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Peptic Ulcer and *Helicobacter Pylori*

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Since the seminal reports in 1983 of Warren and Marshall^[43] describing the presence of *Helicobacter pylori* on gastric mucosa, overwhelming evidence of the link between *H. pylori* and peptic ulcer disease (PUD) has accumulated. This article reviews some of this evidence, but also focuses on emerging concepts and current uncertainties about this relationship.

EVIDENCE IN SUPPORT OF A CAUSATIVE RELATIONSHIP BETWEEN *HELICOBACTER PYLORI* AND PEPTIC ULCER DISEASE

Four lines of evidence support a central role for *H. pylori* and PUD: (1) the natural history of *H. pylori* infection, (2) epidemiologic data, (3) outcomes after cure of *H. pylori* infection in patients with PUD, and (4) the frequent development of gastric ulcers in *H. pylori*-infected Mongolian gerbils. With so much circumstantial evidence and with Koch's postulates arguably fulfilled for a direct link between *H. pylori* and gastric ulceration, the combined weight of all evidence leads to the unequivocal conclusion that PUD is an infectious disease. That PUD also occurs as a result of other factors and in the absence of *H. pylori* infection should not be misinterpreted as casting doubt on the causative link between *H. pylori* and most cases of PUD.

Natural History of Helicobacter pylori Infection

Koch's postulates have been fulfilled with regard to the relationship between *H. pylori* infection and *gastritis*--histologic gastric mucosal inflammation (chronic active gastritis and chronic superficial gastritis--see elsewhere in this issue for a complete review). The converse is true: Histologic inflammation of the stomach is associated with simultaneous histologic detection of *H. pylori* infection in more than 90% of cases (provided that there has been no ingestion of agents suppressing *H. pylori* infection). If reliance is placed on anti-*H. pylori* antibody testing, virtually 100% of patients with gastritis (as defined earlier) have evidence for *H. pylori* infection. Gastritis may be used as a surrogate marker for *H. pylori* infection.

The association between gastritis and PUD has long been recognized. Follow-up over approximately a decade of asymptomatic Northern European subjects with gastritis without known PUD revealed that 11% developed ulcers compared with less than 1% without gastritis.^[34]

In some population groups, primarily from developed countries, PUD may occur in individuals with gastritis and infected with *H. pylori* at the rate of 1% per year.

In other groups, for example, among some African populations, despite a high prevalence of *H. pylori* infection, the incidence of PUD appears to be much lower than in Western countries. *H. pylori* is neither sufficient nor necessary for the development of PUD because in most patients, PUD does not occur in association with this infection, and there are other causes of PUD, especially aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), which cause PUD in the absence of *H. pylori* infection. This fact does not negate the causative relationship between *H. pylori* and PUD in that subset of individuals who, perhaps because of an underlying genetic predisposition, are destined to develop PUD.

Epidemiologic Data Supporting a Causative Link Between Helicobacter pylori and Peptic Ulcer Disease

There is an increased risk for the development of PUD in association with *H. pylori* infection based not only on the natural history data previously outlined, but also on other supportive data. In the United States, the odds ratio for the association between *H. pylori* and PUD is 3.4 (95% confidence interval, 1.8 to 6.3).^[27] There is a consistent worldwide age-independent association of *H. pylori* and PUD. Ninety percent of patients with duodenal ulcers and 70% to 90% of patients with gastric ulcers are infected with *H. pylori*.

Effect of Treatment and Cure of Helicobacter pylori Infection in Peptic Ulcer Disease

The most important evidence supporting a causative relationship between PUD and *H. pylori* is that cure of *H. pylori* infection alters the natural history of PUD (Fig. 1) (Figure Not Available). The recurrence rate of PUD after cure of *H. pylori* infection is less than 10%,^{[8] [14] [41]}

compared with a recurrence rate of approximately 70% in patients in whom the ulcers were healed by acid-suppressive therapy alone. Compared with acid-suppressive therapy alone, concurrent treatment of *H. pylori* infection in the presence of an ulcer crater may shorten the time to healing of the ulcer.^{[12] [15]}

Figure 1. (Figure Not Available) Cure of *Helicobacter pylori* infection radically alters the natural history of PUD. $P < 0.001$. (From Hentschel E, Brandstatter G, Dragosics B, et al: Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 328:308-312, 1993; Copyright © 1993 Massachusetts Medical Society. All rights reserved.)

The importance of *H. pylori* infection in PUD is reinforced further by observations in smokers. As compared with nonsmokers, smokers have about a twofold increase in the risk for developing PUD. There is a direct relationship between the amount of smoking and ulcer incidence. After cure of *H. pylori* infection in patients with PUD, however, smoking no longer appears to be a risk factor for recurrent ulcers.^[2]

Koch's Postulates Fulfilled for Helicobacter pylori in Gastric Ulcer and Gastric Cancer

The pioneering work of Okabe et al^[28] in rat models of peptic ulcer led to the development of *H. pylori*-infected gerbils reported by Hirayama et al^[12A] and Takahashi et al.^[37] Infection with the type strain of *H. pylori* resulted in gastric erosions and ulcers.^[37] In a more recent experiment using their TN2GF4 strain of *H. pylori* (which was motile and urease, catalase, and oxidase positive and produced vacuolating cytotoxin and contained the cytotoxin-associated gene [cagA]), Watanabe et al^[44]

saw ulcers develop in about half of the infected animals after 6 months. Gastric cancers developed in 37% after 14 months. Koch's postulates have been fulfilled substantially for gastric ulcer and gastric adenocarcinoma.

EVIDENCE THAT THE EPIDEMIOLOGIC ASSOCIATIONS BETWEEN PEPTIC ULCER DISEASE AND HELICOBACTER PYLORI ARE CHANGING

Some studies have suggested a prevalence of *H. pylori* infection in association with duodenal ulcer that is lower than the previously indicated value of approximately 90%. Less than 80% of patients with duodenal ulcers were found to be infected with *H. pylori* in one United States multicenter study.^[29] A low prevalence of *H. pylori* infection among Australians with PUD also has been reported.^[46] Laine et al^[22] have reviewed the impact of *H. pylori* therapy on duodenal ulcer recurrence in seven "rigorously designed trials." In contrast to data referred to earlier, despite successful cure of *H. pylori* and denial of NSAID use, recurrence of duodenal ulcers at 6 months occurred in 20% of patients. This situation suggests that *H. pylori* infection was not the cause of some of the ulcers. This suggestion may be explained partly by the occurrence of peptic ulcers among population groups with a high background prevalence (>80%) of *H. pylori* infection: Peptic ulcer may be attributed mistakenly to such infection. The attributable risk for *H. pylori* infection for PUD (the proportion of peptic ulcers resulting from *H. pylori* infection) also decreases as the prevalence of *H. pylori* infection declines in a population.^[18] Although the absolute number of peptic ulcers declines with a decline in the prevalence of *H. pylori* infection, inasmuch as *H. pylori* is the most common cause of ulcer disease, this smaller number of patients with PUD has a relatively low prevalence of *H. pylori* infection. The proportion of ulcers unrelated to *H. pylori* approaches 100% as the prevalence of *H. pylori* approaches 0.

COMPLICATED PEPTIC ULCERS

The previously reviewed data refer to uncomplicated PUD. In contrast, much data regarding bleeding ulcers and perforated ulcers are confusing. One reason for uncertainty is that some *H. pylori* diagnostic tests found to be reliable in uncomplicated ulcer disease may be falsely negative, especially in the setting of bleeding ulcers.

In 1996, Lai et al^[20] were the first to report that biopsy urease tests may be falsely negative in the setting of ulcer bleeding. Although most of their patients had a positive serologic test for *H. pylori*; only approximately 60% of patients had a positive biopsy urease test (type unspecified). Other studies have reinforced this concept. In the most detailed of these reports, Tu et al^[38] compared a biopsy urease test with other endoscopic and nonendoscopic tests for *H. pylori* infection in patients who presented with bleeding ulcers and who were not taking NSAIDs. The gold standard for the diagnosis of *H. pylori* was a positive culture; positive histology using hematoxylin and eosin stain; or a combination of any two tests consisting of a rapid urease test (CLOtest, Ballard Medical Products, Draper, UT),^[13] C-urea breath test (UBT), and a serologic test. Although they studied patients with bleeding (coffee grounds or melena) ulcers, only 22 of 77 patients had evidence of blood in the antrum at the time of endoscopy. The sensitivities of the tests were not significantly different (using a two-tailed test), however, between those with and without blood in the stomach.^[21]

Culture results had poor sensitivity, but this likely reflects their technique. The CLOtest had a sensitivity of only 64%. Histology also was insensitive (73%), but because they obtained only one prepyloric sample and did not use a special stain (e.g., Giemsa or Genta), it is difficult to interpret their stain results, which may reflect sampling or observer error rather than an absence of *H. pylori* infection. The UBT was 95% sensitive, and serology was 97% sensitive. Although the results regarding the rapid urease test are in accordance with other studies (published only as abstracts but reviewed in detail by Laine and Cohen^[21]), they are puzzling. The UBT was performed *within 1 day* of the endoscopic tests and was sensitive, suggesting that urease production was not impaired, or if it was, impairment was short lived. One might have thought that, if anything, blood would cause more false-positive rapid urease biopsy tests by raising the pH of the biopsy site and specimen. In other studies,^[23] however, soaking gastric biopsy specimens in heterologous blood in vitro had no influence on rapid urease testing. Further studies are needed to explore the mechanisms that might be responsible for decreasing the sensitivity of biopsy-based tests in the setting of bleeding ulcers.

Only approximately 70% of patients with bleeding duodenal ulcers are infected with *H. pylori*.^[16] ^[17] The prevalence of NSAID use could not be incriminated as an explanation for the low prevalence of *H. pylori* infection, although surreptitious NSAID use cannot be excluded. The tests used to diagnose *H. pylori* infection in these reports leave much to be desired. Accepting the diagnostic test results at their face value, however, the absence of *H. pylori* infection and lack of NSAID use in association with about 30% of bleeding ulcers might be explained by a more virulent ulcer diathesis in those who are *H. pylori* negative.

Because diagnosis of *H. pylori* may be less accurate in complicated PUD, and because detection of *H. pylori* affects management, it is important to exclude *H. pylori*

in these patients absolutely. A rapid urease test is a useful immediate test at the initial endoscopy, but negative results should prompt additional testing, such as serology. This topic is discussed further under testing for *H. pylori*.

Patients with bleeding ulcers who are infected with *H. pylori* should undergo appropriate anti-*H. pylori* therapy. Cure of *H. pylori* infection reduces to a similar extent as that of maintenance antisecretory therapy the risk of recurrence of a bleeding ulcer,^[3] reinforcing the important interrelationship between *H. pylori* and ulcer disease, even in the setting of complications. Confirmation of cure of *H. pylori* infection is essential in this setting, however.

In one study,^[31] the prevalence of *H. pylori* infection in patients with perforated ulcers was found to be approximately 50%. In other studies of perforated ulcers,^[25] ^[33] the prevalence rates of *H. pylori* were found to be higher (83% to 89%) and similar to those reported in patients with uncomplicated ulcers. This finding may have important implications for the management of such patients. Full-blown ulcer surgery may not be the best option for most patients with perforated ulcers because anti-*H. pylori* therapy probably would be effective in preventing ulcer recurrence.

PATHOGENESIS OF *HELICOBACTER PYLORI*-ASSOCIATED PEPTIC ULCER DISEASE

The factors responsible for the development of PUD and the mechanisms by which *H. pylori* contributes to the ulcer diathesis have not been elucidated fully; however, genetic (host) and environmental cofactors participate in the process leading to ulceration. Gastric and duodenal ulcer models are depicted in Figures 2 (Figure Not Available) and 3 (Figure Not Available) .

Figure 2.

(Figure Not Available) Model of gastric ulcer disease. More severe gastritis permits ulceration even in the presence of relatively low acid secretion. Hp = *Helicobacter pylori*; DU = duodenal ulcer. (From Dooley CP: *Helicobacter pylori* and duodenal ulcer. In Marshall BJ, McCallum RW, Guerrant RL (eds): *Helicobacter pylori* in peptic ulceration and gastritis. Cambridge, Blackwell Scientific Publications, 1991; with permission.)

Figure 3.

(Figure Not Available) Model of duodenal ulcer disease. Acid secretion normal or high. Ulcer occurs in area of most severe histologic damage, that is, duodenal, pyloric or prepyloric. Hp = *Helicobacter pylori*. (From Dooley CP: *Helicobacter pylori* and duodenal ulcer. In Marshall BJ, McCallum RW, Guerrant RL (eds): *Helicobacter pylori* in peptic ulceration and gastritis. Cambridge, Blackwell Scientific Publications, 1991; with permission.)

Genetic Factors

Genetic factors have been difficult to characterize, and *H. pylori* has been found in some *ulcer families* (family members had duodenal ulcer disease and *H. pylori*), suggesting that a common infection rather than heredity may have explained the familial clustering.^[39] A twin study^[30] found that in contrast to a concordance rate of 15% for PUD in dizygotic twins, a concordance rate of 24% for PUD was found in monozygotic twins. Of the liability to PUD, 39% was ascribed to genetic factors.

Environmental Cofactors: Stress and Smoking

Although the role of stress is controversial and in the era of *H. pylori* has been downplayed, *high stress levels* and smoking were significant independent predictors of PUD in men in the twin study referred to previously.

Specific Strains of *Helicobacter pylori*

Host factors probably influence critically the inflammatory and subsequent responses to *H. pylori* infection. These responses may be mediated by characteristics (virulence factors) of the particular infecting strain of *H. pylori*. This discussion addresses aspects specifically related to PUD. One virulence factor considered especially relevant to PUD is *VacA*, a protein causing vacuolation in a cytotoxin assay, and although all *H. pylori* strains possess the *vacA* gene, the *VacA* cytotoxic protein is produced by only about 50% of strains. The gene sequence for *vacA* is variable, particularly at

the signal sequence region (four types) and at the midregion (two types) of the allele, and specific genotypes (associated with phenotypic expression of VacA) are isolated much more commonly from ulcer patients. The prevalence of various *vacA* strains (and VacA expression) varies geographically, however,^[42] and VacA expression is not necessarily associated with ulcer disease. Another current concept is that strains that are ulcerogenic also release virulence factors controlled by specific gene sequences located in a so-called pathogenicity island (which is close but distinct from the site of alleles of the *vacA* gene). CagA protein is a product of one such gene sequence (*cagA* gene) in the pathogenicity island, and this misnamed protein, whose function is unknown, initially was thought to be a virulence marker for ulcer-associated disease. Most patients with PUD are infected with CagA-positive *H. pylori* strains. As with VacA protein expression (which is associated tightly with the presence of the *cagA* gene and CagA expression), however, the prevalence of *H. pylori* with the *cagA* gene also varies geographically without a clear-cut relationship to PUD. It is probable that there are specific *H. pylori* strains that secrete mediators leading to ulceration in patients predisposed to PUD.

Independent Role for Duodenal *Helicobacter pylori* Infection

A confounding factor bearing on possible relationships between various strains of *H. pylori* and duodenal ulcer disease in particular is that more than one strain may coexist in an infected patient. Specifically, there may be differences between antral strains and coexisting strains resident on metaplastic gastric epithelium in the duodenal bulb--the site of ulceration. In contrast to studies of the gastric mucosa, histologic evaluation of the duodenal bulb is apparently much less sensitive for the detection of *H. pylori* than culture of duodenal bulb biopsy specimens because in one study using careful techniques, *H. pylori* was cultured from such biopsy specimens from almost all patients infected with *H. pylori*.^[10] Despite a nearly identical (75% to 86%) prevalence of CagA strains from antral biopsy specimens from patients with duodenal ulcer disease and asymptomatic controls, CagA strains were found in approximately 80% of duodenal isolates from duodenal ulcer patients as compared with only a 30% prevalence in asymptomatic controls. There was a disassociation between CagA status and VacA prevalence because only 38% of patients with duodenal ulcer disease had VacA-positive strains in the duodenum.^[10]

Gastric Metaplasia in the Duodenum

H. pylori resides only on gastric mucosa or areas of gastric metaplasia. *H. pylori* may be found in the duodenal bulb in areas that have undergone gastric metaplasia (see Figs. 2 (Figure Not Available) and 4) . One hypothesis linking *H. pylori* to duodenal ulcer disease is that colonization of gastric metaplasia in the duodenal bulb leads to duodenitis (Fig. 5) and ulcer formation. Duodenal gastric metaplasia is postulated to occur as a result of acidification of the bulb and is thought to represent a protective response. There are conflicting data correlating the relationship between gastric metaplasia and acid secretion, however.^{[13] [32] [45]} In the previously referred to study^[10] regarding the prevalence of CagA and VacA strains of *H. pylori* in the duodenal bulb, gastric metaplasia was detected in 86% of ulcer patients as compared with detection in only 60% of asymptomatic controls. Metaplasia was significantly more extensive in patients with duodenal ulcer disease. Other investigators have found no difference in the prevalence of duodenal gastric metaplasia in ulcer patients versus controls.^[13] Although conceptually attractive, currently there are insufficient data to substantiate a causal association between *H. pylori*, gastric metaplasia, and duodenal ulcer disease.

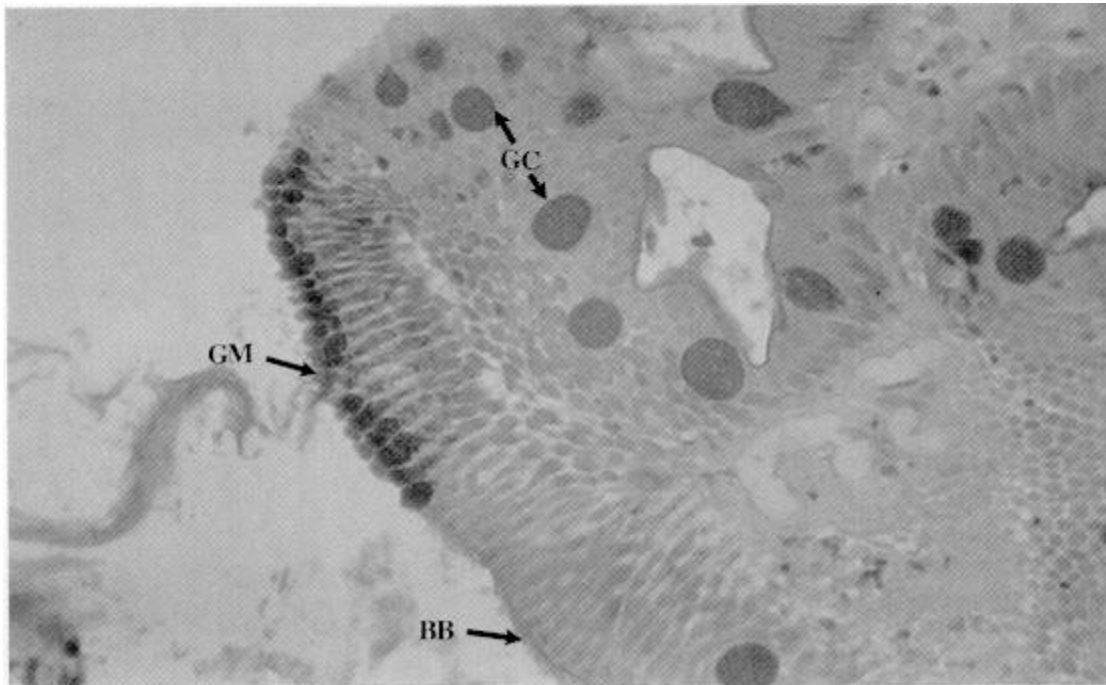


Figure 4. High power periodic acid Schiff's (PAS) stain section of duodenal mucosa from a patient with past duodenal ulcer. The patch of gastric metaplasia (GM) is identified easily by deep pink staining of epithelial cells. In contrast, duodenal mucosa has a delicate, weakly staining brush border (BB) and goblet cells also can be seen (GC).

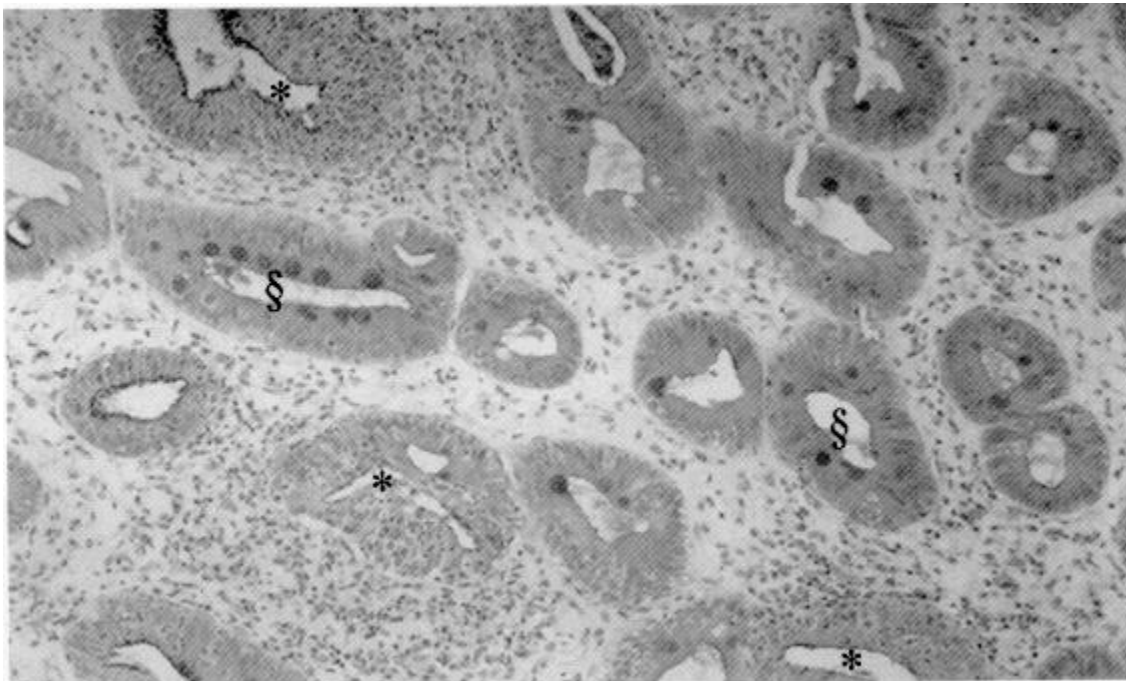


Figure 5. In active duodenal ulcer disease (with duodenitis), neutrophil infiltration is selective for glands with gastric metaplasia (asterisk), whereas glands with normal duodenal mucosa (to which *H. pylori* cannot attach) are spared (section mark).

Gastrin, Acid, and Duodenal Bicarbonate Secretion

H. pylori patients have an increased release of gastrin compared with uninfected controls.^[24] This increase may be secondary to decreased concentration of gastric somatostatin,^[26] but other mechanisms may be operative. Duodenal ulcer disease is heterogeneous, but many patients with *H. pylori*-associated duodenal ulcers have increased basal and stimulated acid secretion. At least some patients also have increased gastric emptying accompanied by a higher duodenal acid load.^[9]

All these factors contribute to excess acid in the bulb leading to injury and ulceration. An additional factor contributing to

a low pH in the bulb is that basal and stimulated duodenal bicarbonate secretion is impaired in patients with duodenal ulcers.^[13] Of particular note, cure of *H. pylori* infection tends to normalize all the previously mentioned responses,^[6] ^[9] ^[11] ^[13] ^[24] ^[26] emphasizing the central, albeit incompletely understood, role of *H. pylori* in duodenal ulcer disease.

Nonsteroidal Anti-Inflammatory Drug's and *Helicobacter pylori* Interactions

Aspirin and NSAIDs are other crucial factors in the development of gastroduodenal ulcers, and one or both of these agents may be used by patients also infected with *H. pylori*. Although one study^[1] suggests that *H. pylori* infection almost doubles the risk of bleeding peptic ulcers among aspirin and nonaspirin NSAID users, the interrelationship between *H. pylori* and these agents in PUD remains uncertain and controversial. In the setting of *H. pylori* infection, aspirin or NSAIDs theoretically may enhance, diminish, or have no influence on the probability of causing ulcers. There is evidence (reviewed elsewhere in this issue) to support all three possibilities. Is it possible to reconcile the data, and how should these data (which include evidence that NSAID-associated ulcers may heal more effectively in the presence of *H. pylori* infection as compared with healing in *H. pylori*-negative patients) influence management? At present, there are insufficient data to answer these questions dogmatically. One may speculate, however, that all three possibilities occur as determined, in part, by the particular pattern of gastritis that occurs in association with *H. pylori* infection in any given individual. For example, patients with duodenal ulcers are characterized by an antral-predominant gastritis. Other patients may have a pangastritis, with diminished acid secretion, which may increase after cure of *H. pylori* infection.

There is a heterogeneous pattern of *H. pylori*

gastritis, with a spectrum of inflammatory activity varying from mild to severe and associated with a variable gastric functional status, including hypochlorhydria and hyperchlorhydria. The outcome of the combination of *H. pylori* infection and NSAID use may be different in different individuals as determined by factors such as those outlined here. *H. pylori* infection may increase the acid-suppressive efficacy of proton-pump inhibitors, and this may explain, in part, the greater efficacy of omeprazole on NSAID-related ulcer healing in patients concurrently infected with *H. pylori*. Until a better understanding of NSAID and *H. pylori*

interactions is acquired, the author recommends that if there is a current ulcer or documentation of previous ulcer disease, *H. pylori* infection should be sought, especially because one study^[1] suggests that the attributable risk for *H. pylori* for bleeding ulcers among elderly (older than 75 years old) NSAID users is 24%. If *H. pylori* is present, anti-*H. pylori*

treatment should be administered. The role of NSAIDs in promoting the ulcer (or more importantly an ulcer complication) must be addressed independently, and depending on such factors as the duration of NSAID treatment and the presence of other established risk factors for complications (e.g., age), cotherapy with potent acid-suppressive treatment, prostaglandin analogues, newer NSAIDs that are selectively cyclooxygenase 2 inhibitors, or nonaspirin and non-NSAID medications (such as acetaminophen) may be appropriate. In the setting in which an ulcer has not occurred previously, the evidence is not sufficiently persuasive that most of those infected with *H. pylori* infection are at increased risk for NSAID-related ulcer complications, and therefore the author does not recommend establishing the *H. pylori* status of patients who are about to receive (or are receiving) NSAIDs to treat "prophylactically" *H. pylori* should it be present.

TESTING FOR *HELICOBACTER PYLORI*

For an overview of diagnostic testing for *H. pylori*,

see elsewhere in this issue. In this section, the considerations related to the diagnosis of *H. pylori* in the setting of PUD that warrant special attention are addressed. Testing for *H. pylori* should be performed in the setting of duodenal ulcer disease. There is increasing evidence (reviewed earlier) that in some population groups the prevalence of *H. pylori* may be lower than the traditionally taught 90%. This situation is especially true in the setting of bleeding ulcers. Biopsy-based tests may be less sensitive in this latter setting, and if negative it may be desirable to perform a UBT, which even in the presence of bleeding is one of the most accurate tests for the diagnosis of *H. pylori*. Positive serologic tests in the setting of PUD have high predictive values. In the setting of a bleeding ulcer, additional confirmatory testing is recommended because serologic tests are less specific than other tests. Gastric biopsy specimens showing more than a mild inflammatory infiltrate would suffice as a confirmatory test if *H. pylori* could not be identified on staining or biopsy urease testing. This more comprehensive diagnostic approach is justified because management of bleeding ulcers may be different depending on the *H. pylori* status--if infection is present, documented cure of *H. pylori* is sufficient (assuming that NSAIDs are not an additional factor to consider). In contrast, maintenance antisecretory therapy may be necessary for patients presenting with bleeding *H. pylori*-negative ulcers.

Confirmation of cure of *H. pylori* is not mandatory in uncomplicated ulcer disease because in the event of failed anti-*H. pylori* treatment, the overwhelming probability is that an ulcer recurrence would be uncomplicated. In the absence of anti-*H.*

pylori

treatment or maintenance acid suppressive therapy, however, approximately one third of patients who present with *H. pylori*-positive bleeding ulcers have a bleeding ulcer recurrence during the ensuing year. The recurrence rate of ulcer bleeding after cure of *H. pylori* and without maintenance therapy is extremely low. Because anti-*H. pylori* therapy is not always successful in curing the infection, confirmation of cure is necessary for patients with bleeding ulcers. Confirmation of cure should not be performed until at least 4 weeks have elapsed between the end of therapy and testing. Unless healing of a gastric ulcer needs to be assessed, endoscopic tests are unnecessary. Breath tests have been found to be accurate posttreatment. Stool tests probably would be satisfactory also.^[40]

TREATMENT OF *HELICOBACTER PYLORI*-ASSOCIATED ULCERS

All patients with *H. pylori* infection and ulcer disease should have anti-*H. pylori* therapy. Treatment regimens are reviewed elsewhere in this issue. For active ulcer disease, the regimen should include antisecretory therapy (which is part of most, but not all, anti-*H. pylori* regimens). Healing of the ulcer is as rapid with anti-*H. pylori* therapy alone (without an antisecretory component) as it is with acid-suppressive therapy. Symptom resolution is faster with acid-suppressive therapy, however.^[1]

Other studies have shown that ulcer healing is more rapid when antisecretory therapy is combined with anti-*H. pylori* therapy as compared with antisecretory therapy alone.^{[12] [15]}

Anti-*H. pylori*

regimens are of various duration but not longer than 2 weeks. Aside from the duration of antisecretory therapy that may be an integral part of the regimen for *H. pylori*, how long is it necessary to maintain antisecretory therapy for ulcer healing? For most patients, this need not be longer than the duration of anti-*H. pylori* therapy, unless the patient continues to be symptomatic. If the ulcer is greater than 1 cm, it might be prudent to administer potent acid-suppressive therapy empirically for at least 2 weeks beyond that administered as part of anti-*H. pylori* treatment. In cases in which confirmation of cure of *H. pylori* is required, diagnostic tests must be delayed not only in relation to the anti-*H. pylori* regimen (at least 4 weeks posttreatment), but also delayed 2 weeks after completion of acid-suppressive therapy using proton-pump inhibitors.

CONSEQUENCES OF CURE OF *HELICOBACTER PYLORI* IN PATIENTS WITH PEPTIC ULCER DISEASE

Cure of *H. pylori*

infection in association with PUD changes dramatically the natural history of ulcer disease (see Fig. 1) (Figure Not Available). After cure of *H. pylori*, recurrence rates of gastric and duodenal ulcers are decreased markedly (<10%)^{[8] [14] [41]} as compared with 60% to 80% recurrence at 1 year in untreated patients. In a study^[22] reviewed earlier (see section on evidence that the epidemiologic associations between PUD and *H. pylori* are changing) in which recurrent duodenal ulcers occurred in 20% of patients cured of *H. pylori* infection, the recurrence rate was markedly lower than in controls. Many of these recurrences were asymptomatic and were detected only because routine endoscopy was performed at regular follow-up intervals. Such ulcers may have little clinical significance and may represent a different entity. There is little doubt that there is an improved clinical outcome associated with cost savings when *H. pylori* is cured in association with duodenal ulcer disease.^[35] As indicated earlier, cure of *H. pylori* infection negates the deleterious effects of cigarette smoking in relation to PUD--the recurrence rate is *normalized* to the same low rate of *H. pylori*-cured nonsmokers.

Despite the beneficial effects of cure of *H. pylori*

as outlined earlier, deleterious consequences have been reported after cure of *H. pylori*. Some^{[3] [19]} but not all investigators have found an increased prevalence of reflux esophagitis after cure of *H. pylori*. This increase has occurred in duodenal ulcer patients and in patients with nonulcer dyspepsia. Only a small proportion of patients have been affected, however, and the data are not persuasive that this should militate current enthusiasm for treatment of *H. pylori* in the setting of documented PUD.

SUMMARY

Although there has been an explosion of data not only since the discovery of *H. pylori* in 1982, but also since the first comprehensive review of *H. pylori* in the *Gastroenterology Clinics* in 1993,⁵ much remains to be learned. In 1993, there were many skeptics doubting the importance of *H. pylori* in ulcer disease. Although this skepticism has dissipated, many ulcer patients infected with *H. pylori* still do not receive appropriate therapy. This situation possibly relates to the safety, efficacy, and simplicity of prescribing acid-suppressive therapy in contrast to the confusion regarding anti-*H. pylori* treatment regimens.

Among the many continuing unanswered questions regarding the role of *H. pylori* and PUD are the still enigmatic nature of host, environmental, and *H. pylori*-related factors that determine outcome. Why do only some infected individuals (and why do more men than women) develop PUD, and what determines whether gastric ulcers or duodenal ulcers develop? What is the explanation for the seasonal variation in ulcer disease? Although PUD is an infectious disease, are other environmental factors critical for the manifestation of ulcers in association with infection? What factors govern the outcome of the combination of *H. pylori* infection and NSAID use? Has attention been too focused first on the pathophysiology of acid secretion and now on *H. pylori*? In curing *H. pylori* in association with PUD, are clinicians going to displace disease northward, substituting erosions, inflammation, and neoplasia (and associated symptoms) in the esophagus and gastroesophageal junction for an ulcer crater (and its associated symptoms) in the duodenum or stomach? The epidemiology of PUD is changing--in more recent reports of ulcer patients, *H. pylori* and NSAID use are less prevalent than in earlier reports. These questions and comments should not be misinterpreted as advocating a lack of aggressiveness in diagnosis and treatment of *H. pylori* in the setting of PUD, however. Nevertheless, the pendulum is swinging.

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