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Helicobacter pylori infection and the use of NSAIDs

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Helicobacter pylori infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) can each result in gastroduodenal ulcers and ulcer complications. Recent studies have suggested that there is an interaction between the two causes such that elimination of *H. pylori* before NSAID treatment decreases the occurrence of ulcers. This led to the conclusion of the Maastricht 2000 meeting that *H. pylori* eradication should be considered before embarking on long-term NSAID therapy. One of the main sources of confusion is related to the fact that prospective endoscopic studies testing various drugs for prevention of NSAID ulcers among chronic NSAID users are probably not directly applicable to problems of clinical ulcers and of ulcer complications. It has become clear that, to be interpretable clinically, such studies must provide separate analyses based on *H. pylori* status, history of ulcer, or an ulcer complication. Overall, the data strongly support the notion that eradication therapy is beneficial for primary prophylaxis. In contrast, one would expect little benefit when NSAIDs caused the clinical ulcer (secondary prevention) and, at best, *H. pylori* eradication has a modest effect on the prevention of recurrent ulcer bleeding in NSAID users who have suffered ulcer complications. The data support the notion that *H. pylori* eradication therapy should be given to all *H. pylori*-infected patients with peptic ulcers irrespective of whether or not they have used NSAIDs. Proton pump inhibitors are superior to placebo for the prevention of ulcer recurrence but are inferior to full-dose misoprostol for the prevention of ulcers among those with NSAID ulcers and no *H. pylori* infection. Selective COX-2 inhibitors appear to reduce markedly, but not eliminate, ulcer complications among chronic NSAID users.

Key words: *Helicobacter pylori*; NSAIDs; peptic ulcer; gastric ulcer; duodenal ulcer; anti-secretory therapy.

Helicobacter pylori infection and non-steroidal anti-inflammatory drugs (NSAIDs) are the main aetiological risk factors for the majority of gastroduodenal ulcers and their

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complications.^{1,2} There are conflicting results regarding the role that *H. pylori* plays in the pathogenesis of ulcers induced by NSAIDs. The interaction between NSAIDs and *H. pylori* is not one of simple addition or multiplication, and the discrepant findings reported reflect complex interaction between *H. pylori* and NSAIDs.³

Over 30 million individuals in the world habitually use NSAIDs; half of the users are over 60 years of age. The fact that the prevalence of *H. pylori* infection in this age group is high (e.g. 80%)⁴ suggests that many, if not most NSAID users with ulcers or ulcer complications will also have an *H. pylori* infection. Knowledge regarding the inter-relationships between *H. pylori* and NSAID-associated gastroduodenal lesions is important for both treatment and prevention of ulcers and ulcer complications.

Both *H. pylori* and NSAIDs are pathogenic factors which exert damaging effects on the mucosa and, in individual cases, could be independent, additive, synergistic, or even antagonistic.⁵ Most of the studies that have been reported have not examined the clinical situation as it occurs in practice. The tendency has been to study the effect of various interventions on 'endoscopic ulcers' which are often asymptomatic lesions found in studies where endoscopy is done as part of a clinical study in chronic NSAID users and which probably differ greatly from those ulcers that cause complications. Many endoscopic ulcers would actually not qualify as 'ulcers' and are typically defined as mucosal breaks 3 mm or greater with apparent depth. We call many of these 'ulcers for study purposes only'. There are far fewer studies where patients presenting with a symptomatic ulcer or with an ulcer complication are followed with or without an intervention. It is likely that studies of the primary prophylaxis of ulcers and ulcer complications or the secondary prophylaxis of endoscopic and clinical ulcers would produce different conclusions. For example, cross-sectional studies of chronic NSAID users from the general population of rheumatology patients have not shown a difference in prevalence of ulcers among those with or without *H. pylori* infection.⁶⁻¹⁰ Similar results have been reported in a follow-up endoscopic ulcer study of what were relatively highly selected chronic NSAID users.

FINDING AN ULCER IN CHRONIC NSAID USERS: EFFECT OF *H. PYLORI* INFECTION

The risk of developing a new ulcer in an *H. pylori*-infected individual is in the range of 0.5 to 1% per year. This contrasts markedly to patients with *H. pylori* ulcer disease where the risk of developing a recurrence over a 1-year period is in the range of 50 to 80%. The risk of a patient with an *H. pylori* ulcer developing an ulcer complication is also in the range of 1 to 2% per year. Again, the likelihood of a recurrent ulcer complication among patients who had previously experienced an ulcer complication is much higher: at least 12% per year. Thus if a clinical study enrolled 500 chronic NSAID users, and followed them for 1 year, the outcome of the trial would be markedly influenced by the proportion of patients from each different risk group entered in the trial. We would expect that approximately 0.5 to 1% of those with *H. pylori* infection would develop new *H. pylori* ulcers irrespective of whether they entered the trial or not. Even if all 500 patients had active *H. pylori* infections, at most five would develop ulcers not directly attributable to the NSAIDs. In contrast, any enrolled patient who had a prior *H. pylori* ulcer would have a high likelihood of an *H. pylori* recurrence (at least 50%) during the study and could have a major influence on the outcome that would be wholly independent of the use of NSAIDs. An example would be a study comparing an H₂-receptor antagonist, which is already known to reduce the rate of

recurrence of *H. pylori* ulcers, and a placebo. Such a study would have a bias against the placebo arm. For example, let us assume that 10% of the 500 patients had prior *H. pylori* ulcers and (luckily) they were randomly distributed between groups (i.e. 25 per group). The proportion of *H. pylori* ulcers in the H₂-receptor antagonist arm would thus be proportional to the effectiveness of the therapy in preventing the recurrence of *H. pylori* ulcers. If the H₂-receptor antagonists were completely effective (0 recurrences) and the recurrence rate of *H. pylori* ulcers in the placebo group was 50%, there would be 12 *H. pylori* ulcers among those receiving placebo. These would be added to the endoscopic ulcers occurring in each group, making the outcome dependent on both the effectiveness of the active therapy in preventing *H. pylori* ulcers and its effectiveness in preventing endoscopic NSAID ulcers. For example, if, as in many trials, the 1-year prevalence of endoscopic NSAID ulcers was 15%, both groups could have 38 NSAID ulcers. If the H₂-receptor antagonist were completely effective in preventing *H. pylori* ulcer recurrences and there was a modest reduction in NSAID ulcers (e.g. 30% reduction in the number of ulcers) the total number of ulcers in the H₂-receptor antagonist group would be 60% of 38, or 27 compared to 50 (38 NSAID plus 12 *H. pylori* ulcer recurrences). The authors would falsely conclude that the H₂-receptor antagonists were highly protective ($P = 0.006$) against NSAID ulcers. In reality, the comparison should have been 27 ulcers in the H₂-receptor antagonist group (10.8%) versus 38 (15.2%) in the placebo group ($P = 1.0$). Overall, one can conclude that if there is no interaction between *H. pylori* and NSAIDs, and the comparison drug has anti-ulcer effects, it is essential to exclude all those with a history of *H. pylori* ulcers or with ulcer complication. Otherwise one runs the risk of a major bias in favour of the drug with anti-ulcer properties. Alternatively, one must keep track of them and be prepared to analyse them separately. Because, as noted below, *H. pylori* and NSAIDs are likely to have an interaction, it is essential to do separate analyses based on *H. pylori* status, history of ulcer, or an ulcer complication.

IDENTIFICATION OF CHRONIC NSAID USERS AT RISK FOR DEVELOPMENT OF AN ULCER OR ULCER COMPLICATION

Dyspeptic symptoms have not proven to be a reliable warning sign for increased risk for either an NSAID ulcer or development of a serious gastrointestinal complication of NSAID use. Uncontroversial factors that are associated with risk include advanced age, past history of an ulcer or ulcer complication (see above), high NSAID dose, the NSAID used, concomitant use of anticoagulants, serious systemic disorders, and (almost certainly) use of corticosteroids at a dose > 10 mg of prednisolone daily. All of these magnify the risk of bleeding peptic ulcers in patients taking NSAIDs. Indications where there is controversy include the indication for the NSAID, sex of the patient, smoking or alcohol history, and *H. pylori* status.¹¹

EPIDEMIOLOGY OF NSAID-ASSOCIATED GASTROINTESTINAL COMPLICATIONS

Numerous studies have shown that the use of NSAIDs is associated with an approximately fourfold enhancement of the risk of gastrointestinal complications and death in elderly patients taking non-aspirin NSAIDs.^{12,13} Population-based studies¹⁴⁻¹⁶ and an endoscopy-based prospective study¹⁷ report discordant results regarding risks

among NSAID users in relation to *H. pylori* infection. The problem is further complicated by the entry criteria in studies, the types of NSAID ulcer, and the different predominant type of *H. pylori* gastric damage (i.e. atrophic pangastritis with reduced acid secretion versus superficial gastritis with normal acid secretion) in different countries. Moreover, many studies suffer from methodological biases, including the use of two or more NSAIDs, lack of knowledge of the type of NSAID, dosage and duration of treatment with NSAIDs. Many studies used univariate analysis, which does allow one to consider possible interactions between multiple factors and coexisting conditions.¹⁸ However, studies of patients with established ulcers who take NSAIDs show a net benefit from *H. pylori* eradication therapy.¹⁹

PATHOPHYSIOLOGY

H. pylori infection causes gastric mucosal inflammation. The critical factors are unknown and could include enzymes such as urease, proteolytic enzymes, antioxidant and metabolic enzymes, lipase and phospholipase A2.²⁰ Epithelium damage is due to direct as well as toxin-mediated and indirect, immunomediated mechanisms. Increased mucosal interleukin-8 promotes neutrophil chemotaxis, followed by macrophage and lymphocyte migration into the gastric mucosa. These defence mechanisms against *H. pylori* infection lead to the release of lysosomal enzymes, platelet-activating factor, oxygen free radicals, chemotactic leukotrienes and an increased synthesis of prostaglandins PGE₂ and PGI₂. *H. pylori* infection is also associated with an increase in the rate of TNF α - and Fas/FasL-mediated apoptosis.²¹

The pathogenesis of NSAID-associated gastropathy is only partially known, but it is well accepted that these drugs can lead to ulcerative lesions through direct epithelial damage with various forms and degrees of desquamation²² and, most prominently, through systemic inhibition of cyclo-oxygenase (COX-1 and COX-2) affecting the cytoprotective role of prostaglandin synthesis. The consequence of prostaglandin inhibition result in a reduced synthesis of mucus and bicarbonate, and alterations in vascular permeability, and in change in the small vessels promoting stasis and ischaemia.²³

It has been suggested that *H. pylori* infection may play a protective role in NSAID users by limiting the decrease in local tissue prostaglandin induced by NSAIDs. Immunohistochemical studies have shown increased expression of COX-2 in the gastric mucosa of infected patients consistent with the presence of acute inflammation with no change in the expression of the 'protective' COX-1.²⁴ In general, *H. pylori* increases mucosal prostaglandins and NSAIDs inhibit them. One would expect that NSAIDs would eliminate or reduce any beneficial anti-NSAID activity related to *H. pylori*-stimulated prostaglandin injury. In fact, Laine et al²⁵ showed a decrease in prostaglandin synthesis in both *H. pylori*-positive and *H. pylori*-negative subjects who were chronically given naproxen. The hypotheses related to a beneficial effect of *H. pylori* related to prostaglandin synthesis are reminiscent of the proposals that mild damaging agents such as antacids or sucralfate might protect by prostaglandin-mediated cytoprotection. It was subsequently recognized that pre-treatment with NSAIDs eliminated any beneficial effect by inhibiting the expected prostaglandin synthesis. For example, sucralfate failed in clinical trials to show any protective effect despite the fact that it was shown to be a mild irritant and to produce adaptive cytoprotection.²⁶ There are few data to support a beneficial effect of an *H. pylori* infection. For example, Lanza et al²⁷ studied the effects of *H. pylori* infection on the severity of acute gastric mucosa damage induced by administration of naproxen and

aspirin in 61 volunteers. They found no relationship between the infection and the severity of the endoscopic lesions. In addition, the percentage of acute endoscopic gastric ulcers was the same in *H. pylori*-positive subjects (16.5%) and *H. pylori*-negative subjects (17.5%). On the other hand, in a recent placebo-controlled, double-blind, randomized trial available only in abstract form, Cryer et al²⁸ prospectively assessed the effect of *H. pylori* on gastric mucosal injury in subjects exposed to low-dose aspirin (ASA). The authors claim that *H. pylori* gastritis significantly worsens gastric mucosal injury in patients chronically taking low-dose ASA and the bacteria appear to be a risk factor for low-dose ASA-induced gastric ulcers. Moreover, two other studies also available only as abstracts^{29,30} suggest that *H. pylori* infection may increase the risk on clinical gastrointestinal events. Lanas and colleagues²⁹ suggest that *H. pylori* is a risk factor associated with peptic ulcer bleeding in low-dose aspirin users, and this risk was associated with duodenal ulcer bleeding but was not influenced by infection with CagA-positive *H. pylori* strains. However, overall, the data are consistent with the notion that *H. pylori* status does not affect the severity of gastric mucosal damage following acute exposure to NSAIDs.^{22,27,31,32} Finally, in a prospective study in volunteers receiving naproxen, Shiotani et al³³ evaluated whether mucosal damage or protection could be related to levels of mucosal nitric oxide or interleukin-8, histological parameters including the density of *H. pylori*, polymorphonuclear cells or luminal pH. The authors demonstrated that only subjects with high intraluminal pH and severe corpus gastritis were protected. In this instance, *H. pylori* acted as a biological antisecretory agent³⁴ as is consistent with the fact that antisecretory therapy can reduce the severity of acute NSAID gastroduodenal injury. The protective effect of severe gastritis was suggested long ago in studies of NSAID-induced gastric micro-bleeding.^{35,36} In summary, there are no creditable data for a protective effect of an *H. pylori* infection for the prevention of NSAID-induced gastric mucosal damage short of *H. pylori*-induced severe gastritis with marked reduction in acid production.

THERAPEUTIC ASPECTS

The role of *H. pylori* infection in patients with NSAID-associated peptic ulcers has been recently addressed in large, randomized, multicenter trials.^{37–39} The OMNIUM study³⁷ compared omeprazole (20 mg given once a day) and misoprostol (200 µg given twice a day) for the prevention of recurrent ulcers in patients with arthritis who were receiving NSAID therapy. After 6 months, 12% of the patients receiving placebo and 10% of those receiving misoprostol, but only 3% of those receiving omeprazole, had duodenal ulcers. Gastric ulcers recurred in 32% of the patients receiving placebo, in 10% of those receiving misoprostol, and in 13% of those receiving omeprazole.⁴⁰ Omeprazole was superior to placebo for the prevention of ulcer recurrence in chronic NSAID users. However, omeprazole was not significantly better than a non-acid inhibiting dose (400 µg/day) of misoprostol (14.5 versus 19.6%, respectively; $P = 0.93$) and 400 µg of misoprostol was actually superior to omeprazole for the prevention of gastric ulcers among chronic NSAID users without *H. pylori* infection (8.2 versus 16.6% for misoprostol and omeprazole, respectively; $P < 0.05$). Omeprazole was also not statistically different from misoprostol for the prevention of gastric ulcers among chronic NSAID users with *H. pylori* infection. Omeprazole was also not significantly different than 300 mg of ranitidine for the prevention of gastric ulcers in chronic NSAID users without an *H. pylori* infection (14.6 versus 116%, respectively; $P = 0.56$).³⁸ Overall, duodenal ulcers were over-represented among *H. pylori*-infected NSAID

users. Over-representation of duodenal ulcer among *H. pylori*-infected chronic NSAID users has now been recognized as a general phenomenon.⁴¹

EFFECT OF *H. PYLORI* INFECTION ON ULCER HEALING

The HELP NSAIDs study⁴² enrolled patients with current or previous endoscopically documented NSAID-associated gastric or duodenal ulceration and/or moderate–severe dyspepsia. Both clinical conditions were studied because the authors felt that *H. pylori* eradication might have a different effect on each end-point. A total of 285 patients were randomized to receive eradication therapy (omeprazole plus two antibiotics) or omeprazole plus placebo (control group) for 1 week. An unexpected finding was a low eradication rate in patients receiving anti-*H. pylori* therapy and a relatively high apparent eradication rate in the control group (respectively 66 versus 14%). Patients who had received eradication therapy had a slight delay in gastric ulcer healing (50 versus 88% at 4 weeks; 72 versus 100% at 8 weeks) consistent with the known reduction in efficacy of proton pump inhibitors associated with eradication of *H. pylori*. Other studies have also shown a slight but generally not significant reduction in gastroduodenal ulcer healing associated with *H. pylori* eradication.^{43–45} While some have suggested that a slight delay in ulcer healing might cause one to reconsider *H. pylori* eradication, few would take that argument seriously. As expected, eradication of *H. pylori* infection did not prevent ulcer recurrence in chronic NSAID users. *H. pylori* eradication would only be expected to prevent recurrence of *H. pylori* ulcers and it was previously shown that ulcer recurrence after *H. pylori* eradication was typically associated with the use of NSAIDs.⁴⁶

The fact that one can never be confident of the actual aetiology of an individual ulcer has complicated the interpretation of clinical studies. For example, some studies have shown a major benefit of *H. pylori* eradication therapy compared to antisecretory drugs for the prevention of bleeding relapse in *H. pylori*-positive patients with NSAID-associated peptic ulcers. In two different studies, Labenz and Borsch⁴⁷ and Jaspersen et al⁴⁸ reported that, 12 to 24 months from ulcer healing, bleeding relapse was documented in 27 to 33% of patients treated with proton pump inhibitors and in no patient treated with eradication therapy for *H. pylori*. Again, one would not expect eradication of *H. pylori* to have a secondary preventive effect against true or unequivocal NSAID ulcers, or their complications.

H. pylori eradication appears to have a primary preventive effect. For example, Chan et al⁴⁹ studied patients who were ulcer-free at an initial endoscopy, who were not taking NSAIDs at the time of study entry and who had no past history suggesting peptic ulcer disease. These patients were randomized to receive eradication therapy or control treatment for 2 weeks, while starting 2-month course of naproxen (250 mg three times daily). At 8 weeks there was a marked reduction in the incidence of gastric ulcers in the eradication treatment group (from 26 to 7%). This observation has apparently been confirmed.⁵⁰

DEVELOPMENT OF SAFER NSAIDS: COX-2 INHIBITORS

Several modifications in the formulation of NSAIDs have been introduced in recent years to reduce their toxicity. COX-2 inhibitors (coxibs) have been recently developed and seem to have markedly reduced the capacity of NSAIDs to cause injury to the

gastrointestinal mucosa.^{51–53} Literature concerning the effects of COX-2 inhibitors on prevention of ulcer complications is only beginning to become available.

Two coxibs that have selectivity for COX-2 at doses substantially higher than those required to affect inflammation are currently available and have been studied extensively: celecoxib and rofecoxib. Coxibs do not cause more mucosal injury than placebo when used in treating osteoarthritis.^{52,53} Goldstein et al⁵⁴ have presented results of a meta-analysis on 14 randomized, controlled trials of 11 008 patients with rheumatoid arthritis and osteoarthritis, treated with placebo ($n = 1864$) or celecoxib ($n = 6376$) or NSAIDs ($n = 2768$) for 2–24 weeks. NSAIDs have been associated with a higher risk of gastrointestinal adverse events clinically significant of 1.48% (95% CI: 0.35–2.62%) than celecoxib, and there has not been shown a higher risk with celecoxib versus placebo (95% CI = 0.08 to 0.47%). Bombardier and colleagues⁵⁵ randomized 8076 patients with rheumatoid arthritis to receive either rofecoxib 50 mg daily or naproxen 500 mg twice daily, their primary target being to evaluate clinical upper gastrointestinal events (ulcers, perforations, bleeding). Although the two drugs had similar efficacy against rheumatoid arthritis, the rate of development of gastrointestinal events per year was 2.1% with rofecoxib versus 4.5% with naproxen (relative risk 0.5; $P < 0.001$) and the respective rates of confirmed complications were 0.6 and 1.4% (relative risk 0.4; $P = 0.005$). Another randomized study⁵⁶ demonstrated that all different dosages of celecoxib (100 mg or 200 mg or 400 mg twice per day) were efficacious in the treatment of rheumatoid arthritis and did not affect COX-1 activity in the gastrointestinal tract.

Data for pooled analysis, obtained from four independent double-blind 12-week endoscopic trials in osteo-rheumatoid arthritis, were collected in a study⁹ to evaluate the effect of *H. pylori* infection on the incidence of gastroduodenal ulcers in patients receiving placebo, celecoxib or NSAIDs. The percentage of ulcers in the celecoxib group was 8% in *H. pylori*-positive patients and 5.1% in those without infection, OR 1.6 (95% CI: 0.90 to 2.84); in the placebo group it was 7.1% in *H. pylori*-positive subjects and 2.2% in those *H. pylori*-negative, OR 3.5 (95% CI: 0.62 to 19.5). In the traditional NSAID group ulcers were seen in 28.4% with *H. pylori* infection versus 20% among the *H. pylori*-negative patients. These results suggest an *H. pylori*–NSAID interaction. The large double-blind comparisons of selective COX-2 inhibitors and NSAIDs for the prevention of ulcer complications are not yet published in full. Preliminary data show that the proportion with ulcer complications was markedly less with the selective COX-2 inhibitors compared to traditional NSAIDs but that the risk was not zero among COX-2 users. It is clear that these studies will require careful reading to understand how much risk remains and how much is attributable to *H. pylori* infection.

Despite the enthusiasm for these promising new NSAIDs, some questions remain regarding COX-2 inhibitors. In fact, COX-2 might generate endogenous prostanoids that are biologically important. Mizuno et al⁵⁷ have suggested that an increase in mucosal COX-2 expression may be necessary for the normal healing of gastroduodenal ulcers. Nonetheless, there has been no evidence for abnormal wound healing seen with the COX-2 inhibitors. McAdam and co-workers⁵⁸ have recently reported that long-term therapy with celecoxib might increase the rate of thrombotic events in patients who were at increased risk for cardiovascular disease. Because the COX-2 inhibitors do not affect platelet function, they cannot substitute for aspirin. An increase in cardiovascular events was not seen in the large studies where low-dose aspirin was allowed.

COX-2 inhibitors inhibit over-expression of the COX-2 gene early in carcinogenesis, and thereby inhibit the proliferation and adhesion of tumour cells, induce

apoptosis and inhibit the formation of aberrant crypts.⁵⁹ In rat models these drugs have been shown to inhibit significantly both the early and the late stages of chemically-induced colonic neoplasia.⁶⁰ However, so far human data are not available and the results of ongoing trials are eagerly awaited.⁶¹ In an Irish study⁶², it was shown, in 76 patients with colorectal cancer, that this neoplasia may be related to survival and that COX-2 may play a role in tumorigenesis. Recently, Steinbach et al⁶³ published the results of a study where, in patients with FAP, the higher dosage of celecoxib (100 mg or 400 mg twice daily) reduced the number of colonic polyps by 28% ($P = 0.003$), and led to a 30.7% reduction in the polyp burden (the sum of poly diameters) ($P = 0.001$) compared with placebo. The results of these studies suggest that although the highly selective COX-2 inhibitors offer considerable promise in the treatment of inflammatory arthritis, careful surveillance will be important to determine whether elimination of *H. pylori* and use of selective COX-2 inhibitors will essentially eliminate ulcer disease.

SUMMARY

Data have accumulated showing an interaction between *H. pylori* and NSAIDs. Overall, the risks of a serious complication appear increased among *H. pylori* infected NSAID users and it is now recommended that *H. pylori* eradication be considered prior to embarking on long term NSAID therapy (The Maastricht Consensus Report 2–2000. Malfertheiner et al. In preparation). The data support the notion that *H. pylori*

Practice points

- *H. pylori* infection increases the risk of complications among NSAID users, and thus consideration should be given to its eradication whenever long-term NSAID therapy is considered
- all patients taking NSAIDs who have ulcer disease should be tested for *H. pylori* and, if present, the infection should be eradicated

Research agenda

- all studies of the effect of NSAIDs on the gastroduodenal mucosa must provide separate analyses based on *H. pylori* status, history of ulcer, or ulcer complications
- endpoints unrelated to the outcome but likely to be favourably influenced by the active therapy, such as heartburn, should not be included as an important outcome measure in endoscopic studies as they provide misleading suggestions regarding the benefits likely to be seen clinically
- studies should focus on primary and secondary prevention of clinically important outcomes, such as clinical ulcers or ulcer complications, and not on endoscopic ulcers which relate poorly to the clinical situation
- the actual risk of selective COX-2 inhibitors in causing life-threatening complications among patients with and without *H. pylori* infection should be determined – as well as identifying the risk factors that predict an untoward outcome

infection increases the risk of duodenal ulcers but may not increase the risk of gastric ulcers in NSAID users. From a clinical point of view, it is impossible to distinguish between *H. pylori* and NSAID-associated peptic ulcers and we believe it is prudent in ulcer patients with both to eradicate *H. pylori* and stop the NSAID. If an NSAID must be restarted, one should consider cotherapy with a prostaglandin, a proton pump inhibitor, or both, or use of a specific COX-2 inhibitor.

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