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Helicobacter pylori: The Etiologic Agent for Peptic Ulcer

Marshall, Barry J. MD

Author Information

From the Department of Medicine, University of Virginia Health Sciences Center, Charlottesville.

Unraveling the puzzle of Helicobacter pylori and its pivotal role in gastric disease was not done in isolation. Many of the pieces were already available but dispersed over 100 years in journals of different languages and sub-specialties. The prevailing dogma was that the stomach was sterile and that bacteria could not survive in gastric acid, but there were articles describing gastric spiral bacteria as far back as 1886. [1] Even after the advent of endoscopy, descriptions of the presence of curved organisms on the surface of the gastric mucosa were ignored by mainstream medicine.

REDISCOVERY OF H PYLORI

Fourteen years have passed since my work on H pylori began. In 1981, Robin Warren at Royal Perth Hospital in Western Australia first showed me the spiral bacteria he had discovered in patients with gastritis. Together we embarked on an attempt to culture the organisms by taking gastric biopsy specimens from patients undergoing endoscopy.

In 1982, we began a prospective study of 100 consecutive patients undergoing endoscopy. We obtained biopsy specimens for culture and histologic diagnosis during the procedure, and Dr Warren read the pathology sections blinded to any clinical details. We hypothesized that the spiral bacteria might be Campylobacter organisms, and if so, that they might have come from contaminated food or milk, from pets, or from poor

dental hygiene. We tried many different culture media, the best choice being blood agar in a microaerophilic atmosphere. When the preliminary results of the study were available in 1983, we published two letters on the new organism in the Lancet [2] and pointed out that these new bacteria, if linked with gastritis, also could be causally linked to other gastritis-associated diseases, such as peptic ulcer and gastric cancer.

Complete analysis of our 100-patient study [3] revealed that (1) 65 percent of patients undergoing endoscopy (mean age, 45 years) had gastritis; (2) there was a strong association between spiral bacteria and gastritis; (3) all patients with duodenal ulcer and 80 percent of those with gastric ulcer had the bacteria; (4) ulcers occurring in the absence of the bacteria were commonly associated with nonsteroidal anti-inflammatory drug ingestion; and (5) the bacteria could be cultured at 37 degrees C using Campylobacter isolation methods and were a new gram-negative genus with features of both Campylobacter and Vibrio bacteria.

In 1983, with colleagues at Fremantle Hospital, I attempted to test various aspects of our hypothesis that were still unsupported by any experimental data. Aware that bismuth had been used to treat ulcers and gastritis for nearly 200 years, I carried out in vitro studies that demonstrated that H pylori and many other spiral organisms (eg, Campylobacter jejuni) were easily killed by bismuth salts. [4] In a search for evidence that H pylori was a pathogen, I used immunofluorescent microscopy to demonstrate presence of antibody in the serum of patients with the bacterium, a finding that led to the development of a passive hemagglutination test. [5] Using serological testing, a prevalence study of H pylori in healthy adults in Australia revealed that 15 percent of those younger than 40 years and 40 percent of those older than 50 years were infected with the organism. [5] Subsequent epidemiological studies certainly made life difficult for those of us who believed H pylori was a pathogen since in many populations it was more normal to have the bacterium than to be free of it.

In clinical studies of patients with gastritis, I found that bismuth cleared H pylori, but the infection relapsed unless metronidazole was added to the regimen. Observation of patients taking H_2 receptor antagonists confirmed that the bacteria always persisted and could therefore be responsible for peptic ulcer relapse that occurred after ceasing H_2 receptor antagonists. In 1983, clinical trials confirmed that gastritis healed when the bacteria disappeared. [6] This was the first therapy ever shown to heal gastritis, although presentation of the data received a cool reception at gastroenterological meetings.

One of the main difficulties with the H pylori theory was our inability to develop an animal model for the disease. After failing to infect rats, mice, and pigs, I decided to infect myself with H pylori to see if chronic

gastritis developed. In July 1984, I drank a pure culture of H pylori (10 [9] organisms). After feeling fine for about 5 days, I experienced early morning nausea and vomiting of acid-free gastric juice. The illness spontaneously resolved after 14 days, but culture and histologic diagnosis on the eighth day demonstrated severe acute gastritis with many H pylori organisms. This experiment allowed me to link epidemic gastritis with hypochlorhydria to H pylori. It is now accepted that the mysterious hypochlorhydric syndrome reported by many authors was actually the acute illness associated with H pylori infection. [7]

In 1984, I received funding for a research grant to study the effect of H pylori eradication on the relapse of peptic ulcer. In 1985, one hundred patients with endoscopically confirmed duodenal ulcer and concurrent H pylori infection were randomized to treatment with cimetidine or one of three antibacterial regimens designed to eradicate H pylori. In that study, ulcers recurred in 90 percent of patients healed with cimetidine. In contrast, when H pylori was eradicated with bismuth plus antibiotic, ulcers recurred in only 21 percent. [8] By the time that article was published in 1988, one other study had shown that relapse of peptic ulcer correlated with persistence of H pylori. By 1989, articles describing "cure of duodenal ulcer" were appearing outside the United States, and in 1991, the first convincing study of the cure within the United States was published. [9]

As success with treatment of duodenal ulcer became known in Western Australia, patients flocked to the endoscopy service at Royal Perth Hospital. Handling larger numbers of patients created difficulty, however. At endoscopy, at least a Gram stain was required to quickly confirm the presence of H pylori. The invention of the rapid urease test in 1984 allowed me to detect H pylori urease in gastric biopsy specimens in a few minutes, without any extra work or special equipment. This test has been available in the United States as the CLOtest (Campylobacter-like organism test) since 1990. [10]

The same year, as more patients were treated for H pylori, it became evident that the endoscopy service was becoming overloaded with patients requiring follow-up diagnostic biopsies to confirm cure of H pylori. The solution to this was found with the development of the rapid carbon 14-labeled urea breath test method, which made it unnecessary to perform endoscopy to confirm cure, [11] and thereby made it possible to embark on large trials of H pylori therapy using only noninvasive diagnosis and follow-up.

H PYLORI 1995: EPIDEMIOLOGY AND DISEASE ASSOCIATIONS

It would have been a simple matter to convince skeptics of the importance of H pylori if the bacterium was

confined to patients with peptic ulcer. However, H pylori is often present in apparently normal persons and, in developing countries, often infects most of the population Figure 1. Whereas persons with H pylori are often asymptomatic, they always have histological changes of chronic gastritis in the gastric mucosa.

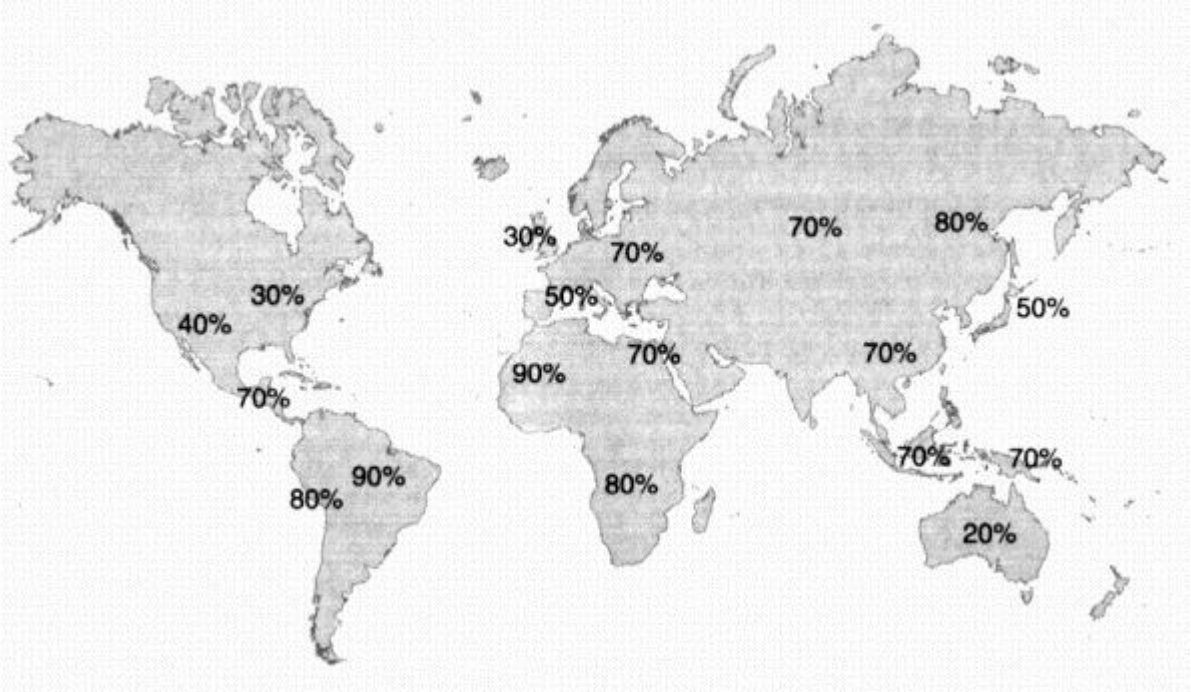

Figure 1. Prevalence of Helicobacter pylori in various countries. [12] Prevalence of H pylori infection correlates with socioeconomic status rather than race. In the United States, probability of being infected is greater for older persons (greater than 50 years, greater than 50 percent), minorities (African Americans, 40 percent to 50 percent), and immigrants from developing countries (Latinos, greater than 60 percent and Eastern Europeans, greater than 50 percent). The infection is less common in more affluent whites younger than 40 years (20 percent).

Although H pylori is more common in older persons, this is due to the fact that the infection is usually acquired in childhood and carried for life. For example, 70-year-old Americans have H pylori that they acquired as children before 1930 when food and water were probably contaminated. Persons born in the United States after 1950 were not exposed to H pylori and have a low prevalence of the infection (20 percent). [12] In Japan, where the standard of living improved remarkably after 1960, persons older than 40 years are usually infected, whereas the prevalence in children younger than 10 years is no more than that seen in the United States.

The fundamental disease association is between H pylori and gastritis Figure 2. The bacterium survives in gastric acid by breaking down urea and generating an alkaline microenvironment for itself. Helicobacter pylori organisms attach only to the mucus-secreting gastric epithelial cells that line the stomach and in this

location occupy a microaerophilic, pH-neutral environment at the junction between the mucosa and the lumen. Technically speaking, H pylori organisms are outside the body and do not invade the tissues. This may be why the bacterium cannot be eradicated by the normal cell-mediated and humoral immune responses.

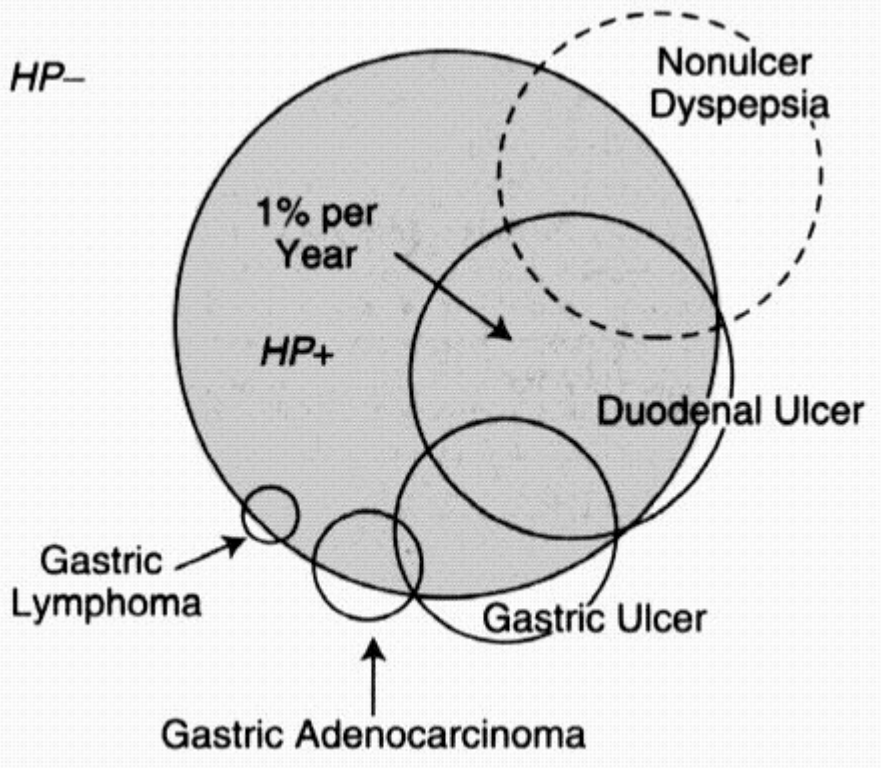

Figure 2. Disease associations with Helicobacter pylori in the United States. The area outside the largest circle represents a population in the United States of uninfected (normal) persons (HP-) within which is a circle representing the 30 percent who are infected (HP+). Persons in the infected group develop duodenal ulcer at the rate of about 1 percent per year, so that approximately one third eventually have peptic ulcer disease. The smaller circles represent diseases associated with H pylori. The dotted circle represents the syndrome nonulcer dyspepsia, a group not yet proven to benefit from antibiotic therapy. Nearly all persons with duodenal ulcer are infected. Conversely, it is unlikely that persons without H pylori will ever develop duodenal ulcer. Gastric ulcer is usually caused by H pylori, but about 30 percent of gastric ulcers in the United States occur in persons without H pylori and can be related to aspirin and other nonsteroidal anti-inflammatory drugs. Most gastric adenocarcinomas and lymphomas occur in persons with current or past infection with H pylori.

Colonization of the mucus cells is associated with the elaboration of various soluble proteins that damage the epithelium and incite an acute (neutrophil) reaction, which is followed, in a few weeks, by a more chronic (lymphocytes, macrophage, and plasma cell) reaction. In acute infection, damage to the parietal cell mucosa is so severe that acid secretion ceases and the patient, after vomiting for a few days, usually becomes asymptomatic since gastric pains are usually related to stomach acid (now absent). After several months, acid secretion may return and the patient may remain in an asymptomatic state, with H pylori and gastritis, for

months, years, or a lifetime.

Peptic ulcer develops in about 1 percent of infected adults per year. [13] The most important factor dictating the development of peptic ulcer appears to be whether the H pylori organism produces soluble cytotoxins that cause vacuolation of the epithelial cells and serve to stimulate the production of interleukin-8 in the mucosa, which in turn leads to more marked attraction of polymorphonuclear leukocytes. Persons who harbor toxin-producing H pylori have, on average, greater numbers of organisms in the mucosa and more acute inflammation. It is likely that peptic ulcer is actually induced by the inflammatory reaction rather than the actual H pylori organism.

Helicobacter pylori also appears to cause the acid hypersecretion seen in patients with duodenal ulcer. Persons with gastritis have diminished numbers of D cells and lower somatostatin levels as a result. Since somatostatin acts locally to suppress antral G-cell gastrin secretion, patients tend to have higher gastrin levels, greater basal acid secretion, and hypertrophy of the gastric corpus (acid-secreting) mucosa. In persons who do not develop peptic ulcer, lifelong H pylori gastritis can lead to intestinal metaplasia (replacement of gastric mucus epithelium with intestinal brush-border and goblet cell-type epithelium). This alteration is usually what is referred to when the term atrophic gastritis was used in older texts. Atrophic gastritis is associated with gastric adenocarcinoma.

Chronic gastritis is often associated with the presence of lymphoid follicles in the lamina propria. In some patients, mucosa-associated lymphoid tissue (MALT) becomes clonal and develops into low-grade lymphoma. When MALT lymphomas are confined to the stomach they are usually associated with H pylori gastritis and can be cured in more than 50 percent of cases by curing the H pylori infection. [14]

TREATMENT OF H PYLORI AND BENEFITS OF ERADICATION

Numerous articles on H pylori treatment exist. [15] Although H pylori is sensitive in vitro to many antibiotics, there is no effective single-antibiotic therapy. All successful treatment regimens require at least one antibiotic (commonly two antibiotics) and either bismuth (eg, Pepto-Bismol) or omeprazole (an acid pump inhibitor). Combinations of H_2 receptor antagonists and antibiotics have generally been less effective than omeprazole-antibiotic combinations. Many of the newest antibiotic regimens have not been fully evaluated in the United States. Currently, there are no drugs or drug combinations in the United States with indications accepted by the Food and Drug Administration for the treatment of H pylori. This may be because clinical

trails of combination therapies are complex and tedious since suitable patients with peptic ulcer are becoming hard to find. A review of therapeutic options was published in 1994. [16]

For patients with peptic ulcer and H pylori as the only risk factor (ie, without nonsteroidal anti-inflammatory drug use), permanent cure of the ulcer occurs in 90 percent. [9] A few patients still require H_2 receptor antagonists or other acid-lowering agents, but this is often because other conditions, such as gastroesophageal acid reflux, are causing the continuation of symptoms.

The current recommendation from the National Institutes of Health Consensus Conference held in February 1994 [15] was that all patients with documented past or present peptic ulcer disease should be investigated and treated for H pylori if the bacterium is detected. Since most ulcer episodes are actually relapses of the chronic condition, this treatment strategy should eliminate 80 percent to 90 percent of H pylori-related peptic ulcer disease in the United States. [15]

Since the cure rate for peptic ulcer disease is so high and the treatment is relatively simple, there is a case to be made for treating all patients with dyspepsia and H pylori as if they had peptic ulcer. Serological or breath test diagnosis is noninvasive, so it may be possible to initially manage these patients with antibiotic therapy rather than having them undergo endoscopy. Currently, this is a controversial topic that will require outcome studies to resolve. Screening asymptomatic persons for H pylori, in an attempt to detect and prevent a gastric cancer risk is not currently recommended in the United States. Exceptions may be siblings of patients with gastric cancer or ethnic groups with a high gastric cancer rate (ie, Japanese). In patients with gastric MALT lymphoma, eradication of H pylori is the primary treatment modality and offers cure to at least 50 percent of patients. [14]

CONCLUSION

Helicobacter pylori infection is now recognized as the major cause of peptic ulcer disease and an important risk factor for gastric malignancy. Early reports of the association between peptic ulcer and H pylori were met with extreme skepticism by physicians convinced that psychic stress, cigarette smoking, and hyperacidity were the main causes of peptic ulcer. Nevertheless, with the advent of bismuth-based triple therapy and omeprazole-based antibiotic therapy, convincing double-blind trials of treatment were completed prompting the National Institutes of Health to recommend antibiotic treatment for H pylori-associated peptic ulcer in 1994. As diagnosis and therapy for H pylori becomes routine in patients with ulcer disease, new controversies

have arisen. For example, should all patients with dyspepsia be screened for H pylori and treated with antibiotics instead of noncurative chronic acid-reducing therapies? Should even healthy people be screened for H pylori and treated in an attempt to prevent future peptic ulcer or gastric cancer? These questions will be the subject of many interesting clinical and basic studies in the coming years.

Dr Marshall is the recipient of the 1995 Albert Lasker Clinical Medical Research Award.

Dr Marshall holds patents related to diagnosis and treatment of Helicobacter pylori and is a shareholder in several companies with similar interests.

Reprint requests to Tri-Med Specialties Inc, 1500 Avon St Ext. Charlottesville, VA 22902 (Dr Marshall).

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Figure 1

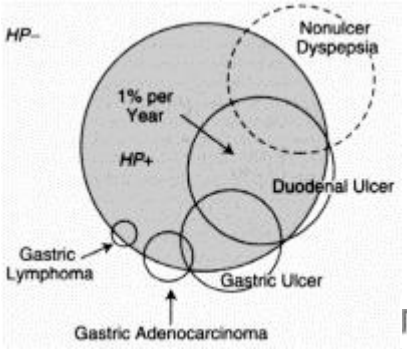

Figure 2

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