

**M. BRIAN FENNERTY, MD**

Division of Gastroenterology

Oregon Health & Science University, Portland, OR

Helicobacter pylori: Why it still matters in 2005

H*elicobacter 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 anti-secretory 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}

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

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

**Permission not granted
to reprint this figure online.**

Please see original source figure (figure 1, page S117) in:
Marshall BJ. *Helicobacter pylori*. *Am J Gastroenterol* 1994;
89(8 Suppl):S116–S128.

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.

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

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.

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 al¹⁵ 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 al¹⁷ 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

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

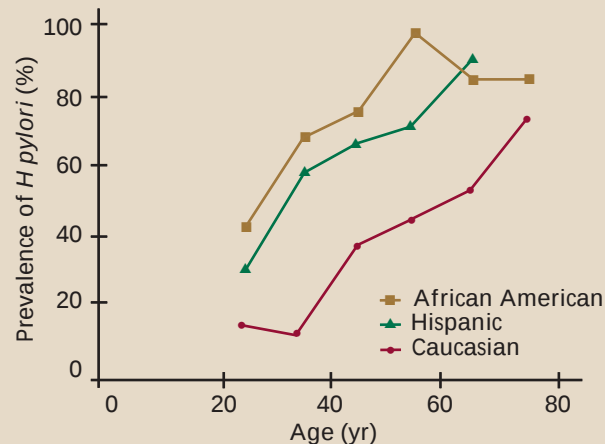


FIGURE 2. The prevalence of *Helicobacter pylori* infection within the United States differs dramatically by race, with racial and ethnic minorities showing prevalence curves more typical of developing nations (see Figure 1). Adapted from *H pylori and Peptic Ulcer*, NIH Publication 97-4225. Bethesda,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

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

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

National Institute for Clinical Excellence³⁰ 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, *non-ulcer* 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

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 al³⁹ 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 complications⁴² 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 esophagitis⁴⁵ and that certain strains of *H pylori* may be protective against serious complications of GERD.⁴⁶

More recent clinical trials have suggested,

Eradication of
H pylori markedly
reduces peptic
ulcer recurrence

TABLE 2

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

	CAUSATIVE/CONTRIBUTORY ROLE FOR <i>H PYLORI</i> ?	EFFECT OF <i>H PYLORI</i> 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 <i>H pylori</i> 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; <i>H pylori</i> 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* eradication⁴⁷ 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*

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.

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

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.

REFERENCES

- Marshall BJ. *Helicobacter pylori*: the etiologic agent for peptic ulcer. JAMA 1995; 274:1064–1066.
- Go MF. Natural history and epidemiology of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2002; 16(Suppl 1):3–15.
- Everhart JE. Recent developments in the epidemiology of *Helicobacter pylori*. Gastroenterol Clin North Am 2000; 29:559–578.
- Peterson WL, Fendrick AM, Cave DR, Peura DA, Garabedian-Ruffalo SM, Laine L. *Helicobacter pylori*-related disease: guidelines for testing and treatment. Arch Intern Med 2000; 160:1285–1291.
- Gold BD, Kruszon-Moran D, Sobel J, McQuillan GM, Everhart J. Decreasing seroprevalence of *Helicobacter pylori* infection in U.S. children ages 6–19 years [abstract]. J Pediatr Gastroenterol Nutr 2003; 37:360. Abstract 99.
- Yip R, Limburg PJ, Ahlquist DA, et al. Pervasive occult gastrointestinal bleeding in an Alaska native population with prevalent iron deficiency. Role of *Helicobacter pylori* gastritis. JAMA 1997; 277:1135–1139.
- Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of *Helicobacter pylori* in the Alaska native population and association with low serum ferritin levels in young adults. Clin Diagn Lab Immunol 2000; 7:885–888.
- Go MF. What are the host factors that place an individual at risk for *Helicobacter pylori*-associated disease? Gastroenterology 1997; 113(Suppl):S15–S20.
- Kuipers EJ, Thijs JC, Festen HPM. The prevalence of *Helicobacter pylori* in peptic ulcer disease. Aliment Pharmacol Ther 1995; 9(Suppl 2):59–69.
- Ciociola AA, McSorley DJ, Turner K, Sykes D, Palmer JB. *Helicobacter pylori* infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. Am J Gastroenterol 1999; 94:1834–1840.
- Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. Am J Gastroenterol 1998; 93:1409–1415.
- Yamagata H, Kiyohara Y, Aoyagi K, et al. Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general Japanese population: the Hisayama study. Arch Intern Med 2000; 160:1962–1968.
- Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001; 345:784–789.
- Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991; 325:1127–1131.
- Uemura N, Mukai T, Okamoto S, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997; 6:639–642.
- Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. J Natl Cancer Inst 2000; 92:1881–1888.
- Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004; 291:187–194.
- Nakamura T, Inagaki H, Seto M, Nakamura S. Gastric low-grade B-cell MALT lymphoma: treatment, response, and genetic alteration. J Gastroenterol 2003; 38:921–929.
- Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991; 338:1175–1176.
- Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med 1994; 330:1267–1271.
- Steinbach G, Ford R, Globler G, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. Ann Intern Med 1999; 131:88–95.
- Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori*. MALT Lymphoma Study Group. Lancet 1995; 345:1591–1594.
- Roggero E, Zucca E, Pinotti G, et al. Eradication of *Helicobacter pylori* infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. Ann Intern Med 1995; 122:767–769.
- Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Malignant tumors of the stomach. Gastric mucosa-associated lymphoid tissue lymphoma and *Helicobacter pylori*. Gastroenterol Clin North Am 2000; 29:593–607.
- Fendrick AM, Chernen ME, Hirth RA, Bloom BS. Alternative management strategies for patients with suspected peptic ulcer disease. Ann Intern Med 1995; 123:260–268.

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



26. Sonnenberg A. Cost-benefit analysis of testing for *Helicobacter pylori* in dyspeptic subjects. *Am J Gastroenterol* 1996; 91:1773–1777.
27. Moayyedi P, Feltbower R, Brown J, et al. Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomised controlled trial. *Leeds HELP Study Group. Lancet* 2000; 355:1665–1669.
28. Silverstein MD, Pettersen T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for *Helicobacter pylori* for dyspepsia: a decision analysis. *Gastroenterology* 1996; 110:72–83.
29. Ofman JJ, Etchason J, Fullerton S, Kahn KL, Soll AH. Management strategies for *Helicobacter pylori*–seropositive patients with dyspepsia: clinical and economic consequences. *Ann Intern Med* 1997; 126:280–291.
30. Dyspepsia: Management of Dyspepsia in Adults in Primary Care. Clinical Guideline 17. London, UK: National Institute for Clinical Excellence; August 2004. Available at: www.nice.org.uk/CG017/NICEguideline. Accessed March 12, 2005.
31. Talley N, Vakil N. Guidelines for the management of dyspepsia. *Am J Gastroenterol*. In press.
32. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998; 339:1869–1874.
33. Blum AL, Talley NJ, O'Morain C, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. Omeprazole plus clarithromycin and amoxicillin effect one year after treatment (OCAY) Study Group. *N Engl J Med* 1998; 339:1875–1881.
34. Talley NJ, Janssens J, Lauritsen K, Racz I, Bolling-Sternevald E. Eradication of *Helicobacter pylori* in functional dyspepsia: randomized double blind placebo controlled trial with 12 months' follow up. The Optimal Regimen Cures *Helicobacter* Induced Dyspepsia (ORCHID) Study Group. *BMJ* 1999; 318:833–837.
35. Talley NJ, Vakil N, Ballard ED 2nd, Fennerty MB. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* 1999; 341:1106–1111.
36. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 134:361–369.
37. Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of *Helicobacter pylori* before nonsteroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* 1997; 350:975–979.
38. Chan FK, To KF, Wu JC, et al. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with nonsteroidal anti-inflammatory drugs: a randomized trial. *Lancet* 2002; 359:9–13.
39. Hawkey CJ, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients on nonsteroidal anti-inflammatory drugs: HELP NSAIDs study. *Helicobacter* Eradication for Lesion Prevention. *Lancet* 1998; 352:1016–1021.
40. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. *N Engl J Med* 1998; 338:727–734.
41. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. *Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med* 1998; 338:719–726.
42. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; 359:14–22.
43. El-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. *Gut* 1998; 43:327–333.
44. El-Serag HB, Sonnenberg A, Jamal MM, Inadomi JM, Crooks LA, Feddersen RM. Corpus gastritis is protective against reflux oesophagitis. *Gut* 1999; 45:181–185.
45. Labenz J, Blum AL, Bayerdorffer E, Meining A, Stolte M, Borsch G. Curing *Helicobacter pylori* infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997; 112:1442–1447.
46. Vicari JJ, Peek RM, Falk GW, et al. The seroprevalence of cagA-positive *Helicobacter pylori* strains in the spectrum of gastroesophageal reflux disease. *Gastroenterology* 1998; 115:50–57.
47. Schwizer W, Thumshirn M, Dent J, et al. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001; 357:1738–1742.
48. Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon AT. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001; 121:1120–1126.
49. Folsom AR, Nieto FJ, Sorlie P, Chambless LE, Graham DY. *Helicobacter pylori* seropositivity and coronary heart disease incidence. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation* 1998; 98:845–850.
50. Ridker PM, Danesh J, Youngman L, et al. A prospective study of *Helicobacter pylori* seropositivity and the risk for future myocardial infarction among socioeconomically similar U.S. men. *Ann Intern Med* 2001; 135:184–188.
51. Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between *Helicobacter pylori* infection, coronary heart disease, and stroke in middle aged men. *Heart* 1996; 75:568–572.
52. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, et al. *Helicobacter pylori* seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst* 2001; 93:937–941.
53. Raderer M, Wrba F, Kornek G, et al. Association between *Helicobacter pylori* infection and pancreatic cancer. *Oncology* 1998; 55:16–19.
54. Milman N, Rosenstock S, Andersen L, Jorgensen T, Bonnevie O. Serum ferritin, hemoglobin, and *Helicobacter pylori* infection: a seroepidemiologic survey comprising 2,794 Danish adults. *Gastroenterology* 1998; 115:268–274.
55. Choe YH, Kwon YS, Jung MK, Kang SK, Hwang TS, Hong YC. *Helicobacter pylori*–associated iron-deficiency anemia in adolescent female athletes. *J Pediatr* 2001; 139:100–104.
56. Annibale B, Marignani M, Monarca B, et al. Reversal of iron deficiency anemia after *Helicobacter pylori* eradication in patients with asymptomatic gastritis. *Ann Intern Med* 1999; 131:668–672.
57. Gasbarrini A, Franceschi F, Tartaglione R, et al. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori* [letter]. *Lancet* 1998; 352:878.
58. Fujimura K. *Helicobacter pylori* infection and idiopathic thrombocytopenic purpura. *Int J Hematol* 2005; 81:113–118.
59. Suzuki T, Matsushima M, Masui A, et al. Effect of *Helicobacter pylori* eradication in patients with chronic idiopathic thrombocytopenic purpura—a randomized controlled trial. *Am J Gastroenterol*. In press.
60. Jaing TH, Yang CP, Hung IJ, Chiu CH, Chang KW. Efficacy of *Helicobacter pylori* eradication on platelet recovery in children with chronic idiopathic thrombocytopenic purpura. *Acta Paediatr* 2003; 92:1153–1157.

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