REVIEW ARTICLE

Drug Safety 2005; 28 (4): 287-300
0114-5916/05/0004-0287/$34.95/0

NSAID-Induced Peptic Ulcers and *Helicobacter pylori* Infection

Implications for Patient Management

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Abstract

The conflicting data about the influence of *Helicobacter pylori* infection on the ulcer risk in patients receiving NSAIDs can be accounted for by the heterogeneity of study designs and the diversified host response to *H. pylori*. Factors that will affect the outcome include the choice of *H. pylori* diagnostic tests, previous ulcer complications, concurrent use of acid suppressants, NSAID-naive versus long-term users, low-dose aspirin (acetylsalicylic acid) versus non-aspirin NSAIDs and whether the result was derived from a pre-specified endpoint or *post hoc* subgroup analysis. Current evidence suggests that *H. pylori* eradication reduces the ulcer risk for patients who are about to start receiving NSAIDs but not for those who are already on long-term NSAID therapy. Since treatment with a proton pump inhibitor (PPI) worsens *H. pylori*-associated corpus gastritis, *H. pylori* should be

tested for, and eradicated if present, before starting long-term prophylaxis with PPIs. Patients with *H. pylori* infection and a history of ulcer complications who require NSAIDs should receive concomitant PPIs or misoprostol after curing the infection. Among patients receiving low-dose aspirin, who have *H. pylori* infection and previous ulcer complications, long-term treatment with a PPI further reduces the risk of complicated ulcers if *H. pylori* eradication fails or if patients use concomitant non-aspirin NSAIDs. Current data on the gastric safety of COX-2 selective NSAIDs in *H. pylori*-infected patients are conflicting. Limited data suggest that the gastroduodenal sparing effect of rofecoxib is negated by *H. pylori* infection in patients who have had prior upper gastrointestinal events. In light of potential cardiovascular risk with COX-2 selective NSAIDs, it is important to weigh the potential adverse effects against the benefits for an individual patient.

Helicobacter pylori and NSAIDs account for the majority of peptic ulcer disease. Defining the precise relationship between *H. pylori* and NSAIDs is important for patient management. However, studies on the interaction between these two factors have generated the most conflicting results in peptic ulcer research. To date there are data suggesting that *H. pylori* increases, has no effect on, or decreases the ulcer risk in patients receiving NSAIDs. The controversy can be largely accounted for by heterogeneity of the study design and a wide spectrum of host response to *H. pylori* infection. This article reviews the influence of *H. pylori* on the risk and severity of NSAID-induced gastric injury and attempts to resolve some of the management controversies.

1. Role of *Helicobacter pylori* in the Pathogenesis of NSAID-Induced Gastric Injury

NSAIDs and *H. pylori* are thought to damage the gastric mucosa via different mechanisms. There is good experimental evidence that NSAIDs induce gastric ulcers via three mechanisms: suppression of gastric prostaglandin synthesis, topical injury and neutrophil-mediated vascular events. In contrast, *H. pylori* infection damages the mucosa by inducing inflammatory infiltration and releasing pro-inflammatory cytokines. Nevertheless, NSAIDs and *H. pylori* do share certain pathways that could influence the severity of mucosal injury.

1.1 Gastric Prostaglandin Synthesis

Gastric prostaglandins play a crucial role in maintaining the integrity of the gastric barrier by regulating mucosal blood flow, mucus and bicarbonate secretion, epithelial proliferation, epithelial restitution and mucosal immunocyte function.[1] *H. pylori* upregulates cyclo-oxygenase (COX) and induces gastric prostaglandin production. A number of animal and human studies have investigated whether the increased prostaglandin synthesis in *H. pylori* gastritis would influence the severity of NSAID-induced mucosal injury.

1.1.1 Animal Studies

In the Mongolian gerbil model of *H. pylori* gastritis,[2] *H. pylori* upregulated COX-2 expression and increased prostaglandin production. The administration of indometacin suppressed prostaglandin levels in normal and infected stomachs to a similar extent. However, gastric injury was more severe in *H. pylori*-infected gerbils. In another study, indometacin induced more severe gastric damage in *H. pylori*-infected gerbils than in uninfected gerbils. Pretreatment with a COX-2 selective NSAID aggravated mucosal damage induced by indometacin in the presence of *H. pylori* infection. The authors postulated that the increased prostaglandin synthesis is a protective response against *H. pylori*. NSAIDs disturb this equilibrium state and thus aggravate mucosal injury.[3]

Animal studies into whether *H. pylori* affects the healing of NSAID-associated ulcers have yielded

conflicting results. In the Mongolian gerbil model of acetic acid-induced gastric ulcers, *H. pylori* infection significantly delayed ulcer healing and induced ulcer relapse.[4] However, in the rat ulcer model, *H. pylori* infection attenuated the delay in ulcer healing induced by aspirin (acetylsalicylic acid).[5]

1.1.2 Human Studies

A number of human studies have investigated the effects of NSAIDs and *H. pylori* on gastric prostaglandin synthesis. In the human stomach, *H. pylori* infection stimulates prostaglandin synthesis. Whether the increased levels of gastric prostaglandins are mediated by upregulation of COX-1 or mediated by COX-2 is controversial.[6,7] The administration of NSAIDs has been shown to suppress gastric prostaglandins to very low levels irrespective of the *H. pylori* status.[8,9] These findings suggest that the modest increased gastric prostaglandin synthesis induced by *H. pylori* infection is not sufficient to alleviate the gastric toxicity of NSAIDs.

1.2 Neutrophil-Mediated Injury

The lack of correlation between gastric prostaglandin levels and the severity of NSAID injury in the presence of *H. pylori* infection suggests that other factors also affect the integrity of the gastric mucosal barrier. There is good evidence from animal experiments that neutrophil-mediated endothelial injury is an early event in NSAID-induced gastropathy. In animal models, NSAIDs induce the expression of adhesion molecules, which leads to neutrophil adherence to the endothelium. Neutrophil adherence damages the mucosa by liberating oxygen free radicals and proteases, and obstructing capillary flow. It has been shown that the severity of mucosal injury is markedly reduced in neutropenic rats.[10,11]

The fact that *H. pylori* also damages the mucosa via a neutrophil-mediated process has led to the suggestion that neutrophil infiltration in *H. pylori* gastritis might aggravate NSAID injury. In Mongolian gerbils, aspirin caused greater neutrophil infiltration, more lipid peroxidation and more extensive haemorrhagic erosions in infected gerbils than in uninfected gerbils. Pre-treatment with anti-neutrophil serum reversed these changes and reduced mucosal erosions.[12] In a subsequent study, it was found that elastase and active oxygen species derived from neutrophils contribute to aspirin-induced mucosal injury in *H. pylori*-infected gerbils.[13] Taha et al.[14] examined the relationship between *H. pylori* infection, gastric neutrophils and NSAID-induced mucosal injury in patients receiving long-term NSAIDs. In this 24-week prospective study, there was a strong correlation between *H. pylori* infection and gastric neutrophils. It was found that ulcers developed in 47.4% of NSAID users with gastric neutrophil infiltration compared with 7.7% of NSAID users without neutrophil infiltration.

Although NSAIDs cause more severe mucosal injury in the presence of *H. pylori*-induced neutrophil infiltration, whether NSAIDs damage the human stomach via a neutrophil-mediated event remains unclear. In the human stomach, NSAID-induced gastropathy is characterised by a paucity of inflammatory infiltrates in the mucosa. Neutrophils are thought to damage the mucosa via a vascular event rather than mucosal inflammation. The significance of neutrophils in NSAID-induced gastropathy of the human stomach requires further studies.

1.3 Acid Secretion

In animal experiments, the severity of NSAID-induced mucosal damage is pH dependent.[15,16] Gastric acid probably aggravates NSAID-induced mucosal injury by converting superficial injury to deeper mucosal necrosis,[17] interfering with haemostasis and platelet aggregation,[18] and impairing ulcer healing.[19]

Gastric acid secretion is influenced by the distribution of *H. pylori*-induced gastritis. Antrum-predominant gastritis causes acid hypersecretion, whereas corpus-predominant gastritis leads to gastric atrophy and hypochlorhydria. In the author's opinion, the distribution of gastritis might influence the susceptibility of *H. pylori*-infected patients to NSAIDs. Patients with antrum-predominant gastritis may be prone to NSAID-induced ulceration, whereas those with corpus-predominant gastritis

may be more resistant to NSAID injury. Before the discovery of *H. pylori*, one study reported that patients with rheumatoid arthritis who tolerated long-term NSAID therapy had a higher prevalence of gastric atrophy and a lower acid secretion than healthy controls.[20] Future studies are needed to verify this hypothesis.

The intragastric acidity of the *H. pylori*-infected stomach is also influenced by the concomitant use of acid suppressants. *H. pylori* has been shown to potentiate the acid-suppressing effect of omeprazole.[21,22] In the subgroup analyses of two large-scale studies that compared omeprazole with ranitidine or misoprostol in preventing NSAID-induced endoscopic injury,[23,24] *H. pylori*-infected patients who received omeprazole had less endoscopic lesions or dyspepsia compared with uninfected patients. In contrast, among NSAID users who did not receive acid suppressants, other studies found that the incidence of ulcers was significantly higher in *H. pylori*-infected subjects than in uninfected subjects.[14,25] These data suggest that *H. pylori* aggravates mucosal injury that is induced by NSAIDs without concomitant acid suppressants, whereas the bacterium reduces the ulcer risk in the presence of acid suppression.

1.4 Gastric Adaptation

Gastric adaptation is a gastric defence mechanism that involves the healing of acute mucosal injury, followed by enhancement of the mucosal defence and the generation of a more resistant mucosa against further injury.[26,27] Although there is considerable debate over the clinical significance of this phenomenon, failure of gastric adaptation is thought to partly account for the marked increase in the risk of ulcer complications during the first few weeks of NSAID treatment.[28-31] Konturek et al.[9] showed that *H. pylori*-infected subjects had impaired adaptation to aspirin, as was evident by persistent occult bleeding from the gastric mucosa. Eradication of *H. pylori* restored gastric adaptation to aspirin. The failure of gastric adaptation might account for the increased ulcer risk in NSAID-naive subjects. Several factors have been implicated in the process of gastric adaptation, including epidermal growth factor, transforming growth factors and heat shock protein 70.[32-34] A recent study has suggested that the expression of heat shock protein 70 plays an important role in gastric adaptation to aspirin. *H. pylori* infection interferes with this adaptation as a result of the reduced expression of heat shock protein 70 in gastric mucosal cells.[34]

1.5 Apoptosis

It has been suggested that augmented apoptosis contributes to ulcer formation.[35] Although *H. pylori* infection[36,37] and NSAIDs[9] have both been shown to induce apoptosis in the gastroduodenal epithelium, the combined effect of NSAIDs and *H. pylori* infection on gastric epithelial apoptosis is very complex. Leung et al.[38] showed that among *H. pylori*-infected individuals, NSAIDs suppressed, rather than induced, gastric apoptotic activities. Similar findings were also reported in a cross-sectional study, which showed a lower level of apoptosis in *H. pylori*-infected NSAID users compared with *H. pylori*-infected non-users.[39] Although these observations raise the possibility that *H. pylori* might ameliorate NSAID-induced mucosal injury, Leung et al.[38] found that patients who received *H. pylori* eradication prior to NSAID treatment had a significantly lower post-treatment apoptosis index than *H. pylori*-infected NSAID users. Moreover, the administration of NSAIDs resulted in similar post-treatment apoptosis indices between *H. pylori*-eradicated patients and non-infected individuals. A recent experiment showed that *H. pylori* and aspirin synergistically accelerate apoptosis via the Fas antigen pathway in rabbit gastric epithelial cells.[40] These findings offer a biological explanation for the success of screen-and-treat *H. pylori* strategies prior to initiating NSAID therapy in the prevention gastroduodenal ulcers.

2. Controversies in Management

2.1 Does *H. pylori* Influence the Ulcer Risk in NSAID Users?

Many investigators had attempted to address this question using case-control or observational studies. To date, there are studies showing that the interaction between *H. pylori* and NSAIDs in ulcer development is synergistic, additive, independent or antagonistic. These conflicting results can be largely accounted for by methodological heterogeneity and diversified host response to *H. pylori* infection.

2.1.1 Case-Control Studies

The most commonly used approach to investigate the relationship between *H. pylori* and NSAIDs in the literature was case-control study. Unfortunately, this is also the major source of bias and confusion. These studies used different endpoints such as dyspepsia, prevalence of *H. pylori* infection, endoscopic lesions and ulcer bleeding. For example, some investigators studied the prevalence of *H. pylori* in NSAID users with or without mucosal lesions; others compared the severity of mucosal injury in NSAID users with or without *H. pylori* infection.[41] The definition of mucosal injury constituted another source of heterogeneity. It varied widely from bleeding ulcers to endoscopic lesions with little clinical significance (e.g. mucosal petechiae or erosions). The heterogeneous study designs rendered direct comparison of the results difficult. In the literature, it is not surprising that even the same investigators reported conflicting results about the interaction between *H. pylori* and NSAIDs.[42-45]

In a meta-analysis that assessed the prevalence of *H. pylori* infection and NSAID use in 893 patients with bleeding ulcer and 1002 controls without bleeding, it was found that the choice of *H. pylori* diagnostic tests influenced the outcome.[46] Overall, *H. pylori* only marginally increased the bleeding risk in NSAID users (odds ratio [OR] 1.67; 95% CI 1.02, 2.72). However, in subgroup analysis on *H. pylori* diagnostic methods, *H. pylori* increased the bleeding risk in NSAID users by 2-fold for studies that used serology (OR 2.16; 95% CI 1.54, 3.04). For studies that used a rapid urease test, histology or culture, *H. pylori* did not increase the bleeding risk in NSAID users (OR 1.24; 95% CI 0.50, 3.08). The discrepant findings could be due to the low sensitivity of non-serological tests for the detection of *H. pylori* infection in patients with bleeding ulcers. There are data suggesting that rapid urease test, culture and histology have significantly higher false negative rates than serology in the presence of blood.[47,48] Several mechanisms probably contribute to the low sensitivity of invasive tests for *H. pylori*. One study showed that albumin in the serum suppressed the colour change of the pH indicator in the biopsy urease test.[49] Others found that human plasma is bacteriocidal against *H. pylori in vitro*.[50]

2.1.2 Observational Studies

There are a number of prospective observational studies that investigated the influence of *H. pylori* infection on the ulcer risk in NSAID users. However, many of these studies were not designed to address this issue. In some studies, the results were derived from *post hoc* subgroup analyses that were not pre-specified in the original study design.

Two studies were primarily designed to investigate how *H. pylori* might affect the risk of developing ulcers in patients receiving NSAIDs.[51,52] One study showed that *H. pylori* increased the ulcer risk, whereas the other did not. In the study by Taha et al.,[51] patients underwent endoscopy at regular intervals for up to 24 weeks. Ulcers developed in 40% of patients with *H. pylori* infection compared with 15% of patients without *H. pylori*. The authors found that *H. pylori*-infected patients with duodenal erosions at baseline were more likely to develop ulcers with NSAID use ($p < 0.05$). Kim et al.[52] prospectively evaluated the development of gastroduodenal ulcers in patients with arthritis who were receiving an NSAID, for up to 3 months. They found that there was no difference in the incidence of ulcers between patients with *H. pylori* infection (12.6%) and those without the infection (14.1%). This study differed from the study by Taha et al.[51] in that patients with erosions at baseline were excluded. The different patient selection criteria prob-

ably accounted for the discrepancy between these two studies.

Other investigators assessed the interaction between *H. pylori* and NSAIDs by analysing data derived from studies that were designed for other purposes.[14,23-25] Taha et al.[14] studied the role of *H. pylori*-induced gastric neutrophils in the development of NSAID-associated ulcers based on data from a randomised controlled trial on the efficacy of famotidine. Among NSAID users who did not receive famotidine, the ulcer incidence was significantly higher in patients with *H. pylori*-induced gastric neutrophils (49.2%, 98.4 per 100 patient years) than in uninfected subjects (7.1%, 14.2 per 100 patient years). This observation disappeared in patients receiving famotidine irrespective of their *H. pylori* status.

Three randomised trials of omeprazole for the prevention of NSAID-induced dyspepsia or endoscopic injury had analysed the effect of *H. pylori* on endoscopic injury.[23-25] Ekstrom et al.[25] found that among patients not receiving omeprazole, *H. pylori* infection significantly increased the incidence of ulcers (26.7% or 106.8 per 100 patient years vs 7% or 28 per 100 patient years for uninfected patients). The OMNIUM (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management) and the ASTRONAUT (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment) studies found that among subjects receiving omeprazole, *H. pylori* infection was a good prognostic factor.[23,24] Using a combined endpoint of dyspepsia, ulcers or multiple erosions, these two studies found that the relapse rates at 6 months were about 25% (50 per 100 patient years) in *H. pylori*-positive patients compared with approximately 45% (90 per 100 patient years) in *H. pylori*-negative patients.[23,24] These conflicting results could be reconciled by the fact that acid suppression modifies the effect of *H. pylori* on the gastric mucosa. Studies showing increased ulcer risk in *H. pylori*-infected NSAID users were based on patients not receiving acid suppressants.[14,25] In contrast, the protective role of *H. pylori* infection reported in the OMNIUM and the ASTRONAUT studies were derived from patients receiving maintenance acid suppressants.[23,24] These findings suggested that although *H. pylori* aggravates NSAID-induced mucosal injury in the absence of acid suppression, the bacterium might alleviate NSAID injury by augmenting the acid-suppressing effect of omeprazole.[21,22]

2.2 Does Eradication of *H. pylori* Alter the Ulcer Risk in Patients Receiving NSAIDs?

Whether *H. pylori* should be eradicated in patients receiving NSAIDs is probably one of the most controversial issues in ulcer research. To date there are eight studies in the literature[53-60] (table I). These studies can be classified according to whether the subjects were NSAID-naive or long term NSAID users and whether they used non-aspirin NSAIDs or low-dose aspirin.

2.2.1 Long-Term NSAID Users

Four randomised trials[53-56] evaluated whether eradication of *H. pylori* would alleviate gastric damage in patients who were already receiving long-term NSAID therapy. All except one study[56] used endoscopic gastroduodenal lesions as a surrogate endpoint for ulcer disease. In the first study by Bianchi Porro et al.,[53] 46 patients with uncomplicated ulcers and *H. pylori* infection were randomly assigned to receive omeprazole alone or omeprazole plus omeprazole-amoxicillin dual therapy. They found that eradication of *H. pylori* did not significantly affect ulcer healing (70% in the eradication group compared with 82% in the omeprazole alone group). Over a period of 6 months, the rate of ulcer relapse was numerically higher in *H. pylori*-positive patients (46%, 92 per 100 patient years) than in *H. pylori*-eradicated patients (31%, 62 per 100 patient years), but the difference did not reach statistical significance. This study was limited by small sample size and poor eradication rate (56%).

Hawkey et al.[54] studied long-term NSAID users with *H. pylori* infection who had dyspepsia or ulcers. Of 285 subjects, only 87 (31%) had ulcers at baseline (41 gastric ulcers and 46 duodenal ulcers). All patients were randomly assigned to receive omeprazole-triple therapy or omeprazole with placebo antibacterials. Ulcer-free patients or patients

Table I. Summary of the effects of *Helicobacter pylori* (HP) eradication on the ulcer risk associated with NSAID use

Study	Patients	Design	Total number of subjects	Duration of follow-up	Outcomes	Remarks
Bianchi Porro et al.[53]	HP+ long-term NSAID users with ulcers	Anti-HP vs HP+	46	6mo	Endoscopic ulcers (31% vs 46%; p = NS)	Poor HP eradication rate: 56%
Hawkey et al.[54]	HP+ long-term NSAID users with ulcers or dyspepsia	Anti-HP vs placebo	285	6mo	Endoscopic ulcers or dyspepsia (44% vs 47%; p = NS)	Of 285 subjects, only 87 (31%) had ulcers at baseline (41 gastric ulcers and 46 duodenal ulcers)
Lai et al.[55]	HP+ long-term NSAID users without ulcer or dyspepsia	Anti-HP vs placebo	140	3mo	Endoscopic ulcers (7% vs 9% p = NS)	
Chan et al.[56]	HP+ long-term NSAID or aspirin users with ulcer bleeding	Anti-HP vs PPI	150 (NSAID users)	6mo	Recurrent ulcer bleeding NSAID users (18.8% vs 4.4%; p = 0.005)	Patients in the PPI group remained HP+
			250 (aspirin users)		Aspirin users (1.9% vs 0.9%; p = NS)	
Chan et al.[57]	HP+ NSAID-naive subjects without ulcer or dyspepsia	Anti-HP+ vs HP+	100	2mo	Endoscopic ulcers (7% vs 26%; p = 0.01)	
Chan et al.[58]	HP+ NSAID-naive subjects with ulcers or dyspepsia	Anti-HP + vs placebo	100	6mo	Endoscopic ulcers (12% vs 34%; p = 0.0085)	
					Complicated ulcers (4% vs 27%; p = 0.0026)	
Labenz et al.[59]	HP+ NSAID-naive subjects without ulcer	Anti-HP vs anti-HP + PPI vs PPI vs placebo	660	5wk	Endoscopic ulcers (1.2% vs 1.2% vs 0% vs 5.8%; p < 0.05 vs placebo)	
Lai et al.[60]	HP+ long-term aspirin (acetylsalicylic acid) users with ulcer bleeding	Anti-HP + placebo vs anti-HP + PPI	123	12mo	Recurrent ulcer bleeding (14.8% vs 1.6%; p = 0.008)	In the placebo group, 4 of 9 patients with recurrent bleeding had recurrent HP and 2 used concomitant NSAIDs. Only 4.9% (3 patients) with successful HP eradication had recurrent bleeding

HP+ = *H. pylori*-positive; **anti-HP** = HP eradication therapy; **NS** = not significant; **PPI** = proton pump inhibitor.

with healed ulcers continued NSAIDs without anti-ulcer treatment for up to 6 months. Relapse was broadly defined as recurrent ulcers (≥3mm in diameter) or dyspepsia. *H. pylori* was eradicated in 66% of patients in the eradication group and 14% of patients in the control group. There was no difference in terms of ulcer relapse or dyspeptic symptoms between the two groups. On subgroup analysis of 41 patients with baseline gastric ulcers, ulcer healing was significantly slower in *H. pylori*-eradicated patients (72%) than in *H. pylori*-infected patients (100%).

The study by Hawkey et al.[54] raised concern as to whether eradication of *H. pylori* infection would impair ulcer healing in patients with arthritis. A note of caution about this study is that ulcer healing was not a predefined endpoint and there was a possibility of type I error. Using ulcer healing as the primary endpoint, our group investigated whether eradication of *H. pylori* would affect the healing of complicated ulcers in NSAID users. 195 *H. pylori*-infected patients with NSAID-associated bleeding ulcers (112 gastric ulcers and 83 duodenal ulcers) were randomly assigned to *H. pylori* eradication therapy plus omeprazole or omeprazole alone. The result showed that eradication of *H. pylori* did not have any significant adverse effect on the healing of gastric (*H. pylori*-positive vs *H. pylori*-eradicated: 94% vs 88%; p = 0.29) or duodenal (*H. pylori*-positive vs *H. pylori*-eradicated: 100% vs 98%; p = 1.0) ulcers.[61] Recently, Lai et al.[55] evaluated the effect of *H. pylori* eradication on low-risk, long-term NSAID users who did not have baseline endoscopic ulcers. The 12-week incidence of ulcers was similar between *H. pylori*-eradicated and control subjects (7% vs 9%). The result suggested that screen-and-treat *H. pylori* in low-risk subjects is not worthwhile, although the study was not powered to detect a treatment difference.

Previously we compared *H. pylori* eradication with omeprazole for the prevention of recurrent ulcer bleeding in arthritic patients with *H. pylori* infection and a history of ulcer bleeding who received naproxen.[56] Over 6 months, 18.8% (37.6 per 100 patient years) of patients who received eradication therapy alone developed recurrent bleeding whereas 4.4% (8.8 per 100 patient years) of patients who received omeprazole had recurrent bleeding (p = 0.005). Although this is the first study suggesting that a proton pump inhibitor (PPI) is effective against ulcer bleeding in NSAID users who are infected with *H. pylori,* current evidence indicates that the efficacy of PPI is reduced in the absence of *H. pylori* infection (see section 2.1.2). With the exception of the study by Bianchi Porro et al.,[53] the overall results suggest that eradication of *H. pylori* does not reduce the ulcer risk or dyspepsia in patients who are already receiving long-term NSAIDs.

2.2.2 NSAID-Naive Subjects

Three randomised trials[57-59] investigated whether eradication of *H. pylori* before starting NSAID treatment would reduce the subsequent risk of ulcer development. In the first study, patients with *H. pylori* infection who had no prior NSAID use were randomly assigned to bismuth-triple therapy followed by naproxen or naproxen alone. The endpoint was endoscopic ulcers (≥5mm diameter).[58] Over 8 weeks, 7% of patients (45.5 per 100 patient years) in the eradication group developed ulcers and 26% (169 per 100 patient years) in the naproxen alone group developed ulcers (p = 0.01). This study had several limitations, which included a short duration of follow-up, the inclusion of only low-risk patients who had no dyspepsia or ulcers, the use of bismuth that possesses a mucosal protective effect, the requirement of screening endoscopy to exclude baseline ulcers, the lack of double-blinding and the use of endoscopic ulcer as the endpoint.

In the second study, we sought to overcome these limitations by studying NSAID-naive patients who had dyspepsia or a history of ulcer, replacing bismuth with omeprazole in the eradication regimen, substituting screening endoscopy with urea breath tests, extending NSAID treatment to 6 months, using a double-blind design and assessing the outcome using both endoscopic and complicated (symptomatic or bleeding) ulcers. The rates of endoscopic ulcers were 12% (24.2 per 100 patient years) in the eradication group compared with 34.4% (68.8 per 100 patient years) in the placebo group (relative risk

[RR] reduction 65%, p = 0.0085). The incidence of complicated ulcers was 4.2% (8.4 per 100 patient years) in the eradication group and 27.1% (54.2 per 100 patient years) in the placebo group (RR reduction 85%, p = 0.0026).[59]

In a double blind, multi-centre study by Labenz et al.,[59] 660 *H. pylori*-infected patients requiring NSAID therapy, who had no past or current peptic ulcers, were enrolled. They received diclofenac for 5 weeks in combination with one of the four randomly assigned treatments: anti-*H. pylori* therapy, anti-*H. pylori* therapy followed by omeprazole, omeprazole alone or placebo. All three active treatments significantly reduced the occurrence of ulcer (the rates of endoscopic ulcers were 12.5 per 100 patient years for *anti-H. pylori* therapy, 12.5 per 100 patient years for anti-*H. pylori* therapy followed by omeprazole, 0 per 100 patient years for omeprazole, and 60.3 per 100 patient years for placebo; $p < 0.05$) and dyspeptic symptoms.

Unlike eradication of *H. pylori* for long-term NSAID users, curing the infection significantly reduces the ulcer risk in NSAID-naive subjects. In a decision analysis model of screen-and-treat *H. pylori* for patients requiring NSAID therapy,[62] *H. pylori* screening reduces NSAID-related adverse events for average-risk patients at an acceptable incremental cost. For patients who are at twice the average ulcer risk, screen-and-treat *H. pylori* improves clinical outcome and lowers per patient expenditures if the strategy can reduce the ulcer risk by 50%.

2.2.3 NSAID-Naive Patients versus Long-Term NSAID Users

How can we explain the different outcomes of *H. pylori* eradication between long-term NSAID users and NSAID-naive subjects? There is good epidemiological evidence that the ulcer risk is substantially increased during the first few months of NSAID treatment.[28-31] The author hypothesised that *H. pylori* contributes to the excessive ulcer risk at the start of NSAID treatment, whereas NSAIDs cause the majority of ulcer disease in long-term users irrespective of their *H. pylori* status. *H. pylori* has been shown to impair gastric adaptation to aspirin, which leads to persistent microbleeding from the mucosa.[9] The administration of NSAIDs induces ulcer or precipitates ulcer complications in these susceptible patients. Excluding these susceptible individuals naturally selects patients who can tolerate long-term NSAIDs irrespective of their *H. pylori* status. This may account for the lack of benefit of *H. pylori* eradication in patients who are already receiving long-term NSAIDs.

2.2.4 Low-Dose Aspirin (Acetylsalicylic Acid) Users

Unlike non-aspirin NSAIDs, there are more data from animal experiments and observational studies to suggest that *H. pylori* aggravates mucosal damage or increases the ulcer risk associated with aspirin. However, whether eradication of *H. pylori* could effectively reduce the risk of ulcer complications in an increasing population of aspirin users remains unresolved. To date, only two studies have been published as full articles in the literature.[56,60] In the first study, 250 aspirin users with *H. pylori* infection and a recent history of ulcer bleeding were randomly assigned to *H. pylori* eradication therapy alone or maintenance therapy with omeprazole. The 6-month incidence of recurrent ulcer bleeding in the eradication therapy group (1.9%, 3.8 per 100 patient years) was comparable to that of the omeprazole group (0.9%, 1.8 per 100 patient years [difference: 1.0%; 95% CI, −1.9, −3.9]).[56] One limitation of this study is the relatively short follow-up period. It is uncertain whether curing *H. pylori* infection without acid suppressive treatment will confer long-lasting gastric protection against aspirin.

In the second study by Lai et al.,[60] 123 aspirin users with *H. pylori* infection and a history of ulcer bleeding received eradication therapy. After confirmation of ulcer healing and eradication of *H. pylori,* patients were randomly assigned to lansoprazole or placebo for 12 months. One of the 62 patients in the lansoprazole group (1.6%, 1.6 per 100 patient years) compared with nine of the 61 patients in the placebo group (14.8%, 14.8 per 100 patient years) had recurrent ulcer complications (adjusted hazard ratio [HR_{adj}], 9.6; 95% CI, 1.2, 76.1). Contrary to the first study, the result of this study suggests that eradication of *H. pylori* alone is not sufficient to prevent

ulcer complications in high-risk users of low-dose aspirin.

What are the possible explanations for the conflicting results of these two studies? First, the high incidence of recurrent bleeding in the placebo group (14.8 per 100 patient years) observed in the study by Lai et al.[60] was attributed to an unexpectedly high relapse rate of *H. pylori* infection and concomitant use of NSAIDs. Of the nine patients with recurrent bleeding in the placebo group, four had a relapse of *H. pylori* infection and two received concomitant NSAIDs. Excluding these six patients, only 4.9% (three patients) with successful eradication of *H. pylori* had recurrent ulcer bleeding with aspirin therapy in 12 months. Second, the study excluded patients with *H. pylori* infection who had ulcer bleeding within 30 days of aspirin use. This would eliminate patients with pre-existing *H. pylori* ulcers who developed complications with aspirin. The true benefit of *H. pylori* eradication for prevention of ulcer complications with low-dose aspirin needs to be evaluated by large-scale, long-term studies.

2.3 Is *H. pylori* Infection Relevant in the Era of Cyclo-Oxygenase Selective NSAIDs?

The development of NSAIDs that selectively inhibit COX-2 offers the prospect of providing effective anti-inflammatory action with minimal gastric toxicity. With the much improved gastric safety profiles of COX-2 selective NSAIDs, the relative importance of *H. pylori* infection in inducing gastric damage may arguably increase. Furthermore, there is good evidence that COX-2 is upregulated in *H. pylori* gastritis.[7] Selective inhibition of COX-2 might become a disadvantage since COX-2 may be an important source of gastric prostaglandins in *H. pylori* gastritis. However, current data on the gastric safety profile of selective COX-2 inhibitors in *H. pylori*-infected patients were derived from subgroup analysis on studies designed for different aims.

In a double-blind, 12-week endoscopic study of celecoxib versus naproxen,[63] among patients who received celecoxib the incidence of ulcer was 12.9% (57.6 per 100 patient years) in patients with *H. pylori* infection compared with 2.9% (11.6 per 100 patient years) in uninfected patients (p = 0.023). *H. pylori* did not influence the ulcer risk in patients receiving naproxen. However, in a pooled analysis of four double-blind, 12-week endoscopic studies of celecoxib that collectively enrolled 4000 patients with arthritis, the same group of investigators reported contradictory results.[64] Among patients who received celecoxib, the incidences of ulcer was not significantly different between *H. pylori*-infected and uninfected subjects (8.0% or 32 per 100 patient years vs 5.1% or 20.4 per 100 patient years, respectively; [OR 1.6; 95% CI 0.9, 2.8]). In contrast, among patients who received nonselective NSAIDs, the incidence of ulcer was significantly higher in *H. pylori*-infected subjects (28.4%, 113.6 per 100 patient years) than in uninfected patients (20%, 80 per 100 patient years [OR 1.6; 95% CI 1.1, 2.3]).

Contrary to the conflicting results generated from celecoxib studies, there are data to suggest that *H. pylori* infection may negate the gastric sparing effect of rofecoxib. Laine et al.[65] analysed the risk factors for upper gastrointestinal (GI) events[65] from the VIGOR (Vioxx® [1] Gastrointestinal Outcomes Research) study.[66] Major risk factors identified for upper GI clinical events were old age (≥75 years of age) and prior complicated or uncomplicated GI events. Interestingly, *H. pylori* infection was found to alter the outcomes of certain groups of patients. First, patients receiving rofecoxib had fewer gastric ulcers than those receiving naproxen, irrespective of the *H. pylori* status. In contrast, rofecoxib did not reduce the risk of duodenal ulcers compared with naproxen in *H. pylori*-infected subjects. Second, among those with prior GI events, the rate of events in the rofecoxib group was 3.5-fold higher in *H. pylori*-positive patients than in *H. pylori*-negative patients. The results suggest that the upper GI sparing effect of rofecoxib was offset by the presence of *H. pylori* infection in patients with prior upper GI events and the superiority of rofecoxib over naproxen in reducing the risk of complicated duodenal ulcers disappeared in the presence of *H. pylori* infec-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tion. The discrepant findings between celecoxib and rofecoxib were probably because of *post hoc* subgroup analysis.

2.4 What is the Significance of *H. pylori* Infection in Patients Receiving Proton Pump Inhibitors for Prophylaxis Against NSAID Ulcers?

Current evidence indicates that PPIs are more effective in the presence of *H. pylori* infection. On subgroup analysis of the study by Ekstrom et al.,[25] omeprazole was superior to placebo for the prevention of gastric ulcers in NSAID users with *H. pylori* infection (rates of gastric ulcer in the groups receiving omeprazole and placebo were 13.6 and 70.4 per 100 patient years, respectively). In contrast, omeprazole was not superior to placebo in uninfected subjects (12.0 vs 10.4 per 100 patient years). Two large-scale studies showed that omeprazole was superior to standard-dose ranitidine and half-dose misoprostol for prevention of NSAID-associated gastroduodenal injury.[23,24] However, in the omeprazole group, patients with *H. pylori* infection had significantly less mucosal lesions than those who were *H. pylori* negative.[23,24] To eliminate the confounding effect of *H. pylori*, Graham et al.[67] compared full-dosages of misoprostol (200μg four times daily) with two dosages of lansoprazole (15mg and 30mg daily) in NSAID users without *H. pylori* infection. The results showed that both doses of lansoprazole were inferior to misoprostol for the prevention of gastric ulcers (the rates of ulcer were 43, 47 and 15 per 100 patient years in the groups receiving two dosages of lansoprazole and misoprostol).

Should we save *H. pylori* to increase the efficacy of PPIs? This cannot be justified since *H. pylori* infection is an important risk factor for peptic ulcer and gastric cancer. Since long-term treatment with PPIs is associated with the worsening of *H. pylori* corpus gastritis,[68] it is advisable to test for *H. pylori* and eradicate the infection if it is present before starting long-term PPI therapy.

3. Conclusion

The complex interaction between *H. pylori* infection and NSAIDs indicates that it would be inappropriate to recommend eradicating or saving the bacterium without considering other concomitant factors. Factors such as the choice of *H. pylori* diagnostic tests, previous ulcer complications, concurrent use of acid suppressants, NSAID-naive versus long-term users, low-dose aspirin versus non-aspirin NSAIDs, and whether the result was derived from a pre-specified endpoint or *post hoc* subgroup analysis will alter the outcome (table II). Based on current evidence, the author would like to suggest a number of recommendations regarding the indication of *H. pylori* testing and eradication for NSAID users. First, patients who have a history of ulcer complication should undergo *H. pylori* testing. *H. pylori* should be eradicated in all infected patients because it is not plausible to determine whether the ulcer complications were caused by the *H. pylori*, NSAIDs or both. Patients who continue to require NSAIDs should receive either a PPI or misoprostol to prevent ulcer recurrence. Although *H. pylori* infection enhances the efficacy of PPIs, it is unethical to keep a gastric pathogen, as well as carcinogen, for a modest therapeutic gain. Second, for patients with a history of ulcer complications who require low-dose aspirin, eradication of *H. pylori* substantially reduces the risk of recurrent ulcer bleeding. Whether these patients require long-term acid suppressants depends on the outcome of *H. pylori* eradication and

Table II. Checklist for reading a research paper on the interaction between *Helicobacter pylori* infection and NSAIDs

Was the result derived from a pre-specified primary endpoint or *post hoc* subgroup analysis?
What was the *H. pylori* diagnostic test used (serological vs non-serological tests) in case-control studies?
Were the patients NSAID-naive or long-term users?
What was the proportion of patients with a history of ulcer or ulcer complications?
Did the patients receive concomitant acid suppressants?
Did the patients receive low-dose aspirin (acetylsalicylic acid) or non-aspirin NSAIDs?

concurrent use of non-aspirin NSAIDs. Current evidence suggests that long-term treatment with a PPI is beneficial for these patients if *H. pylori* eradication has failed and they use concomitant non-aspirin NSAIDs. Third, for patients who are about to start receiving NSAIDs, *H. pylori* testing and treatment reduces the ulcer risk at an affordable incremental cost. Fourth, since treatment with PPIs has been shown to aggravate *H. pylori* corpus gastritis, it is advisable to test for *H. pylori* and eradicate the infection if it is present before starting long-term therapy with a PPI for prophylaxis against NSAID-induced ulcers. Current data on the gastric safety of COX-2 selective NSAIDs in *H. pylori*-infected patients are conflicting. Limited data suggest that *H. pylori* infection probably negates the gastroduodenal sparing effect of rofecoxib in patients who have had prior upper GI events. With a reduced gastric toxicity of COX-2 selective NSAIDs, the relative contribution of *H.pylori* infection to peptic ulcer disease is likely to increase. Recently, there is much concern about the cardiovascular risk of COX-2 selective NSAIDs. Rofecoxib has been withdrawn from the market, but other COX-2 selective NSAIDs probably share similar cardiovascular risk. The use of this new class of NSAIDs needs to be critically reconsidered.

Acknowledgements

The author did not receive any financial support in preparing this article and does not have any potential conflicts of interest that are relevant to the contents of the article.

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