
Current indications for acid suppressants in *Helicobacter pylori*-negative ulcer disease

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Although *Helicobacter pylori* infection remains the single most common cause of peptic ulcer, an increasing proportion of patients have *H. pylori*-negative ulcers. The proportion is higher in the USA – and possibly Australia – than elsewhere. Although the precise aetiology of these ulcers is often unknown, some are caused by the use of aspirin or non-steroidal anti-inflammatory drugs. In areas with a high prevalence of *H. pylori*-negative ulcers, the empirical treatment of *H. pylori* infection for newly diagnosed peptic ulcer disease should be discouraged. All such patients should have documentation of their *H. pylori* status before treatment. Patients with *H. pylori*-negative ulcers may have the more serious ulcer diathesis and are likely to require long-term management with acid-suppressing drugs. Proton pump inhibitors are likely to be the drugs of choice; patients may be relatively refractory to H₂-receptor antagonists. The optimal duration of treatment is undefined but might be lifelong. There are no prospective studies of the efficacy of surgery or mucosal-protective agents in the treatment of *H. pylori*-negative ulcers.

Key words: *Helicobacter pylori*; peptic ulcer; H₂-receptor antagonists; proton pump inhibitors; non-steroidal anti-inflammatory drugs.

Helicobacter pylori infection is recognized as being the single most common cause of peptic ulcer disease. Some countries, however, report an increasing proportion of peptic ulcers that are unrelated to *H. pylori* infection. Although the proportion of these *H. pylori*-negative ulcers has been increasing, their absolute number may have been relatively constant as the natural fall in the population prevalence of *H. pylori* infection and the successful eradication of the infection following its treatment in peptic ulcer patients has resulted in an increase in the proportion of *H. pylori*-negative ulcers.

This paper will review the epidemiology and geographical variation of *H. pylori*-negative ulcer disease and will consider some possible explanations for the phenomenon before examining the place of acid-suppressant drugs in the management of affected patients.

EPIDEMIOLOGY AND GEOGRAPHICAL VARIATION

The prevalence of *H. pylori*-negative ulcer disease is highly variable geographically. In 10 studies from the USA, the proportion of ulcers that were *H. pylori*-negative was as high as 61% (Table 1).¹⁻¹⁰ In seven studies of patients with uncomplicated duodenal ulcer^{1-3,6,8-10}, 27% out of 3122 individuals were *H. pylori* negative; in three studies of patients with uncomplicated gastric ulcer^{1,8,9}, 26% out of 315 were *H. pylori* negative.

In contrast, the reported prevalence of *H. pylori*-negative ulcers from elsewhere – particularly from Europe – is much lower (Table 2).¹¹⁻¹⁸ One exception to this is when complicated ulcers are studied in isolation. In a British study of patients with a perforated duodenal ulcer, 53% were *H. pylori*-negative (Table 2).¹² One other exception is Australia, where there is a high reported prevalence of *H. pylori*-negative duodenal ulcers (Table 2).¹⁵ In the study by Henry and Batey¹⁵, 40% of the patients with a duodenal ulcer had been taking aspirin or another non-steroidal anti-inflammatory drug

Table 1. Recent US-based studies of the prevalence of *Helicobacter pylori*-negative ulcers.

Reference	N	Ulcer type	<i>H. pylori</i> negative (%)
1	100	DU	1
		GU	8
2	183	DU	30
3	59	DU	52
4	80	PUD	61
5	166	PUD	40
6	201	DU	20
7	339	Bleeding DU	27
		Bleeding GU	36
8	144	DU	39
		GU	39
9	41	DU	39
		GU	47
10	2394	DU	27

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

Table 2. Recent non-US-based studies of the prevalence of *H. pylori*-negative ulcers.

Reference	N	Ulcer type	<i>H. pylori</i> negative (%)	Country
11	435	DU	3	UK
12	80	Perforated DU	53	UK
13	707	DU, pyloric	2	Finland
14	125	PUD	30	Finland
15	125	DU	45	Australia
16	774	DU	5	Spain
17	14	DU	43	Australia
		GU	58	
18	215	DU + GU	43	Japan
		GU	3	
		DU	2	

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

(NSAID), and there was a trend towards higher NSAID use in *H. pylori*-negative patients ($P = 0.09$). Another study from Australia also found a high prevalence of *H. pylori*-negative ulcers but did not specifically report the rate of aspirin or NSAID use.¹⁷

The explanation for the higher prevalence of *H. pylori*-negative ulcers in the USA compared with Europe and Japan, but not apparently with Australia, is unclear. However, the incidence of new infection in the USA is probably lower than in some European countries, and the population prevalence may have been falling more rapidly.

HELICOBACTER PYLORI-NEGATIVE ULCER DISEASE: ROLE OF ASPIRIN AND NSAIDS

Aspirin or NSAID use – conscious, unconscious or surreptitious – may be a more substantial problem in the USA¹⁹ and in Australia¹⁵ than elsewhere. Aspirin or NSAID use must always be considered in those patients with ulcer disease that is negative for *H. pylori* and in those patients whose ulcers appear slow or difficult to heal or relapse soon after treatment.¹⁹ This may sometimes be overlooked in routine clinical practice. Apart from their prescription use, some NSAIDs are available in low doses for over-the-counter purchase. Patients may, however, take more than the recommended or approved doses of these drugs and may combine them with aspirin or with various proprietary combinations that contain aspirin. They could, therefore, take a cumulatively large, and potentially ulcerogenic, dose of aspirin and NSAIDs.

Not all of the studies that are outlined in Tables 1 and 2 above have rigorously excluded surreptitious or unreported aspirin or NSAID use. Many of the US-based studies are available only in abstract form^{2–5,7,9}, from which it is difficult to ascertain the contribution of aspirin or NSAID use to the toll of *H. pylori*-negative ulcers. Jyotheeswaran et al, from Rochester, NY, USA, interviewed patients about their use of these drugs; when admitted, aspirin or NSAID use was excluded, but 39% of ulcers were still found not to be associated with *H. pylori* infection.⁸ Ciociola and colleagues reviewed six multicentre clinical trials on duodenal ulcer conducted in the USA. Aspirin and NSAID use was a specific exclusion criterion for these trials, in which the rate of *H. pylori*-negative ulcers ranged from 21 to 33%.¹⁰ In McColl et al's initial series from Scotland¹¹, 12 out of 435 patients with duodenal ulcer were *H. pylori*-negative, four of whom were using NSAIDs. Gisbert et al from Spain found that 95.3% of 774 consecutive duodenal ulcer patients were *H. pylori* positive. If patients with admitted aspirin or NSAID use were excluded, the proportion of duodenal ulcer patients who were *H. pylori* positive increased to 99.1%.¹⁶

POSSIBLE CAUSES OF HELICOBACTER PYLORI-NEGATIVE ULCER DISEASE

Assuming that the use of aspirin and NSAIDs has been formally excluded, other possible aetiologies of *H. pylori*-negative ulcers need to be considered. Some of these are discussed here and summarized in Table 3.

Zollinger–Ellison syndrome

Zollinger–Ellison syndrome probably accounts for at most only 1% of duodenal ulcers²⁰, and for even fewer gastric ulcers. A history of complicated ulcers or ulcers at

Table 3. Uncommon causes of peptic ulcer disease unrelated to *Helicobacter pylori* infection.

- Crohn's disease
- *Helicobacter heilmannii* infection
- Hypercalcaemia
- Portal hypertension
- Carcinoma
- Tuberculosis
- Lymphoma
- Ischaemia
- Cytomegalovirus infection
- Herpes simplex infection
- Systemic mastocytosis
- Rare genetic syndromes, not always adequately characterized or defined (e.g. ulcer–tremor–nystagmus syndrome and ‘stiffman’ syndrome)

multiple or unusual sites should raise the suspicion of Zollinger–Ellison syndrome, especially if tests for *H. pylori* infection are negative. The combination of duodenal ulceration and severe erosive oesophagitis, or duodenal ulcer and diarrhoea, is another possible presentation of Zollinger–Ellison syndrome. A strong family history of peptic ulcer disease, perhaps suggesting multiple endocrine neoplasia type I, is also suggestive. Hypercalcaemia may indicate underlying hyperparathyroidism in multiple endocrine neoplasia type I.

False-negative tests for *Helicobacter pylori* infection

A false-negative result from a test for *H. pylori* infection might be another explanation for apparent ‘*H. pylori*-negative’ ulcers. The sensitivity of endoscopic methods, the ^{13}C - and ^{14}C -urea breath tests (UBTs) and the ^{13}C -urea blood test is reduced in patients receiving proton pump inhibitors (PPIs) and in those who are taking, or have recently been taking, antibiotics or bismuth-containing compounds. Laine and colleagues reported that 33% of 93 patients with known *H. pylori* infection had a false-negative ^{13}C -UBT while taking the PPI lansoprazole.²¹ The sensitivity of the ^{13}C -UBT increased to 91, 97 and 100% after, respectively, 3, 7 and 14 days off lansoprazole. Bravo et al found that lansoprazole produced false-negative rates of 30–40% for the ^{13}C -UBT and 15–25% for the HpSA stool antigen test.²² Bismuth subsalicylate treatment was associated with a false-negative rate of 45–55% for the ^{13}C -UBT and 10–15% for the HpSA stool antigen test.²² Ranitidine had no significant effect on the sensitivity of either test.

Helicobacter heilmannii infection

Helicobacter heilmannii is a gram-negative bacterium isolated from the human stomach and probably transmitted zoonotically. Previously called *Gastrospirillum hominis*, it is morphologically distinct from *H. pylori*. Infection is associated with a mild antral-predominant gastritis and has been preliminarily linked to peptic ulcer.

In a retrospective study of gastric biopsies from 946 patients with duodenal ulcer, Jhala and colleagues found *H. heilmannii* in only four, all of whom had negative cultures for *H. pylori*.²³ Among the biopsies from 281 patients with NSAID-related gastric ulcers, only two had evidence of *H. heilmannii*.²³ The gastritis of *H. heilmannii* infection appears to be patchier and milder than that of *H. pylori* and more likely to be confined

to the gastric antrum.^{23,24} In Stolte's series of 202 patients with *H. heilmannii* gastritis, only eight had ulceration, which was usually associated with NSAID use.²⁴

Crohn's disease

Oberhuber and colleagues in Austria examined gastric and duodenal biopsies from 792 patients with known intestinal Crohn's disease but without specific upper gastrointestinal manifestations.²⁵ They found histological evidence of Crohn's disease in the gastric corpus in 37%, the antrum in 42%, the duodenal bulb in 13% and the descending duodenum in 12%. Overt Crohn's disease of the duodenum usually occurs in association with active disease elsewhere. In the series of Yamamoto et al from Birmingham, UK, 96% of 54 patients with gastroduodenal Crohn's had expression of the disease elsewhere in the gastrointestinal tract.²⁶ Ulceration was only found in 4 out of 54 patients; the most common presentation was with stricture, which occurred in 41 patients.

Hypercalcaemia

Steinberg et al studied 268 elderly patients consecutively admitted to an acute care geriatric medicine facility in South Carolina, USA.²⁷ The mean age of the patients was 77 (range 61–98). Thirty-five patients (13%) had hypercalcaemia at the time of admission. Upper gastrointestinal endoscopy was performed on all patients in whom there was clinical suspicion of peptic ulcer disease. Of the 42 patients who underwent endoscopy, 27 (64%) had a peptic ulcer. Of the 27 with ulcer disease, 6 had a normal serum calcium level and an *H. pylori*-positive duodenal ulcer, 10 displayed hypercalcaemia and an *H. pylori*-positive duodenal ulcer, 5 had hypercalcaemia and an *H. pylori*-positive gastric ulcer and only 6 out of the 27 (22%) demonstrated hypercalcaemia and an *H. pylori*-negative gastric ulcer. This preliminary study highlighted the unexpectedly high prevalence of hypercalcaemia in elderly patients. Most of the patients with ulcer disease were hypercalcaemic; most were, however, also positive for *H. pylori* infection. Hypercalcaemia is, therefore, unlikely to contribute much to the high rate of *H. pylori*-negative ulcers that has been reported in the USA.

Miscellaneous

Rare causes of peptic ulcer have occasionally been uncovered when patients have gastrointestinal bleeding in unusual clinical circumstances. Examples include Wegener's granulomatosis²⁸, adult Still's disease²⁹ and misplaced chemotherapy catheters for hepatic artery infusion.³⁰

ANTI-SECRETORY DRUGS

Both H₂-receptor antagonists (H₂RAs) and PPIs produce healing of duodenal and gastric ulcers through the suppression of gastric acid secretion. The cumulative healing rates of duodenal and gastric ulcers have been related mathematically to the degree and duration of suppression of intragastric acidity that these drugs produce and to the duration of treatment.^{31–34} Since PPIs produce a greater degree of suppression of gastric acid secretion than H₂RAs, they have been associated with higher ulcer healing rates in blinded, randomized comparative trials. Similarly, in gastro-oesophageal reflux disease that is associated with erosive oesophagitis, mucosal healing is related to the

degree and duration of suppression of acidity that an anti-secretory drug produces and to the duration of treatment.³⁵

Although these mathematical relationships still hold true, these observations were made before the recognition of the importance of *H. pylori* infection in ulcer disease. The *H. pylori* status of the subjects in whom the anti-secretory effects of the H₂RAs and PPIs were tested is unknown. This is important since it is now recognized that *H. pylori* status is one of the most important determinants of the anti-secretory potency of PPIs and, to a lesser extent, H₂RAs. In general, these drugs produce a more profound degree of suppression of acidity in subjects who are *H. pylori* positive than in those who are *H. pylori* negative.^{36–39} Furthermore, the eradication of *H. pylori* infection from individual subjects is associated with a reduction in anti-secretory potency when a PPI continues to be administered in the same dose.³⁷

When the H₂RAs and PPIs were undergoing clinical development, they were extensively examined in randomized, double-blind, placebo-controlled trials of duodenal and gastric ulcers. Since most of these trials were conducted before the recognition of *H. pylori*, the infection status of the patients who were included is unknown. Once the importance of *H. pylori* infection in peptic ulcer disease became established, it was generally assumed that all – or almost all – ulcer patients were *H. pylori* positive unless they had been known to be using an NSAID. Therefore, the treatment of peptic ulcer disease with anti-secretory drugs went from a state of blissful ignorance of *H. pylori* to a state of blind acceptance of its role. There have been to date no specific trials examining the role of either PPIs or H₂RAs in a group of patients with predetermined *H. pylori*-negative peptic ulcer disease.

CHARACTERISTICS OF *H. PYLORI*-NEGATIVE ULCER DISEASE

In McColl et al's series from Scotland¹¹, the small group of patients with *H. pylori*-negative ulcer disease had some characteristics similar to those of the majority of patients who had *H. pylori*-positive ulcer disease. Stimulated gastric acid secretion and serum gastrin level were similar in the two groups. However, the patients with *H. pylori*-negative ulcers had more rapid gastric emptying and an absence of the blood group A antigen and gene. Furthermore, the patients with *H. pylori*-negative ulcers had a particularly severe form of ulcer disease with frequent relapses and complications despite treatment with H₂RAs.

Lanas et al in Spain identified 80 patients with resistant ulcer disease.⁴⁰ Of this group, 58 had *H. pylori* infection either with or without concomitant NSAID use, and another 10 were using an NSAID in the absence of *H. pylori* infection. The remaining 12 were *H. pylori* negative by UBT and had normal platelet cyclo-oxygenase (COX) function, thereby excluding aspirin use within the preceding 5 days, although not entirely excluding the use of other NSAIDs showing COX-1 inhibition.

The mean age of the 12 patients was 52 and the male to female ratio was 7 to 5. Eight patients had a duodenal ulcer, 2 a gastric ulcer and 2 had both duodenal and gastric ulcers. The mean duration of their ulcer history was almost 13 years. The mean basal acid output was 1.2 mmol per hour, which was significantly lower than that seen in the patients with ulcer disease related to *H. pylori* infection and/or aspirin or NSAID use. Of the group of 12, however, two had had a previous vagotomy and two had gastric ulcers. None of the patients had a basal acid output greater than 10 mmol per hour, which was the arbitrary criterion used to define idiopathic gastric acid hypersecretion. Mean maximal acid output in the 12 patients with idiopathic ulcer disease was 18 mmol per

hour, which was numerically – but not significantly – lower than that of the other groups of patients. Five of the 12 patients had a history of ulcer complications; 7 had a family history of ulcer disease. Ulcer healing with PPI therapy was successful in 9 of the patients, the remaining 3 having continuous ulcer-related problems despite PPI therapy. No additional aetiological factors – other than cigarette smoking and a family history of ulcer disease – were identified in these patients.

TREATMENT OF *H. PYLORI*-NEGATIVE ULCER DISEASE

We have conducted a formal literature search using the MEDLINE and PRE-MEDLINE databases from 1984 to 2000. The search string was: ('Peptic Ulcer' [MESH] OR 'peptic ulcer' OR 'duodenal ulcer' OR 'gastric ulcer') AND ('proton pump inhibitors' OR 'proton-pump inhibitors' OR 'proton pump inhibitor' OR 'proton-pump inhibitor' OR PPI OR PPIs OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole OR 'Histamine H₂ antagonists' [MESH] OR cimetidine OR ranitidine OR famotidine OR nizatidine). Although this uncovered 5584 citations, a perusal of all the available abstracts did not reveal any that had stratified patients according to pre-treatment *H. pylori* status. Since there are no prospective, randomized controlled clinical trials that have focused on patients with *H. pylori*-negative ulcers, any conclusions and recommendations about treatment must be extrapolated from other existing data.

Treatment of NSAID-associated ulcer according to *H. pylori* status

When an ulcer is found in a patient who is taking an NSAID, it is important to check the *H. pylori* status. It has been unclear whether *H. pylori* infection and NSAID use are additive or synergistic risk factors for ulcer disease, or whether *H. pylori* infection might even be protective against NSAID-related peptic ulcer.

Huang et al at McMaster University in Canada have performed a meta-analysis of studies that have looked at ulcer incidence according to *H. pylori* status and the use or non-use of NSAIDs.⁴¹ In the absence of *H. pylori* infection, NSAID use was associated with an odds ratio (OR) for ulcer disease of 5.99, whereas in the presence of *H. pylori* infection, NSAID use was associated with an OR for ulcer disease of 2.9. Among NSAID non-takers, *H. pylori* infection was associated with an OR for ulcer disease of 5.7; among NSAID takers, however, the OR with *H. pylori* infection was 2.8. Compared with *H. pylori*-negative individuals who did not take NSAIDs, *H. pylori*-positive individuals who used NSAIDs had a 16.5-fold increased risk of peptic ulcer. These findings strongly suggest that the two factors of *H. pylori* infection and NSAID use are independent and additive risks for ulcer disease.

Despite the apparently additive nature of the risks of using an NSAID and having *H. pylori* infection, two important trials unexpectedly reported that NSAID-related ulcers healed more rapidly in those patients who had *H. pylori* infection.^{42,43} Neither trial had, however, been designed to address the influence of *H. pylori* status on the healing of NSAID-related ulcers. The OMNIUM study of Hawkey et al⁴² showed a superiority of omeprazole over misoprostol in healing duodenal and gastric ulcers in patients who continued to use NSAIDs. Subsequent analysis demonstrated a higher duodenal ulcer healing rate in omeprazole-treated patients who were *H. pylori* positive than in those who were *H. pylori* negative. The ASTRONAUT study, reported by Yeomans et al, demonstrated the superiority of omeprazole over ranitidine in healing duodenal or gastric ulcers related to NSAID use in patients who continued to use

NSAIDs for the duration of the study.⁴³ It was subsequently found that omeprazole-treated patients who were *H. pylori* positive had a higher healing rate than those who were *H. pylori* negative, a similar relationship between healing rate and *H. pylori* status being established for ranitidine-treated patients.

Both the OMNIUM and the ASTRONAUT study had extensions to look at the efficacy of omeprazole, misoprostol and ranitidine for the secondary prevention of relapse of NSAID-related ulcers. In the OMNIUM study, *H. pylori* positivity was associated with a reduced ulcer recurrence during omeprazole maintenance treatment. In the ASTRONAUT study, *H. pylori* positivity was associated with a lower ulcer recurrence rate during either omeprazole or ranitidine maintenance treatment.

One obvious explanation for the apparently beneficial effect of *H. pylori* infection on the healing and subsequent prevention of relapse of NSAID-related ulcers during treatment with omeprazole or ranitidine is that these drugs exert a more powerful pharmacodynamic effect on gastric acid secretion in the presence of *H. pylori* infection. Two subsequent trials have, however, compared the efficacy of lansoprazole and ranitidine in healing NSAID-related ulcers in patients who continued to use NSAIDs^{44,45}, neither finding a beneficial effect of *H. pylori* infection. In both trials, once-daily lansoprazole was significantly better than twice-daily ranitidine in healing NSAID-related ulcers irrespective of *H. pylori* status, and there was no difference between *H. pylori*-positive and *H. pylori*-negative patients.

It is unclear why these two lansoprazole trials have not found the same influence of *H. pylori* status on ulcer healing rate as the two previous trials with omeprazole.^{42,43} Each PPI would be expected to exert a greater degree of suppression of intragastric acidity in *H. pylori*-positive than *H. pylori*-negative patients. However, taken together, these trials demonstrate a consistent superiority of a PPI taken once-daily over an H₂RA taken twice-daily in healing NSAID-related ulcers that are either *H. pylori* positive or *H. pylori* negative.

A study from Italy has demonstrated the superiority of omeprazole over sucralfate in healing NSAID-related gastric and duodenal ulcers in patients who continued to take NSAIDs during the study.⁴⁶ In that study, *H. pylori* status did not influence the efficacy of omeprazole or sucralfate.

Therefore, for ulcers – including *H. pylori*-negative ulcers – that are related to known NSAID use, treatment with a PPI is superior to treatment with an H₂RA, misoprostol or sucralfate if the NSAID has to be continued. PPI treatment is also preferable to misoprostol treatment based on the superior quality of life that was demonstrated in the OMNIUM study.⁴² It is thus logical to conclude, based on the available evidence, that PPIs are the drugs of choice for NSAID-related ulcers, a proportion of which will be *H. pylori*-negative. In patients in whom NSAID therapy can be stopped, the healing rate with H₂RAs is high⁴⁷, although the effect of *H. pylori* status has not been specifically studied.

Therefore, patients with NSAID-related ulcers should be checked for *H. pylori* infection. Those patients who are *H. pylori*-positive should receive appropriate treatment for the infection. Those who are *H. pylori*-negative should be treated with a PPI to heal the ulcer. If NSAID therapy is to be continued, a PPI should be given as maintenance treatment irrespective of initial *H. pylori* status. There are to date no data to demonstrate that PPIs will reduce the risk of clinically significant ulcer complications in patients taking NSAIDs. However, since they reduce the incidence of endoscopically demonstrated gastric and duodenal ulcers, it is reasonable to presume that they should do so.

Management of *H. pylori*-negative ulcer disease in other conditions

Although not definitively excluded in some published series, the use of aspirin and other NSAIDs probably accounts for many of the *H. pylori*-negative ulcers encountered in clinical practice. US-based clinical trials sponsored by pharmaceutical companies and conducted to standards required by the United States Food and Drug Administration have carefully tried to exclude patients taking aspirin or other NSAIDs. Such trials have still, however, uncovered a substantial proportion of ulcers that are not apparently related to *H. pylori* infection.¹⁰ Although many other conditions can produce ulceration in the upper gastrointestinal tract (see Table 3 above), most of these should be suggested by individual patients' clinical presentations. Crohn's disease, for example, usually only affects the duodenum in conjunction with lower intestinal disease and even then most often manifests with stricture rather than ulceration.²⁶

When faced with a patient with ulcer disease that is apparently *H. pylori*-negative, the clinician should first review the manner in which the patient was tested for *H. pylori* infection in order to exclude the possibility of a false-negative result. Then the consumption of aspirin, aspirin-containing products and other NSAIDs should be carefully explored. Ideally, a test of platelet COX function should be undertaken if there is any doubt about surreptitious or unconscious aspirin use.^{19,40} If aspirin or other NSAID use is confidently excluded, a fasting serum gastrin level should be checked when the patient is not taking any gastric anti-secretory medicines. Consideration might then be given to other possible causes of ulceration, as briefly reviewed here and listed in Table 3 above.

Finally, there will remain a proportion of patients with ulcer disease that is *H. pylori*-negative, unrelated to aspirin or NSAID use and genuinely 'idiopathic'. The optimal management for such patients is unclear at this point. They will not benefit from treatment directed towards *H. pylori* infection and are likely to require indefinite treatment with gastric anti-secretory drugs. Although surgery might be a reasonable option in some, this has not been studied in an exclusively *H. pylori*-negative group of patients.

In countries with a high prevalence of *H. pylori*-negative peptic ulcers, it is mandatory to check the *H. pylori* status before initiating treatment. In these countries, it cannot be assumed that a newly diagnosed peptic ulcer is caused by *H. pylori* infection. It may, however, be reasonable to embark on 'semi-empirical' treatment for *H. pylori* infection without documentation in some European countries where *H. pylori* still accounts for almost all peptic ulcers encountered in clinical practice. Whenever *H. pylori* infection is diagnosed in patients with peptic ulcer disease, it must be treated with a regimen of proven efficacy, the choice of antibiotics being influenced by local rates of antimicrobial resistance.

If there is no evidence of *H. pylori* infection in a patient with peptic ulcer disease, the method(s) of testing for the infection should be reviewed in case of the possibility of a false-negative test. The patient should be questioned about the use of aspirin or an NSAID; if doubt about such use exists, platelet COX activity should be tested. If *H. pylori* infection is definitively excluded, the patient should be regarded as having *H. pylori*-negative ulcer disease and treated with an anti-secretory drug. Evidence in support of PPI – rather than H₂RA – treatment is indirect and is based largely on the observation that small groups of these patients have frequently relapsing disease that is often associated with complications, and are often refractory to H₂RA treatment.^{11,40} Our current recommendation is therefore for long-term PPI treatment for proven *H. pylori*-negative ulcer disease.

SUMMARY

The characteristics of patients with *H. pylori*-negative ulcer disease have not been adequately defined. The exact role of aspirin or NSAID use – which, it is acknowledged, may be surreptitious in some – also remains to be defined. Presumably, however, different rates of NSAID use may explain some of the apparent geographical differences in prevalence. Once aspirin and NSAID use have been definitively excluded, other recognized causes of ulceration in the upper gastrointestinal tract probably account for only a small proportion of *H. pylori*-negative ulcers, most currently remaining idiopathic.

Current evidence regarding optimum treatment is extremely limited since the clinical syndrome of *H. pylori*-negative ulcer disease has not been studied in isolation. The best recommendation that can currently be given is that these patients be managed with a PPI, which may have to be continued long term. If aspirin or NSAID therapy can be stopped, it should be. The current and future role of the COX-2

Practice points

- not all peptic ulcers are caused by *H. pylori* infection
- although many *H. pylori*-negative peptic ulcers result from aspirin or NSAID use, the aetiology of some remains unknown
- patients with *H. pylori*-negative ulcers will not benefit from treatment for *H. pylori* infection
- in countries with a high prevalence of *H. pylori*-negative ulcers, it is not advisable to initiate anti-*H. pylori* treatment for patients with newly diagnosed peptic ulcer disease without first documenting their *H. pylori* status
- patients with *H. pylori*-negative ulcers – whether or not these are associated with NSAID use – should probably be treated with a PPI. Treatment may have to be long term
- clinical trials of PPI and other drugs in peptic ulcer have not focused on patients with *H. pylori*-negative ulcers. In general, patients have not been stratified pre-treatment according to *H. pylori* status

Research agenda

- to identify those demographic characteristics which better identify patients with *H. pylori*-negative ulcer disease
- in view of conflicting existing evidence, to determine the gastric secretory profile in people with proven *H. pylori*-negative ulcers that are unrelated to aspirin or NSAID use
- to determine why the prevalence of *H. pylori*-negative ulcer disease varies geographically and ascertain how far this is explained by different rates of aspirin/NSAID use
- to assess whether *H. pylori*-negative and *H. pylori*-positive ulcers heal at different rates during treatment with anti-secretory drugs
- to determine the risk of ulcer complications in *H. pylori*-negative ulcer disease and whether long-term treatment with anti-secretory drugs helps to control these

selective inhibitors is beyond the scope of this article. Patients who have *H. pylori*-negative ulcers related to NSAID use, and who must continue to take NSAIDs, are best managed with long-term PPI treatment.

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