The Role of *Helicobacter pylori* in Acid-Peptic Disease

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ABSTRACT: Acid peptic disease is common, and its management is costly. Less than a decade ago, the traditional theories regarding the etiology and pathogenesis of acid peptic disease were upset by the discovery of *Helicobacter pylori* infection in association with chronic active gastritis. A substantial body of investigation after that discovery has established this infection as the major cause of human chronic active gastritis and has defined a critical role for *H. pylori* in the etiology, pathophysiology, and treatment of duodenal ulcer disease. Furthermore, evidence is accumulating to link *H. pylori* to gastric ulcers, nonulcer dyspepsia, and even gastric carcinoma. Research has clarified some unique features of the organism that have been put to advantage in the development of diagnostic tests, and it has also clarified some features of the infection that make it difficult to treat. Although treatment is decidedly beneficial for certain patient subsets, simpler and more effective therapy is needed.
KEY INDEXING TERMS: Helicobacter pylori; History; Pathophysiology; Gastritis; Duodenal ulcer; Gastric ulcer; Non-ulcer dyspepsia; Gastric carcinoma; Diagnosis; Therapy. [Am J Med Sci 1993;306(6):381–392.]

The ubiquitous and recurrent nature of the peptic diseases make their long-term management expensive. The prevalence of peptic ulcer disease (gastric and duodenal ulcer disease) is approximately 4 million cases in the United States, with an incidence of about 350,000 new cases per year.[1] The National Center for Health Statistics reports that about 1.2 million patients required hospitalization in 1990 for peptic disease. Total health care and other costs (eg, time lost from work) of peptic disease was more than $3.2 billion, according to a 1975 estimate.[2]

The pathophysiology of peptic disease can be viewed as an imbalance between mucosal aggressive and mucosal defensive factors. Historically, the major aggressive factor underlying peptic disease has been touted to be gastric acid,[3] although more recently the contribution of peptic enzyme activity has been acknowledged as indispensable to the ulcerogenic potential of acid.[4] Gastric acid hypersecretion, which, in the extreme, accompanies such conditions as Zollinger-Ellison syndrome, can overwhelm the body's defensive mechanisms and produce unremitting ulcer disease. However, only about one third of patients with duodenal ulcer, and virtually none with gastric ulcer, secrete any excess gastric acid at all.[5] Furthermore, Zollinger-Ellison syndrome is associated with less than 0.1% of duodenal ulcers.[6] The balance of peptic ulcer disease is thought to result from a weakening of mucosal defense, involving various alterations in bicarbonate secretion, mucosal blood flow, prostaglandin synthesis, mucus properties, or epithelial cell turnover. Cigarette smoking, alcohol use, and nonsteroidal antiinflammatory agents (NSAIAs) are thought to impair defenses and increase susceptibility to gastric acid as a consequence of such alterations.[5]

Until recently, the treatment of peptic ulcer disease has focused on reestablishing mucosal balance through inhibition of acid (antacids, histamine-receptor antagonists, or proton-pump inhibitors) and cytoprotection (coating of ulcerated tissue or prostaglandin analogs).[7] The avoidance of smoking, alcohol, and NSAIAS during the acute healing phase of a peptic ulcer generally has been considered desirable. However, although these various therapies are effective in providing symptom relief and promoting healing of the peptic diseases, these conditions tend to recur frequently.[8]

The discovery of *Helicobacter pylori* in 1982 and the subsequent extensive research that has accompanied this discovery has upset some traditional theories and shed new light on the pathophysiology and treatment of the peptic diseases.

Historical Perspective

Almost a century ago, spiral bacteria were described in the stomachs of animals[9–11] and, later, of humans.[12]

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Further refinement of these early observations was hampered by a lack of advanced laboratory methods. Coincidentally, however, the first half of this century witnessed an awareness and investigation of gastric urease activity (not then realized to be of bacterial origin) present in animals[13] and in most human surgical stomach specimens, the majority of which had been resected for peptic ulcer disease.[14] It was even found that antibiotic therapy could abolish gastric urease activity.[15,16]

However, a series of mid-century investigations diminished the significance of gastric bacteria and helped establish the traditional notion of the stomach as a sterile site. A postmortem study confirmed a high prevalence of gastric bacteria (43%), but without significant histopathologic changes.[17] A study of fresh surgical specimens also found a high prevalence of gastric bacteria (37%), but only in the necrotic tissues surrounding a lesion. The investigators concluded that the presence of bacteria was merely a secondary infestation.[18] The coup de grace was delivered by one large study of 1,180 gastric suction biopsy specimens from individuals with different upper-gastrointestinal conditions. No evidence of any bacterial infection was found in the specimens.[19] It is now recognized that this study was flawed, particularly by obtaining specimens from the proximal stomach, where *H. pylori* is least prevalent, and by the failure to apply special staining techniques required to reliably identify the organisms. Nonetheless, it was several decades before the issue of gastric bacteria was reexamined.

The availability of fiberoptic endoscopy during the 1970s led to the "rediscovery" of gastric bacteria. Histopathologists receiving endoscopically guided gastric mucosal biopsies from patients with gastroduodenal pathology noticed the presence of gram-negative spiral bacteria in association with acute inflammatory changes.[20–22] The presence of these organisms was thought to be more consistent with infection than with contamination, for several reasons. These reasons included finding the bacteria consistently located upon the surface of the gastric epithelium beneath the mucus layer, finding bacteria often phagocytized by neutrophils, and preparing the biopsies with immediate tissue fixation, which minimizes contamination. An association was made between the presence of the organisms and active chronic gastritis.[23,24] The organism was finally isolated in culture in 1982 by Dr. Barry Marshall at the Royal Perth Hospital in Perth, West Australia.[22] Marshall later went on to fulfill Koch's postulates for the role of *H. pylori* in antral gastritis during a self administration experiment, which has been confirmed and repeated by others.[25–27]

Pathogenic Features of *Helicobacter Pylori*

General. Initially classified as a species of Campylobacter, a number of genomic, biochemical, and morphologic dissimilarities led to the bacteria's reclassification as *H. pylori* in 1989.[28] This spiral-shaped gram-negative bacterium possesses a number of features that not only permit survival in the harsh gastric environment but also can result in tissue injury. A summary list of these putative virulence features is presented in Table 1.

The gastric microenvironment presents a formidable challenge to bacterial colonization. Constantly bathed and protected by a flowing mucus layer, the gastric epithelium is not readily exposed to the luminal contents. Powerful gastric peristaltic waves do not permit the prolonged stasis of any potential invaders. The routine secretion of hydrochloric acid, generating a gastric juice pH level of 1 to 2, is perhaps the most discouraging hurdle for the potential pathogen. *H. pylori* has evolved uniquely to overcome these obstacles; the success of this organism is implicit in its widespread prevalence. Although varying with age and ethnicity, the prevalence of *H. pylori* among adults is about 20% to 40% in Western nations and 60% to 80% in Third World countries.[29]

Motility. Most strains of the bacteria possess 4 to 6 unipolar sheathed flagella, each with a bulbous tip.[30] These contribute significantly to the motility of the organism, which can penetrate viscous solutions such as the gastric mucus layer.[31] Motility has been confirmed as a virulence factor in an animal model. Highly motile strains proved to be 100% infective compared with nonmotile (aflagellate) strains, which infected only 17% of the animals.[32] Some degree of motility is also conferred by virtue of the organism's spiral morphology.[31,33]

Adhesion. *H. pylori* has a selective affinity for gastric epithelium. When closely apposed to gastric epithelial microvilli, the bacterial polysaccharide glycocalyx is capable of fusing with gastric epithelial polysaccharide structures to form an adherence pedestal.[31,34,35] Although the organism can be demonstrated deep within the gastric pits and glands, *H. pylori* is only rarely seen to invade the gastric mucosa, except as has been described in the setting of acquired immunodeficiency syndrome.[36] Within the stomach, the organism has a predilection for the antrum, but it has been reported colonizing heterotopic gastric mucosa in the proximal esophagus,[37,38] the rectum,[39] and even in Meckel's diverticulum.[40,41] Most important, however, has been the demonstration of *H. pylori* colonization of gastric metaplasia in the duodenal bulb,[42] even in association

Table 1. Putative Virulence Factors of Helicobacter Pylori

Motility in viscous solution
Selective adherence for gastric epithelium
Urease
Catalase
Mucolytic enzymes
Toxins
Immunologic escape

with duodenitis.[43] Gastric metaplasia of the duodenal bulb is a common condition thought to correlate with acid exposure; it has been described as a condition sine qua non for duodenal ulcer occurrence.[44]

Urease and Other Enzymes. One key to *H. pylori*'s survival in an acid milieu may lie in the organism's powerful urease activity. Urease is a surface-bound enzyme that cleaves urea to form ammonia; therefore, the microenvironment surrounding *H. pylori* is rendered relatively alkaline. This permits survival at a pH level as low as 1.5 in the presence of physiologic concentrations of urea.[45] Urease may fulfill more than one function, however; the other product of urea hydrolysis is carbon dioxide (CO_2), a required carbon source for heterotrophic bacteria.[46] Furthermore, urease is thought to augment the damaging effects of acid on the gastric mucosa.[47–49]

In fact, *H. pylori* elaborates a host of enzymes that may be of pathologic significance. Catalase, for one, has long been secondary to urease in the *H. pylori* literature. Catalase acts to protect against the damaging effects of oxygen metabolites, especially hydrogen peroxide (H_2O_2). This effect is thought to be important to some bacteria as a means of resistance to destruction by neutrophils,[50–52] a source of exogenous H_2O_2. Data suggests not only that *H. pylori* possesses a relatively high catalase activity, but also that this catalase is not inhibited by high concentrations of H_2O_2,[53] a feature also present in mycobacteria.[54]

Furthermore, *H. pylori* appears resistant to high concentrations of exogenous H_2O_2.[53] Moreover, catalase-negative phenotypes of *H. pylori* are not found in vivo. The occasional in vitro spontaneous mutation of *H. pylori* to a catalase-negative phenotype has not been shown to affect growth characteristics, suggesting that the enzyme is not required by *H. pylori* in the metabolism of endogenous H_2O_2.[55] These features suggest that the catalase activity of this organism is not required for intrinsic bacterial metabolism, but rather may be required in its adaptation to the environment of inflamed gastric mucosa. Even so, the precise role for catalase is not entirely clear. Although neutrophils have been demonstrated to phagocytize *H. pylori*,[56] these leucocytes typically do not migrate into the gastric lumen. Although some H_2O_2 may be secreted extracellularly to leucocytes, it is uncertain whether this can clearly justify the catalase activity of *H. pylori*.

H. pylori also produces proteases, lipases, and phospholipases, which are presumably capable of degrading mucus. In fact, infection has been shown to lead to a depletion of the surface mucus layer.[57–59] Weakening of this mucosal defense factor will result in the increased back diffusion of hydrogen ions with consequent tissue injury.

Toxins. Several enteric pathogens have been recognized as producing cytotoxins thought to play a role in their virulence. These include *Shigella* species, enterohemorrhagic *E. coli*, *Clostridium difficile*, and *Campylobacter jejuni*.[60] *H. pylori* possesses at least two distinct cytotoxins. The first is a cytolethal toxin produced in reasonably high titers by more than half of *H. pylori* clinical isolates.[60] The second is a vacuolating cytotoxin produced in slightly less than half of the isolates.[61,62] Yet, this second toxin has been found in up to 67% of *H. pylori* isolated from patients with peptic ulcer disease, as compared with only 30% ($p < 0.01$) of strains from patients with asymptomatic gastritis.[63]

Immunologic Features. Several aspects of the immune response to *H. pylori* infection have been described, although their precise significance is not yet well understood.

The acidity of the gastric lumen and the flowing mucus barrier have been the more recognized nonspecific gastric defense factors, but other factors have been described as well. Lysozyme (a bacteriolytic enzyme) and lactoferrin (an iron-binding glycoprotein) have been demonstrated to be present in increased concentration in inflamed gastric mucosa as compared with normal mucosa.[64] The origin of these luminal factors is debated, with evidence pointing to both gastric epithelium and granulocytes. It is presently not clear what interactions, if any, these factors have with *H. pylori*.

Clearly, both systemic and local immune responses occur. Specific local immune responses can be thought of in terms of humoral and cell-mediated responses. Studies on the local gastric humoral response to *H. pylori* reveal the presence of immunoglobulin A (predominantly) as well as immunoglobulin M in the gastric juice of 30% of patients with *H. pylori* gastritis.[65] These antibodies are specific for *H. pylori*, and are not found in healthy control patients. Organ culture studies using gastric and duodenal tissue have shown that these antibodies are produced by plasma cells within the mucosa.[66] These antibodies can be shown to coat the surface of *H. pylori*,[67] but do not result in clearance of the infection. Although *H. pylori* have been shown in vitro to be sensitive to an antibody-dependent complement-mediated bactericidal activity of serum from infected patients, this does not occur in vivo.[68] Immunoglobulin A does not activate complement, and the very presence of complement at the epithelial surface is currently uncertain. Immunoperoxidase studies have shown that *H. pylori* present in the depths of the gastric pits remain uncoated with immunoglobulins, as opposed to surface organisms, despite the presence of immunoglobulin A in these pits and the reliability of the immunoperoxidase assay in staining specific *H. pylori* antigens in these pits.[69]

The characteristic local cell-mediated immune response has been the presence of intra-epithelial neutrophils, which define active chronic gastritis in *H. pylori* infection.[67] As discussed previously, phagocytosis of *H. pylori* by neutrophils has been shown,[56] although the leucocytes are rarely present in the gastric lumen. Neutrophils can be shown to remit after the *H. pylori* has been treated, which supports the notion that the

neutrophil response is focused on the presence of the organism, rather than the organism colonizing previously inflamed mucosa.[70] Macrophages are also increased in active chronic gastritis, and *H. pylori* has been shown to stimulate them to produce inflammatory mediators.[71] There have been conflicting data regarding the lymphocyte response, with increases reported for the suppressor-cell subset by some[72] and for the helper-cell subset by others.[73] Of final consideration in the cell-mediated immune response, it is of interest that inflamed gastric mucosal cells have been reported to become human leukocyte antigen DR-positive, enabling these cells to be capable, theoretically, of antigen sampling and presentation.[74,72]

The systemic humoral response, predominantly immunoglobulin G- based (immunoglobulin G1 and immunoglobulin G2 account for almost the entire immunoglobulin G response), does not appear to play a role in vivo in the course of *H. pylori* infection.[75] However, serology serves as a useful diagnostic tool in screening and population studies, as antibody levels remain elevated in untreated individuals.[76,77]

The mechanisms by which *H. pylori* escapes destruction from the immunologic responses remain unclear. It is likely, however, that these escape mechanisms lead to mucosal damage by permitting persistent mucosal inflammation. However, there is another facet to this concept of misdirected damage; there is some evidence to support the existence of an antibody raised against *H. pylori* that will cross-react with the mucosa, and this has been shown to be a strain-specific phenomenon.[78]

Helicobacter Pylori and Upper Gastrointestinal Disease

Gastritis. *H. pylori* is now considered the major cause of active chronic antral gastritis. The organism is recoverable in the vast majority of cases of antral inflammation characterized by mononuclear cell and neutrophilic infiltration.[79,80] Furthermore, epidemics of *H. pylori*-associated gastritis have occurred secondary to upper gastrointestinal instrumentation;[81,82,27] human volunteer studies have indicated a cause-effect relationship;[25,26] studies have shown that antimicrobial eradication of *H. pylori* infection leads to healing of histologic abnormalities;[83,70] and both natural[84] and experimental[85,86] animal models of chronic gastritis exist. However, it should be noted that the organism plays no role in the gastritis associated with autoimmunity,[87,88] post gastrectomy bile reflux,[89,90] Crohn's disease, or Menetrier's disease.[91] The role of *H. pylori* in nonsteroidal anti-inflammatory drug gastropathy remains controversial. It should also be noted that gastritis is a histologic description that is not uniformly associated with symptoms. Therefore, many patients with *H. pylori* are clinically asymptomatic.

Duodenal Ulcer. Although the revelation that an infection is the etiologic agent of antral gastritis was unexpected, the magnitude of confirmatory scientific evidence, especially the fulfillment of the revered Koch's postulates, led to an eventual acceptance of this point, even by the most skeptical opponents. However, battle was truly joined over the idea that *H. pylori* could be the etiologic agent of peptic ulcer disease. Much of the controversy lies in the inherent difficulty of proving causal associations in chronic disease.

Originally, when the rudimentary principles of infectious diseases were being established, Koch's[92] postulates were welcomed as a guide to establishing an agent as the etiology of a disease. These postulates state that the infectious agent: 1) must be found in patients with the disease only; 2) must be grown outside the body; 3) must reproduce the same disease when inoculated into a susceptible animal; and 4) must be grown from the lesions observed. *H. pylori* does not fulfill these criteria with respect to peptic ulcer disease, as there is a well-defined asymptomatic carrier state, and no animal model of *H. pylori*-induced peptic ulcer yet exists. These points are frequently misapplied as arguments against the clinical relevance of *H. pylori* infection. However, many infectious diseases could not meet these criteria; cholera and meningococcal disease are two such examples of acute bacterial infections with chronic asymptomatic carrier states. Also, many infectious diseases lack animal models.

Recognizing that the concept of disease causality needs to embrace not only infectious diseases but also other diseases, Bradford Hill[93] proposed several criteria in 1965 to overcome the limitations of Koch's postulates. These well-accepted criteria were initially applied to prove the causal association between smoking and lung cancer. These include the characteristics of association (strength, consistency, specificity), temporal relationship, biologic gradient, biologic plausibility, effect of an intervention, and coherence of the data with what is known about the disease.

Applying these criteria to *H. pylori* as an etiologic agent in duodenal ulcer disease, we find the evidence to be compelling. Many series of patients with duodenal ulcers, on every continent, have found the prevalence of infection to be between 90% and 100%.[94] This establishes the strength and the consistency of the association. Although the temporal sequence of *H. pylori* infection leading to duodenal ulcer has not been prospectively assessed, there are data to support a temporal association. One large study of 454 patients who had been endoscoped and biopsied 10 years earlier showed that chronic gastritis was the major risk factor for the development of peptic ulcer: 34 out of 321 patients with chronic gastritis developed peptic ulcer during follow-up, compared with 1 out of 133 patients without chronic gastritis.[95]

The effect of interventions, or the capacity to alter the natural history of a disease, is a strong argument for causation. In the case of *Helicobacter pylori,* antibiotic therapy heals duodenal ulcers at the same rate

itidine was decreased (13%) when compared with the recurrence after healing with ranitidine alone (95%, $p < 0.01$).[119]

Non-ulcer Dyspepsia. Non-ulcer dyspepsia describes chronic symptoms referable to the upper gastrointestinal system without identifiable organic disease.[120] Clinical studies on this entity are notoriously difficult, largely because of problems in defining a consistent population and in following objective measures of disease. The population prevalence of vague dyspeptic complaints is estimated at 20% to 30%.[121] The prevalence of *H. pylori* infection within this group is generally between 40% and 70%.[121] Several studies have attempted to assess whether *H. pylori* eradication leads to symptomatic improvement among patients with non-ulcer dyspepsia, with variable results.[122] However, this issue may become clearer in the future as we become more precise in defining which dyspeptic symptoms may be referable to *H. pylori* infection. For example, investigators are now starting to classify non-ulcer dyspepsia according to whether the patient predominantly has complaints of reflux (chest pain, dysphagia, and heartburn), dysmotility (nausea, satiety, belching, bloating, distention, and intermittently altered bowel habits), or epigastric pain (burning, gnawing, and aching). One recent investigation found that epigastric pain was significantly associated with *H. pylori* infection, whereas dysmotility symptoms were significantly associated with delayed gastric emptying and a lack of *H. pylori* infection.[123]

Gastric Carcinoma. Although the prevalence of gastric carcinoma is falling in the United States, it remains the world's second most common cancer.[124] As alluded to when gastric ulcer was discussed previously, *H. pylori* infection is thought to result in atrophic gastritis, an established precursor of the intestinal type of gastric carcinoma.[116,117] Two studies have now shown that *H. pylori* infection is a strong risk factor for the development of gastric adenocarcinoma.[125,126] This information needs to be placed in the proper context. The vast majority of individuals infected with *H. pylori* will not develop gastric cancer. However, of all those infected, some will go on to develop a fertile substrate (atrophic gastritis), upon which other environmental or genetic carcinogenic factors may operate. Even with this qualification, there is discussion regarding the efficiency of screening high-risk groups for the treatment of *H. pylori* infection. Although now just speculation, it is a worthy ideal to consider that someday an effective approach to the eradication of this infection may lead to a significant reduction in the prevalence of gastric cancer.

Diagnosis

Culture of the organism from the antral mucosa is certainly the standard against which other tests should be validated, but the process is tedious and dependent upon the techniques and sophistication of the lab. At this time, a gastric biopsy for culture is most appropriately reserved for the evaluation of *H. pylori* treatment failures, to test for antimicrobial sensitivity.

The test of choice at the initial endoscopy is a rapid urease test, such as the commercially available Campylobacter-Like—Organism test (CLOtest^R, Delta West Pty Ltd, Western Australia). A pinch biopsy from the antrum is placed into a well containing urea, phenol red, and a bacteriostatic agent. If *H. pylori* is present, its powerful urease enzyme will cleave the urea to form ammonia, producing a color change in the phenol red from yellow to red. A biopsy for histologic examination can be a useful confirmatory test. However, histology adds to the expense of the procedure, and it is not strictly required in the clinical setting. The CLOtest^R is presently the gold standard biopsy urease test, with a sensitivity of 90% to 98%, and a specificity of 98% to 100%.[127–130] Histology has a sensitivity of 80% to 95% and a specificity of 99%.[94]

Breath testing has the advantage of being noninvasive and less expensive than diagnostic methods dependent on endoscopy. During a breath test for *H. pylori,* the patient ingests a capsule of labeled urea (either ^{14}C-urea or ^{13}C-urea). If *H. pylori* is present, its urease activity will hydrolyze the labeled urea to release ammonia and labeled CO_2, which can be collected and measured in the exhaled breath. The ^{14}C-urea breath test only takes 20 minutes to perform, and is likely to be widely available soon. However, it is limited to nonpregnant adults because of its radioactivity. The ^{13}C-urea breath test is nonradioactive but takes longer to perform. Although breath testing is an effective way to demonstrate an active *H. pylori* infection and document bacterial eradication after treatment, it is limited as an initial diagnostic tool because it cannot provide an assessment of gastroduodenal pathology.

Serologic testing has received a great deal of attention because of its potential to be the most widely available, simplest, and least expensive diagnostic test. Serologic assays with an enzyme-linked immunosorbent assay detect an immunoglobulin G antibody against an outer membrane protein of *H. pylori.* Although serology is a useful tool for epidemiologic studies, it presently has a limited clinical applicability. A positive test may only indicate an infection at some point in the recent past, and by no means does a positive serology indicate the presence of an upper gastrointestinal lesion that merits investigation or an infection that merits therapy. This test is of limited use in following the results of therapy, because it will take months to years for a positive titer to fall after successful eradication of the infection.[130] Table 3 highlights the clinical use of the diagnostic tests.

Therapy

As with any infectious disease, the haphazard and indiscriminate use of antibiotics in the treatment of *H. pylori* is to be condemned. The treatment of asymp-

Table 3. Application of Diagnostic Tests for *Helicobacter Pylori*

Test	Application
CLOtest	Biopsy done at endoscopy; useful initial diagnostic study.
Histology	Done at endoscopy; useful complement to the CLOtest.
Culture	Done at follow-up endoscopy; reserved for evaluation of treatment failures, to test antibiotic sensitivities.
Breath test (^{14}C or ^{13}C)	Useful to document eradication of infection post-therapy.
Serology	Useful for epidemiologic studies; falling titers can be used to document eradication of infection post-therapy.

tomatic infected individuals is not recommended. For patients with upper gastrointestinal symptoms, it is only recommended to treat *H. pylori* infection in the presence of duodenal ulcer disease that is a significant management problem requiring either continuous medication or consideration of surgery, or after bleeding or perforation have occurred.[131] This recommendation has not yet been revised to incorporate the new data with respect to *H. pylori*-positive gastric ulcers. For now, the treatment of *H. pylori* in the setting of gastric ulcer or nonulcer dyspepsia should be reserved for research studies and referral centers. Spouses and other close family members of an infected patient do not need to be tested or treated, as it has been our experience that reinfection of the patient is the exception rather than the rule, with an apparent reinfection rate at the University of Virginia of about 3% at 1 year.[132] Symptomatic spouses will usually request treatment, and should be appropriately investigated for their complaints. These recommendations are summarized in Table 4.

H. pylori presents some unique obstacles to antibiotic therapy. First, the organism largely inhabits the surface of the gastric epithelium beneath and within the mucus layer, but often it can be found deep within the lumen of gastric glands and pits. This would suggest, as has been borne out, that agents with primarily luminal or topical activity will usually fail to eradicate the organism (when given as monotherapy), although temporary suppression is easily achieved. In fact, suppression of the infection can be so thorough that true eradication (or "cure") is operationally defined by a negative diagnostic test for *H. pylori* not earlier than 1 month after the completion of therapy.[131]

In our experience, even 3 to 4 doses of an effective antibiotic will render a breath test negative for up to 2 weeks. Agents with only topical activity against *H. pylori* include the bismuth compounds (bismuth subsalicylate—"Pepto Bismol" [Proctor and Gamble, Cincinnati, OH]; bismuth subcitrate—"DeNol" [Gist Brocades, Delpht, Holland]). A few antibiotics are active within the gastric lumen, although they may also be absorbed and secreted across mucosa. These include amoxicillin/ampicillin, tetracycline, metronidazole, and, if accompanied by acid suppression, erythromycin and clarithromycin. Although an argument can be generated over which route of activity is more important, it should be noted that oral consumption of any one of these agents—as monotherapy—can render a breath test negative without having completely eradicated the infection. Presumably, the antibiotics will topically deplete that population of *H. pylori* that would have been most readily available to hydrolyze the labeled urea ingested during the breath test.

Second, the gastric environment is hostile for many antibiotics that are not acid stable. Third, *H. pylori* has a propensity for rapidly acquiring resistance to several classes of antibiotics after exposure to the agent as monotherapy. These include the flouroquinolones (ofloxacin, ciprofloxacin, and norfloxacin); the nitroimidazoles (metronidazole and tinidazole); the macrolides (erythromycin and clindamycin); and rifampin.[131] These last two points may explain the failure of several systemically active antibiotics to achieve in vivo eradication of *H. pylori* when it is clear the agent is not only effective in vitro but is also capable of achieving high concentrations in the gastric mucosa.[133] Resistance has not yet been shown by the organism for the beta-lactams, the bismuth salts, and tetracycline.

It is of historical interest that Sir William Osler himself may have been among the first physicians to treat *H. pylori* infections. He sometimes offered bismuth subnitrate lozenges for acute and chronic gastritis.[134] Unfortunately, effective monotherapy for *H. pylori* does not yet exist. A variety of antibiotics have been tested in vivo, based on the organism's susceptibility in vitro. Only a few (bismuth, tetracycline, metronidazole, amoxicillin, and ofloxacin) were capable of achieving any response, and the eradication rates for these monotherapies were between 5% and 27%.[131]

Table 4. When to Treat *Helicobacter pylori*

Disease	*H. pylori* Treatment?
Gastritis	Not recommended, except in research settings.
Uncomplicated duodenal ulcer (no bleed/perforation, good response to H2-blocker).	Not required, but relapse rate can be dramatically lowered after *H. pylori* eradicated.
Complicated duodenal ulcer	Recommended. (Status post bleed/perforation, excessive H-2 blocker requirement, surgical therapy contemplated).
Gastric ulcer	Not yet recommended, except in research settings.
Non-ulcer dyspepsia	Not recommended, except in research settings.

as histamine-receptor antagonists,[96–99] and long-term ulcer recurrence rates are much lower when the organism is eradicated (0% to 25% at 1 year) than when the organism persists (75% at 1 year).[100–103]

The biologic plausibility of the association is another strong point favoring *H. pylori* as an etiologic agent of duodenal ulcer. As discussed above, there are many pathogenic mechanisms that have evolved to uniquely suit this organism to survival in the gastroduodenal environment and to injury of the gastroduodenal epithelium. These include motility in viscous solution, survival at a low pH level, strong and specific adherence to gastric epithelium, escape from the immune system, weakening of the mucus layer, and toxin-stimulated epithelial damage.

It should be noted that there has not been an extensive study of these virulence factors with respect to assessing a biologic gradient in asymptomatic subjects versus patients with duodenal ulcers. However, there clearly are differences in the proportions of virulent *H. pylori* strains between patients with asymptomatic gastritis and patients with duodenal ulcers, as exemplified by our previous discussion on vacuolating cytotoxin. The emergence of *H. pylori* as an etiologic candidate for duodenal ulcers does not threaten the coherence of all the previous data that have been accumulated on ulcer disease. Rather, it serves to enhance the concept of ulcer disease resulting from an imbalance in mucosal aggressive and defensive factors, with the organism contributing to both enhanced aggressive and weakened defensive elements. It is clearly consistent to embrace *H. pylori* as an etiologic cofactor in duodenal ulcer disease without contradicting the existence of duodenal ulcers due to NSAIAs or the healing of ulcers based on acid suppression alone. A summary of the chief evidence favoring *H. pylori* as an etiologic agent of duodenal ulcer disease is presented in Table 2.

The few remaining opponents of the infectious theory of duodenal ulcer disease have largely highlighted the lack of specificity of *H. pylori* for duodenal ulcers. The organism is found in patients with gastric ulcer, non-ulcer dyspepsia, and antral gastritis. As pointed out by MeGraud and Lamouliatte,[44] this lack of specificity is not uncommon in infectious diseases, and is best exemplified by the model of meningococcal disease, which affects many as asymptomatic carriers, a few with pharyngitis, and even fewer with meningitis. Differences in virulence with meningococcal disease are due to strain differences, which may be analagous to the differences in virulence with different *H. pylori* strains, as discussed previously.

Gastric Ulcer. The role of *H. pylori* in the formation of gastric ulcers has been less clear. This is due, in part, to the prominence of NSAIAs in the etiology of many gastric ulcers. There has not been a consensus among studies as to whether *H. pylori* infection confers an added risk for nonsteroidal anti-inflammatory drug-induced gastric ulcers.[104–109] Another confounding factor is that the pathophysiology of gastric ulcers not related to NSAIAs is still poorly understood. We will confine our remarks to gastric ulcers not related to nonsteroidal anti-inflammatory drug use.

Table 2. Evidence Favoring Helicobacter Pylori as an Etiologic Agent of Duodenal Ulcer

The prevalence of *Helicobacter pylori* in duodenal ulcers is 90%–100%.
Approximately 11% of cases of chronic gastritis will go on to develop peptic ulceration over 10 years.
Antibiotic therapy heals duodenal ulcers at the same rate as histamine-receptor antagonists.
Long-term duodenal ulcer recurrence rates are much lower after *Helicobacter pylori* has been eradicated.
Virulence factors lend biologic plausibility to the hypothesis.

H. pylori is found in only about 80% of all patients with gastric ulcers, whereas almost all gastric ulcers occur in the setting of chronic gastritis.[110] Furthermore, this gastritis tends to be a pan-gastritis, involving gastric corpus as well as antrum.[111] It appears that glandular atrophy and intestinal metaplasia are consistent findings in this setting, with their degree and extent increasing with age.[112] The atrophy appears to commence in the antrum and progress along the lesser curvature into the corpus mucosa,[113] with the border of intestinal metaplasia advancing proximally with age. Gastric ulcers are generally found in the boundary between gastric corpus mucosa and intestinal metaplasia,[114] and it follows that there is a known association between increasing age and more proximally situated ulcers.[115] The advancing atrophic gastritis is responsible for a gradual reduction in the acid-producing mucosa, resulting in the classic hypochlorhydria of patients with gastric ulcers. Atrophic gastritis has also been found to be a substrate for potential gastric carcinomas.[116,117]

The strength of the association between *H. pylori* and gastric ulcer is weaker than that for duodenal ulcer. However, it is now suspected that this probably is a consequence of atrophic gastritis providing a hostile environment for *H. pylori*,[87] thereby hindering the recovery of the organism from patients with gastric ulcers. A leading theory has been that atrophic gastritis is an end result of untreated *H. pylori*-active chronic antral gastritis, in a manner likened to a "burn-out" of the infection. Recently, an important contribution toward elucidating the role of *H. pylori* in gastric ulcer has been made by demonstrating that the eradication of this organism alters the natural history of the disease. Specifically, the eradication of *H. pylori* has been shown to increase the rate of initial healing of *H. pylori*-positive gastric ulcer (92% healed at 12 weeks when eradication was successful versus 72% healed at 12 weeks when eradication failed, $p < 0.05$);[118] and the recurrence within 1 year of *H. pylori*-positive gastric ulcers after healing with eradicative therapy and ran-

itidine was decreased (13%) when compared with the recurrence after healing with ranitidine alone (95%, $p < 0.01$).[119]

Non-ulcer Dyspepsia. Non-ulcer dyspepsia describes chronic symptoms referable to the upper gastrointestinal system without identifiable organic disease.[120] Clinical studies on this entity are notoriously difficult, largely because of problems in defining a consistent population and in following objective measures of disease. The population prevalence of vague dyspeptic complaints is estimated at 20% to 30%.[121] The prevalence of *H. pylori* infection within this group is generally between 40% and 70%.[121] Several studies have attempted to assess whether *H. pylori* eradication leads to symptomatic improvement among patients with non-ulcer dyspepsia, with variable results.[122] However, this issue may become clearer in the future as we become more precise in defining which dyspeptic symptoms may be referable to *H. pylori* infection. For example, investigators are now starting to classify non-ulcer dyspepsia according to whether the patient predominantly has complaints of reflux (chest pain, dysphagia, and heartburn), dysmotility (nausea, satiety, belching, bloating, distention, and intermittently altered bowel habits), or epigastric pain (burning, gnawing, and aching). One recent investigation found that epigastric pain was significantly associated with *H. pylori* infection, whereas dysmotility symptoms were significantly associated with delayed gastric emptying and a lack of *H. pylori* infection.[123]

Gastric Carcinoma. Although the prevalence of gastric carcinoma is falling in the United States, it remains the world's second most common cancer.[124] As alluded to when gastric ulcer was discussed previously, *H. pylori* infection is thought to result in atrophic gastritis, an established precursor of the intestinal type of gastric carcinoma.[116,117] Two studies have now shown that *H. pylori* infection is a strong risk factor for the development of gastric adenocarcinoma.[125,126] This information needs to be placed in the proper context. The vast majority of individuals infected with *H. pylori* will not develop gastric cancer. However, of all those infected, some will go on to develop a fertile substrate (atrophic gastritis), upon which other environmental or genetic carcinogenic factors may operate. Even with this qualification, there is discussion regarding the efficiency of screening high-risk groups for the treatment of *H. pylori* infection. Although now just speculation, it is a worthy ideal to consider that someday an effective approach to the eradication of this infection may lead to a significant reduction in the prevalence of gastric cancer.

Diagnosis

Culture of the organism from the antral mucosa is certainly the standard against which other tests should be validated, but the process is tedious and dependent upon the techniques and sophistication of the lab. At this time, a gastric biopsy for culture is most appropriately reserved for the evaluation of *H. pylori* treatment failures, to test for antimicrobial sensitivity.

The test of choice at the initial endoscopy is a rapid urease test, such as the commercially available Campylobacter-Like—Organism test (CLOtest^R, Delta West Pty Ltd, Western Australia). A pinch biopsy from the antrum is placed into a well containing urea, phenol red, and a bacteriostatic agent. If *H. pylori* is present, its powerful urease enzyme will cleave the urea to form ammonia, producing a color change in the phenol red from yellow to red. A biopsy for histologic examination can be a useful confirmatory test. However, histology adds to the expense of the procedure, and it is not strictly required in the clinical setting. The CLOtest^R is presently the gold standard biopsy urease test, with a sensitivity of 90% to 98%, and a specificity of 98% to 100%.[127–130] Histology has a sensitivity of 80% to 95% and a specificity of 99%.[94]

Breath testing has the advantage of being noninvasive and less expensive than diagnostic methods dependent on endoscopy. During a breath test for *H. pylori,* the patient ingests a capsule of labeled urea (either ^{14}C-urea or ^{13}C-urea). If *H. pylori* is present, its urease activity will hydrolyze the labeled urea to release ammonia and labeled CO_2, which can be collected and measured in the exhaled breath. The ^{14}C-urea breath test only takes 20 minutes to perform, and is likely to be widely available soon. However, it is limited to nonpregnant adults because of its radioactivity. The ^{13}C-urea breath test is nonradioactive but takes longer to perform. Although breath testing is an effective way to demonstrate an active *H. pylori* infection and document bacterial eradication after treatment, it is limited as an initial diagnostic tool because it cannot provide an assessment of gastroduodenal pathology.

Serologic testing has received a great deal of attention because of its potential to be the most widely available, simplest, and least expensive diagnostic test. Serologic assays with an enzyme-linked immunosorbent assay detect an immunoglobulin G antibody against an outer membrane protein of *H. pylori.* Although serology is a useful tool for epidemiologic studies, it presently has a limited clinical applicability. A positive test may only indicate an infection at some point in the recent past, and by no means does a positive serology indicate the presence of an upper gastrointestinal lesion that merits investigation or an infection that merits therapy. This test is of limited use in following the results of therapy, because it will take months to years for a positive titer to fall after successful eradication of the infection.[130] Table 3 highlights the clinical use of the diagnostic tests.

Therapy

As with any infectious disease, the haphazard and indiscriminate use of antibiotics in the treatment of *H. pylori* is to be condemned. The treatment of asymp-

Table 3. Application of Diagnostic Tests for *Helicobacter Pylori*

Test	Application
CLOtest	Biopsy done at endoscopy; useful initial diagnostic study.
Histology	Done at endoscopy; useful complement to the CLOtest.
Culture	Done at follow-up endoscopy; reserved for evaluation of treatment failures, to test antibiotic sensitivities.
Breath test (^{14}C or ^{13}C)	Useful to document eradication of infection post-therapy.
Serology	Useful for epidemiologic studies; falling titers can be used to document eradication of infection post-therapy.

tomatic infected individuals is not recommended. For patients with upper gastrointestinal symptoms, it is only recommended to treat *H. pylori* infection in the presence of duodenal ulcer disease that is a significant management problem requiring either continuous medication or consideration of surgery, or after bleeding or perforation have occurred.[131] This recommendation has not yet been revised to incorporate the new data with respect to *H. pylori*-positive gastric ulcers. For now, the treatment of *H. pylori* in the setting of gastric ulcer or nonulcer dyspepsia should be reserved for research studies and referral centers. Spouses and other close family members of an infected patient do not need to be tested or treated, as it has been our experience that reinfection of the patient is the exception rather than the rule, with an apparent reinfection rate at the University of Virginia of about 3% at 1 year.[132] Symptomatic spouses will usually request treatment, and should be appropriately investigated for their complaints. These recommendations are summarized in Table 4.

H. pylori presents some unique obstacles to antibiotic therapy. First, the organism largely inhabits the surface of the gastric epithelium beneath and within the mucus layer, but often it can be found deep within the lumen of gastric glands and pits. This would suggest, as has been borne out, that agents with primarily luminal or topical activity will usually fail to eradicate the organism (when given as monotherapy), although temporary suppression is easily achieved. In fact, suppression of the infection can be so thorough that true eradication (or "cure") is operationally defined by a negative diagnostic test for *H. pylori* not earlier than 1 month after the completion of therapy.[131]

In our experience, even 3 to 4 doses of an effective antibiotic will render a breath test negative for up to 2 weeks. Agents with only topical activity against *H. pylori* include the bismuth compounds (bismuth subsalicylate—"Pepto Bismol" [Proctor and Gamble, Cincinnati, OH]; bismuth subcitrate—"DeNol" [Gist Brocades, Delpht, Holland]). A few antibiotics are active within the gastric lumen, although they may also be absorbed and secreted across mucosa. These include amoxicillin/ampicillin, tetracycline, metronidazole, and, if accompanied by acid suppression, erythromycin and clarithromycin. Although an argument can be generated over which route of activity is more important, it should be noted that oral consumption of any one of these agents—as monotherapy—can render a breath test negative without having completely eradicated the infection. Presumably, the antibiotics will topically deplete that population of *H. pylori* that would have been most readily available to hydrolyze the labeled urea ingested during the breath test.

Second, the gastric environment is hostile for many antibiotics that are not acid stable. Third, *H. pylori* has a propensity for rapidly acquiring resistance to several classes of antibiotics after exposure to the agent as monotherapy. These include the flouroquinolones (ofloxacin, ciprofloxacin, and norfloxacin); the nitroimidazoles (metronidazole and tinidazole); the macrolides (erythromycin and clindamycin); and rifampin.[131] These last two points may explain the failure of several systemically active antibiotics to achieve in vivo eradication of *H. pylori* when it is clear the agent is not only effective in vitro but is also capable of achieving high concentrations in the gastric mucosa.[133] Resistance has not yet been shown by the organism for the beta-lactams, the bismuth salts, and tetracycline.

It is of historical interest that Sir William Osler himself may have been among the first physicians to treat *H. pylori* infections. He sometimes offered bismuth subnitrate lozenges for acute and chronic gastritis.[134] Unfortunately, effective monotherapy for *H. pylori* does not yet exist. A variety of antibiotics have been tested in vivo, based on the organism's susceptibility in vitro. Only a few (bismuth, tetracycline, metronidazole, amoxicillin, and ofloxacin) were capable of achieving any response, and the eradication rates for these monotherapies were between 5% and 27%.[131]

Table 4. When to Treat *Helicobacter pylori*

Disease	*H. pylori* Treatment?
Gastritis	Not recommended, except in research settings.
Uncomplicated duodenal ulcer (no bleed/perforation, good response to H2-blocker).	Not required, but relapse rate can be dramatically lowered after *H. pylori* eradicated.
Complicated duodenal ulcer	Recommended. (Status post bleed/perforation, excessive H-2 blocker requirement, surgical therapy contemplated).
Gastric ulcer	Not yet recommended, except in research settings.
Non-ulcer dyspepsia	Not recommended, except in research settings.

Table 5. Triple Therapy and Some Alternatives

Standard therapy		
"Pepto Bismol"	2 tab q.i.d.	day 1–14
Metronidazole	250 mg q.i.d.	day 1–14
Tetracycline	500 mg q.i.d.	day 1–14
Modified standard (If intolerant of tetracycline)		
"Pepto Bismol"	2 tab q.i.d.	day 1–14
Metronidazole	250 mg q.i.d.	day 1–14
Amoxicillin	500 mg t.i.d.	day 1–14
Second-line therapy (for metronidazole-resistant strains)		
"Pepto Bismol"	2 tab q.i.d.	day 1–14
Tetracycline	500 mg q.i.d.	day 1–14
Erythromycin base	500 mg q.i.d.	day 1–14
Omeprazole	40 mg q.d.	day 1–14
Second-line therapy (if intolerant of all of above)		
Amoxicillin	500 mg q.i.d.	day 1–14
Omeprazole	40 mg b.i.d.	day 1–14
	or	
Clarithromycin	500 mg t.i.d.	day 1–14
Omeprazole	40 mg q.d.	day 1–14

Dual antibiotic therapies are generally more effective but are still only modestly successful, with eradication rates between 30% and 60%.[131] These rates seem to reflect an additive effect of the monotherapies. There is one notable exception; bismuth combined with metronidazole achieves an eradication rate of 75% in unselected patients, suggesting a synergism that so far has been noted only between these two agents.[131] The eradication rate is better than 90% with this combination in patients with metronidazole-sensitive *H. pylori,* but falls to 13% in those with metronidazole-resistant strains.[135,136] In developed countries, about 75% of *H. pylori* isolates are metronidazole-sensitive.[137] However, in many Third World countries, where common parasitic infections are treated with metronidazole, sensitive isolates are in the minority.[138] The clinical use of metronidazole-sensitivity testing before the first attempt of eradicative *H. pylori* therapy has not been fully evaluated.

However, there are other forms of dual therapy which do not strictly involve two antibiotics. The combination of high-dose omeprazole (40 mg to 80 mg daily) with amoxicillin has been reported recently to achieve an 82% eradication rate, and it appears to be a well-tolerated though not inexpensive therapy.[139] The combination of high-dose omeprazole with clarithromycin (a new, acid-stable macrolide) has recently been shown to result in an 80% eradication rate.[140]

The officially recommended therapy for *H. pylori* infection is commonly referred to as "triple therapy". This originally consisted of a 2-week course of bismuth subsalicylate (one tablet four times daily), tetracycline (500 mg four times daily), and metronidazole (500 mg three times daily).[131] Most studies in the Western literature that have examined the effect of *H. pylori* eradication on the natural history of peptic ulcer disease have used this triple therapy with slight modifications, often in combination with an H2-blocker. The modifications on standard triple therapy involve doubling the bismuth dose to two tablets four times daily and reducing the metronidazole dose to 250 mg four times daily. The eradication rate with triple therapy is between 80% and 90%. Failure of therapy has been reported to correlate most closely with patient compliance, with eradication rates of 96% in patients who took more than 60% of the prescribed therapy compared with 69% in patients who took less.[141]

Amoxicillin (500 mg four times daily) may be substituted for tetracycline in patients allergic to tetracycline, without compromising efficacy. It is our practice at the University of Virginia to use erythromycin base combined with an acid-suppressing medication as a substitute for metronidazole in triple therapy, used only as a second-line therapy in cases of known metronidazole resistance. This has resulted in a cure rate of 70%.[132] Erythromycin base appears to be more ef-

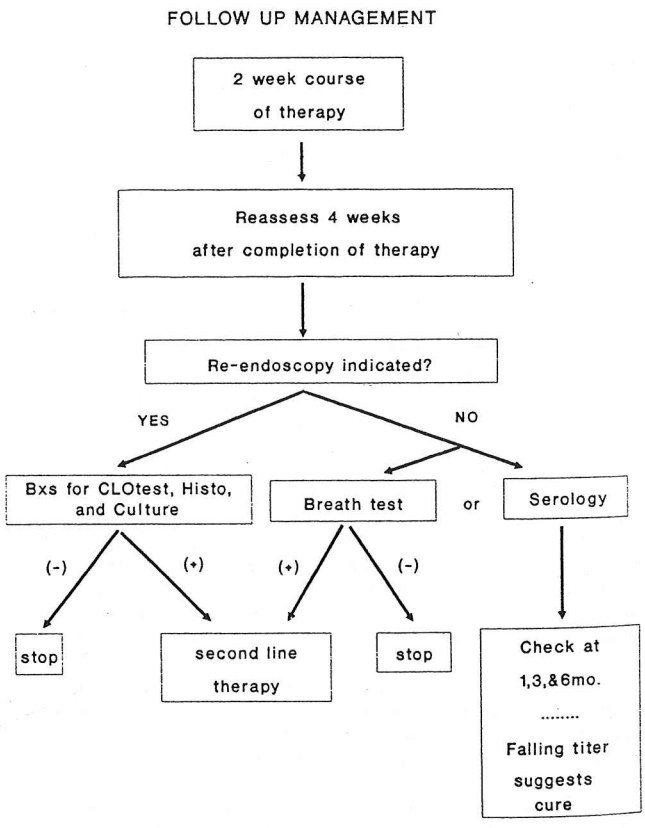

Figure 1. Flow chart for the assessment and management of patients after therapy for *Helicobacter pylori* infection. Adapted with permission from Marshall.[132]

fective than the acid stable erythromycin pro-drugs, erythromycin stearate, and erythromycin ethylsuccinate. Clarithromycin has shown promise to be as least as efficacious as erythromycin base. Table 5 reviews standard triple therapy and some alternative therapeutic regimens.

Many patients are intolerant of the side effects of multiple antibiotic therapy, which in general include malaise, nausea, diarrhea, sore mouth, and fungal infections. In particular, each antibiotic has its own profile of side effects. Bismuth is perhaps the most benign medication, often causing only darkened stools. Excessive bismuth ingestion in a patient with poor renal function has been rarely reported to lead to toxic bismuth levels, with reversible encephalopathy as a consequence.[142] Metronidazole may cause a metallic taste, may have a disulfiram-like effect, and should be avoided in pregnancy. Penicillin allergy and pseudomembranous colitis may complicate therapy with amoxicillin, although it is our experience that pseudomembranous colitis is not seen when the patient is receiving cotherapy with metronidazole.

Eradication of the infection must be documented after therapy. The success of *H. pylori* eradication is established 1 month after the completion of therapy. At that time, if a repeat endoscopy is indicated, biopsies for a CLOtest, histology, and culture can be obtained. Antimicrobial sensitivities can be tested against a positive culture. If a repeat endoscopy is not clinically indicated, a breath test can be checked. If the breath test is not available, serology can be checked at 1, 3, and 6 months post-therapy. A falling titer is evidence of cure. If retreatment is necessary but antimicrobial sensitivities are not available, metronidazole resistance should be presumed if the initial therapy included metronidazole. Figure 1 outlines a management scheme for the clinical follow-up of *H. pylori* therapy.

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