ClinicalEvidence

Helicobacter pylori infection

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ABSTRACT

INTRODUCTION: The principal effect of Helicobacter pylori infection is lifelong chronic gastritis, affecting up to 20% of younger adults but 50% to 80% of adults born in resource-rich countries before 1950. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of H pylori eradication treatment in people with a confirmed duodenal ulcer, a confirmed gastric ulcer, confirmed gastro-oesophageal reflux disease (GORD), confirmed non-ulcer dyspepsia, uninvestigated dyspepsia, localised B cell lymphoma of the stomach, and non-steroidal anti-inflammatory drug (NSAID)-related peptic ulcers? What are the effects of H pylori eradication treatment for preventing NSAID-related peptic ulcers in people with or without previous ulcers or dyspepsia? What are the effects of H pylori eradication treatment on the risk of developing gastric cancer? Do H pylori eradication treatments differ in their effects? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 58 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: effects of H pylori eradication in different populations; relative effects of triple regimens, quadruple regimens, and sequential regimens.

QUESTIONS

INTERVENTIONS

TREATING DUODENAL ULCER

Beneficial

TREATING GASTRIC ULCER

Beneficial

TREATING NSAID ULCERS

Unknown effectiveness

PREVENTING NSAID ULCERS WITH PREVIOUS ULCERS OR DYSPEPSIA

Unknown effectiveness

PREVENTING NSAID ULCERS WITHOUT PREVIOUS ULCERS

Likely to be beneficial

TREATING GORD

Unlikely to be beneficial

TREATING B CELL LYMPHOMA

Unknown effectiveness

Key points

- The principal effect of *Helicobacter pylori* infection is lifelong chronic gastritis, affecting up to 20% of younger adults but 50% to 80% of adults born before 1950 in resource-rich countries.

  H pylori infection can be identified indirectly by the C13 urea breath test and stool antigen tests, which are more accurate than serology.

  Transmission and prevalence rates are higher in areas of childhood poverty. Adult reinfection rates are less than 1% a year.

  In people with *H pylori* infection, about 15% will develop a peptic ulcer and 1% will develop gastric cancer during their lifetime.

- Eradication of *H pylori* makes healing of duodenal ulcers more likely and reduces the risk of bleeding with gastric and duodenal ulcers, either alone or when added to antisecretory drug treatment. Eradication also greatly reduces the risk of recurrence of a duodenal ulcer.

  Eradication reduces recurrence after healing of a gastric ulcer; however, we don't know whether it increases healing of gastric ulcers.

  Eradication of *H pylori* may reduce the risk of NSAID-related ulcers in people without previous ulcers; however, we don't know whether it reduces NSAID-related ulcers or bleeding in people with previous ulcers.

- In areas of low prevalence of *H pylori*, few ulcers are caused by *H pylori* infection. Eradication may be less effective in preventing ulcers in these areas compared with higher-prevalence areas.

- Eradication of *H pylori* reduces symptoms of dyspepsia, but not of GORD.

  Eradicating *H pylori* has been shown to reduce dyspeptic symptoms in people with non-ulcer dyspepsia or uninvestigated dyspepsia compared with placebo.

- Despite the association between *H pylori infection* and gastric cancer, no studies have shown a reduced risk after eradication treatment.

  Gastric B cell lymphoma lesions may regress after *H pylori* eradication, but we don't know this for sure.

- Quadruple and triple regimens seem equally effective at eradicating *H pylori* as first-line treatments. Quadruple regimens may be more effective as second-line treatment than triple regimens when a first-line triple regimen has failed to eradicate the infection. However, the evidence is limited in that, in comparisons of second-line quadruple versus triple regimens, most triple regimens did not contain a nitroimidazole.

- Ten-day sequential therapy may be more effective at eradicating *H pylori* than a 7-day triple regimen.

- Nitroimidazole-based triple regimens and amoxicillin-based triple regimens seem equally effective at eradicating *H pylori.* High-dose clarithromycin within an amoxicillin-based triple regimen seems more effective at eradicating *H pylori* than low-dose clarithromycin. However, the dose of clarithromycin within a nitroimidazole-based triple regimen does not seem to have an effect on eradication rates.

- Triple regimens using different proton pump inhibitors seem equally effective at eradicating *H pylori*.

Pre-treatment with a proton pump inhibitor before triple regimen does not seem to increase *H pylori* eradication rates compared with no pre-treatment.

Two-week triple proton pump inhibitor regimens may be more effective than 1-week regimens for eradicating *H pylori*.

- Lower eradication rates are achieved in people infected with strains of *H pylori* that are resistant to antibiotics included in the eradication regimen than are achieved in people infected with sensitive strains of *H pylori*.
- Antibiotics can cause adverse effects such as nausea and diarrhoea. Bismuth may turn the stools black.

Clinical context

DEFINITION

Helicobacter pylori is a gram-negative flagellated spiral bacterium found in the stomach. Infection with *H pylori* is predominantly acquired in childhood. *H pylori* infection is not associated with a specific type of dyspeptic symptom. The organism is associated with lifelong chronic gastritis and may cause other gastroduodenal disorders. [1] **Diagnosis:** *H pylori* can be identified indirectly by serology or by the C13 urea breath test. The urea breath test is more accurate than serology, with a sensitivity and specificity greater than 95%, and indicates active infection, whereas serology may lack specificity and cannot be used reliably as a test of active infection. Thus, the urea breath test is the test of choice where prevalence (and hence predictive value of serology) may be low, or where a "test of cure" is required. In some areas, stool antigen tests that have a similar performance to the urea breath test are now available. **Population:** This review focuses on *H pylori*-positive people throughout.

INCIDENCE/ PREVALENCE

In the developed world, *H pylori* prevalence rates vary with year of birth and social class. Prevalence in many resource-rich countries tends to be much higher (50%–80%) in individuals born before 1950 compared with prevalence (<20%) in individuals born more recently. [2] In many resource-poor countries, the infection has a high prevalence (80%–95%) irrespective of the period of birth. [3] Adult prevalence is believed to represent the persistence of a historically higher rate of infection acquired in childhood, rather than increasing acquisition of infection during life.

AETIOLOGY/ RISK FACTORS

Overcrowded conditions associated with childhood poverty lead to increased transmission and higher prevalence rates. Adult reinfection rates are low — less than 1% a year. [3]

PROGNOSIS

H pylori infection is believed to be causally related to the development of duodenal and gastric ulceration, B cell gastric lymphoma, and distal gastric cancer. About 15% of people infected with *H pylori* will develop a peptic ulcer, and 1% of people will develop gastric cancer during their lifetime. [4] One systematic review of observational studies (search date 2000; 16 studies, 1625 people) found that the frequency of peptic ulcer disease in people taking non-steroidal anti-inflammatory drugs (NSAIDs) was greater in those who were *H pylori* positive than in those who were *H pylori* negative (peptic ulcer: 341/817 [42%] in *H pylori*-positive NSAID users *v* 209/808 [26%] in *H pylori*-negative NSAID users; OR 2.12, 95% CI 1.68 to 2.67). [5]

AIMS OF INTERVENTION

Eradication of *H pylori*; improvement in dyspeptic symptoms; improvement in ulcer healing; reduction in ulcer recurrence and complications; reduced mortality from peptic ulcer complications of gastric cancer; improved quality of life.

OUTCOMES

Under questions on treatments in people with confirmed ulcers: **ulcer healing**, **ulcer recurrence**, **ulcer bleeding**, and **ulcer perforation or obstruction**. Under questions on preventing ulcers: **prevention of ulcers**. Under questions on people with symptoms (confirmed GORD, non-ulcer dyspepsia, uninvestigated dyspepsia): **symptom improvement** (includes quality of life). Under the question on people at risk of developing gastric cancer: **prevention of gastric cancer** and **regression of pre-cancerous lesions**. Under the question on whether eradication treatments differ in their effects: **eradication rates of *H pylori*.**

METHODS

Clinical Evidence search and appraisal September 2007. The following databases were used to identify studies for this review: Medline 1966 to September 2007, Embase 1980 to September 2007, and The Cochrane Library, Issue 3, 2007 (all databases). Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for all databases, Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved were assessed independently by two information specialists using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language and including more than 20 individuals of whom more than 80% were followed up. Open studies were excluded unless the interventions could not be blinded. There was no minimum length of follow-up required to include studies. There is a wide range of combinations of

eradication therapy available, and we have restricted our coverage to those regimens in common clinical use. In the question, "Do *H pylori* eradication regimens differ in their effects?", when assessing triple regimens, we have included only regimens consisting of a proton pump inhibitor plus two antibiotics chosen among clarithromycin, amoxicillin, or a nitroimidazole (either metronidazole or tinidazole). When assessing quadruple regimens, we have included only regimens consisting of a proton pump inhibitor, a bismuth salt (either bismuth citrate, bismuth subsalicylate, bismuth subnitrate, or tripotassium dicitratobismuthate), a nitroimidazole (either metronidazole or tinidazole), and tetracycline. Dose comparisons have been restricted to high-dose versus low-dose clarithromycin in triple regimens. When assessing sequential therapy, we have assessed only 5 days of dual therapy using a proton pump inhibitor plus amoxicillin followed by 5-day triple therapy using a proton pump inhibitor plus a macrolide plus a nitroimidazole. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 42). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of H pylori eradication treatment in people with a confirmed duodenal ulcer?

OPTION ERADICATION TREATMENT IN PEOPLE WITH A CONFIRMED DUODENAL ULCER

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradication of *H pylori* makes healing of duodenal ulcers more likely and reduces the risk of bleeding with gastric and duodenal ulcers, either alone or when added to antisecretory drug treatment. Eradication also greatly reduces the risk of recurrence of a duodenal ulcer.
- We found no clinically important results from RCTs about the effects of eradication therapy on the prevention of gastrointestinal perforation or obstruction in people with duodenal ulcers.

Benefits and harms

Eradication treatment versus no eradication treatment:

We found one systematic review (search date 2005). [6]

Ulcer healing

Eradication treatment compared with no eradication treatment Eradication treatment seems more effective at increasing duodenal healing (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[6] Systematic review	207 people 2 RCTs in this analysis	**Healing** 76% with eradication treatment 42% with no treatment	RR for persistence 0.37 95% CI 0.26 to 0.53 NNT 3 95% CI 2 to 4	●●○	eradication treatment

Ulcer recurrence

Eradication treatment compared with no eradication treatment Eradication treatment may be more effective at reducing ulcer recurrence (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer recurrence					
[6] Systematic review	2509 people 27 RCTs in this analysis	**Recurrence** 14% with eradication treatment 64% with no treatment	RR 0.20 95% CI 0.15 to 0.26 Results were heterogeneous because of differing eradication regimens and lengths of follow-up	●●○	eradication treatment
[6] Systematic review	531 people 5 RCTs in this analysis Analysis of regimens using proton pump inhibitors	**Ulcer recurrence** 8% with eradication treatment containing proton pump inhibitors 65% with no treatment	RR 0.14 95% CI 0.09 to 0.20	●●●	eradication treatment containing proton pump inhibitors

Ulcer bleeding

No data from the following reference on this outcome. [6]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	5614 people with duodenal ulcer or gastric ulcer 42 RCTs in this analysis	**Adverse effects** 22% with eradication treatment 8% with antisecretory drugs or no treatment	RR 2.24 95% CI 1.72 to 2.93 The review did not perform a separate analysis for people with duodenal ulcer and gastric ulcer	●●○	antisecretory drugs or no treatment

Eradication treatment versus antisecretory drugs:

We found one systematic review (search date 2003). [7] The review assessed the effects of eradication treatment in people with previous peptic ulcer bleeding and did not differentiate between duodenal and gastric ulcers.

Ulcer bleeding

Eradication treatment compared with antisecretory drugs Eradication treatment is more effective at reducing ulcer bleeding compared with short-term or maintenance antisecretory drugs in people with duodenal or gastric ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer bleeding					
[7] Systematic review	355 people with previous peptic ulcer bleeding 6 RCTs in this analysis The review did not differentiate between duodenal and gastric ulcers	**Bleeding** 5% with eradication treatment 24% with short-term antisecretory drugs alone with no maintenance antisecretory treatment	RR 0.23 95% CI 0.12 to 0.43	●●○	eradication treatment
[7] Systematic review	470 people with previous peptic ulcer bleeding 3 RCTs in this analysis The review did not differentiate between duodenal and gastric ulcers	**Bleeding** 2% with eradication treatment 6% with short-term antisecretory drugs plus maintenance antisecretory treatment	RR 0.27 95% CI 0.09 to 0.77	●●○	eradication treatment

Ulcer healing

No data from the following reference on this outcome. [7]

Ulcer recurrence

No data from the following reference on this outcome. [7]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [7]

Adverse effects

No data from the following reference on this outcome. [7]

Eradication treatment plus antisecretory drugs versus antisecretory drugs alone:
We found one systematic review (search date 2005). [6]

Ulcer healing

Eradication treatment plus antisecretory drugs compared with antisecretory drugs alone Adding *H pylori* eradication treatment to antisecretory drugs is more effective at increasing duodenal ulcer healing than antisecretory drugs alone (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[6] Systematic review	3910 people 34 RCTs in this analysis	**Healing** 83% with eradication treatment plus antisecretory drugs for 1 month 81% with antisecretory drugs alone for 1 month	RR for ulcer persistence 0.66 95% CI 0.58 to 0.76 NNT for persistence 14 95% CI 11 to 20	●○○	eradication treatment plus antisecretory drugs

Ulcer recurrence

Eradication treatment plus antisecretory drugs compared with antisecretory drugs alone Adding eradication treatment to antisecretory drugs may be no more effective than antisecretory drugs alone (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer recurrence					
[6] Systematic review	319 people 4 RCTs in this analysis	**Recurrence after ulcer healing** 12% with eradication treatment plus antisecretory drugs for 1 month 16% with ongoing maintenance antisecretory drugs alone	RR 0.73 95% CI 0.42 to 1.25	⟷	Not significant

Ulcer bleeding

No data from the following reference on this outcome. [6]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [6]

Adverse effects

No data from the following reference on this outcome. [6]

Further information on studies

Comment: We excluded analyses that grouped people by *H pylori* status at the end of the trial.

Adverse effects:
A systematic review (search date 1995) [8] found that minor adverse effects were common with bismuth (40% of people), metronidazole (39%), clarithromycin (22%), and tinidazole (7%). Discon-

tinuation of treatment because of severe adverse effects was rare (bismuth 4%, metronidazole 2%, clarithromycin 1%, and tinidazole <1%).

Ulcer recurrence:
Observational evidence from RCTs suggests that duodenal ulcer recurrence rates 1 year after treatment are lower in people with successful *H pylori* eradication treatment (recurrence rates in US RCTs: 20%, 95% CI 14% to 26% in people cured of *H pylori* *v* 56%, 95% CI 50% to 61% in people remaining infected). [9] The recurrence rate in non-US trials was lower than in the US trials (6% for people cured of *H pylori*). The difference in recurrence rates may be partially explained by the marked loss to follow-up in the US trials (9%–41%). However, countries with low prevalence of *H pylori* infection also have a low prevalence of duodenal ulcers, but a greater proportion of those ulcers arise from causes other than *H pylori*; therefore, eradication may be less effective where *H pylori* prevalence is low. Poor adherence to *H pylori* eradication treatment, and the use of less effective regimens, may lead to increased antibiotic resistance in *H pylori*, but we found no direct evidence to support this. The harms of *H pylori* eradication treatment are mainly the minor short-term effects of the antibiotics, particularly nausea from metronidazole or clarithromycin, and diarrhoea. Bismuth may turn the stools black.

Clinical guide:
H pylori eradication is the treatment of choice for duodenal ulcers; it heals ulcers as effectively as acid suppression and effectively prevents recurrence.

QUESTION **What are the effects of H pylori eradication treatment in people with a confirmed gastric ulcer?**

OPTION **ERADICATION TREATMENT IN PEOPLE WITH A CONFIRMED GASTRIC ULCER**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradication reduces recurrence after healing of a gastric ulcer; however, we don't know whether it increases healing of gastric ulcers.
- Eradication of *H pylori* reduces the risk of bleeding with gastric and duodenal ulcers when compared with antisecretory therapy alone.
- We found no clinically important information from RCTs about the effects of eradication treatment on prevention of gastrointestinal obstruction or perforation in people with gastric ulcers.

Benefits and harms

Eradication treatment versus no eradication treatment:

We found one systematic review (search date 2005). [6]

Ulcer recurrence

Eradication treatment compared with no eradication treatment Eradication treatment is more effective at reducing recurrence of gastric ulcer (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer recurrence					
[6] Systematic review	1104 people 11 RCTs in this analysis	**Recurrence of gastric ulcer** 14% with eradication treatment 58% with no treatment	RR 0.29 95% CI 0.20 to 0.42 NNT 3 95% CI 2 to 5	●●○	eradication treatment

Ulcer healing

No data from the following reference on this outcome. [6]

Ulcer bleeding

No data from the following reference on this outcome. [6]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] Systematic review	5614 people with duodenal ulcer or gastric ulcer 42 RCTs in this analysis	**Adverse effects** 22% with eradication treatment 8% with antisecretory drugs or no treatment	RR 2.24 95% CI 1.72 to 2.93 The review did not perform a separate analysis for people with duodenal ulcer and gastric ulcer	●●○	antisecretory drugs or no treatment

Eradication treatment versus antisecretory drugs:

We found one systematic review (search date 2003). [7] The review assessed the effects of eradication treatment in people with previous peptic ulcer bleeding and did not differentiate between duodenal and gastric ulcers.

Ulcer bleeding

Eradication treatment compared with antisecretory drugs Eradication treatment is more effective at reducing ulcer bleeding compared with short-term or maintenance antisecretory drugs in people with duodenal or gastric ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer bleeding					
[7] Systematic review	355 people with previous peptic ulcer bleeding 6 RCTs in this analysis The review did not differentiate between duodenal and gastric ulcers	**Bleeding** 5% with eradication treatment 24% with short-term antisecretory drugs alone with no maintenance antisecretory treatment	RR 0.23 95% CI 0.12 to 0.43	●●○	eradication treatment
[7] Systematic review	470 people with previous peptic ulcer bleeding 3 RCTs in this analysis The review did not differentiate between duodenal and gastric ulcers	**Bleeding** 2% with eradication treatment 6% with short-term antisecretory drugs plus maintenance antisecretory treatment	RR 0.27 95% CI 0.09 to 0.77	●●○	eradication treatment

Ulcer healing

No data from the following reference on this outcome. [7]

Ulcer recurrence

No data from the following reference on this outcome. [7]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [7]

Adverse effects

No data from the following reference on this outcome. [7]

Eradication treatment plus antisecretory drugs versus antisecretory drugs alone:

We found one systematic review (search date 2005). [6]

Ulcer healing

Eradication treatment plus antisecretory drugs compared with antisecretory drugs alone Eradication treatment plus antisecretory drugs is no more effective at increasing endoscopic healing compared with antisecretory drugs alone in people with gastric ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[6] Systematic review	1572 people with gastric ulcers 14 RCTs in this analysis	**Healing** 78% with eradication treatment plus antisecretory drugs 86% with antisecretory drugs alone	RR for ulcer persistence 1.25 95% CI 0.88 to 1.76	⟷	Not significant

Ulcer recurrence

No data from the following reference on this outcome. [6]

Ulcer bleeding

No data from the following reference on this outcome. [6]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [6]

Adverse effects

No data from the following reference on this outcome. [6]

Further information on studies

Comment: None.

QUESTION **What are the effects of H pylori eradication treatment in people with NSAID-related peptic ulcers?**

OPTION **ERADICATION TREATMENT IN PEOPLE WITH NSAID-RELATED PEPTIC ULCERS**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- We don't know whether eradication therapy is more effective than a single antisecretory drug alone at healing ulcers at 8 weeks in people taking NSAIDs who have bleeding peptic ulcers.

Benefits and harms

Eradication treatment versus antisecretory drugs alone:

We found one RCT comparing *H pylori* eradication treatment versus a proton pump inhibitor alone in people with NSAID-related peptic ulcer. [10]

Ulcer healing

Eradication treatment compared with antisecretory drugs alone Eradication treatment may be no more effective than a single antisecretory drug alone at healing ulcers in people taking NSAIDs who have bleeding peptic ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[10] RCT	195 people with *H pylori*, using NSAIDs, and with bleeding peptic ulcers	**Healing rate , 8 weeks** 77/93 (83%) with eradication treatment (bismuth subcitrate plus tetracycline plus metronidazole plus omeprazole) 88/102 (86%) with omeprazole alone	P = 0.50	⟷	Not significant

Ulcer recurrence

No data from the following reference on this outcome. [10]

Ulcer bleeding

No data from the following reference on this outcome. [10]

Ulcer perforation or obstruction

No data from the following reference on this outcome. [10]

Adverse effects

No data from the following reference on this outcome. [10]

Further information on studies

Comment: None.

QUESTION **What are the effects of H pylori eradication treatment for preventing recurrence of NSAID-related peptic ulcers in people with previous ulcers or dyspepsia?**

OPTION **ERADICATION TREATMENT FOR PREVENTING RECURRENCE OF NSAID-RELATED PEPTIC ULCERS IN PEOPLE WITH PREVIOUS ULCERS OR DYSPEPSIA**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- We don't know whether eradication of *H pylori* reduces NSAID-related ulcers in people with previous ulcers.

Benefits and harms

Eradication treatment versus antisecretory drugs alone:

We found two RCTs. [11] [12]

Ulcer prevention

Eradication treatment compared with antisecretory drugs alone We don't know how eradication treatment and antisecretory drugs alone compare at preventing peptic ulcers or bleeding from ulcers in people taking NSAIDs who have had previous ulcers (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer prevention					
[11] RCT	102 people with *H pylori* and taking NSAIDs, with a history of dyspepsia or peptic ulceration, but without active ulcers	**Cumulative 6-month risk of peptic ulcer** 12% with 1-week quadruple eradication regimen 34% with omeprazole alone for 1 week	P = 0.009	○○○	quadruple eradication regimen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[11] RCT	102 people with *H pylori* and taking NSAIDs, with a history of dyspepsia or peptic ulceration, but without active ulcers	**Cumulative 6-month risk of bleeding peptic ulcer** 4% with 1-week quadruple eradication regimen 27% with omeprazole alone for 1 week Absolute numbers not reported	P = 0.003	○○○	quadruple eradication regimen
[12] RCT	150 people taking naproxen with *H pylori* and a bleeding peptic ulcer that healed with omeprazole treatment Subgroup analysis Total population of 400 people who were taking naproxen or low-dose aspirin	**Cumulative 6-month risk of developing a bleeding ulcer** 19% with 1-week triple eradication regimen (bismuth subcitrate plus tetracycline plus metronidazole) 4% with 6 months' maintenance treatment with omeprazole Absolute numbers not reported	ARI 14.4% 95% CI 4.4% to 24.4%	○○○	omeprazole
[12] RCT	250 people taking low-dose aspirin with *H pylori* and a bleeding peptic ulcer that healed with omeprazole treatment Subgroup analysis Total population of 400 people who were taking naproxen or low-dose aspirin	**Cumulative 6-month risk of developing a bleeding ulcer** 1.9% with 1-week triple eradication regimen (bismuth subcitrate plus tetracycline plus metronidazole) 0.9% with 6 months' maintenance treatment with omeprazole Absolute numbers not reported	Absolute difference +1.0% 95% CI –1.9% to +3.9% Given the much lower risk of bleeding with low-dose aspirin compared with naproxen, the RCT may have been underpowered with respect to aspirin, although a large absolute effect can be excluded	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [11] [12]

Further information on studies

Comment: **Clinical guide:**
The evidence on the effects of *H pylori* eradication treatment on recurrent bleeding from an NSAID-induced peptic ulcer is conflicting. However, even when *H pylori* eradication treatment is effective in reducing recurrent bleeding from an NSAID-induced peptic ulcer, the absolute risk of bleeding remains significant. Therefore discontinuation of NSAID treatment, or use of an additional preventative treatment, is desirable.

QUESTION **What are the effects of H pylori eradication treatment for preventing NSAID-related peptic ulcers in people without previous ulcers?**

OPTION **ERADICATION TREATMENT FOR PREVENTING NSAID-RELATED PEPTIC ULCERS IN PEOPLE WITHOUT PREVIOUS ULCERS**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradication of *H pylori* may reduce the risk of NSAID-related ulcers in people without previous ulcers.

Benefits and harms

H pylori eradication versus no treatment or placebo:

We found two RCTs. [13] [14]

Ulcer prevention

Eradication treatment compared with no treatment/placebo *H pylori* eradication treatment seems more effective at reducing the risk of developing a peptic ulcer at 5 to 8 weeks compared with placebo or no treatment in people without previous ulcers taking NSAIDs (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peptic ulcers					
[13] RCT	100 *H pylori*-positive people requiring NSAID treatment and without any history of peptic ulceration or gastric surgery	**Peptic ulcer , 8 weeks** 3/45 (7%) with 1-week triple eradication regimen 12/47 (26%) with no eradication treatment After treatment, all patients were given NSAIDs for 8 weeks	P = 0.01	○○○	triple eradication regimen
[14] RCT **4-armed trial**	832 people with *H pylori* and no history of ulcer, and requiring treatment with an NSAID The remaining arms evaluated omeprazole alone and 1-week triple eradication regimen plus 4 weeks of omeprazole	**Peptic ulcers , 5 weeks** 2/161 (1%) with 1-week triple eradication regimen 10/171 (6%) with placebo for 5 weeks	P <0.05 for 1-week triple eradication regimen *v* placebo Analysis not by intention to treat	○○○	triple eradication regimen
[14] RCT **4-armed trial**	832 people with *H pylori* and no history of ulcer, and requiring treatment with an NSAID The remaining arms evaluated omeprazole alone and 1-week triple eradication regimen	**Peptic ulcers , 5 weeks** 2/173 (1%) with 1-week triple eradication regimen plus 4 weeks of omeprazole 10/171 (6%) with placebo for 5 weeks	P <0.05 for 1-week triple eradication regimen plus 4 weeks of omeprazole *v* placebo Analysis not by intention to treat	○○○	triple eradication regimen

Adverse effects

No data from the following reference on this outcome. [13] [14]

H pylori eradication treatment versus antisecretory drugs:

We found one RCT, which compared two eradication regimens, omeprazole alone, and placebo. [14] The results of eradication treatment versus placebo from this RCT are reported above.

Ulcer prevention

Eradication treatment compared with antisecretory drugs We don't know how 1 week of triple eradication treatment and 1 week of triple eradication treatment plus omeprazole for 4 weeks compare at preventing peptic ulcers at 5 weeks in people without previous ulcers taking NSAIDs (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Peptic ulcers					
[14] RCT **4-armed trial**	832 people with *H pylori* and no history of ulcer, requiring treatment with an NSAID The remaining arm evaluated placebo alone	**Peptic ulcers , 5 weeks** 2/161 (1%) with 1-week triple eradication regimen 2/173 (1%) with 1-week triple eradication regimen plus 4 weeks of omeprazole 0/155 (0%) with omeprazole alone for 5 weeks	Reported no significant difference among active treatment groups P value not reported Analysis not by intention to treat	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [13] [14]

Further information on studies

Comment: **Clinical guide:**
It is likely that *H pylori* eradication will reduce the risk of ulceration with NSAIDs (but that risk is not reduced to zero), and other prophylactic treatments should be considered.

QUESTION What are the effects of H pylori eradication treatment in people with confirmed GORD?

OPTION ERADICATION TREATMENT IN PEOPLE WITH GORD

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradication of *H pylori* does not reduce symptoms of GORD.

Benefits and harms

H pylori eradication treatment versus placebo:

We found two RCTs. [15] [16]

Symptom improvement

Eradication treatment compared with placebo H pylori eradication treatment is no more effective at reducing symptoms at 1 to 2 years in people with GORD (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom recurrence					
[15] RCT	190 *H pylori*-positive people with GORD but no duodenal ulcer	**Symptomatic relapse , 1 year** 83% with *H pylori* eradication treatment 83% with placebo	difference 0% 95% CI –11% to +11%	⟷	Not significant
[16] RCT	People with GORD symptoms at baseline (number of people not clear) Subgroup analysis Total population was 1558 *H pylori*-positive people with or without GORD symptoms at baseline	**Heartburn , 2 years** with *H pylori* eradication treatment with placebo	OR 0.90 95% CI 0.71 to 1.14	⟷	Not significant
[16] RCT	People with GORD symptoms at baseline (number of people not clear) Subgroup analysis Total population was 1558 *H pylori*-positive people with or without GORD symptoms at baseline	**Reflux , 2 years** with *H pylori* eradication treatment with placebo	OR 0.89 95% CI 0.62 to 1.29	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [15] [16]

Further information on studies

Comment: Case control studies have found an increased risk of reflux symptoms after *H pylori* eradication. [17] However, discontinuation of antisecretory treatment after *H pylori* eradication might have unmasked symptoms of co-existing GORD.

QUESTION **What are the effects of H pylori eradication treatment in people with localised B cell lymphoma of the stomach?**

OPTION **ERADICATION TREATMENT IN PEOPLE WITH LOCALISED B CELL LYMPHOMA OF THE STOMACH**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Gastric B cell lymphoma lesions may regress after *H pylori* eradication, but we don't know this for sure.
- We found no clinically important results from RCTs about the effects of *H pylori* eradication treatment in people with localised B cell gastric lymphoma (also known as mucosa-associated lymphoid tissue [MALT] lymphoma).

Benefits and harms

H pylori eradication therapy versus placebo or no treatment:

We found no systematic review or RCTs.

Further information on studies

Comment: We found six prospective cohort studies of *H pylori* eradication in people with localised low-grade lymphomas. [18] Tumour regression occurred in 60% to 93% of people, but responses were sometimes delayed, and some people relapsed within 1 year of treatment. A further uncontrolled study (28/34 [82%] people with B cell gastric lymphoma were found to be *H pylori* positive, and were given eradication treatment) found that 14/28 people (50%, 95% CI 31% to 69%) achieved complete remission at 18 months' follow-up. [19]

Clinical guide:
Treatment options for primary gastric lymphoma include surgery, radiotherapy, chemotherapy, and *H pylori* eradication. We found no direct comparative studies.

QUESTION **What are the effects of H pylori eradication treatment on the risk of developing gastric cancer?**

OPTION **ERADICATION TREATMENT FOR PREVENTION OF GASTRIC CANCER**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Despite the association between *H pylori* infection and gastric cancer, no studies have shown a reduced risk after eradication treatment.

Benefits and harms

H pylori eradication treatment versus placebo for the prevention of gastric cancer in people at high risk of cancer:

We found no systematic review but found two RCTs of the effects of *H pylori* eradication on the development of gastric cancer. [20] [21] Both were conducted in populations at high risk of gastric cancer.

Prevention of gastric cancer

Eradication treatment compared with placebo Eradication treatment is no more effective at reducing the risk of developing gastric cancer in people at high risk of cancer (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of gastric cancer					
[20] RCT	1630 people at high risk of gastric cancer	**Gastric cancer , 7 years** 7/817 (0.86%) with eradication treatment 11/813 (1.35%) with placebo	HR 0.63 95% CI 0.24 to 1.62 P = 0.34	⟷	Not significant
[21] RCT	2258 people at high risk of gastric cancer	**Gastric cancer , 7 years** 19/1130 (1.7%) with eradication treatment 27/1128 (2.4%) with placebo	HR 0.70 95% CI 0.39 to 1.27 P = 0.14	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [20] [21]

H pylori eradication treatment versus placebo for regression of pre-cancerous lesions:

We found one RCT. [22]

Regression of pre-cancerous lesions

Eradication treatment compared with placebo Eradication treatment is more effective at increasing regression of pre-cancerous lesions in people with gastric atrophy or intestinal metaplasia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Regression of pre-cancerous lesions					
[22] RCT **4-armed trial**	852 people with gastric atrophy or intestinal metaplasia found at screening endoscopy The four arms evaluated *H pylori* eradication treatment, beta-carotene, ascorbic acid, and placebo	**Atrophy** with eradication treatment with no eradication treatment Absolute numbers not reported	RR 4.8 95% CI 1.6 to 14.2 Result calculated by multivariate modelling	●●○	eradication treatment
[22] RCT **4-armed trial**	852 people with gastric atrophy or intestinal metaplasia found at screening endoscopy The four arms evaluated *H pylori* eradication treatment, beta-carotene, ascorbic acid, and placebo	**Intestinal metaplasia** with eradication treatment with no eradication treatment Absolute numbers not reported	RR 3.1 95% CI 1.0 to 9.3 Result calculated by multivariate modelling	●●○	eradication treatment

Adverse effects

No data from the following reference on this outcome. [22]

H pylori eradication treatment versus placebo for the prevention of gastric cancer in people not at high risk:

We found no systematic review or RCTs.

Further information on studies

Comment: In two of the identified RCTs, [20] [21] post hoc analysis suggested that gastric cancer is more likely to develop in people with pre-cancerous lesions at baseline. [20] We found one systematic review of nested case control studies (search date 1999; 12 studies, 1228 cases, 3406 controls). [23] In the absence of trial data, this is the best evidence of an association between *H pylori* infection and gastric cancer. The review found that overall there was a significant association between *H pylori* infection and the subsequent development of gastric cancer (OR 2.36, 95% CI 1.98 to 2.81). The review found no significant association between *H pylori* and cardia cancer (OR 0.99, 95% CI 0.72 to 1.35). It did find a significant association for non-cardia (distal) cancer (OR 2.97, 95% CI 2.34 to 3.77). The review also found a strong interaction with age and time from sample collection. *H pylori* does not colonise areas of cancer, intestinal metaplasia, or atrophy, and antibodies may be lost with increasing age. Prospective studies with a short time period between the collection of the serum sample and the development of the cancer, or retrospective studies, may underestimate the association. The review found a significant association between *H pylori* and non-cardia cancer, where the time from sampling to cancer was more than 10 years (OR 5.93, 95% CI 3.41 to 10.3). [23] A systematic review of the role of eradication therapy in preventing gastric cancer in high-risk populations is registered with the Cochrane Collaboration, and is due for completion imminently. [24]

QUESTION What are the effects of H pylori eradication treatment in people with confirmed non-ulcer dyspepsia?

OPTION ERADICATION TREATMENT IN PEOPLE WITH CONFIRMED NON-ULCER DYSPEPSIA

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradicating *H pylori* has been shown to reduce dyspeptic symptoms in people with non-ulcer dyspepsia compared with placebo.

Benefits and harms

H pylori eradication treatment versus placebo:

We found one systematic review (search date 2004). [25] Two RCTs identified by the review assessed the effect of *H pylori* eradication on endoscopically assessed oesophagitis (see Adverse effects). [26] [27] See also adverse effects in option on eradication treatment for *H pylori* in people with confirmed duodenal ulcer, p 4 .

Symptom improvement

Eradication treatment compared with placebo H pylori eradication treatment is more effective at reducing dyspeptic symptoms in people with non-ulcer dyspepsia at 3 to 12 months (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Dyspeptic symptoms					
[25] Systematic review	3186 people with *H pylori* and non-ulcer dyspepsia 13 RCTs in this analysis	**Proportion with dyspeptic symptoms , 3–12 months** 1118/1742 (64%) with eradication treatment 1016/1444 (70%) with placebo	RR 0.92 95% CI 0.88 to 0.97 NNT 18 95% CI 12 to 48	●○○	eradication treatment
Quality of life					
[25] Systematic review	839 people with *H pylori* and non-ulcer dyspepsia 3 RCTs in this analysis	**Quality of life scores , 3–12 months** with eradication treatment with placebo	WMD –0.25 95% CI –3.49 to +2.99	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Oesophagitis					
[26] [27]	People with non-ulcer dyspepsia In review [25]	**Endoscopically assessed oesophagitis** 5.7% with eradication treatment 2.9% with placebo	ARI +2.8% 95% CI –0.5% to +6.0% RR 2.1 95% CI 0.9 to 4.6 No trial evaluated individual dyspeptic symptoms, so the effect on reflux symptoms cannot be estimated separately from epigastric pain	⟷	Not significant

Further information on studies

Comment: **Clinical guide:**
H pylori eradication treatment results in a small but significant benefit in symptoms. This is similar to the benefit achieved by treatment with a proton pump inhibitor, but more cost-effective as the effect persists after treatment for at least 2 years and possibly longer.

QUESTION **What are the effects of H pylori eradication treatment in people with uninvestigated dyspepsia?**

OPTION **ERADICATION TREATMENT IN PEOPLE WITH UNINVESTIGATED DYSPEPSIA**

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Eradicating *H pylori* has been shown to reduce dyspeptic symptoms in people with uninvestigated dyspepsia compared with placebo.
- Delaying endoscopy is not safe in people at increased risk of gastrointestinal malignancy.

Benefits and harms

H pylori eradication treatment versus placebo in people with uninvestigated dyspepsia:

We found two RCTs. [28] [29]

Symptom improvement

Eradication treatment compared with placebo Eradication treatment is more effective at increasing relief from dyspeptic symptoms at 1 year in people with *H pylori* infection (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[28] RCT	294 people with dyspeptic symptoms and confirmed *H pylori* infection	**Proportion of people free of dyspeptic symptoms , 1 year** 41/145 (28%) with eradication treatment 22/149 (15%) with placebo	ARI 13% 95% CI 4% to 24% P = 0.008	○○○	eradication treatment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT	184 people with *H pylori* infection and long-term proton pump inhibitor use	**Mean change in dyspepsia symptom scores from baseline (measured by Leeds Dyspepsia Questionnaire, score range 0–40) , 1 year** –2.7 with eradication therapy +0.4 with placebo Dyspepsia was assessed as a secondary outcome; primary outcome was the change in number of proton pump inhibitor prescriptions (not reported here)	Mean difference –3.1 95% CI –5.3 to –0.9 P = 0.005	○○○	eradication treatment

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	184 people with *H pylori* infection and long-term proton pump inhibitor use	**Change in heartburn** +9% with eradication treatment –5% with placebo	P = 0.13	⟷	Not significant

No data from the following reference on this outcome. [28]

Initial *H pylori* testing plus eradication treatment versus management based on initial endoscopy or versus empirical eradication treatment:

We found two systematic reviews (search dates 2004 [30] and 2005) [31] of people with dyspepsia not considered at high risk of gastrointestinal malignancy (see comment). Both reviews identified five RCTs, with four RCTs common to both reviews. However, the reviews performed different meta-analyses, and so we report both reviews here. Both reviews included open-label RCTs. We also found two subsequent RCTs. [32] [33]

Symptom improvement

H pylori testing plus eradication compared with management based on initial endoscopy H pylori testing and eradication treatment strategies and management based on initial endoscopy may be equally effective at reducing dyspepsia at 1 year in people at low risk of gastrointestinal malignancy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Dyspeptic symptoms					
[30] Systematic review	2222 people with dyspeptic symptoms including those of GORD 5 RCTs in this analysis	**Proportion of people with dyspeptic symptoms** 264/836 (31%) with test-and-treat strategy 283/846 (33%) with endoscopy-based management	RR 0.95 95% CI 0.79 to 1.15 Calculated using random effects model Significant statistical heterogeneity among studies; see further information on studies for full details Results may not be generalisable to primary care; see further information on studies for full details	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] Systematic review	1924 people with dyspeptic symptoms including those of GORD 5 RCTs in this analysis 4 RCTs in analysis carried out by review [30]	**Dyspeptic symptoms , 1 year** with test-and-treat strategy with endoscopy-based management Absolute results reported graphically	RR 0.95 95% CI 0.2 to 0.99 Individual patient data meta-analysis No heterogeneity among RCTs; see further information on studies for full details	●○○	endoscopy-based management
[32] RCT **3-armed trial**	234 people with dyspeptic symptoms	**Decrease in mean dyspepsia severity score (assessed on a 12-item dyspepsia symptom severity score) , 6 weeks** 5.6 with empirical endoscopy 5.6 with eradication treatment 4.4 with empirical treatment with cisapride If no symptom improvement after 2 weeks, endoscopy was performed on eradication and empirical groups	Significance not assessed		
[32] RCT **3-armed trial**	234 people with dyspeptic symptoms	**Decrease in mean dyspepsia severity score (assessed on a 12-item dyspepsia symptom severity score) , 1 year** with empirical endoscopy with eradication treatment with empirical treatment with cisapride If no symptom improvement after 2 weeks, endoscopy performed on eradication and empirical groups. Everyone had received endoscopy by 1 year, which makes interpretation of the results difficult	Among-group difference reported as not significant P value not reported	⟷	Not significant
[33] RCT **3-armed trial**	722 people with dyspeptic symptoms Data from 1 RCT	**Proportion of people who were asymptomatic , 1 year** 26% with test-and-eradicate strategy 23% with empirical proton pump inhibitor for 1 week 22% with empirical proton pump inhibitor for 1 week, plus, if symptoms improved, test-and-eradicate strategy as needed Absolute numbers not reported	Among-group difference reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[34] RCT	People with dyspeptic symptoms In review [30] [31]	**Adverse effects** with test-and-eradicate strategy			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with endoscopy-based management A small proportion of people (14/104 [13%]) given *H pylori* eradication treatment discontinued treatment because of short-term adverse effects, which were not specified			
[35] RCT	People with dyspeptic symptoms In review [30] [31]	**Adverse effects** with test-and-eradicate strategy with endoscopy-based management A small proportion of people (4/80 [5%]) given *H pylori* eradication treatment discontinued treatment because of short-term adverse effects, which were not specified			

No data from the following reference on this outcome. [30] [31] [32] [33]

Further information on studies

[30] **Heterogeneity** The review reported significant statistical heterogeneity (P = 0.035; review set statistical heterogeneity as significant if P <0.05) among the RCTs because of inclusion of one RCT [36] that found positive results in favour of endoscopy; the other four did not. [30] **Generalisability** The results of the review might not apply directly to primary care, where people with less severe dyspepsia might be treated and *H pylori* eradication rates might be lower, and the reassuring or anxiety-provoking effect of specialist consultation might not be replicated.

[31] The review found no heterogeneity among the RCTs and suggested that this was possibly because of its exclusion of non-dyspeptic symptoms or because the analysis contained two primary care trials. One of the included RCTs was conducted in a hospital setting, three in primary care, and the fifth in both primary and secondary care. The RCT conducted in a hospital setting stipulated that all eligible people with dyspepsia consulting with a general medical practitioner should be included.

Comment:

Clinical guide:
The results of the systematic review [30] were in people at low risk of gastrointestinal malignancy and are not applicable to all people with dyspepsia. People with "alarm" symptoms (e.g., dysphagia, weight loss, jaundice, epigastric mass, or anaemia) or over the age of 55 years, with either continuous epigastric pain or first onset of symptoms in the previous year, may have a significant risk of upper gastrointestinal malignancy, and may benefit from prompt endoscopy. The small effects of endoscopy on symptoms observed in this review must be interpreted in the light of cost-effectiveness. In particular, the cost of endoscopy in many locations would not be warranted on the basis of such a small effect, and most guidelines (such as that of NICE) [37] advocate either *H pylori* "test and treat" or empirical acid suppression, rather than initial endoscopy, on the grounds of cost-effectiveness.

QUESTION Do H pylori eradication treatments differ in their effects?

OPTION QUADRUPLE REGIMENS VERSUS TRIPLE REGIMENS AS FIRST-LINE TREATMENT

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Quadruple and triple regimens seem equally effective at eradicating *H pylori* as first-line treatments.

Benefits and harms

Quadruple regimen versus triple regimen as first-line treatment:

We found one systematic review that was updated soon after its initial publication (search dates 2002 [38] and 2003) [39] comparing triple regimens versus quadruple regimens (either 7 or 10 days; both given for the same duration) as a first-line treatment.

Eradication rates

Quadruple regimens compared with triple regimens Quadruple regimens are no more effective as first-line treatment at clearing *H pylori* infection (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[38] [39] Systematic review	1128 people 5 RCTs in this analysis	**Eradication rates , time of measurement not reported** 451/569 (79%) with triple regimen 449/559 (80%) with quadruple regimen	OR 1.00 95% CI 0.64 to 1.57 P = 1.00 Updated meta-analysis reported here was published as a letter to the editor; results should be interpreted with caution	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] [39] Systematic review	1128 people 5 RCTs in this analysis	**Adverse effects** 34% with triple regimen 37% with quadruple regimen	OR 1.14 95% CI 0.76 to 1.7 P = 0.54 Updated meta-analysis reported here was published as a letter to the editor; results should be interpreted with caution	⟷	Not significant

Further information on studies

Comment:

When assessing quadruple regimens, we have included only regimens consisting of a proton pump inhibitor, a bismuth salt (either bismuth citrate, bismuth subsalicylate, bismuth subnitrate, or tripotassium dicitratobismuthate), a nitroimidazole (either metronidazole or tinidazole), and tetracycline.

Clinical guide:

The rationale for quadruple regimens is that they can be used as second-line treatment, giving different antibiotics than those commonly given with current triple treatments, thus reducing the likelihood of resistance (see option on quadruple versus triple regimens for second-line treatment, p 25).

OPTION QUADRUPLE REGIMENS VERSUS TRIPLE REGIMENS AS SECOND-LINE TREATMENT

N e w

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Quadruple regimens may be more effective as second-line treatment than triple regimens when a first-line triple regimen has failed to eradicate the infection. However, the evidence is limited in that, in comparisons of second-line quadruple versus triple regimens, most triple regimens did not contain a nitroimidazole.

Benefits and harms

Quadruple regimens versus triple regiments as second-line treatment:

We found no systematic review but found three RCTs assessing the effects of salvage therapy after failure of first-line treatment. [40] [41] [42]

Eradication rates

Quadruple regimens compared with triple regimens Quadruple regimens may be more effective at clearing *H pylori* infection as second-line treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[40] RCT **3-armed trial**	60 people with dyspepsia and persistent *H pylori* infection after treatment with amoxicillin-based or metronidazole-based triple regimens The remaining arm evaluated a repeat triple regimen for 14 days	**Eradication rates** 15/22 (68%) with quadruple regimen for 7 days 4/12 (33%) with repeat triple regimen for 7 days 34 people in this analysis See further information on studies for full details of the regimens used	P = 0.02 for quadruple regimen *v* repeat triple regimen (7 days)	○○○	quadruple regimen
[40] RCT **3-armed trial**	60 people with dyspepsia and persistent *H pylori* infection after treatment with amoxicillin-based or metronidazole-based triple regimens The remaining arm evaluated a repeat triple regimen for 7 days	**Eradication rates** 15/22 (68%) with quadruple regimen for 7 days 16/22 (73%) with repeat triple regimen for 14 days 44 people in this analysis See further information on studies for full details of the regimens used	P = 0.71 for quadruple regimen *v* repeat triple regimen (14 days)	⟷	Not significant
[41] RCT	48 people with persistent *H pylori* infection after treatment with a triple regimen	**Eradication rates** 20/28 (71%) with 14-day quadruple regimen 15/20 (75%) with 14-day triple regimen 41/47 (87%) received a metronidazole-based triple regimen; see further information on studies for details of the regimens used	P = 0.78	⟷	Not significant
[42] RCT	84 people with persistent *H pylori* infection after treatment with a metronidazole-based triple regimen	**Eradication rates** 27/40 (68%) with 7-day quadruple regimen 19/44 (43%) with 7-day triple regimen	P = 0.03 The RCT was terminated early (after recruiting 84 people); see further information on studies for full details	○○○	quadruple regimen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for full details of the regimens used			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	48 people with persistent *H pylori* infection after treatment with a triple regimen	**Adverse effects** 84% with quadruple regimen 82% with triple regimen Absolute numbers not reported 41/47 (87%) received a metronidazole-based triple regimen; see further information on studies for full details of the regimens used The most common adverse effects reported included nausea (33%), upset stomach (25%), diarrhoea (36%), abdominal pain (16%), lightheadedness or dizziness (4%), and fatigue (8%)	P = 0.85	⟷	Not significant
[42] RCT	84 people with persistent *H pylori* infection after treatment with a metronidazole-based triple regimen	**Mild or moderate adverse effects** 45% with quadruple regimen 66% with triple regimen Absolute numbers not reported See further information on studies for full details of the regimens used The most frequently reported adverse effect was abdominal pain (no further data reported)			

No data from the following reference on this outcome. [40]

Further information on studies

[40] The RCT compared a quadruple regimen containing omeprazole plus tripotassium dicitratobismuthate plus metronidazole plus tetracycline (22 people) for 7 days, repeat triple regimens for 7 days (12 people), and repeat triple regimens for 14 days (22 people). Repeat triple regimens were prescribed on the basis of previous antimicrobial resistance profiles, with alternative regimens to first-line treatment being given.

[41] The RCT compared a 14-day quadruple regimen containing lansoprazole plus bismuth subsalicylate plus metronidazole plus tetracycline versus a 14-day triple regimen containing lansoprazole plus amoxicillin plus clarithromycin.

[42] The RCT compared a 7-day quadruple regimen containing omeprazole plus bismuth subsalicylate plus metronidazole plus tetracycline versus a 7-day triple regimen containing omeprazole plus amoxicillin plus clarithromycin. **Early termination** The RCT was terminated early (after recruiting 84 people) because of poor *H pylori* eradication rates in people receiving the triple regimen and because the difference in eradication rates between the two regimens was larger than anticipated.

Comment: None.

OPTION SEQUENTIAL REGIMENS VERSUS TRIPLE REGIMENS AS FIRST-LINE TREATMENT New

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Ten-day sequential therapy may be more effective at eradicating *H pylori* than a 7-day triple regimen.
- Adverse effects were similar between sequential and triple regimens.

Benefits and harms

Sequential eradication regimens versus triple eradication regimens as first-line treatment:

We found one systematic review (search date not reported) [43] comparing sequential therapy versus triple regimens for 7 or 10 days.

Eradication rates

Sequential eradication regimens compared with 1-week triple regimens Sequential regimens may be more effective than triple regimens given for 7 or 10 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[43] Systematic review	2146 people 6 RCTs in this analysis	**Eradication rates** with sequential regimens with 7-day triple regimens Absolute numbers not reported Timeframe of outcome measurement not reported	RR 0.81 95% CI 0.78 to 0.84 Results must be interpreted with caution; the review was published as a commentary article and has not been peer reviewed	●○○	sequential regimens
[43] Systematic review	770 people 6 RCTs in this analysis	**Eradication rates** with sequential regimens with 10-day triple regimens Absolute numbers not reported Timeframe of outcome measurement not reported	RR 0.86 95% CI 0.81 to 0.91 Results must be interpreted with caution; the review was published as a commentary article and has not been peer reviewed	●○○	sequential regimens

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] Systematic review		**Adverse effects** with sequential regimen with 7-day or 10-day triple regimens The review did not pool data on adverse effects, but reported that the frequency of adverse effects was similar with sequential regimens and triple proton pump inhibitor regimens			

Further information on studies

Comment: When assessing sequential therapy, we have assessed only 5 days of dual therapy using a proton pump inhibitor plus amoxicillin followed by a 5-day triple regimen using a proton pump inhibitor plus a macrolide plus a nitroimidazole.

Clinical guide:
The authors of the review [43] noted that the RCTs identified were often written by similar authors and originated from the same centres in Italy. Therefore, more trials are needed by other groups comparing sequential regimens versus proton pump inhibitor triple therapy and quadruple therapy before we can be certain of the efficacy of this approach in the general population.

OPTION DIFFERENT TRIPLE REGIMENS VERSUS EACH OTHER AS FIRST-LINE TREATMENT

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Nitroimidazole-based triple regimens and amoxicillin-based triple regimens seem equally effective at eradicating *H pylori*. High-dose clarithromycin within an amoxicillin-based triple regimen seems more effective at eradicating *H pylori* than low-dose clarithromycin. However, the dose of clarithromycin within a nitroimidazole-based triple regimen does not seem to have an effect on eradication rates.
- Triple regimens using different proton pump inhibitors seem equally effective at eradicating *H pylori*.
- Pre-treatment with a proton pump inhibitor before triple regimen does not seem to increase *H pylori* eradication rates compared with no pre-treatment.

Benefits and harms

Nitroimidazole-based versus amoxicillin-based triple regimens as first-line treatment:

We found one systematic review (search date 1999; 22 RCTs; number of people not reported) [44] and three subsequent RCTs [45] [46] comparing nitroimidazole-based triple regimens versus amoxicillin-based triple regimens. Two of the RCTs were of a similar design and were reported in one publication. [46]

Eradication rates

Nitroimidazole-based compared with amoxicillin-based triple regimens Nitroimidazole-based triple regimens and amoxicillin-based triple regimens are equally effective at eradicating *H pylori* (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[44] Systematic review	2862 people 18 RCTs in this analysis	**Eradication rates** 1174/1456 (81%) with nitroimidazole-based regimens 1133/1406 (81%) with amoxicillin-based regimens All regimens contained a proton pump inhibitor and clarithromycin	OR 1.00 95% CI 0.83 to 1.22 Significant statistical heterogeneity among RCTs (P = 0.14; statistical heterogeneity defined by the review as significant if P <0.2)	⟷	Not significant
[44] Systematic review	893 people 7 RCTs in this analysis	**Eradication rates** 360/443 (81%) with amoxicillin-based regimens containing lower-dose clarithromycin (250 mg twice daily) 388/450 (86%) with nitroimidazole-based regimens containing lower-dose clarithromycin (250 mg twice daily) All regimens contained a proton pump inhibitor and clarithromycin	Peto OR 0.68 95% CI 0.48 to 0.98	●○○	nitroimidazole-based regimens

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[45] RCT **3-armed trial**	120 people with *H pylori* infection and dyspeptic symptoms or a history of peptic ulcer The remaining arm evaluated a 14-day metronidazole-based regimen (containing omeprazole plus clarithromycin)	**Eradication rates** 83% with 7-day metronidazole-based regimen (containing omeprazole plus clarithromycin) 92% with 7-day amoxicillin-based regimen (containing omeprazole plus clarithromycin) Absolute numbers not reported 74 people in analysis	Significance not assessed		
[46] RCT Two RCTs reported in one publication	People with *H pylori* infection and active peptic ulcers or a history of peptic ulcer Total population of 1016 people in two trials (trials A and B combined), 581 of whom received a triple regimen	**Eradication rates** 73%, 95% CI 65% to 81% with metronidazole-based regimen 65%, 95% CI 57% to 75% with amoxicillin-based regimen Absolute numbers not reported Data reported from trial A: for full details of regimens, see further information on studies	Significance of between-group difference not assessed		
[46] RCT Two RCTs reported in one publication	People with *H pylori* infection and active peptic ulcers or a history of peptic ulcer Total population of 1016 people in two trials (trials A and B combined), 581 of whom received a triple regimen	**Eradication rates** 81%, 95% CI 73% to 88% with metronidazole-based regimens 65%, 95% CI 56% to 73% with amoxicillin-based regimens Absolute numbers not reported Data reported from trial B: for full details of regimens, see further information on studies	Significance of between-group difference not assessed		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT **3-armed trial**	120 people with *H pylori* infection and dyspeptic symptoms or a history of peptic ulcer The remaining arm evaluated a 14-day metronidazole-based regimen	**Proportion of people reporting an adverse effect** 16/35 (46%) with 7-day metronidazole-based regimen 19/39 (48%) with 7-day amoxicillin-based regimen The RCT found that adverse effects were generally mild (no further data reported)	Significance assessment between groups not reported		
[45] RCT **3-armed trial**	120 people with *H pylori* infection and dyspeptic symptoms or a history of peptic ulcer The remaining arm evaluated a 14-day metronidazole-based regimen	**Total number of adverse effects reported (could be >1 per person)** 31 with 7-day metronidazole-based regimen 19 with 7-day amoxicillin-based regimen	P = 0.02	○○○	amoxicillin-based regimen
[46] RCT	1016 people with *H pylori* infection and	**Adverse effects**			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Two RCTs reported in one publication	active peptic ulcers or a history of peptic ulcer, 581 of whom received a triple regimen	with metronidazole-based regimens with amoxicillin-based regimens Absolute numbers not reported Results for trials A and B: for full details see further information on studies Adverse effects were similar in both groups and generally mild (no further data reported) The most commonly reported adverse effects in both RCTs included: taste perversion (13%); diarrhoea (9%); abdominal pain (7%); headache (7%); dyspepsia (6%); and nausea (5%)			

No data from the following reference on this outcome. [44]

Triple regimens using different proton pump inhibitors versus each other as first-line treatment:

We found four systematic reviews (search date 2000; [47] search date 2002) [48] [49] [50] and three subsequent RCTs. [51] [52] [53] All systematic reviews identified some RCTs in common but none completely superseded another and all performed different meta-analyses. Therefore, we report results of all the reviews here.

Eradication rates

Triple regimens using different proton pump inhibitors compared with each other No one proton pump inhibitor-based regimen is more effective at eradicating *H pylori* compared with other proton pump inhibitor regimens (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[47] Systematic review	2159 people 11 RCTs in this analysis	**Eradication rates** 963/1117 (86%) with esomeprazole-based triple regimens 843/1029 (82%) with omeprazole- or pantoprazole-based triple regimens	OR 1.38 95% CI 1.09 to 1.75	●○○	esomeprazole-based regimens
[49] Systematic review	833 people 2 RCTs in this analysis	**Eradication rates** 364/415 (88%) with omeprazole-based triple regimen 372/418 (89%) with esomeprazole-based triple regimen	OR 0.89 95% CI 0.58 to 1.35	⟷	Not significant
[47] Systematic review	1596 people 6 RCTs in this analysis Sensitivity analysis of 6 high-quality RCTs	**Eradication rates** 689/811 (85%) with esomeprazole-based triple regimens 649/785 (83%) with omeprazole- or pantoprazole-based triple regimens	OR 1.17 95% CI 0.89 to 1.54	⟷	Not significant
[48] Systematic review	1337 people 7 RCTs in this analysis	**Eradication rates** 444/534 (83%) with pantoprazole-based triple regimens	OR 1.00 95% CI 0.61 to 1.64	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		486/603 (81%) with triple regimens based on other proton pump inhibitors			
[48] Systematic review	2226 people 12 RCTs in this analysis	**Eradication rates** 852/1076 (79%) with rabeprazole-based triple regimens 886/1150 (77%) with triple regimens based on other proton pump inhibitors	OR 1.21 95% CI 0.97 to 1.52 The analysis includes one RCT comparing rabeprazole-based triple regimen versus a proton pump inhibitor-based dual regimen	⟷	Not significant
[49] Systematic review	550 people 3 RCTs in this analysis	**Eradication rates** 264/326 (81%) with lansoprazole-based triple regimen 192/224 (86%) with rabeprazole-based triple regimen	OR 0.77 95% CI 0.48 to 1.22	⟷	Not significant
[49] Systematic review	1085 people 6 RCTs in this analysis	**Eradication rates** 399/534 (75%) with omeprazole-based triple regimen 419/551 (76%) with lansoprazole-based triple regimen	OR 0.91 95% CI 0.69 to 1.21	⟷	Not significant
[49] Systematic review	825 people 4 RCTs in this analysis	**Eradication rates** 328/421 (78%) with omeprazole-based triple regimen 328/404 (81%) with rabeprazole-based triple regimen	OR 0.81 95% CI 0.58 to 1.15	⟷	Not significant
[51] RCT	101 people with *H pylori* infection and active duodenal ulcers	**Eradication rates** 81% with rabeprazole-based triple regimen for 7 days (including clarithromycin plus amoxicillin) 70% with omeprazole-based triple regimen for 7 days (including clarithromycin plus amoxicillin) Absolute results not reported ITT analysis	P >0.05	⟷	Not significant
[52] RCT	345 people with *H pylori* infection and current or previously active peptic ulcers	**Eradication rates** 77% with rabeprazole-based triple regimen for 7 days 75% with omeprazole-based triple regimen for 7 days Triple regimens contained clarithromycin and either amoxicillin or metronidazole ITT analysis	difference: +2% 95% CI −7% to +10%	⟷	Not significant
[53] RCT	90 people with *H pylori* infection and non-ulcer dyspepsia	**Eradication rates , 6 weeks** 28/45 (62%) with pantoprazole-based triple regimen for 14 days (including clarithromycin plus amoxicillin) 27/45 (60%) with lansoprazole-based triple regimen for 14 days (including clarithromycin plus amoxicillin)	P >0.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[52] RCT	345 people with *H pylori* infection and current or previously active peptic ulcers	**Adverse effects** with rabeprazole-based triple regimen for 7 days with omeprazole-based triple regimen for 7 days The RCT reported that mild to moderate adverse effects were reported by 162 people (47%) across both groups. The most frequently reported were diarrhoea (43/345 [12%]) and taste disturbances (39/345 [11%])			
[53] RCT	90 people with *H pylori* infection and non-ulcer dyspepsia	**Rate of adverse effects** with pantoprazole-based triple regimen for 14 days (including clarithromycin plus amoxicillin) with lansoprazole-based triple regimen for 14 days (including clarithromycin plus amoxicillin) Adverse effects were reported in 17 people (22%) and included nausea (7/79 [9%]), metallic taste (5/79 [6%]), and diarrhoea (5/79 [6%]) No further comparative data reported	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [47] [48] [49] [50] [51]

Higher-dose clarithromycin-based triple regimens versus lower-dose clarithromycin-based triple regimens as first-line treatment:

We found one systematic review (search date 1998; 4 RCTs; 385 people) [54] and three subsequent RCTs [55] [56] [57] comparing higher versus lower doses of clarithromycin within triple regimens.

Eradication rates

Higher-dose clarithromycin compared with lower-dose clarithromycin within triple regimens Amoxicillin-based triple regimens are more effective at eradicating *H pylori* when higher-dose clarithromycin is used. The dose of clarithromycin does not seem to affect the efficacy of nitroimidazole-based triple regimens (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[54] Systematic review	Number of people in analysis not reported The review included 385 people in total	**Eradication rates** 80% with triple regimen with clarithromycin 250 mg twice daily (with proton pump inhibitor and amoxicillin) 90% with triple regimen with clarithromycin 500 mg twice daily (with proton pump inhibitor and amoxicillin) Absolute numbers not reported	RR 0.89 95% CI 0.81 to 0.97 NNT 11 95% CI 6 to 38	●○○	higher-dose clarithromycin (with amoxicillin)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] Systematic review	Number of people in analysis not reported The review included 385 people in total	**Eradication rates** 87% with triple regimen with clarithromycin 250 mg twice daily (with proton pump inhibitor and metronidazole) 89% with triple regimen with clarithromycin 500 mg twice daily (with proton pump inhibitor and metronidazole) Absolute numbers not reported	RR 0.98 95% CI 0.93 to 1.04	⟷	Not significant
[55] RCT	288 people with *H pylori* infection and peptic ulcers	**Eradication rates** 116/143 (81%) with triple regimen using 200 mg clarithromycin twice daily (with omeprazole and amoxicillin) 116/145 (80%) with triple regimen using 400 mg clarithromycin twice daily (with omeprazole and amoxicillin)	Significance not assessed		
[56] RCT	189 people with gastric ulcers, all positive for *H pylori* Subgroup analysis Full RCT included 377 people with either gastric or duodenal ulcers	**Eradication rates** 88% with triple regimen with clarithromycin 200 mg twice daily (with lansoprazole and amoxicillin) 89% with triple regimen with clarithromycin 400 mg twice daily (with lansoprazole and amoxicillin)	Significance not assessed		
[56] RCT	188 people with duodenal ulcers, all positive for *H pylori* Subgroup analysis Full RCT included 377 people with either gastric or duodenal ulcers	**Eradication rates** 91.3% with triple regimen with clarithromycin 200 mg twice daily (with lansoprazole and amoxicillin) 84% with triple regimen with clarithromycin 400 mg twice daily (with lansoprazole and amoxicillin)	Significance not assessed		
[57] RCT	100 people with *H pylori* infection and a healed peptic ulcer or non-ulcer dyspepsia	**Eradication rates** 43/50 (86%) with 7-day triple regimen with clarithromycin 200 mg twice daily (with rabeprazole and amoxicillin) 47/50 (94%) with 7-day triple regimen with clarithromycin 400 mg twice daily (with rabeprazole and amoxicillin) ITT analysis	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[54] Systematic review	Number of people in analysis not reported	**Proportion of people with adverse effects** 21% with triple regimen with clarithromycin 500 mg twice daily	P = 0.77	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The review included 385 people in total	(with proton pump inhibitor and amoxicillin) 22% with triple regimen with clarithromycin 250 mg twice daily (with proton pump inhibitor and amoxicillin) Absolute numbers not reported			
[54] Systematic review	Number of people in analysis not reported The review included 385 people in total	**Proportion of people with adverse effects** 40% with triple regimen with clarithromycin 500 mg twice daily (with proton pump inhibitor and metronidazole) 30% with triple regimen with clarithromycin 250 mg twice daily (with proton pump inhibitor and metronidazole) Absolute numbers not reported	P <0.0001	○○○	triple regimen with lower-dose clarithromycin (with metronidazole)
[55] RCT	288 people with *H pylori* infection and peptic ulcers	**Adverse effects (not specified)** 67/143 (47%) with triple regimen with 200 mg clarithromycin twice daily (with omeprazole and amoxicillin) 76/145 (52%) with triple regimen with 400 mg clarithromycin twice daily (with omeprazole and amoxicillin)	Significance not assessed		
[56] RCT	377 people with either gastric or duodenal ulcers, all positive for *H pylori*	**Adverse effects** 47% with triple regimen with clarithromycin 200 mg twice daily (with lansoprazole and amoxicillin) 54% with triple regimen with clarithromycin 400 mg twice daily (with lansoprazole and amoxicillin) There were no treatment withdrawals because of adverse effects	Significance not assessed		
[57] RCT	100 people with *H pylori* infection and a healed peptic ulcer or non-ulcer dyspepsia	**Adverse effects** with 7-day triple regimen with clarithromycin 400 mg twice daily (with rabeprazole and amoxicillin) with 7-day triple regimen with clarithromycin 200 mg twice daily (with rabeprazole and amoxicillin) There were two cases of severe adverse effects reported: pneumothorax with low-dose clarithromycin and haemorrhagic colitis with high-dose clarithromycin No further comparative data reported	Reported as not significant P value not reported	⟷	Not significant

Pre-treatment with proton pump inhibitor versus no pre-treatment:

We found one systematic review (search date 2004; 9 RCTs; 773 people) comparing *H pylori* eradication rates with a pre-treatment proton pump inhibitor versus no pre-treatment. [58] The review carried out separate meta-analysis

assessing the effects of proton pump inhibitor pre-treatment on two different triple proton pump inhibitor triple regimens: trials assessing a proton pump inhibitor plus clarithromycin plus amoxicillin (172 people), and trials assessing a proton pump inhibitor plus a macrolide plus a nitroimidazole (241 people).

Eradication rates

Pre-treatment with proton pump inhibitor compared with no pre-treatment Pre-treatment with a proton pump inhibitor is no more effective at increasing eradication rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[58] Systematic review	172 people	**Eradication rates** 71% with pre-treatment 70% with no pre-treatment Analysis of RCTs assessing a proton pump inhibitor plus clarithromycin plus amoxicillin for eradication treatment	ARR +3% 95% CI −10% to +16%	⟷	Not significant
[58] Systematic review	241 people	**Eradication rates** 91% with pre-treatment 83% with no pre-treatment Analysis of RCTs assessing a proton pump inhibitor plus a macrolide plus a nitroimidazole	ARR +7% 95% CI −1% to +16%	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [58]

Further information on studies

[46] People were randomised into one of two study groups (A or B) and received triple regimens containing: pantoprazole plus clarithromycin plus metronidazole (289 people); or pantoprazole plus clarithromycin plus amoxicillin (292 people). The RCTs did not directly compare *H pylori* eradication rates between the two triple regimens.

Comment:

When assessing triple eradication regimens, we have included only regimens consisting of a proton pump inhibitor plus two antibiotics chosen among clarithromycin, amoxicillin, or a nitroimidazole (either metronidazole or tinidazole).

We identified one Chinese RCT comparing short-term triple regimen with omeprazole plus tinidazole plus clarithromycin for eradication of *H pylori* infection in older adults. [59] However, we could not obtain a copy of the full paper for assessment.

Clinical guide:
Antibiotic resistance with different triple regimens:
We found one systematic review (search date 1995; 19 RCTs; 1006 people with metronidazole-sensitive *H pylori*, 452 with metronidazole-resistant *H pylori*) [8] and three subsequent RCTs [60] [61] [62] in which data were analysed to examine effects of resistance on eradication rate.

We found two additional RCTs that did not meet our quality inclusion criteria but provided useful data on eradication rates in people with *H pylori* strains resistant or sensitive to antibiotics included in the eradication regimen. [63] [64]

The systematic review found that, in laboratory tests, nitroimidazole-based regimens achieved *H pylori* eradication in significantly fewer people showing nitroimidazole-resistant strains than in people with nitroimidazole-sensitive strains (99%, 95% CI 97% to 100% with sensitive strains *v* 69%, 95% CI 60% to 77% with resistant strains). [8] The review concluded that a clinically important reduction of eradication rates is unlikely if the proportion of resistant strains is below 25%. [8]

The first subsequent RCT (114 people with a confirmed duodenal ulcer and *H pylori* infection, 33 of whom had primary metronidazole resistance and 81 of whom had no resistance) found that metronidazole resistance significantly decreased the *H pylori* eradication rate with an omeprazole plus metronidazole plus clarithromycin regimen (77/81 [95%] with no metronidazole resistance *v* 25/33 [76%] with metronidazole resistance; RR 0.79, 95% CI 0.62 to 0.93). [60]

The second subsequent RCT (112 people with dyspeptic symptoms and *H pylori* infection) assessed the effects of antimicrobial resistance on *H pylori* eradication rates with 7-day proton pump inhibitor-based triple regimens containing metronidazole or clarithromycin. The RCT found that people with metronidazole-resistant isolates (primary metronidazole resistance) had significantly higher eradication failure rates compared with people with metronidazole-susceptible isolates (failure rates: 9/19 [47%] with metronidazole-resistant isolates *v* 7/44 [16%] with metronidazole-susceptible isolates; P <0.05). Similarly, people with clarithromycin-resistant isolates (primary clarithromycin resistance) had significantly higher eradication failure rates compared with people with clarithromycin-susceptible isolates (failure rates: 4/4 [100%] with clarithromycin-resistant isolates *v* 7/66 [11%] with clarithromycin-susceptible isolates; P <0.05). [61]

The third subsequent RCT (122 people with dyspeptic symptoms and *H pylori* infection) stratified people into a metronidazole-resistant and a metronidazole-susceptible group prior to randomisation. It compared omeprazole plus metronidazole plus clarithromycin with omeprazole plus amoxicillin plus clarithromycin for 1 week. The RCT found no significant difference in *H pylori* eradication rates between the amoxicillin-based regimen and metronidazole-based regimens in people with metronidazole-susceptible strains (23/26 [88%] with an amoxicillin-based regimen *v* 21/26 [81%] with metronidazole-based regimen; P = 0.11; ITT analysis). However, the RCT found that *H pylori* eradication rates were significantly higher with the amoxicillin-based regimen compared with the metronidazole-based regimen in people with metronidazole-resistant strains (30/35 [86%] with an amoxicillin-based regimen *v* 29/35 [83%] with a metronidazole-based regimen; P = 0.02; ITT analysis). [62]

The first additional open-label RCT (287 people with *H pylori* infection and a history of peptic ulcer or dyspeptic symptoms) assessed *H pylori* eradication rates with second-line therapy according to antibiotic susceptibility in people who had failed first-line eradication therapy. The RCT found that, in a subgroup of 118 people given clarithromycin plus omeprazole plus amoxicillin, *H pylori* eradication rates were lower in people with primary clarithromycin resistance compared with people with no clarithromycin resistance (9/58 [16%] with clarithromycin-resistant strains *v* 48/60 [80%] with clarithromycin-susceptible strains; significance assessment between groups not reported). [63]

The second additional RCT (228 people with *H pylori* infection and dyspeptic symptoms) assessed *H pylori* primary resistance to antibiotics within lansoprazole-based triple regimens. Results for antibiotic resistance were only available for 98 people (43%), randomised because samples were lost in an earthquake. The RCT found that a regimen of lansoprazole plus clarithromycin plus either amoxicillin or metronidazole achieved significantly higher *H pylori* eradication rates in people with no clarithromycin resistance compared with people with clarithromycin-resistant strains (62/68 [91%] with no clarithromycin resistance *v* 0/10 [0%] with clarithromycin resistance; P <0.001; per-protocol analysis). [64] The RCT found that metronidazole-containing regimens achieved similar *H pylori* eradication rates in people with metronidazole-susceptible and metronidazole-resistant strains (metronidazole plus lansoprazole plus amoxicillin: 23/27 [85%] with no metronidazole resistance *v* 14/17 [82%] with metronidazole resistance; metronidazole plus lansoprazole plus clarithromycin:15/18 [83%] with no metronidazole resistance *v* 10/16 [63%] with metronidazole resistance; significance assessment not reported). [64]

OPTION DURATION OF H PYLORI ERADICATION AS FIRST-LINE TREATMENT

- For GRADE evaluation of interventions for Helicobacter pylori infection, see table, p 42 .
- Two-week triple proton pump inhibitor regimens may be more effective than 1-week regimens for eradicating *H pylori*.

Benefits and harms

14-day triple regimen versus 7-day triple regimen as first-line treatment:

We found one systematic review (search date 1999; 7 RCTs; 906 people) [65] and three subsequent RCTs. [66] [67] [68]

Eradication rates

Two-week compared with 1-week triple regimen Two-week triple regimens seem more effective at eradicating *H pylori* (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication rates					
[65] Systematic review	906 people 7 RCTs in this analysis	**Eradication rates** 339/470 (72%) with 7-day treatment with proton pump inhibitor-based triple regimens 353/436 (81%) with 14-day treatment with proton pump inhibitor-based triple regimens	RR 0.89 95% CI 0.83 to 0.96 NNT 11 95% CI 7 to 33	●○○	14-day treatment
[68] RCT **3-armed trial**	909 people with *H pylori* infection and duodenal ulcer The remaining arm evaluated a 14-day dual regimen	**Eradication rates , 4 weeks** 240/301 (80%) with 7-day treatment with proton pump inhibitor-based triple regimen 246/301 (82%) with 14-day treatment with proton pump inhibitor-based triple regimen ITT analysis	P = 0.53 The RCT adjusted results to allow for multiple comparisons	⟷	Not significant
[67] RCT	598 people with *H pylori* infection and peptic ulcer disease	**Eradication rates , 5 weeks** 240/337 (71%) with 7-day treatment with proton pump inhibitor-based triple regimen 197/261 (76%) with 14-day treatment with proton pump inhibitor-based triple regimen Proton pump inhibitor-based triple regimen contained omeprazole plus clarithromycin plus amoxicillin ITT analysis	ARR −4% 95% CI −11% to +3% RCT designed as an equivalence trial; the high predetermined non-inferiority margin of 15% means that the results must be treated with caution	⟷	Not significant
[66] RCT	243 people with *H pylori* infection and dyspepsia having amoxicillin-based triple eradication therapy Subgroup analysis Total population of 486 people; RCT compared 7 days *v* 14 days of amoxicillin- and metronidazole-based triple regimens	**Eradication rates** 67/117 (57%) with 7-day treatment with amoxicillin-based triple regimen 88/126 (70%) with 14-day treatment with amoxicillin-based triple regimen ITT analysis; see further information on studies for additional detail	P = 0.05 Result is of borderline significance A multivariate analysis found that the 2-week duration of treatment was the only independent factor associated with a higher rate of *H pylori* eradication both at ITT and per-protocol analysis	⟷	Not significant
[66] RCT	243 people with *H pylori* infection and dyspepsia having metronidazole-based triple eradication therapy Subgroup analysis	**Eradication rates** 63/122 (52%) with 7-day treatment with metronidazole-based triple regimen 68/121 (56%) with 14-day treatment with metronidazole-based triple regimen	Significance not assessed A multivariate analysis found that the 2-week duration of treatment was the only independent factor associated with a higher rate of *H pylori* eradication both at ITT and per-protocol analysis		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Total population of 486 people; RCT compared 7 days *v* 14 days of amoxicillin- and metronidazole-based triple regimens	ITT analysis (see further information on studies)			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[68] RCT **3-armed trial**	909 people with *H pylori* infection and duodenal ulcer The remaining arm evaluated a 14-day dual regimen	**Adverse effects** 5.0% with 7-day treatment with proton pump inhibitor-based triple regimen 4.6% with 14-day treatment with proton pump inhibitor-based triple regimen Absolute numbers not reported	P = 0.80	⟷	Not significant
[67] RCT	598 people with *H pylori* infection and peptic ulcer disease	**Adverse effects** 9.6% with 7-day treatment with proton pump inhibitor-based triple regimen 9.9% with 14-day treatment with proton pump inhibitor-based triple regimen Absolute numbers not reported Proton pump inhibitor-based triple regimen contained omeprazole plus clarithromycin plus amoxicillin	P = 0.88	⟷	Not significant
[66] RCT	486 people with *H pylori* infection and dyspepsia having amoxicillin- or metronidazole-based triple eradication therapy The RCT assessed 7 days *v* 14 days of amoxicillin- and metronidazole-based regimens	**Adverse effects** with 7-day treatment with 14-day treatment Compliance was low; the RCT reported that the incidence of adverse effects was similar between the 7-day and 14-day regimens (absolute results tabulated) Adverse effects were primarily gastrointestinal: 23/486 (5%) people withdrew from treatment because of severe adverse effects	Significance not assessed		

No data from the following reference on this outcome. [65]

Further information on studies

[66] The ITT analysis overall included 75 (15%) people who withdrew from treatment: 23 people (5%) withdrew because of severe adverse effects; 32 (7%) people were lost to follow-up; and 20 (4%) people had poor compliance.

Comment: **Clinical guide:**
The risk of failure of a 7-day regimen as opposed to a 14-day regimen in any particular individual will relate to the local prevalence of antibiotic resistance, as 14-day regimens may overcome resistance to one of the antibiotics used. As longer regimens have a longer duration of minor adverse effects, the balance between local failure rate and adverse effects must be decided on the basis of locally validated data.

GLOSSARY

Sequential therapy Involves 10-day *H pylori* eradiction treatment: 5-day dual therapy with proton pump inhibitor plus amoxicillin followed by 5-day triple therapy with proton pump inhibitor plus macrolide plus a nitroimidazole.

Quadruple regimens *Helicobacter pylori* eradication regimen consisting of a proton pump inhibitor plus bismuth plus metronidazole plus tetracycline.

Antisecretory treatment A treatment that reduces the production of acid by the stomach. These treatments may either be H_2 receptor antagonists or proton pump inhibitors.

Bismuth A compound containing a bismuth salt, such as bismuth subsalicylate or bismuth citrate.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

MALT Mucosa-associated lymphoid tissue (MALT) is constitutionally found in the intestine but not in the stomach. MALT lymphoma is also known as B cell gastric lymphoma.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Proton pump inhibitor A drug that directly inhibits the mechanism within the stomach that secretes acid; examples are esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole.

Quadruple regimens *H pylori* eradication regimen consisting of four components: a proton pump inhibitor, a bismuth salt, a nitroimidazole (either metronidazole or tinidazole), and tetracycline.

Triple regimens *H pylori* eradication regimen consisting of three components: a proton pump inhibitor plus two antibiotics (either clarithromycin or amoxicillin), and a nitroimidazole (either metronidazole or tinidazole).

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

***H pylori* eradication treatments (quadruple regimens compared with triple regimens as second-line treatment)** New option for which we found three RCTs. [40] [41] [42] The RCTs found that quadruple regimens as second-line therapies were more effective than triple regimens at eradicating *H pylori*. Most triple regimens given did not contain a nitroimidazole. Categorised as Likely to be beneficial.

***H pylori* eradication treatments (sequential regimens compared with triple regimens as first-line treatment)** New option for which we found one systematic review. [43] The review found sequential therapy was more effective at increasing *H pylori* eradication rates compared with proton pump inhibitor triple regimens. Categorised as Likely to be beneficial.

***H pylori* eradication (in uninvestigated dyspepsia)** Three RCTs added. The first RCT found that eradication treatment was more effective at improving dyspepsia symptoms than placebo in long-term proton pump inhibitor users. [29] The other two RCTs found similar dyspepsia scores with test and treat, prompt endoscopy, and empirical eradication treatment. [32] [33] Categorisation unchanged (beneficial).

***H pylori* eradication treatments (different triple regimens compared with each other)** Four systematic reviews and 12 RCTs added. One systematic review [44] and three RCTs [45] (2 RCTs reported in 1 publication) [46] found that nitroimidazole-based triple regimens and amoxicillin-based triple regimens were equally effective at eradicating *H pylori*. Two RCTs [56] [57] found no significant difference in *H pylori* eradication rates between higher- and lower-dose clarithromycin within nitroimidazole-based triple regimens. Three systematic reviews [47] [49] [50] and three subsequent RCTs [51] [52] [53] found no significant difference in *H pylori* eradication rates between different proton pump inhibitor-based triple regimens. [47] [49] [50] Four RCTs [61] [62] [63] [64] found lower eradication rates in people infected with strains of *H pylori* resistant to antibiotics included in the eradication regimen compared with people infected with sensitive strains. It is unclear whether any one triple regimen is more effective than another. Categorisation unchanged (Unknown effectiveness).

***H pylori* eradication treatments (duration of *H pylori* eradication as first-line treatment)** Three RCTs [66] [67] [68] added, which found no significant difference in *H pylori* eradication rates between 1-week and 2-week triple

regimens, although in all three RCTs eradication rates were higher with 2-week regimens. Categorisation unchanged: both Likely to be beneficial, but the 2-week triple regimen is more effective than the 1-week triple regimen.

***H pylori* eradication treatments (quadruple regimens compared with triple regimens as first-line treatment)** One systematic review results updated and published as a letter to the editor. [39] The review found no significant difference in eradication rates between quadruple regimens and triple regimens. Categorisation changed from Likely to be beneficial to Unlikely to be beneficial with the rationale that quadruple regimens are no more effective than triple regimens. Adding a fourth drug to initial eradication treatment confers no additional benefit.

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Competing interests: GIL has received fees for speaking at conferences from AstraZeneca and has received travel grants in order to attend conferences from AstraZeneca, Janssen-Cilag, Sanofi-Aventis, and GlaxoSmithKline. ACF is the author of three systematic reviews referenced in this review. PM is the author of six systematic reviews and one RCT referenced in this review and has accepted fees for speaking from AstraZeneca, Wyeth, Mareda, and Abbott Laboratories.
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Disclaimer

GRADE **Evaluation of interventions for Helicobacter pylori infection.**

Important outcomes	Eradication rates, Prevention of gastric cancer, Regression of pre-cancerous lesions, Symptom improvement, Ulcer bleeding, Ulcer healing, Ulcer perforation or obstruction, Ulcer prevention, Ulcer recurrence								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of H pylori eradication treatment in people with a confirmed duodenal ulcer?									
2 (207) [6]	Ulcer healing	Eradication treatment versus no eradication treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
At least 27 (at least 2509) [6]	Ulcer recurrence	Eradication treatment versus no eradication treatment	4	0	–1	0	0	Moderate	Consistency point deducted for statistical heterogeneity owing to inclusion of different regimens
9 (825) [7]	Ulcer bleeding	Eradication treatment versus antisecretory drugs	4	0	0	–1	+1	High	Directness point deducted for inclusion of both duodenal and gastric ulcer. Effect-size point added for RR <0.5
34 (3910) [6]	Ulcer healing	Eradication treatment plus antisecretory drugs versus antisecretory drugs alone	4	0	0	0	0	High	
4 (319) [6]	Ulcer recurrence	Eradication treatment plus antisecretory drugs versus antisecretory drugs alone	4	0	0	0	0	High	
What are the effects of H pylori eradication treatment in people with a confirmed gastric ulcer?									
11 (1104) [6]	Ulcer recurrence	Eradication treatment versus no eradication treatment	4	0	0	0	+1	High	Effect-size point added for RR <0.5
9 (825) [7]	Ulcer bleeding	Eradication treatment versus antisecretory drugs	4	0	0	–1	+1	High	Directness point deducted for inclusion of both duodenal and gastric ulcer. Effect-size point added for RR <0.5
14 (1572) [6]	Ulcer healing	Eradication treatment plus antisecretory drugs versus antisecretory drugs alone	4	0	0	0	0	High	
What are the effects of H pylori eradication treatment in people with NSAID-related peptic ulcers?									
1 (195) [10]	Ulcer healing	Eradication treatment versus antisecretory drugs alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
What are the effects of H pylori eradication treatment for preventing recurrence of NSAID-related peptic ulcers in people with previous ulcers or dyspepsia?									
2 (502) [11] [12]	Ulcer prevention	Eradication treatment versus antisecretory drugs alone	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inclusion of different populations
What are the effects of H pylori eradication treatment for preventing NSAID-related peptic ulcers in people without previous ulcers?									

Important outcomes	Eradication rates, Prevention of gastric cancer, Regression of pre-cancerous lesions, Symptom improvement, Ulcer bleeding, Ulcer healing, Ulcer perforation or obstruction, Ulcer prevention, Ulcer recurrence								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (607) [13] [14]	Ulcer prevention	*H pylori* eradication versus no treatment or placebo	4	–1	0	0	0	Moderate	Quality point deducted for no ITT analysis
1 (489) [14]	Ulcer prevention	*H pylori* eradication treatment versus antisecretory drugs	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of events (2 with triple eradication treatment, none with omeprazole)
What are the effects of H pylori eradication treatment in people with confirmed GORD?									
2 (1748) [15] [16]	Symptom improvement	*H pylori* eradication treatment versus placebo	4	0	0	0	0	High	
What are the effects of H pylori eradication treatment on the risk of developing gastric cancer?									
2 (3888) [20] [21]	Prevention of gastric cancer	*H pylori* eradication treatment versus placebo for the prevention of gastric cancer in people at high risk of cancer	4	0	0	0	0	High	
1 (852) [22]	Regression of pre-cancerous lesions	*H pylori* eradication treatment versus placebo for regression of pre-cancerous lesions	4	–1	0	0	+1	High	Quality point deducted for incomplete reporting of results. Effect-size point added for RR >2
What are the effects of H pylori eradication treatment in people with confirmed non-ulcer dyspepsia?									
13 (3186) [25]	Symptom improvement	*H pylori* eradication treatment versus placebo	4	0	0	0	0	High	
What are the effects of H pylori eradication treatment in people with uninvestigated dyspepsia?									
2 (478) [28] [29]	Symptom improvement	*H pylori* eradication treatment versus placebo in people with uninvestigated dyspepsia	4	0	0	0	0	High	
8 (at least 3178) [30] [31] [32] [33]	Symptom improvement	Initial *H pylori* testing plus eradication treatment versus management based on initial endoscopy or versus empirical eradication treatment	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for uncertainty of applicability of results to both primary and secondary care settings
Do H pylori eradication treatments differ in their effects?									
5 (1128) [38] [39]	Eradication rates	Quadruple regimen versus triple regimen as first-line treatment	4	0	0	0	0	High	
3 (184) [40] [41] [42]	Eradication rates	Quadruple regimens versus triple regimens as second-line treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of regimens of different durations

Important outcomes	Eradication rates, Prevention of gastric cancer, Regression of pre-cancerous lesions, Symptom improvement, Ulcer bleeding, Ulcer healing, Ulcer perforation or obstruction, Ulcer prevention, Ulcer recurrence								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
6 (2146) [43]	Eradication rates	Sequential eradication regimens versus triple eradication regimens as first-line treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of data. Directness point deducted for all studies being conducted in centres in a single country
21 (3998) [44] [45] [46]	Eradication rates	Nitroimidazole-based versus amoxicillin-based triple regimens as first-line treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
25 (5324) [47] [48] [49] [50] [51] [52] [53]	Eradication rates	Triple regimens using different proton pump inhibitors versus each other as first-line treatment	4	0	0	0	0	High	
7 (892) [54] [55] [56] [57]	Eradication rates	Higher-dose clarithromycin-based triple regimens versus lower-dose clarithromycin-based triple regimens as first-line treatment	4	0	–1	0	0	Moderate	Consistency point deducted for different results between SR and subsequent RCTs
9 (773) [58]	Eradication rates	Pre-treatment with proton pump inhibitor versus no pre-treatment	4	0	0	0	0	High	
10 (2592) [65] [66] [67] [68]	Eradication rates	14-day triple regimen versus 7-day triple regimen as first-line treatment	4	0	–1	0	0	Moderate	Consistency point deducted for different results between SR and subsequent RCTs

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.