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# *Helicobacter pylori* and Non-Steroidal Anti-inflammatory Drugs: Does Infection Affect the Outcome of NSAID Therapy?

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## INTRODUCTION

Over the past decade, we have come to recognize that most peptic ulcers arise in the setting of either *H. pylori* infection or the use of aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs). The pathogenetic mechanisms involved are still far from clear; both *H. pylori* infection and NSAIDS have many effects on tissues and are associated with many clinical problems other than peptic ulcer.

Infection with *H. pylori* usually leads in time to chronic active gastritis ("type B" gastritis or "superficial active gastritis") involving both the antrum and body of the stomach and characterized by the presence of polymorphonuclear leukocytes in the tissue. Organisms are visible on microscopy at the surface of gastric glandular cells, just beneath the mucus coat, adhering exclusively to columnar epithelial cells of the gastric mucosa. Long-term infection is associated not only with chronic active gastritis and ulcers, but in time, with gastric atrophy, gastric cancer, gastric MALT lymphoma, hypertrophic gastropathy with protein-loosing enteropathy (Menetriere's Disease), and probably with the condition known as "Epidemic Hypochlorhydria" [1].

In like manner, acetyl salicylic acid (ASA)[b] and nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a variety of injuries to any part of the gastrointestinal (GI) tract, but their use, as discussed here, is particularly associated with erosive injury to the gastric mucosa, often associated with "chemical" or "reactive" gastritis, characterized by foveolar hyperplasia, vasodilation, edema, relatively few inflammatory cells and the appearance of muscle cells in the lamina propria [2, 3]. Both types of gastritis are associated with an increased risk of "peptic" ulceration [3], not only in the stomach but also in the duodenal cap, which may or may not be similarly inflamed.

Over 25 years, as the incidence, prevalence and rates of hospitalization for peptic ulcer disease have fallen, we have noted no overall decline in incidence rates for GI hemorrhage, bleeding ulcers or ulcer perforations; while these have become far less common in those under 60 years of age, in those over 60 they have risen rapidly, in some countries to almost epidemic proportions.

We recognize that the burden of ulcer disease has shifted to the elderly, most ulcer deaths occurring over age 75 years. Some of the increase in ulcer complications has been linked to increasing use of both prescription and over-the-counter NSAIDs and aspirin-containing products, due not only to their "ulcerogenic" or "erosive" effects on gastroduodenal tissues and on the GI mucosa in general, but also to their potent anti-platelet effects (especially ASA) that increase bleeding from a variety of lesions located anywhere in the GI tract [4].

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[b]*Abbreviations:* ASA, aspirin; NSAID, non-steroidal inflammatory drug.

More recently, both hemorrhage and ulcer perforation have also been linked epidemiologically to the presence of *H. pylori* gastritis, with suggestions, based on small studies, that eradication of infection significantly reduces the risk of subsequent hemorrhage from non-NSAID ulcers. Realization that many peptic ulcers were silent and subclinical has prompted the suggestion that the high rate of GI complications, particularly bleeding, surrounding the start of NSAID or ASA therapy in practice, was due to antiplatelet effects of the drugs in patients with underlying ulcer disease, much of it caused by *H. pylori*. This has raised many questions as to the need to eradicate *H. pylori* in ulcer patients using ASA or NSAIDs, in the hope of influencing the main adverse outcome of NSAID therapy, namely the hospitalization of elderly patients for GI bleeding or perforation. Such outcomes have not been formally studied.

The failure to perform the appropriate outcome studies has stemmed from several sources including: unwillingness to allow the relevant "high-risk" patients to enter clinical trials; the fear that large numbers would be required to provide the statistical power to resolve the issue, with consequent high costs incurred by those performing the trials; the consequent search for a surrogate marker, such as an endoscopic lesion, that would accurately predict the relevant outcome—an effort that has failed; and interests, largely commercial, that opposed the identification of relevant high-risk subgroups requiring expensive care, as a sensible alternative to subjecting the whole NSAID-consuming population to expensive co-therapy or the use of expensive but safer NSAIDs. The willingness of gastroenterologists to perform lucrative endoscopy, however irrelevant, must also be recognized as hindering the progress of research in this area.

Thus, although there has been considerable interest in studying the possible interactions of NSAIDs and *H. pylori* as risk factors for the development of serious gastrointestinal maladies requiring hospitalization, there has been a consistent failure to fund or perform the kinds of studies needed to answer the clinically relevant questions. For this reason, we are compelled to review a large number of small studies, many published only as abstracts, to try to discern in what directions the data point.

Additional problems stem from our lack of understanding of the biology of *H. pylori*, particularly of those properties of the organism that contribute to the pathogenesis of peptic ulcers. While currently available serologic studies are useful in identifying subjects who at some time have had exposure to *H. pylori* infection with consequent gastritis, serologic tests tell us nothing about the current state of the patient, who by now may have little gastritis. The severity of the gastritis cannot be predicted by easily available serologic tests. Furthermore, only 10 to 15 percent of those infected ever develop an ulcer, the lesion of greatest concern in studying interactions with NSAIDs. It is axiomatic that the absence of an ulcer precludes the development of ulcer complications, but not the development of bleeding from other gastrointestinal sites due to platelet dysfunction.

Problems surrounding the use of serologic diagnosis of *H. pylori* in clinical research have been discussed elsewhere [5-7] but include poor sensitivity, specificity and predictive value for peptic ulcer and some further reductions in these values associated with the use of NSAIDs [7]. Suffice it to say that studies relying solely upon serologic evidence of *H. pylori* as a risk factor should be discounted as of little value, except that a negative test, in the absence of evidence to the contrary may generally be used to discount *H. pylori* contributing to an illness in an individual patient. Other tests, including breath tests, histologic diagnosis, biopsy culture and various urease tests of gastric tissues or contents, all have some limitations, especially in the area of thresholds below which negative tests may be unreliable. For these reasons, in studying its interactions with NSAIDs or ASA, the best studies confirm the diagnosis of *H. pylori* infection by at least two methods other than serology. Since these drugs vary considerably in their platelet inhibiting and ulcerogenic

properties, and in their *in vitro* effects on *H. pylori* [8], studies on *H. pylori* and NSAIDs should exclude ASA, a compound that deserves separate study.

What then is the scope of this review? It is to examine a number of individual pieces of a puzzle, using methodologies and underpinning assumptions that may or may not be valid, in the hope of defining a basis for the design of effective future studies. These last need to employ the techniques of outcomes research to quantitate the impact of *H. pylori*-NSAID and *H. pylori*-ASA interactions on hospitalization rates, morbidity and mortality from adverse gastrointestinal events in those using NSAIDs.

## *H. PYLORI* INFECTION AND DYSPEPTIC SYMPTOMS DUE TO NSAIDS

A large number of studies have examined the relationship between underlying chronic active gastritis due to *H. pylori* and susceptibility to developing dyspeptic symptoms while taking a variety of NSAIDs [9, 10]. Many of these studies relied on serological characterization of the patients; this, for reasons described above, confounds the problem. Nevertheless, among a dozen major articles, eight concluded that underlying *H. pylori* infection or gastritis increased the likelihood that a patient would develop dyspeptic symptoms when given either one or a succession of different NSAIDs; four studies failed to find such an association. Overall, the emerging picture is that, at least in some cases, the development of symptoms and their severity are attributable to underlying *H. pylori* gastritis, although symptoms can also accompany NSAID use in the absence of such (type B, chronic active) gastritis. Stated another way, patients with *H. pylori* gastritis appear more likely to develop troublesome dyspeptic symptoms when given NSAIDs.

## NSAIDS, ASA AND *H. PYLORI* GASTRITIS

Much of the background to this discussion has been reviewed previously [9]. For present purposes, suffice it to say that true inflammatory active gastritis, characterized by polymorphonuclear neutrophilic infiltrates in the gastric mucosae of NSAID users, is due to co-incident *H. pylori* infection, and not to NSAIDs or ASA; these latter can cause chemical gastritis, described above, in which mucosal neutrophils are rare. Both types of gastritis are risk factors for ulcer disease [3] but rarely co-exist. It is well accepted that NSAID therapy does not increase the incidence or prevalence of *H. pylori* infection or gastritis, or the susceptibility of the patient to acquiring *H. pylori* infection *de novo*. The prevalence of *H. pylori* infection/gastritis may, if anything, be somewhat lower in all NSAID users [9], especially in studies that include ASA as an NSAID. When full-dose ASA therapy is in use, it is distinctly uncommon to find *H. pylori* in biopsies, suggesting either that ASA therapy, by destroying the mucus layer, unfavorably alters the habitat or "biologic niche" in which *H. pylori* survives or that the demonstrated *in vitro* activity of ASA against *H. pylori* also occurs *in vivo* [8, 9].

The converse of the above relationship is less clear and less well examined. It remains a possibility that underlying *H. pylori* gastritis alters the host susceptibility to NSAID injury, not as reflected by altered incidence or prevalence, but as reflected in the course and severity of the gastritis. Few studies have examined the issue of severity carefully in prospective studies with repeated biopsies of the patients. Those that have attempted to do so for the most part evaluated the effect of NSAIDs as a categorical variable and have ignored quantitative parameters such as type and dose of NSAID, duration of exposure and follow-up, type of patient studied, co-therapy with potentially protective drugs like antacids, sucralfate, $H_2$-antagonists, proton pump inhibitors, bismuth compounds, etc., and have lumped together those with any evidence of exposure to *H. pylori* with the critical

sub-group of those who had *H. pylori* and peptic ulcer prior to the onset of NSAID therapy. Only this last group provides any indication of the existence of the host and *H. pylori* virulence factors most relevant to questions of interaction clinically.

The interactions of *H. pylori* and chemical gastritis may be complex, and some effects may cancel out or oppose other effects [10]. For instance, at least two studies have shown that gastric mucosal and lumenal concentrations of prostaglandin $E_2$ are higher in *H. pylori* infected patients than in normals [11, 12]. If the mechanisms by which ASA and NSAIDs lead to chemical gastritis in healthy mucosa involve inhibition of prostaglandin synthesis, then it is possible that *H. pylori* infection might be protective, by countering such inhibitory effects on prostaglandin synthesis.

In fact, a recent study in "normal" volunteers supports such a hypothesis [13]. After an initial endoscopy to establish the baseline state of their gastric antral mucosal histology, 19 patients were given naproxen 1 g/d for one week, and then re-endoscoped and re-biopsied to examine the incidence of *de novo* chemical gastritis [13]. Among eight subjects with *H. pylori* infection, none developed chemical gastritis, compared to five cases developing among 11 patients who were free of *H. pylori* infection. While the numbers are small, they support the notion that *H. pylori* may protect against chemical gastritis. Unfortunately, the study did not quantitate whether or not active gastritis changed in the infected group.

In the same way, treating ASA consumption as a categorical variable, ignores several important considerations, such as dose-response effects of ASA on the gastric mucosa with, for example, adaptation at low dosage overwhelmed at high dosage, and dose-response effects on platelets, which could increase the risk of bleeding while limiting the survival of *H. pylori* on the mucosal surface.

Despite several studies claiming that NSAIDs had no effect on chronic active gastritis, there are some indications that this warrants more careful study. Early observations in arthritis patients studied before and after NSAID therapy showed significant worsening of active gastritis during therapy with sulindac, with a similar trend observed in four of seven patients treated with indomethacin [14]; based on the histology, these patients were almost certainly infected with *H. pylori* although this was not determined in 1982. A very careful double-blind study [15], which performed endoscopy and obtained biopsies at baseline and four weeks after commencing therapy with either tenoxicam 20 mg/d or diclofenac 100 mg/d, quantitated endoscopic injury scores, histopathologic changes (severity of gastritis) and intensity of mucosal colonization with *H. pylori*. The study found that, of those with no or mild active gastritis due to *H. pylori* at baseline, only one of 22 treated for four weeks with an NSAID progressed to severe gastritis. However, among 14 patients with moderate gastritis at baseline, severe gastritis developed in five, and one developed a duodenal ulcer ($p < .02$). Similarly, in another study in which 51 subjects were randomized to treatment with placebo, meloxicam 5 mg/d or piroxicam 20 mg/d (double-blind) for 28 days, there was a strong positive association between *H. pylori* infection and the severity of mucosal damage (Lanza scale) or with increases in serum concentrations of pepsinogen A and C (markers of mucosal damage) [16].

While the only other studies that prospectively studied patients present before and after NSAID therapy failed to document such an effect of NSAIDs on the severity of gastritis [11, 17], both studies had features that militated against conclusiveness. In the first study [17], normal volunteers were treated for only seven days, and assessments of effects were confined to recording endoscopic scores for mucosal hemorrhage (not a feature of active gastritis); the diagnosis of *H. pylori* was serologic, and no histology was obtained before or after therapy.

In the second study, normal volunteers were again employed: 52 were randomized to placebo (17), naproxen (18), and etodolac (17). However, the highest percentage of *H.*

*pylori* infected patients (59 percent) received etodolac, a very non-injurious NSAID, the second highest group (47 percent) received placebo, and only 45 percent of the 18 receiving naproxen, another comparatively safe NSAID [18], were infected. This study lacked the statistical power to accept or reject any hypothesis with confidence. Other studies that failed to show NSAID effects on severity of active gastritis either did not have repeated biopsies in the same subjects before and after drug, or lacked careful quantitative microscopy of damage or inflammation. Thus, the present data favor the notion that therapy with potent NSAIDs may increase the severity of gastritis due to *H. pylori* over the course of four weeks. The importance of this is that severity and activity of gastritis have been shown to be greater in *H. pylori* subjects with ulcers, particularly duodenal ulcers, than in infected subjects without ulcers [19]. Another study also noted that antral gastritis was predictive of developing ulcers during NSAID therapy [20].

As mentioned previously, both "chemical" or "reactive" gastritis appear to predispose to ulcer development [3]. Many pathologists are much better at recognizing neutrophils in the mucosa than at finding *H. pylori* organisms, particularly in patients who have been treated with anti-ulcer or anti-microbial drugs. The presence of neutrophils is also common to both chemical and active gastritis. A recent study [21] has shown that the density of neutrophils per high-powered field in antral biopsies, was strongly correlated with the risk of ulcer development during NSAID therapy. However, the risk could be substantially reduced by co-therapy with famotidine 20 mg or 40 mg b.i.d.. This finding, if substantiated in other studies, could prove to be very useful clinically in identifying which patients using NSAIDS need special attention to preventing ulcers and their complications.

## NSAIDS, ASA, *H. PYLORI* AND ULCERS

*NSAID ulcers and infection status.*

Over the past decade, a growing number of studies suggests that among long-term users of NSAIDs, the occurrence of ulcer is statistically significantly higher in *H. pylori* infected than in uninfected patients: these data are summarized in Table 1. If these are averaged, almost three times as many lesions are found in *H. pylori*-infected subjects. Some studies have failed to confirm this observation [28, 29], but the first study selected only symptomatic gastric ulcer patients undergoing endoscopy, rather than prospectively studying a cohort of patients taking NSAIDs [28], and the second depended solely on serologic diagnosis of *H. pylori* status, and also had exclusion criteria that would bias the study [29]. A third study, based on endoscopic studies and strict criteria for the diagnosis of *H. pylori* gastritis, showed, among 75 NSAID users 13 ulcers, 11 of which were in *H. pylori*-infected patients. Thus, overall data indicate that the majority of ulcers found in NSAID users are in those infected with *H. pylori* [30].

Two studies, published only in abstracts, [31, 32] have drawn attention to the high percentage of gastric ulcers in NSAID users that were associated with *H. pylori* infection: only 11 percent of 161 patients [31] and 14 percent of 26 patients [32] were uninfected, emphasizing that both factors are present in the majority of gastric ulcers associated with NSAID use. The study by Publig (Table 1) found that 81.5 percent of those with gastric ulcers on NSAIDs were also infected with *H. pylori* [24]. In an older but similar study of 107 patients undergoing endoscopy, but relying on serologic diagnosis of *H. pylori*, 25 percent of gastric ulcers were solely related to NSAID use, without *H. pylori* infection, but, despite NSAID use among 14 duodenal ulcers, none occurred in an uninfected subject [33].

**Table 1. Occurrence of peptic ulcers and erosions (one study) in patients with and without *H. pylori* on long-term NSAIDs.**

| Author Year, [Ref.] | | Hp +ve (%) | Hp -ve (%) | p value |
|---|---|---|---|---|
| Armstrong and Blower 1987 [22] | GU | 31 | 15 | $p < .02$ |
| Taha et al. 1992 [3] | GU/DU | 48 | 22 | $p < .01$ |
| Heresbach et al. 1992 [23] | GU/DU | 37 | 11 | $p < .02$ |
| Publig et al. 1994 [24] | GU/DU | 83 | 17 | $P < .02$ |
| Taha et al. 1995 [25] | Ulcers<br>Erosions | 40<br>60 | 15<br>25 | $p < .01$<br>$p < .05$ |
| Ekstrom et al. 1995 [26] | GU/DU | 26 | 7 | $p < .02$ |
| Bianchi Porro [27] | GU/DU | 70 | 30 | $p < .01$ |

Two of the studies listed in Table 1, that of Ekstrom et al., 1995 [26], and Taha et al., 1995 [25], are prospective studies and yield data on the incidence of new ulcers after initiation of NSAID therapy as related to *H. pylori* status. Both provide only combined totals of gastric and duodenal ulcers, not broken down by site. Nevertheless, 16.7 percent of patients developed an ulcer in three months on NSAIDs in the Scandinavian study, lesions occurring almost four times more frequently in *H. pylori*-infected patients [26]. The smaller of the two studies showed, during six months of NSAID therapy, that ulcers developed in 40 percent (12) of *H. pylori*-infected patients compared to 15 percent (3) in uninfected patients ($p < .01$) [25].

*Does H. pylori gastritis affect the response to low-dose aspirin therapy?*

A nested case-control study of sera of 166 of 22,071 male physicians taking 325 mg. ASA per day [34] who developed ulcers were compared with sera from age and treatment matched controls. In patients taking ASA, sera of significantly more patients with ulcers were positive for anti-bodies to *H. pylori*, (HP+), 63.8 percent, compared to those without ulcers, 51 percent. A smaller study from Turkey [35] prospectively took 32 patients beginning therapy with enteric coated ASA, 300mg/d and randomized them to receive initial *H. pylori* eradication therapy with omeprazole and amoxicillin, or placebo eradication; at endoscopy those with *H. pylori* by CLO test and histology, had higher base-line endoscopically evaluated gastric injury scores than those without infection. Following ASA therapy, scores rose in both infected and post-eradication-therapy patients, but final injury scores were significantly higher in those who remained infected ($1.94 \pm 0.33$) than in those who were infection free ($0.80 \pm 0.22$, $p < .05$). Histologic grading of gastritis was not performed. In the group who remained infected, two of 17 developed ulcers, compared to none of 15 patients free of infection (NS). This issue warrants further study.

*Does eradication of H. pylori reduce the occurrence of NSAID-associated ulcers?*

The cleanest study [36], involving 92 patients with musculoskeletal pain and in need of NSAID therapy, randomized all patients to either naproxen 750 mg/d, or one week of triple therapy with tetracycline, metronidazole and bismuth, followed by naproxen 750 mg/day. After two months, among evaluable patients, three of 45 (6.7 percent) patients given triple therapy and 12 of 47 treated with naproxen alone (25 percent) developed ulcers ($p = .014$): two of the three were failures of eradication with, thus, only one ulcer in an uninfected patient. About half of the ulcers bled or became symptomatic in the naproxen treated group, compared to none in those who received triple therapy with eradication.

A second study from Poland [37] examined the ulcer recurrence rate over the eight months following initial treatment-to-healing with various drug regimens: only those treated with omeprazole, amoxicillin and metronidazole triple therapy showed no diminution in healing (92 percent) between one and eight months after eradication, despite continued NSAID therapy.

A third rather complicated study examined the role of *H. pylori* in ulcer healing during omeprazole therapy or in recurrence following eradication of infection [27]. The study essentially failed to find a difference in ulcer recurrence rates between those in whom *H. pylori* was eradicated and those in whom infection persisted, although numbers were small. However, no information of any kind is given as to what NSAIDs were used or in what dosage. Furthermore, in some patients, post-eradication status of *H. pylori* infection was determined after they had been allowed alternative therapy such as sucralfate, which may not be devoid of *H. pylori* suppressive activity. Finally, based on a large Finnish study of cure of gastric ulcer associated with eradication of *H. pylori* infection, Seppala [38] commented that "after eradication ulcer recurrence was very rare, even when patients continued to take NSAIDs," but gave us no actual data. On balance, therefore, it appears likely that *H. pylori* eradication lowers the risk of ulcer recurrence during continued NSAID therapy, but more data are needed.

## NSAIDS, *H. PYLORI* GASTRITIS AND GASTROINTESTINAL BLEEDING

In this area, few data are available beyond those found in abstracts. Several preliminary reports have found that in patients not using NSAIDs, *H. pylori* infected patients presenting with acute peptic ulcer bleeding have benefited strongly from eradication therapy as judged by reductions in recurrences of both ulcers and bleeding. This would appear to establish that *H. pylori* is a risk-factor for gastrointestinal hemorrhage, largely from gastroduodenal lesions.

To what extent this applies to patients who bleed in the context of NSAID use is much less clear. It is apparent that patients using NSAIDs can bleed from ulcers or other GI lesions, in the complete absence of *H. pylori* infection. Thus, ASA and NSAIDs are both independent risk factors for ulcer bleeding and for GI bleeding in general, less than 50 percent of which comes from ulcers, and some of which comes from the lower GI tract.

At least five groups have published abstracts [39-43] in which NSAIDs and *H. pylori*, studied in the same patient groups, emerge as independent risk factors for bleeding, but allegedly show no interaction. The fact that risk factors are independent does not exclude the possibility that they are also additive or interactive in complex ways. The largest of these studies [39] had 128 patients and 128 controls. The numbers needed to reject interaction with 95 percent confidence are an order of magnitude higher than this, so that the claims for "no interaction" must be taken with reservation.

One Danish study, published only in abstract form, seems to cast doubt on the absence of interaction. A group of 132 consecutive patients with NSAID-related bleeding peptic ulcers were matched by age, sex and other factors in a case-control study, with similar NSAID users who had not bled. Based on odds ratios, *H. pylori* emerged as increasing the risks of NSAID-associated bleeding about two-fold. My main reservation about this study is that ASA was included among NSAIDS, and it is possible that differences in the numbers of ASA users, or the doses of ASA consumed, were not the same in bleeders and controls. Such an imbalance could alter the odds ratio appreciably. In the meantime, it intuitively seems reasonable to argue that since both NSAIDs and *H. pylori* are independent risk factors for bleeding ulcer, *H. pylori* should be treated to eradication in elderly NSAID users, who have high usage of NSAIDs, a high prevalence of *H. pylori* infection and gastritis, and a high prevalence of peptic ulcers, many of which are clinically silent. This issue remains unresolved. Seropositive patients with ulcers or a history of peptic ulcer or bleeding should certainly receive eradication therapy before starting NSAID/ASA therapy.

## NSAIDS, *H. PYLORI* INFECTION AND ULCER PERFORATION

From epidemiologic studies, it is apparent that ulcer perforation is increasingly common in elderly subjects. In the United Kingdom, this has appeared to be linked to a rise in the consumption of NSAIDs by the elderly, but in Scandinavia, Germany, Australia and the United States, this linkage is far less clear, and not more than 20 to 30 percent of the increase is attributable to NSAID use. Much of the increase must be attributed to other factors, among which is smoking. Nevertheless, a group exists in which perforation seems linked to NSAID or ASA use, and it is in this group that the question arises as to whether or not *H. pylori* infection or gastritis poses an additional risk that could be abolished by eradicating the infection. Because perforation is so much less common than bleeding, progress has been slow in this area. From animal studies, NSAIDs vary greatly in the likelihood of perforation associated with their oral use. Only parenteral use of Ketorolac is commonly associated with perforation, and I know of no data on the prevalence of *H. pylori* in affected versus unaffected patients. A single clinical study by Reinbach in 1993 [45] suggested that the prevalence of *H. pylori* did not differ significantly between patients perforating duodenal ulcers during NSAID therapy, regular NSAID users without perforation and matched hospital controls. The question remains open at the present time.

## SUMMARY

1. *H. pylori* gastritis appears to increase the likelihood of developing dyspeptic symptoms on NSAID therapy.

2. There is preliminary evidence that the histologic severity of *H. pylori* gastritis may be adversely affected by NSAID therapy, with a consequent increase in the risk of developing a peptic ulcer, possibly with complications. Whether this results from an effect on the inflammatory process or results from a quantitative increase in *H. pylori* colonization is unknown. In these respects, ASA may differ from other NSAIDs.

3. Ulcers are more likely to develop during the course of NSAID therapy in those infected with *H. pylori*; eradication of the infection reduces ulcer recurrence in the face of continued NSAID therapy, and it seems likely that this must reduce but not abolish the risk of GI bleeding in

those using NSAIDs. Eradication also reduces the damage (and possibly risks) of low-dose aspirin therapy.

4. While *H. pylori* and NSAID use are independent risk factors for GI bleeding, whether or not they are interactive remains unresolved.

5. The effect of *H. pylori* infection on the risk of perforation during NSAID therapy, or conversely, the contribution of NSAID therapy to the risk of perforation in *H. pylori*-infected subjects, is also unclear at the present time.

6. Only large outcome studies of accurately diagnosed patients (with regard to *H. pylori* gastritis), and with much more specific detail as to the type of NSAID, dose and duration of therapy, employing only well-defined end-points, such as significant hemorrhage, perforation or death, and avoiding all surrogate markers short of these end points can hope to unravel this tangled web.

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