestinal evaluation via endoscopy and an ulcer has been ruled out.

Some epidemiologic studies have suggested an increased prevalence of *H pylori* in patients with nonulcer dyspepsia. However, numerous large interventional trials of *H pylori* eradication therapy in patients with nonulcer dyspepsia have yielded conflicting results, failing to confirm a cause-and-effect relationship.[32–36] The differences in trial results can be explained by differences in the settings, definitions, and instruments used.[36] The preponderance of evidence suggests that there is little, if any, effect of *H pylori* eradication in patients with nonulcer dyspepsia.[36]

Eradication of *H pylori* markedly reduces peptic ulcer recurrence

NSAID-induced ulcer

Although synergism in the development of peptic ulcer between NSAID use and *H pylori* infection has been suggested, NSAIDs and *H pylori* cause ulcers via different pathophysiologic mechanisms. Because *H pylori* infection induces local prostaglandin production, it is biologically plausible that *H pylori* could even be protective against NSAID-induced ulcer. A number of prevalence and incidence studies have investigated proposed ulcer-inducing interactions between *H pylori* and NSAIDs, yielding conflicting results.

Generally, the results appear to differ according to whether the subjects were naïve or chronic NSAID users. In short-term and long-term studies in NSAID-naïve Asian patients infected with *H pylori*, Chan et al[37,38] demonstrated significant reductions in ulcer rates in patients who received *H pylori* eradication therapy prior to naproxen therapy compared with those who received no eradication therapy. These results, together with findings from other studies, have fairly well established the notion that *H pylori* eradication prior to NSAID therapy will reduce ulcer incidence in NSAID-naïve Asian patients.

There is currently no evidence, however, that this is true in US populations or in chronic NSAID users, because similar studies in chronic NSAID users have found no benefit from *H pylori* eradication. In fact, Hawkey et al[39] found that *H pylori* eradication in long-term NSAID users with past or current ulcer was associated with impaired ulcer healing, suggesting that prostaglandin-related protection was perhaps at work. Similarly, *H pylori* infection was associated with higher rates of maintenance of NSAID ulcer healing in two other large studies in chronic NSAID users.[40,41]

The risks of ulcer bleeding in NSAID users infected with *H pylori* have likewise been variable, precluding clear conclusions.

At this time, it appears that *H pylori* infection may increase the rate of NSAID ulcer complications[42] and that *H pylori* eradication may reduce the incidence of ulcers in new NSAID users, particularly among Asians. However, it also appears that *H pylori* could possibly be protective against NSAID-induced ulceration in chronic NSAID users. Further research is needed in all of these areas.

Gastroesophageal reflux disease

The existence and nature of any association between *H pylori* and gastroesophageal reflux disease (GERD) is one of the most complicated questions concerning *H pylori*.

It has been hypothesized that the loss of acid secretory capacity (gastric atrophy) over time that is related to chronic *H pylori* infection might reduce the incidence of GERD. Proponents of this hypothesis point to the opposing time trends of peptic ulcer disease and reflux disease, suggesting that the decline in *H pylori* prevalence could be associated with an increase in GERD and its complications.[43] They also point to evidence of an inverse relationship between corpus gastritis and esophagitis.[44] Additionally, some clinical trial evidence has suggested that *H pylori* eradication may increase the risk of reflux esophagitis[45] and that certain strains of *H pylori* may be protective against serious complications of GERD.[46]

More recent clinical trials have suggested,

TABLE 2

The role of *H pylori* in various diseases: What we know today

	CAUSATIVE/CONTRIBUTORY ROLE FOR *H PYLORI*?	EFFECT OF *H PYLORI* ERADICATION
Peptic ulcer disease	Yes	Reduces ulcer recurrence rate
Gastric adenocarcinoma	Yes	Uncertain
MALT lymphoma	Yes	Partial or complete remission in more than half of patients
Uninvestigated dyspepsia	Yes, in some patients	Symptom improvement in some patients
Iron-deficiency anemia	Likely	May lead to anemia resolution when *H pylori* is the cause
Idiopathic thrombocytopenic purpura	Yes, in some patients	Platelet counts improve after eradication
Nonulcer dyspepsia	Controversial	Little effect, if any
NSAID-induced ulcer	Controversial; perhaps only in naïve NSAID users	May reduce ulcer incidence in Asian naïve NSAID users
GERD	Unlikely, at least for most patients; *H pylori* may protect against GERD	Uncertain
Pancreatic cancer	Uncertain	Unknown
Coronary artery disease	Unlikely	Probably none

MALT = mucosa-associated lymphoid tissue; NSAID = nonsteroidal anti-inflammatory drug; GERD = gastroesophageal reflux disease

however, that a subset of patients with GERD may benefit from *H pylori* eradication[47] or that *H pylori* eradication has no effect on GERD relapse rates.[48]

More research is clearly needed before firm conclusions can be made. In the meantime, clinical practice should be guided by the premise that there is no clear relation between *H pylori* infection and GERD.

Chronic inflammation in coronary disease

Chronic inflammation appears to be an integral pathophysiologic mechanism for plaque disruption and the precipitation of coronary symptoms and events. Several early epidemiologic and clinical reports suggested an increased prevalence of *H pylori* in patients with coronary artery disease, but subsequent case-control investigations have largely dismissed such an association.[49–51]

Pancreatic cancer

Several case-control studies have indicated a possible modest association between *H pylori* infection and pancreatic cancer,[52,53] although the biologic plausibility of such an association has not been clearly elucidated. Prospective studies are needed to further examine this question.

CONDITIONS IN WHICH EMERGING DATA SUGGEST A ROLE FOR *H PYLORI*

A test-and-treat strategy for *H pylori* is increasingly supported for patients with uninvestigated dyspepsia

Iron-deficiency anemia

An association between *H pylori* and iron-deficiency anemia was first observed in the late 1990s in a group of Native Americans in Alaska with widespread iron deficiency attributable to occult gastrointestinal bleeding.[6] Potential mechanisms for this association include iron sequestration by the *H pylori*–infected antrum, altered iron absorption related to the degree of gastritis and pH elevation, and increased microscopic blood loss from the mucosa.

The findings from Alaska were followed by similar findings from a case-control study in a Danish population showing an odds ratio of 1.4 (95% CI, 1.1 to 1.8) for reduced serum iron levels in *H pylori*–infected individuals.[54] Since then, interventional trials have shown successful resolution of iron-deficiency anemia following *H pylori* eradication.[55,56]

While additional studies are encouraged, *H pylori* appears to be a risk factor for iron-deficiency anemia. For patients in whom there is no other explanation for iron-deficiency anemia, *H pylori* testing and eradication may be an effective management approach.

Idiopathic thrombocytopenic purpura

H pylori causes an inflammatory response and provokes an immunologic reaction. It has been proposed that other chronic immune disorders may be caused by an immunologic reaction to *H pylori* antigens, resulting in antibodies that cross-react with human tissues. Uncontrolled studies have suggested a role for *H pylori* in chronic idiopathic thrombocytopenia,[57,58] and recent controlled trials confirm that some patients with this disorder may benefit from therapy to eradicate *H pylori*.[59,60]

SUMMARY

Despite falling prevalence rates in the developed world, *H pylori* is still present in the United States and is particularly prevalent among racial minorities and recent immigrants. *H pylori* infection is clearly associated with an increased risk of peptic ulcer disease, gastric cancer, and MALT lymphoma, and it is associated with some cases of uninvestigated dyspepsia. Identification and eradication of *H pylori* improves outcomes in patients with peptic ulcer disease and causes tumor regression in patients with MALT lymphoma. It is uncertain whether *H pylori* eradication will improve outcomes in patients with gastric cancer. Decision analytic models suggest that a test-and-treat strategy for *H pylori* is rational and cost-effective for patients with uninvestigated dyspepsia.

***H pylori* cure has little, if any, effect in patients with nonulcer dyspepsia**

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Practice should be guided by the premise that there is no clear relation between *H pylori* and GERD