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The problem of *Helicobacter pylori*-negative idiopathic ulcer disease

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Ulcer disease is an infectious disease, but for how much longer? Reports of a large number of non-infectious ulcers are becoming more frequent, parallelling the changing prevalence of *Helicobacter pylori* (*H. pylori*) in many parts of the world. This chapter will address factors involved in the increasing proportion of *H. pylori*-negative ulcers, the probable cause of such ulcers and the clinical implications related to their management. This discussion is currently most relevant to those regions of the world where the prevalence of *H. pylori* is already low or rapidly decreasing. However, it is possible that, even in other areas of the world, the prevalence of infection will also eventually change and *H. pylori*-negative ulcer disease will become more important.

Key words: *H. pylori*; ulcer disease; non-steroidal anti-inflammatory drugs; acid hypersecretion.

Helicobacter pylori (*H. pylori*), which infects 50% of the world's population, is unquestionably the most common cause of ulcer disease. In most parts of the world, ulcers are uncommon, virtually non-existent in those not infected with the bacterium. In fact *H. pylori*-associated active chronic gastritis appears to be the pre-requisite for most duodenal and gastric ulcers world-wide. Curing the infection resolves the gastritis, heals the ulcers and, most importantly, prevents ulcer complications and recurrence.

It, however, remains to be seen how long this will continue to be the case. In many areas of the world, the prevalence of *H. pylori* infection is rapidly decreasing, partly as a result of optimizing sanitation, public health education efforts and a lower childhood acquisition rate.[1] Fewer infection-related clinical events, especially duodenal ulcers, are the result of this change in prevalence. A greater proportion of ulcer patients today do not have *H. pylori* infection, particularly the very young[2], the elderly[3] and those with ulcer complications.[4,5] Other causes of ulcer disease are becoming more evident, but an increasing number of individuals are found to have no obvious cause for their ulcer. This change in demographics, the expanding list of aetiologies and the absence in some patients of an obvious cause will undoubtedly impact on future ulcer diagnosis and management. As *H. pylori* becomes less prevalent, testing for infection may become less important or at least require the use of very sensitive and specific diagnostic techniques. Management strategies will change since non-infectious ulcers cannot be cured with antibiotics and will probably recur unless treated with maintenance acid anti-secretory medications. This is particularly relevant since acid suppression with

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traditional maintenance doses of H_2-receptor antagonist and proton pump inhibitors may be less effective in those with *H. pylori*-negative ulcer disease.[6]

PREVALENCE OF *HELICOBACTER PYLORI*-NEGATIVE ULCERS

The prevalence of *H. pylori*-negative ulcers varies considerably between regions of the world and even between areas within the same geographical locality. Although the sensitivity of bacterial testing, non-steroidal anti-inflammatory drug (NSAID) use and other infections or conditions can explain some of these differences, the population prevalence of infection is the major factor influencing the frequency of *H. pylori*-negative ulcer disease. Circumstances that determine bacterial acquisition, for example ethnicity, socio-economic status and childhood living conditions, also determine the percentage of ulcers that are related or unrelated to infection. Figure 1 illustrates this concept. Let us assume that the absolute number of *H. pylori*-negative ulcers stays constant over time (an assumption that may not, however, be true given the increased use of NSAIDs), and that the number of *H. pylori*-positive ulcers declines during this same period, reflecting the change in community prevalence of infection. The net result is a reduction in the total number of ulcers, although the proportion of *H. pylori*-negative ulcers will actually increase.

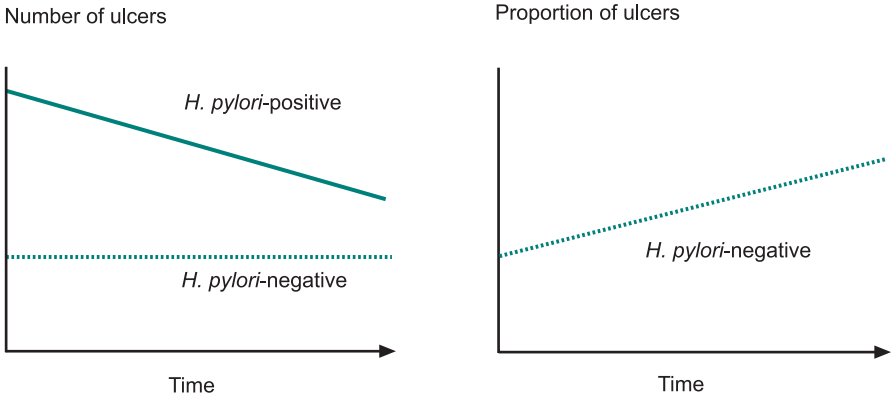

Figure 1. Increasing proportion of *H. pylori*-negative ulcers.

Graham has constructed a hypothetical model to further illustrate the relationship between *H. pylori* prevalence and *H. pylori*-negative ulcer disease.[7] If for example in his model, *H. pylori* prevalence changes from 80% to 40% and the total number of duodenal ulcers from other causes remains stable at 250 per 100 000, the total number of ulcers will decline from 1050 to 650 per 100 000, while the proportion of *H. pylori*-negative ulcers will increase from 24% to 38%. Therefore, a greater proportion of *H. pylori*-negative ulcers will be diagnosed clinically.

Is this *H. pylori*-negative ulcer phenomenon a clinical reality? In the past, centres from around the world, including the USA, have reported a greater than 90% and 80% prevalence of *H. pylori* infection in patients with duodenal and gastric ulcers respectively.[8] The elimination of the bacteria virtually obviated subsequent ulcer recurrence.[8] In 1994, based on such data, a National Institutes of Health Consensus Conference

concluded that ulcer disease was an infectious disease that could be cured by bacterial eradication.[9] In fact, the association between infection and ulcers, especially duodenal ulcers, was so strong that some even questioned the need to test for bacteria if an ulcer were found at the time of endoscopy.[10] More recent reports suggest that a considerable proportion of ulcers now may be non-infectious in origin. Some of these reports were compiled retrospectively, used less than ideal methods to exclude infection and failed entirely to account for the use of NSAIDs or other confounding medications. Nevertheless, the results summarized in Tables 1 and 2 from the USA and other countries do suggest that the proportion of *H. pylori*-negative ulcers, while varying somewhat, appears to be rising and may relate to community *H. pylori* prevalence. These reports also point to other factors such as NSAID use and, surprisingly, older age, which may predispose to non-infectious ulcers.

Table 1. *H. pylori*-negative ulcers: United States reports.

Year	Reference	Location	N	Ulcer type	% *H. pylori* negative
1996	11	Houston	100	DU	1
			145	GU	8
1996	16	Multicentre	183	DU	30
1997	12	Orlando	59	DU	52
1997	13	Baltimore	80	PUD	61
1997	14	Multicentre	166	PUD	40
1997	15	Multicentre	201	DU	20
1997	5	Los Angeles	339	Bleeding	
				DU	27
				GU	36
1998	18	Rochester	144	DU	39
			127	GU	39
1999	19	Richmond	41	DU	39
			43	GU	47
1999	17	Multicentre	2394	DU	27

DU=duodenal ulcer; GU=gastric ulcer; PUD=unspecified peptic ulcer.

Table 2. *H. pylori*-negative ulcers: other countries' reports.

Year	Reference	Location	N	Ulcer type	% *H. pylori* negative
1993	20	Glasgow, Scotland	435	DU	3
1993	4	Glasgow, Scotland	80	Perforated DU	53
1997	21	Glasgow, Scotland	76	DU	4
			28	GU	14
1996	22	Espoo, Finland	707	DU and Pyloric	2
1997	3	Turku, Finland	125	PUD	30
1998	24	New Castle, Australia	125	DU	45
1999	23	Madrid, Spain	774	DU	5
1999	25	Sydney, Australia	14	DU	43
			33	GU	58
			7	DU and GU	43

DU=duodenal ulcer; GU=gastric ulcer; PUD=unspecified peptic ulcer.

Let us first examine details of US studies. In 1996, workers from Houston, Texas demonstrated a high prevalence of *H. pylori* in 100 duodenal and 145 gastric ulcer patients.[11] Ninety-nine percent of those with duodenal ulcers and 92% of those with gastric ulcer were infected; those few uninfected were taking NSAIDs. These data confirmed the strong association between *H. pylori* and ulcers, but the Veterans Affairs (VA) hospital population from which the patients were drawn presumably has a high prevalence of infection. In contrast, reports from a community practice in Orlando[12], a University hospital endoscopy unit in Baltimore[13] and a large national physician health study centred in Boston[14] suggest that *H. pylori* may account for only 40–60% of ulcers in populations where the prevalence of *H. pylori* is possibly lower.

While NSAIDs have been shown to be responsible for many non-infectious ulcers, others have no obvious cause found. Two multicentre trials found no evidence of *H. pylori* infection in 20% and 30% respectively of subjects with endoscopically documented duodenal ulcer.[15,16] These individuals presumably had idiopathic duodenal ulcer disease since they had been pre-screened for NSAID use, known acid hypersecretion and other confounding medical conditions. A recent analysis of data from six multicentre pharmaceutical trials (including data from Peterson et al[15] and Lanza et al[16]) involving more than 2300 subjects revealed that 27% of endoscopically confirmed duodenal ulcers were unrelated to *H. pylori* infection or NSAIDs.[17] Jensen et al observed that 30% of bleeding duodenal or gastric ulcer patients were *H. pylori* negative, a relatively high proportion in an area such as Los Angeles where the background prevalence of *H. pylori* would be expected to be quite high.[5] NSAIDs accounted for some of these non-infectious complicated ulcers, yet for others no cause was identified.

Jyotheeswaran et al illustrated the relationship between race, population prevalence of *H. pylori* and bacteria-associated ulcers.[18] Of a total of 1272 patients reviewed, 160 were found with duodenal ulcer and 145 with gastric ulcer. Thirty-nine per cent of ulcer patients were *H. pylori* negative. However, when the data were analysed according to race, 47% of whites had *H. pylori*-negative ulcers compared with 22% of non-whites. The background prevalence of *H. pylori* in those without ulcers was 24% in whites and 54% in non-whites. NSAID users were excluded from this analysis, so most *H. pylori*-negative ulcers were presumably idiopathic. In Richmond, Virginia, where the prevalence of *H. pylori* is low, 40% of ulcers at a VA medical centre were not caused by *H. pylori*.[19] Further characterization of these ulcers suggested that one third were truly idiopathic, not being associated with *H. pylori*, NSAIDs or acid hypersecretion. Finally, in large multicentre US duodenal ulcer trials, up to 20% of ulcers recurred following successful bacterial eradication. This suggests that some individuals may have an *H. pylori*-negative ulcer diathesis and coincidentally be infected with the bacterium.[20]

Physicians in the USA are clearly seeing a larger proportion of *H. pylori*-negative ulcers, some resulting from NSAIDs but others apparently idiopathic. What about other parts of the world? In 1993, McColl et al identified only 12 *H. pylori*-negative ulcer patients in a group of 435 individuals with duodenal ulcer cared for in a large hospital in Glasgow.[21] Of these 12 patients, 4 used NSAIDs, 1 presumably had duodenal Crohn's disease and 1 Zollinger–Ellison syndrome. Thus, in this series of over 400 duodenal ulcer patients, only six 'idiopathic' ulcers were identified. From Glasgow in the same year, Reinbach et al reported that of 80 patients with perforated duodenal ulcer, only 47% were infected with *H. pylori*.[4] They concluded that unlike chronic duodenal ulcer, which is an infectious disease, acute perforated duodenal ulcer has a different pathogenesis. A later report from Glasgow confirmed the high prevalence of *H. pylori* in those with uncomplicated ulcers.[22] Infection was found in 96%

of those with duodenal, and 86% of those with gastric, ulcers. The prevalence of *H. pylori* was 50% in non-ulcer dyspeptic and hospital controls.

Two studies from different regions of Finland report different rates of *H. pylori*-negative ulceration. Investigators from Espoo[23] found *H. pylori* in 98% of 707 individuals with duodenal and/or pylori ulcers, while those from Turku[3] noted infection in only 70% of 125 peptic ulcer disease patients (duodenal and gastric ulcers combined). In Turku, older and younger patients were compared. In those older than 65 years of age, gastric ulcers were more common, bleeding more often present, and NSAID use more frequent. Interestingly, *H. pylori* was less common in the older age group (56% versus 92%), and of those elderly patients who did not use NSAIDs, 35% were *H. pylori* negative. The prevalence of *H. pylori* in a non-ulcer dyspeptic control population was 30%. Investigators from Madrid noted a strong association between duodenal ulcer and *H. pylori* infection: 95% of 774 individuals with duodenal ulcer were infected.[24] Most of the remaining 5% were taking NSAIDs or antibiotics, which may have interfered with *H. pylori* testing, and only 6 of the 774 duodenal ulcers could be considered idiopathic.

As is the case in the USA, ulcers in Australia are less frequently caused by *H. pylori* infection. During a retrospective analysis of 125 duodenal ulcer patients, Henry and Batey found that 56 (45%) were not infected with *H. pylori*.[25] Eight had previously been treated for infection and presumably had *H. pylori*-negative ulcer recurrence. A number were taking NSAIDs, were heavy smokers and/or drinkers, or were taking proton pump inhibitors, which may have decreased the sensitivity of testing. Of the 35 individuals with recent ulcer bleeding, 40% were *H. pylori* negative. Henry and Batey suggested that the prevalence of *H. pylori* was lower than expected in their duodenal ulcer population and that other factors such as NSAIDs remain important in ulcer pathogenesis. Xia et al, from Sydney, studied 54 patients with ulcer disease; 14 had duodenal ulceration, 33 gastric ulceration and 7 both. The prevalence of *H. pylori* was 57%, 42% and 57% respectively in these groups.[26] NSAID use was not reported by Xia et al, but since *H. pylori*-negative duodenal ulcers tended to be multiple and gastric ulcers located in the antrum (NSAID-associated characteristics), it is probable that NSAIDs were responsible for at least some of these ulcers.

North American and Australian reports suggest that *H. pylori*-negative ulcers are more common than was previously thought. NSAIDs account for many of these lesions, but some are true idiopathic ulcers. In Europe, where the population prevalence of infection is presumably higher than in the USA and Australia, ulcer remains primarily an infectious disease. However, in Europe, complicated ulcers and ulcers in the elderly are less often the result of infection. Thus, even in parts of the world where the prevalence of *H. pylori* is high, idiopathic mechanisms may cause some ulcers.

THE AETIOLOGY OF *HELICOBACTER PYLORI*-NEGATIVE ULCER DISEASE

There are several reasons why an individual with a gastric or duodenal ulcer might not have associated *H. pylori* infection. First, the test for infection may be inaccurate. For example, serology detects antibodies to *H. pylori* in serum or whole blood, the presence of such antibodies in a previously untreated ulcer patient being taken as indirect evidence of active infection. While serology is convenient, inexpensive, non-invasive, widely available and often the first test of choice in primary care practice to diagnose *H. pylori* infection, it is not 100% sensitive. In fact, false-negative test results occur in 10–15% of cases, especially when blood is obtained by a finger stick.[27]

Furthermore, tests that identify active infection, for example histology, bacterial culture, the biopsy urease test and the urea breath test, are all negatively influenced by the recent use of bismuth, antibiotics and/or proton pump inhibitors.[10] Therefore, before concluding that an ulcer is unrelated to *H. pylori*, several tests should be negative and/or a test for active infection should be repeated after stopping bismuth, antibiotics or proton pump inhibitors for an appropriate length of time.

Aspirin and NSAID use are common in the general population, many individuals using prescription or over-the-counter forms of these medications on a daily basis. The prevalence of ulcers in chronic NSAID users is at least 15%, gastric ulcers being more common than duodenal.[28,29] The elderly, those using high doses or multiple NSAIDs, and those with a previous ulcer appear to be at greatest risk of NSAID-associated ulcer. Whether or not *H. pylori* and NSAIDs interact to affect ulcer risk remains controversial, but NSAID-associated ulcers occur frequently in those with no evidence of bacterial infection.[29] Therefore, in any *H. pylori*-negative ulcer patient, NSAID or aspirin use should be strongly suspected as a cause and systemically excluded. Whether the new COX-2-specific NSAIDs will appreciably reduce medicinal ulcer disease remains to be seen, although early clinical experience suggests that these drugs are quite safe, are well tolerated and produce fewer gastroduodenal lesions.[30]

Other less common causes of gastric and duodenal ulcers include acid hypersecretory conditions such as Zollinger–Ellison syndrome, and gastroduodenal Crohn's disease. McColl et al diagnosed two such patients in a series of more than 400 individuals with duodenal ulcer.[21] Cytomegalovirus and other organisms can cause gastric and duodenal ulcers, usually as a manifestation of systemic infection, especially in an immunocompromised patient.[31] Other helicobacter species cause ulcers but do so less frequently than infection with *H. pylori*. Stolte et al reported 202 patients with *H. heilmannii* gastritis, of whom only eight had ulcers, which were usually associated with NSAID use.[32] Debongie et al also reported an association between *H. heilmannii* and gastric ulcer.[33] Fourteen patients were described, all with newly diagnosed, non-recurring gastric ulcer. None had evidence of *H. pylori* infection, and gastric histology demonstrated only mild inflammatory changes. The healing of these ulcers was associated with the disappearance of *H. heilmannii* infection and a resolution of the inflammatory changes.

Kemppainen et al described a group of elderly patients whose ulcers were associated with neither *H. pylori* nor NSAIDs.[3] They speculated that age-related changes could lead to a weakening of the mucosal defence mechanisms, rendering the mucosa more susceptible to peptic ulceration. These authors proposed that since mucosal blood flow was particularly important in delivering nutrients to epithelial cells, transporting neutralizing bicarbonate and disposing of back-diffused acid, some ulcers in the elderly might be due to reduced mucosal blood flow from underlying vascular disease.

Ulcers not associated with *H. pylori*, NSAID use or other obvious causes should for the present be viewed as 'idiopathic'. McColl et al encountered only six such patients during 5 years while treating 435 individuals suffering from duodenal ulcer.[21] Five of the six had normal antral histology. Their median integrated gastrin responses and peak acid outputs were similar to those of *H. pylori*-positive duodenal ulcer patients but significantly higher than those seen in non-ulcer controls. All had accelerated gastric emptying, and each lacked a specific blood group A antigen gene, suggesting a genetic basis for the disturbed gastric function. These *H. pylori*-negative ulcer patients were very difficult to manage clinically; all had longstanding (median 8 years) recurrent dyspepsia and ulcers that had been difficult to control with medication. Four patients

failed to heal their ulcers despite 3 months on H_2-receptor antagonists, 2 were subsequently treated with omeprazole, and 1 required highly selective vagotomy. Two had ulcer bleeding, requiring transfusion. Bleeding occurred in one despite maintenance H_2-receptor antagonist therapy.

The phenomenon of *H. pylori*-negative complicated ulcer disease has also been described by a number of other investigators, even those from areas of the world with a high prevalence of *H. pylori*.[3–5,25] This observation was so conflicting that some actually questioned the accuracy of testing for infection in the bleeding ulcer patient.[34] The issue appears now to have been resolved: testing is accurate, but a greater proportion of complicated ulcers are non-infectious. Many are caused by NSAIDs (occasionally surreptitious), but some are idiopathic, possibly due to uniquely altered gastric acid physiology.

Harris et al studied seven men who had symptomatic, endoscopically documented ulcer recurrence at least 6 months after successful *H. pylori* eradication therapy.[35] NSAID use and other unusual causes of ulcer recurrence were excluded. Comparing gastric acid secretory studies in these 7 men with *H. pylori*-negative healthy controls and 10 *H. pylori*-positive duodenal ulcer patients before and 6 months after *H. pylori* eradication, these authors confirmed McColl et al's observations of acid hypersecretion in those with *H. pylori*-negative duodenal ulcer.[21] Harris et al speculated that hypersecretion was caused by an increased parietal cell mass and that perhaps the *H. pylori* infection that had been cured was not the cause of these duodenal ulcers. They further noted that maintenance anti-secretory treatment or possibly surgery would remain necessary for a subset of duodenal ulcer patients, those who could not be cured with antibiotics, to prevent recurrence.

CLINICAL IMPLICATIONS OF *HELICOBACTER PYLORI*-NEGATIVE ULCER DISEASE

As the proportion of *H. pylori*-negative ulcers increases, the clinical management of patients will undoubtedly change. For example, an *H. pylori* test-and-treat strategy has been proposed as a cost-effective method to manage individuals with dyspepsia.[36] A cost analysis of such a management strategy assumes that the number of endoscopic procedures will be reduced since eradicating *H. pylori* should improve the outcome in some individuals. The elimination of dyspeptic symptoms in those with non-ulcer dyspepsia remains controversial, and a reduction of subsequent gastric cancer risk by bacterial cure is not a major issue in most developed areas of the world. Therefore, the basis of the test-and-treat strategy is curing peptic ulcer disease, thereby eliminating recurrent dyspeptic symptoms. As the number of *H. pylori*-associated ulcers decreases in the population, this test-and-treat strategy will become less favourable economically. This is especially true since 20% or more of those cured of *H. pylori* infection may develop subsequent *H. pylori*-negative ulcers.[20]

As management changes, so too will testing for infection. The positive predictive value of the various diagnostic tests depends on the prevalence of *H. pylori* in the population being tested. As the *H. pylori* prevalence decreases, serology will become less useful, being associated with more false-positive test results. Non-invasive techniques assessing for active infection, for example the urea breath test and stool antigen test, will assume greater importance in the primary care setting.

Ulcer treatment will also change. *H. pylori*-negative ulcers cannot be cured with antibiotics. *H. pylori*-negative ulcer patients will undoubtedly have recurrent symptoms

and possibly be at greater risk of complications. Since the apparent underlying mechanism of 'idiopathic' *H. pylori*-negative ulcer disease relates to altered gastric acid physiology, such patients will be candidates for chronic maintenance acid anti-secretory therapy, which presents potential problems. Studies establishing the efficacy of standard low doses of H_2-receptor antagonists or proton pump inhibitors in preventing ulcer recurrence were presumably performed mainly in *H. pylori*-positive ulcer patients. Whether such doses will be effective in preventing *H. pylori*-negative ulcer recurrence is unknown. Anti-secretory medications are less effective in controlling gastric pH in *H. pylori*-negative than *H. pylori*-positive individuals.[6] This reduced anti-secretory efficacy could result in a reduced ability to prevent *H. pylori*-negative ulcer recurrence. Pending data to the contrary, one should use full doses of H_2-receptor antagonists or proton pump inhibitors as maintenance therapy in *H. pylori*-negative ulcer patients, especially since non-infectious ulcers appear to be especially prone to complications.

SUMMARY

Prior to the 1980s, no-one seriously implicated infection as a major cause of ulcer disease. Now, to question the association between ulcers and *H. pylori* would be viewed as heretical. In the future, as the population demographics of infection change, non-infectious ulcers will again predominate, and scientists will be challenged to find a cause(s) for these idiopathic ulcers in the hope of delivering a long-term cure. Clinicians will also be challenged. Faced with a number of possible aetiologies of ulcers, they will need correctly to identify the unique cause in each individual patient in order to manage symptoms appropriately and prevent recurrence. Acid peptic disease is about to go back to the future. This journey will hopefully be unencumbered with the biases of the past.

REFERENCES

1. Parsonnet J. The incidence of *Helicobacter pylori* infection. *Alimentary Pharmacology and Therapeutics* 1995; **9 (supplement 2):** 45–51.
2. Kennedy NH, Friedman CR, Stockwell J & Gold BD. Pediatric hospitalizations due to peptic ulcer disease in the era of *Helicobacter pylori*: analysis of the pediatric hospital information system. *Gastroenterology* 1999; **116:** A212.
3. Kemppainen H, Raiha I & Sourander L. Clinical presentation of peptic ulcer in the elderly. *Gerontology* 1997; **43:** 283–288.
4. Reinbach DH, Cruickshank G & McColl KEL. Acute perforated duodenal ulcer is not associated with *Helicobacter pylori* infection. *Gut* 1993; **34:** 1344–1347.
5. Jensen DM, Cheng S, Jensen ME et al. Risk factors and recurrence of ulcer haemorrhage. *Gastroenterology* 1997; **112:** A160.
* 6. Gillen D, Wirz AA, Neithercut WD et al. *Helicobacter pylori* infection potentiates the inhibition of gastric acid secretion by omeprazole. *Gut* 1999; **44:** 468–475.
7. Graham DY. Large U.S. clinical trials report a high proportion of *H. pylori* negative duodenal ulcers at study entry as well as a high recurrence rate after cure of the infection: Have we all been wrong? *Gastroenterology* 1998; **114:** A17.
8. Kuipers EJ, Thijs JC & Festen HPM. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Alimentary Pharmacology and Therapeutics* 1995; **9 (supplement 2):** 59–69.
* 9. Anonymous. *Helicobacter pylori* in peptic ulcer disease. *Journal of the American Medical Association* 1994; **272:** 65–69.

10. Cutler AF. Testing for *Helicobacter pylori* in clinical practice. *American Journal of Medicine* 1996; **100:** 35S–41S.
11. al-Assi MT, Genta RM, Karttunen TJ & Graham DY. Ulcer site and complications: relation to *Helicobacter pylori* infection and NSAID use. *Endoscopy* 1996; **28:** 229–233.
12. Sprung DJ & Gano B. The natural history of duodenal ulcer disease and how it relates to *H. pylori* – a community study. *American Journal of Gastroenterology* 1997; **92:** 1655–A286.
13. Gislason GT, Emu B, Okolo P III et al. Where have all the Helicobacter gone? Etiologic factors in patients with duodenal ulcers (DU) presenting to a university hospital. *Gastrointestinal Endoscopy* 1997; **45:** AB90.
14. Greenberg PD, Albert CM, Ridker PM et al. *Helicobacter pylori* as a risk factor for peptic ulcers in patients taking low-dose aspirin. *Gastroenterology* 1977; **112:** A133.
15. Peterson WL, Ciociola AA, Sykes DL et al. Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating *H. pylori* and reducing ulcer recurrence. *Alimentary Pharmacology and Therapeutics* 1996; **10:** 251–261.
16. Lanza F, Ciociola AA, Sykes D et al. Ranitidine bismuth citrate plus clarithromycin is effective in eradicating *H. pylori*, healing duodenal ulcers, and preventing ulcer relapse. *Gastroenterology* 1996; **110:** A172.
*17. Ciociola AA, McSorley DJ, Turner K et al. *Helicobacter pylori* infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. *American Journal of Gastroenterology* 1999; **94:** 1834–1840.
18. Jyotheeswaran S, Shah AN, Jin HO et al. Prevalence of *Helicobacter pylori* in peptic ulcer patients in greater Rochester, NY: is empirical triple therapy justified? *American Journal of Gastroenterology* 1998; **93:** 574–578.
19. Schubert M, DeWitt JM & Taylor CA. Prospective evaluation of the prevalence of *H. pylori* in duodenal and gastric ulcer: is its role overstated? *Gastroenterology* 1999; **116:** A305.
*20. Laine L, Hopkins RJ & Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. *American Journal of Gastroenterology* 1998; **93:** 1409–1415.
*21. McColl KEL, El-Nujumi AM, Chittajallu RS et al. A study of the pathogenesis of *Helicobacter pylori* negative chronic duodenal ulceration. *Gut* 1993; **34:** 762–768.
22. McColl KEL, El-Nujumi A, Murray L et al. The *Helicobacter pylori* breath test: a surrogate marker for peptic ulcer disease in dyspeptic patients. *Gut* 1977; **40:** 302–306.
23. Hyvarinen H, Salmenkyla S & Sipponen P. *Helicobacter pylori*-negative duodenal and pylori ulcer: role of NSAIDs. *Digestion* 1996; **57:** 305–309.
24. Gisbert JP, Blanco M, Mateos JM et al. *H. pylori*-negative duodenal ulcers. Prevalence and causes in 774 patients. *Gastroenterology* 1999; **116:** A171.
25. Henry A & Batey RG. Low prevalence of *Helicobacter pylori* in an Australian duodenal ulcer population. NSAIDitis or the effect of ten years of *H. pylori* treatment? *Australia and New Zealand Journal of Medicine* 1998; **28:** 345.
26. Xia H, Phung N, Kalander J & Talley NJ. Characteristics of *Helicobacter pylori* positive and negative peptic ulcer disease. *Gastroenterology* 1999; **116:** A359.
27. Lopez-Brea M, Alarcon T & Megraud F. Diagnosis of *Helicobacter pylori* infection. *Current Opinion in Gastroenterology* 1997; **13 (supplement 1):** 13–19.
28. Singh G & Ramey DR. NSAID induced gastrointestinal complications: the ARAMIS perspective – 1997. *Journal of Rheumatology* 1998; **25 (supplement 51):** 8–16.
29. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointestinal Endoscopy Clinics of North America* 1996; **6:** 489–504.
30. Hawkey CJ. COX-2 Inhibitors. *Lancet* 1999; **353:** 307–314.
31. Fantry GT & Tramont EC. Gastric infection. In Brandt LJ (ed.) *Clinical Practice of Gastroenterology*, pp 373–384. Philadelphia: Current Medicine, 1999.
32. Stolte M, Kroher G, Meining A et al. A comparison of *Helicobacter pylori* and *H. heilmannii* gastritis. A matched control study involving 404 patients. *Scandinavian Journal of Gastroenterology* 1997; **32:** 28–33.
33. Debongnie JC, Donnay M, Mairesse J et al. Gastric ulcers and *Helicobacter heilmannii*. *European Journal of Gastroenterology and Hepatology* 1998; **10:** 251–254.
34. Laine L & Cohen H. *Helicobacter pylori*: drowning in a pool of blood? *Gastrointestinal Endoscopy* 1999; **49:** 398–402.
*35. Harris AW, Gummett PA, Phull PS et al. Recurrence of duodenal ulcer after *Helicobacter pylori* eradication is related to high acid output. *Alimentary Pharmacology and Therapeutics* 1997; **11:** 331–334.
36. Fendrick AM. Outcomes research in *Helicobacter pylori* infection. *Alimentary Pharmacology and Therapeutics* 1997; **11 (supplement 1):** 95–101.