The Role of *Helicobacter pylori* in Peptic Ulcer Disease

Maria L. Partipilo, Pharm.D., and Patricia S. Woster, Pharm.D.

The pathophysiology of peptic ulcer disease (PUD) is often described as an imbalance between aggressive factors such as acid and pepsin and alterations in the mucosal protective mechanisms. *Helicobacter pylori* is a gram-negative organism that has been identified as a potential causative agent in the pathogenesis of PUD. The exact mechanism by which it contributes to mucosal damage is unknown. It is thought that the organism may disrupt the protective mucous layer, allowing the underlying epithelium to be injured by gastric acid. Significant evidence indicates that *H. pylori* is a major etiologic factor in type B gastritis. Data confirming its etiologic role in duodenal ulcer (DU) disease is not conclusive; however, eradication of the organism is associated with a reduction in the recurrence of DU. Optimum therapy to eradicate *H. pylori* has not been established, although several multidrug regimens have been evaluated. Treatment of *H. pylori* infection should be reserved for individuals in whom conventional therapy for DU is unsuccessful and those whose ulcers relapse during maintenance therapy.

(Pharmacotherapy 1993;13(4):330–339)

OUTLINE

The etiology of peptic ulcer disease (PUD) remains largely unknown despite extensive investigation. Most of the investigation and treatment over the past 30 years have focused on the role of acid in the generation of ulceration. Treatment with agents that suppress acid secretion, such as histamine$_2$-receptor antagonists (H_2RAs), is a highly effective means of healing acute duodenal ulcers. Although these drugs can heal ulcers, they do not cure the disease. Recurrence rates among patients from whom treatment was withdrawn after 8 weeks are as high as 80% in the first year and reach 100% at 2 years.[1, 2] Even in patients who continue therapy, cumulative recurrence is reportedly as high as 48% after 1 year.[3] Therefore, it appears that an imbalance between aggressive factors, such as acid and pepsin, and alterations in the mucosal protective mechanisms contribute to the pathophysiology of PUD.

This theory suggests that the underlying pathophysiologic mechanisms of ulcerogenesis are unaltered with current treatment. Gastric acid is necessary for duodenal ulcers to form, but in most cases it appears that an alteration in the protective mechanisms of the duodenal mucosa must also play a role. This fact has prompted intense continuing investigation into the factors that might weaken the defenses of the gastric and duodenal epithelium.

Helicobacter pylori is a gram-negative bacterium that has been identified as a potential causative agent in the pathogenesis of PUD.[4] The organism

From the College of Pharmacy, University of Michigan, and the Department of Pharmacy Services, University of Michigan Medical Center, Ann Arbor, Michigan (both authors).

Address reprint requests to Maria L. Partipilo, Pharm.D., University of Michigan Hospitals, Department of Pharmacy Services, UH B2 D301 Box 0008, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0008.

Table 1. Methods of Detecting *H. pylori*

Method	Advantages	Disadvantages
Invasive		
Histology Warthin-Starry silver stain Giemsa stain Gram stain	Specificity and sensitivity 85–100%; direct visualization of gastrointestinal tract; gold standard with culture; inexpensive.	Two or more biopsies required.
Culture of biopsy specimens	Specificity approaches 100%; in vitro susceptibility can be determined.	Sensitivity 50–90%; may require 1 wk for growth; recent use of antibiotic or H_2RA may lead to false negatives; poor negative predictive value when used without histology.
Rapid urease test CLO test	Rapid (75% positive within 20 min); represents entire mucosa; may replace culture if susceptibility not required.	
Noninvasive		
Urea breath test Nonradioactive C^{13}	Specificity and sensitivity 90–100%.	Expensive equipment required; radioactivity limits repeated tests, therefore reserved for follow-up.
Radioactive C^{14}	Rapid (60 min); represents entire mucosa.	Presence of PUD not determined.
Serology ELISA	Ideal for mass screening.	Questionable reliability; possible cross-reactivity with similar bacteria.

has been isolated from beneath the mucous layer and from the surface of gastric epithelium in a high percentage (70–100%) of patients with active chronic gastritis and duodenal ulcer (DU) disease.[2, 4–6] Although its role in PUD is now well established, the mechanisms by which *H. pylori* predisposes patients to PUD remain controversial.

The Organism

In 1982 Warren and Marshall successfully cultured a spiral-shaped microorganism from the gastric antral mucosa of patients with gastritis or peptic ulcer.[7] These organisms were originally designated as *Campylobacter pyloridis* due to their prepyloric location and their biochemical similarity with other campylobacteria. The species name was later changed to *pylori*, which was grammatically consistent with the nomenclature of other bacteria such as *Campylobacter jejuni*. After its successful culture, the taxonomic features of *C. pylori* underwent intense evaluation. A number of important morphologic and biochemical dissimilarities existed between it and true campylobacteria, including ultrastructure, cellular fatty acid composition, respiratory quinones, growth characteristics, RNA sequences, and enzymes.[8–10] Therefore, evidence existed that a new bacterial genus had been discovered, and thus in 1989 *C. pylori* was renamed *Helicobacter pylori*.[11]

Helicobacter pylori has adapted to its environment by developing four to six unipolar sheathed flagella that allow it to move freely in and beneath the mucous layer of the gastric epithelium.[6, 7] It tends to cluster in the junctions between cells, rarely invading the cells. It is not viable in an acid environment; however, its location beneath the mucous layer and the release of urease, which produces a local alkaline environment capable of neutralizing gastric acid, allows its survival.[2, 6, 12] *Helicobacter pylori* has been found only on gastric epithelial cells.[2, 5, 13] Persons in whom it is colonized in the stomach may also harbor organisms in the metaplastic gastric epithelium of the esophagus (Barrett's esophagus) or duodenum.[2]

Methods of Detection

Helicobacter pylori may be detected invasively or noninvasively (Table 1). The gold standard is a combination of culture and histologic staining of biopsy specimens. Appropriate culture techniques can lead to the recovery of bacteria in 50–90% of infected individuals.[2, 6] Biopsies of both the antrum and the body of the stomach (due to the bacterium's nonuniform distribution) and prompt, careful handling of the culture are required to maximize the likelihood of detection. Warthin-Starry silver stain and Giemsa preparations are preferred for histologic detection.[6] Histologic identification of *H. pylori* on the gastric epithelium surface correlates well with culture results, with a sensitivity and specificity range of 85–100%.

The high urease activity exhibited by *H. pylori*

allows simple biochemical tests to detect the presence of the products of hydrolysis (ammonium) and, by inference, the presence of the organism. In the *Campylobacter*-like organism (CLO) test, a gastric biopsy specimen is placed in a solution that contains a small amount of urea, a pH indicator, and a bacteriostatic agent. If *H. pylori* is present, the urease produced will hydrolyze the urea, producing ammonia and a color change. This reaction is rapid, with broad sensitivity and specificity ranges of 65–95% and 60–100%, respectively.[2, 6, 14, 15]

The urea breath test, which also depends on bacterial urease activity, is a noninvasive way to detect *H. pylori*. A small dose of radiolabeled C^{13}- or C^{14}-urea is administered to subjects with a test meal to delay gastric emptying. Due to hydrolysis of a labeled carbon from the urea molecule by urease, radiolabeled carbon dioxide can be detected in the breath within 1 hour using a mass spectrometer to detect the stable C^{13} isotope, or a scintillation counter for the radioactive C^{14} isotope, if *H. pylori* is present in the stomach. This test has the advantage of being noninvasive, sensitive (90–100%), and specific (95–100%). In addition, the results represent the entire mucosa rather than the small area provided by a random biopsy specimen.[2, 6, 14, 15] Disadvantages are that access to the necessary equipment may not be available, and repeat testing must be avoided due to the radioactivity. Further validation of this test is required before its routine use can be recommended.

Antibodies directed against various *H. pylori* antigens can be detected in gastric juice and serum of infected persons, thus forming the basis of another noninvasive method of detection. Immunologic techniques using enzyme-linked immunosorbent assay (ELISA) demonstrate a strong correlation between high serum IgG and IgA antibody to *H. pylori* and gastric infection and inflammation. Use of whole-cell extracts of *H. pylori* as an antigen for ELISA should be avoided due to the cross-sensitivity with antibodies against other bacteria, resulting in loss of specificity. Further studies are necessary to determine if these tests are reliable indicators of the organism's eradication.[2, 6, 14, 15]

Epidemiology

The association of *H. pylori* with PUD is well documented.[2, 6, 13, 15] Most infected people never develop ulcers, however, suggesting that the organism is not the only cause of PUD, but rather a requisite risk factor. The overall endoscopic isolation rate for *H. pylori* in patients complaining of dyspepsia ranges from 32–62% (mean 56%).[15] Studies performed in the Netherlands and the United States indicate the prevalence of *H. pylori* in healthy, asymptomatic subjects to be approximately 20%.[16, 17] The prevalence is age dependent: *H. pylori* can be isolated in 10% of healthy individuals less than 30 years old and increases to 60% in those over age 60 years.[2, 5, 13, 18–20] It is rare in asymptomatic children.[15]

The mode of transmission of *H. pylori* is still unknown, although person-to-person is most likely.[5, 21, 22] Clustering within families and reports of higher than expected prevalence rates in nursing home residents support this concept.[5] Spread of the organism in endoscopy personnel also suggests this mode of transmission; the frequency in gastroenterologists is twice as high as expected.[21, 22] The organism has been isolated from swine and nonhuman primates, but these sources cannot account for all infections.[23] Acquisition from food and environmental sources has not been determined.[24] Clearly, infection from a common exogenous source cannot be completely ruled out.[5]

Mechanism of Injury

Although the exact mechanism by which *H. pylori* contributes to mucosal damage is unknown, several mechanisms have been suggested. The inflammatory response associated with the organism may interfere with the production of gastric mucus and alter the hydrogen ion diffusion properties.[2, 6, 15, 25] These changes may disrupt the protective mucous layer and allow injury to the underlying epithelium by gastric acid. In addition, local production of ammonia may damage cells through direct toxic effects or by raising pericellular pH, potentially leading to altered cellular permeability or active transport processes.[2, 13, 15] Alternatively, *H. pylori* may produce an unidentified toxin or chemotactic factor that promotes injury and inflammation. Finally, the pathogen adheres to the gastric metaplastic tissue in the duodenum; however, the role of attachment in the development of mucosal injury is not yet understood.

Virtually all patients with duodenal ulcer, as well as many healthy individuals, experience gastric metaplasia in the duodenum.[26] *Helicobacter pylori* may induce duodenitis in those areas, thereby disrupting the structure and function of the mucosa, and predisposing it to ulceration.[2, 15] Furthermore, in the gastric antrum it may stimulate gastrin release, which increases gastric acid secretion and leads to ulceration. Gastrin release is decreased after eradication of the organism.[27]

Prevalence in PUD

Chronic Nonspecific Gastritis

The prevalence of *H. pylori* in patients with chronic nonspecific gastritis (type B) ranges from 70–100%.[5] Type B gastritis primarily affects

Table 2. Evidence Refuting and Implicating a Pathogenic Role of *H. pylori* in Duodenal Ulcer Disease

Refuting Evidence	Implicating Evidence
DU predominant in men; *H. pylori* has no sex predilection.	Persistence of *H. pylori* after ulcer healing leads to higher relapse rate.
DU occurs in younger population; *H. pylori* most prevalent in elderly.	DU healing rate comparable with either H_2RAs or antibiotics plus bismuth.
Many individuals with *H. pylori* never develop DU.	Recurrence of DU less likely after antimicrobial therapy vs H_2RAs.
Acid hypersecretion can cause DU without presence of *H. pylori* (Zollinger-Ellison).	Prevalence of *H. pylori* in patients with DU approaches 100%.
Ulcers heal in presence of bacteria.	

mucus-secreting antral-type gastric epithelium and the pyloris. It is characterized by chronic active inflammation, patchy gastric atrophy, and neutrophilic infiltration.[28]

Several factors support a causal role of *H. pylori* in this disease. Patients almost always show evidence of infection with the organism, and asymptomatic patients colonized with the organism always have histologic evidence of gastritis.[2, 9] An association exists between the number of organisms seen and the number of polymorphonuclear leukocytes in the infected tissue.[2] In addition, eradication of *H. pylori* is associated with histologic improvement.[17, 29, 30] When two investigators with normal mucosa ingested live cultures of *H. pylori*, both developed acute gastritis.[31] The symptoms resolved with eradication of the organism. Even though it is agreed that *H. pylori* causes chronic nonspecific gastritis, it is unclear and perhaps unlikely that histologic gastritis causes dyspeptic symptoms or gross pathologic changes.

Duodenal Disease

The pathogen's role in chronic duodenal disease is currently an area of great interest because the prevalence of *H. pylori*-associated gastritis in patients with DU approaches 100%.[2, 6, 32, 33] However, preliminary observations do not support the theory of a pathogenic role in duodenal disease (Table 2). Epidemiologically, DU predominantly occurs in men, and generally in young people (< 30 yrs). In contrast, *H. pylori* is most prevalent in the elderly and has no sex predilection. In addition, patients with acid hypersecretion (Zollinger-Ellison syndrome) develop DU in the absence of *H. pylori*; in this patient population DU can be healed with therapy directed at acid suppression. Moreover, many individuals infected with the organism never develop DU.[2, 16, 17]

Conversely, overwhelming evidence to support *H. pylori* in the pathogenesis of DU can be found in antimicrobial treatment trials.[34–36] These trials suggest that persistence of *H. pylori* after ulcer healing leads to a significantly high relapse rate, 70–80% within 1 year. A comparable DU healing rate can be achieved with either H_2RAs or antibiotics plus bismuth.[24, 37, 38] However, recurrence of DU is less common after antimicrobial therapy than conventional therapy with the H_2RAs.[34, 36, 39] If *H. pylori* is eradicated, 1-year recurrence falls to 5–20%.[40]

Gastric Ulcer

In comparison with the prevalence of *H. pylori* in DU or chronic nonspecific gastritis, in gastric ulcer it is 60–80%.[24] However, there is little difference in the prevalence in patients with gastric ulcer compared with that in age-matched controls without gastric ulcer.[2, 15, 28] Because gastric ulcers are frequently associated with nonsteroidal antiinflammatory drug (NSAID) use, chronic active gastritis is typically not seen. If NSAID-associated gastric ulcers are excluded, however, the frequency of *H. pylori* and gastric lesions increases to 90%, a rate similar to that in duodenal disease.[24] The *H. pylori*-associated gastric ulcers are usually found along the transition zone between areas of inflammation and normal mucosa.

Nonulcer Dyspepsia

Nonulcer dyspepsia is a vague clinical syndrome that may comprise a variety of unexplained functional and inflammatory disorders of the upper gastrointestinal tract. Establishing a relationship between its symptoms, which include belching, nausea, and indigestion, and those of *H. pylori* infection is complicated by several factors. First, no universally accepted definition of nonulcer dyspepsia exists.[33] Furthermore, there is no difference in complaints of patients who have nonulcer dyspepsia with or without *H. pylori*. The frequency of *H. pylori* in patients with nonulcer dyspepsia is reported to be between 40% and 60% and is comparable to that in age-matched, asymptomatic controls. Some investigators demonstrated a higher percentage of *H. pylori* colonization in patients with symptoms of nonulcer dyspepsia, but the number of subjects was

Table 3. Treatment to Eradicate *H. pylori*

	Underlying Disease	Agent	Dose (mg/day)	Duration of Therapy	Time of Post-therapy Assessment	Eradication (%)
Bismuth alone						
	Gastritis[30]	BSS	3000	3 wks	2 days	78
	DU, GU, NUD[59]	BSS	2700	28 days	Immediately	47
					3 mo	18
	NA[48]	CBS	960	2 wks	Immediately	80
					3 mo	0
	NA[48]	CBS	480	1–2 mo	Immediately	81
					3 mo	27
	NUD[42]	CBS	480	8 wks	2 days	83
	DU[36]	CBS	480	8 wks	2 wks	32
					1 yr	27
Antibiotic alone						
	Antral gastritis[46]	Amoxicillin	2000	8 days	2 days	91
					2 wks	0
		Amoxicillin	2000	14 days	7 days	72
					1 mo	0
	Antral gastritis[45]	Furazolidone	400	14 days	1 day	86
					1.5 mo	34
		Nitrofurantoin	400	14 days	1 day	58
					1.5 mo	0
Bismuth plus antibiotic						
	DU, GU, NUD[59]	BSS	2700	15 days	Immediately	60
		Nitrofurantoin	400	10 days	2 wks	17
	NA[48]	CBS	480	2 mo	Immediately	100
		Amoxicillin	750	2 wks	3 mo	42
	DU[36]	CBS	480	8 wks	2 wks	74
		Tinidazole	1000	10 days	1 yr	70
Triple therapy						
	NA[63]	BSS	1800	2 wks	Immediately	100
		Amoxicillin	1500	2 wks	4 wks	90
		Metronidazole	1500	2 wks		
	DU, NUD[64]	CBS	480	4 wks	4 wks	94
		Tetracycline	2000	4 wks	19.3 mo	94
		Metronidazole	800	10 days		
	DU[65]	Tetracycline	2000	2 wks	Immediately	37
		Metronidazole	750	2 wks	3 mo	96
		BSS	750	2 wks		
	DU[67]	Furazolidone	600	5 days	6.5 mo	54
		Metronidazole	750	5 days		
		Amoxicillin	1500	5 days		

DU = duodenal ulcer; GU = gastric ulcer; NUD = nonulcer dyspepsia; BSS = bismuth subsalicylate; CBS = colloidal bismuth subcitrate; NA = not available.

inadequate, and these trials failed to evaluate therapy in noninfected symptomatic controls.[41–44]

Considerable variation exists in *H. pylori* eradication rates after treatment with colloidal bismuth subcitrate (CBS) in patients with nonulcer dyspepsia.[28, 41–44] Although CBS (DeNOL) 480 mg resulted in transient clearance of the organism and histologic improvement of the associated gastritis, literature reports disagree as to whether the agents improve symptoms.[41–44] Two studies that administered antibiotics (nitrofurans or amoxicillin) alone described no improvement of symptoms.[45, 46] Studies are necessary to compare directly the frequency of *H. pylori* in patients with nonulcer dyspepsia with that in asymptomatic, age-related controls to determine a clinically convincing causal role in the disorder.

Treatment of *Helicobacter pylori* Infection

Eradication is the absence of *H. pylori* 1 month after discontinuation of therapy.[6, 47] Early studies are misleading because relapse, rather than reinfection, was not appreciated.[5, 25] Follow-up of patients in whom the infection was thought to be eradicated showed that recurrent infections due to relapse are frequent and generally occur within a few weeks.[35, 48, 49] Since the strain of organism that

emerges is usually identical to the original infecting strain, recurrent infections likely reflect relapse of the initial infection rather than reinfection.[25] The optimum therapy to eradicate *H. pylori* is being evaluated (Table 3).

Although the organism shows in vitro susceptibility to the β-lactams, macrolides, nitrofurans, and quinolones, in vivo eradication with a single-drug regimen is difficult.[30, 35, 46, 50] Rapidly acquired resistance to antibiotics may be responsible for the lack of clinical efficacy. In addition, development of resistance may be due to the inoculum effect; that is, the significant increase in the minimum inhibitory concentration of an antibiotic when the number of organisms inoculated is increased. Since large numbers of the organism are present in the stomach, relative resistance due to the inoculum effect may occur. Furthermore, subpopulations of *H. pylori* that develop antimicrobial resistance may be present.[47] Recrudescence of the infection after single-agent therapy with amoxicillin or bismuth without the development of resistance indicates that other factors may influence the effectiveness of therapy.[47, 50]

The development of resistance or relapse may be due to the patchy distribution of antibiotics over gastric mucosa, which results in a wide variation of drug concentration in the esophagus, stomach, and duodenum.[50] Antimicrobial agents must reach the site of infection, attain sufficient concentration, and maintain activity in the local environment to be effective in vivo. The limited penetration of drug into the protected location of *H. pylori*, embedded in and covered by gastric mucus, and the decreased antibiotic activity due to local inactivation of the drug at a low pH may account for clinical failures.[24, 50] Although H_2RAs lack in vitro activity against *H. pylori*, they may serve as adjunctive agents by potentiating the gastric mucosal concentration of pH-sensitive antibiotics.[51]

Omeprazole

Omeprazole decreases colonization rates of *H. pylori* when used as a single agent in the treatment of refractory DU and associated gastritis.[52, 53] Recent studies demonstrated that it causes temporary suppression rather than eradication of the organism.[54, 55] Omeprazole causes a rise in gastric pH due to hydrogen ion pump inhibition. At this neutral pH, the ammonia produced by *H. pylori* is no longer neutralized by hydrogen ions and therefore may cause direct bacterial damage.[54] In addition, omeprazole-induced achlorhydria may suppress *H. pylori* urease secretion, resulting in a biologically inactive bacteria. In its inactive state, it is postulated that the organism does not secrete phospholipases responsible for its pathogenicity.[55] Because temporary suppression has been observed with omeprazole, its inclusion in regimens aimed at eradicating *H. pylori* is currently being evaluated.

Bismuth

Bismuth subsalicylate (Pepto-Bismol) and colloidal bismuth subcitrate (CBS; DeNOL) have been used in the treatment of gastrointestinal disorders for many years and are as effective as H_2RAs in healing gastric and duodenal ulcers.[15, 40, 56] Bismuth may contribute to healing by several cytoprotective mechanisms, including altering the mucous layer (making it more effective as a diffusion barrier to hydrogen ions), stimulating the synthesis of prostaglandins and reducing pepsin output, and modulating the immune response.[25, 33, 51, 56, 57] In addition, bismuth preparations exhibit bactericidal action against *H. pylori*.[58] Monotherapy with bismuth subcitrate lyses organisms in vivo within 30–90 minutes after administration.[58] Eradication ranging from 1 month to 1 year is poor, however, with rates of 0–27%.[49, 59, 60] Successful regimens under investigation combine a bismuth preparation and one or two antibiotics.[49, 59, 60] Coadministration seems to decrease antibiotic resistance.[47]

Bismuth subcitrate 120 mg 4 times/day is the most extensively studied, but the agent is not available in the United States.[39, 61, 62] Bismuth subsalicylate 525 mg (30 ml, or 2 tablets) is a safe and effective substitution.[5] Both preparations appear to be safe when used in the recommended dosages for up to 8 weeks.[30, 39, 42] Treatment for longer than 8 weeks with blood bismuth levels greater than 100 μg/L has been associated with neurologic toxicity.[39, 56, 60] Most cases were reported in the 1970s with large doses (up to 20 g elemental bismuth) of bismuth subnitrate, subgallate, or subcarbonate and are rarely reported with bismuth preparations available today. Treatment should be followed by an 8-week, bismuth-free interval, however, and patients with levels between 50 and 100 μg/L should be monitored for adverse reactions.[39] The salicylate component also has the potential for toxic effects. Therefore, bismuth subsalicylate should be used with caution in children, individuals with salicylate sensitivity or bleeding disorders, those who are taking high-dose salicylates, and patients taking other drugs that may clinically interact with salicylate (e.g., anticoagulants, uricosuric agents, sulfonylureas, corticosteroids, methotrexate).[56, 60]

Combination Therapy

Although the ideal treatment of *H. pylori* is unknown, bismuth salts seem to be an important component of therapy in patients with DU disease. Three prospective, randomized studies combining

a bismuth preparation and an antibiotic have been reported in sufficient detail to allow an adequate assessment of therapy.[36, 49, 59] The first long-term results were with a combination of bismuth and tinidazole, an investigational agent that is similar to metronidazole. In a double-blind study, 100 patients with DU and *H. pylori* infection were randomly assigned to 8 weeks of cimetidine or CBS therapy with concurrent tinidazole or placebo during the first 10 days.[36] Even when combined with tinidazole, cimetidine was ineffective against *H. pylori*; the infection persisted in 95% of patients. The organism was eradicated in 27% of the CBS-placebo group and in 70% of the CBS-tinidazole group. In patients in whom *H. pylori* persisted after treatment, only 61% had healed duodenal ulcers and 84% of these patients relapsed at 12 months. When *H. pylori* was cleared, 92% of ulcers were healed, and only 21% of patients relapsed during the 12-month follow-up period. This study suggests that eradication of the pathogen is a determining factor in ulcer relapse rates. However, ulcers did recur in some patients without persistent *H. pylori* infection. In other studies, therapy with drugs active against *H. pylori* (bismuth, metronidazole, amoxicillin) was associated with a significantly reduced rate of relapse compared with regimens without activity against the organism in patients with DU disease.[34, 35]

Results of studies using combination therapy with bismuth plus nitrofurantoin or amoxicillin are less impressive, with eradication rates of 17% 2 weeks after the completion of a 14-day course of therapy and 42% 4 weeks after therapy, respectively.[49, 59] The duration of therapy in these studies was significantly shorter than that of the other study.[36]

Failure of single- and two-drug regimens led to several multidrug regimens. Preliminary studies examining the treatment of *H. pylori* with bismuth and two antibiotics show reasonably good eradication rates. A nonblinded, uncontrolled trial evaluated the efficacy of chewable bismuth salicylate tablets 600 mg, amoxicillin suspension 500 mg, and metronidazole 500 mg 3 times/day for 2 weeks in 23 patients with peptic ulcers.[63] All patients were *H. pylori* negative at the end of therapy. Ten patients were reassessed 4 weeks after the cessation of therapy and 90% remained *H. pylori* negative by culture and biopsy. The time of follow-up in this study was short, and late relapses were not reported. Similarly, a 94% eradication rate was observed in 100 patients with nonulcer dyspepsia or DU 8 weeks after coadministration of chewable CBS tablets 120 mg, tetracycline 500 mg 4 times/day for 4 weeks, and metronidazole 200 mg 4 four times/day for 2 weeks.[64] Of the 64 patients available for reassessment in whom *H. pylori* remained eradicated at 8 weeks, 60 (94%) remained free of infection after a mean follow-up of 19.3 months.[64]

Ranitidine 300 mg/day alone was compared with ranitidine plus tetracycline 500 mg 4 times/day, metronidazole 250 mg 3 times/day, and bismuth subsalicylate 151-mg tablets 5–8 times/day in 105 patients.[65] Triple-antibiotic therapy was administered only during the first 2 weeks of the 16-week trial. More rapid ulcer healing was reported with ranitidine plus triple-antibiotic therapy within 16 weeks. The respective cumulative percentages of patients with healed ulcers in this group and in the group receiving ranitidine alone were 37% and 18% after week 2, 84% and 68% after week 8, and 98% and 84% after week 16. A follow-up study evaluated the recurrence of gastric and duodenal ulcer after eradication of *H. pylori* in 109 patients (83 with DU and 26 with gastric ulcer) for an average of 13 months.[66] The investigators concluded that eradication leads to a significant reduction in the recurrence of symptomatic ulcers. The results of these studies provide further evidence that *H. pylori* infection plays a role in the pathogenesis of DU.

In the first trial of 5-day, bismuth-free, triple-drug therapy for the eradication of *H. pylori*, 61 patients with DU received furazolidone 200 mg, metronidazole 250 mg, and amoxicillin 500 mg in combination 3 times a day for 5 days.[67] Fifty-four percent of patients were negative for the organism 6.5 months after the end of treatment, and 46% continued to be positive. Furthermore, 92% of the patients in whom the organism was eradicated showed endoscopically healed ulcers. The authors suggest that a shorter regimen may increase patient adherence to treatment, lower costs, and lessen the possibility of serious adverse effects with prolonged use of antibiotics.

Although triple-drug therapy initially appears to be effective in eradicating the bacteria, the risks of antibiotic-associated diarrhea (*Clostridium difficile* disease) and antibiotic resistance must be weighed against the benefit. To date, no long-term studies on the efficacy of a long-term regimen to prevent relapse have been performed. Until an optimum regimen is established, only patients who have failed other treatment (H_2RAs) should be considered to receive an antimicrobial plus bismuth.

Investigational Agents

An investigational product that combines ranitidine and bismuth citrate is currently undergoing phase III clinical trials in the United States. The new preparation, GR-122311X, at a dosage of 391 mg twice/day was as effective as ranitidine 150 mg twice/day in decreasing 24-hour intragastric acidity in 30 healthy men volunteers.[68] This combination is aimed at enhancing the ulcer-healing benefit of an H_2RA and may prove to be

very useful in the treatment of *H. pylori*. It remains to be determined whether it will enhance the healing as well as decrease the recurrence of PUD.

Recommendations

Since many patients with *H. pylori* are asymptomatic, the question becomes who would benefit from eradication of the bacteria. Strong evidence exists that *H. pylori* is the major cause of chronic nonspecific gastritis (type B). It is clear that eradicating the organism with amoxicillin, furazolidone, or bismuth salts leads to resolution of gastritis.[17, 45, 46] However, asymptomatic patients with *H. pylori*-positive gastritis should not be treated because chronic nonspecific gastritis is not clearly associated with any specific symptoms or long-term sequelae. Furthermore, this subset of patients usually do not seek medical attention.

The decision to eradicate *H. pylori* routinely when treating patients with nonulcer dyspepsia remains unclear. First, there is no convincing evidence that *H. pylori* has a pathogenic role in nonulcer dyspepsia. Second, the gastric mucosa of patients complaining of similar dyspeptic symptoms is normal and the organism often is not detected. Finally, the optimum eradication therapy has not been established. Therefore, at the present time, specific treatment directed against *H. pylori* is not recommended for patients with nonulcer dyspepsia.[6, 47, 50]

In general, investigators suggest that eradication therapy be reserved for patients in whom the benefits (reduced recurrence, cure) outweigh the risks (side effects of therapy, antibiotic resistance, etc.). Some suggest that patients with DU and gastric ulcer are most likely to benefit, and that this therapy is best aimed at preventing relapse.[47] Three well-controlled studies support the idea of treating patients with *H. pylori* infection.[34, 36, 66] Eradication in patients with healed DU resulted in a significantly lower relapse rate than those in patients not cleared of the organism.[34, 36] Eradication may be associated with drug-related complications such as antibiotic-associated diarrhea. Failure to eradicate the organism may cause the development of antibiotic-resistant *H. pylori*, which could render the disease incurable using currently available antibiotics. Furthermore, eradication may not necessarily result in clinical cure because the patient may experience reinfection. While reinfection was uncommon in the present studies, the duration of follow-up was limited. Therefore, the best candidates in whom to attempt eradication of *H. pylori* are patients who have had no success with conventional treatment for DU and those whose ulcers recur.

Currently, no agent is approved by the Food and Drug Administration for the treatment of *H. pylori* infection. Although most authors believe that therapy should be limited to controlled trials, several drug regimens have been proposed. One suggestion is bismuth subsalicylate 525 mg 4 times/day plus metronidazole 250 mg 3 times/day, administered over 4 weeks to patients in whom all other forms of therapy have failed but who remain symptomatic.[5] Gastric mucosal cultures and sensitivities should be obtained, and eradication of the organism confirmed 4–6 weeks after the cessation of therapy. A triple-drug regimen administers metronidazole 500 mg, chewable bismuth subsalicylate tablets 600 mg, and amoxicillin suspension 500 mg 4 times/day for 2 weeks in patients with ulcers that fail to heal within 12 weeks and whose symptoms are severe enough to make them candidates for surgery.[24, 47] A third recommendation is a combination of tinidazole 500 mg 2 times/day plus either bismuth subcitrate 120-mg tablets or amoxicillin 500 mg suspension 4 times/day for long-term eradication of *H. pylori*, provided the initial infecting strain is susceptible to nitroimidazoles.[47, 50, 69] Cultures should be obtained both before and after treatment to monitor the organism's susceptibility to antimicrobial agents.[50] A final suggestion is two 151-mg bismuth subsalicylate tablets chewed 4 times/day 30 minutes before each meal for 2 weeks, plus tetracycline or amoxicillin 500 mg 4 times/day for 2 weeks, plus metronidazole 250 mg 4 times/day for 10 days.[28]

Factors to enhance therapy have also been investigated. Administration of bismuth salts with meals will allow the drug to remain in the stomach as long as possible. The grinding and mixing functions of the stomach may also ensure maximum distribution within the stomach. In addition, since antacid tablets have a longer action than antacid liquids (possibly due to slower gastric emptying), bismuth tablets may be more effective than bismuth liquid.[47] Finally, to ensure compliance, patients should be informed at the onset of therapy that two to three drugs will have to be taken several times a day for up to 4 weeks, and they must be willing to adhere to this regimen.

Conclusion

Significant evidence indicates that *H. pylori* is the major etiologic factor in type B gastritis. It is also associated with duodenal and gastric ulceration, and its eradication is associated with elimination of the recurrence of DU. Treatment should be considered on an individual basis. Patients should not be subjected to possibly ineffective or potentially toxic triple-drug regimens when safer treatment with H_2RAs is available. The best candidates in whom to attempt eradication of *H. pylori* at the present time are individuals who have not had success with conventional treatment for

DU and those whose ulcers relapsed during maintenance therapy.

The optimum therapy to eradicate *H. pylori* and the preferred duration of treatment remain to be established. Most investigators now agree that bismuth salts are an important component of eradication therapy. Evaluation of various other antimicrobial agents and H_2RAs in combination with bismuth must be completed, as well as studies comparing dosage formulations, salts, and administration of bismuth in relationship to meals. Well-designed, controlled trials with prolonged follow-up to ensure long-term eradication of *H. pylori* are also needed. Questions remain concerning the best methods to detect the organism, and which one or combination of several is reliable and least expensive. Clinical trials to confirm that eradication leads to clinical improvement in symptomatic patients will have a major influence on the treatment of peptic ulcer disease in the future.

References

1. **Bardhan K, Cole DS, Hawkins BW, et al.** Does treatment with cimetidine extended beyond initial healing of duodenal ulcer reduce the subsequent relapse rate? Br Med J 1982;284:621–3.
2. **Chamberlain CE, Peura DA.** *Campylobacter* (*Helicobacter*) *pylori*: is peptic disease a bacterial infection? Arch Intern Med 1990;150:951–5.
3. **Boyd EJS, Penston JG, Johnston DA, et al.** Does maintenance therapy keep duodenal ulcers healed? Lancet 1988;1:1324–7.
4. **Marshall BJ, McGechie DB, Rogers PA, et al.** Pyloric *Campylobacter* infection and gastroduodenal disease. Med J Aust 1985;142:439–44.
5. **Peterson WL.** *Helicobacter pylori* and peptic ulcer disease. N Engl J Med 1991;324:1043–8.
6. **Ormand JE, Talley NJ.** *Helicobacter pylori*: controversies and an approach to management. Mayo Clin Proc 1990;65:414–26.
7. **Warren JR, Marshall BJ.** Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273–5.
8. **Goodwin CS, McCulloch RK, Armstrong JA, et al.** Unusual cellular fatty acids and distinctive ultrastructure in a new spiral bacterium (*Campylobacter pyloridis*) from the human gastric mucosa. J Med Microbiol 1985;19:257–67.
9. **Goodwin CS, Armstrong JA, Marshall BJ.** *Campylobacter pyloridis*, gastritis, and peptic ulceration. J Clin Pathol 1986; 39:353–65.
10. **Romaniuk PJ, Zoltowska B, Trust TJ, et al.** *Campylobacter pylori*, the spiral bacterium associated with human gastritis, is not a true *Campylobacter* sp. J Bacteriol 1987;169:2137–41.
11. **Goodwin CS, Gordon A, Burke V.** *Helicobacter pylori* (*Campylobacter pylori*) and duodenal ulcer. Med J Aust 1990;153:66–7.
12. **Sidebotham RL, Baron JH.** Hypothesis: *Helicobacter pylori*, urease, mucus, and gastric ulcer. Lancet 1990;335:193–5.
13. **Wyle FA.** *Helicobacter pylori*: current perspectives. J Clin Gastroenterol 1991;13(suppl):S114–24.
14. **Maddocks AC.** Helicobacter pylori (formerly *Campylobacter pyloridis*/*pylori*) 1986–1989: a review. J Clin Pathol 1990;43:353–6.
15. **Korman MG.** *Helicobacter pylori*: fact or fiction? Scand J Gastroenterol 1990; 25(suppl 175):159–65.
16. **Barthel JS, Westblom JU.** Gastritis and *Campylobacter pylori* in healthy, asymptomatic volunteers. Arch Intern Med 1988;148: 1149–51.
17. **Rauws EAJ, Langenberg W, Houthoff HJ, et al.** *Campylobacter pyloridis*-associated chronic active antral gastritis: a prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. Gastroenterology 1988;94:33–40.
18. **Morris A, Nicholson G, Lloyd G, et al.** Seroepidemiology of *Campylobacter pyloridis*. N Z Med J 1986;99:657–9.
19. **Marshall BJ, McGechie DB, Francis GJ, et al.** Pyloric *Campylobacter* serology [letter]. Lancet 1984;2:281.
20. **Rawles JW, Paull G, Yardley JH, et al.** Gastric *Campylobacter*-like organisms (CLO) in a US hospital population [abstr]. Gastroenterology 1986;90:1599.
21. **Landenberg W, Rauws EAJ, Oudbier JH, et al.** Patient-to-patient transmission of *Campylobacter pylori* infection by fiberoptic gastroduodenoscopy and biopsy. J Infect Dis 1990;161:507–11.
22. **Mitchell HM, Lee A, Carrick J.** Increased incidence of *Campylobacter pylori* infection in gastroenterologists: further evidence to support person-to-person transmission of *C. pylori*. Scand J Gastroenterol 1989;24:396–400.
23. **Blaser MJ.** Epidemiology and pathophysiology of *Campylobacter pylori* infections. Rev Infect Dis 1990;12(suppl 1):S99–106.
24. **Goodman LJ, Lisowski JM.** *Helicobacter pylori* and the upper GI tract: a bug for all lesions? Hosp Formulary 1991;26:792–800.
25. **Soll AH.** Pathogenesis of peptic ulcer and implications for therapy. N Engl J Med 1990;322:909–16.
26. **Blaser M.** *Helicobacter pylori* and the pathogenesis of gastroduodenal inflammation. J Infect Dis 1990;161:626–33.
27. **Levi S, Beardshall K, Haddad G, et al.** *Campylobacter pylori* and duodenal ulcers: the gastrin link. Lancet 1989;1:1167–8.
28. **Clearfield HR.** *Helicobacter pylori*: aggressor or innocent bystander? Med Clin North Am 1991;75:815–29.
29. **Lambert JR, Dunn KL, Turner H, et al.** Effect of histological gastritis following eradication of *Campylobacter pyloridis*. Gastroenterology 1986;90:1509.
30. **McNulty CAM, Gearty JC, Crump B, et al.** *Campylobacter pyloridis* and associated gastritis: investigator blind, placebo controlled trial of bismuth salicylate and erythromycin ethylsuccinate. Br Med J 1986;293:645–9.
31. **Morris A, Nicholson G.** Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. Am J Gastroenterol 1987;82:192–9.
32. **Loffeld RJLF.** *Helicobacter pylori* in gastroduodenal disease. Pharm Weekbl [Sci] 1990;12:46–50.
33. **McKinlay AW, Upadhyay R, Gemmell CG, et al.** *Helicobacter pylori*: bridging the credibility gap. Gut 1990;31:940–5.
34. **Coghlan JG, Humphries H, Dooley C, et al.** *Campylobacter pylori* and recurrence of duodenal ulcers. Lancet 1987;1:1109–11.
35. **Rauws EAJ, Tytgat GNJ.** Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990;335:1233–5.
36. **Marshall BJ, Goodwin CS, Warren JR, et al.** Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet 1988;2:1437–42.
37. **Diaz MQ, Escobar AS.** Metronidazole versus cimetidine in treatment of gastroduodenal ulcer [letter]. Lancet 1986;1:907.
38. **Lambert JR, Borromeo M, Korman MG, et al.** Effect of colloidal bismuth (De-Nol) on healing and relapse of duodenal ulcers: role of *Campylobacter pyloridis* [abstr]. Gastroenterology 1987;92:1489.
39. **Bader JP.** The safety profile of De-Nol. Digestion 1987;37(suppl 2):53–9.
40. **Lind CD, Blaser MJ.** *Helicobacter pylori* and duodenal ulceration. Hosp Pract 1991;26(2A):45–63.
41. **Loffeld RJ, Potters HV, Stobberingh E, et al.** *Campylobacter* associated gastritis in patients with non-ulcer dyspepsia: a double blind placebo controlled trial with colloidal bismuth subcitrate. Gut 1989;30:1206–12.
42. **Rokkas T, Pursey C, Uzoechina E, et al.** Non-ulcer dyspepsia and short term De-Nol therapy: a placebo controlled trial with particular reference to the role of *Campylobacter pylori*. Gut 1988;29:1386–91.
43. **Lambert JR, Dunn K, Borromeo M, et al.** *Campylobacter pylori*. A role in non-ulcer dyspepsia? Scand J Gastroenterol 1989; 160(suppl):7–13.
44. **Kang Y, Tay HH, Wee A, et al.** Effect of colloidal bismuth subcitrate on symptoms and gastric histology in non-ulcer dyspepsia. A double blind placebo controlled study. Gut 1990;31:476–80.
45. **Morgan D, Kraft W, Bender M, et al.** Nitrofurans in the treatment of gastritis associated with *Campylobacter pylori*. Gastroenterology 1988;95:1178–84.
46. **Glupczynski Y, Burett A, Labbe M, et al.** *Campylobacter pylori*-associated gastritis: a double-blind placebo-controlled trial with amoxycillin. Am J Gastroenterol 1988;83:365–72.
47. **Graham DY, Borsch GMA.** The who's and when's of therapy for *Helicobacter pylori*. Am J Gastroenterol 1990;85:1552–5.
48. **O'Riordan T, Mathai E, Tobin E, et al.** Adjuvant antibiotic therapy in duodenal ulcers treated with colloidal bismuth subcitrate. Gut 1990;31:999–1002.
49. **Weil J, Bell GD, Powell K, et al.** *Helicobacter pylori* infection treated with a tripotassium dicitrate bismuthate and metronidazole combination. Aliment Pharmacol Ther 1990;4:651–7.
50. **Glupczynski Y, Burette A.** Drug therapy for *Helicobacter pylori* infection: problems and pitfalls. Am J Gastroenterol 1990;85: 1545–51.
51. **Westblom TU, Duriex DE.** Enhancement of antibiotic

concentrations in gastric mucosa by H_2-receptor antagonist: implications for treatment of *Helicobacter pylori* infections. Dig Dis Sci 1991;36:25–8.
52. **Hui WM, Lam SK, Ho J, et al.** Effect of omeprazole on duodenal ulcer-associated antral gastritis and *Helicobacter pylori*. Dig Dis Sci 1991;36:577–82.
53. **Mainguet P, Delmee M, Debongnie JC.** Omeprazole, *Campylobacter pylori* and duodenal ulcer. Lancet. 1989;2:389–90.
54. **Weil J, Bell GD, Powell K, et al.** Omeprazole and *Helicobacter pylori*: temporary suppression rather than true eradication. Aliment Pharmacol Ther 1991;5:309–13.
55. **Daw MA, Deegan P, Leen E, O'Morain C.** Short report: the effect of omeprazole on *Helicobacter pylori* and associated gastritis. Aliment Pharmacol Ther 1991;5:435–9.
56. **Gorbach SL.** Bismuth therapy in gastrointestinal diseases. Gastroenterology 1990;99:863–75.
57. **Burns R, Thomas DW, Barron VJ.** Reversible encephalopathy possibly associated with bismuth subgallate ingestion. Br Med J 1974;1:220–3.
58. **Marshall BJ, Armstrong JA, Francis GJ, et al.** Antibacterial action of bismuth in relation to *Campylobacter pyloridis* colonization and gastritis. Digestion 1987;37(suppl 2):16–30.
59. **Borsch G, Mai U, Muller KM.** Monotherapy of polychemotherapy in the treatment of *Campylobacter pylori*-related gastroduodenal disease. Scand J Gastroenterol 1988;142(suppl):101–6.
60. **Marshall BJ.** The use of bismuth in gastroenterology. Am J Gastroenterol 1991;86:16–25.
61. **Weller MPJ.** Neuropsychiatric symptoms following bismuth intoxication. Postgrad Med J 1988;64:308–10.
62. **Beckingham IJ, Baird G, Kesteven PJL.** Acute thrombocytopenia after De-Nol. Gut 1989;30:1016–17.
63. **Borsch G, Mai U, Opferkuch W.** Oral triple therapy (OTT) may effectively eradicate *Campylobacter pylori* in man: a pilot study [abstr]. Gastroenterology 1988;94:a44.
64. **Borody T, Cole P, Noonan S, et al.** Recurrence of duodenal ulcer and *Campylobacter pylori* infection after eradication. Med J Aust 1989;151:431–5.
65. **Graham DY, Lew GM, Evans DG, et al.** Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. Ann Intern Med 1991;115:266–9.
66. **Graham DY, Lew GM, Klein PD, et al.** Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 1992;116:705–8.
67. **Coelho LGV, Passos MDF, Chausson Y, et al.** Five-day bismuth-free triple therapy for the eradication of *Helicobacter pylori* and reduction of duodenal ulcer relapse. Am J Gastroenterol 1991;86:971–5.
68. **Pewett EJ, Nwokolo CU, Hudson M, et al.** The effect of GR122311X, a bismuth compound with H_2-antagonist activity, on 24-hour intragastric acidity. Aliment Pharmacol Ther 1991;5:481–90.
69. **Glupczynski Y, Burrette A.** On the who's and when's of therapy for *Helicobacter pylori* [letter]. Am J Gastroenterol 1991;86:924–5.