

CLINICAL REVIEWS

Management of Peptic Ulcer Disease Not Related to *Helicobacter pylori* or NSAIDs

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ABSTRACT

Helicobacter pylori (*H. pylori*) infection is widely accepted as the most important factor in the pathogenesis of duodenal ulcer. However, in parallel with more effective eradication of *H. pylori*, the prevalence of *H. pylori* is changing, and *H. pylori*-negative peptic ulcer disease appears to be increasing. When making a diagnosis of *H. pylori*-negative peptic ulcer disease, it is essential to avoid misclassification because of inaccurate diagnosis. In addition, secondary causes may need to be excluded with appropriate investigations. In the absence of *H. pylori*, nonsteroidal anti-inflammatory drug usage is the most common cause of peptic ulcer; surreptitious nonsteroidal anti-inflammatory drug usage is a cause of unexplained ulcer disease in up to 60% of patients. Hypersecretory syndromes such as Zollinger-Ellison syndrome, although rare, need to be excluded. Once all known etiological factors are excluded, there remains a group of patients with so-called "idiopathic ulcers." The interplay of etiological factors in the pathogenesis of idiopathic peptic ulcer disease is poorly defined but may include a genetic predisposition, altered acid secretion, rapid gastric emptying, defective mucosal defense mechanisms, psychological stress, and smoking. The management of idiopathic peptic ulcers is not defined; they appear to be more resistant to standard therapy, can be associated with more frequent complications, and those that relapse may require long-term maintenance therapy. (Am J Gastroenterol 2002;97:2950–2961. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

It is established that chronic peptic ulceration is causally linked to *Helicobacter pylori* (*H. pylori*) infection and traditional nonsteroidal anti-inflammatory drugs (NSAIDs). In the 1980s and early 1990s, *H. pylori* was found to be present in more than 90% of patients with duodenal ulceration and 70% of gastric ulcers (1). However, the epidemiology of peptic ulcer disease has begun to dramatically change. In the new millennium, the proportion of peptic ulcers that are *H. pylori* negative appears to be increasing based on endoscopic series from around the world (2–4). This has paralleled a decline of *H. pylori* in Western countries, and is likely to be further influenced by the greater use of cyclooxygenase (Cox)-2 specific NSAIDs.

We aimed to systematically review the prevalence of unexplained ulceration and the possible mechanisms inducing idiopathic peptic ulcer. We also aimed to formulate a management plan for this problematic group of patients. A MEDLINE search using the following key words in combination with peptic ulcer were used: *Helicobacter pylori* negative (480), idiopathic (63), smoking (663), psychological stress (638), nonsteroidal anti-inflammatory agents (2673), genetics (642), and prevalence (205) from 1995 to 2001. Sixty-eight articles that were relevant to the topic were selected from the search.

Prevalence of *H. pylori*-Negative Peptic Ulceration

A number of studies have reported a lower prevalence of *H. pylori* infection in duodenal ulcer disease; the results are summarized in Table 1 (2–25). In the United States, a retrospective study by Jyotheeswaran *et al.* reported that only 61% of 144 patients with duodenal ulcers had *H. pylori* in New York, even when 16 patients taking NSAIDs were excluded (22). However, because of the retrospective nature of the study, an underestimation of NSAID use may have occurred. Gislason *et al.* found that only 39% of their patients with duodenal ulcer had *H. pylori*, although this increased to 50% when patients exposed to antibiotics and bismuth were excluded (23). In a recent prospective study by Schubert *et al.*, *H. pylori* was present in 61% with duodenal ulceration and 53% with gastric ulceration (8). The low prevalence of *H. pylori* was confirmed by six large controlled trials in the United States (comprising a total of 2394 patients), which found that only 73% of patients with duodenal ulcers were infected with *H. pylori* (4). Further review of medical histories in those who were definitely *H. pylori* negative found that 20% might have surreptitiously ingested NSAIDs despite having negative tests for salicylates (4).

In northern Italy, the prevalence of *H. pylori*-negative peptic ulcer disease was found to be only 8% (3). Patients with *H. pylori*-negative peptic ulcer were significantly older by a decade (60.5 ± 3.3 vs 51.6 ± 0.74 yr, respectively) and had a higher prevalence of complications (35% vs 12%) than *H. pylori*-positive patients. Even after considering all known risk factors, 58% of the *H. pylori*-negative peptic ulcers were idiopathic ulcers (3). In a recent Danish study, 12% of duodenal ulcers were *H. pylori* negative with 31% of these associated with NSAID usage. In addition, they demon-

Table 1. Prevalence of *H. pylori*-Negative Ulcers

Author (Reference), Yr	Type of Study	Population Recruited	<i>H. pylori</i> -Negative Ulcers (%)	NSAIDs in <i>H. pylori</i> -Negative Ulcers (%)	Total Idiopathic Ulcers (%)	Comment, Serum Gastrin
Ciociola <i>et al.</i> (4), 1999	Randomized, controlled	2394 DU	657/2394 (27)	133/657 (20) Surreptitious	524/2394 (22)	
Arakawa <i>et al.</i> (5), 2000	Prospective	889 total 521 GU 368 DU	26/889 (2.9) 13/521 (2.5) GU 13/368 (3.5) DU	*9/889 (1) 6/521 (1.2) GU 3/368 (0.8) DU	16/889 (1.8) 7/521 (1.3) GU 9/368 (2.4) DU	1 Crohn's disease
Gisbert <i>et al.</i> (7), 1999	Prospective	774 DU	36 (4.65)	21/36 (58)	6/774 (0.8)	Gastrin checked in 467
Schubert <i>et al.</i> (8), 1999	Prospective	84 total 43 GU 41 DU	36/84 (43) 20/43 (47) GU 16/41 (39) DU	24/36 (67) 14/20 (70) GU 10/16 (63) DU	12/84 (14) 6/43 (30) GU 6/41 (15) DU	Gastrin checked
Ng <i>et al.</i> (9), 1996	Prospective	73 perforated DU	22/73 (30)	10/22 (45)	12/73 (16)	Gastrin not checked
Xia <i>et al.</i> (2), 2000	Cross-sectional, prospective	54 total 34 GU/14 DU/6 GU and DU	22/51 (43) 17 GU/5 DU	4/22 (18) 3 GU/1 DU	18/54 (33)	
Bytzer <i>et al.</i> (5), 2001	Cross-sectional, prospective	275 DU	32/275 (12)	10/32 (31)	22/275 (8)	
Sprung and Apter (10), 1998	Retrospective Prospective	112 DU 52 36 GU 16 DU	76/112 (68) 36/52 (69) 25/36 (69) GU 11/16 (69) DU	37/76 (49) 13/36 (36) 7/25 (28) GU 6/11 (55) DU	39/112 (35) 23/52 (44) 18/36 (50) GU 5/16 (31) DU	
Aoyama <i>et al.</i> (11), 2000	Cross-sectional	302 total 146 GU 111 DU 45 DU/GU	11/302 (3.6) 9/146 (6.2) GU 2/111 (1.8) DU 0/45 DU/GU	2/11 (18) 2/9 (22) GU 0/2 DU	8/302 (2.6) 6/146 (4.1) GU 2/111 (1.8) DU	
Meucci <i>et al.</i> (3), 2000	Cross-sectional	409 84 GU 317 DU 8 DU/GU	31/409 (7.6) 7/84 (8.3) GU 24/314 (7.6) DU 0/8 DU/GU	12/31 (39)	19/409 (4.6)	1 Crohn's disease, no ZES
Nishikawa <i>et al.</i> (12), 2000	Cross-sectional	398 total 246 GU 152 DU	14/398 (3.5) 12/246 (4.9) GU 2/152 (1.3) DU	9/14 (64)	5/398 (1.3)	Gastrin and pepsinogen checked
Higuchi <i>et al.</i> (13), 1999	Cross-sectional	330 DU	12 (3.6)	3/12 (25)	8/330 (2.4)	1 Crohn's disease, gastrin checked
Tsuji <i>et al.</i> (14), 1999	Cross-sectional	335 total 215 GU 120 DU	9/335 (2.7) 7/215 (3) GU, 5 undetermined 2/120 (1.7) DU, 3 undetermined	3/9 (33) 2/7 (28.6) GU 1/2 (50) DU	6/335 (1.8) 5/215 (2.3) 1/120 (0.8)	Gastrin checked
Henriksson <i>et al.</i> (15), 1998	Cross-sectional	106 acute bleeding ulcers 53 GU 53 DU	24/106 (23) 11/53 (21) GU 13/53 (25) DU	14/24 (58)	10/106 (94)	
Uyub <i>et al.</i> (16), 1994	Cross-sectional	55 total 21 GU 32 DU 2 DU/GU	37/55 (67) 20/21 (95) GU 15/32 (43) DU 2/2 (100) DU/GU	13/21 0/32	7/21 15/32 (47) DU	
Borody <i>et al.</i> (17), 1992	Cross-sectional	115 GU	44/115 (38)	29/44 (66)	13/115 (11)	2 malignant GU
Borody <i>et al.</i> (18), 1991	Cross-sectional	302 DU	18/302 (6)	8/18 (44)	1/303 (0.3)	2 Crohn's disease, 2 <i>Gastrospirillum hominis</i> , 1 with pancreatic cancer, Serum gastrin checked
Nensey <i>et al.</i> (19), 1991	Cross-sectional	52 DU	12/52 (23)	9/12 (75)	3/52 (6)	1 ZES

(continued)

Table 1. Continued

Author (Reference), Year	Type of Study	Population Recruited	<i>H. pylori</i> -Negative Ulcers (%)	NSAIDs in <i>H. pylori</i> -Negative Ulcers (%)	Total Idiopathic Ulcers (%)	Comment, Serum Gastrin
Vu and Ng (20), 2000	Retrospective	107 total 53 GU 47 DU 7 GU/DU	25/107 (23) 17/53 (32) GU 7/47 (15) DU 1/7 (14) GU/DU		12/107 (11) 7/53 (13) GU 5/47 (11) DU	
Henry and Batey (21), 1998	Retrospective	125 DU	56 (44.8)	50/125 (40)		
Jyotheeswaran <i>et al.</i> (22), 1998	Retrospective	305 total 145 GU 160 DU	140/305 (46) 68/145 (47) GU 72/160 (45) DU	34/140 (24) 18/68 (26) GU 16/72 (22) DU	106/305 (35) 50/145 (34) GU 56/160 (35) DU	
Gislason <i>et al.</i> (23), 1997	Retrospective	80 DU	39/80 (50)	15/39 (38)	24/80 (30)	
Hyvarinen <i>et al.</i> (24), 1996	Retrospective	707	16/707 (2.3)	13/16 (81)	3/707 (0.4)	
McColl <i>et al.</i> (25), 1993	Case control	12 <i>H. pylori</i> -negative DU		4/12 (30)	6/12 (50)	1 Crohn's disease, 1 ZES

DU = duodenal ulcer; GU = gastric ulcer; ZES = Zollinger-Ellison syndrome.

* % of NSAIDs in all ulcers.

strated that *H. pylori*-negative duodenal ulcers were associated with a poorer prognosis mainly because of a higher rate of ulcer and symptom relapse (5).

In Australia, Henry and Batey observed that only 55% of patients with duodenal ulcers were infected with *H. pylori* (21). Similarly, Xia *et al.* observed that only 56% with active ulcer disease had *H. pylori*; of the patients with *H. pylori*-negative ulcers, 5% were NSAID users (2). Moreover, Xia *et al.* reported that gastric ulcers had become more common than duodenal ulcers, a reverse of the gastric to duodenal ulcer prevalence 15 yr ago in Australia (2).

In Japan, where the prevalence of *H. pylori* infection in the general population is high, the prevalence of *H. pylori*-negative peptic ulcer is reportedly very low (2.7–3.6%) (11–14). Although the majority of the *H. pylori*-negative peptic ulcer patients were taking NSAIDs in Nishikawa's study (12), in other studies, about two thirds of the *H. pylori*-negative ulcers were idiopathic (6, 11, 13). The true prevalence of *H. pylori*-negative peptic ulcer could have been underestimated, as it was unclear whether patients taking recent antibiotics and antisecretory treatment were excluded. Interestingly, the prevalence of *H. pylori* appears to be decreasing in Japan, as evident in a recent prospective study by Fujisawa *et al.* (26). A clear cohort shift in the overall prevalence of *H. pylori* infection was demonstrated over the last 20 yr, with the prevalence decreasing from 73% to 39% (26). However, despite the fall in prevalence of *H. pylori* infection, the attributable risk of *H. pylori* infection in peptic ulcer disease has not changed, based on a cross-sectional study of 396 patients with active peptic ulcers or ulcer scars found by endoscopic examination (27). Thus, the apparent increase in the frequency of non-*H. pylori* ulcers cannot be entirely explained by the declining prevalence of infection.

Ethnic differences in ulcer rates caused by *H. pylori* appear to occur in the northeastern peninsular of Malaysia.

Uyub *et al.* (16) found that 47% of duodenal ulcers and 95% of gastric ulcers were *H. pylori* negative, although 62% of the subjects with a gastric ulcer were NSAID users. When ethnic groups within Malaysia were considered, *H. pylori*-negative duodenal ulcers were significantly more common in Malays (15 of 20) compared with non-Malays (two of 14). This finding correlates with the low *H. pylori* infection rates of duodenal ulcers among Malays (27.8%) compared with the rate in non-Malays (86%). However, they did not take recent antibiotics and antisecretory drug use into consideration. In Goh's study (28), where recent antibiotic and bismuth or proton pump inhibitor (PPI) therapy was excluded, only 15% with peptic ulcer disease were *H. pylori* negative. Similarly, Goh found a higher prevalence of *H. pylori*-negative duodenal ulcers in the Malays and Chinese than in the Indians (28). Hence, ethnic differences exist in the prevalence of *H. pylori*-negative peptic ulcers, which appear to correlate with the background prevalence of *H. pylori* infection in Malaysia.

In southern China, the prevalence of *H. pylori*-negative peptic ulcers was reported to be 13% for duodenal ulcers and 10% for gastric ulcers. However, when patients taking bismuth or antibiotics within 4 wk of the endoscopy were excluded, there were no *H. pylori*-negative gastric ulcers and only 1% *H. pylori*-negative duodenal ulcers (29). In contrast, in a case-control study performed in Shanghai factory workers, 19% of peptic ulcers were *H. pylori* negative after excluding NSAID use (30). In addition, a recent retrospective study performed in Singapore with predominant Chinese subjects showed that 29% of all peptic ulcers were *H. pylori* negative after excluding NSAID use (20). The prevalence of *H. pylori* in the Chinese may also be decreasing. In a recent review of 1414 patients with peptic ulcers in Hong Kong, the prevalence of *H. pylori* in duodenal ulcers had decreased from 97% to 81% and in gastric ulcers, from 88% to 58% (31).

The true incidence of idiopathic peptic ulcer disease remains difficult to determine because of the cross-sectional nature of the studies to date. There is conflicting evidence on the relationship between *H. pylori*-negative ulcers and age. Kemppainen *et al.* showed that in a group of elderly patients who did not use NSAIDs, 35% were *H. pylori* negative, but no controls were evaluated (32). Interestingly, this is despite the increased prevalence of *H. pylori* infection with age. Moreover, others do not agree. Higuchi *et al.* demonstrated that there was a significantly higher incidence of idiopathic duodenal ulcers in the younger generation (<40 yr) (13). This is supported by Xia *et al.* who also demonstrated that patients with idiopathic ulcers were significantly younger (average age of 48.3 yr) (2). Hence, idiopathic ulcers appear to be a younger person's disease. There appears to be no sex predisposition.

Notably, there are a substantial number of patients with *H. pylori*-associated peptic ulcer disease who after eradication develop ulcer disease relapse. Hirschowitz *et al.* reported that 45% (five of 11) of duodenal ulcer patients without NSAID use who were cured of *H. pylori* infection then experienced symptomatic recurrences within 7 months after discontinuation of therapy (33). Peterson *et al.* reported a 32% ulcer recurrence rate in 19 patients during a 24-wk follow-up after having successfully eradicated *H. pylori* infection (34). Although there was no corroborative history, surreptitious NSAID use was a concern as five of 49 *H. pylori*-negative patients had osteo- or rheumatoid arthritis, or other painful conditions. The recent meta-analysis by Laine *et al.* showed that 20% had a duodenal ulcer recurrence within 6 months despite successful eradication of *H. pylori* and no reported use of NSAIDs (35). Similarly, Marshall *et al.* found that 21% of patients had a duodenal ulcer relapse during 12 months of follow-up after confirmed eradication of *H. pylori* and no NSAID usage (36). One possible explanation for these observations is that *H. pylori* infection-induced ulceration leaves a weakened mucosa that can break down despite the removal of a primary causal factor. The results overall suggest that etiological factors other than *H. pylori* play a significant role in a subset of ulcer patients.

Complicated Ulcer Disease

The prevalence of *H. pylori* infection has been reported to be lower in those with complicated ulcers than in those with uncomplicated ulcers. In a Scottish study, the prevalence of *H. pylori* infection in patients presenting with acute perforated duodenal ulcer was only 47%, suggesting a different pathogenesis from chronic recurrent duodenal ulcer disease (37). Although 44% of the acute perforated duodenal ulcer patients were taking NSAIDs, other pathogenic factors must be relevant. In another study where NSAID usage was excluded, 20% of acute perforated duodenal ulcers were *H. pylori* negative (38).

Hosking *et al.* (39) reported that there was a significant difference in prevalence of *H. pylori* in patients presenting

with bleeding duodenal ulcers. Twenty-nine percent of patients (31 of 102) with bleeding duodenal ulcers were *H. pylori* negative compared with 7% (nine of 121) with non-bleeding duodenal ulcers; only 19 of the 102 in the bleeding group were taking NSAIDs at the time of the bleeding (39). This was also demonstrated by Lee *et al.* who found that only 27% of patients with bleeding duodenal ulcers were *H. pylori* negative compared with 7% of patients with non-bleeding ulcers (40). However, NSAID use may have contributed to this difference in Lee *et al.*'s study, as 40% of patients reported NSAID use among both *H. pylori*-positive and *H. pylori*-negative patients presenting with bleeding. Meucci *et al.* reported that NSAID use (39% vs 12%) as well as ulcer-related complications (35% vs 10%) were significantly higher in *H. pylori*-negative than *H. pylori*-positive patients; even in the non-NSAID users, the complication rate remained high (3).

Definition of *H. pylori*-Negative Peptic Ulcers

Endoscopic evaluation is essential for an accurate diagnosis. Small ulcers and erosions can be difficult to differentiate, but any mucosal defect of at least 3 mm in diameter with depth is usually defined as a chronic ulcer (41). *H. pylori*-negative peptic ulcers should only be diagnosed after an adequate evaluation to exclude the presence of *H. pylori*. There are a number of possible explanations for *H. pylori*-negative peptic ulcers. Each of these will be reviewed in turn.

Misclassification of *H. pylori* Peptic Ulcers

Recent or current use of antibiotic or bismuth preparations can cause false-negative results for *H. pylori*. A number of studies have reported lower *H. pylori* prevalence rates in those who had recently received antibiotics. The study by Gisbert *et al.* observed that, although 96% who had not received antibiotics had *H. pylori* associated with their duodenal ulcer, only 78% appeared to have *H. pylori* among those who had recent antibiotic exposure (42). Borody *et al.* reported similar findings in a small cohort of *H. pylori*-negative duodenal ulcer patients (18).

In addition, PPI therapy has been shown to cause suppression of *H. pylori*. Laine *et al.* demonstrated that in patients whose *H. pylori* infection was not eradicated, 33% had a negative breath test after 28 days of PPI treatment (lansoprazole 30 mg/day); all of these patients reverted back to a positive test result by 2 wk after completion of therapy (43). Moreover, Chey *et al.* showed that the accuracy of the urea breath test was reduced in the presence of lansoprazole as well as to a lesser extent, with high-dose ranitidine (44). The false-negative results may be partly related to the ability of these drugs to suppress acid secretion *per se* and hence exert an inhibitory effect on *H. pylori* (44).

Sampling error is an issue as *H. pylori* can be patchy, and inappropriate diagnostic testing protocols may miss the infection (45–48). This is particularly true in the setting of current or recent use of PPI therapy or high-dose hista-

mine-2 antagonist therapy where proximal migration of *H. pylori* can occur and antral biopsies alone may be misleading (49, 50). However, Graham *et al.* has challenged this concept of proximal migration; omeprazole therapy resulted in a reduction in the density of *H. pylori* in both the antrum and the corpus, although there was a more pronounced effect in the antrum (51). In most patients, the number of *H. pylori* in the corpus was less post treatment than it was pretreatment but still detectable (51). In addition, the presence of atrophic gastritis and intestinal metaplasia can be associated with a lower infection rate because of reduced density of *H. pylori*. This increases the chance of sampling error; histopathology, culture, and the urease test may be negative and only serology positive (52–54).

The use of the rapid urease test alone to diagnose *H. pylori* in patients presenting with duodenal ulcer hemorrhage has been shown by Lee *et al.* to be associated with a lower sensitivity when compared with current “gold standard” criteria (antral and corpus biopsies or successful culture) (40). The false-negative rate was 25% (10 of 40). The failure to detect pH change by the urease test is mediated by albumin, and possibly other buffer systems in blood (55). Although blood in the antrum interferes with the sensitivity of the urease test, there is no effect on other tests; serology is the most sensitive followed by ¹³C-labeled urea breath test (56). This emphasizes that further diagnostic accuracy may be obtained by combining diagnostic tests.

The pretest prevalence of *H. pylori* infection is critical in interpreting any single test for the infection. For example, if the prevalence of *H. pylori* is 90% in duodenal ulceration, then a negative test for *H. pylori* that is 90% sensitive and specific has a 50% false-negative rate. On the other hand, if the prevalence of *H. pylori* is 50%, then a negative *H. pylori* test will be false in only one in 10 patients.

Hence, unless a combination of test methods is used, misclassification is more likely, and this may well explain some of the negative *H. pylori* duodenal ulcers in the literature that appear otherwise to be idiopathic. Use of two or more tests together (parallel testing) increases the sensitivity and the negative predictive value, but unfortunately decreases the specificity and positive predictive value. That is, *H. pylori* is less likely to be missed, but false-positive diagnoses are also more likely to be made (57). One strategy to consider is obtaining a rapid urease test initially and only perform a second test in those patients with a negative initial test to save on costs. Gastric biopsies for histopathology can be secured at endoscopy but not sent to the pathologist unless the rapid urease test was negative. However, even if two diagnostic tests are negative, a third may be needed in certain circumstances such as in the presence of widespread intestinal metaplasia. In addition, at least two biopsies should be taken at separate sites such as the body and antrum. Moreover, delaying testing for *H. pylori* for 4 wk after antibiotic use or for 1–2 wk after PPI use should be routine (58, 59).

H. pylori-Negative Peptic Ulcers and NSAIDs

In the past, the role of NSAIDs in duodenal ulcer disease was controversial, despite convincing evidence that NSAIDs are causally linked to gastric ulceration. Recently, NSAID use has been identified as the most frequent possible cause of ulceration in duodenal ulcer patients who are not infected with *H. pylori*. Studies have shown that 30–75% of *H. pylori*-negative ulcers are associated with the use of NSAIDs (19, 25). Moreover, large clinical trials testing prophylactic therapy for NSAID-induced ulceration have supported a causal link between duodenal ulcer disease and NSAID ingestion (41). In addition, the risk of ulcer bleeding, perforation, and death in elderly patients taking non-aspirin NSAIDs may be greater in those who are *H. pylori* negative (8.1-, 3.6-, to 18.4-fold, respectively) than in those who are *H. pylori* positive (3.5-, 1.4-, to 8.6-fold, respectively) (60). The protective effect of higher gastric prostaglandin levels in patients taking NSAIDs who are *H. pylori* positive may explain the difference (60).

The prevalence of drug-induced *H. pylori*-negative ulcer patients may even be higher because of surreptitious NSAID use. In several studies, NSAIDs have not been implicated in *H. pylori*-negative duodenal ulceration, but misclassification of non-NSAID users remains a methodological concern (61, 62). In a study of patients who have presented with GI perforation, 13% who claimed not having used aspirin previously had objective evidence of current aspirin use based on the platelet cyclo-oxygenase activity (63). Even more convincing is that in the majority (57%) of patients, intractable peptic ulcer disease in one study appeared to be caused by surreptitious aspirin use (64). Furthermore, Chinese herbal medicines and other alternative therapies may sometimes contain anti-inflammatory compounds that are not recognized by those taking the treatment (65, 66). Thus, serum salicylate levels especially in the context of intractable peptic ulcer disease can be useful. However, NSAID assays can be difficult and costly as they are only specific for each NSAID.

The position of the ulcer may provide additional clues to the etiology of peptic ulceration. *H. pylori* duodenal ulcers occur more commonly in the cap, whereas duodenal ulcers in the second part of the duodenum are more associated with NSAID use or the Zollinger-Ellison syndrome.

To heal NSAID ulcers, acid suppression with a PPI remains optimal therapy (41, 67). The prescription of Cox-2 inhibitors or cotherapy with potent acid suppressants or misoprostol in high-risk patients remains the mainstay of management and reduces the risk associated with NSAID use (60).

Other Drug-Related Ulcers

Apart from NSAIDs, it is recognized that other drugs, albeit more rarely, are potentially ulcer inducing. These include potassium chloride, nitrogen-containing bisphosphonates, and immunosuppressive medications such as mycophenolate. Graham and Malaty showed that in healthy volunteers

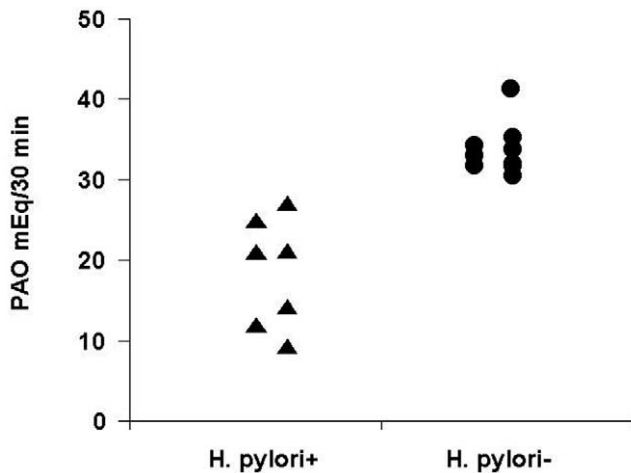


Figure 1. Peak acid output (PAO) in patients with Zollinger-Ellison syndrome who have and do not have *H. pylori*-associated gastritis histologically. From Fich et al. *Dig Dis Sci* 1991;36: 10–14 with permission.

who received 10 mg of alendronate, 8% (two of 24) developed antral ulcers, and 17% (four of 24) had large superficial antral erosions, which was significantly greater than in the placebo group (68). Of interest is that all the ulcers occurred in *H. pylori*-negative subjects. In addition, Blank *et al.* reported in animal experimentation that concomitant administration of bisphosphonates and indomethacin resulted in significant antral mucosal damage more than either drug alone (69). This suggests that bisphosphonates and traditional NSAIDs may act synergistically to induce damage in the antral region. Although the mechanism of GI intolerance associated with bisphosphonate therapy is unknown, a direct local reaction of the mucosa to contact with concentrated drug has been postulated, as the occurrence of gastritis and esophagitis is uncommon with *i.v.* dosing (70). GI ulceration and perforation have been described with wax/polymer matrix potassium chloride tablets predominantly in the small bowel, but peptic ulceration has also been reported (71). However, GI injury appears to be significantly less with microencapsulated potassium products.

Crack cocaine and/or amphetamine use has been reported to be associated with duodenal ulceration and perforation (72). Focal tissue ischemia induced by mucosal vasoconstriction may explain the perforation of gastroduodenal ulcers (73). In addition, chemotherapy has been implicated in gastric ulceration after hepatic arterial infusion of floxuridine (74).

Duodenal Ulcers Caused by Zollinger-Ellison Syndrome

An important, albeit rare, explanation for *H. pylori*-negative peptic ulcer disease is the Zollinger-Ellison syndrome. It is established that over 90% of patients with a gastrinoma will develop peptic ulceration sometime during their disease course (75). In one study, only 44% of ulcer patients with Zollinger-Ellison syndrome had *H. pylori* identified, and this was associated with a lower peak acid output (Fig. 1)

(76). Other groups have confirmed similar results (77, 78). Hence, the absence of *H. pylori* infection and NSAID use should raise the consideration of a gastrinoma.

Although gastrinoma-associated ulcers may be indistinguishable from ordinary peptic ulcers, several features should raise the level of suspicion including multiple ulcers, ulcers occurring distal to the duodenal bulb, and recurrent, refractory, or complicated peptic ulcer disease. The presence of diarrhea, weight loss, hypercalcemia, and prominent gastric folds are other important clues to the diagnosis of Zollinger-Ellison syndrome (79). Fasting serum gastrin determinations and provocative studies should be performed to confirm the diagnosis. Once a diagnosis of Zollinger-Ellison syndrome is made, consideration should be given to whether there is evidence of a multiple endocrine neoplasia type 1. Tumor localization can be sought by a somatostatin receptor scintigraphy or contrast CT scan, and an endoscopic ultrasound may be used to identify small tumors (80). However, if these tests fail to localize the tumor, the patient can be further examined with angiography, arterial stimulation venous sampling (81), or the tumor may still be located by surgery. The tumor should be resected where feasible; otherwise, patients are managed with high-dose PPI to control gastric acid.

Helicobacter heilmannii

Helicobacter heilmannii, another spiral-like nonspirochetal bacteria previously named *Gastrospirillum hominis*, causes a similar range of gastroduodenal pathology and has been reported in association with *H. pylori*-negative duodenal ulcers (18, 82, 83). However, it is much rarer than *H. pylori* and has a lower pathogenicity (84). It can be differentiated from *H. pylori* by routine histology. *Helicobacter heilmannii* in human gastric mucosa is thought to be transmitted from domestic animals such as dogs, cats (85, 86), monkeys (87), and pigs (88). Thus, changes in handling domestic animals may prevent transmission, but this has not been proven. Although it has been implicated in the pathogenesis of peptic ulcer disease in animals, additional studies are necessary before a causal relationship can be firmly established in humans. Small series and isolated case reports to date have demonstrated that bacterial eradication can be achieved with bismuth, omeprazole, metronidazole, and amoxicillin in variable combinations (82, 83, 87, 89).

Other Uncommon Infections Causing Ulcers

Cytomegalovirus was first associated with peptic ulcers in renal transplant recipients (90, 91). Peptic ulcers are infrequent in HIV-positive patients who present with upper GI symptoms; cytomegalovirus is the only organism to be significantly associated with peptic ulceration in HIV-positive patients (90). However, there have been case reports in nonimmunocompromised hosts (91). The ulcers in these patients are usually gastric and multiple. The diagnosis is made by finding intranuclear inclusion bodies and/or cyto-

megalovirus DNA in the gastric mucosa in biopsy specimens taken from the base of the ulcer.

The involvement of Herpes simplex virus type 1 in patients with peptic ulcer disease has been suggested by an increased incidence of antibodies and the detection of DNA and protein specific for this virus in the mucosa of the ulcer margin (92). These patients had antral or prepyloric ulcers; none had systemic disease or evidence of compromised immune function.

Other uncommon infectious causes of peptic ulceration include tuberculosis and syphilis. Endoscopic biopsies and appropriate cultures should be performed especially in the immunosuppressed and HIV-positive patients to exclude opportunistic infections.

Uncommon Disorders

Systemic mastocytosis causes duodenal ulcer, diarrhea, and skin manifestations (pruritus, flushing, or a maculopapular rash); serum histamine may be elevated, and mast cells infiltrate affected tissue (93). There are several other uncommon diseases that can cause ulceration in the duodenum or stomach, and may be misdiagnosed as ordinary peptic ulcer disease. These include Crohn's disease, lymphoma, carcinoma, radiation, and duodenal obstruction such as from an annular pancreas (94, 95). Biopsies from the ulcer can be helpful in distinguishing among these causes, and should be considered in any patient with idiopathic peptic ulceration.

IDIOPATHIC PEPTIC ULCER DISEASE

Mechanisms

There does appear to be a true subset of patients who do not have *H. pylori* infection, have not been exposed to NSAIDs, and after appropriate testing have unexplained peptic ulceration. These patients can be referred to as having idiopathic ulcer disease. The prevalence of idiopathic ulcers appears to be increasing, and in some studies, it accounts for up to 50% of peptic ulcers (23, 25). Harris *et al.* demonstrated that patients with recurrent idiopathic duodenal ulcers have significantly higher pentagastrin-stimulated peak acid output suggesting that acid hypersecretion may be a special feature in idiopathic ulcer disease (96). However, in a study by McColl *et al.*, where gastric function in patients with *H. pylori*-positive duodenal ulcers, idiopathic duodenal ulcers, as well as healthy volunteers were compared, these results were not confirmed (25). Both gastrin responses and peak acid output were similar in idiopathic duodenal ulcer patients and those with *H. pylori*-positive duodenal ulcer disease (Fig. 2). However, patients with idiopathic duodenal ulcer had less retention of both a liquid and solid meal (Fig. 3). McColl *et al.* (25) suggested that patients with idiopathic duodenal ulcer disease develop ulceration because of increased acid exposure in the duodenum, caused by rapid gastric emptying into the duodenal cap in the setting of a high acid secretory background rate.

There is some evidence to suggest that genetic factors

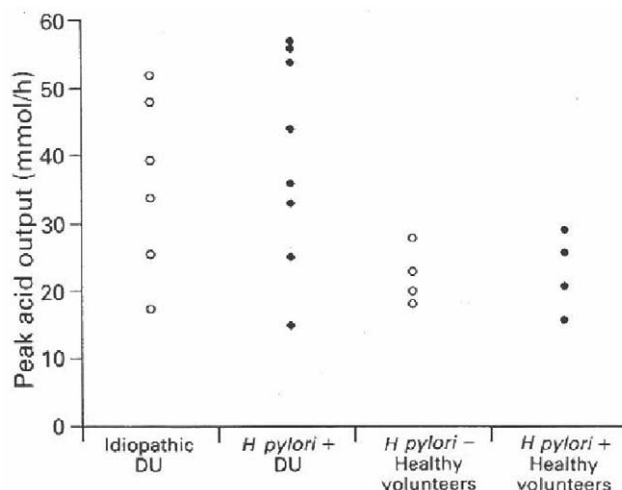


Figure 2. Peak acid output in patients with idiopathic duodenal ulcer (DU), *H. pylori*-positive patients with DU, and healthy volunteers with and without *H. pylori*. From McColl *et al.* Gut 1993;34:762-8 with permission.

play an important role in the etiology of peptic ulcer disease (97, 98); twin studies have suggested a modest genetic association (98, 99). Blood group O and nonsecretor status are genetic traits associated with duodenal ulcer disease, and when both are present, they increase the risk of the disease by 150% (97). McColl *et al.* showed that the presence of blood group O and the total absence of A1 antigen and gene were associated with idiopathic ulcers (25). Importantly, the genetic effects linked to the development of peptic ulcer

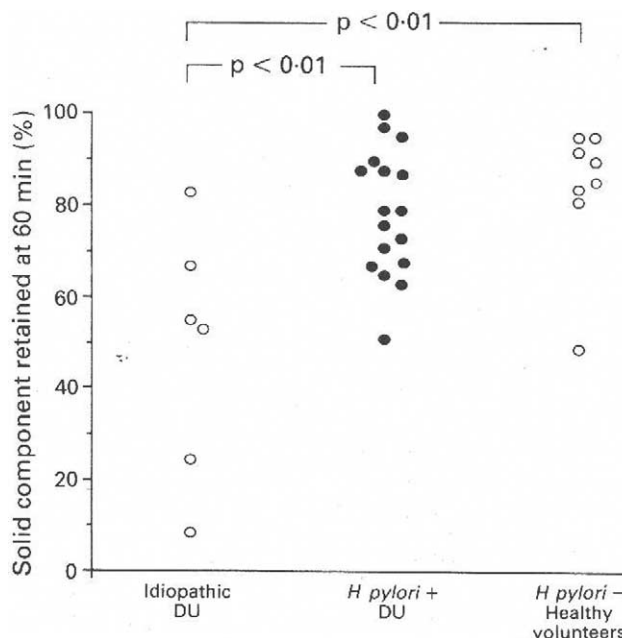


Figure 3. Gastric emptying of solids in patients with idiopathic duodenal ulcer (DU), *H. pylori*-positive patients with DU, and *H. pylori* healthy volunteers. From McColl *et al.* Gut 1993;34:762-8 with permission.

appear to be independent of the genetic influences for acquiring *H. pylori* infection (98).

An association between cigarette smoking and peptic ulcer disease has been observed for many years. Friedman *et al.* showed that the prevalence rates of peptic ulcers in current smokers as compared with those who had never smoked was increased 2-fold in men and slightly less in women (100). In addition, the quantity of cigarettes smoked and duration of use were positively associated with peptic ulcer disease. A significant difference was noted in those who smoked 10 or more cigarettes per day (101, 102). Smokers are more likely to develop ulcers that are more difficult to heal and more likely to relapse (101, 103, 104). In a recent meta-analysis, 23% of peptic ulcers could be attributed to cigarette smoking (105). However, other data suggest that once *H. pylori* has been eradicated, cigarette smoking has no effect on ulcer healing and does not influence the risk of ulcer recurrence, suggesting it is not an essential cause (36, 106).

Nicotine is the major toxic component of cigarette smoke. Although conflicting data exist in regards to the mechanism by which cigarette smoking could adversely affect the gastric mucosa, the bulk of the evidence supports the hypothesis that nicotine is harmful to the gastric mucosa (107). The development of a peptic ulcer is presumably determined by the balance of defensive and aggressive forces acting on the gastric mucosa (108). Smoking adversely affects many of the defensive mechanisms and enhances the aggressive ones. Although nicotine has no consistent effect on acid secretion, it increases pepsin secretion, gastric motility, duodenogastric reflux of bile salts, levels of free radicals, platelet-activating factor, endothelin generation, and vasopressin secretion (107). In addition, nicotine interferes with the therapeutic effect of histamine-2 antagonists, decreases prostaglandin synthesis, gastric mucosal blood flow, mucus, and epidermal growth factor secretion (107). However, these effects are transient, and the affected physiological functions return to normal within hours after cessation of smoking (109).

It remains controversial whether psychological stress contributes to the pathogenesis of peptic ulcer disease. It has been suggested that between 30–65% of peptic ulcers may be influenced by psychosocial factors such as objective life stresses, personality patterns, anxiety, and depression (110, 111). In longitudinal studies, the onset and recurrence of ulcer symptoms was found to correlate with stressful life events in subjects with peptic ulcers (112, 113). Peters and Richardson described two patients who had evidence of acid hypersecretion and ulcer disease during periods of severe emotional stress (114). When the stress was alleviated, the acid hypersecretion diminished, and the ulcers healed. However, other studies have found no temporal relationship between chronic gastric ulcer and stressful life events (115, 116). The mechanism by which emotional stress may contribute to ulcer disease is unclear. It has been postulated that stress affects the stimulation of gastric acid secretion, alters

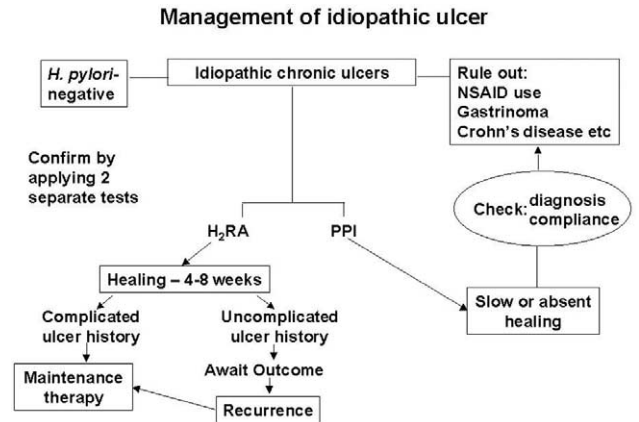


Figure 4. Management plan to diagnose and treat *H. pylori*-negative peptic ulcers.

gastric motility, modifies gastric blood flow, or affects cytokines interfering with the gastric mucosal barrier (113). Although psychological stress may contribute to the pathogenesis of peptic ulcer disease, multiple confounding variables exist making it difficult to clarify the relevance of this factor.

Another possible explanation for idiopathic ulcer disease is relapse of previous ulcer disease initially caused by *H. pylori*, where there has been disappearance of the organism. There is good evidence that a subset of patients with *H. pylori* ulcer disease still relapse after successful *H. pylori* eradication (33–36). An explanation for this remains unclear, but it may be that once there is a mucosal defect through the muscularis layer, patients are more prone to recurrence of ulceration at the same site because an inherent weakness is retained. In Hawkey *et al.*'s study when NSAID-induced peptic ulcers relapsed after treatment with omeprazole or misoprostol, the nature and site of the lesions at relapse tended to be the same as the initial ulcer, supporting the theory that local mucosal factors play a significant role (67). This might explain why patients already exposed to traditional NSAIDs may not receive additional protection from eradication of *H. pylori*, but those never exposed may be partially protected (117, 118). Keppainen *et al.* described a group of elderly patients whose ulcers were associated with neither *H. pylori* nor NSAIDs and postulated that age-related changes could lead to a weakening of the mucosal defense mechanisms, rendering the mucosa more susceptible to peptic ulceration (119). In support of this, Cryer *et al.* demonstrated that gastric and duodenal prostaglandins decline with age, and this decrease was associated with an increase in gastric acid secretion (120).

Management

The long-term management of unexplained chronic duodenal and gastric ulcer disease remains ill defined. A proposed management plan is shown in Figure 4. As a first step, it is important to ensure that misdiagnosis of *H. pylori* infection has not occurred. At least two different gold standard tests

should be negative before a confident diagnosis of *H. pylori* infection-negative peptic ulcer disease is made. Testing for *H. pylori* should be delayed for 4 wk after antibiotic use or for 1–2 wk after PPI use (58, 59). Secondly, surreptitious or unrecognized NSAID use must be excluded as accurately as possible. Serum salicylate levels especially in the context of intractable peptic ulcer disease should be considered. Thirdly, it is reasonable to measure serum gastrin as a screening test in these patients. Although the Zollinger-Ellison syndrome is rare, it is certainly a diagnosis that should not be missed. In the small series of 12 patients by McColl *et al.*, one patient was found to have the Zollinger-Ellison syndrome (25). Fourthly, it is essential to obtain biopsies from idiopathic ulcers to exclude other rare diseases that may mimic peptic ulceration. This applies not only to gastric ulcers, which are routinely biopsied to rule out malignancy, but also any unexplained duodenal ulcer, which reflects a change in management strategy.

A repeat endoscopy is necessary only in those patients who have symptom recurrence, to determine if their symptoms are linked to persistent ulceration and to exclude secondary causes. However, it is essential that all gastric ulcers are re-endoscoped to exclude refractory ulceration associated with malignancy.

Antisecretory drugs remain the mainstay of treatment for promoting healing of idiopathic peptic ulceration. However, in the absence of *H. pylori* infection, antisecretory drugs are less effective in inhibiting gastric acidity (25, 121). Gillen *et al.* (121) showed that during omeprazole treatment, the median fasting intragastric pH in *H. pylori*-negative subjects was 3.75 compared with 7.95 in the *H. pylori*-positive subjects. In addition, during omeprazole therapy, the mean basal, submaximal (180 pmol/kg/h G-17) and maximal acid outputs (800 pmol/kg/h G-17) in response to gastrin stimulation were lower in *H. pylori*-positive subjects (0.0, 3.6, 6.0 mmol/h, respectively) versus negative subjects (0.3, 14.2, 18.6 mmol/h, respectively) (121). Therefore, higher doses or longer duration of PPI therapy may be required in a subset of patients, but this is unproven.

Several key issues in terms of long-term management remain. For example, should maintenance therapy be considered for these patients? In practice, the main group where this requires serious consideration is those patients who have presented with ulcer complications. In this group, lifelong maintenance appears to be a reasonable therapeutic strategy until clinical studies define optimal management. Smoking cessation appears sensible but is an unproven intervention, and it has been suggested that the unfavorable effects of smoking on ulcer relapse may be overcome by low-dose, long-term, antisecretory treatment (104).

CONCLUSIONS

H. pylori and NSAIDs remain important causes of peptic ulcer, but the epidemiology is changing. It is unclear whether there is, in fact, a real increase in non-*H. pylori*/

NSAID-negative ulcers occurring, or whether this is just a change in proportion caused by the disappearance of the infection because of a cohort effect. The introduction of the Cox-2 inhibitors (which do not cause peptic ulceration) will presumably further accelerate the recognition of idiopathic peptic ulcers. Management needs to be further defined and will require new clinical studies.

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