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• *REVIEW* •

Role of *Helicobacter pylori* eradication in aspirin or non-steroidal anti-inflammatory drug users

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Abstract

Helicobacter pylori (*H pylori*) infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin at any dosage and formulation represent well-established risk factors for the development of uncomplicated and complicated peptic ulcer disease accounting for the majority of such cases. Although the interaction between *H pylori* and NSAID/aspirin use in the same individuals was questioned in some epidemiological studies, it has now become widely accepted that they are at least independent risk factors for peptic ulcer disease. According to data from randomized intervention trials, naive NSAID users certainly benefit from testing for *H pylori* infection and, if positive, *H pylori* eradication therapy prior to the initiation of NSAID. A similar strategy is also suggested for naive aspirin users, although the efficacy of such an approach has not been evaluated yet. Strong data also support that chronic aspirin users with a recent ulcer complication should be tested for *H pylori* infection and, if positive, receive *H pylori* eradication therapy after ulcer healing, while they appear to benefit from additional long-term therapy with a proton pump inhibitor (PPI). A similar approach is often recommended to chronic aspirin users at a high risk of ulcer complication. *H pylori* eradication alone does not efficiently protect chronic NSAID users with a recent ulcer complication or those at a high-risk, who certainly should be treated with long-term PPI therapy, but *H pylori* eradication may be additionally offered even in this setting. In contrast, testing for *H pylori* or PPI therapy is not recommended for chronic NSAID/aspirin users with no ulcer complications or those at a low risk of complications.

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INTRODUCTION

Salicylates have been used in therapeutic medicine since the Hippocrates' era and their use is still growing. During the last 50 years, there is a continuously increasing consumption of aspirin for cardioprotection and for secondary prophylaxis of recurrent stroke or other vascular occlusion, while the drug seems to have a possible role in chemoprevention of cancer and Alzheimer's disease[1-4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are also widely used agents[5]. In the USA, it is estimated that more than 50% of the population over 65 years take aspirin or NSAIDs frequently[6].

The increasing widespread consumption of aspirin/NSAIDs, however, is associated with an increasing incidence of their well-known gastrointestinal complications, which include dyspepsia, gastric and/or duodenal erosions and ulcers and peptic ulcer complications. Peptic ulcer complications, usually bleeding, represent the most frequent serious adverse events of the use of aspirin/NSAIDs[1,7]. Peptic ulcer(s) may be found at endoscopy in up to 20-25% and ulcer complications requiring hospital admission develop in 2-5% of chronic users of NSAIDs[7-12]. Use of NSAIDs has also been shown to increase the risk of lower gastrointestinal bleeding[13]. The damaging effect of aspirin on the gastric mucosa may be less potent than the effect of NSAIDs[14]. Thus, it is estimated that the chronic use of aspirin increases the absolute annual risk of gastrointestinal bleeding by 0.04% (absolute annual risk of bleeding with and without aspirin: 0.09% and 0.05% respectively)[15]. Nevertheless, despite the relatively low absolute risk of bleeding in aspirin users, the numbers of aspirin related acute gastrointestinal bleeding episodes are rather high probably due to the huge numbers of individuals who take the drug regularly for long periods often having additional factors with increased risk for bleeding, such as old age and history of peptic ulcer disease. The use of selective NSAIDs, such as selective cyclo-oxygenase 2 (COX-2) inhibitors, significantly reduces but does not completely eliminate the risk of gastrointestinal complications[11,12,16], while their gastrointestinal benefit appears to be significantly restricted in cases of concomitant use of aspirin, even at low doses[11,17].

Helicobacter pylori (*H pylori*) is undoubtedly associated with the development of gastritis and uncomplicated and complicated peptic ulcer diseases[18]. Although the presence of two factors that can damage the gastric mucosa, such as *H pylori* and aspirin/NSAIDs, would be reasonably considered

to increase the risk for development of uncomplicated and complicated peptic ulcer, data from several, mainly epidemiological, studies appear to be controversial and do not always confirm such an assumption[19]. This review focuses on the role of *H pylori* infection and the need for its eradication for prevention of gastrointestinal complications among aspirin/NSAIDs users by evaluating the relevant pathophysiological and epidemiological data as well as the results of the randomized, controlled clinical trials of therapeutic intervention.

PATHOPHYSIOLOGY

Aspirin or NSAIDs use is associated with the development of peptic erosions or ulcers through several mechanisms. First, aspirin acts locally through the release of salicylic acid in the stomach, which is not ionized by the gastric acid. Salicylic acid enters and accumulates within the gastric epithelial cells, is ionized intracellularly and disrupts cell metabolic functions increasing mucosal permeability and permitting the back diffusion of H^+ ions[20]. Moreover, aspirin promotes topical inflammation by inducing recruitment of leukocytes, which eventually results in capillary constriction and topical ischemia. The topical gastrotoxic effect of aspirin, however, does not seem to be particularly important, since it is associated only with superficial ulcerations that often resolve spontaneously despite the continued aspirin use[20]. The systemic gastrotoxic effect of aspirin is related to the inhibition of cyclo-oxygenase-1 (COX-1) and the subsequent disruption of prostaglandin synthesis and to the antiplatelet function that promotes bleeding complications[20]. The key role of the systemic effects of aspirin in the development of gastrointestinal complications is strongly supported by the data showing that the risk of such complications is independent of the drug formulation[17,21,22]. Even low doses of aspirin, such as 75 mg/d, have been shown to increase the risk of gastroduodenal ulcerations[21,22]. Inhibition of COX-1 with disruption of prostaglandin production is also the main mechanism of NSAIDs induced gastroduodenal complications[11-13].

H pylori infection induces a substantial inflammatory reaction in the gastric mucosa with recruitment of leukocytes and production of several inflammatory cytokines, which eventually result in attenuation of mucosal defense mechanisms[18]. Thus, *H pylori* infection and aspirin/NSAID use impaired gastric mucosal defense by different mechanisms and therefore an interaction between these two factors is biologically plausible.

EPIDEMIOLOGICAL STUDIES

The interaction between *H pylori* infection and aspirin/NSAIDs use in the development of ulcer and ulcer complications has been initially evaluated in several cohort or case-control studies. The findings of these studies, however, have been controversial, since some studies suggested an independent or additive role of *H pylori* infection and aspirin/NSAIDs use in gastrointestinal complications[21-30] and others proposed no association or even a protective role of *H pylori* infection in users of aspirin/NSAIDs[31-33]. Moreover, in one study, *H pylori* infection was found to increase the risk of gastric but not of duodenal ulceration in this setting[34]. The heterogeneity in study design and methodology, definitions, power, outcome, and selection of controls have been suggested to be responsible for such conflicting results[19].

In a systemic review published in 2002, the combined analysis of the data available up to October 2000 showed that there is synergism for the development of peptic ulcer and ulcer bleeding between *H pylori* infection and aspirin/NSAID use[35]. In particular, the presence of *H pylori* infection was found to increase 3-5-fold the risk of peptic ulcer in aspirin/NSAID users (prevalence of peptic ulcer in *H pylori* positive: 53% and *H pylori* negative: 21%, OR: 3.5) and 18-fold in subjects not taking aspirin/NSAID (prevalence of peptic ulcer in *H pylori* positive: 18% and *H pylori* negative: 0%, OR: 18.1)[35]. Thus, the risk of peptic ulcer is approximately 60-fold higher in *H pylori* positive aspirin/NSAID users compared with *H pylori* negative subjects not taking aspirin/NSAID[35]. Moreover, *H pylori* infection was shown to increase the risk of ulcer bleeding 1.8-fold, aspirin/NSAID use 4.85-fold, and the presence of both factors 6.1-fold compared with the risk of bleeding among *H pylori* negative subjects not taking aspirin/NSAID[35]. *H pylori* infection has also been found to increase the risk of upper gastrointestinal bleeding even in chronic users of low dose aspirin[27]. In a more recent case-control study from our group, *H pylori* infection was again found to increase the risk for upper gastrointestinal bleeding in aspirin/NSAID users 2.9-fold, or 1.7-fold when adjustment for other risk factors for bleeding was performed[28]. Taking all together, it seems that aspirin/NSAID use and presence of *H pylori* infection are at least independent risk factors for peptic ulcer and bleeding from peptic ulcer.

RANDOMIZED CLINICAL TRIALS

H pylori eradication in naive aspirin/NSAID users

If *H pylori* gastritis does enhance the risk for ulcer bleeding in aspirin/NSAID users, then *H pylori* eradication should substantially reduce such a risk in this setting. Since the risk of bleeding in aspirin/NSAID users is strongly related to the duration of drug use, being higher in subjects with new or recent drug onset (<1-3 mo) than in chronic drug users (>1-3 mo)[36-38], the possible beneficial effect of *H pylori* eradication on naive aspirin/NSAID users was initially evaluated. In fact, only naive users of non-aspirin NSAIDs have been included in the relevant clinical trials to date, while the possible benefit of *H pylori* eradication in naive users of aspirin has not been evaluated yet.

H pylori eradication before NSAID use was found to significantly reduce the occurrence of peptic ulcers in 92 *H pylori* positive, NSAID naive patients with musculoskeletal pain treated with an 8-wk course of naproxen at a daily dose of 750 mg (peptic ulcers: 3/45 or 7% of patients in the *H pylori* eradication group *vs* 12/47 or 26% of patients in the placebo group, $P = 0.01$)[39]. In a longer trial with a similar design, *H pylori* eradication before NSAID use was again found to significantly reduce the risk of peptic ulcers in 100 *H pylori* positive, NSAID naive, patients with arthritis and a history of peptic ulcer or dyspepsia treated with a 6-mo course of diclofenac slow release at a daily dose of 100 mg (peptic ulcers: 5/51 or 12% *vs* 15/49 or 34%, $P = 0.0085$)[40]. In the latter trial, *H pylori* eradication

was also found to significantly reduce the risk of ulcer complications as well [6-mo probability: 4.2% (1.3-9.7) *vs* 27.1% (14.7-39.5), $P = 0.0026$][40].

H pylori eradication in chronic aspirin/NSAID users without a history of peptic ulcer complications

The results of the first large clinical trial of *H pylori* eradication in chronic NSAID users raised several questions for the benefit of such an intervention. In this trial[41], 285 *H pylori* positive chronic NSAID users with past or current peptic ulcers or NSAID-associated dyspepsia who continued a minimum dosage of NSAID for at least 6 mo were randomized to receive *H pylori* eradication therapy with omeprazole, amoxycillin and clarithromycin ($n = 142$) or omeprazole plus placebo antibiotics ($n = 143$) for 1 wk. Subsequently, all patients received omeprazole 20 mg daily for 3 wk followed by an additional 4-wk omeprazole course in cases with endoscopically detected peptic ulcers at 4th wk. The probability of being peptic ulcer free at 6th mo was similar in the *H pylori* eradication [0.56 (95%CI: 0.47-0.65)] and the omeprazole-control group [0.53 (95%CI: 0.44-0.62)], while healing of gastric ulcers was significantly impaired in the *H pylori* eradication group (gastric ulcers healed at 8th wk: 72% in the *H pylori* eradication group *vs* 100% in the omeprazole-control group, $P = 0.006$)[41].

The design of the latter trial, however, was different from the design of the trials in naive NSAID users, since *H pylori* eradication therapy was given to subjects with ulcers or at high-risk of ulcers, who had already been on long-term NSAID consumption. Moreover, both the *H pylori* eradication and control groups were treated with 4-8 wk of omeprazole for ulcer healing. The lower probability of gastric ulcer healing at 8th wk in the *H pylori* eradication group should be associated with the more potent antisecretory activity of the PPIs including omeprazole in the presence than absence of *H pylori* infection[42]. Similar findings have also been observed in another large study including 692 chronic NSAID users, in which gastric ulcer healing with ranitidine or lansoprazole was shown to be significantly enhanced in the presence of *H pylori* infection (healing of gastric ulcers at 8th wk: 70% in *H pylori* positive *vs* 61% in *H pylori* negative, $P<0.05$)[43]. According to these data, it has been reasonably suggested that any attempt to eradicate *H pylori* infection should follow ulcer healing in the management of chronic NSAID users, although the efficacy of such an approach remains to be tested. The efficacy of *H pylori* eradication in chronic aspirin users has not been evaluated yet.

H pylori eradication in chronic aspirin/NSAID users with a recent peptic ulcer complication

Subjects with a history of upper gastrointestinal bleeding or other peptic ulcer complications represent a particular subgroup of aspirin/NSAID users who are at a high risk for recurrent bleeding during continued aspirin/NSAID use[44,45]. Strategies that may prevent bleeding in this setting include concurrent therapy with a PPI or eradication of *H pylori* infection in *H pylori* positive subjects. The efficacy of these two strategies was evaluated in a large clinical trial including 400 *H pylori* positive aspirin/NSAID users with a history of upper gastrointestinal bleeding[46]. All patients initially discontinued aspirin or NSAID therapy and were treated with omeprazole 20 mg daily for at least 8 wk to promote ulcer healing. Once the healing of ulcer was confirmed, 250 patients who were given 80 mg of aspirin daily for heart disease or stroke and 150 patients who were given 500 mg of naproxen twice daily for arthritis, both for at least 6 mo, were separately randomized to receive 20 mg of omeprazole daily for 6 mo or a 7-d course of *H pylori* eradication therapy followed by placebo once daily for 6 mo. In patients taking aspirin, no significant difference in the probability of recurrent bleeding during the 6-mo follow-up period was observed between those who received *H pylori* eradication therapy (1.9%) and those who received omeprazole (0.9%) (absolute difference: 1%, 95%CI: -1.9-3.9%). In contrast, in patients taking naproxen, the 6-mo probability of recurrent bleeding was significantly lower in the omeprazole (4.4%) than in the *H pylori* eradication group (18.8%) (absolute difference: 14.4%, 95%CI: 4.4-24.4%, $P = 0.005$)[46]. According to these data, it seems that, after ulcer healing, *H pylori* eradication may be effective in preventing recurrence of upper gastrointestinal bleeding in chronic aspirin users, but not in chronic NSAID users, who require long-term potent antisecretory therapy with a PPI.

Whether the combination of *H pylori* eradication and long-term use of PPIs may further decrease the risk of recurrence of peptic ulcer complications in chronic aspirin users was evaluated in a recent clinical trial[47]. Thus, 123 *H pylori* positive patients with a history of an aspirin-related peptic ulcer complication and current peptic ulcer were initially treated with a 7-d *H pylori* eradication therapy followed by 40 mg of famotidine daily for 5 or 13 additional weeks until ulcer healing. Then, they all restarted taking 100 mg of aspirin daily and randomized to receive 30 mg of lansoprazole daily or placebo. During a median follow-up of 12 mo, recurrence of ulcer complications was observed in 9 (14.8%) of 61 patients in the placebo group and in only 1 (1.6%) of 62 patients in the lansoprazole group (adjusted hazard ratio: 9.6, 95%CI: 1.2-76.1, $P = 0.008$)[47]. It should be noted, however, that four of the nine placebo treated patients with a recurrence of ulcer complications were reinfected with *H pylori* and an additional two patients of this group took other NSAIDs. Despite these problems in the latter trial, it is becoming widely accepted that long-term therapy with a PPI after *H pylori* eradication offers additional benefit in preventing peptic ulcer complications in high risk *H pylori* positive chronic aspirin users[19].

DISCUSSION

All existing data suggest that the presence of *H pylori* infection represents an additional risk factor for peptic ulcer complications in aspirin/NSAID users[19,48]. However, in current clinical practice which should be guided by the evidence-based medicine and should take into account the cost/benefit analysis of any major intervention, the management of *H pylori* infection and generally the gastrointestinal prevention in aspirin/NSAID users should probably be individualized (Table 1). Thus, the optimal management of such subjects appears to depend on the main factors affecting the risk of ulcer complications, which are: (1) whether the subject is a

Table 1 Recommendations[19,48] and evidence for the *H pylori* test-and-treat approach and/or the long-term therapy with a proton pump inhibitor (PPI) in users of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs)

	H pylori test-and-treat approach	Long-term PPI therapy
Naive aspirin users	Recommendation	No
Naive NSAIDs users	Recommendation-evidence[39,40]	No
Chronic aspirin users		
With a recent ulcer complication	Recommendation[1]-evidence[46,47]	Recommendation-evidence[47]
At high risk for ulcer complication	Recommendation[1]	Recommendation
At low risk for ulcer complication	No	No
Chronic NSAIDs users		
With a recent ulcer complication	Potential benefit[1,2]	Recommendation-evidence[46]
At high risk for ulcer complication	Potential benefit[1,2]	Recommendation
At low risk for ulcer complication	No	No

[1]*H pylori* eradication therapy in chronic users of aspirin or NSAIDs with a recent ulcer complication or those at a high-risk should be administered after confirmation of ulcer healing. [2]*H pylori* eradication therapy in chronic NSAIDs users with a recent ulcer complication or those at a high-risk may be given as a potentially beneficial intervention in addition to the long-term PPI therapy.

naive aspirin/NSAID user or already on long-term (>1-3 mo) or chronic drug use[36-38]; (2) whether the subject is at high risk for bleeding or other complication of peptic ulcer (history of complicated or uncomplicated peptic ulcer, age older than 60-65 years, recent dyspepsia, treatment with anticoagulants)[6,36-38,49]; and (3) perhaps whether they take aspirin or non-aspirin NSAID[19,48].

In naive NSAID users, it is well accepted and supported by strong data[39,40] that they should be tested for the presence of *H pylori* infection and, if positive, receive *H pylori* eradication therapy before NSAID use[19-48]. A similar strategy is also suggested for naive aspirin users[19], although the efficacy of such an approach has not been evaluated yet.

In chronic aspirin/NSAIDs users, the recommendations may depend on the risk for peptic ulcer complications[6] and the type of drug. The indication for use of aspirin or NSAIDs should be first evaluated in all such users at high risk for peptic ulcer complications. Moreover, the probability and the cost/benefit of replacement of aspirin or NSAID with a less gastrotoxic antiplatelet agent or a selective COX-2 inhibitor respectively may be considered[6,11,12].

All individuals, who should continue taking aspirin after development of a peptic ulcer complication, should be tested for the presence of *H pylori* infection and, if positive, receive *H pylori* eradication therapy after peptic ulcer healing. In addition, they should subsequently receive long-term therapy with a PPI[19,47]. A similar approach may be recommended in chronic aspirin users without a recent ulcer complication but at high risk for ulcer complication, such as those with a history of peptic ulcer[19]. It should be noted, however, that there are no strong data to support the combined prophylactic approach with both *H pylori* eradication and long-term PPI therapy in this setting.

All individuals, who should continue taking NSAIDs being at high-risk for peptic ulcer complication, certainly benefit from long-term therapy with a PPI[19,46,48]. The risk of relapse of ulcer complication in chronic NSAIDs users taking PPI, however, is higher than the risk of such a relapse in aspirin users irrespective of the type of gastroprotection[46]. Thus, given that *H pylori* infection represents an independent risk factor for gastrointestinal bleeding in chronic NSAIDs users[35], it is often recommended that testing for *H pylori* infection and, if positive, *H pylori* eradication therapy should be offered to high-risk chronic NSAIDs users in addition to the long-term PPI therapy[19], despite that there are no strong data to support such an approach.

Finally, testing for *H pylori* infection or PPI therapy is not recommended for chronic users of aspirin or NSAIDs with no peptic ulcer or complication or those at a low risk of the same[19].

REFERENCES

1 **Lauer MS.** Aspirin for primary prevention of coronary events. *N Engl J Med* 2002; **346**: 1468-1474

2 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories. *Br Med J* 1994; **308**: 81-106

3 **Giovannucci E,** Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, Speizer FE. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995; **333**: 609-614

4 **Arber N,** DuBois RN. Nonsteroidal anti-inflammatory drugs and prevention of colorectal cancer. *Curr Gastroenterol Rep* 1999; **1**: 441-448

5 **Baum C,** Kennedy DL, Forbes MB. Utilization of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1985; **28**: 686-692

6 **Laine L.** Approaches to nonsteroidal anti-inflammatory drugs use in the high-risk patient. *Gastroenterology* 2001; **120**: 594-606

7 **Singh G,** Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med* 1996; **156**: 1530-1536

8 **Hawkey CJ,** Laine L, Simon T, Quan H, Shingo S, Evans J. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 wk of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study. *Gut* 2003; **52**: 820-826

9 **Geis GS.** Update on clinical developments with celecoxib, a new specific COX-2 inhibitor: what can we expect? *J Rheumatol* 1999; **26** (Suppl 56): 31-36

10 **Silverstein FE,** Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, Geis GS. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid ar-

thritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **123**: 241-249

11 **Silverstein FE,** Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib *vs* nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; **284**: 1247-1255

12 **Bombardier C,** Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343**: 1520-1528

13 **Laine L,** Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, Yu Q, Bombardier C. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003; **124**: 288-292

14 **Singh G,** Ramey DR, Morfeld D, Fries JF. Comparative toxicity of non-steroidal anti-inflammatory agents. *Pharmacol Ther* 1994; **62**: 175-191

15 **Sanmuganathan PS,** Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001; **85**: 265-271

16 **Hawkey CJ,** Laine L, Harper SE, Quan HU, Bolognese JA, Mortensen E. Influence of risk factors on endoscopic and clinical ulcers in patients taking rofecoxib or ibuprofen in two randomized controlled trials. *Aliment Pharmacol Ther* 2001; **15**: 1593-1601

17 **Sorensen HT,** Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, Olsen JH. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000; **95**: 2218-2224

18 **Suerbaum S,** Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002; **347**: 1175-1186

19 **Hunt RH,** Bazzoli F. Should NSAID/low-dose aspirin takers be tested routinely for *H pylori* infection and treated if positive? Implications for primary risk of ulcer and ulcer relapse after initial healing. *Aliment Pharmacol Ther* 2004; **19** (Suppl 1): 9-16

20 **Kaufman G.** Aspirin-induced gastric mucosal injury: lessons learned from animal models. *Gastroenterology* 1989; **96**: 606-614

21 **Derry S,** Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *Br Med J* 2000; **321**: 1183-1187

22 **Kelly JP,** Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996; **348**: 1413-1416

23 **Lichtenstein DR,** Syngal S, Wolfe MM. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. *Arthritis Rheum* 1995; **38**: 5-18

24 **Labenz J,** Peitz U, Kohl H, Kaiser J, Malfertheiner P, Hackelsberger A, Borsch G. *Helicobacter pylori* increases the risk of peptic ulcer bleeding: a case-control study. *Ital J Gastroenterol Hepatol* 1999; **31**: 110-115

25 **Aalykke C,** Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. *Helicobacter pylori* and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. *Gastroenterology* 1999; **116**: 1305-1309

26 **Ng TM,** Fock KM, Khor JL, Teo EK, Sim CS, Tan AL, Machin D. Non-steroidal anti-inflammatory drugs, *Helicobacter pylori* and bleeding gastric ulcer. *Aliment Pharmacol Ther* 2000; **14**: 203-209

27 **Lanas A,** Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. *Aliment Pharmacol Ther* 2002; **16**: 779-786

28 **Papatheodoridis GV,** Papadelli D, Cholongitas E, Vassilopoulos D, Mentis A, Hadziyannis SJ. Effect of *Helicobacter pylori* infection on the risk of upper gastrointestinal bleeding in users of non-steroidal anti-inflammatory drugs: a prospective, case-control study. *Am J Med* 2004; **116**: 601-605

29 **Laine L,** Marin-Sorensen M, Weinstein WM. Nonsteroidal anti-inflammatory drug associated gastric ulcers do not require *Hepicobacter pylori* for their development. *Am J Gastroenterol* 1992; **87**: 1398-1402

30 **Cullen DJ,** Hawkey GM, Greenwood DC, Humphreys H, Shepherd V, Logan RF, Hawkey CJ. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. *Gut* 1997; **41**: 459-462

31 **Loeb DS,** Talley NJ, Ahlquist DA, Carpenter HA, Zinsmeister AR. Long-term nonsteroidal anti-inflammatory drug use and gastroduodenal injury: the role of *Helicobacter pylori* infection. *Gastroenterology* 1992; **102**: 1899-1905

32 **Pilotto A,** Leandro G, Di Mario F, Franceschi M, Bozzola L, Valerio G. Role of *Helicobacter pylori* infection on upper gastrointestinal bleeding in the elderly: a case-control study. *Dig Dis Sci* 1997; **42**: 586-591

33 **Stack WA,** Atherton JC, Hawkey GM, Logan RF, Hawkey CJ. Interactions between *Helicobacter pylori* and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther* 2002; **16**: 497-506

34 **Santolaria S,** Lanas A, Benito R, Perez-Aisa M, Montoro M, Sainz R. *Helicobacter pylori* infection is a protective factor for bleeding gastric ulcers but not for bleeding duodenal ulcers in NSAID users. *Aliment Pharmacol Ther* 1999; **13**: 1511-1518

35 **Huang JQ,** Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; **359**: 14-22

36 **Gabriel SE,** Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991; **115**: 787-796

37 **Griffin MR,** Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991; **114**: 257-263

38 **Langman MJ,** Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF, Murphy M, Vessey MP, Colin-Jones DG. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343**: 1075-1078

39 **Chan FK,** Sung JJ, Chung SC, To KF, Yung MY, Leung VK, Lee YT, Chan CS, Li EK, Woo J. Randomised trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. *Lancet* 1997; **350**: 975-979

40 **Chan FK,** To KF, Wu JC, Yung MY, Leung WK, Kwok T, Hui Y, Chan HL, Chan CS, Hui E, Woo J, Sung JJ. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. *Lancet* 2002; **359**: 9-13

41 **Hawkey CJ,** Tulassay Z, Szczepanski L, van Rensburg CJ, Filipowicz-Sosnowska A, Lanas A, Wason CM, Peacock RA, Gillon KR. Randomised controlled trial of *Helicobacter pylori* eradication in patients on non-steroidal anti-inflammatory drugs: HELP NSAIDs study. Helicobacter Eradication for Lesion Prevention. *Lancet* 1998; **352**: 1016-1021

42 **van Herwaarden MA,** Samsom M, van Nispen CH, Mulder PG, Smout AJ. The effect of *Helicobacter pylori* eradication on intragastric pH during dosing with lansoprazole or ranitidine. *Aliment Pharmacol Ther* 1999; **13**: 731-740

43 **Campbell DR,** Haber MM, Sheldon E, Collis C, Lukasik N, Huang B, Goldstein JL. Effect of *H pylori* status on

gastric ulcer healing in patients continuing nonsteroidal anti-inflammatory therapy and receiving treatment with lansoprazole or ranitidine. *Am J Gastroenterol* 2002; **97**: 2208-2214

44 **Lanas A,** Bajador E, Serrano P, Fuentes J, Carreno S, Guardia J, Sanz M, Montoro M, Sainz R. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000; **343**: 834-839

45 **Garcia Rodriguez LA,** Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343**: 769-772

46 **Chan FK,** Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, Chan HL, Sung JJ. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001; **344**: 967-973

47 **Lai KC,** Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, Lau GK, Wong WM, Yuen MF, Chan AO, Lai CL, Wong J. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002; **346**: 2033-2038

48 **Malfertheiner P,** Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of *Helicobacter pylori* infection-the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167-180

49 **Laine L,** Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C, Reicin A. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 2002; **123**: 1006-1012

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