



Management of Peptic Ulcers: Emerging Issues

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Abstract. Most peptic ulcers are caused by *Helicobacter pylori* infection. The infection is best diagnosed by a radiolabeled carbon urea breath test, which also can prove that eradication therapy was successful. Serologic testing is useful for establishing prior or present infection but not to determine if the infection has been eradicated. Endoscopic tests usually are not needed to establish a diagnosis. Modern ulcer treatment consists of *H. pylori* eradication in infected patients. A combination of a proton pump inhibitor plus clarithromycin and amoxicillin or a proton pump inhibitor plus bismuth, metronidazole, and tetracycline are the most effective regimens. Reinfection is less than 2% per year in developed countries. Evidence suggests that *H. pylori* eradication may foster the development of erosive esophagitis, but confirmatory studies are needed. Studies also suggest an interaction between *H. pylori* infection and peptic ulcers related to the use of nonsteroidal antiinflammatory drugs (NSAIDs). However, the studies are conflicting: One shows that *H. pylori* eradication protects against NSAID-related ulcers; another suggests protection afforded by the infection. Non-*H. pylori* peptic ulcers remain a challenge, especially in the United States, where one study showed that 42% of peptic ulcers were not due to the infection. Some non-*H. pylori* ulcers are refractory to usual doses of antisecretory drugs.

The last few years have seen an explosion of interest in the pathogenesis and management of peptic ulcer disease since recognition of the role of *Helicobacter pylori* infection. A series of consensus conferences held in various countries served to consolidate the vast quantity of new information about clinical aspects of *H. pylori* infection [1–4]. The purpose of this article is to summarize the newer concepts of peptic ulcer management, highlighting areas of consensus and addressing controversial and problematic areas.

Peptic Ulcers and *H. pylori*

Epidemiology

Helicobacter pylori is the most common cause of peptic ulcer and the most common chronic bacterial infection afflicting humans. Most infections are acquired during childhood and become chronic or lifelong. The rising prevalence of infection with increasing age represents a cohort effect in which patients became infected as children and have remained infected into adult life. Prevalence is higher in lower socioeconomic groups. In the United States, infection rates are higher in Hispanics and African Americans than in whites [5–7]. This is thought to reflect differences in the economic status of these groups.

The mode of transmission is unknown. Evidence supports either a predominantly fecal-oral or oral-oral route. The fecal-oral route may be important in less developed nations where the infection is likely to be water-borne. The infection may be spread among children through exposure to gastric juice in vomit. Apart from humans, no animal reservoir has been identified.

Diagnosis

The appropriate selection of tests depends on an understanding of their characteristics (Table 1) and the clinical situation at hand. Nonendoscopic tests include antibody testing and urea breath tests (UBTs). Immunoglobulin G (IgG) antibodies to *H. pylori* can be determined quantitatively or qualitatively in blood or serum. Some qualitative tests can be used in physicians' offices with a result available within minutes. However, sensitivity and specificity are lower than with laboratory-based tests [8]. Although convenient and relatively inexpensive, blood and serum antibody tests do not prove *current* infection. Furthermore, because antibody tests may remain positive for months after successful eradication of infection, they are not recommended to prove that eradication therapy has been successful.

In UBTs, urea labeled with ^{13}C or ^{14}C is given by mouth. Urease elaborated by *H. pylori* splits the urea to produce NH_3 and CO_2 ; the latter carries the ^{13}C or ^{14}C and is detected in a breath sample. These tests are simple to perform and have excellent operating characteristics. False-negative tests with the UBT may occur in patients receiving antibiotics, bismuth compounds, or acid-suppressing medicines because these agents suppress the ability of *H. pylori* to produce NH_3 [9, 10].

Endoscopic diagnostic methods include biopsy urease tests, histology, and culture. At least three biopsy urease tests are commercially available; all have good operating characteristics and are simple to use [11]. A gastric mucosal biopsy is placed in a small well or semipermeable membrane that contains urea and a pH indicator. *H. pylori* urease in the biopsy metabolizes urea to produce NH_3 and CO_2 . NH_3 alkalizes the medium and produces a change in the color of the pH indicator. A positive biopsy urease test is virtually diagnostic of *H. pylori* infection. False-negative tests occur in patients who have recently been taking antibiotics, bismuth compounds, or acid-suppressing medicines for the reason stated previously. *H. pylori* can be identified with standard hematoxylin-eosin (HE) staining, but the diagnostic yield (and cost)

Table 1. Comparison of diagnostic tests for *H. pylori* on 268 patients in the United States.

Test	Sensitivity	Specificity	PPV	NPV
Histology (WS)	93.1	99	99.4	88.7
Urease (CLO test)	89.6	100	100	84.1
Urea breath test	90.2	95.8	87.5	84.3
Serology (IgG)	91.3	91.6	95.2	85.3

From Cutler et al. [8], with permission.

PPV: positive predictive value; NPV: negative predictive value; WS: Warthin-Starry stain; CLO: commercial urease test for *H. pylori* performed on a gastric mucosal biopsy; IgG: immunoglobulin G.

increases with the use of special stains including the Warthin-Starry, Giemsa, or Genta stain. The finding of acute and chronic inflammation of the gastric mucosa is virtually diagnostic of *H. pylori* infection, regardless of whether bacteria are visible microscopically. Conversely, the absence of chronic inflammation is a good indicator for the absence of *H. pylori* infection.

Culture for detection of *H. pylori* is rarely necessary in clinical practice. Culture is time- and labor-intensive; *H. pylori* requires special microaerophilic conditions in which to grow. The main role of culture is to test for bacterial antibiotic sensitivities in patients in whom the infection had proved difficult to eradicate [12].

Although it has been argued that patients with an endoscopic diagnosis of duodenal ulcer do not require confirmation of *H. pylori* infection, *H. pylori*-negative duodenal ulceration is a growing problem particularly in the United States, as discussed below. Therefore the cause of the duodenal ulcer should be confirmed before embarking on a course of eradication therapy.

How to test for *H. pylori* infection depends on the clinical situation [3]. The UBT is the method of choice for diagnosing infection and for documenting cure of infection after treatment. If an ulcer is detected at upper endoscopy, a biopsy urease test is recommended. Blood or serum antibody tests may be used to confirm the presence of infection in patients with a previous diagnosis of peptic ulcer. They should be used when the UBT is unavailable. In patients with bleeding ulcers, it is relatively easy to detect *H. pylori* infection by upper endoscopy. However, the presence of blood in the stomach may produce a false-negative result on a biopsy urease test. Patients with bleeding peptic ulcer and *H. pylori* infection should start treatment for the infection prior to hospital discharge [3, 13].

Treatment of Peptic Ulcers and *H. pylori* Infection

Most peptic ulcers heal following treatment with H₂-receptor antagonists (H₂RAs) or proton pump inhibitors (PPIs) or with certain "site-protective" drugs (e.g., sucralfate). However, since the majority of ulcers are due to chronic infection with *H. pylori*, such treatment alone is no longer considered adequate or appropriate [1–4]. Because eradication of *H. pylori* infection in ulcer patients usually provides a permanent cure of the ulcer diathesis, eradication is now the recommended treatment for all infected patients with peptic ulcers [1–4]. In patients with a benign gastric ulcer, it may not be possible to determine the precise etiology, as both nonsteroidal antiinflammatory drug (NSAID) use and *H. pylori* infection may be present. If so, *H. pylori* infection should be

Table 2. Metaanalysis of *H. pylori* eradication regimens (119 studies, 6416 patients).

Regimen	Days	Nonadjusted eradication rate (%)	Compliance-adjusted eradication rate (%)	Δ
PBMT	7	96	85	11
PCM	7	91	84	7
BMT	14	90	80	10
PCA	14	89	82	7
PMA	7	84	76	8
PC	14	72	65	7
BMA	14	70	62	8
PA	14	63	58	5

From Taylor et al. [14], with permission, copyright 1997, American Medical Association.

P: proton pump inhibitor; B: bismuth; M: metronidazole; T: tetracycline; C: clarithromycin; A: amoxicillin.

treated as part of the overall management, and NSAID use should be addressed separately (see below).

The comparative efficacy of the various eradication regimens has been analyzed by meta-analysis [14–16] (Table 2).⁴ Bismuth-based regimens with two antibiotics ("triple") and a PPI ("quadruple") and regimens containing a PPI plus two antibiotics are the most effective. Ranitidine bismuth citrate (RBC), a unique entity, 400 mg b.i.d. with clarithromycin 500 mg t.i.d. for 2 weeks produced eradication rates of 73% and 84%, respectively, in U.S. trials [17].

The consensus conferences that addressed goals of therapy, generally recommended regimens that achieved eradication rates in controlled trials of >90% on a "per-protocol" analysis, and >80% on an "intent-to-treat" analysis. The regimens that meet this goal are relatively few and include triple combinations of a PPI plus clarithromycin and amoxicillin or metronidazole or the quadruple regimen of a PPI plus bismuth, metronidazole, and tetracycline (Table 3) [18]. The combination of RBC plus two antibiotics may also reach this goal, but more published results are needed. The duration of therapy remains somewhat unsettled. Most consensus conferees [1, 2, 4] have recommended PPI triple therapies for a duration of just 1 week based on the results of large European trials of omeprazole or lansoprazole in combination with clarithromycin and metronidazole or amoxicillin. The consensus conference in the United States recommended therapy for 2 weeks because of skepticism that U.S. trials would produce 1-week results comparable to those of the European trials [3, 19].

Vaccination against *H. pylori* infection is a possibility for the future. It would have to be administered orally with a suitable, safe adjuvant. Preliminary trials of the use of a vaccine therapeutically (rather than prophylactically) have produced reduced colonization with *H. pylori* in some patients [20].

Outcomes of *H. pylori* Eradication

Eradication of *H. pylori* infection produces a fundamental change in the natural history of ulcer disease and virtually eliminates recurrence of duodenal or gastric ulcers (i.e., eradication cures the disease). There are also important economic benefits to eradicating *H. pylori* infection in ulcer patients, as most of the cost of treating the disease is expended on managing recurrence. Reinfection following cure of *H. pylori* infection is less than 2% of adult

Table 3. Treatment regimens requiring a proton pump inhibitor to achieve *H. pylori* eradication rates of $\geq 90\%$ and $\geq 80\%$ by per-protocol and intent-to-treat analyses.

Treatment	Duration (days)	Studies	No.	Eradication rates (%)	
				Per protocol	Intent to treat
PC250A	7	20	1236	87 (83–91)	84 (79–90)
PC500A	7	9	514	91 (88–97)	90 (86–94)
PC250M	7	27	1635	89 (85–92)	86 (82–90)
PC500A	7	4	253	91 (85–99)	91 (81–100)
P+BMT	7	17	1006	95 (91–98)	87 (81–92)

From Huang et al. [18], with permission.

P: proton pump inhibitor; C250: clarithromycin 250 mg b.i.d.; C500: clarithromycin 500 mg b.i.d.; B: bismuth; M: metronidazole; A: amoxicillin; T: tetracycline.

patients per year in developed countries [21]. Reinfection is more frequent in young children and in underdeveloped nations with relatively poor standards of hygiene and sanitation. In patients who have bled from a duodenal ulcer, cure of *H. pylori* infection produces a substantial reduction in the rate of recurrent hemorrhage for at least the next 1 to 2 years [13, 22].

Why Patients Fail in Eradication Therapy

Clinicians are increasingly encountering treatment failures. The reasons for failure have been reviewed [23, 24].

Use of Ineffective Regimens. In a recent survey, U.S. physicians reported using 103 different eradication regimens; many were ineffective or of unknown effectiveness [25]. Altogether 18% of family physicians and general internists and 16% of gastroenterologists reported using dual therapies despite evidence that triple and quadruple regimens are superior in efficacy and cost-effectiveness.

Noncompliance. The impact of noncompliance on eradication rates with bismuth triple therapy was well documented by Graham and colleagues [26]. They found a 30% reduction in efficacy in patients who took less than 60% of their medication. Taylor and colleagues [14] calculated the impact of noncompliance with several *H. pylori* eradication regimens at 5% to 11% (Table 2). The largest reductions in eradication rates were found with PPI-bismuth-metronidazole-tetracycline (PBMT) quadruple therapy for 7 days (11% reduction) and BMT for 14 days (10%). However, after adjusting for these reductions in efficacy, these regimens were still among the most cost-effective regimens. Vakil and Fennerty [27] determined eradication rates for a variety of widely used dual and triple regimens in patients treated in the community. With the possible exception of the BMT and omeprazole-BMT regimens, eradication rates were similar to those reported in large meta-analyses [14, 15, 26]. Overall, the available evidence indicates that clinicians should be less concerned with noncompliance than with prescribing the most effective regimen.

Resistance to Antibiotics. *H. pylori* resistance to antimicrobial agents is a major cause of failed eradication therapy, having been reported in about two-thirds of treatment failures [28]. Resistance to metronidazole is ubiquitous and increasing in most regions of the world. Eradication rates for otherwise effective regimens drop to 20% to 65% in the presence of metronidazole resistance [29]. The incidence of primary resistance to clarithromycin remains

under 10% in most countries and seems to be relatively stable [30].

The most practical approach to the problem of resistance is to use regimens that are effective regardless of the presence of metronidazole resistance. A large European trial determined that the combination of omeprazole, amoxicillin, and clarithromycin was effective in more than 90% of patients with metronidazole resistance compared to eradication rates of 76% and 42% with omeprazole-metronidazole-clarithromycin and metronidazole-clarithromycin combinations, respectively [31].

H. pylori and Gastroesophageal Reflux Disease

The relation between *H. pylori* infection and gastroesophageal reflux disease (GERD), once thought to be nonexistent, has become a clinically relevant issue in light of reports suggesting that the presence of *H. pylori* infection may in some way afford some protection against the development of GERD. Hallerback and colleagues [32] found that the prevalence of GERD relapses was lower in *H. pylori*-positive patients than in *H. pylori*-infected patients treated continuously with omeprazole 10 or 20 mg per day; and Mihara et al. [33] found that the presence of moderate to severe *H. pylori* gastritis appeared to be protective against the development of severe GERD. The latter finding might be attributable to reduced acid secretion in patients with severe corpus gastritis with atrophy [34]. Labenz and colleagues [35] reported that *H. pylori* eradication in duodenal ulcer patients was followed by a significant increase in the prevalence of erosive esophagitis after 3 years. This observation, if confirmed, obviously has clinical implications and is relevant to the debate about whether *H. pylori* eradication is universally beneficial.

Another area of confusion is the possible risk of embarking on long-term PPI therapy for GERD in patients who also harbor *H. pylori* infection. The concern arose from the report by Kuipers and colleagues [36] that *H. pylori*-positive Dutch patients treated with omeprazole for 5 years for GERD had a higher prevalence of corpus atrophic gastritis than did a cohort of Swedish *H. pylori*-positive GERD patients treated with antireflux surgery. However, new information caused the U.S. Food and Drug Administration (FDA) to conclude that the evidence did not support the conclusion that PPI therapy accelerates the development of atrophic gastritis, intestinal metaplasia, or gastric adenocarcinoma [37]. Of particular relevance to the FDA's conclusion was the study by Lundell and colleagues [38]. This study was similar to the Kuipers study in that two cohorts of patients were studied. One cohort was treated with omeprazole chronically, and the other cohort was

treated with antireflux surgery. The Lundell study differed, however, in that it was a randomized trial of patients of comparable age. No significant difference was found in the prevalence of corpus atrophic gastritis in omeprazole- and surgery-treated patients. These conflicting reports need to be resolved by a definitive study of the influence of PPI therapy on *H. pylori*-induced atrophic gastritis.

Peptic Ulcers and NSAIDs

Interactions between H. pylori Infection and NSAIDs

Helicobacter pylori infection and NSAID use are generally regarded as independent risk factors for ulcer disease. The prevalence of *H. pylori* infection is not altered in patients taking NSAIDs. Use of NSAIDs does not affect rates of infection with *H. pylori*. There is no convincing evidence that *H. pylori* plays a role in dyspeptic symptoms in patients taking an NSAID. However, a study from Hong Kong found a reduced incidence of new ulcers in patients in whom *H. pylori* eradication was undertaken before initiating treatment with an NSAID, suggesting an interaction between *H. pylori* infection and NSAID usage [39]. To complicate matters, a large multinational study reported *higher* NSAID-related ulcer healing rates with either an H₂RA or a PPI in patients who have *H. pylori* infection, suggesting that *H. pylori* infection *protects* against the development of NSAID-related ulcers [40]. Clearly, no recommendations can yet be made about eradicating *H. pylori* infection to protect against NSAID-related ulcers.

Prevention of NSAID-related Ulcers

Various drugs reduce the occurrence of new gastric or duodenal ulcers when given along with an NSAID. Ranitidine was initially shown to reduce the incidence of new duodenal ulcers, but not gastric ulcers, in patients taking NSAIDs. Another study found that famotidine 40 mg b.i.d. reduced the incidence of both duodenal and gastric ulcers in patients taking an NSAID [41]. Misoprostol, a synthetic derivative of prostaglandin E₁, reduces the incidence of new gastric and duodenal ulcers in patients taking an NSAID and reduces the incidence of NSAID-related ulcer complications in patients taking an NSAID [42].

The PPIs have not been extensively studied in regard to the prevention of NSAID-induced ulcer. Omeprazole was shown to be superior to both misoprostol and ranitidine in preventing recurrent gastric or duodenal ulceration in patients with recently healed NSAID-related ulcers and in whom NSAID use was continued [40].

Treatment of NSAID-related Ulcers

Ulcer healing is delayed if the NSAID is continued. For treatment of NSAID-related gastric ulcer, 8 weeks of ranitidine 150 mg b.i.d. healed 100% of ulcers in patients in whom the NSAID was stopped and 79% of ulcers in patients in whom the NSAID was continued [43]. Omeprazole 40 mg daily is superior to ranitidine 150 mg b.i.d. for healing NSAID-related gastric ulcers [44]. Omeprazole is also superior to misoprostol for healing these ulcers [40].

H. pylori-negative Ulcers

Absence of *H. pylori* infection has been documented in the United States in up to 42% of patients with peptic ulcer [45]. Many of the *H. pylori*-negative patients were elderly. Some of these results may be explicable on the basis of false-negative tests for *H. pylori* infection, the surreptitious or unconscious use of aspirin or NSAIDs [46], or Zollinger-Ellison syndrome. However, some patients have truly "idiopathic" *H. pylori*-negative peptic ulcer disease [47]. These patients may have a particularly severe ulcer diathesis characterized by refractoriness to H₂RAs, rapid recurrence after healing, and a high incidence of complications. Long-term medical treatment with a PPI is the most appropriate form of management.

Résumé

La plupart des ulcères gastro-duodénaux sont en rapport avec une infection à *Helicobacter pylori* (*H. pylori*). La meilleure façon d'en faire le diagnostic est le test respiratoire à l'urée, qui sert également à témoigner de l'efficacité de l'éradication. La sérologie est utile pour témoigner d'une infection antérieure ou actuelle, mais pas pour déterminer si l'infection a été efficacement éradiquée. En général, on n'a pas besoin d'examen endoscopique pour le diagnostic. Le traitement moderne de la maladie ulcéreuse consiste en l'éradication de l'infection à *H. pylori*. Les régimes thérapeutiques les plus efficaces sont un inhibiteur de la pompe à protons combiné à la clarithromycine et à l'amoxicilline ou un inhibiteur de la pompe à protons combiné au bismuth, au métronidazole et à une tétracycline. Le taux de ré-infections est de moins de 2% par an dans les pays «développés». On dispose de certaines preuves suggérant que l'éradication de l'*H. pylori* peut favoriser la survenue d'une œsophagite érosive mais on doit encore le confirmer. Des études récentes suggèrent également une interaction entre l'infection à *H. pylori* et les ulcères gastroduodénaux en rapport avec l'utilisation de médicaments anti-inflammatoires non-stéroïdiens (AINS). Cependant, les études sont en contradiction : l'une a montré que l'éradication de l'*H. pylori* protège contre les ulcères en rapport avec les AINS, une autre a suggéré que c'est l'infection qui protège. Il est plus difficile de traiter les ulcères qui ne sont pas en rapport avec l'*H. pylori*, surtout aux Etats-Unis, où une étude récente a montré que 42% des ulcères n'ont pas de rapport avec l'infection. Certains de ces ulcères non-*H. pylori* sont réfractaires aux doses usuelles de médicaments anti-sécrétoires.

Resumen

Muchas de las úlceras pépticas se deben a la infección por "*Helicobacter pylori*" ("*H. pylori*"). La infección se detecta fácilmente mediante el test del radiocarbono-urea, que también es capaz de demostrar si se ha conseguido erradicar el germen mediante un adecuado tratamiento. Los tests serológicos son útiles antes o durante la infección, pero son incapaces de determinar si se ha conseguido o no la erradicación del germen. Los tests endoscópicos, generalmente, no son necesarios para establecer el diagnóstico. El tratamiento actual de la úlcera péptica consiste en la erradicación del "*H. pylori*" en pacientes infectados por dicho germen. Para ello, la combinación de un inhibidor de la bomba de protones asociado a la claritromicina y

amoxicilina o bien, el inhibidor de la bomba de protones más bismuto, metronidazol y tetraciclinas, constituyen los tratamientos más efectivos. Reinfecciones anuales menores al 2% se observan en los países desarrollados. Estudios recientes sugieren que la erradicación del “*H. pylori*” podría favorecer el desarrollo de esofagitis erosivas; sin embargo, se necesita un mayor número de estudios para confirmar o no, esta posibilidad. Trabajos actuales sugieren la existencia de una interacción entre la infección por “*H. pylori*” y úlceras pépticas producidas por el uso de drogas antiinflamatorias no esteroideas (NSAIDs). Sin embargo, los estudios al respecto son contradictorios: unos, demuestran que la erradicación del “*H. pylori*” ejerce una acción protectora sobre la génesis de úlceras secundarias al uso de los NSAID; otros, sugieren que la infección proporciona una protección contra el desarrollo de la úlcera. Úlceras pépticas no-“*H. pylori*” constituyen un auténtico desafío, sobre todo en USA, en donde un estudio reciente ha demostrado que el 42% de las úlceras pépticas no eran debidas a la infección por el “*H. pylori*”. En efecto, algunas úlceras no-“*H. pylori*” son refractarias a los medicamentos antisecretoarios administrados en dosis normales.

References

- Lee, J., O'Morain, C.: Who should be treated for Helicobacter pylori infection? A review of consensus conferences and guidelines. *Gastroenterology* 113(Suppl. 1):S99, 1997
- European Helicobacter pylori Study Group (EHPG): Current European concepts in the management of H. pylori infection: the Maas-tricht consensus report. *Gut* 41:8, 1997
- Report of the Digestive Health Initiative International Update Conference on Helicobacter pylori. *Gastroenterology* 113:(Suppl. 1):S4, 1997
- Hunt, R.H., Thompson, A.: Canadian Helicobacter pylori consensus conference. *Can. J. Gastroenterol.* 12:31, 1998
- Cave, D.R.: How is Helicobacter pylori transmitted? *Gastroenterology* 113(Suppl. 1):S9, 1997
- Cover, T.L.: Commentary: Helicobacter pylori transmission, host factors, and bacterial factors. *Gastroenterology* 113(Suppl. 1):S29, 1997
- Malfetheriner, P., Freston, J.W.: Helicobacter pylori-induced gastric and ulceration: epidemiology, pathophysiology and therapeutics. In: *Gastrointestinal Pharmacology and Therapeutics*, E.D. Jacobson, editor, Philadelphia, Lippincott-Raven, 1997, pp. 21–29
- Cutler, A.F., Havstad, S., Ma, C., Blaser, M., Perez-Perez, G., Shubert, T.: Accuracy of invasive and noninvasive tests to diagnose Helicobacter pylori infection. *Gastroenterology* 109:136, 1995
- Chey, W.D., Spybrook, M., Carpenter, S., Nostrant, T.T., Elta, G.H., Scheiman, J.M.: Prolonged effect of omeprazole on the ¹⁴C urea breath test. *Am. J. Gastroenterol.* 91:89, 1996
- Chey, W.D., Woods, M., Scheiman, J.M., Nostrant, T.T., DelValle, J.: Lansoprazole and ranitidine affect the accuracy of the ¹⁴C-urea breath test by a pH-dependent mechanism. *Am. J. Gastroenterol.* 92:446, 1997
- Laine, L., Lewin, D., Naritoku, W., Estrada, R., Cohen, H.: Prospective comparison of commercially available rapid urease tests for the diagnosis of Helicobacter pylori. *Gastrointest. Endosc.* 44:523, 1996
- Megraud, F.: How should Helicobacter pylori infection be diagnosed? *Gastroenterology* 113(Suppl. 1):S93, 1997
- Howden, C.W.: For what conditions is there evidence-based justification for treatment of Helicobacter pylori infection? *Gastroenterology* 113(Suppl. 1):S78, 1997
- Taylor, J.L., Zagari, M., Murphy, K., Freston, J.W.: Pharmacoeconomic comparison of treatments for the eradication of H. pylori. *Arch. Intern. Med.* 157:87, 1997
- Unge, P.: What other regimens are under investigation to treat Helicobacter pylori infection? *Gastroenterology* 113(Suppl. 1):S131, 1997
- Huang, J.Q., Chiba, N., Wilkinson, J.M., Hunt, R.H.: One week clarithromycin 500 mg bid is better than 250 mg bid for eradicating Helicobacter pylori (H. pylori) infection when combined with proton pump inhibitor and metronidazole or amoxicillin: a meta-analysis [abstract]. *Gastroenterology* 112:A153, 1997
- Peterson, W.L., Ciociola, A.A., Sykes, D.L., McSorley, D.J., Webb, D.D.: Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H. pylori and reducing ulcer recurrence. *Aliment. Pharmacol. Ther.* 10:251, 1996
- Huang, J.Q., Chiba, N., Wilkinson, J.M., Hunt, R.H.: Which combination therapy can eradicate > 90% Helicobacter pylori (H. pylori) infection? A meta-analysis of amoxicillin, metronidazole, tetracycline and clarithromycin containing regimens [abstract]. *Gastroenterology* 112:A19, 1997
- Freston, J.W.: What remaining questions regarding Helicobacter pylori and associated diseases should be addressed by future research? View from North America. *Gastroenterology* 113:(Suppl. 1):S163, 1997
- Czinn, S.J.: What is the role for vaccination in Helicobacter pylori? *Gastroenterology* 113(Suppl. 1):S149, 1997
- Forbes, G.M., Glasser, M.E., Cullen, D.J.E., Warren, J.R., Christiansen, K.J., Marshall, B.J., Collins, B.J.: Duodenal ulcer treated with Helicobacter pylori eradication: seven-year follow-up. *Lancet* 343:258, 1994
- Vaira, D., Menegatti, M., Miglioli, M.: What is the role of Helicobacter pylori in complicated ulcer disease? *Gastroenterology* 113(Suppl. 1):S78, 1997
- Borody, T.J., Shortis, N.P.: Treatment of patients with failed eradication: a personal view. In: *Helicobacter pylori: Basic Mechanisms to Clinical Cure 1996*, R. Hunt, G.N.J. Tytgat, editors, Dordrecht, Kluwer, 1996, pp. 357–365
- Freston, J.W.: Helicobacter pylori: The Clinical Agenda. In: *Helicobacter pylori: Basic Mechanisms to Clinical Cure 1998*, R. Hunt, G.N.J. Tytgat, editors, Dordrecht, Kluwer, 1998, pp. 1–9
- Breuer, T., Goodman, K.J., Malaty, H.M., Sudhop, T., Graham, D.Y.: How do clinicians practicing in the U.S. manage Helicobacter pylori-related gastrointestinal diseases? A comparison of primary care and specialist physicians. *Am. J. Gastroenterol.* 93:553, 1998
- Graham, D.Y., Lew, G.M., Malaty, H.M., Evans, D.J., Klein, P.D., Alpert, L.C., Genta, R.M.: Factors influencing the eradication of Helicobacter pylori with triple therapy. *Gastroenterology* 102:493, 1992
- Vakil, N., Fennerty, B.: Cost-effectiveness of treatment regimens for H. pylori-infection based on a community practice effectiveness study [abstract]. *Gastroenterology* 112:A28, 1997
- Cayla, R., Zerbib, F., Talbi, P., Megraud, F., Lamouliatte, H.: Pre and post treatment clarithromycin resistance of Helicobacter pylori strains: a key factor of treatment failure [abstract]. *Gut* 37(Suppl. 1):A55, 1995
- Megraud, F.: What is the relevance of resistance of Helicobacter pylori to antimicrobial agents? In: *Helicobacter pylori: Basic Mechanisms to Clinical Cure 1996*, R. Hunt, G.N.J. Tytgat, editors, Dordrecht, Kluwer, 1996, pp. 348–356
- Megraud, F., Camou-Juncas, C., Occhialini, A., Birac, C.: Helicobacter pylori resistance levels to clarithromycin remain stable [abstract]. *Gastroenterology* 100:A192, 1996
- Lind, T., Megraud, F., Bardhan, K.D., Bayerdorffer, E., Hellblom, M., O'Morain, C., Spiller, R.C., Unge, P., Veldhuyzen van Zanten, S.J.O., Wrangstadh, M., Zeijlon, L., Cederberg, C.: The MACH2 study: antimicrobial resistance in Helicobacter pylori therapy—the impact of omeprazole [abstract]. *Gut* 41(Suppl. 1):A89, 1997
- Hallerback, B., Unge, P., Carling, L., Edwin, B., Glise, H., Havu, N., Lyrenas, E., Lundberg, K.: Omeprazole or ranitidine in long-term treatment of reflux esophagitis: the Scandinavian Clinics for United Research group. *Gastroenterology* 107:1305, 1994
- Mihara, M., Haruma, K., Kamada, T., Kiyohira, K., Goto, T., Sumii, M., Tanaka, S., Yoshihara, M., Sumii, K., Kajiyama, G.: Low prevalence of Helicobacter pylori infection in patients with reflux esophagitis [abstract]. *Gut* 39(Suppl. 2):A94, 1996
- Kuipers, E.J., Uterlinde, A.M., Pena, A.S., Roosendaal, R., Pals, G., Nelis, G.F., Festen, H.P., Meuwissen, S.G.: Long-term sequelae of Helicobacter pylori gastritis. *Lancet* 345:1525, 1995
- Labenz, J., Blum, A.L., Bayerdorffer, E., Meining, A., Stolte, M., Borsch, G.: Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 112: 1442, 1997

36. Kuipers, E.J., Lundell, L., Klinkenberg-Knol, E.C., Havu, N., Festen, H.P., Liedman, B., Lamers, C.B., Jansen, J.B., Dalenback, J., Snel, P., Nelis, G.F., Meuwissen, S.G.: Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N. Engl. J. Med.* 334:1018, 1996
37. Freston, J.W.: Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective. *Am. J. Gastroenterol.* 4(Suppl. 1):51S, 1997
38. Lundell, L., Havu, N., Andersson, A., Miettinen, P., Myrvold, H.E., Pedersen, S.A., Thor, K.: Gastritis development and acid suppression therapy revisited: results of a randomized clinical study with long-term follow-up [abstract]. *Gastroenterology* 112:A28, 1997
39. Chan, F.K.L., Sung, J.J.Y., Chung, S.C.S., To, K.F., Yung, M.Y., Leung, V.K., Lee, Y.T., Chan, C.S., Li, E.K., Woo, J.: Randomized trial of eradication of Helicobacter pylori before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* 350:975, 1997
40. Hawkey, C.J., Karrasch, J.A., Szczepanski, L., Walker, D.G., Barkun, A., Swannell, A.J., Yeomans, N.D.: Omeprazole compared with misoprostol for ulcers associated with non-steroidal anti-inflammatory drugs: omeprazole vs. misoprostol for NSAID-induced ulcer management. (OMNIUM) Study Group. *N. Engl. J. Med.* 338:727, 1998
41. Taha, A.S., Hudson, N., Hawkey, C.J., Swannell, A.J., Tyre, P.N., Cottrell, J., Mann, S.G., Simon, T.J., Sturrock, R.D., Russell, R.I.: Famotidine for the prevention of gastric and duodenal ulcers caused by non-steroidal anti-inflammatory drugs. *N. Engl. J. Med.* 334:1435, 1996
42. Silverstein, F.E., Graham, D.Y., Senior, J.R., Davies, H.W., Struthers, B.J., Bittman, R.M., Geis, G.S.: Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs. *Ann. Intern. Med.* 123:241, 1995
43. Lancaster-Smith, M.J.: Ranitidine in the treatment of non-steroidal anti-inflammatory drug-associated gastric and duodenal ulcers. *Gut* 32:252, 1991
44. Walan, A., Bader, J.P., Classen, M., Lamers, C.B., Piper, D.W., Rutgersson, K., Eriksson, S.: Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N. Engl. J. Med.* 320:69, 1989
45. Maher, W., Jyotheeswaran, S., Potter, G., Shaw, A., Malkin, M., Joseph, D., Wagner, D., Faiello, P., Chey, W.Y.: An epidemiological study of peptic ulcer disease patients in greater Rochester, New York [abstract]. *Gastroenterology* 113:A206, 1997
46. Hirschowitz, B.I., Lanas, A.: Intractable peptic ulceration due to aspirin (ASA) abuse in patients who have not had gastric surgery [abstract]. *Gastroenterology* 113:A149, 1997
47. McColl, K.E.L., El-Nujumi, A.M., Chittajallu, R.S., Dahill, S.W., Dorrain, C.A., El-Omar, E., Penman, I., Fitzsimons, E.J., Drain, J., Graham, H., Ardill, J.E.S., Bessent, R.: A study of the pathogenesis of Helicobacter pylori negative chronic duodenal ulceration. *Gut* 34:762, 1993