H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer

[Reviews]

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Abstract

Background: Peptic ulcer is the main cause for upper gastrointestinal haemorrhage, and Helicobacter pylori infection is the main etiologic factor for peptic ulcer disease. Maintenance antisecretory therapy has been the standard long-term treatment for patients with bleeding ulcers to prevent recurrent bleeding. On the other hand, the precise efficacy of H. pylori eradication for the prevention of rebleeding from peptic ulcer is unknown.

Objectives: To compare the efficacy of H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

Search strategy: We searched the Cochrane Controlled Trials Register (the Cochrane Library issue 4, 2003), MEDLINE (January 1966 to January 2004), EMBASE (January 1988 to January 2004), CINAHL (January 1982 to January 2004), and reference lists of articles. We also conducted a manual search from several congresses. The search strategy was re-run in January 2005, but no new trials were found.

Selection criteria: Controlled clinical trials comparing the efficacy of H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

Data collection and analysis: Extraction and quality assessment of studies were done by two reviewers. Study authors were contacted for additional information.

Main results: Seven studies with a total of 578 patients were included in the first meta-analysis: mean percentage of rebleeding in H. pylori eradication therapy group was 2.9%, and in the non-eradication therapy group without subsequent long-term maintenance antisecretory therapy it was 20% (OR 0.17, 95% CI 0.10 to 0.32; there was no statistical evidence of heterogeneity; NNT was 7, 95% CI 5 to 11). Three studies with a total of 470 patients were included in the second meta-analysis: mean percentage of rebleeding in H. pylori eradication therapy group was 1.6%, and in non-eradication therapy group with long-term maintenance antisecretory therapy it was 5.6% (OR 0.25, 95% CI 0.08 to 0.76; heterogeneity was not demonstrated; NNT was 20, 95% CI 12 to 100).
Subanalysis. Excluding patients taking non-steroidal anti-inflammatory drugs (NSAIDs) at the
time of recurrent bleeding resulted in a rebleeding rate of 2.7% (first meta-analysis) or 0.78%
(second meta-analysis) in the group receiving H. pylori eradication therapy. When only patients
with H. pylori eradication success were included, rebleeding rate was 1.1% in H. pylori eradication
therapy group, and NNT decreased from 7 to 6. In some cases, recurrence of H. pylori infection
seemed to be responsible for recurrence of bleeding.

Authors' conclusions: Treatment of H. pylori infection is more effective than antisecretory
non-eradicating therapy (with or without long-term maintenance antisecretory therapy) in
preventing recurrent bleeding from peptic ulcer. Consequently, all patients with peptic ulcer
bleeding should be tested for H. pylori infection, and eradication therapy should be prescribed to H.
pylori-positive patients.

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Plain language summary

For people who have had a bleeding peptic ulcer caused by Helicobacter pylori, treatment with
antibiotics more effectively prevents gastrointestinal re-bleeding than acid-suppressing drugs.

Peptic ulcers are caused by acidic stomach juices damaging the lining of the stomach (gastric
ulcer) or upper small intestine (duodenal ulcer). This causes pain, indigestion and sometimes,
bleeding. Bleeding in the gut can be life-threatening. Several treatments aim to heal the ulcer and
prevent future bleeding. These include acid-suppressing drugs and antibiotics to treat Helicobacter
pylori, a bacterium that causes most peptic ulcers. The review found that antibiotics more
effectively prevented re-bleeding than acid-suppressing drugs in people with peptic ulcers.
Antibiotics when Helicobacter pylori infection is present are also cheaper and more convenient than
long-term acid-suppressing drugs.

Background

Upper gastrointestinal haemorrhage is a major cause of morbidity, mortality and medical care
costs, with peptic ulcer being the most frequent source of bleeding (Laine 1994). It has been
estimated that approximately 2-3% of duodenal ulcer patients who are not receiving antisecretory therapy are likely to develop haemorrhage during each year of follow-up study, giving a cumulative risk of haemorrhage after 5 years of approximately 10-14% (Mignon 1994). Furthermore, patients whose ulcers have bled once have an increased risk of further rebleeding, compared with those with uncomplicated ulcer disease. Thus, among patients who present with a bleeding ulcer, approximately one-third will develop recurrent bleeding in the following 1-2 years, and 40-50% within the subsequent 10 years, if left untreated after ulcer healing (Petersen 1995; Laine 1996). Furthermore, patients with bleeding ulcers account for an overall mortality rate that has remained around 5 to 10% for the past 50 years, despite improved medical and surgical treatments, the development of diagnostic and therapeutic endoscopy, and the availability of intensive care units (Gilbert 1990; Penston 1992; Laine 1994).

Maintenance antisecretory therapy has been the standard long-term treatment for patients with bleeding ulcers to prevent recurrent bleeding, despite the fact that only two randomised studies have specifically examined such options in patients with peptic ulcer haemorrhage (Murray 1988; Jensen 1994). The first study found no significant difference in the rate of recurrent bleeding between ranitidine maintenance therapy and placebo, but the number of bleeding episodes was so small that a treatment benefit could not be demonstrated (Murray 1988); the second study reported significantly fewer episodes of haemorrhage among patients taking ranitidine maintenance antisecretory regimen when compared with placebo (Jensen 1994).

Helicobacter pylori (H. pylori) infection is the main etiologic factor for peptic ulcer disease. However, although the role of this micro-organism on non-complicated peptic ulcer has been definitively established (Kuipers 1995), the precise relationship between H. pylori and complicated ulcer disease has hardly been studied (Gisbert 2003). H. pylori eradication has been demonstrated to dramatically reduce the rate of ulcer recurrence (Hopkins 1996). Therefore, it would seem logical to assume that H. pylori cure would also represent an effective strategy to prevent recurrence of ulcer bleeding. In 1994, the National Institutes of Health (NIH) Consensus Conference panel stated that, although preliminary studies indicate that cure of H. pylori infection prevents recurrent ulcer bleeding at rates equal to those of maintenance antisecretory therapy, until these studies can be confirmed, maintenance antisecretory 'may be prudent' in such patients even after H. pylori eradication, in view of high risks associated with rebleeding (NIH 1994). Two years later, in 1996, the NIH Consensus Conference did not go any further, stating that 'several trials indicate that H. pylori eradication also reduces the recurrence of ulcer complications, but the magnitude of this reduction remains to be firmly established' (Soll 1996).

Although several authors have administered H. pylori eradication treatment to patients with a history of peptic ulcer haemorrhage with the intention to prevent recurrence of bleeding, only a few studies have included a control group treated with 'traditional' antisecretory non-eradicating therapy (followed or not by long-term maintenance antisecretory therapy). Furthermore, the number of patients included in these 'eradication' studies has been small and, as the incidence of rebleeding episodes is relatively low (especially when antisecretory maintenance treatment is prescribed and follow-up limited), efficacy differences between groups may not be demonstrated due to a problem of statistical power of individual studies. Consequently, as the true efficacy of H. pylori eradication for the prevention of recurrent bleeding from peptic ulcer is unknown, it remains
unclear whether maintenance antisecretory therapy must be continued or stopped in patients with a history of peptic ulcer haemorrhage and prior H. pylori eradication.

Finally, in addition to efficacy reasons, other relevant arguments may advocate the use of eradication therapy instead of maintenance antisecretory treatment. Firstly, the cost of antibiotic therapy is lower than long-term management by antisecretory drugs, mainly because the financial outlay for medication in the former approach is not cumulative as with the later. Secondly, one disadvantage of maintenance antisecretory therapy is the requirement for long-term compliance, which may not be sustained but wane, especially when symptoms are absent. And thirdly, it seems obvious that 7-10 days of antibiotic therapy is more convenient for the patients than many years of daily continuous antisecretory treatment.

With these antecedents, we aimed to perform a systematic review and a meta-analysis to compare the efficacy of H. pylori eradication therapy vs. antisecretory non-eradication therapy (followed or not by long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

**Objectives**

To compare the efficacy of H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer.

**Criteria for considering studies for this review**

**Types of studies**

Controlled clinical trials were eligible for inclusion in the review.

**Types of participants**

Patients with a previous episode of peptic ulcer bleeding.

Patients were included if bleeding was severe enough to warrant hospitalisation, haematemesis or melena was evident, or a drop in haemoglobin level of more than 2 g/dL occurred.

The presence of an ulcer had to be documented endoscopically and no other potential bleeding source had to be found during initial evaluation.

Studies designed to follow patients up for less than 6 months were excluded.

Studies with all patients taking NSAIDs were excluded. H. pylori infection and NSAIDs seem to be mainly independent risk factors for peptic ulcer bleeding ([Hawkey 2001](#)). If all patients were taking NSAIDs prior to the bleeding episode, then the efficacy of H. pylori eradication for the prevention of recurrent bleeding in these patients would be masked, as most complications would be attributable to NSAIDs and therefore not prevented by eradicating the organism.

**Types of intervention**

H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy).
Types of outcome measures

Recurrence of bleeding during follow-up (after prescribing eradication or antisecretory treatment) of more than 6 months.

Rebleeding during follow-up was assessed with the same criteria used for initial evaluation.

Search methods for identification of studies

See: methods used in reviews.

Searches were conducted to identify all published and unpublished controlled clinical trials. Articles published in any language were included.

Trials were identified by searching the Cochrane Library (Issue 4 - 2003), MEDLINE (January 1966 - January 2004), EMBASE (January 1980 - January 2004) and CINAHL (January 1982 - January 2004). The search strategy was re-run in January 2005, but no new trials were found.

The following search strategy was constructed by using a combination of subject headings and textwords relating to the use of antisecretory therapies in the prevention of rebleeding in peptic ulcer patients. The standard Cochrane search strategy filter for identifying randomised controlled trials was applied to all searches.

MEDLINE search strategy:
randomized controlled trial.pt.
controlled clinical trial.pt.
ratedinated controlled trials.sh.
random allocation.sh.
double blind method.sh.
single-blind method.sh.
or/1-6
(animal not human).sh.
7 not 8
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 blind$).mp. or mask$.ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/10-17
18 not 8
19 not 9
comparative study.sh.
ext exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$).mp. or volunteer$.ti,ab.
or/21-25
26 not 8
27 not (9 or 20)
9 or 20 or 28
exp peptic ulcer hemorrhage/
exp peptic ulcer perforation/
(bleed$ adj5 ulcer$).tw.
(rebleed$ adj5 ulcer$).tw.
(recurrent adj5 bleed$ adj5 ulcer$).tw.
(acute adj5 bleed$ adj5 ulcer$).tw.
gastrointestinal adj5 bleed$.tw.
gastrointestinal adj5 rebleed$.tw.
gastrointestinal adj5 hemorrhag$.tw.
gastrointestinal adj5 haemorrhag$.tw.
ulcer adj5 hemorrhag$.tw.
ulcer adj5 haemorrhag$.tw.
The Trials Search Co-ordinator for the Cochrane UGPD Group scanned the results of the electronic searches and removed all the obviously irrelevant references. These results were then independently assessed by two reviewers to ascertain if they were eligible for inclusion in the review.

Reference lists from the trials selected by electronic searching were handsearched to identify further relevant trials. Review articles examining the role of H. pylori infection on gastroduodenal haemorrhage were also searched to identify articles which met the inclusion criteria.

We also conducted a manual search of abstracts from 1995 to 2003 from the International Workshop on Gastroduodenal Pathology and Helicobacter pylori (EHPSG) published in Gut, the American Digestive Disease Week (DDW) published in Gastroenterology and the United European Gastroenterology Week (UEGW) published in Gut.

We included abstracts from congresses on the grounds that many negative studies are never published as a full paper, and the inclusion of abstracts thus prevents, or at least reduces, publication bias. Authors of trial reports published only as abstracts were contacted and asked to contribute full datasets or completed papers.

Abstracts of the articles selected in each of these multiple searches were reviewed and those meeting the inclusion criteria were recorded.

**Methods of the review**

**Selection of studies.**

Only studies that clearly state information about the number of treated patients and the number of patients with recurrent bleeding in each therapeutic group (H. pylori eradication group and non-eradication group) were included.

The success of eradication therapy had to be based on the negative results of two tests or one test repeated twice during follow-up in order to make sure that H. pylori has been eliminated.

H. pylori eradication success or failure had to be confirmed at least 4 weeks after antibiotic treatment has been completed.
The selection criteria were applied independently by two reviewers according to the pre-stated eligibility criteria, and where disagreements occurred they were resolved by consensus.

Assessment of study quality

The quality of the studies was assessed using the score proposed by Jadad et al (Jadad 1996) based on 3 items: 1) Randomisation; 2) Double blinding; and 3) Description of withdrawals and dropouts. The items are presented as questions to elicit yes or no answers. Points awarded for items 1 and 2 depended on the quality of the description of the methods to generate the sequence of randomisation and/or on the quality of the description of the method of double blinding. If the trial had been described as randomised and/or double blind, but there was no description of the methods used to generate the sequence of randomisation or the double blinding conditions, one point was awarded in each case. If the method of generating the sequence of randomisation and/or blinding had been described, one additional point was given to each item if the method was appropriate. A method to generate randomisation sequences was regarded as adequate if it allowed each study participant to have the same chance of receiving each intervention, and if the investigators could not predict which intervention was next. Double blinding was considered appropriate if it was stated or implied that neither the person doing the assessment nor the study participant could identify the intervention being assessed. Conversely, if the method of generating the sequence of randomisation and/or blinding was described but not appropriate, the relevant item was given zero points. The third item, withdrawals and dropouts, was awarded as zero points for a negative answer and one point for a positive. For a positive answer, the number of withdrawals and dropouts and the reasons had to be stated in each of the comparison groups. If there were no withdrawals, it should have been stated in the report.

Quality assessment of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus.

Data extraction

The following variables were extracted in a predefined data extraction form (see table of included studies): author, year of publication, type of publication (complete article or abstract), type of participants (duodenal or gastric ulcer, or both), NSAID use previous to the inclusion in the study (yes/no; if yes, percentage of patients taking NSAIDs), intervention (H. pylori eradication treatment or antisecretory treatment; including drugs, dose, schedule and duration), maintenance antisecretory therapy (yes/no; if yes, drug, dose and schedule of administration), follow-up (months), quality score (see Jadad score in previous section, including items of randomisation, double blinding, and description of withdrawal/dropouts; concealment of allocation of the sequence of randomisation was also separately assessed), and rebleeding rate (raw numbers and percentages in each therapeutic group).

Publications identified as duplicates were excluded; when more than one version of the same trial was retrieved, only the most recent data were considered.

Extraction of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus.
Data synthesis

The main outcome considered in this study was 'percentage of patients having recurrence of bleeding' due to peptic ulcer.

Dropouts were considered as not having recurrent bleeding, as it is the most frequent outcome (see introduction section). In addition, it seems to be exceptional that patients having recurrent bleeding are lost for follow-up, as it is logical to assume that these patients will be finally included in the analysis.

The heterogeneity of effects throughout studies was appraised using a heterogeneity test based on the chi-square test. Due to the low power of this test, a minimum cut-off p value of 0.1 was established as a threshold of homogeneity: lower values indicated heterogeneity, and prevented us from relying on the combination of the study results.

Separate meta-analysis were performed for studies comparing: 1) H. pylori eradication therapy vs. non-eradication therapy with antisecretors without subsequent long-term maintenance antisecretory therapy; and 2) H. pylori eradication therapy vs. non-eradication therapy with antisecretors followed by long-term maintenance antisecretory therapy.

Meta-analysis was performed combining the Odds Ratios (OR) of the individual studies in a global OR, using both a random effect model (DerSimonian and Laird) and a fixed effect model (Peto method). Significance and 95% confidence intervals (95% CI) were provided for the combined OR. All calculations were performed with the Cochrane freeware program Review Manager 4.2.

'Absolute risk reduction' (ARR; or 'risk difference'), 'relative risk reduction' (RRR), and 'numbers needed to treat' (NNT) to prevent one episode of rebleeding were also calculated for the pooled data.

Subanalysis/Sensitivity analysis

Subanalyses were planned a priori depending on: Quality of the studies (based on quality score proposed by Jadad, see appropriate section), type of ulcer disease (duodenal/gastric), and duration of follow-up. Furthermore, subanalyses excluding those studies where rebleeding could be potentially explained by NSAID use were also planned. Finally, assessment of potential role for H. pylori eradication failure, or recurrence of H. pylori infection, in patients with rebleeding were also planned.

Description of studies

Excluded studies and respective causes of exclusion are summarized in the table 'Characteristics of excluded studies'. As shown in the table, causes of exclusion were: rebleeding not evaluated, less than six-month follow-up, no control group (all patients received H. pylori eradication therapy), no previous upper gastrointestinal bleeding, all patients received NSAIDs, no H. pylori eradication group, or control group included only H. pylori-negative patients or patients with unknown H. pylori status.
Hence, 7 studies finally fulfilled the inclusion criteria and contained data for the first planned meta-analysis: H. pylori eradication therapy vs. non-eradication therapy with antisecretors without subsequent long-term maintenance antisecretory therapy (Arkkila 2003; Bataga 1997; Graham 1993; Jaspersen 1995a; Lai 2000; Rokkas 1995; Vcev 1996). Detailed characteristics of the studies are shown in the table 'Characteristics of included studies'. Three-hundred and seventy five patients were included in the eradication therapy group, while 203 were included in the group receiving non-eradication therapy. Details of eradication and antisecretory treatment of included studies are summarized in Table 01. Three studies prescribed, as eradication regimen, a bismuth-based triple therapy, three other studies prescribed omeprazole-based dual therapy (omeprazole plus amoxicillin), and in one study both eradication regimens were used. These eradication regimens were administered for 10 to 14 days.

With respect to the second planned comparison (H. pylori eradication therapy vs. non-eradication therapy with antisecretors followed by long-term maintenance antisecretory therapy), 3 studies fulfilled the inclusion criteria (Riemann 1997; Santander 1996; Sung 1997), detailed characteristics of them also being shown in the table 'Characteristics of included studies'. Two-hundred and fifty seven patients were included in the eradication therapy group, while 213 received long-term maintenance antisecretory therapy. Details of eradication and antisecretory treatment of included studies are summarized in Table 01. One study prescribed, as eradication regimen, a bismuth-based triple therapy, a second study prescribed omeprazole-based dual therapy (omeprazole plus amoxicillin), and in a third study both regimens were used. These eradication regimens were administered for 7 to 12 days. Antisecretory maintenance therapy with ranitidine 150 mg od was administered in two studies, while in a third study ranitidine 150 mg od or omeprazole 20 mg od was used as maintenance regimen.

**Methodological quality**

From the 7 studies included in the first meta-analysis (eradication therapy vs. non-eradication therapy without subsequent maintenance antisecretory therapy), 2 studies had a Jadad’s quality score of 1, two more studies had a score of 2, and the three remaining studies had a score of 3 (see table of 'Characteristics of included studies') (a score > or = 3 has been reported to indicate high quality; Jadad 1996). All studies were randomised, but none of them were double-blinded. Allocation concealment was adequate in only 2 studies. One study was only in abstract form (and not in complete article form) (Vcev 1996).

From the 3 studies included in the second meta-analysis (H. pylori eradication therapy vs. non-eradication therapy with long-term maintenance antisecretory therapy), two studies had a Jadad’s quality score of 2, and the remaining study had a score of 1 (see table of 'Characteristics of included studies'). This last study was controlled but not randomised, although it was stated that 'prospective allocation into the H. pylori treatment regimen or the maintenance regimen was performed'. None of the studies were double-blinded. Allocation concealment was adequate in only one study. All the studies were in complete article form.

**Results**

Seven studies with a total of 578 patients were included in the first meta-analysis: mean
percentage of rebleeding in H. pylori eradication therapy group was 2.9% (95% CI 1.6 to 5.2%), and in non-eradication therapy group without subsequent long-term maintenance antisecretory therapy it was 20% (95% CI 14 to 25%). The OR for this comparison was 0.17 (95% CI 0.10 to 0.32) using a fixed effect model, and 0.20 (95% CI 0.10 to 0.41) with a random effect model. Respective values for the RR were 0.22 (95% CI 0.12 to 0.40) and 0.26 (95% CI 0.14 to 0.48). There was no statistically significant heterogeneity (test for heterogeneity chi-square = 6.14, p=0.41). ARR or 'risk difference' between the two groups was -0.15 (95% CI -0.21 to -0.09) with the fixed and -0.17 (95% CI -0.26 to -0.08) with the random effect models. The NNT with eradication therapy to prevent one episode of rebleeding, compared with non-eradication therapy, was 7 (95% CI 5 to 11) with the fixed effect model.

Three studies with a total of 470 patients were included in the second meta-analysis: mean percentage of rebleeding in H. pylori eradication therapy group was 1.6% (95% CI 0.6 to 3.9%), and in non-eradication therapy group with long-term maintenance antisecretory therapy it was 5.6% (95% CI 2.5 to 8.7%). The OR for this comparison was 0.25 (95% CI 0.08 to 0.76) using a fixed effect model, and 0.26 (95% CI 0.08 to 0.80) with a random effect model. Respective values for RR were 0.27 (95% CI 0.09 to 0.77) and 0.28 (95% CI 0.10 to 0.82). There was no statistically significant heterogeneity (test for heterogeneity chi-square = 0.89, p=0.64). ARR or 'risk difference' between the two groups was -0.05 (95% CI -0.08 to -0.01) with the fixed effect model, and -0.04 (95% CI -0.08 to -0.01) with the random effect model. The NNT with eradication therapy to prevent one episode of rebleeding, compared with long-term maintenance antisecretory therapy, was 20 (95% CI 12 to 100) with the fixed effect model.

Subanalyses.

Quality of studies. Regarding the first meta-analysis, when only the 3 high quality studies (having a Jadad's quality score of 3) were included (see table of 'Characteristics of included studies'), OR was 0.27 (95% CI 0.12 to 0.61), RR 0.33 (95% CI 0.15 to 0.70), ARR -0.10 (95% CI -0.17 to -0.03), and NNT 10 (95% CI 6 to 33) (fixed effect model). When trying to perform separate comparisons depending on the quality of studies in the second meta-analysis, all studies were classified as low quality ((one of which was non-randomised (Santander 1996)), and therefore the influence of this variable could not be adequately assessed.

Type of ulcer disease. In the first meta-analysis, all but 2 studies included patients with only duodenal ulcers (see table of 'Characteristics of included studies'), thus precluding adequate subanalysis of the results depending on the ulcer location (duodenal or gastric). Furthermore, in the second meta-analysis, the 3 studies included patients with both duodenal and gastric ulcer, precluding again planned subanalysis.

Duration of follow-up. From the 10 studies included in the two meta-analyses, all but two had a similar follow-up of 12 months (see table of 'Characteristics of included studies'). Therefore, the influence of this variable on the outcome of the review (e.g., rate of rebleeding) could not be adequately assessed.

NSAID use. In the first meta-analysis, one of the patients who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) took NSAIDs at the time of rebleeding. Thus, subanalysis of the
data excluding this patient resulted in rebleeding rate of 10/374 (2.7%, 95% CI 1.5 to 5%) in the group receiving H. pylori eradication therapy, OR of 0.17 (95% CI 0.08 to 0.33), RR of 0.20 (95% CI 0.11 to 0.38), ARR of -0.15 (95% CI -0.21 to -0.10), and NNT of 7 (95% CI 5 to 10) (fixed effect model). In the second meta-analysis, the 2 patients suffering from recurrence of haemorrhage in the study by Riemann et al (Riemann 1997) had taken NSAIDs at the time of rebleeding (and they were H. pylori-negative). Subanalysis of the data excluding these 2 patients in the group receiving H. pylori eradication therapy were: rebleeding rate of 2/255 (0.78%, 95% CI 0.22 to 2.8%), RR of 0.16 (95% CI 0.04 to 0.58), OR of 0.15 (95% CI 0.04 to 0.55), ARR of -0.05 (95% CI -0.09 to -0.02), and NNT of 20 (95% CI 11 to 50) (fixed effect model).

H. pylori eradication failure. In the study by Lai et al (Lai 2000), 4 out of the 6 patients with a rebleeding episode in the eradication treatment group had failed to eradicate H. pylori infection. In the study by Vcev et al (Vcev 1996), all the 3 patients with recurrence of bleeding had failed to eradicate H. pylori infection with antibiotic therapy. Therefore, when these 7 patients were excluded from the analysis, rebleeding occurred in 4/371 patients (1.1%, 95% CI 0.4 to 2.7%) in H. pylori eradication therapy group, OR was 0.10 (95% CI 0.05 to 0.19), RR 0.10 (95% CI 0.05 to 0.24), ARR -0.17 (95% CI -0.23 to -0.12), and NNT 6 (95% CI 3 to 7) (fixed effect model).

Recurrence of H. pylori infection. In the first meta-analysis one of the patients who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) had recurrence of H. pylori infection at the time of rebleeding, while in the second meta-analysis H. pylori recurrence occurred in the 2 patients having recurrence of haemorrhage in the study by Santander et al (Santander 1996).

Rebleeding in patients with H. pylori eradication success. Rebleeding in patients in whom H. pylori eradication was achieved (and did not receive maintenance antisecretory therapy) in studies included in the meta-analysis and in other uncontrolled studies from the literature are summarized in Table 02. Overall, from 1370 patients in whom H. pylori infection had been eradicated, mean rate of rebleeding (weighted mean) was 1.24% (95% CI 0.8 to 2%). However, as the follow-up time markedly varied among studies, this factor needs to be taken into account. Thus, follow-up periods in each study, measured in patient-years, and respective yearly bleeding (in patient-years⁻¹), are also included in Table 02. A total of 2179 patient-years of follow-up was calculated from all studies. A total of 17 rebleedings was observed among patients with H. pylori eradication success, yielding a yearly recurrence of 0.78% (95% CI 0.5 to 1.2) patient-years⁻¹.

Discussion

The main result of the present meta-analysis is that rebleeding is less frequent after H. pylori eradication therapy than after non-eradication antisecretory therapy, both with or without subsequent long-term maintenance antisecretory therapy, with ORs of about 0.17-0.25. This advantage is expressed by a NNT with eradication therapy to prevent one episode of rebleeding of only 7 when compared with ulcer healing treatment alone, and of 20 when compared with long-term maintenance antisecretary therapy (mainly because the risk of rebleeding with maintenance antisecretory therapy was relatively low), in agreement with results of previous report (Sharma 2001).

The decision of whether maintenance antisecretory therapy must be continued or stopped in
patients with a history of peptic ulcer haemorrhage and prior H. pylori eradication will depend on the true efficacy of H. pylori eradication for the prevention of recurrent bleeding. Thus, mean rebleeding rate in patients in whom H. pylori eradication was achieved (and did not receive maintenance antisecretory therapy) in studies included in the meta-analysis and in other uncontrolled studies from the literature (see Table 02) was of only 1.24%. However, as the follow-up time markedly varied among studies (many of them being higher than 12 months), the risk of rebleeding is better expressed as 'yearly' recurrence of bleeding, which was of only 0.78% patient-years⁻¹.

In brief, probability of having recurrence of haemorrhage after H. pylori eradication is less than 1% per year, which arguments against the necessity or prescribing maintenance antisecretory therapy in these cases. Two recent randomised studies (Lai 1998; Pellicano 2001) have directly compared, after anti-H. pylori therapy had been prescribed and eradication confirmed, long-term maintenance antisecretory therapy vs. no treatment, reporting no differences in rebleeding rates, during a mean follow-up period of up to 47 months. Furthermore, the protective effect of H. pylori eradication seems to be maintained at least in the medium-term follow-up, as rebleeding rates of 0% have been reported even after 24 months (Amendola 1999; Loperfido 2001; Macri 1998; Pellicano 2001). This observation seems to agree with the relatively low incidence of reinfection reported after H. pylori eradication, at least in developed countries, as discussed later.

Therefore, the results of our systematic review support the recommendation that it is unnecessary to continue antisecretory maintenance therapy in patients with a history of peptic ulcer bleeding and prior H. pylori eradication (Laine 1995; McColl 1995; Laine 1996). It must be emphasized, therefore, that in patients with previous peptic ulcer bleeding the success of H. pylori eradication should always be confirmed (McColl 1995; Howden 1998; van Leerdam 2002). In case of initial eradication failures, re-treatment should be prescribed. In clinical practice, several studies have demonstrated that H. pylori eradication can finally be achieved in almost all patients if several rescue therapies are consecutively given (Gisbert 2002). The rare patients with a hypersecretory state or true idiopathic ulcers with coincident H. pylori infection may have recurrent bleeding despite H. pylori eradication (Laine 1995). However, this should be a very uncommon occurrence and, probably, does not justify the routine use of maintenance antisecretory therapy after H. pylori eradication (Laine 1995; Laine 1996).

Nevertheless, as it has been shown by the present meta-analysis, the prescription of H. pylori eradication therapy does not always prevent recurrence of bleeding, and several explanations could be suggested. Firstly, as antibiotic regimens are not 100% effective to treat H. pylori infection, eradication failures may explain, obviously, some of the rebleedings. For example, in the study by Lai et al (Lai 2000), 4 out of the 6 patients with a rebleeding episode in the eradication treatment group had failed to eradicate H. pylori infection; and in the study by Vcev et al (Vcev 1996), all the 3 patients with recurrence of bleeding had failed to eradicate H. pylori infection with antibiotic therapy. Therefore, when these 7 patients were excluded from the analysis, the rebleeding rate in the eradication therapy group was of only 1.1%.

Secondly, as recurrence of H. pylori infection seems to be an important cause of subsequent ulcer recurrence (and consequent rebleeding) (Gisbert 1998), the study of incidence of the
organism's recurrence represents an important issue, as high reinfection rate offsets the expected beneficial effects of H. pylori eradication. In the first meta-analysis, one of the patients who had recurrence of haemorrhage in the study by Lai et al (Lai 2000) had recurrence of H. pylori infection at the time of rebleeding, while in the second meta-analysis H. pylori recurrence occurred in the 2 patients having recurrence of haemorrhage in the study by Santander et al (Santander 1996). Other studies have also reported rebleeding only in patients with reinfection (Jaspersen 1995b). Fortunately, recurrence of H. pylori infection seems to be a relatively infrequent event in developed countries (Cutler 1993; Forbes 1994; Elta 1994; Bell 1996; Xia 1997; Gisbert 1998) and, therefore, initial H. pylori eradication is likely to confer long-term protection from rebleeding. Nevertheless, in countries where the rate of reinfection is higher, rebleeding may be a relevant problem even in patients with initial successful eradication.

Thirdly, NSAID intake probably explain a major percentage of rebleedings occurring despite H. pylori eradication. The use of these drugs at the time of rebleeding seemed to explain some of the episodes in the studies included in this meta-analysis (Lai 2000; Riemann 1997), and also in other studies (Huellin 1998). Although excluding from the analysis those patients with NSAID use will give us more strict data about the true role of H. pylori eradication in the prevention of recurrent bleeding, in clinical practice a relevant group of patients will probably take these drugs. Because clinical research, unlike basic science research, has clinical practicality as its foundation and not pure knowledge, we must probably accept the real results (including patients taking NSAIDs) as predictive of outcome for the population in question (Barthel 1997).

Several advantages are associated with H. pylori eradication therapy, when compared with long-term maintenance antisecretory therapy in patients with previous peptic ulcer bleeding. Firstly, as previously shown, the first strategy is more effective than the second. It must be emphasized that the prevention of rebleeding with antisecretory maintenance therapy is, in any case, incomplete, since about 5-10% of the patients who receive this regimen have recurrent bleeding (Jensen 1994; Laine 1996; Jaspersen 1995c). Furthermore, some data exist suggesting that continued administration of H2 receptor antagonist leads to pharmacological tolerance, with a decrease in its effect in controlling gastric acid secretion (Lachman 2000). Secondly, one disadvantage of maintenance antisecretory therapy is the requirement for long-term compliance; patient compliance with antisecretors may not be sustained but wane, especially when symptoms are absent. Thirdly, it is obvious that 7-10 days of antibiotic therapy is more convenient for the patients than many years of continuous antisecretory treatment; therefore, even if these two forms of therapy would be equivalent (in terms of efficacy), it makes much more sense to choose the treatment that requires only a few days of therapy rather than the one that requires daily medication forever.

Finally, maintenance therapy is expensive. The cost of antibiotic therapy is lower than long-term management by antisecretory drugs, mainly because the financial outlay for medication in the former approach is not cumulative as with the later (Jonsson 1996; Sonnenberg 1999). The present meta-analysis clearly shows that the strategy of testing for H. pylori and treating if positive in patients with previous upper gastrointestinal haemorrhage secondary to peptic ulcer is considerably more effective than PPI maintenance therapy or no treatment. In addition, cost-effectiveness analysis underlines that this strategy is also the most favourable from a financial
point of view even when wide variations of the current scenario are considered. Sharma et al (Sharma 2001) compared treatment of H. pylori infection with other approaches to prevent recurrent ulcer haemorrhage to determine the least costly strategy. Decision model-based cost minimization analysis demonstrated that treatment of H. pylori infection was the least costly strategy unless the incidence of complicated recurrences after treatment was over 6%, or the cost of confirming eradication was over 741 $. Other authors have compared several strategies for the prevention of recurrent ulcer-related haemorrhage, from a cost-effectiveness perspective (Ofman 2002). Decision analysis was used to compare the cost-per-recurrent hemorrhage prevented for 11 strategies over 1 year. The test/retest eradication strategy with maintenance PPI therapy for H. pylori-negative patients was most effective (prevention of recurrence in 96%). The test/retest eradication strategy with maintenance H2 receptor antagonist therapy for H. pylori-negative patients was least costly (1070 $). The test/retest strategies were dominant with average cost-effectiveness ratios of 1118-1310 $/recurrent hemorrhage prevented with maintenance antisecretory therapy. These studies shows that the strategies based on the diagnosis and treatment of H. pylori are cost-effective for the prevention of recurrent ulcer-related hemorrhage because they result in fewer recurrent hemorrhages and fewer patients requiring antisecretory therapy. In summary, these studies emphasize that the relative 'small' advantage in preventing rebleeding results in a substantial health-care cost saving.

Although, based on aforementioned arguments, it seems logical to test all patients with peptic ulcer bleeding for H. pylori infection, and to prescribe eradication therapy to H. pylori-positive patients, in clinical practice this strategy seems to have limited divulgation. Thus, it is disappointing that relatively few patients admitted to hospital with peptic ulcer haemorrhage appear to be tested for the infection or to be treated when present. In this respect, a recent study on a high number of such patients admitted to US hospitals found that only 56% were tested for H. pylori infection or appropriately treated for it (Hood 1999). These discouraging results regarding the implementation of H. pylori testing and treating have been confirmed in a review of case notes and endoscopy records of patients presenting to Auckland Hospital (Garrigan 1999). Finally, in another study aimed to investigate current management of ulcer haemorrhage in the Netherlands, it was found that H. pylori eradication was confirmed by only 64% of the physicians (van Leerdam 2002). In summary, it seems evident that management of patients with previous peptic ulcer haemorrhage is only partly in accordance with evidence-based medicine.

The present meta-analysis suffers from several possible limitations. Firstly, some limitation of the studies included need to be recognized: they were relatively small, none of them were double-blinded (the overall quality of the studies was low), and the follow-up period was limited to only one year in most cases. In this respect, it remains to be demonstrated that the beneficial effects of H. pylori eradication are maintained in the future, mainly because, as previously mentioned, H. pylori reinfection could be a problem in the long-term management. Secondly, the studies included in the meta-analysis were not homogeneous regarding H. pylori eradication regimen (and therefore regarding efficacy to successfully eradicate the organism); however, it seems that the prophylactic effect of H. pylori eradication on recurrence of haemorrhage depends mainly, or perhaps exclusively, on the capacity to eradicate the infection, which is supported by the encouraging results obtained with many different antibiotic regimens. Thirdly, antisecretory maintenance therapy also differed among different studies; thus, while some authors prescribed H2
receptor antagonist, others used PPI. Nevertheless, the findings of the meta-analysis were not statistically heterogeneous, thus suggesting that the combination of the study results is reasonable.

**Authors' conclusions**

**Implications for practice**

Treatment of H. pylori infection is more effective than antisecretory non-eradicating therapy (with or without long-term maintenance antisecretory therapy) in preventing recurrent bleeding from peptic ulcer. When H. pylori eradication therapy is compared with ulcer healing treatment alone (without subsequent long-term maintenance antisecretory therapy), the magnitude of the beneficial effect of the first strategy is remarkable (NNT of only about 7, and even 6 if H. pylori eradication success is confirmed). However, when the comparison is performed against long-term maintenance antisecretory therapy, the 'clinical impact' on the recurrence of bleeding is smaller (NNT of 20), mainly because the risk of rebleeding with maintenance therapy is relatively low. Nevertheless, in addition to efficacy, other relevant advantages of H. pylori eradication treatment, such as better compliance, better convenience, and lower cost, advised also for the use of antibiotic therapy. Finally, it seems unnecessary to continue antisecretory maintenance therapy in patients with a history of peptic ulcer bleeding and prior H. pylori eradication. Consequently, all patients with peptic ulcer bleeding should be tested for H. pylori infection, and eradication therapy should be prescribed to H. pylori-positive patients.

**Implications for research**

The findings of this review are relatively robust and unlikely to change with the result of further short- or medium-term follow-up trials. Although further short term trials of greater sample size would be useful, the main area of uncertainly is the assessment of the long-term beneficial results of H. pylori eradication and the role of the factors which could explain recurrence of bleeding despite H. pylori eradication success (especially NSAID use and H. pylori reinfection).

**Potential conflict of interest**

None known.

**Acknowledgements**

We thank Dr. D. Forman, Dr. E. Gardener, Dr. R. Laheij, Dr. P. Moayyedi and Dr. Savarino for their valuable advice and constructive comments on our review. We also appreciate Miss J. Lilleyman, Miss G. Sutherington and Miss I. Gordon in the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group for their helpful suggestions.

**Characteristics of included studies**

**Study Arkkila 2003**

**Methods** Randomized

Not double-blinded

**Participants** Duodenal and gastric ulcer
Some patients used NSAIDs (19%) or ASA (35%)

**Interventions** OBAM/OA vs. O

No maintenance antisecretory therapy

**Outcomes** Rebleeding

Follow-up 12 months in all patients

**Notes** Q=3

Eradication rates: 92% in eradication groups, and 4% in antisecretory group

**Allocation concealment** B - Unclear

**Study Bataga 1997**

**Methods** Randomized

Not double-blinded

**Participants** Duodenal ulcer

NSAID use unknown

**Interventions** BAM (with or without endoscopic hemostasis) vs. H2-antagonist

No maintenance antisecretory therapy

**Outcomes** Rebleeding

Follow-up 12 months in all patients

**Notes** Q=1

Eradication rates not provided in any group

Abstract form only (no complete article)

**Allocation concealment** B - Unclear

**Study Graham 1993**

**Methods** Randomized

Not double-blinded

**Participants** Duodenal and gastric ulcer

Some patients (28%) used NSAIDs

**Interventions** BMT vs. ranitidine
No maintenance antisecretory therapy

**Outcomes** Rebleeding

Mean follow-up 12 months in eradication group, and 9 months in antisecretory group

**Notes** Q=2

Eradication rates: 81% in eradication group, and 0% in antisecretory group

**Allocation concealment** B - Unclear

**Study Jaspersen 1995a**

**Methods** Randomized

Not double-blinded

**Participants** Duodenal ulcer

No patient used NSAIDs

**Interventions** OA vs. O

No maintenance antisecretory therapy

**Outcomes** Rebleeding

Follow-up 12 months in all patients

**Notes** Q=2

Eradication rates: 83% in eradication group, and 5% in antisecretory group

**Allocation concealment** B - Unclear

**Study Lai 2000**

**Methods** Randomized

Not double-blinded

**Participants** Duodenal ulcer

No patient used NSAIDs

**Interventions** BAM vs. B

No maintenance antisecretory therapy

**Outcomes** Rebleeding

Mean follow-up 53 months
Notes  Q=3
Eradication rates: 85% in eradication group, and 2% in antisecretory group

Allocation concealment  A - Adequate

Study Riemann 1997
Methods  Randomized
Not double-blinded
Participants  Duodenal and gastric ulcer
No patient used NSAIDs
Interventions  OA vs. ranitidine (as maintenance antisecretory therapy)
Outcomes  Rebleeding
Mean follow-up 19 months

Notes  Q=2
Eradication rates: 89% in eradication group, and not provided in antisecretory group

Allocation concealment  A - Adequate

Study Rokkas 1995
Methods  Randomized
Not double-blinded
Participants  Duodenal ulcer
Some patients (6%) used NSAIDs
Interventions  OA vs. O
No maintenance antisecretory therapy
Outcomes  Rebleeding
Follow-up 12 months in all patients

Notes  Q=3
Eradication rates: 81% in eradication group, and 13% in antisecretory group

Allocation concealment  A - Adequate

Study Santander 1996
Methods Not randomized
Not double-blinded

Participants Duodenal and gastric ulcer
No patient used NSAIDs

Interventions OA/OC/BAM vs. ranitidine/O (as maintenance antisecretory therapy)

Outcomes Rebleeding
Follow-up 12 months in all patients

Notes Q=1

Eradication rates: 100% in eradication group (retreatment was prescribed in failures), and not provided in antisecretory group

Allocation concealment B - Unclear

Study Sung 1997

Methods Randomized
Not double-blinded

Participants Duodenal and gastric ulcer
No patient used NSAIDs

Interventions BAM vs. ranitidine (as maintenance antisecretory therapy)

Outcomes Rebleeding
Median follow-up 12 months

Notes Q=2

Eradication rates: 98% in eradication group, and 6% in antisecretory group

Allocation concealment B - Unclear

Study Vcev 1996

Methods Randomized
Not double-blinded

Participants Duodenal ulcer
NSAID use unknown
**Interventions** OA vs. O

No maintenance antisecretory therapy

**Outcomes** Rebleeding

Follow-up 12 months in all patients

**Notes** Q=1

Eradication rates: 72% in eradication group, and 0% in antisecretory group

**Allocation concealment** B - Unclear

Intervention (treatment): B: bismuth; A: amoxicillin; M: metronidazole; O: omeprazole; C: clarithromycin; T: tetracycline; details of eradication and antisecretory treatment are provided in additional table (01).

NSAIDs: non-steroidal anti-inflammatory drugs (taken by the patient previous to the inclusion in the study).

ASA: acetylsalicylic acid (taken by the patient previous to the inclusion in the study).

Q: quality score (Jadad scale, from 0 to 5 points, see appropriate section).

**Characteristics of excluded studies**

**Study** Reason for exclusion

**Adamek 1994** Rebleeding not evaluated

**Altorjay 2000** Rebleeding not evaluated

Less than six-month follow-up

**Amendola 1999** No control group (all patients received H. pylori eradication therapy)

**Arkkila 2001** Insufficient data (no response from the authors)

**Capurso 2001** No previous upper gastrointestinal bleeding

No control group (all patients received H. pylori eradication therapy)

**Chan 1997** All patients received NSAIDs

**Chan 1998** Rebleeding not evaluated

**Chan 2001** All patients received NSAIDs

**Chan 2002a** All patients received NSAIDs

**Chan 2002b** All patients received NSAIDs
No previous upper gastrointestinal bleeding in one group

**Chen 1996** No control group (all patients received H. pylori eradication therapy)

Less than six-month follow-up

**Chen 1998** No control group (all patients received H. pylori eradication therapy)

Less than six-months follow-up

**Di Mario 1997** No control group (all patients received H. pylori eradication therapy)

**Fakhreih 1995** No control group (all patients received H. pylori eradication therapy)

**Gisbert 1995** No control group (all patients -one- received H. pylori eradication therapy)

**Gisbert 1999** No control group (all patients received H. pylori eradication therapy)

**Hsieh 2001** Rebleeding not evaluated

**Huellin 1998** No control group (all patients received H. pylori eradication therapy)

**Jaspersen 1994a** No control group (all patients received H. pylori eradication therapy)

**Jaspersen 1994b** No control group (all patients received H. pylori eradication therapy)

Less than six-month follow-up

**Jaspersen 1995b** No control group (all patients received H. pylori eradication therapy)

**Krizman 1997** No control group (all patients received H. pylori eradication therapy)

**Kung 1997** No control group (all patients received H. pylori eradication therapy)

Less than six-month follow-up

**Labenz 1994** No control group (all patients received H. pylori eradication therapy)

**Lai 1998** No control group (all patients received H. pylori eradication therapy)

**Lai 2000b** Rebleeding not evaluated.

**Lee 1998** Rebleeding not evaluated

**Lee 1999** No control group (all patients received H. pylori eradication therapy)

**Lin 1999** No H. pylori eradication group

**Loperfido 2001** No control group (all patients received H. pylori eradication therapy)

**Macri 1998** No control group (all patients received H. pylori eradication therapy)

**Martino 1998** No control group (all patients received H. pylori eradication therapy)
No previous upper gastrointestinal bleeding

**Pamos 1998** Control group included only H. pylori-negative patients or patients with unknown H. pylori status

**Pauly 1997** No control group (all H. pylori-positive patients received eradication therapy)

**Pazzi 1996** No control group (all patients received H. pylori eradication therapy)

**Pazzi 1999** No control group (all patients received H. pylori eradication therapy)

**Pellicano 2001** No control group (all patients received H. pylori eradication therapy)

**Pica 1996** No control group (all patients received H. pylori eradication therapy)

**Romero 2000** Rebleeding not evaluated

**Ruiz Gomez 2002** Rebleeding not evaluated

**Seppala 1995** Insufficient data (no response from the authors)

**Sheu 1996** Rebleeding not evaluated

**Sheu 1999** Rebleeding not evaluated

**Sheu 2002** No control group (all patients received H. pylori eradication therapy)

Less than six-month follow-up

**Siu 1999** No control group (all patients received H. pylori eradication therapy)

**Sonnenberg 1999** No previous upper gastrointestinal bleeding

**Vergara 2000** No control group (all patients received H. pylori eradication therapy)

**van der Voort 2001** Stress ulcer bleeding

No previous upper gastrointestinal bleeding

NSAIDs: non-steroidal anti-inflammatory drugs

**Additional tables**

Table 01

Table 02

**Analyses**

Comparison 01

Comparison 02
Sources of support

External sources of support
* Supported in part by a Grant from the Instituto de Salud Carlos III (C03/02) SPAIN

Internal sources of support
* No sources of support supplied

<table>
<thead>
<tr>
<th>Study</th>
<th>Eradication tr. n/N</th>
<th>No eradication tr. n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
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<td>0/27</td>
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<td>0.8</td>
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<td>0.00 [0.01, 0.88]</td>
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<td>0.4</td>
<td>10.0</td>
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<td>8/22</td>
<td>12.5</td>
<td>10.0</td>
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</tr>
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<td>7.7</td>
<td>10.0</td>
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</table>

Total (50% CI) 375/203
Test for heterogeneity chisquare 14 df 0.01 P=0.22
Test for overall effect z=-5.8 P=0.00001

Comparison 01 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 01 Recurrent bleeding

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<tr>
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</tr>
</tbody>
</table>

Total (50% CI) 374/203
Test for heterogeneity chisquare 14 df 0.01 P=0.22
Test for overall effect z=-5.8 P=0.00001

Comparison 01 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 02 Recurrent bleeding excluding NSAID users
Comparison 01 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 03 Recurrent bleeding excluding H. pylori eradication failures

Comparison 01 Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy), Outcome 04 Recurrent bleeding considering high quality studies

Comparison 02 Eradication therapy vs. long-term maintenance antisecretory therapy, Outcome 01 Recurrent bleeding
Comparison 02 Eradication therapy vs. long-term maintenance antisecretory therapy, Outcome 02 Recurrent bleeding excluding NSAID users

Details of eradication and antisecretory treatment of included studies

**Study ID:** Arkkila 2003

**Eradication tx.:** Bismuth subcitrate, 120 q.i.d., for 14 days, amoxicillin, 500 mg q.i.d., metronidazole, 400 mg t.i.d., and omeprazole, 40 mg o.d., for 28 days; amoxicillin, 500 mg q.i.d., for 14 days, and omeprazole, 40 mg o.d., for 28 days

**Antisecretory tx.:** Omeprazole, 40 mg o.d., for 28 days plus placebo q.i.d., for 14 days

**Study ID:** Bataga 1997

**Eradication tx.:** H2-antagonist (dose not stated) for 7 days, followed by bismuth subcitrate, 240 mg b.i.d., metronidazole, 500 mg t.i.d., and amoxicillin 500 mg t.i.d., for 10 days (with and without endoscopic hemostasis with pure ethanol)

**Antisecretory tx.:** H2-antagonist (dose not stated) and antiacids for 7 days

**Study ID:** Graham 1993

**Eradication tx.:** Bismuth subsalicylate 5-8 tablets daily, metronidazole, 250 mg t.i.d., and tetracycline, 500 mg q.i.d., for 14 days, and ranitidine, 300 mg o.d., until ulcer healing

**Antisecretory tx.:** Ranitidine, 300 mg o.d., until ulcer healing

**Study ID:** Jaspersen 1995a

**Eradication tx.:** Omeprazole, 40 mg o.d. and amoxicillin, 1 g b.i.d., for 14 days

**Antisecretory tx.:** Omeprazole, 40 mg o.d., for 14 days

**Study ID:** Lai 2000

**Eradication tx.:** Metronidazole, 300 mg q.i.d., and amoxicillin, 500 mg q.i.d., for 14 days, and tripotassium dicitrato bismuthate, 120 mg q.i.d., until ulcer healing

**Antisecretory tx.:** Tripotassium dicitrato bismuthate, 120 mg q.i.d., until ulcer healing

**Study ID:** Riemann 1997
**Eradication tx.**: Omeprazole, 60 mg b.i.d, and amoxicillin, 750 mg t.i.d., for 10 days, followed by omeprazole, 20 mg o.d., for 30 days

**Antisecretory tx.**: Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d.

**Study ID**: Rokkas 1995

**Eradication tx.**: Omeprazole, 20 mg o.d. for 30 days, followed by omeprazole, 20 mg t.i.d., and amoxicillin, 500 mg q.i.d., for 14 days

**Antisecretory tx.**: Omeprazole, 20 mg o.d., for 30 days, followed by omeprazole, 20 mg t.i.d., for 14 days

**Study ID**: Santander 1996

**Eradication tx.**: Omeprazole, 20 mg b.i.d., and clarithromycin, 500 mg t.i.d., for 12 days; or omeprazole, 20 mg b.i.d., and amoxicillin, 500 mg t.i.d., for 10 days; or bismuth subsalicylate, 240 mg b.i.d., for 30 days, metronidazole, 500 mg t.i.d., for 10 days, and amoxicillin, 500 mg t.i.d., for 10 days

**Antisecretory tx.**: Antisecretory maintenance therapy with ranitidine, 150 mg o.d., or omeprazole, 20 mg o.d.

**Study ID**: Sung 1997

**Eradication tx.**: Bismuth subsalicylate, 120 mg q.i.d., metronidazole, 400 mg q.i.d., tetracycline, 500 mg q.i.d., and ranitidine, 300 mg o.d., for 7 days

**Antisecretory tx.**: Ranitidine, 300 mg o.d., for 6 weeks, followed by antisecretory maintenance therapy with ranitidine, 150 mg o.d.

**Study ID**: Vcev 1996

**Eradication tx.**: Omeprazole, 20 or 40 mg o.d, and amoxicillin, 500 mg q.i.d. or 1 g b.i.d., for 14 days, followed by omeprazole, 20 mg o.d., for 14 days

**Antisecretory tx.**: Omeprazole, 20 mg o.d., for 30 days

**Study ID**: Footnotes:

**Eradication tx.**: o.d.: once per day; b.i.d.: two times per day; t.i.d.: three times per day; q.i.d.: four times per day

**Antisecretory tx.**:

**Rebleeding in H. pylori eradicated patients and no maintenance antisecretory tx.**

**Author & year**: Arkkila 2003
<table>
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<tr>
<th>Author &amp; Year</th>
<th>N. of Patients</th>
<th>Mean Follow-up (mo.)</th>
<th>Rebleeding (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bataga 1997</td>
<td>176</td>
<td>12</td>
<td>2 (1.1%)</td>
<td>The two patients had Dieulafoy's ulcer</td>
</tr>
<tr>
<td>Graham 1993</td>
<td>13</td>
<td>12</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Jaspersen 1995</td>
<td>24</td>
<td>12</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Author &amp; year</td>
<td>N. of patients</td>
<td>Mean follow-up (mo.)</td>
<td>Rebleeding (%)</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
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<td>----------------</td>
<td>-------</td>
</tr>
<tr>
<td>Lai 2000</td>
<td>41</td>
<td>53</td>
<td>2 (4.9%)</td>
<td>One of these patients took NSAIDs at the time of rebleeding; another patient had recurrence of H. pylori infection at the time of rebleeding</td>
</tr>
<tr>
<td>Riemann 1997</td>
<td>42</td>
<td>19</td>
<td>2 (4.8%)</td>
<td>The two patients took NSAIDs at the time of rebleeding (and were H. pylori-negative)</td>
</tr>
<tr>
<td>Rokkas 1995</td>
<td>13</td>
<td>12</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Santander 1996</td>
<td>84</td>
<td>12</td>
<td>2 (2.4%)</td>
<td>The two patients had recurrence of H. pylori infection at the time of rebleeding</td>
</tr>
</tbody>
</table>
Follow-up (p-y): 84
Yearly rebleeding (%): 2.4
Author & year: Sung 1997
N. of patients: 108
Mean follow-up (mo.): 12
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 108
Yearly rebleeding (%): 0
Author & year: Vcev 1996
N. of patients: 36
Mean follow-up (mo.): 12
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 36
Yearly rebleeding (%): 0
Author & year: Studies not included in the meta-analysis
N. of patients:
Mean follow-up (mo.):
Rebleeding (%):
Notes:
Follow-up (p-y):
Yearly rebleeding (%):
Author & year: Amendola 1999
N. of patients: 42
Mean follow-up (mo.): 24
Rebleeding (%): 0 (0%)
Notes:

Follow-up (p-y): 84
Yearly rebleeding (%): 0
Author & year: Di Mario 1997
N. of patients: 40
Mean follow-up (mo.): 21
Rebleeding (%): 0 (0%)

Notes:

Follow-up (p-y): 70
Yearly rebleeding (%): 0
Author & year: Fakhreih 1995
N. of patients: 61
Mean follow-up (mo.): 12
Rebleeding (%): 3 (4.9%)

Notes:

Follow-up (p-y): 61
Yearly rebleeding (%): 4.9
Author & year: Gisbert 1999
N. of patients: 111
Mean follow-up (mo.): 12
Rebleeding (%): 0 (0%)

Notes:

Follow-up (p-y): 111
Yearly rebleeding (%): 0
Author & year: Huelin 1998
N. of patients: 80
Mean follow-up (mo.): 18
Rebleeding (%): 1 (1.2%)

Notes: This patient took NSAIDs at the time of rebleeding

Follow-up (p-y): 120

Yearly rebleeding (%): 0.8

Author & year: Jaspersen 1995b

N. of patients: 29

Mean follow-up (mo.): 12

Rebleeding (%): 1 (3.4%)

Notes: This patient had recurrence of H. pylori infection at the time of rebleeding

Follow-up (p-y): 29

Yearly rebleeding (%: 3.4

Author & year: Krizman 1997

N. of patients: 33

Mean follow-up (mo.): 17

Rebleeding (%: 0 (0%)

Notes:

Follow-up (p-y): 47

Yearly rebleeding (%: 0

Author & year: Labenz 1994

N. of patients: 42

Mean follow-up (mo.): 17

Rebleeding (%: 0 (0%)

Notes:

Follow-up (p-y): 59

Yearly rebleeding (%: 0

Author & year: Lai 1998

N. of patients: 29
Mean follow-up (mo.): 11
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 27
Yearly rebleeding (%: 0
Author & year: Lee 1999
N. of patients: 92
Mean follow-up (mo.): 15
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 115
Yearly rebleeding (%: 0
Author & year: Loperfido 2001
N. of patients: 38
Mean follow-up (mo.): 24
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 76
Yearly rebleeding (%: 0
Author & year: Macri 1998
N. of patients: 21
Mean follow-up (mo.): 48
Rebleeding (%): 0 (0%)
Notes:
Follow-up (p-y): 84
Yearly rebleeding (%: 0
Author & year: Pamos 1998
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N. of Patients</th>
<th>Mean Follow-up (mo.)</th>
<th>Rebleeding (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazzi 1999</td>
<td>39</td>
<td>47</td>
<td>4 (10.3%)</td>
<td>Follow-up (p-y): 153 Yearly rebleeding (%): 2.6</td>
</tr>
<tr>
<td>Pica 1996</td>
<td>6</td>
<td>12</td>
<td>0 (0%)</td>
<td>Follow-up (p-y): 6 Yearly rebleeding (%): 0</td>
</tr>
<tr>
<td>Pellicano 2001</td>
<td>46</td>
<td>47</td>
<td>0 (0%)</td>
<td>Follow-up (p-y): 180 Yearly rebleeding (%): 0</td>
</tr>
</tbody>
</table>
**Author & year:** Vergara 2000

**N. of patients:** 93

**Mean follow-up (mo.):** 27

**Rebleeding (%):** 0 (0%)

**Notes:**

Follow-up (p-y): 209

Yearly rebleeding (%): 0

**Author & year:** Total

**N. of patients:** 1370

**Mean follow-up (mo.):**

**Rebleeding (%):** 17 (1.24%)

**Notes:**

Follow-up (p-y): 2179

Yearly rebleeding (%): 0.78

**Author & year:** Footnotes:

**N. of patients:** p-y: patient-years

**Mean follow-up (mo.):** NSAIDs: non-steroidal anti-inflammatory drugs

**Rebleeding (%):**

**Notes:**

Follow-up (p-y): 

Yearly rebleeding (%): 

---

**Eradication vs non-eradication therapy (without long-term maintenance antisecretory therapy)**

**Outcome title:** 01 Recurrent bleeding

**No. of studies:** 7

**No. of participants:** 578

**Statistical method:** Peto Odds Ratio 95% CI
Effect size: 0.17 [0.10, 0.32]

Outcome title: 02 Recurrent bleeding excluding NSAID users
No. of studies: 7
No. of participants: 577
Statistical method: Peto Odds Ratio 95% CI

Effect size: 0.16 [0.09, 0.30]

Outcome title: 03 Recurrent bleeding excluding H. pylori eradication failures
No. of studies: 7
No. of participants: 574
Statistical method: Peto Odds Ratio 95% CI

Effect size: 0.10 [0.05, 0.19]

Outcome title: 04 Recurrent bleeding considering high quality studies
No. of studies: 3
No. of participants: 374
Statistical method: Peto Odds Ratio 95% CI

Effect size: 0.27 [0.12, 0.61]

**Eradication therapy vs. long-term maintenance antisecretory therapy**

Outcome title: 01 Recurrent bleeding
No. of studies: 3
No. of participants: 470
Statistical method: Peto Odds Ratio 95% CI

Effect size: 0.24 [0.09, 0.67]

Outcome title: 02 Recurrent bleeding excluding NSAID users
No. of studies: 3
No. of participants: 468
Statistical method: Peto Odds Ratio 95% CI

Effect size: 0.14 [0.05, 0.43]
Contribution of Reviewer(s)

JP Gisbert developed the protocol, performed the main search strategy, assessed eligibility, extracted the data, performed the statistical analyses (meta-analysis), and wrote the manuscript.

S Khorrami, X Calvet and E Gene were involved in the search strategy, checked eligibility and data extraction.

F Carballo and E Dominguez-Munoz were involved in developing the protocol and provided senior support in overseeing the project.

References

References to studies included in this review

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Rokkas 1995

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Chan 1998


Chan 2001


Chan 2002a


Chan 2002b


Chen 1996


Chen 1998


Di Mario 1997


Fakhreih 1995


Gisbert 1995


Gisbert 1999

(Barc) 1999;112(5):161-5. Bibliographic Links

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Jaspersen 1994a


Jaspersen 1994b


Jaspersen 1995b


Krizman 1997


Kung 1997

Kung NN, Sung JJ, Yuen NW, Ng PW, Wong KC, Chung EC, Lim BH, Choi CH, Li TH, Ma HC, Kwok SP. Anti-Helicobacter pylori treatment in bleeding ulcers: randomized controlled trial comparing 2-day versus 7-day bismuth quadruple therapy. Am J Gastroenterol 1997;92(3):438-41. Bibliographic Links

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Lai 1998


Lai 2000b

Lee 1998


Lee 1999


Lin 1999


Loperfido 2001

Loperfido S, Priora R, Monica F, Salvat HH. Effect of Helicobacter pylori eradication on recurrence of bleeding duodenal ulcer and dyspeptic symptoms: A two-year prospective study. Gastroenterology. 2001; Vol. 120 (Suppl.1):A585. [Context Link]

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Martino 1998


Pamos 1998


Pauly 1997


Pazzi 1996


Pazzi 1999


Pellicano 2001

**Pica 1996**


**Romero 2000**


**Ruiz Gomez 2002**


**Seppala 1995**


**Sheu 1996**


**Sheu 1999**

Sheu BS, Chi CH, Yang HB, Jen CM, Lin XZ. A three-day course of intravenous omeprazole plus antibiotics for H. pylori-positive bleeding duodenal ulcer. Hepatogastroenterology 1999;46(28):2363-71. [Bibliographic Links]

**Sheu 2002**


**Siu 1999**


**Sonnenberg 1999**


**van der Voort 2001**

Vergara 2000


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Cutler 1993


Elta 1994


Forbes 1994


Garrigan 1999


Gilbert 1990


Gisbert 1998


Gisbert 2002

Gisbert 2003


Hawkey 2001


Hood 1999


Hopkins 1996


Howden 1998


Jadad 1996


Jaspersen 1995c


Jensen 1994


Jonsson 1996


Kuiipers 1995


Lachman 2000

Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine

**Laine 1994**


**Laine 1995**


**Laine 1996**


**McColl 1995**


**Mignon 1994**


**Murray 1988**


**NIH 1994**


**Ofman 2002**


**Penston 1992**


**Petersen 1995**


**Sharma 2001**

Sharma VK, Sahai AV, Corder FA, Howden CW. Helicobacter pylori eradication is superior to ulcer healing
with or without maintenance therapy to prevent further ulcer haemorrhage. Aliment Pharmacol Ther 2001;15(12):1939-47. Bibliographic Links [Context Link]

Soll 1996


Sonnenberg 1999


van Leerdam 2002


Xia 1997


GASTRODUODENAL DISORDERS; Complicated gastroduodenal disease (haemorrhage); prevention; anti H. pylori therapy; Humans; *Anti-Ulcer Agents/tu (therapeutic use); *Helicobacter Infections/dt (drug therapy); *Helicobacter pylori; *Peptic Ulcer/dt (drug therapy); Peptic Ulcer/mi (microbiology); *Peptic Ulcer Hemorrhage/pc (prevention & control); Recurrence/pc (prevention & control)

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