Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis

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Authors' objectives
The objectives were three-fold:

- to review the relation between Helicobacter pylori (H. pylori) infection and non-steroidal anti-inflammatory drug (NSAID)-associated gastropathy;
- to assess the presence and magnitude of any possible interaction between these two risk factors on peptic-ulcer disease; and
- to examine any possible interaction between the two risk factors with respect to the site of the ulcer or bleeding.

Searching
MEDLINE, PubMed and the Cochrane Library were searched from 1984 to October 2000 using the following search terms (both as MeSH terms and as keywords): 'NSAIDs', 'pylori', and 'ulcer' or 'ulcer bleeding'. Articles written in any language were considered. A search on links to related articles was conducted wherever possible. The reference lists of all the articles reviewed and the original studies retrieved were also checked. The following journals were manually searched from January 1989 to October 2000 for potential relevant articles: Gastroenterology; Gut; American Journal of Gastroenterology; Alimentary Pharmacology and Therapeutics; Digestive Disease Sciences; European Journal of Gastroenterology and Hepatology; Scandinavian Journal of Gastroenterology; Journal of Clinical Gastroenterology; The Lancet; New England Journal of Medicine; Archives of International Medicine; British Medical Journal; JAMA; Annals of Internal Medicine; and Quarterly Journal of Medicine.

Study selection
Study designs of evaluations included in the review
Cross-sectional, case-control, or cohort studies. Review articles, duplicate publications, and studies published in abstract form were excluded.

Specific interventions included in the review
NSAIDs. Studies looking at the eradication of H. pylori were excluded.

Participants included in the review
Adult patients taking NSAIDs or patients with peptic-ulcer bleeding or disease. Studies in which patients had reported recent use (3 to 4 weeks before study entry) of antibiotics or anti-ulcer drugs, or a history of gastric surgery, were excluded. Studies that included all patients with peptic-ulcer disease, patients recently exposed to H2-receptor antagonists, or patients with ulcer perforation were also excluded. For the analysis of ulcer bleeding, studies that allowed the enrolment of patients with non-ulcer gastrointestinal bleeding or gastric tumours and those receiving corticosteroids or anticoagulants, were excluded.

For studies that examined the relationship between H. pylori infection and NSAID use in patients with uncomplicated peptic-ulcer disease, the mean age (where reported) ranged from 48 to 79.5 years. The definition of NSAID use (where reported) ranged from daily use for less than 4 weeks, to chronic use. The ulcer size (where reported) in the majority of studies was greater than or equal to 0.5 cm. Most of the studies included patients that used NSAIDs for osteo- or rheumatoid arthritis.

For studies that examined the relationship between H. pylori infection and NSAID use in patients with peptic-ulcer bleeding, the mean age (where reported) ranged from 55 to 80 years. NSAID use (where reported) ranged from taken less than one week before study entry, to within 4 weeks before entry.
Outcomes assessed in the review
The studies investigated the prevalence of peptic-ulcer disease in patients taking NSAIDs; the prevalence of H. pylori infection and NSAID use in patients with peptic-ulcer bleeding; or the relationship between H. pylori infection and NSAID-associated peptic-ulcer disease. Peptic-ulcer disease or ulcer bleeding had to be documented by endoscopy, and H. pylori infection had to be confirmed by histopathology, culture, serology, or urea breath test.

How were decisions on the relevance of primary studies made?
The titles and abstracts of all potentially relevant studies were screened for their relevance to the study question before the full articles were retrieved. If the title and abstract were ambiguous then the full article was scrutinised for relevance. Two independent reviewers went through the searches.

Assessment of study quality
Validity was assessed using criteria modified from the guidelines for reading case-control studies proposed by Lichtenstein et al. (see Other Publications of Related Interest). The criteria were: an explicit statement of the research question and its relevance to the question of the review; the methods for identifying cases and controls and their matching techniques; a clear statement of the exclusion criteria for cases and controls; definition of NSAID exposure and peptic ulcer; the methods used for the data collection; and a description of analytical methods and sample size. The validity criteria were used to rank studies. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Any disagreements were resolved by discussion and consensus between the researchers.

Data extraction
The data were extracted by two reviewers by means of a structured spreadsheet. A third reviewer was consulted in the case of disagreement. The major items extracted were: the primary question of an individual study; study design; characteristics of the case and control populations; the major exclusion criteria; definition of ulcer or ulcer bleeding; the diagnostic method for ulcer or ulcer bleeding; the site of the ulcer; definition of NSAID use; the type of NSAID; the test for H. pylori infection; the total number of cases and controls; the percentage of smokers; concurrent treatment; and prevalence of H. pylori infection and ulcer. Where necessary, the original investigators were contacted for further information on the site of the ulcer or H. pylori status.

Methods of synthesis
How were the studies combined?
The summary odds ratio (OR) and 95% confidence intervals (CIs) were calculated using the DerSimonian and Laird method (random-effects model). Subgroup or sensitivity analyses were carried out where possible.

How were differences between studies investigated?
The following considerations were applied to determine the homogeneity of the individual studies for meta-analysis: study design, matching techniques in case-control studies, methods used for measuring outcome, and biological plausibility. The authors also took into account the summary estimate of the OR and the results of the tests for homogeneity. The Breslow-Day method was used to test for homogeneity and, in the presence of statistical heterogeneity, the authors searched for any sources of clinical heterogeneity.

Results of the review
Twenty-five studies were included. Sixteen case-control, cohort and cross-sectional studies examined the relation between H. pylori infection and NSAID use in patients with uncomplicated peptic-ulcer disease (1,625 patients taking NSAIDs). Nine case-control studies examined the relation between H. pylori infection and NSAID use in patients with peptic-ulcer bleeding (893 patients).

Uncomplicated peptic-ulcer disease (1 cohort study, 7 case-controlled studies and 8 cross-sectional studies).
Uncomplicated peptic-ulcer disease was statistically significantly more common in patients positive for H. pylori, than in those negative: 41.7% (341 out of 817) versus 25.9% (209 out of 808). The OR was 2.12 (95% CI: 1.68, 2.67; Breslow-Day test, p=0.43).

Similar results were found when studies were grouped by study design. In five controlled studies (matched for age and/or gender), H. pylori infection was diagnosed in 46.8% (180 out of 385) of the NSAID takers and 46.0% (127 out of 276) of the controls. There was no statistically-significant difference in the pooled prevalence of the infection between the two groups: the OR was 0.88 (95% CI: 0.28, 2.79; Breslow-Day test, p<0.001). However, peptic ulcer disease was statistically significantly more common in NSAID takers than in controls, irrespective of H. pylori infection: 35.8% (138 out of 385) versus 8.3% (23 out of 276). The OR was 5.14 (95% CI: 1.35, 19.6; Breslow-Day test, p<0.001).

The risk of peptic-ulcer disease associated with H. pylori infection, without NSAID exposure, was 18.1 (95% CI: 2.64, 124).

The risk of peptic-ulcer disease associated with NSAID use, without H. pylori infection, was 19.4 (95% CI: 3.14, 120).

In the presence of H. pylori infection, the use of NSAIDs increased the risk of peptic-ulcer disease 3.55-fold (95% CI: 1.26, 9.96).

H. pylori infection increased the risk of peptic ulcer disease in NSAID takers 3.53-fold (95% CI: 2.16, 5.75).

Compared with H. pylori negative individuals not taking NSAIDs, the risk of ulcer in H. pylori infected NSAID takers was 61.1 (95% CI: 9.98, 373). Four controlled studies provided data on site of ulcer.

The risk of developing a gastric ulcer associated with H. pylori infection was 1.72 (95% CI: 0.92, 3.20) among patients taking NSAIDs, and 4.07 (95% CI: 0.39, 42.9) among patients not taking NSAIDs.

The risk of developing a duodenal ulcer associated with H. pylori infection was 2.77 (95% CI: 1.12, 6.88) among patients taking NSAID, and 9.14 (95% CI: 1.02, 81.8) among patients not taking NSAIDs.

Peptic-ulcer bleeding (9 case-control studies).

Overall, the prevalence of H. pylori infection was 73.6% (657 out of 893) in the cases and 67.3% (674 out of 1,002) in the controls. The OR was 1.67 (95% CI: 1.02, 2.72; Breslow-Day test, p<0.001).

The prevalence of NSAID use (7 studies) was 59.7% (391 out of 655) in the cases and 27.4% (230 out of 839) in the controls. The OR was 4.79 (95% CI: 3.78, 6.06; Breslow-Day test, p=0.3).

For six studies that had controls matched for age and/or gender, the pooled prevalence of H. pylori infection was 70.2% (450 out of 641) in the cases and 56.1% (368 out of 656) in the controls. The OR was 1.79 (95% CI: 0.97, 3.32; Breslow-Day test, p<0.001).

The prevalence of NSAID use was 58.6% (357 out of 609) in the cases and 23.5% (150 out of 637) in the controls. The OR was 4.85 (95% CI: 3.77, 6.23; Breslow-Day test, p=0.21).

The risk of developing ulcer bleeding increased to 6.13 (95% CI: 3.93, 9.56) when both factors were present.

Authors' conclusions
Both H. pylori infection and NSAID use independently and significantly increased the risk of peptic ulcer and ulcer bleeding. There was synergism for the development of peptic ulcer and ulcer bleeding between H. pylori infection and NSAID use. Peptic-ulcer disease was rare in H. pylori negative non-NSAID takers.

CRD commentary
This was a fairly well-conducted review. The aims were clearly stated and the inclusion and exclusion criteria were well-defined. The electronic database search was not extensive, no attempt was made to look for unpublished data, and studies published in abstract form were excluded. The possibility of publication bias was not evaluated and cannot, therefore, be ruled out. The selection of the papers for inclusion and the data extraction were undertaken in a systematic way by more than one reviewer. The validity of the included trials was assessed, although it was not reported how many of the reviewers were involved in this process. However, it was noted that disagreements were resolved by discussion, which implies that more than one reviewer was involved.

Relevant details of the primary studies were tabulated. Studies were pooled appropriately using a random-effects model and, where statistical heterogeneity was present, the source of clinical heterogeneity was investigated and the pooled effect recalculated.

The authors’ conclusions follow from the results.

**Implications of the review for practice and research**
The authors did not report any implications for further research and practice.

**Bibliographic details**

**PubMedID**
11809181

**DOI**
10.1016/S0140-6736(02)07273-2

**Other publications of related interest**

This additional published commentary may also be of interest. Helicobacter pylori and peptic-ulcer disease [correspondence]. Lancet 2002;359:1943-4.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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**Record Status**
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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.