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# Use of NSAIDs and infection with *Helicobacter pylori*—what does the rheumatologist need to know?

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**Objectives.** NSAID-induced gastroduodenal lesions are a frequent and potentially serious health problem in patients with rheumatic diseases. *Helicobacter pylori* (*H. pylori*) has also been recognized as a major risk factor for the development of ulcer disease. However, the role of *H. pylori* in the pathogenesis of NSAID-induced gastroduodenal lesions has remained controversial, and there is currently no clear consensus on the management of NSAID users who are infected with *H. pylori*.
**Methods.** To clarify this situation we have performed a systematic literature search to find randomized controlled trials comparing the efficacy of eradication in patients receiving NSAIDs to prevent ulcer development.
**Results.** Seven randomized controlled trials and one meta-analysis were identified. There were three papers on NSAID-naive patients. According to this data, NSAID-naive users benefit from testing for *H. pylori* infection and subsequent *H. pylori* eradication therapy prior to the initiation of NSAID. In contrast, *H. pylori* eradication alone does not protect chronic NSAID users with recent ulcer complications from further gastrointestinal (GI) events. To prevent recurrent ulcer bleeding long-term acid suppressive therapy is needed.
**Conclusions.** In conclusion, ulcer risk reduction after *H. pylori* eradication therapy is clearly more marked in patients beginning NSAID therapy than in patients who were already receiving and tolerating NSAID therapy. Thus, the management of *H. pylori* infection and the prevention of GI complications in NSAID users need to be individualized on the basis of recently published data.

**Key words:** Non-steroidal anti-inflammatory drugs, *Helicobacter pylori*, Eradication, Gastroduodenal lesions, Rheumatoid arthritis.

## Introduction

*Helicobacter pylori* (*H. pylori*) have been recognized as a major risk factor for the development of gastroduodenal ulcer disease. The lifetime risk of peptic ulcer in a person infected with *H. pylori* ranges from 3% in the United States to 25% in Japan [1]. Peptic ulcers may remain asymptomatic, cause different degrees of dyspepsia or cause severe complications such as bleeding and perforation. *H. pylori* are causally linked to a diverse spectrum of gastrointestinal (GI) diseases, including peptic ulcer disease (PUD), gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [2]. Two prospective studies, both in high-risk populations of gastric cancer, have reported *H. pylori* infection as a definitive risk factor for the development of gastric cancer [3, 4]. In addition, the International Agency for Research on Cancer has categorized *H. pylori* as a group I carcinogen [5].

An infection with *H. pylori* can be diagnosed by both non-invasive and invasive methods. Non-invasive methods include the urea breath test, serological tests and stool antigen assays [6]. Invasive methods are mainly based on endoscopy and biopsies [7]. The selection of the most appropriate test to detect *H. pylori* depends on the clinical setting (Table 1) [8].

In general, testing for *H. pylori* is recommended only if there is a reasonable option for treatment. Recommendations have been issued by the European Maastricht III Consensus (Table 2) [9].

Effective anti-microbial therapy for eradication of *H. pylori* is available, but there is still no ideal treatment. Clinically relevant *H. pylori* eradication regimens must have cure rates of at least 80% without major side-effects and with minimal induction of bacterial resistance. Similar success rates have not been achieved with antibiotics alone. The so-called triple therapies, combinations of two antibiotics with one anti-secretory drug, twice daily for 7 days, have been evaluated in randomized trials [10]. The recommended first-line therapy is based on proton-pump inhibitors (PPI) in combination with 500 mg clarithromycin and either 1 g of amoxicillin or 400 mg of metronidazole, if the primary resistance to clarithromycin in the area is <15–20%. Following first-line treatment failure, 14-day PPI triple therapy employing alternative antibiotics or quadruple therapy could be used. The main anti-microbial agents used in those regimens are tetracycline, levofloxacin, rifabutin and bismuth.

Although chronic *H. pylori* infection is associated with gastric carcinoma, the effect of *H. pylori* treatment on prevention of gastric cancer development in chronic carriers is unknown. In a randomized controlled trial in a high-risk population in China, the incidence of gastric carcinoma was found to be similar in patients receiving *H. pylori* eradication and placebo over a period of 7.5 yrs. Only in a subgroup of *H. pylori*-positive participants without pre-cancerous lesions, *H. pylori* eradication led to a significant decrease of gastric cancer [11]. It is important in that context that there is some evidence for an association of use of NSAIDs with a decreased risk of gastric cancer in a dose-dependent manner [12].

However, NSAIDs are also well-established risk factors for the development of uncomplicated and complicated PUD [13]. In patients with rheumatic diseases, NSAID-induced gastroduodenal lesions are a frequent and potentially serious health problem. The incidence of NSAID gastropathy is in the range of 1.2–1.6% per year in patients with RA [14]. Evidence suggests that co-prescription of NSAIDs with PPIs reduce gastroduodenal lesions [15]. Simultaneously, the rate of acquisition of *H. pylori* has decreased substantially over recent decades in industrialized countries [1]. Hence, there may be uncertainty about the further development of the incidence of gastroduodenal ulcer diseases induced by *H. pylori* and NSAIDs.

The precise contribution of *H. pylori* to ulcerogenesis and to upper intestinal bleeding in NSAID users is not clear. Accordingly, the role of *H. pylori* eradication in the prevention of GI pathology is not well defined, despite the role of PPIs being well established [16]. There is, therefore, no good consensus on the optimal management of NSAID users who are infected with *H. pylori*.

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TABLE 1. Characteristics of methods for detection of *H. pylori*

| Method | Indication | Sensitivity (%) | Specifity (%) |
|---|---|---|---|
| Non-invasive | | | |
| Urea breath test | Diagnosis, follow-up[a] | 95 | 100 |
| Serological test | Screening, diagnosis[b] | 95 | 91 |
| Stool antigen | Diagnosis, follow-up[c] | 89–96 | 96 |
| Invasive | | | |
| Urease test | Diagnosis | 80–100 | 92–90 |
| Histology | Diagnosis | 90 | 90 |
| Culture | Antibiotic sensitivity testing | 80–90 | 95 |

Adapted from Dzierzanowska-Fangrat K *et al.* [43]. [a]Should not be performed earlier than 4 weeks after eradication. [b]Local validation is necessary. [c]Should not be performed earlier than 8 weeks after eradication.

TABLE 2. Guideline for the treatment of *H. pylori* infection, according to the Maastricht III Consensus Report

| Treatment is recommended | Treatment is advised |
|---|---|
| PUD | Functional dyspepsia |
| MALT Lymphoma | PPI maintenance therapy |
| Atrophic gastritis | Use of NSAIDs |
| Gastric cancer, including first-degree relative | Iron deficiency anaemia |
| Desire of the patient | |

Adapted from Malfertheiner *et al.* [9].

To analyse this situation we have performed a systematic literature search to review all randomized controlled trials addressing this problem. Based on a critical review of the studies, proposals are made for clinical practice about indications for *H. pylori* eradication in patients who are already treated or who are about to be treated with NSAIDs with special regard to RA patients as a high-risk patient group.

## Methods

Electronic searches of Medline, Embase and the Cochrane Library from 1966 to August 2006 were carried out using search terms for *H. pylori*, GI disease, eradication therapy and anti-inflammatory therapies. Medical Subject Heading terms were exploded where appropriate. All randomized controlled trials and meta-analyses of randomized controlled trials in any language comparing the efficacy of eradication in patients receiving NSAIDs to prevent ulcer development were included. A recursive hand search of the references of all articles reviewed and of the retrieved original studies was done to look for studies not identified by the computer search. A manual search of abstract submitted to the Digestive Disease Week between 1984 and 2006 was also performed. The following criteria were used to include published studies: first, they had to be randomized controlled trials investigating patients with *H. pylori* infection and NSAIDs treatment. Second, the *H. pylori* infection had to be confirmed by histology, culture, serology or urea breath test. Third, NSAID and PPI use had to be defined in duration and dosage of medication. Fourth, the trial profile had to compare eradication regimen *vs* placebo or *vs* PPI treatment.

## Results

The literature search in the three databases generated 55 citations. Manual search did not yield any new studies. Of these, 47 studies were subsequently excluded because they did not allow adequate evaluation. No review articles were included. Altogether, seven randomized controlled trials and one meta-analysis were identified [17–24]. The main characteristics and major differences between these studies are presented in Table 3.

### *NSAID-naive patients*

There were three papers on NSAID-naive patients. According to these, NSAID-naive users benefit from testing for *H. pylori* infection and, if positive, *H. pylori* eradication therapy prior to the initiation of NSAID. In one trial, triple therapy was compared with NSAIDs alone without use of PPIs [17]. The other two studies compared triple therapy *vs* PPIs with different regimes [21, 22]. Notably, in two studies with RA patients, no corticosteroid use was allowed.

### *Chronic NSAID users*

There were four papers looking at chronic NSAID users. *Helicobacter pylori* eradication alone did not protect chronic NSAID users with recent ulcer complications from further GI events. In two trials, triple therapy was compared with PPIs. In another one, triple therapy was tested against placebo [18–20, 23]. In the remainder, eradication therapy was compared with maintenance of PPI medication [19].

### *Study heterogeneity*

Critical review of the studies revealed some heterogeneity in the design and the definitions used. For example, the definition of an ulcer varied almost 2-fold between studies from >3 mm to >5 mm on endoscopy. Clearly, a diameter of 3 mm will result in a higher prevalence and incidence of ulcers than a diameter of 5 mm. Similarly, there were different definitions for NSAID user as well as the types, doses, duration and their indications for NSAID use. The main confounding factors were the differences in the choice of the PPI, the obtained history of PUD and the regimes used for eradication of *H. pylori*. The eradication regimes were different in all studies. The regime most frequently used was 1-week triple therapy with PPI, while Chan *et al.* [17, 20] also used a 1-week bismuth triple therapy and Lai *et al.* [23] used a 2-weeks triple antibiotic therapy without PPIs. In all studies, the use of PPIs varied between no PPI use, 1-week use and 6 months use.

Nevertheless, the recent meta-analysis by Vergara *et al.* [24] showed a significant reduction of the ulcer risk for NSAID-naive patients receiving *H. pylori* eradication therapy [odds ratio (OR) = 0.26; 95% CI 0.14, 0.49] but not for chronic NSAID users (OR = 0.95; 95% CI 0.53, 1.72).

## Discussion

Although the strategies to reduce the risk for PUD in patients with ongoing analgesic therapy are controversial, several conclusions can be drawn from the available data.

### *Role of* H. pylori

The nature of the contribution of NSAIDs and *H. pylori* infection to the pathogenesis of PUD has not yet been elucidated. There are studies showing that the interaction between *H. pylori* and NSAIDs in ulcer development may be synergistic, additive, independent or antagonistic [25–30]. These conflicting data can be accounted for in part by the heterogeneity of study designs and by diversified host responses to *H. pylori* infection. Nevertheless, in the meta-analysis by Huang *et al.* [31], NSAID use and *H. pylori* infection were identified as independent risk factors for ulcer development which, in combination, seem to act in an additive manner. The presence of *H. pylori* infection was calculated to increase the risk of peptic ulcer in NSAID users by >3-fold (OR = 3.5). The prevalence of peptic ulcer in *H. pylori*-positive patients in that study was 53% and 21% in *H. pylori*-negative patients. These data suggest either that some patients with an *H. pylori* infection are prone to develop ulcers on exposure to NSAIDs, or that NSAIDs may worsen complications in patients with pre-existing *H. pylori*-induced ulcers.

TABLE 3. Major differences in the studies on *H. pylori* eradication for the prevention of NSAID-associated ulcers

| | Chan *et al.* [17] | Hawkey *et al.* [18] | Pilotto *et al.* [19] | Chan *et al.* [20] | Chan *et al.* [21] | Labenz *et al.* [22] | Lai *et al.* [23] |
|---|---|---|---|---|---|---|---|
| Baseline characteristics of the patients | | | | | | | |
| Number of patient | 92 | 279 | 66 | 400 | 100 | 660 | 140 |
| Median age in years | 62.5 | 54.9 | 75.4 | 67.5 | 62.5 | 54.7 | 58.2 |
| Sex (M/F) | 26/66 | 84/195 | 29/37 | 247/153 | 33/67 | 253/407 | 38/102 |
| RA (%) | 4.3 | 41.5 | Not provided | 4.6 (naproxen group) | 100.0 | 14.6 (systemic inflammatory diseases) | 35.0 |
| Major differences | | | | | | | |
| Trial profile | Triple therapy *vs* NSAID alone | Triple therapy *vs* omeprazole | Triple therapy *vs* pantoprazole | Triple therapy *vs* omeprazole | Triple therapy *vs* omeprazole | Triple therapy plus 4 weeks omeprazole/placebo *vs* omeprazole plus 4 weeks omeprazole/placebo | Triple therapy *vs* placebo |
| Prior NSAID use | NSAID naive | Chronic users | Chronic users | Chronic users incl. aspirin | NSAID naive, concurrent use of aspirin are allowed | NSAID naive, concurrent use of aspirin are allowed | Chronic users |
| PPI use in the study | No PPI used in both groups | 20 mg omeprazole for 3 weeks in both groups | 40 mg pantoprazole for 1 week (eradication) or for 1 month (control) | 20 mg omeprazole for 8 weeks (eradication) or for 6 months (control) | 20 mg omeprazole for 1 week in both groups | 20 mg omeprazole for 1 week (eradication) followed by 4 weeks omeprazole/placebo or for 1 week omeprazole plus 4 weeks omeprazole (control/placebo) | No PPI used in both groups |
| Exclusion of corticosteroid | Yes | Dose equivalent $\geq$10 mg prednisolone | Not provided | Yes | Yes | Dose equivalent $\geq$10 mg prednisolone | Yes |
| Ulcer history | Excluded | Included | Included | Included | Included | Excluded | Excluded |
| Dyspepsia | Excluded | Included | Included | Not provided | Included | Not provided | Included |
| Schedule of endoscopy | 2 months | 1, 3 and 6 months | 1 month | Only in case of upper GI bleeding | 6 months | 5 weeks | 12 weeks |
| Definition of ulcer | $>$5 mm | $>$3 mm | $>$3 mm | $>$5 mm | $>$5 mm | $>$3 mm | $>$5 mm |
| NSAIDs used | Naproxen | Variable | Diclofenac | Naproxen or aspirin | Diclofenac SR | Diclofenac | Variable |
| Eradication regimen | 1-week bismuth triple therapy | 1-week omeprazole triple therapy | 1-week pantoprazole triple therapy | 1-week bismuth triple therapy | 1-week omeprazole triple therapy | 1-week omeprazole triple therapy | 2-weeks triple antibiotic therapy |
| Follow-up | 2 months | 6 months | 1 month | 6 months | 6 months | 5 weeks | 3 months |
| End-points | Primary: endoscopic ulcer | Endoscopic ulcer or dyspepsia | Gastroduodenal lesions | Recurrent upper GI bleeding | Primary: endoscopic ulcer/secondary: complicated ulcer | Endoscopic ulcer | Endoscopic ulcer |
| Eradication rate | | | | | | | |
| Intervention (%) | 89* | 66* | 88.5* | 92.0 | 90.0 | 83.3 | 77.6 |
| Control (%) | 0.0 | 14.0 | 51.6 | 8.5 | 6.0 | 16.8 | 0.0 |
| Endoscopic ulcer | | | | | | | |
| Intervention (%) | 7* | 11.0 (endoscopy at 8 weeks)* | 29* | 8.6 (only naproxen group)* | 9.8* | 1.2 | 7.0 |
| Control (%) | 26.0 | 0.0 (endoscopy at 8 weeks) | 9.0 | 2.0 (only naproxen group) | 30.6 | Omeprazole: 0.0, placebo 5.8* | 8.5 |

*$P \leq 0.05$.

TABLE 4. Patient's individual risk factors

| Chronic NSAID users | | | Risk factors |
|---|---|---|---|
| Low risk | No risk factors | | Use of high dose or multiple NSAIDs<br>Age over 65 yrs<br>Comorbidity |
| Moderate risk | 1 or 2 risk factors | | |
| High risk | Multiple risk factors | or | Taking concomitant aspirin, corticosteroids or anti-coagulants |
| Very high risk | Multiple risk factors | or | History of ulcer bleeding |

Adapted from Chan *et al.* [41].

TABLE 5. Individualized strategy for patients with NSAID use

| | Risk for ulcer complications | *H. pylori* test-and-treat approach | Long-term PPI therapy |
|---|---|---|---|
| Naive NSAID users | | Recommendation-evidence | No |
| Chronic NSAID users | Very high risk | Potential benefit | Recommendation-evidence |
| | High risk | Potential benefit | Recommendation |
| | Moderate risk | Potential benefit | Potential benefit |
| | Low risk | No | No |

Adapted from Papatheodoridis *et al.* [42].

### *Role of NSAIDs*

Epidemiological studies have consistently shown that the risk of ulcer complications is substantially increased during the first 3 months of NSAID treatment [32]. Probably, initiation of NSAIDs aggravates PUD in susceptible patients, which will result in a group who can tolerate long-term NSAIDs, irrespective of their *H. pylori* status. A number of clinical factors have been identified which increase the risk of developing serious GI complications in NSAID users: age, concomitant medication (anti-coagulation, corticosteroid use), history of PUD and high-dose NSAID use [33]. Since NSAID-associated ulceration occurs asymptomatically, the actual frequency of gastroduodenal ulceration associated with NSAIDs is different from the number of patients who present with dyspepsia (cumulative incidence of endoscopic gastroduodenal ulcers: 25–30% after 3 months of NSAID therapy) [34]. Several mechanisms are associated with the development of PUD: in addition to certain local effects (topical injury, neutrophil adherence) the main mechanism of NSAIDs induced gastroduodenal complications is the inhibition of cyclo-oxygenase (COX)-1 and disruption of prostaglandin production [35]. Thus, NSAID use and *H. pylori* infection may impair the gastric mucosal defence by different mechanisms: *H. pylori* infection induces mucosal inflammation whereas NSAIDs inhibit the gastric prostaglandin synthesis.

### *Strategy in* H. pylori*-positive patients with NSAID use*

Strategies that may prevent GI complications in *H. pylori*-positive patients with NSAID use include eradication of *H. pylori* infection and/or concurrent therapy with a PPI. Management of *H. pylori*-infected chronic NSAID users is believed to depend on the duration of NSAID use and the presence of risk factors (Table 4). An expert committee has recommended a treatment strategy stratified in different risk categories (Table 5).

### H. pylori *eradication*

In patients commencing NSAIDs, *H. pylori* eradication reduces the incidence of GI ulceration in patients who are about to start NSAID therapy but by itself is insufficient to prevent recurrent ulcer bleeding in chronic NSAID users with recent PUD. NSAID-naive users benefit from testing for *H. pylori* infection and, eradication therapy prior to the initiation of NSAID (test-and-treat approach). Chan *et al.* [21] showed a significant reduction in the incidence of peptic ulcers after *H. pylori* eradication in NSAID-naive patients with a history of PUD compared with a group with omeprazole and placebo antibiotics (peptic ulcers: 9.8% in the eradication group and 30.6% in the placebo group). In 1997, the same group had already shown that in NSAID-naive patients without a history of PUD, eradication of *H. pylori* before NSAID therapy does reduce the occurrence of NSAID-induced peptic ulcers (peptic ulcers: 7% in the eradication group and 26% in the NSAID group without eradication) [17]. The value of primary prophylaxis by eradication of *H. pylori* was also evaluated in a trial comparing four different interventions (three active *vs* one placebo group). The rate of ulcer development was significantly higher in the placebo group than in all actively treated patients, but there was no difference between the three arms (peptic ulcers: 1.2% in the eradication group and 5.8% in the placebo group) [22].

In contrast, *H. pylori* eradication alone does not protect chronic NSAID users with recent ulcer complications from further GI events. Furthermore, it has been shown that among chronic NSAID users with a history of ulcer bleeding, the eradication of *H. pylori* alone is not sufficient to prevent recurrent ulcer bleeding. However, patients receiving PPI maintenance in addition to NSAIDs (long-term PPI therapy) showed a significant reduction of recurrent bleeding compared with the patient who has had *H. pylori* eradication (probability of recurrent bleeding 4.4 *vs* 18.8%) [20]. Similar findings have been described by Hawkey *et al.* [18], who showed that curing *H. pylori* infection did not reduce the risk of ulcer in chronic NSAID users.

High-risk patients with RA often need anti-phlogistic therapy and they do have additional risk factors such as a concomitant medication with corticosteroids. Pilotto *et al.* [19] showed in a risk group with elderly patients that in the prevention of gastroduodenal damage, long-term PPI therapy is more effective than *H. pylori* eradication (peptic ulcers: 29% in the eradication group *vs* 9% in controls). In contrast, Lai *et al.* [23] failed to show a benefit of *H. pylori* eradication when no PPIs were taken concomitantly.

### *PPI prophylaxis*

As discussed, PPI therapy is superior to the eradication of *H. pylori* for the secondary prevention of upper GI bleeding in *H. pylori*-infected patients who continue to take NSAIDs [20]. Any of the patients at high-risk for PUD, who need to continue taking NSAIDs, benefit from long-term PPI therapy (Fig. 1).

There has been a lot of controversy on the role of coxibs in the prevention of GI side-effects and the associated cardiovascular risk. Most data show that the GI risk is reduced by up to 50% in comparison with conventional NSAIDs, and that the cardiovascular risk is rather similar to conventional NSAIDs in subsets of patients with cardiovascular disease [36]. As mentioned previously, a history of ulcer bleeding is the single most important risk factor for NSAID-related ulcer complications, but the safety of COX-2 inhibitors in patients with a prior history of ulcer bleeding is not precisely known at present [37]. In a recently published study, Chan *et al.* [38] show that in patients at very high risk for recurrent ulcer bleeding, combination treatment with COX-2 inhibitor and PPI was more effective than COX-2 inhibitor alone.

### *Strategy in* H. pylori*-positive patients with NSAID use and RA*

Withdrawal of NSAIDs or dose reduction is often not possible in patients with RA. Moreover, many of the patients with RA receive high-dose NSAID therapy with several concomitant

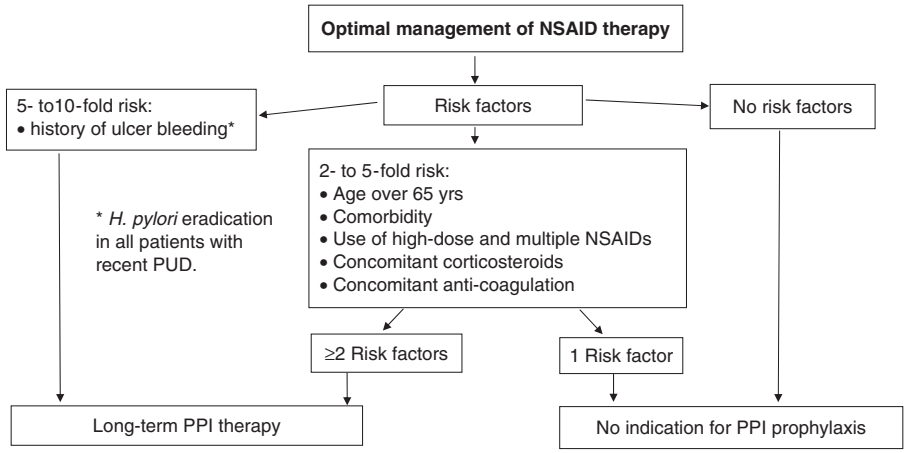


FIG. 1. PPI use in NSAID therapy.

medications such as corticosteroids, resulting in an increased risk for GI complications. These patients are at a very high risk for bleeding recurrence and it seems advisable to remove as many risk factors as possible. Many of the studies on NSAID use were conducted in RA patients [1, 21, 33, 35]; however, no detailed data are given regarding DMARDs or other concomitant medications. Corticosteroid use is a recognized independent risk factor for the development of gastric ulcers: an OR of 6.8 (95% CI 1.3–36.0) was found in one study, and 45% of the RA population with ulcers was *H. pylori* positive [39]. In addition, some DMARDs seem to have an interaction with *H. pylori*: use of SSZ may increase the incidence of gastric ulcers [40].

## Conclusion

Ulcer risk reduction after *H. pylor*i eradication therapy is clearly more marked in patients starting to commence NSAIDs than in patients who tolerate and were already receiving NSAID therapy. Thus, the management of *H. pylori* infection and the prevention of GI complications in NSAID users need to be individualized on the basis of recently published data.

### Rheumatology key messages

- NSAID-naive users benefit from treatment of *H. pylori* infection prior to the initiation of NSAIDs.
- Eradication alone does not protect chronic NSAID users from further GI events.

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