Peptic Ulcer Bleeding Risk. The Role of *Helicobacter Pylori* Infection in NSAID/Low-Dose Aspirin Users

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OBJECTIVES: **_Helicobacter pylori_ (_H. pylori_) infection and NSAID/low-dose aspirin (ASA) use are associated with peptic ulcer disease. The risk of peptic ulcer bleeding (PUB) associated with the interaction of these factors remains unclear. The objective of this study was to determine the risk of PUB associated with the interaction between _H. pylori_ infection and current nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose ASA use.**

METHODS: **This was a case-control study of consecutive patients hospitalized because of PUB. Controls were matched by age, sex, and month of admission. _H. pylori_ infection status was determined in all cases and controls by serology. Drug use was determined by structured questionnaire. Adjusted relative risk (RR) associated with different factors, and the interaction between NSAID/ASA and _H. pylori_ infection was estimated by logistic regression analysis.**

RESULTS: **The study included 666 cases of PUB and 666 controls; 74.3% cases and 54.8% controls (RR: 2.6; 95% confidence interval (CI): 2.0–3.3) tested positive for _H. pylori_ infection; 34.5% of cases had current NSAID use compared with 13.4% of controls (RR: 4.0; 95% CI: 3.0–5.4). Respective proportions for low-dose ASA use were 15.8 and 12%, respectively (RR: 1.9; 95% CI: 1.3–2.7). The RR of PUB for concomitant NSAID use and _H. pylori_ infection suggested an additive effect (RR: 8.0; 95% CI: 5.0–12.8), whereas no interaction was observed with ASA use (RR: 3.5; 95% CI: 2.0–6.1).**

CONCLUSIONS: **NSAID, low-dose ASA use, and _H. pylori_ infection are three independent risk factors for the development of PUB, but there were differences in the interaction effect between low-dose ASA (no interaction) or NSAID (addition) use and _H. pylori_ infection, which may have implications for clinical practice in prevention strategies.**

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and low-dose aspirin (ASA) use are three independent and the most important modifiable risk factors in the pathogenesis of gastroduodenal peptic ulcers (1). In clinical practice, the coincidence of *H. pylori* infection with the intake of one of those drugs in the same patient is frequent and may have important clinical consequences. In this way, whether NSAID intake in the presence of *H. pylori* infection may further increase the risk of peptic ulcer is still under intense debate. Clinicians might expect at least an additive if not a synergistic effect on the risk of peptic ulcer. However, despite *H. pylori* and NSAID sharing a number of pathogenic mechanisms, studies on the interaction between these two risk factors has yielded conflicting data leaving this relationship uncertain (2). In addition, in the last years, the use of low-dose ASA has increased as a result of accumulating evidence for its benefits in primary and secondary prevention of cardiovascular and cerebrovascular events (3–5). Low-dose ASA damages the upper gastrointestinal (GI) tract through both local and systemic effects (4,5). Although it is commonly asserted that *H. pylori* infection will increase the risk of ASA-associated GI side effects, the impact and influence of *H. pylori* infection on the incidence of upper GI bleeding (UGIB) in patients taking ASA is also still unclear (6). These conflicting

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data are the result of variability in methods, selection biases, and outcome definition. Furthermore, most studies involve a limited number of patients. A highly quoted meta-analysis (7) analyzed all available endoscopic studies at that time but included only a limited number of studies with serious outcomes such as UGIB.

Therefore, we aimed at evaluating the risk of peptic ulcer bleeding (PUB) associated with the interaction between *H. pylori* infection and current use of NSAIDs or low-dose ASA in a large group of patients presenting with PUB requiring hospitalization.

METHODS

Study design and population

Hospital-based, case–control study with prospective case ascertainment and data collection carried out between 2006 and 2012. Cases and controls were collected in three general hospitals of the Spanish National Health System. Eligible participants were 20–85-year old and free of liver disease, coagulation disorders, or malignancies in the previous 5 years.

Definitions

Case. Patient hospitalized because of major UGIB (hematemesis or melena), which was confirmed by hospital personnel and caused by a peptic ulcer lesion as determined in an endoscopic procedure. Cases with the following conditions were excluded: (a) any other cause of bleeding (gastro-esophageal varices, vascular lesions, tumors, Mallory–Weiss, associated coagulopathy, and esophagitis); (b) patients with unreliable sources of information; (c) patients refusing to participate; and (d) in-hospital bleeding patients. The index date was the first day when the GI bleeding episode was objectively noticed.

Control. Controls matched by age (±5 years), gender, hospital, and month of admission were selected. Controls were obtained either from people accompanying hospitalized patients or from unselected people referred to the hospital outpatient's office for blood extraction as part of general analysis. The index date for controls was the day of the interview.

Exposure. Drug use was considered to be current when the drug was taken up to 7 days before the index date. It was considered to be past when the use ended earlier than 1 week before the index date. Non-use was individual referring no mention of drug use. Cardioprotective ASA (low dose) was defined as any dose no greater than 300 mg/day.

GI disorder history. We classified cases and controls as having a history of ulcer, dyspepsia, or neither condition. A person was defined as having no history of GI disorder if he or she reported no history of dyspepsia or ulcer (uncomplicated or complicated) before the index date. A person was defined as having a history of dyspepsia only if he or she did not report also a history of peptic ulcer. Finally, a person was defined as having a history of peptic ulcer with or without complications (bleeding or perforation) when he or she reported so and found or provided previous hospital reports that confirmed the diagnosis. All of these groups were mutually exclusive.

Data collection

Cases and controls were interviewed by the same persons (a gastroenterologist or a gastroenterology trainee) in each participating center, in general, within 48 h of admission. To ensure reliable data collection, cases and controls were accompanied during the interview by a relative or someone who lived with them. A structured questionnaire of marketed drugs and a careful review of prescriptions were used. Interview data were completed with the patient's family and hospital clinical records concerning endoscopy data. To avoid bias, interviewers were not involved in the design, were not the investigators at each center of the study, and were unaware of the actual objectives of the study. *H. pylori* status infection (positive or negative) was determined in all cases and controls by serology (*H. pylori* enzyme-linked immunosorbent assay immunoglobulin G, Vircell, Santa Fé, Granada, Spain). In a subset of patients, this test showed a good agreement (kappa coefficient =0.608 with previously validated western blot test (Bioblot Helicobacter Biokit SA, Barcelona, Spain)) in other studies conducted by our group (8,9). According to the manufacturer information, the test used in this study has 97% sensitivity and 100% specificity. These figures were obtained by comparing our test in local Spanish patients with other enzyme-linked immunosorbent assay test previously validated in the literature (10,11). Blood samples were obtained at the time of interview. A committee was designated to respond to any questions or doubts arising during the study, and all data were introduced into a single database.

Statistical analysis

Results of continuous variables are expressed as mean with standard deviation (s.d.), whereas qualitative variables are expressed as frequencies and percentages. Bivariate analysis of all clinical variables and drug use was performed by the chi-square test and Student's *t*-test. Conditional logistic-adjusted regression analyses were carried out to compute relative risks (RR) of PUB and their 95% confidence intervals (95% CI). The final multivariate model included age, sex, ulcer history, smoking status, proton pump inhibitor use, anticoagulant use, NSAID, and ASA. We assessed interactions between NSAID or low-dose ASA and *H. pylori*, using one simple term in the model for the join effect. For all tests, a two-sided *P*-value <0.05 was considered statistically significant. The statistical analyses were performed using the SPSS software v 15.00 for Windows (SPSS Ibérica, Madrid, Spain).

RESULTS

Clinical variables, drug use, and *H. pylori* infection

Overall, 666 cases and 666 controls meeting all eligibility criteria were included in the analysis. Mean Hb level was 9.1±2.4 g/dl, and the mean of transfused blood units was 1.6±2.1 in cases. **Table 1** presents frequency distribution and crude and adjusted RRs for age, gender, smoking, complicated or uncomplicated ulcer history, dyspepsia, current drug use, and *H. pylori* infection status.

Table 1. Adjusted relative risk and 95% confidence intervals of upper gastrointestinal peptic ulcer bleeding associated with different clinical risk factors

	Case (*n*, %) *n*=666	Control (*n*, %) *n*=666	*P*[a]	Crude RR (95% CI)	Adjusted RR (95% CI)
Gender (female)	192 (28.8)	192 (28.8)	NS		
Age (mean, s.d.)	61.6 (16.1)	60.4 (15.6)	NS		
Smoking status	168 (25.2)	129 (19.4)	0.010	1.4 (1.1–1.8)	1.4 (1.0–2.0)
Complicated ulcer history	106 (16.0)	12 (1.8)	<0.001	10.4 (5.6–19.0)	6.1 (3.2–11.8)
Uncomplicated ulcer history	165 (24.8)	58 (8.7)	<0.001	3.5 (2.5–4.8)	4.4 (3.1–6.2)
Dyspepsia	77 (11.6)	40 (6.0)	<0.001	2.1 (1.4–3.1)	2.0 (1.3–3.2)
ASA	105 (15.8)	80 (12.0)	0.048	1.4 (1.0–1.9)	1.9 (1.3–2.7)
NSAID	230 (34.5)	89 (13.4)	<0.001	3.4 (2.6–4.5)	4.0 (3.0–5.4)
NSAID and ASA	22 (3.3)	11 (1.7)	0.051	2.0 (1.0–4.2)	2.6 (1.2–5.7)
NSAID or ASA	313 (47.0)	158 (23.7)	<0.001	2.9 (2.3–3.6)	—
PPI	107 (16.1)	166 (24.9)	<0.001	0.6 (0.4–0.8)	0.4 (0.3–0.6)
Anticoagulant	58 (8.7)	26 (3.9)	<0.001	2.3 (1.5–3.8)	1.1 (0.9–1.2)
Helicobacter pylori infection	495 (74.3)	365 (54.8)	<0.001	2.4 (1.9–3.0)	2.6 (2.0–3.3)

ASA, aspirin; CI, confidence interval; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RR, relative risk.
Relative risks were adjusted for age, gender, ulcer history, smoking status, proton pump inhibitors, anticoagulant, NSAIDs, and aspirin use.
[a]A χ^2-test or Student's *t*-test.

Age and gender were matched by protocol; 75.4% of patients were older than 50 years. ASA, NSAID, and anticoagulant current use were significantly more frequent in cases compared with controls. However, current proton pump inhibitor intake was significantly higher in controls. A total of 107 (16.1%) of cases had taken at least one proton pump inhibitor in the week before hospital admission compared with 166 (24.9%) among controls (P<0.001). Tests for *H. pylori* infection were performed in all cases and controls, with positive results in 74.3 and 54.8%, respectively (P<0.001). We found that peptic ulcers in cases were evenly distributed between the duodenum and the stomach (48% in the duodenum and 47.8% in the stomach; in 4.2% of cases, the ulcers were present in both sites).

NSAID and/or low-dose ASA use

Overall, 230 (34.5%) of cases had taken NSAIDs at least in the week before the onset of bleeding compared with 89 (13.4%) among controls, adjusted RR: 4.0 (95% CI; 3.0–5.4). Ibuprofen was the most frequently used NSAID (11.3 vs. 5.9%) followed by ASA (high dose; 12.3 vs. 0.5%), Diclofenac (4.2 vs. 1.2%), and Naproxen (2.1 vs. 1.5%) among cases and controls, respectively. The corresponding percentages for low-dose ASA in cases and controls were 15.8% and 12.0%, respectively, adjusted RR: 1.9 (95% CI; 1.3–2.7).

NSAID or low-dose ASA interaction with *H. pylori* infection

Table 2 describes adjusted RRs for the joint effect of NSAID or ASA use with *H. pylori* infection, taking as reference individuals free of *H. pylori* infection, NSAID, or ASA use, respectively. Both NSAIDs and *H. pylori* infection independently increased the risk of PUB bleeding, although the effect of NSAID use was greater compared with the one estimated for *H. pylori*. The increased risk of PUB for the interaction between current NSAID users with *H. pylori* infection was slightly greater than a simple additive effect. The magnitude of the risk of PUB associated with current ASA use was similar to that observed for *H. pylori* infection. There was no positive interaction between low-dose ASA use and *H. pylori* infection, as the RR of PUB among patients with both factors was less than additive and similar to the risk observed with each of the

Table 2. RRs for the development of peptic ulcer bleeding associated with NSAID/ASA use and *Helicobacter pylori* (*Hp*) status

Factor	RR[a] (95% CI)	Case (*n*)	Control (*n*)
No NSAID—No *Hp*	1	103	261
NSAID—No *Hp*	3.5 (2.0–6.0)	68	40
No NSAID—*Hp*	2.7 (1.9–3.8)	333	316
NSAID—*Hp*	8.0 (5.0–12.8)	162	49
No ASA—No *Hp*	1	136	265
ASA—No *Hp*	2.2 (1.2–4.2)	35	36
No ASA—*Hp*	2.8 (2.0–3.8)	425	321
ASA—*Hp*	3.5 (2.0–6.1)	70	44

ASA, aspirin; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.
[a]Adjusted for age, gender, ulcer history, smoking status, proton pump inhibitors, anticoagulant, NSAIDs, and aspirin use.

Table 3. RRs for the development of either upper gastric or duodenal ulcer bleeding associated with NSAID or ASA use and *Helicobacter pylori* (*Hp*) infection

Factor	Gastric ulcer	Duodenal ulcer
	RR[a] (95% CI)	RR[a] (95% CI)
No NSAID—No *Hp*	1	1
NSAID—No *Hp*	6.2 (2.8–13.8)	2.2 (1.0–4.8)
No NSAID—*Hp*	2.1 (1.3–3.5)	3.3 (2.0–5.5)
NSAID—*Hp*	8.6 (4.3–17.0)	7.8 (4.0–15.2)
No ASA—No *Hp*	1	1
ASA—No *Hp*	2.2 (0.9–5.6)	2.3 (0.9–6.1)
No ASA—*Hp*	2.1 (1.3–3.4)	3.5 (2.2–5.6)
ASA—*Hp*	2.4 (1.1–5.2)	6.3 (2.8–14.1)

ASA, aspirin; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.
[a]Adjusted for age, gender, ulcer history, smoking status, proton pump inhibitors, anticoagulant, NSAIDs, and aspirin use.

individual factors alone. Sub-analysis performed with high-dose ASA (>500 mg/day) showed similar interaction pattern to that seen with NSAIDs (data not shown).

Table 3 shows the adjusted RRs of PUB for the interaction between NSAID or low-dose ASA current use and *H. pylori* infection, separately for gastric and duodenal ulcer. A synergistic interaction was present between NSAID use and *H. pylori* infection for the risk of duodenal ulcer bleeding, whereas the effect of these two risk factors was additive for gastric ulcer bleeding. No interaction was observed among ASA users with *H. pylori* infection for gastric ulcer bleeding, whereas there was an additive effect for duodenal ulcer bleeding.

DISCUSSION

This large case–control study has confirmed that *H. pylori* infection and NSAID or low-dose ASA current use are independent risk factors for the development of PUB (1). In our study, low-dose ASA increased the risk of PUB twofold, *H. pylori* infection threefold, and NSAIDs fourfold. However, the combination between these factors shows that the joint effect between *H. pylori* infection and NSAID or low-dose ASA use is different.

A systematic review including 25 different studies (7) concluded that there was synergism for the development of peptic ulcer disease between *H pylori* infection and NSAID use. When they looked specifically at ulcer bleeding, the RR for the interaction between these two factors was marginally additive. This meta-analysis had several limitations. For instance, the prevalence of *H pylori* infection could not be adjusted by age because of the lack of individual patients' data; NSAID takers had various underlying disorders, and different control populations were used. Furthermore, definitions of patients exposed to NSAIDs or ASA were also diverse. Different definitions of ulcer could also be a source of bias. Finally, the conclusions drawn from subgroup analyses (like PUB) were limited by small sample sizes. Our case–control study tried to solve most of these limitations. The presence of *H. pylori* infection in NSAID users increased the RR of PUB similar to the addition of each individual factor alone, suggesting that these two factors act independently and in an additive manner. Therefore, patients having these two factors are at an increased risk of developing a bleeding peptic ulcer event compared with patients taking NSAIDs alone or infected only by *H. pylori*. These results may have clear implications for clinical practice, as elimination of both factors is essential to maximally reduce the risk, and eradication of *H. pylori* infection among NSAID users should have an impact on the resulting risk.

However, a different association was observed with low-dose ASA and *H. pylori* infection. Both were independent risk factors for PUB, but there was no suggestion of a positive interaction between these two factors. This also may have important clinical implications, as, based on these data, *H. pylori* eradication in low-dose ASA users should not have a major impact on the risk of developing PUB, which differs from previously reported studies (12–14). Reasons for the difference in our findings with previous reports may be partly due to study designs, heterogeneous patient populations, validity of exposure information, and different clinical outcomes evaluated. Actually, the vast majority of data concerning the interaction between *H. pylori* and low-dose ASA are for the most part limited to Asian population and to extrapolation of data from studies evaluating NSAIDs, despite major mechanistic differences between the two types of agents. Only two randomized controlled trials (RCTs) have been published on this issue with low-dose ASA (15), both of them in Asian population and for secondary prevention of UGIB: one from Chan and colleagues (14) and the other from Lai and colleagues (16). In addition, a recent systematic review by Fletcher *et al.* (17), including 13 studies, concluded that the current available evidence was insufficient to perform a meta-analysis and that no firm conclusion could be drawn regarding the impact of *H. pylori* on UGIB risk in low-dose ASA users. Our study provides additional evidence to evaluate this interaction. Compared with individuals free of *H. pylori* infection and no low-dose ASA use, the RR for PUB in low-dose ASA users and *H. pylori*-infected individuals was 2.2 and 2.8, respectively, with a similar increased risk when both factors are present (RR: 3.5), supporting no major interaction between low-dose ASA use and *H. pylori* infection for the development of UGIB.

Another important finding concerning the interaction between these factors is ulcer location, as the pathogenesis of gastric and duodenal ulcers is somehow different (1). Most published studies did not separate patients by ulcer location and reported data for both ulcers together (18–21). It is widely believed that NSAID intake increases the risk of gastric ulcer to a greater extent compared with duodenal ulcer, whereas the location of ulcers associated with *H. pylori* infection strongly depends on the distribution of gastritis, which in turn is related to the level of gastric acid output (2). Our analysis suggests that NSAID use alone has a greater effect in the development of gastric than duodenal ulcers (RR: 6.2 (2.8–13.8) vs. 2.2 (1.0–4.8), respectively), whereas the risk of duodenal ulcer related to *H. pylori* infection was greater compared

with gastric ulcer (RR: 3.3 (2.0–5.5) vs. 2.1 (1.3–3.5), respectively): yet, it should be noted that all these difference were not statistically significant. The joint effect of NSAID use and *H. pylori* infection was additive for gastric ulcer bleeding and nearly synergistic for duodenal ulcer bleeding (**Table 3**). However, the effect of low-dose ASA and *H. pylori* infection in gastric and duodenal ulcer seems, in some way, different. When examining the joint effect of low-dose ASA and *H. pylori* infection according to ulcer site, no interaction was observed with gastric ulcer bleeding and close to an additive effect with duodenal ulcer bleeding.

Strengths of our study include the large sample size, the well-defined logistics of case ascertainment and control selection, the validation of the cause of the bleeding in all patients with the original clinical records, and the structured data collection methods of data on prescription and non-prescription drug consumption equally implemented among cases and controls. Limitations are *H. pylori* diagnosis based on serology, which may reflect not only present but also recent or past *H. pylori* infection. Yet, this minor misclassification will have equally applied to cases and controls and should not have an impact on the estimations of the RR. On the other hand, *H. pylori* status was determined among all cases and controls with the same method reducing internal variability, and, although the test showed good correlation with previous *H. pylori* tests used in former studies, no specific local validation was performed. Observational studies are always open to residual confounding that can not always be completely controlled. Here, we reported estimates of RR adjusted by most widely recognized independent risk factors. In addition, it is also important to mention that bleeding from the lower small intestine was not examined.

In summary, our data provide additional evidence that NSAID use, low-dose ASA use, and *H. pylori* infection are all independent risk factors for the development of PUB due to either gastric or duodenal peptic ulcer. We have shown that there is at least an additive effect between *H. pylori* infection and NSAID use. More importantly, the data show no interaction between low-dose ASA and *H. pylori* infection for the development of bleeding peptic ulcer, especially gastric ulcer bleeding, which may have clear implications for clinical practice as low-dose ASA intake in patients infected by *H. pylori* will carry a similar risk of developing PUB to patients not infected by *H. pylori*, making unnecessary the eradication in this frequent clinical scenario. Therefore, prevention strategies in low-dose ASA users should be implemented based on the presence of other risk factors in this population.

CONFLICT OF INTEREST

Guarantor of the article: Carlos Sostres, MD.

Specific author contributions: Carlos Sostres—involved in the study design, as well as the planning, conducting, interpretation of data, and in drafting/editing the manuscript. Patricia Carrera—involved in statistical analysis, interpretation of data, and drafting/editing the manuscript. Rafael Benito—involved in the performance of serological determination of *Helicobacter pylori* infection, analysis, and interpretation of data. Pilar Roncales—involved in patient collection, sample collection, and acquisition of data. María Arruebo—involved in patient collection, sample collection, and acquisition of data. Maria Teresa Arroyo—involved in the study design, as well as the planning, conducting, interpretation of data, and in drafting/editing the manuscript. Luis Bujanda—involved in patient collection, sample collection, and acquisition of data. Luis Alberto García-Rodriguez—involved in the study design, as well as the planning, conducting, interpretation of data, and in drafting/editing the manuscript. Angel Lanas—involved in the study design, as well as the planning, conducting, interpretation of data, and in drafting/editing the manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ NSAID/ASA use and *Helicobacter pylori* (*H. pylori*) infection are independent risk factors for the development of peptic ulcers.
- ✓ The true effect of the interaction between these factors and peptic ulcer bleeding (PUB) is still unclear.
- ✓ *H. pylori* eradication in naive nonsteroidal anti-inflammatory drug (NSAID) users is associated with a significant reduction in the incidence of endoscopic ulcers in patients starting NSAIDs.
- ✓ The effect of *H. pylori* eradication on the incidence of endoscopic ulcers in naive aspirin (ASA) users is unknown.
- ✓ Current European and US guidelines recommend test and treat *H. pylori* infection in NSAID or ASA users who are at risk of PUB.

WHAT IS NEW HERE

- ✓ There is an additive interaction between *H. pylori* infection and NSAID use on the risk of PUB.
- ✓ There is no interaction between low-dose ASA use and *H. pylori* infection for the development of PUB.
- ✓ These data suggest that *H. pylori* eradication might not reduce the risk of low-dose ASA-related PUB.

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