World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i28.9439

World J Gastroenterol 2014 July 28; 20(28): 9439-9450
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Interaction between *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs and/or low-dose aspirin use: Old question new insights

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Received: October 25, 2013 Revised: January 15, 2014
Accepted: April 8, 2014
Published online: July 28, 2014

Abstract

Previous reports clearly demonstrated that *Helicobacter pylori* (*H. pylori*) infection, nonsteroidal anti-inflammatory drugs (NSAID) or low dose aspirin (ASA) use significantly and independently increased the risk for the development of peptic ulcer disease. Today, the presence of *H. pylori* infection associated with low dose ASA and/or NSAID use in the same patient is becoming more frequent and therefore the potential interaction between these factors and the consequences of it has important implications. Whether NSAID intake in the presence of *H. pylori* infection may further increase the risk of peptic ulcer carried by the presence of only one risk factor is still a matter of debate. Studies on the interaction between the two risk factors yielded conflicting data and no consensus has been reached in the last years. In addition, the interaction between *H. pylori* infection and low-dose ASA remains even more controversial. In real clinical practice, we can find different clinical scenarios involving these three factors associated with the presence of different gastrointestinal and cardiovascular risk factors. These huge variety of possible combinations greatly hinder the decision making process of physicians.

Key words: Nonsteroidal anti-inflammatory drugs; Low dose aspirin; *Helicobacter pylori* infection; *Helicobacter pylori* eradication; Peptic ulcer disease

Core tip: *Helicobacter pylori* (*H. pylori*) infection, nonsteroidal anti-inflammatory drugs (NSAID) or low dose aspirin use independently increases the risk for the development of peptic ulcer disease. In clinical practice, the presence of *H. pylori* infection associated with low dose aspirin and/or NSAID use in the same patient is becoming more frequent and therefore the potential interaction between these factors and the consequences of it has important implications. In real clinical practice, we can find different clinical scenarios involving these three factors associated with the presence of different gastrointestinal and cardiovascular risk factors. These huge variety of possible combinations greatly hinder the decision making process of physicians.

Sostres C, Gargallo CJ, Lanas A. Interaction between *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs and/or low-dose aspirin use: Old question new insights. *World J Gastroenterol* 2014; 20(28): 9439-9450 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i28/9439.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i28.9439

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection, NSAID or low dose

aspirin (ASA) use independently and significantly increases the risk for the development of peptic ulcer disease. In a systematic review, the reported pooled relative risk for traditional NSAID-related gastrointestinal (GI) bleeding was 4.50 (95%CI: 3.82-5.31)[1]. In addition, meta-analysis published in 2006 of 14 randomized, placebo-controlled trials showed a relative risk of 2.07 (95%CI: 1.61-2.66) for major GI bleeding attributable to low-dose ASA when compared with placebo[2]. Finally, the association between *H. pylori* infection and the relative risk of peptic ulcer bleeding was further studied in a meta-analysis which confirmed that *H. pylori* infection increased the risk of ulcer bleeding (OR = 1.79)[3]. Today, in clinical practice, the presence of *H. pylori* infection associated with low dose ASA and/or NSAID use in the same patient is becoming more frequent and therefore the potential interaction between these factors and the consequences of it has important implications. Whether NSAID intake in the presence of *H. pylori* infection may further increase the risk of peptic ulcer carried by the presence of only one risk factor is still a matter of debate. Studies on the interaction between the two risk factors yielded conflicting data and no consensus has been reached in the last years[4]. In addition, the interaction between *H. pylori* infection and low-dose ASA use is complex poorly defined and remains even more controversial[5]. In real clinical practice, we can find different clinical scenarios involving these three factors associated with the presence of different GI and cardiovascular risk factors. These huge variety of possible combinations greatly hinder the decision making process of physicians. In this review we present current knowledge on the upper GI risk associated with NSAID and/or low-dose ASA use and *H. pylori*, and discuss the expanding clinical data on *H. pylori* infection and eradication in NSAID and low-dose ASA users. Finally, we review current consensus recommendations.

NSAID-RELATED GI DAMAGE

It has been estimated that over 30 million people consume NSAIDs worldwide and the per capita consumption averages 278 prescriptions per 1000 patient[6]. In Europe, NSAIDs represents more than 7.7% of all prescriptions and probably these figures are underestimated because of over-the-counter use is not included[7]. In 2004, a total of 111 million NSAID prescriptions were written in the United States[8], and it is expected that the use of NSAIDs will increase because the incidence of rheumatic diseases also is growing. NSAIDs have emerged as one of the most important cause of peptic ulcer complications in many developed countries where the incidence of *H. pylori*-related ulcer is rapidly declining. NSAIDs injure the whole gut by causing topical injury to the mucosa and/or systemic effects associated with mucosal prostaglandin depletion derived from COX-1.

From an endoscopic point of view, NSAIDs produced a wide range of lesions including petechia and erosions with little clinical consequences[9] to more serious life-threatening events. From a clinical point of view, NSAID-related upper GI adverse events could be categorized in different types depending on the consequences for the patients:

Symptoms like *dyspepsia*, nausea, vomiting, abdominal pain and heartburn are the most frequent side GI effects associated with NSAID intake, and can be present in up 40% of NSAIDs users[10]. Sadly, about 50%-60% of patients with complications will not have predictive warming signs or symptoms[11] and conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa[12].

NSAIDs related gastroduodenal injury with unclear clinical significance

This damage occurs in 30%-50% of patients taking NSAIDs but most lesions are asymptomatic[9]. Only 15%-30% of NSAIDs users have endoscopically confirmed GI ulcers[12].

Symptomatic ulcers and GI complications (GI bleeding, ulcer perforation and obstruction)

Approximately 1%-1.5% of patients will develop GI complications in the first year of treatment[13-16] and when symptomatic ulcers are included this figure rises up to 4%-5%[17].

Mortality

In the different population based surveys regarding all-cause upper GI bleeding, mortality ranges between 3% and 14%. In a systematic review, Tramér *et al*[18] reported a mortality rate for NSAID exposure of more than 2 mo as high as 12% in 11000 cases of GI bleed or perforation, although there was a large variation Therefore mortality data associated with NSAIDs treatment are still scant[19]. It is important to note that the increase in NSAID consumption or the introduction of potent antisecretory medications has not affected the long-term downward trends of ulcer mortality. In Spain, in the year 2001, 50114 GI bleeding events were reported with 18191 GI complications and 1022 deaths attributed to aspirin or other NSAIDs use. The mortality rate in this study[20] was estimated as 15.3 deaths/100000 NSAID/aspirin users. However, this lower rate estimate could be due to fact that both NSAIDs associated GI complications have been decreasing in recent years. It is also important to highlight that recent data indicate that most PUB-linked deaths are not direct sequelae of the bleeding ulcer itself. Instead, mortality derives from multiorgan failure, cardiopulmonary conditions, or terminal malignancy, suggesting that improving treatments of the bleeding ulcer may affect mortality very little[21].

The GI risk factors for NSAID induced ulcer complications are widely reported[22], but not all risk factors are equally important. Patients with a previous ulcer bleeding are at the highest risk[22,23]. GI risk factors also include patients older than 65 years, a previous ulcer history, and concomitant use of NSAIDs with anticoagulants, and

aspirin or clopidogrel[24,25].

LOW-DOSE ASPIRIN RELATED GI DAMAGE

Today, low dose ASA, commonly defined as 75-325 mg daily, is one of the most widely used drugs in the world and the cornerstone of therapy for cardiovascular disease[26]. One survey suggested that over one-third of the United States adult population use low dose ASA regularly[27]. In England in 2007, over 30 million primary care prescriptions were issued for low dose ASA[28]. Guidance from the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents state that low dose ASA is associated with a two to four fold increase in GI adverse events, increasing with concomitant medication use[29-31]. Low dose ASA is associated with a wide range of side effects in the upper GI tract, including ulcers, GI bleeding, perforation and even death[32]. Gastro-oesophageal reflux and dyspeptic symptoms seem to be the most frequent low dose ASA related symptoms[30,33]. Low dose ASA users can also develop mucosal injury through the whole GI tract even at very low doses. However, low dose ASA related mucosal lesions developed more frequently in upper GI tract. This mucosal damage includes petechiaes, ecchymosis, erosions and ulcers[34]. Endoscopically-controlled studies have shown that the prevalence of erosions in gastroduodenal mucosa in low dose ASA users is about 60%[35,36]. One recent study of 187 patients taking low dose ASA without gastroprotective drugs showed that ulcer prevalence was 11% (95%CI: 6.3%-15.1%) and ulcer incidence in patients followed for 3 mo was 7% (95%CI: 2.4%-11.8%)[30], identical figures to ulcer incidence were found by Laine *et al*[37] in patients who were taking enteric-coated low dose ASA. The main clinical problem occurs when an ulcer erodes a vessel and starts bleeding or, less commonly, perforates. American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents state that low dose ASA is associated with a 2-4 fold increase in symptomatic or complicated ulcer, increasing with concomitant medication use[29-31]. Death is the worst outcome of GI complications, but mortality data associated with low dose ASA use are scarce. A nationwide study in Spain of mortality associated with hospital admission because of GI complication events found an aspirin-associated death rate of 24.8 cases per 1000000 people[20]. Low-dose ASA use was responsible for between 8.2% and 12.2% of all complications and deaths. There are some factors that put patients on low dose ASA treatment at increased risk of upper GI complications. The most important risk factors include a history of an ulcer a history of a bleeding ulcer[29], age > 70 years[35], *H. pylori* infection and concomitant drug therapy with NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, other antiplatelet agents (clopidogrel) or anticoagulants[29,38,39]. Multiple risk factors have a cumulative effect on complications; not all patients who take ASA are at the same risk of upper GI bleeding. A case-control study of hospitalizations for bleeding ulcer revealed that low-dose ASA alone was associated with an adjusted OR of 3.3 (2.5-4.4), while the combination of low-dose ASA plus an NSAID had an OR of 7.7 (3.6-16.4)[29]. In another case-control study[40] of hospitalizations for bleeding peptic lesions, NSAID plus low-dose ASA use also increased the risk when compared with low dose ASA alone [OR = 3.8 (1.8-7.8)]. Although *H. pylori* is a frequently reported risk factor for upper GI bleeding in aspirin users, the real effect of *H. pylori* eradication on reducing the risk of bleeding remains unclear and we are going to discuss it in the next paragraphs.

ROLE OF *H. PYLORI* INFECTION IN PEPTIC ULCER DISEASE

H. pylori is one of the most common chronic bacterial infections in humans, with almost 50% of the world population infected[41]. The prevalence rates of *H. pylori* infection are highly inconsistent worldwide. Recent international studies have shown that *H. pylori* prevalence varies from 7% (in Czech population)[42] to 92% (in Pakistani population)[43], finding lower prevalences in North America and in Western European countries. At any rate, there is now evidence that *H. pylori* infection prevalence is declining during the last few decades in both developing and developed nations.

It is well known that acidic environment of human stomach is the ideal environment to *H. pylori*. The influence of *H. pylori* on gastric pH is not simple, depends on severity and phenotype of the induced gastritis. Acute infection leads to a transient hypochlorhydria, which facilitates the survival of bacteria and helps in its colonization of the stomach[44,45]. However, chronic infection may be associated with both, hypochlorhydria and hyperchlorhydria, depending on distribution of inflammation[46,47]. Most of chronically infected patients manifest a corpus predominant gastritis and produces decreased amounts of acid that non infected stomachs. With time, loss of oxyntics glands occurs, resulting in an irreversible achlorhydria, intestinal metaplasia, dysplasia and even cancer. Therefore, it is not surprising that patients with gastric ulcers have normal o decreased acid production. Conversely, some chronic infected patients have antral predominant gastritis with high gastric acid output[48]. This hyperacidity might predispose to gastric metaplasia of duodenal mucosa and it allows *H. pylori* colonization of duodenum and further propagate duodenal ulceration. Normally, patients with duodenal ulcers have increased acid output.

Although most infected patients remain asymptomatic, *H. pylori* infection predisposes to peptic ulcer disease (PUD), gastric carcinoma and mucosa-associated lymphoid tissue lymphoma.

In a recent meta-analysis that evaluated the current global incidence and prevalence of PUD over the last decade by systematic review of 18 large population based studies from mainly Western countries, the 1-year inci-

dence rates of PUD were 0.10% to 0.19% for physician-diagnosed and 0.03% to 0.17% when based on hospitalization data[49]. There is not doubt that *H. pylori* infection plays an important role in the occurrence of this PUD. In early studies it was estimated that *H. pylori* was responsible for up to 95% of all gastro-duodenal ulcers[50], but more recent studies have found the prevalence of *H. pylori* in patients with PUD to range from 36% to 73%, depending on several factors: geographic location, socioeconomics level, *etc.*[51,52].

PUD can lead to serious complications including acute upper GI bleeding and perforation. The mortality from these complications ranges between 4% and 30%[53]. There are discrepancies concerning time trends of hospitalizations owing to complicated ulcers. Generally, studies that reported decreasing peptic ulcer bleeding rates are more recent and are populations based. In this regard, it is interesting a Spanish study by Lanas *et al*[54] published in 2011. Authors showed that the incidence per 100000 person-years of hospitalizations due to upper GI ulcer bleeding and perforations decreased over time [from 54.6 and 3.9 in 1996 (r^2 = 0.944) to 25.8 and 2.9 in 2005 (r^2 = 0.410) respectively], being bleeding peptic ulcer the most common cause of upper GI bleeding. A recent systematic review of 71 articles, including 8496 patients showed that the mean prevalence of *H. pylori* infection in peptic ulcer bleeding was 72 %[55]. This prevalence varied based on geographic area, gastrolesive drugs use, age of patients, and time and diagnosis test used.

It is now well known that *H. pylori* eradication improves peptic ulcer healing and reduce risk of ulcer bleeding recurrence. In 2001, Leodolter *et al*[56], published a meta-analysis (included 24 trials) that found that the 12 month ulcer remission rate was 97 and 98% for gastric and duodenal ulcer respectively in patients with successfully eradicated infection, *vs* 61% and 65% in patients in whom infection persisted. Another meta-analysis compared eradication of infection with ulcer healing treatment (ranitidine or omeprazole) to prevent recurrent ulcer bleeding. Treatment of *H. pylori* infection reduced recurrent bleeding by 17% compared with ranitidine for 16 weeks or omeprazole for 2 wk and by 4% compared with ranitidine or omeprazole for 1-2 years[57]. A more recent Cochrane Database meta-analysis that included 56 trials found that in duodenal ulcer healing, eradication therapy was superior to ulcer healing drug and no treatment[58]. In gastric ulcer healing, no significant differences were detected between eradication therapy and ulcer healing treatment. In preventing duodenal and gastric ulcer recurrence no significant differences were detected between eradication therapy and maintenance therapy with ulcer healing drugs, but eradication therapy was superior to no treatment.

Concerning duodenal ulcer perforation, the data showed by a recent systematic review and meta-analysis, that the simple closure surgery method plus *H. pylori* eradication is better than operation plus antisecretory non eradication therapy for preventing ulcer recurrence[59].

INTERACTION BETWEEN *H. PYLORI* INFECTION AND NSAID/LOW DOSE ASA USE

NSAIDs, low dose ASA and *H. pylori* infection damage the gastric mucosa by different or shared mechanisms than can result in a synergist or antagonist effect.

Interaction between H. pylori infection and NSAIDs use

Mechanisms of upper GI damage with NSAIDs and *H. pylori* infection: NSAIDs damage the gastric mucosa by two broad mechanisms, a systemic effect due to inhibition of the enzyme cyclooxigenase-1 and consequent depletion of prostaglandin synthesis and also through a direct topical injury. Topical damage is initiated because most of NSAIDs are weak acids. Due to a low dissociation constant, which varies according to the particular agent, these weak acids remain in their non-ionized lipophilic form in the highly acidic gastric lumen. Such conditions favour migration through the gastric mucus across plasma membranes and into surface epithelial cells, where NSAIDs are dissociated into the ionized form, resulting in trapping of hydrogen ions that induced mucosal damage. However, the systemic effects of NSAIDs on the GI mucosa have apparently the predominant role. NSAIDs inhibit cyclo-oxygenases (COX), and the biosynthesis of prostaglandins. COX-1 derived prostaglandins play an important protective role in the gut by stimulating the synthesis and secretion of mucus and bicarbonate, increasing mucosal blood flow and promoting epithelial proliferation. When NSAIDs inhibit this enzyme create a gastric environment that is more susceptible to damage induced by other endogenous or exogenous factors, like *H. pylori*. On the other hand, *H. pylori* infection also decreases mucosal blood flow, induced apoptosis and produces a local inflammatory response and may render the mucosa more susceptible to damage induced by other factors such as NSAID or ASA. The interaction of mechanisms between these two factors is not well understood. A decrease in the viscosity of mucus or the effect on gastric pH associated with hypo or hyperchlorhydria depending on the phenotype of the induced *H. pylori*-induced gastritis have been proposed to explain the variability of effects reported by the interaction of *H. pylori* infection and NSAID or ASA gastroduodenal mucosal damage[46,47]. From a pathophysiologic point of view, it has been suggested that *H. pylori* infection could protect against, and even accelerating the healing of NSAID induced ulcers as a result of acid suppression favored by *H. pylori* induced pangastritis, especially in the presence of proton pump inhibitors[60,61]. This hypothesis however has not been confirmed by clinical studies. An interesting discovery related to the gastric injury induced by NSAIDs is an increase in mucosal tolerance or adaptation to this damage that developed with their more prolonged administration. This adaptation has been first demonstrated in rats[62] and then confirmed in human. Several studies[63,64] revealed that intragastric

aspirin when administered repeatedly induces acetylation of COX-2 which is upregulated during continued treatment with this NSAIDs resulting in the local generation of 15-(R)epilipoxin A4. This lipoxin exterts gastroprotective effect in the gastric mucosa and was also implicated in the enhanced gastric mucosal resistance to aspirin induced damage in animal model. *H. pylori* is though to worse this adaptation *via* mechanism involving oxygen and pro-inflammatory mediators[65].

Role of NSAID and *H. pylori* infection in peptic ulcer disease development: It is widely accepted that the risk of NSAID-induced ulcers varies according to the presence of some host risk factors like advanced age, comorbility, co-prescription of other drugs, history of peptic ulcer, and *H. pylori* infection.

It has been established that the presence of both, *H. pylori* infection and NSAID use, increases the risk of uncomplicated and complicated PUD. Huang *et al*[3] published in 2002 an interesting meta-analysis that included data from 25 observational studies and evaluated the role of these risk factors in the development of PUD. They showed that uncomplicated PUD was significantly more common in NSAID users with *H. pylori* infection than in those without infection and also was significantly more common in NSAID takers than in controls, irrespective of *H pylori* infection. When the comparison was between NSAIDs users with *H. pylori* infection and individuals not taking NSAIDs and without infection, the risk of PUD in the patients with both risk factors was 61.1 (9.98-373). Data analysis showed that *H. pylori* infection increased the risk of PUD in NSAIDs users 3.53 folds in addition to the risk associated with NSAID use (OR = 19.4) and use of NSAID increased the risk of PUD 3.55 fold in *H. pylori* positive patients in addition to the risk associated with *H. pylori* infection (OR = 18.1). It is important to note that the extremely large odds ratios seen in the comparisons between control populations might have resulted from a zero event rate in *H pylori* negative controls. Also, they evaluated the prevalence of *H. pylori* infection and NSAIDs use in 893 patient with bleeding ulcer and 1002 controls without bleeding. *H. pylori* infection and NSAIDs use increased the risk of ulcer bleeding 1.79 fold and 4.85 fold, respectively. If both risk factor were present the risk increased to 6.13. Therefore, with this evidence, we can summarize that both, *H. pylori* infection and NSAIDs use, are independent risk factor for development of complicated and uncomplicated PUD, and probably, both have a synergistic effect.

Role of *H. pylori* eradication in the primary prevention of PUD in NSAIDs users: Two recent meta-analysis have evaluated whether eradication of *H. pylori* prevents PUD in NSAIDs users.

Vergara *et al*[66], in 2005, analyzed 5 studies that included 939 patients. The analysis of data showed that 7.4% of patients in the eradicated group developed a PUD *vs* 13.3 % in the control group (OR = 0.43, 95%CI: 0.20-0-93). Sub-analysis of these data showed that eradication was significantly effective when performed in NSAIDs naïve users (OR = 0.26, 95%CI: 0.14-0.49), but is not so effective in chronic users (OR = 0.95, 95%CI: 0.53-1.72). Regarding data on ulcer complications, eradication was significantly effective to prevent ulcer bleeding in those patients. None of eradicated patients (332) *vs* four of non eradicated patients (340) presented a bleeding ulcer (OR = 0.13, 95%CI: 0.02-0.92). In 2012, Tang *et al*[67] developed a meta-analysis with a similar objective than Vergara´s meta-analysis. The analysis of data of seven randomized controlled studies showed that 6.4% and 11.8% of NSAIDs users, with and without eradication treatment, respectively, developed PUD (OR = 0.50; 95%CI: 0.36-0.74). This preventive effect was also more significant in NSAIDs naïve takers (OR = 0.26, 95%CI: 0.14-0.49) than in chronic users (OR = 0.74, 95%CI: 0.46-1.20).

Role of *H. pylori* eradication in the secondary prevention of PUD in NSAIDs users: Although the data summarized above suggest a beneficial effect of *H. pylori* eradication in the prevention of PUD, one of the remaining key issues is whether the effect is sufficient to prevent PUD in NSAIDs users at higher risk as those with history of prior ulcer[68].

Chan *et al*[22] have developed two very interesting studies in which they try to provide evidence on this key issue. In the first study, published in 2001, they examined ulcer reebleding in NSAID or low dose ASA users with history of upper GI bleeding and who were infected with *H. pylori*. They enrolled 150 NSAIDs users with history of prior ulcer which was healed with PPI (at least during 8 wk). After healing of ulcers patients were randomized to receive either eradication treatment or long term maintenance PPI therapy. Treatment with PPI was more effective in as much as the probability of recurrent bleeding, over 6 mo, was 18.8% for eradicated group *vs* 4.4% for maintenance PPI therapy group (absolute difference 14.4%, 95%CI: 4.4-24.4%, P = 0.005). In the second study, published in 2002, they evaluated the role of eradication in NSAIDs naïve users who had *H. pylori* infection and prior history of dyspepsia or peptic ulcer. The rate of endoscopic ulcers in the eradication group compared with control group were 12% *vs* 34.4% (RR = 0.65; P = 0.0085) and the corresponding 6 month probabilities of complicated PUD were 4.2% *vs* 27.1 % (RR = 0.85; P = 0.0026). With these data *H. pylori* eradication seems to be insufficient to prevent ulcer recurrence in NSAIDs users.

In summary, current evidence suggests that, in NSAIDs naïve users, eradicating *H. pylori* for both, primary and secondary prophylaxis can reduce effectively ulcer risk, however, in those patients who are already long-term NDAIDs users there is no clear benefit. Furthermore *H. pylori* eradication seems insufficient to prevent ulcer recurrence in NSAID users and PPI co-therapy has been recommended as necessary for appropriate prevention in this population. Treatment of both risk factors, eradica-

Table 1 Mechanisms of upper gastrointestinal injury with *Helicobacter pylori* infection, low dose aspirin and non steroidal anti-inflammatory drugs

Mechanism	LDA	NSAID	*H. pylori*
Prostaglandin/effect on COX enzyme	Selective and irreversible inhibition of COX-1	Inhibition of both isoforms of COX enzyme (COX-1 and 2)	Increase/up regulation COX-2
Gastric pH	Decrease	Decrease	Decrease or increase or no effect
PMN mediated gastric mucosa injury	Increase	Increase	Increase
Gastric mucosal flow	Decrease	Decrease	Increase
Gastric adaptation to LDA and NSAIDs			Reduce

Adapted from reference [5]. LDA: Low dose aspirin; NSAID: Non steroidal anti-inflammatory drugs; *H. pylori*: *Helicobacter pylori*; PMN: Polimorphonuclear cells; COX: Cicloxigenase.

tion of infection and PPI treatment, is likely to afford the greatest protection. The reasons for the differences observed on the effects of *H. pylori* eradication between NSAIDs naïve and chronic NSAIDs users are not clear, but a plausible explanation has been proposed. Early epidemiological studies showed that the risk of ulcer complications with NSAID use is increased during the first months. Initiation of NSAIDs treatment may precipitate ulcer complications in *H. pylori* positive patients who are susceptible to develop complication ulcers. Weeding of these susceptible patients in the initiation of treatment will select a group of chronic NSAIDs takers who can tolerate these drugs irrespective of *H. pylori*. Because of that, eradication seems to be more beneficial in NSAIDs naïve patients than in chronic users.

Interaction between H. pylori infection and low dose ASA use

Literature about interaction between *H. pylori* infection and low dose ASA is scarce and also controversial.

Mechanisms of upper gastrointestinal damage with low dose ASA and *H. pylori* infection: *H. pylori* and low dose ASA exert their gastric damage through different mechanism that may interact in a synergistic or antagonistic manner (Table 1).

Low dose ASA increases gastric acidity by decreasing prostaglandin. The influence of *H. pylori* infection on gastric pH depends on the severity and phenotype of the induced gastritis like we have explained previously, and its role in ASA induced injury will depend on its modulation of gastric acidity. The different phenotypes of *H. pylori* gastritis may contribute to contradictory data concerning its effect on gastric damage in low dose ASA takers. Thereby it has been argued that *H. pylori* infection could protect against low dose ASA induced ulcers. But, there are other mechanisms through which low dose ASA damages gastric mucosa: exposure of gastric epithelial cells to luminal acid, reduction of mucosal blood flow, increase of apoptosis of epithelial cells, and recruitment of polymorphonuclear cells. And *H. pylori* also may further aggravate this local injury by reducing viscosity of mucus and impairing the gastric adaptation to prolonged use of low dose ASA.

Low dose ASA inhibits selectively and irreversibly of COX-1 that suppresses prostaglandin synthesis and platelet production of thromboxane A2. This irreversible nature of COX-1 inhibition and its antitrombotic effect is what differentiate low dose ASA from NSAIDs. These differences may explain why low dose ASA is less ulcerogenic than NSAIDs but, at the same time, increases more the risk of bleeding from pre-existing ulcers such as those caused by *H. pylori*[5]. Because of that, *H. pylori* may have a more significant role in low dose ASA induced gastric damage than with other NSAIDs. And it is important to note that, although *H. pylori* promote gastric mucosa prostaglandin secretion by up regulating COX-2, it is probably insufficient to counteract the potent prostaglandin inhibition by low dose ASA.

Role of low dose ASA and *H. pylori* infection in peptic ulcer disease development: A recent systematic review about the influence of *H. pylori* on upper GI bleeding risk in low dose ASA users concluded that the current data are insufficient to allow meta-analyses and that no firm conclusion could be drawn on this issue[69]. Ten of 13 studies evaluated were cohort studies that comprise heterogeneous group of patients whit different dosages of ASA, different inclusion criteria and different techniques to detect *H. pylori*. Moreover, the existing RCT had a small sample size and short follow up.

Lanas *et al*[40] performed the first study that suggested that *H. pylori* infection is a significant risk factor to upper GI bleeding in low dose ASA takers (OR = 4.7; 95%CI: 2.0-10.9). In this case-control study, the prevalence of *H. pylori* infection was 89.9% in cases of upper GI bleeding *vs* 68.7% in controls (P = 0.0001). *H. pylori* was found to be an independent risk factor for ulcer bleeding (OR = 4.7, 95%CI: 2.0-10.9).

Role of *H. pylori* eradication in the primary prevention of PUD in low dose ASA users: Nowadays there are not large studies that evaluate the effect of *H. pylori* eradication in preventing PUD in medium risk low dose ASA users.

It is interesting a small randomized controlled trial (RCT) developed by Giral *et al*[70] that included 32 patients and evaluated the role of eradication of *H. pylori* in primary prevention previous to begin long term low dose ASA treatment (300 mg). In this study, eradication of *H. pylori* seemed to have a protective effect at 4 mo follow-up. In contrast, a recent cohort study that examined the potential risk factors for the development of erosions in long term low dose ASA users showed that *H. pylori* infection may be a protective factor against low dose ASA induced gastric erosions due to the gastric acid reducing effect of infection[71]. Gastric erosions appeared more frequently and were more numerous in *H. pylori* negative patients compared to *H. pylori* positive patiens. At

baseline, 48.5 % of positive *H. pylori* patients had gastric erosions *vs* 66.4% in negative *H. pylori* patients ($P = 0.17$) and at 3 mo 40% *vs* 64% ($P = 0.029$). It is important to note, that although gastric erosions may be a precursor to PUD, this endpoint is less clinical relevant that peptic ulcer bleeding.

The ongoing HEAT (Helicobacter Eradication Aspirin Trial) study whose objective is to evaluate the role of *H. pylori* eradication in low dose ASA users and the occurrence of peptic ulcer bleeding can provide quality evidence on the role of eradication of infection in primary prevention of PUD in low dose ASA users.

Role of *H. pylori* eradication in the secondary prevention of PUD in low dose ASA users: Several studies have focused on the role of *H. pylori* eradication in secondary prophylaxis of ulcers (uncomplicated and complicated) and most of them have suggested an increased risk of upper GI bleeding in low dose ASA users with *H. pylori* infection.

Chan *et al*[22] developed a RCT that evaluated the roles of *H. pylori* eradication and long term maintenance PPI as secondary prevention strategies in low dose ASA users who were *H. pylori* positive and had suffered upper GI bleeding. After healing of ulcers cause bleeding with PPI, patients were randomized to receive either eradication treatment or long term maintenance PPI therapy. At 6 mo follow up, the probability of rebleeding was comparable in both groups [1.9% in the eradication group *vs* 0.9% in PPI group (absolute difference 1%; 95%CI: 1.9%-3.9%)].

Lai *et al*[72] performed a RCT that examined whether long term maintenance PPI treatment provided some benefit in preventing recurrent ulcer bleeding in long term low dose ASA users who had already received *H. pylori* eradication therapy; 1.6% (1/62) of patients who were treated with PPI had a recurrent ulcer complication *vs* 14.8% (9/61) in placebo group during a median follow up of 1 year. According to these data, treatment with PPI, in addition to eradication, appears to reduce the rate of rebleeding in those patients. However it is important to note that 4 patients who had recurrent bleeding had a relapse of *H. pylori* infection and 2 had taken NSAIDs before recurrent complication.

Interestingly, the largest long-term prospective cohort study has been published recently[73]. One of the points of interest is that, unlike previous studies, the study has a long follow-up period (patients were censored at the first occurrence of ulcer bleeding, after 10 years of follow-up or death). They recruited a total of 904 low dose ASA users that were divided into 3 cohorts: (1) *H. pylori* positive ASA users with bleeding ulcers in which *H. pylori* were eradicated; (2) *H. pylori* negative ASA users with bleeding ulcers; and (3) new users of ASA without prior peptic ulcer. None of the subjects received regular PPI. The adjusted incidence of ulcer bleeding (cases per 100 patients-years) were not significantly different between the *H. pylori* eradicated cohort (1.09; 95%CI: 0.61-1.98) and the average risk cohort (0.67; 95%CI: 0.42-1.06), which, according to author's conclusion, would confirm the hypothesis that *H. pylori* eradication is beneficial in ASA users as secondary prevention strategy. However, ASA users without current or past *H pylori* infections who develop ulcer bleeding have a high risk of recurrent bleeding (incidence of recurrent bleeding 5.22; 95%CI: 3.04-8.96). The study is of great interest, but the lack of direct comparisons and the clinical differences between the cohorts reduces the impact of the findings.

In summary, current evidence suggests that *H. pylori* infection increases the risk of PUD (complicated and uncomplicated ulcers) in low dose ASA users. Still, there is insufficient evidence on the role of *H. pylori* eradication in primary and secondary prevention in ASA users. *H. pylori* eradication seems to reduce the risk of ulcer bleeding in high-risk low dose ASA users. In fact, the available evidence suggests that *H. pylori* eradication is probably as effective as long term maintenance PPI treatment in secondary prevention of peptic ulcer bleeding in these patients. In any case, the evidence is scant and comes from studies with small sample size and short follow up, and probably recommending not using maintenance PPI treatment in the high risk patient with previous peptic ulcer may be yet too risky. In average-risk low dose ASA users, the role of *H. pylori* eradication is controversial.

INTERNATIONAL GUIDELINES STATEMENTS

In this section, we summarize in a table (Table 2) the statements and recommendations of the Maastricht Ⅳ/Florence Consensus Report (2012)[74], Second Asia-Pacific Consensus Guidelines for *H. pylori* (2009)[75], American College of Gastroenterology Guideline on the Management of *H. pylori* (2007)[76] and Ⅲ Spanish Consensus Conference on *H. pylori* infection (2013) about *H. pylori* eradication in NSAIDs and low dose ASA users (2013)[77].

The four revised clinical guidelines agree that *H. pylori* infection and NSAIDs use are independent risk factors for the development of PUD. Therefore, regardless of whether or not a patient is taking NSAIDs or low dose ASA, all patients with peptic ulcer should be tested and when infected, treated for *H. pylori*. American Guideline recommends cotherapy with a PPI in all NSAIDs users with history of complicated peptic ulcer. Asian and European Guidelines recommend co-therapy in chronic NSAIDs user with history of complicated ulcer, without recommendations on naïve NSAIDs users, and Spanish consensus recommends co-therapy according to risk factors.

European and Asian Guidelines recommend *H. pylori* eradication before starting NSAIDs treatment. No clinical guidelines makes a firm recommendation on what attitude to take to (chronic and naïve) low dose ASA and chronic NSAIDs users without history of peptic ulcer.

NEW INSIGHTS

Recently low-dose ASA has emerged as the most impor-

Table 2 Summary of statements and recommendations of main international guidelines about *Helicobacter pylori* eradication in non steroidal anti-inflammatory drugs and low dose aspirin users

Statements and recommendations	Guideline/consensus	EL GR
H. pylori infection is a risk factor of PUD in NSAIDs and low dose ASA users	Maastricht Ⅳ Consensus	EL: 2a GR: B
	American Guideline	
Eradication of *H. pylori* infection reduces the risk of complicated an uncomplicated gastroduodenal ulcers in NSAID and low dose ASA users	Maastricht Ⅳ Consensus	EL: 1b GR: A
In NSAIDs naïve users, H.pylori eradication is beneficial. It is mandatory in patients with a peptic ulcer history	Maastricht Ⅳ Consensus	EL: 1b GR: A
	Ⅱ Asian-Pacific Guidelines	EL: 1a GR: A
	Ⅲ Spanish Consensus	EL: weak GR: low
In chronic NSAIDs users with history of peptic ulcer, eradication alone is insufficient to prevent ulcer recurrence and/or bleeding. They require continued PPI treatment	American Guideline	
	Maastricht Ⅳ Consensus	EL: 1b GR: A
In low dose ASA naïve users with peptic ulcer history, eradication of *H. pylori* infection is indicated	Maastricht Ⅳ Consensus	EL: 1b GR: A
	Ⅱ Asian-Pacific Guidelines	EL: 2b GR: B
	Ⅲ Spanish Consensus	EL: 1b GR: B
In chronic low dose ASA users with a history of peptic ulcer, eradication of *H. pylori* infection is indicated	American Guideline	EL: weak GR: low
	Maastricht Ⅳ Consensus	EL: 2b GR: B
	Ⅱ Asian-Pacific Guidelines	EL: 1b GR: B
	Ⅲ Spanish Consensus	EL: weak GR: low
	American Guideline	
The long-term incidence of peptic ulcer bleeding is low in low dose ASA users after receiving eradication even in the absence of gastroprotective treatment	Maastricht Ⅳ Consensus	EL: 2b GR: B

EL: Evidence level; GR: Grade of recommendation; PUD: Peptic ulcer disease; ASA: Aspirin; NSAID: non steroidal anti-inflammatory drugs; *H. pylori*: *Helicobacter pylori*.

tant cause of PUB in Western countries. In addition, a secondary analysis of cardiovascular trials showed that daily use of ASA also reduces the risk of all cancers[78]. With increasing use of ASA for cardiac thrombosis diseases and cancer prevention due to the increase of elderly population, the global burden of low dose ASA-related PUD is expected to increase in the next years. Therefore, last years most research efforts are focus on the interaction between *H. pylori* and low dose ASA use. Current European and United States guidelines recommend test and treat *H. pylori* infection in low dose ASA users who are at risk of ulcer bleeding[21,31,74] Despite these guidelines, the long-term benefit of eradicating *H. pylori* in high-risk ASA users is uncertain. Chan *et al*[73] recently found that the long-term incidence of recurrent ulcer bleeding with ASA use is low after *H. pylori* infection is eradicated, however ASA users without current or past *H. pylori* infections who develop ulcer bleeding have a high risk of recurrent bleeding. On the other hand, PPI cotherapy should be given selectively to *H. pylori* eradicated ASA users who use concomitant NSAIDs, anticoagulants, corticosteroids, or other antiplatelet drugs. They hypothesize that most of the ulcers in *H. pylori* positive ASA users were related to *H. pylori* alone. Therefore ASA probably provoked bleeding from pre-existing *H. pylori* induced ulcers. *H. pylori* eradication lead to mucosal integrity such that resumption of ASA was not ulcerogenic enough to induce recurrent ulceration and bleeding. In contrast, the *H. pylori* negative low dose ASA users represented a group of patients who were susceptible to the GI toxicity of low-dose ASA. It is important to highlight that this was not a randomized trial. Given the very low incidence rate of ulcer bleeding, a long-term prospective cohort study may provide the best alternative to a randomized trial to address this important clinical question. In addition study cohorts were all ethnic Chinese so that generalizability of study results to other populations needs further evaluation.

There are a few studies of the association between genetic polymorphisms and the risks of ASA/NSAID induced ulcer or bleeding. A recent Japanese study[79] indicated that the number of COX-1-1676T alleles was a significant risk factor for peptic ulcer in NSAID users. Carrying the CYP2C9 variants is reported a significantly increased risk of NSAID-related GI bleeding[80,81]. The polymorphisms of interleukin-1β (IL-1β)[82] and tumor necrosis factor-α (TNF-α)[83] have been associated with development of peptic ulcer. In a recent investigation, carriage of the IL-1b-511 T allele was significantly associated with peptic ulcer among low-dose ASA users. Recently, one study from Japan[84] showed that SLCO1B1 1b haplotype may identify patients at increased risk for aspirin-induced peptic ulcer. Data on which polymorphisms are significant risk factors for GI events in aspirin/NSAID users are still lacking and further large-scale clinical studies are required and future development in this research area will provide important results for patient individualized management.

Interestingly, a Japanese study[85] reported that the interaction between *H. pylori* infection and low dose ASA use depends on gastric acid. They concluded that in the presence of sufficient amounts of gastric acid, *H. pylori* infection and ASA could synergistically damage gastric mucosal integrity, while in the absence of sufficient amounts of gastric acid, the synergistic effect could be completely counteracted and the infection could even suppress the ASA-related gastropathy. Further studies in larger and different population are needed in order to

confirm these results.

In clinical practice the coincidence of *H. pylori* infection with the intake of low dose ASA and/or NSAID in the same patient is becoming more frequent and may have important clinical and economic consequences. Therefore it is mandatory to establish clear strategies for the management of these patients. Further clinical studies focused on the combined effect of *H. pylori* infection with low dose ASA/NSAID intake should be performed. In addition, economical cost-effectiveness studies of the different strategies (*H. pylori* "test and treat", long term PPI use) should be carried out.

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P- Reviewer: Skok P, Sung J **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Zhang DN

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