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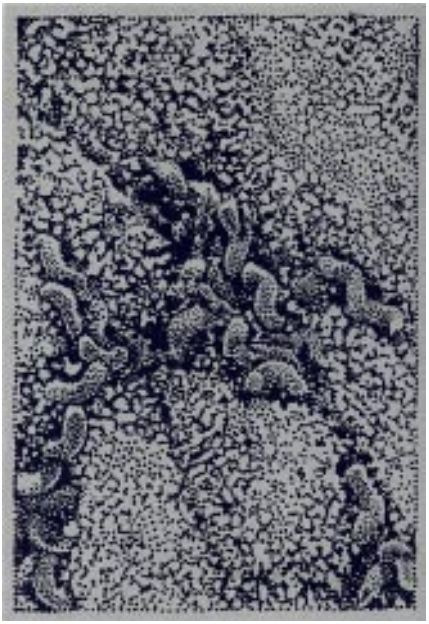

Helicobacter pylori *in Peptic Ulcer Disease*

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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

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Abstract

The National Institutes of Health Consensus Development Conference on *Helicobacter pylori* in Peptic Ulcer Disease brought together specialists in gastroenterology, surgery, infectious diseases, epidemiology, and pathology, as well as the public, to address the following questions: (1) What is the causal relationship of *H. pylori* to upper gastrointestinal disease? (2) How does one diagnose and eradicate *H. pylori* infection? (3) Does eradication of *H. pylori* infection benefit the patient with peptic ulcer disease? (4) What is the relationship between *H. pylori* infection and gastric malignancy? (5) Which *H. pylori*–infected patients should be treated? (6) What are the most important questions that must be addressed by future research in *H. pylori* infections? Following 1½ days of presentations by experts and discussion by the audience, a consensus panel weighed the evidence and prepared their consensus statement.

Among their findings, the consensus panel concluded that: (1) ulcer patients with *H. pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or on recurrence; (2) the value of treating nonulcer dyspepsia patients with *H. pylori* infection remains to be determined; and (3) the interesting relationship between *H. pylori* infection and gastric cancers requires further exploration.

The full text of the consensus panel's statement follows.

Introduction

Peptic ulcer disease is a chronic inflammatory condition of the stomach and duodenum that affects as many as 10 percent of people in the United States at some time in their lives. The disease has relatively low mortality, but it results in substantial human suffering and high economic costs.

In the early 20th century, the pathogenesis of the disorder was believed to be related to stress and dietary factors. Thus, treatment focused on hospitalization with bed rest and prescription of special bland foods. Later the concept arose that peptic ulcer disease was caused by the injurious effects of digestive secretions such as gastric acid; hence, antacids became the standard of therapy. In 1971, Sir James Black identified a subtype of the histamine receptor (H_2 receptor) that appeared to be the principal mediator of gastric acid secretion. Antagonists of this receptor proved to be safe and effective therapy for peptic ulcer disease. More recently, inhibitors of the proton pump (H^+,K^+-ATPase) in gastric parietal cells have proved to be rapidly effective and extremely potent antiulcer drugs. Other drugs that appear to enhance mucosal defense such as bismuth compounds, sucralfate, and prostaglandins have also been applied to the treatment of peptic ulcers. Despite these sophisticated therapeutic agents, the disturbing problem of the high recurrence rate of peptic ulcer, even after complete healing, remains.

In 1982, Warren and Marshall provided the first insight into another important pathogenic factor in peptic ulcer disease. They isolated a spiral urease-producing organism (later identified as *Helicobacter pylori*) nestled in the narrow interface between the gastric epithelial cell surface and the overlying mucus gel. In their early studies, the presence of this organism was shown to be highly correlated with antral gastritis as well as with gastric and duodenal ulcers, and eradication of this organism effectively eliminated ulcer recurrences. Furthermore, a disturbing epidemiologic relationship between *H. pylori* infection and gastric malignancies was reported. Such studies have given rise to

the hypothesis that *H. pylori* is a major etiologic factor in peptic ulcer disease and that diagnosis and eradication of the organism are necessary for optimal therapy of the disorder.

To address these issues, the National Institute of Diabetes and Digestive and Kidney Diseases, together with the Office of Medical Applications of Research of the National Institutes of Health, convened a Consensus Development Conference on *Helicobacter pylori* in Peptic Ulcer Disease. The conference was cosponsored by the National Institute of Allergy and Infectious Diseases. Following a day and a half of presentations by experts in the relevant fields and discussion from the audience, an independent consensus panel composed of specialists and generalists from the medical and other related scientific disciplines, as well as representatives from the public, considered the evidence and formulated a consensus statement in response to the following six previously stated questions:

- What is the causal relationship of *H. pylori* to upper gastrointestinal disease?
- How does one diagnose and eradicate *H. pylori* infection?
- Does eradication of *H. pylori* infection benefit the patient with peptic ulcer disease?
- What is the relationship between *H. pylori* infection and gastric malignancy?
- Which *H. pylori*–infected patients should be treated?
- What are the most important questions that must be addressed by future research in *H. pylori* infections?

What Is the Casual Relationship of *H. pylori* to Upper Gastrointestinal Disease?

A strong association between *H. pylori* and upper gastrointestinal disease has been reported. The causal relationship between *H. pylori* and chronic superficial gastritis is well established. The evidence for this statement is as follows:

1) Virtually all *H. pylori*-positive patients demonstrate antral gastritis.

2) Eradication of *H. pylori* infection results in resolution of gastritis.

3) The lesion of chronic superficial gastritis has been reproduced following intragastric administration of the isolated organism in some animal models and oral administration in two humans.

A causal relationship between *H. pylori* and peptic ulcer disease is more difficult to establish from the available data in part because of the lack of an animal model and because only a small proportion of individuals harboring the organism develop ulceration. However, nearly all patients with duodenal ulcer have *H. pylori* gastritis. Thus infection with the organism may be a prerequisite for the occurrence of almost all duodenal ulcers in the absence of other precipitating factors such as nonsteroidal anti-inflammatory drug (NSAID) use or Zollinger-Ellison syndrome. The association between *H. pylori* infection and gastric ulcer is only slightly less strong, in that 80 percent of patients with non-NSAID-induced gastric ulcers are infected. Nevertheless, it is important to note that the majority of *H. pylori*–infected individuals do not develop duodenal or gastric ulcers. These facts imply that host characteristics, strain variability, or other factors play a role in the pathogenesis of peptic ulcer disease.

The strongest evidence for the pathogenic role of H. *pylori* in peptic ulcer disease is the marked decrease in the recurrence rate of ulcers following the eradication of infection. The prevention of recurrence following *H. pylori* eradication is less well documented for gastric ulcer than for duodenal ulcer, but the available data suggest similar efficacy.

In the case of duodenal ulcer, it is curious that in some studies the organism is more often present in the antrum than in the duodenum, where the ulcer is found. Suggested mechanisms by which an antral organism causes a duodenal lesion include bacterial colonization of gastric metaplasia in the duodenum, secondary changes in gastric acid or duodenal bicarbonate secretion, or changes caused by products of the infecting organism and/or the inflammatory response of the host. Further studies are needed to clarify the mechanisms of bacterial pathogenesis and host responses leading to duodenal ulceration.

To date there is no convincing evidence for an association of *H. pylori* infection with nonulcer dyspepsia. The prevalence of *H. pylori* infection is no higher in patients with nonulcer dyspepsia than in the general population. Although some patients with nonulcer dyspepsia may have symptoms that are related to the presence of *H. pylori*, there are no data to demonstrate how to identify such a subject. Studies are needed to determine whether *H. pylori*–infected patients with nonulcer dyspepsia would benefit from treatment of the infection.

How Does One Diagnose and Eradicate *H. pylori* Infection?

A fundamental principle of specific antimicrobial therapy is accurate diagnosis. Numerous validated methods to diagnose patients with *H. pylori* infection are in use. These methods can be divided into invasive and noninvasive diagnostic tests.

The invasive tests include endoscopy followed by gastric biopsy and histologic demonstration of organisms, biopsy with direct detection of urease activity in the tissue specimen, and biopsy with culture of the *H. pylori* organism. Although culturing the organism is traditionally considered the "gold standard" for diagnosis of many infectious agents, it is the least sensitive diagnostic test (approximately 70–80 percent positivity). Both histologic demonstration of the organism by Giemsa or Warthin-Starry stains and urease testing have sensitivities and specificities above 90 percent.

Excellent diagnostic sensitivities and specificities (>95 percent) are also obtained with noninvasive tests for the initial diagnosis of *H. pylori* infection. These include serology for immunoglobulin G antibodies to *H. pylori* antigens and breath tests of urease activity using orally administered ^{14}C- or ^{13}C-labeled urea. A number of highly accurate serologic kits for diagnosis of *H. pylori* infection are available. Labeled urea breath tests have had restricted availability as research tools in the past, but commercial assays will be available in the near future.

It is important to note that with the exception of the serologic assays all of the tests for diagnosis of *H. pylori* infection may be falsely negative in patients who have taken antibiotics, bismuth compounds, or omeprazole in the recent past.

Presently, there is no readily available, inexpensive, and accurate noninvasive method to monitor eradication of *H. pylori*. Without such an assay, routine monitoring for relapse, reinfection, or treatment failure cannot be recommended. Even if such a test were available, testing all patients treated for *H. pylori* infection probably would

not be necessary in view of the high efficacy of treatment and low reinfection rate. Important exceptions would be patients with complicated, recurrent, or refractory peptic ulcers who should be evaluated for successful eradication of infection before cessation of antiulcer therapy. Antibody levels decrease slowly following successful eradication of *H. pylori* infection. If the same well-standardized assay is used, a dramatic fall in antibody titer 6–12 months following antimicrobial treatment indicates successful eradication. However, variability among serology tests applied in commercial laboratories may limit their usefulness in confirming *H. pylori* eradication. Although breath testing is the best noninvasive assay for evaluating success of eradication, there are unresolved issues of availability, cost, and ease of use in the practical application of this method. Invasive tests can also be used for documenting cure, but these incur the cost and morbidity associated with endoscopy.

Therapy of *H. pylori* poses several unique challenges. The organism resides under a mucus gel layer in the highly acidic milieu of the stomach, where rapid removal of ingested antimicrobials may occur. These and other factors may contribute to the variable correlation between *in vitro* and *in vivo* antimicrobial activity. A problem in selection of a therapeutic regimen has been the lack of a suitable animal model. For these reasons, much of the available information concerning choice of antimicrobial agents is based on small empirical trials in humans. Multiple agents that have been studied in various combinations include metronidazole, tetracycline, amoxicillin, clarithromycin, bismuth compounds, H_2-receptor antagonists, and proton-pump inhibitors. The choice of a particular regimen must be tempered by the rapidly developing data on optimal therapy.

Consideration of the therapeutic options should take into account efficacy, compliance, side effects, and cost. A triple antimicrobial regimen consisting of bismuth subsalicylate, tetracycline, and metronidazole has been studied extensively and can yield eradication rates of approximately 90 percent. Substitution of amoxicillin for tetracycline or

metronidazole lowers efficacy only slightly (greater than 80 percent). One promising study reported efficacy of approximately 90 percent with the combination of ranitidine, metronidazole, and amoxicillin. Although variable, eradication rates of greater than 80 percent have also been reported with the combination of omeprazole (a proton-pump inhibitor) and amoxicillin. Omeprazole should be given at least twice daily, and the two agents begun at the same time because immediate pretreatment with omeprazole lowers efficacy of the omeprazole–amoxicillin combination. Two- or three-drug regimens should last 2 weeks. If therapy is begun at the time of active peptic disease, treatment with antisecretory agents in addition to antimicrobials is recommended. When multiple drugs are administered at various times in the day, patient compliance may become an important factor affecting efficacy. If symptoms persist or recur after initial treatment, diagnostic reevaluation should be undertaken and a second course of therapy considered. Side effects are more frequent with the three-drug regimen than with the two-drug regimen but have been mild in either case and infrequently have prevented completion of therapy. Serious but rare events such as anaphylaxis, Stevens-Johnson syndrome, and pseudomembranous colitis should be expected as antimicrobial regimens are used more widely. Safety and efficacy of antimicrobial therapy in *H. pylori*–infected children and adolescents have not been studied in detail.

Resistance to antimicrobials, in particular to nitroimidazoles such as metronidazole, is an important problem and a cause for treatment failure in some studies. Resistance to metronidazole varies worldwide, with the highest rates (40–50 percent) in underdeveloped countries. Application of currently available one-drug regimens has led to enhanced antimicrobial resistance and thus is strongly discouraged. The widespread application of antimicrobial regimens to treat *H. pylori* infection may magnify the problem of drug resistance. Thus alternative treatment or prevention strategies such as vaccines or immunotherapy may deserve attention in the future.

Does Eradication of *H. pylori* Infection Benefit the Patient With Peptic Ulcer Disease?

Helicobacter pylori infection is strongly associated with the predominant forms of peptic ulcer disease and appears to play an important contributory role in their pathogenesis; thus, it is reasonable to suggest that eradication of *H. pylori* infection may benefit patients with peptic ulcer disease. Although further studies are needed to delineate fully the role of *H. pylori* eradication in many other patient populations, available studies have demonstrated clearly the principal benefit of eradication in patients with peptic ulcers, a substantial reduction in the risk of ulcer recurrence (to less than 10 percent in 1 year). The evidence is more complete for patients with duodenal ulcers than for those with gastric ulcers, although the benefits to the two sets of patients appear to be comparable. The side effects of current regimens for eradication of *H. pylori* infection are generally minor and are outweighed by the benefit of reduced ulcer recurrence. When combined with standard antisecretory therapy, *H. pylori* eradication may contribute to a modest reduction in time to ulcer healing. Moreover, eradication of *H. pylori* infection may enhance healing of ulcers refractory to conventional therapy.

A separate question is whether *H. pylori* eradication prevents future problems in peptic ulcer patients with a history of bleeding or other complications. Although preliminary data indicate such efficacy, more definitive data are needed.

The benefits of eradicating *H. pylori* infection in patients with peptic ulcer disease may vary depending on a variety of factors including those related to the host, the organism, and the environment. Such factors include patient demographics (age, socioeconomic status, concurrent illness, behavioral factors), frequency of reinfection, mode of transmission, and strain variation.

The potential cost savings associated with treating *H. pylori* infection have not been established but may be substantial. Carefully designed economic analyses are needed to assess more completely the cost-effectiveness of *H. pylori* eradication in peptic ulcer disease patients.

What Is the Relationship Between *H. pylori* Infection and Gastric Malignancy?

Adenocarcinoma of the stomach is one of the most common malignancies in the world, although it is relatively uncommon in the United States (24,000 new cases and 14,000 deaths per year). There is evidence that *H. pylori* infection is associated with adenocarcinoma of the body and antrum of the stomach. However, gastric cancer occurs in some individuals with no evidence of *H. pylori* infection, and in the United States, fewer than 1 percent of *H. pylori*–infected individuals will ever develop gastric cancer. The effect of prevention or treatment of *H. pylori* infection on gastric cancer risk has not been studied adequately.

Descriptive epidemiologic data indicate that gastric cancer occurs more frequently in some populations that have higher rates of *H. pylori* infection. Rates of both *H. pylori* infection and gastric cancer correlate inversely with socioeconomic status, increase as a function of age, have declined in successive birth cohorts in developed countries, and occur less commonly in whites than in African Americans and Hispanics in the United States. A geographic correlation has been found between *H. pylori* infection and gastric cancer death rates. However, some clear examples exist of disparity in the epidemiology of the two diseases. Gastric cancer is more common in men than in women, whereas the rates of *H. pylori* infection are not different between the sexes. Some populations are reported to have a high rate of *H. pylori* infection but low rates of gastric cancer. These disparities indicate that factors other than *H. pylori* infection are also important in gastric cancer risk.

Some but not all of the retrospective serologic studies have shown that patients with gastric cancer more frequently have *H. pylori* infection than do controls. The strongest evidence that *H. pylori* infection is associated with gastric cancer comes from three prospective

cohort serologic studies, which indicate that *H. pylori*–infected individuals have a significantly increased rate of gastric cancer. There is no association in any of these studies between *H. pylori* infection and cancer in the gastric cardia and gastroesophageal junction, which is increasing in incidence in the United States.

Non-Hodgkin's lymphoma of the stomach is a rare disorder that accounts for only 3 percent of gastric malignancies. Mucosa-associated lymphoid tissue (MALT) lymphomas, which constitute a subset of non-Hodgkin's lymphoma, are low-grade clonal neoplasms that are thought to arise from lymphoid aggregates in the lamina propria. Preliminary epidemiologic data suggest that *H. pylori* infection is associated with both non-Hodgkin's lymphoma and MALT lymphomas of the stomach. Further study of the relationship between *H. pylori* infection and gastric lymphomas is warranted.

In summary, if there is any causal relationship between *H. pylori* infection and gastric cancer, clearly other factors are also important in gastric carcinogenesis. *H. pylori* eradication for the purpose of preventing gastric cancer cannot be recommended at this time.

Which *H. pylori*–Infected Patients Should Be Treated?

There are ample data to support the antimicrobial eradication of *H. pylori* infection in patients with peptic ulcer disease. All patients with gastric or duodenal ulcers who are infected with *H. pylori* should be treated with antimicrobials regardless of whether they are suffering from the initial presentation of the disease or from a recurrence. *H. pylori*–infected peptic ulcer patients who are receiving maintenance treatment with antisecretory agents or who have a history of complicated or refractory disease should also be treated for the infection. The presence of NSAID's, including aspirin, as a contributing factor should not alter the antimicrobial regimen, but whenever possible, these drugs should be discontinued. However, in asymptomatic *H. pylori*–infected patients without ulcers, the data are not sufficient to support prophylactic antimicrobial therapy to prevent ulcer disease in the future or to reduce the likelihood of developing gastric neoplasia. Also, no convincing data exist to support routine treatment of patients with nonulcer dyspepsia who are infected with *H. pylori*. Thus, at the present time there is no reason to consider routine detection or treatment of *H. pylori* infection in the absence of ulcers. Carefully controlled prospective studies are needed to assess the benefits of treating nonulcer dyspepsia patients with *H. pylori* infection. It is self-evident that no patient should be treated for *H. pylori* unless one of the sensitive and specific tests previously discussed demonstrates infection.

Bleeding is the complication of peptic ulcer disease associated with the highest mortality rate and, therefore, demands aggressive therapy. The available data suggest that after these ulcers heal, the likelihood of recurrence with bleeding is significantly reduced by maintenance antisecretory therapy. Preliminary studies indicate that eradication of *H. pylori* infection may be equally efficient in preventing the recurrence of ulcer bleeding. Until these studies can

be confirmed, maintenance antisecretory therapy may be prudent in such patients even after *H. pylori* eradication in view of the high risks associated with rebleeding.

Guidelines for the routine antimicrobial treatment of *H. pylori* infection

Patient status	*H. pylori* negative	*H. pylori* positive
Asymptomatic (no ulcer)	No	No
Nonulcer dyspepsia	No	No
Gastric ulcer	No	Yes
Duodenal ulcer	No	Yes

What Are the Most Important Questions That Must Be Addressed by Future Research in *H. pylori* Infections?

Although much is known about the role of H*. pylori* in gastrointestinal disease, many issues are still unresolved.

Further well-designed studies on the role of *H. pylori* eradication in the management of peptic ulcer disease are needed, particularly in populations not well studied to date, including children, patients with gastric ulcers, and patients with duodenal or gastric ulcers with complications. These studies should utilize standard definitions, be randomized, be analyzed on an intent-to-treat basis, have sample size adequate to detect clinically meaningful differences between treatment arms, and be double-blind whenever possible.

Fundamental questions remain concerning the initial evaluation of a patient who presents with dyspepsia. Should that patient be tested for *H. pylori* infection? Should that patient be treated empirically for *H. pylori* infection if it is present? The answers to these questions depend in part on whether antimicrobial therapy relieves symptoms in some or all symptomatic patients with *H. pylori* infection and gastritis but without ulcers. If the answer is yes, patients presenting to the physician with dyspepsia should be tested for *H. pylori* infection and, if the results are positive, be treated with antimicrobial therapy. However, if symptomatic *H. pylori*–infected patients without ulcers do not respond to antimicrobial therapy, it will continue to be imperative to confirm the diagnosis of peptic ulcer disease in order to identify the patients who will benefit from treatment of their infection. Under these circumstances, the question arises as to whether it is necessary, appropriate, and cost-effective to perform endoscopy in dyspeptic patients at initial presentation.

Another major question that remains to be answered is whether eradication of *H. pylori* infection prevents gastric cancer. Such a question cannot be answered directly without a long and costly study. Thus, an alternative approach might be to conduct studies looking at intermediate endpoints that are thought to predict the evolution of malignancy and their response to *H. pylori* eradication. Epidemiologic studies are also needed to define more precisely the subset of *H. pylori*–infected individuals who will develop gastric cancer.

A major opportunity for additional studies is in the area of mechanisms by which *H. pylori* infection leads to gastrointestinal disease. Virulence factors, bacterial genetics, mechanisms of immunity, animal models, antibiotic resistance, and modes of transmission are all issues that should be examined in future studies. Furthermore, the natural history of *H. pylori* infections and the nature of the host-organism interaction require further study. The pathogenic consequences of *H. pylori* infection in childhood and adolescence and the optimal management of infection are additional important questions. More information is needed on the value of testing to confirm eradication after antimicrobial therapy, and antimicrobial regimens need to be optimized to improve treatment efficacy. A comprehensive economic analysis should be conducted to examine the cost-effectiveness of treating *H. pylori* infection.

Conclusion

The discovery of *H. pylori* as a gastrointestinal pathogen has had a profound effect on current concepts of peptic ulcer disease pathogenesis. Evidence presented at this Consensus Development Conference has led to the following conclusions:

- Ulcer patients with *H. pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs whether on first presentation with the illness or on recurrence.
- The value of treatment of nonulcer dyspepsia patients with *H. pylori* infection remains to be determined.
- The interesting relationship between *H. pylori* infection and gastric cancers requires further exploration.

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