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Periodontal therapy as adjunctive treatment for gastric *Helicobacter pylori* infection (Review)

Ren Q, Yan X, Zhou Y, Li WX

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[Intervention Review]

Periodontal therapy as adjunctive treatment for gastric *Helicobacter pylori* infection

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ABSTRACT

Background

Helicobacter pylori is estimated to affect about half the world's population and is considered as the main cause of chronic gastritis and peptic ulcer disease. Eradication of *H. pylori* infection accelerates ulcer healing and prevents relapse, reducing incidence of *H. pylori*-related gastric diseases. Numerous studies have provided evidence that the oral cavity could be a potential reservoir for *H. pylori.* The presence of oral*H. pylori* might affect the efficiency of eradication therapy and act as a causal force for its recurrence. Conversely, other investigators have indicated that the colonization and growth of *H. pylori* differs between the oral cavity and the stomach. Considering the open debate on the topic, it's necessary to clarify whether periodontal therapy is an effective adjunctive treatment for gastric *H. pylori* infection.

Objectives

To assess the effects of periodontal therapy plus eradication therapy versus eradication therapy alone for gastric *H. pylori* infection. The secondary objective is to compare the non-recurrence rate at long-term follow up in different treatment groups.

Search methods

We identified randomized controlled trials (RCTs) by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 8), MEDLINE (1946 to August 2015), EMBASE (1980 to August 2015), and the Chinese Biomedical Database (1978 to August 2015). We also searched both ClinicalTrials.gov and the WHO ICTRP portal in October 2015. We handsearched the reference lists of included studies to identify relevant trials.

Selection criteria

RCTs comparing periodontal therapy plus eradication treatment with eradication treatment alone, regardless of language of publication.

Data collection and analysis

Two reviewers selected the trials that met the inclusion criteria and extracted the details of each study independently. The data were pooled using both fixed-effect and random-effects models and results calculated as odds ratios (OR) with their 95% confidence intervals (CIs) based on an intention-to-treat analysis. However, because there was little difference in the results from these two models, we only reported the results from the fixed-effect model.

Main results

We included seven small RCTs involving 691 participants aged 17 to 78 years in our meta analyses. The primary result showed that periodontal therapy combined with *H. pylori* eradication treatment increased the eradication rate of gastric *H. pylori* compared with

eradication treatment alone (OR 2.15; 95% CI 1.47 to 3.14; P < 0.0001) in people with *H. pylori* infection. In addition, periodontal therapy also had benefits on long-term gastric *H. pylori* eradication. After eradication of *H. pylori*, the non-recurrence rate of gastric *H. pylori* infection increased in participants treated with periodontal therapy compared with those who received eradication therapy alone (OR 3.60; 95% CI 2.11 to 6.15; P < 0.00001). According to the GRADE approach, the overall quality of the evidence was 'moderate' for eradication rate of gastric *H.pylori* and 'low' for non-recurrence rate of gastric *H. pylori.*

Authors' conclusions

Overall, periodontal therapy could increase the efficiency of *H. pylori* eradication and the non-recurrence rate of gastric*H. pylori*. In view of the limited number and quality of included studies, it will be necessary to conduct more well-designed, multicenter, and large-scale RCTs to determine the effects of periodontal therapy in eradicating gastric *H. pylori* and suppressing the recurrence of this bacterium in the stomach.

PLAIN LANGUAGE SUMMARY

Dental hygiene in addition to drug treatment for *Helicobacter pylori* eradication

Background

Helicobacter pylori is a bacteria that is considered to be the main cause of long-term inflammation and ulcers of the stomach, and research has also linked it to diseases such as cancer of the stomach and lymph nodes. Globally, the bacteria affects about half the world's population. To eliminate *H. pylori* infection and prevent its recurrence, physicians can use various combinations of medications, including antibiotics and proton pump inhibitors (which reduce stomach acid production). This is known as eradication therapy. However, *H. pylori* may also reside inside the mouth, and researchers do not know whether or not its presence there changes the effectiveness of eradication therapy aimed at the stomach. Given this open debate, it is necessary to clarify whether periodontal therapy is an effective added treatment for*H. pylori* infection of the stomach and whether its use combined with eradication therapy can prevent recurrence better than eradication therapy alone. Periodontal therapy consists of procedures carried out to support the health of the structures in the mouth that support teeth, such as the jaw bone and gums. It includes oral hygiene instruction, toothbrushing, the use of mouthwash, and the professional removal of dental plaque and tartar from the teeth and gum line. This summary of a Cochrane review represents what we know about the benefits and harms of periodontal therapy as an accompanying treatment for *H. pylori* infection of the stomach in adults.

Study characteristics

After searching for all relevant studies to August 2015, we found seven small randomized controlled trials (considered the highest quality study design) involving 691 participants aged 17 to 78 years.

Key results

The results indicated that periodontal therapy as an added treatment had some benefits on eradication of gastric*H. pylori* for short-term and long-term follow-up. The eradication (the reduction of the prevalence of *H. pylori* in stomach to normal range) and non-recurrence (the proportion of participants that remained free of gastric *H. pylori* after successful eradication therapy) rates increased in people who received periodontal therapy plus eradication treatment, when compared with those who received eradication treatment alone.

Quality of the evidence

Because there were not very many participants or trials included in our analyses, we cannot draw a firm conclusion about the use of periodontal therapy for all patients with gastric *H. pylori* infection in clinical practice.

Based on the results in this review, large-scale randomized controlled trials comparing periodontal therapy plus eradication treatment with eradication treatment alone would be useful to generate stronger evidence on the use of periodontal therapy as an additional treatment for patients with gastric diseases caused by *H. pylori*.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Eradication therapy combined with periodontal therapy versus eradication therapy alone for gastric Helicobacter pylori infection

Eradication therapy combined with periodontal therapy versus eradication therapy alone for gastric Helicobacter pylori infection

Patient or population: patients with gastric *Helicobacter pylori* infection
Settings: outpatient clinic
Intervention: eradication therapy combined with periodontal therapy versus eradication therapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Eradication therapy alone	Eradication therapy combined with periodontal therapy			
Eradication rate of gastric *H. pylori*	**60 per 100**	**76 per 100** (69 to 82)	**OR 2.15** (1.47 to 3.14)	543 (6 studies)	⊕⊕⊕⊖ **moderate** [a]
Non-recurrence rate of gastric *H. pylori*	**29 per 100**	**60 per 100** (47 to 72)	**OR 3.60** (2.11 to 6.15)	299 (3 studies)	⊕⊕⊖⊖ **low** [b,c,d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[a]Downgraded one level due to risk of bias (only Zaric 2009 described methods of randomization).
[b]Downgraded one level due to risk of bias (all patients in Jia 2009a were successfully treated for gastric *H. pylori* after triple eradication therapy).
[c]Although OR value was 3.60, we decided not to upgrade the quality of evidence because all patients in Jia 2009a were successfully treated for gastric *H. pylori* after triple eradication therapy.
[d]Downgraded one level due to imprecision (less than 400 total participants).

BACKGROUND

Description of the condition

The prevalence of *Helicobacter pylori (H. pylori)* is estimated to affect about half the world's population, possibly reaching between 70% to 90% in developing countries and hovering between 25% to 50% in developed countries (Go 2002). Of all individuals infected with *H. pylori*, only a small percentage develops related diseases. Diseases associated with *H. pylori* infection commonly happen at earlier ages in developing countries (Balaban 1997), which is probably due to various host-related factors, the difference in strains of *H. pylori*, and the duration of infection and environmental factors, including socioeconomic status (Yamaoka 2010). *H. pylori* infection is considered to be the main cause of chronic gastritis and peptic ulcer disease (Suerbaum 2002). Most individuals infected with *H. pylori* have also have gastritis. Many of them are never diagnosed because they have so few or no symptoms, but about 10% to 20% of them will develop gastric or duodenal ulcer, with the latter being much more prevalent (Schlemper 1996). A paper from Serbia showed that 15% to 25% of patients had duodenal ulcer, while 13% had gastric ulcer (Sokić-Milutinović 2004). *H. pylori* is also linked with gastric adenocarcinoma (cancerous tumour) and mucosa-associated lymphoid tissue (MALT) lymphoma. An *H. pylori*-positive individual has less than 3% lifetime risk of developing adenocarcinoma and a 1% risk of developing MALT lymphoma (Balaban 1997; Kusters 2006; Peek 2002). Eradication of *H. pylori* infection accelerates ulcer healing and prevents relapse, reducing the incidence of *H. pylori*-related gastric diseases (Ford 2006; Graham 1991; Hopkins 1996; Kim 1998; Tytgat 1994).

Description of the intervention

Triple therapy, including a proton pump inhibitor (PPI, a drug that reduces gastric acid secretion in the stomach and accelerates the healing of peptic ulcer) plus two antibiotics, such as clarithromycin and amoxicillin or metronidazole, is the most common first-line clinical intervention regimen (Asaka 2001; Hunt 1999; Shirin 2004; Wolle 2007). Taking into account the high prevalence of clarithromycin resistance, quadruple therapy (PPI + bismuth + metronidazole + tetracycline) is used as an alternate strategy. In recent years, there have also been reports proposing sequential therapy (agents administered in sequence) and concomitant therapy (non-bismuth quadruple therapy) as alternatives that produce eradication rates similar to PPI-triple therapy. In fact, however, the results of recent studies have shown that documented eradication rates are at their lowest level in history (Vakil 2009).This could be due to incomplete elimination of *H. pylori*, leading to recrudescence of the same strain, or to reinfection with a new strain, with recrudescence being the more common cause of recurrence (Gisbert 2006; Xia 1997). Generally, the recurrence rate of *H. pylori* in developing countries is about 13%, although one report from India indicated that in that setting it may be as high as 40% (Rimbara 2011); on the other hand, in developed countries estimates of recurrence are under 3% (Niv 2008). The causes of this imbalance seem to be the limitations related to hygiene and socioeconomic constraints.

How the intervention might work

It is critical to identify factors contributing to the recrudescence of gastric*H. pylori.* Apart from the stomach, *H. pylori* also has been found in the distal esophagus, the proximal duodenum, the colonic contents, and the oral cavity, including tonsil and adenoid tissue (Cover 2009; Eyigor 2009). Considerable research has been published on the relationship between the oral cavity and gastric *H. pylori* infection, with numerous studies providing evidence that the oral cavity may be a potential reservoir for *H. pylori*. The bacteria has been detected in saliva, dental plaques, and gingival pockets (Burgers 2008; Dowsett 2003; Gebara 2006; Liu 2009; Pytko-Polonczyk 1996; Song 2000b). Conversely, other investigators have indicated that the oral cavity may not be a reservoir of *H. pylori* (Olivier 2006; Silva Rossi-Aguiar 2009). This contention is largely based upon different detection methods for oral *H. pylori*, compounded by the fact that there are several types of urease-producing bacteria in the mouth including *Streptococcus*, *Haemophilus* sp., and *Actinomyces* sp. The test based on urease activity is not applicable for diagnosis; culture is a more sensitive method. However, culture is difficult to gather successfully due to the potential for the formation of a viable coccus (Chaudhry 2008). Currently, polymerase chain reaction (PCR) is the most effective method for testing oral *H. pylori* in clinical settings with high sensitivity and specificity. The specificity depends on the different sets of primers (Song 1999; Song 2000b). A meta-analysis published in 2011 reported a strong connection between the presence of*H. pylori* in the oral cavity and in the stomach (Zou 2011): between 39.5% and 64.0% of patients with gastric *H. pylori* also have oral *H. pylori*. In contrast, other studies have found that 83.3% of people with oral *H. pylori* also test positive for the bacteria in gastric samples (Medina 2010; Song 2000a). However, triple eradication therapy has no or little effect on elimination of oral *H. pylori*; studies have recorded eradication rates for oral infection below 40% (Gebara 2006; Czesnikiewicz-Guzik 2007; Miyabayashi 2000). The presence of oral *H. pylori* might diminish the effect of eradication therapy and act as a causal element in the recurrence of *H. pylori* infection. Furthermore, Sheu 2007 have proposed that the presence of dental disease could predispose patients to recurrent *H. pylori* infection even after successful eradication.

Considering the important role of the oral cavity in gastric *H. pylori* infection, periodontal therapy, including oral hygiene procedures and dental plaque and dental calculus control measures, may be a potentially effective adjunctive treatment for gastric *H. pylori* infection (Namiot 2007; Jia 2009b; Zaric 2009).

Why it is important to do this review

It is important to clarify whether periodontal therapy is an effective adjunctive treatment for gastric *H. pylor*i infection. Therefore, it is necessary to perform a meta-analysis on the basis of current randomized controlled trials (RCTs) to understand the available data more comprehensively and to evaluate the evidence for the effectiveness of periodontal therapy in eradication of gastric *H. pylori* infection.

OBJECTIVES

To assess the effects of periodontal therapy plus eradication therapy versus eradication therapy alone for gastric *H. pylori* infection. The secondary objective is to compare the non-recurrence rate at long-term follow up in different treatment groups.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) comparing periodontal therapy plus eradication therapy versus eradication therapy alone.

Types of participants

Adults (≥ 17 years) objectively diagnosed as positive for gastric *H. pylori*, with or without oral *H. pylori* infection, were eligible for inclusion. Investigators confirmed presence of gastric *H. pylori* by serology, rapid urease test (RUT), histology or culture of endoscopic antral/body biopsy specimens, or urea breath test (UBT). The sensitivity and specificity of these methods were similar (Ricci 2007). For our meta-analyses, at least one positive result of above tests confirmed the positive gastric *H. pylori* diagnosis. For oral *H. pylori*, investigators used the PCR analysis to obtain an accurate result.

We excluded studies that involved participants who had received any eradication treatment of *H. pylori* infection within four weeks prior to the study.

Types of interventions

We included all RCTs that used periodontal therapy combined with eradication therapy for the treatment of gastric *H. pylori* infection. Eligible *H. pylori* eradication regimens included triple therapy, quadruple therapy, sequential therapy, and concomitant therapy. We excluded trials or trial arms that treated participants with dual therapy because of the low eradication rate. Periodontal therapy considered for this review comprises oral hygiene training, removal of supragingival and accessible subgingival bacterial plaque and calculus by periodontal scaling, periodontal root planing and chemotherapeutic agents (e.g. irrigation of periodontal pockets). However, we excluded trials with oral surgical treatment. Periodontal therapy began with eradication therapy.

Types of outcome measures

Primary outcomes

Eradication rate of gastric *H. pylori.*

We assessed eradication at four weeks after therapy. We considered eradication successful in case of a negative result for that UBT, serology, RUT, or histology or culture of an endoscopic antral/body biopsy specimen.

Secondary outcomes

Non-recurrence rate of gastric *H. pylori (*at least six months after eradication therapy*).*

Search methods for identification of studies

We conducted searches to identify all published and unpublished trials for this review, applying no restriction with regard to language of publication.

Electronic searches

We identified trials by searching the following electric databases.

1. The Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 8); see Appendix 1.
2. MEDLINE (1946 to August 2015); see Appendix 2.
3. EMBASE (1980 to August 2015); see Appendix 3.
4. Chinese Biomedical Database (1978 to August 2015).
5. ClinicalTrials.gov (last searched October 2015).
6. WHO ICTRP portal (last searched October 2015).

The Cochrane UGPD Group ran the searches in CENTRAL, MEDLINE, and EMBASE, while QR searched the Chinese Biomedical Database (CBM) in parallel.

Searching other resources

We handsearched the reference list of each included study to identify relevant trials. We also searched reference lists of abstracts from all relevant conference proceedings.

Data collection and analysis

Selection of studies

In order to assess studies for inclusion, two review authors independently reviewed abstracts from relevant trials using pre-specified inclusion criteria. When we could not include or exclude a record solely on the basis of the abstract, we reviewed the article in full. In case of disagreement, a third author decided whether to include the study in the review.

Data extraction and management

Two authors independently extracted details of each study using a pre-defined data collection form. We recorded the study design, participants, setting, timing, interventions, participant characteristics, and outcomes, in as much detail as possible. We resolved disagreements by consultation with the senior author. We also entered outcome data into an Excel database to check for potential input errors.

Assessment of risk of bias in included studies

Two review authors independently assessed the methodological quality of each study in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The senior author participated by resolving discrepancies in order to reach a consensus.

We assessed trials according to the following criteria.

Did the trial use adequate random sequence generation?

We assessed the allocation sequence as truly random, unclear, or not stated. We defined 'truly random' as: computer-generated random numbers, published random number table, coin toss, shuffled cards.

Was there adequate allocation concealment?

We assessed allocation concealment as adequate, inadequate, or unclear.

We defined adequate concealment as follows: trialists were ignorant of the allocation of each recruited participant when they were entered in the study. Appropriate methods included central randomization schemes, pharmacy-based schemes, opaque sealed envelopes.

Did trials adequately prevent knowledge of the allocated interventions during the study?

We assessed allocation concealment as triple blind, double blind, single blind, not blinded, or unclear.

When the participants, investigator and outcome assessors were not aware of the treatments, we defined the trial as 'triple blind'.

If two of them were not aware of the treatments, we defined the trial as 'double blind'.

If only one was not aware of the treatments, we defined the trial as 'single blind'.

We judged trials as blinded, not blinded, or unclear on the basis of the available information.

Did investigators adequately address incomplete outcome data?

We noted the completeness of follow-up and whether investigators reported the intention-to-treat (ITT) analysis.

Measures of treatment effect

We calculated the odds ratio to analyze data on the eradication rate of *H. pylori* and the non-recurrence rate of gastric*H. pylori* infection.

Dealing with missing data

We tried to contact the authors of original RCTs for missing information. We calculated the outcome with the intention-to-treat analytical approach. We considered drop-outs as individuals for whom treatment failed.

Assessment of heterogeneity

We assessed statistical heterogeneity with the Chi^2 test with significance set at P value 0.10. We quantified heterogeneity using the I^2 statistic (Higgins 2002). We judged I^2 greater than 25% as heterogeneous. We considered clinical heterogeneity and the heterogeneity of study quality.

Assessment of reporting biases

According to the number of included trials, we determined whether it was necessary to prepare a funnel plot for assessing publication bias (Egger 1997); as there were relatively few trials, we decided that this step was not necessary.

Data synthesis

We used Review Manager software (RevMan 2011) to pool and analyze the trial data and used forest plots to present the results of this meta-analysis. All data were dichotomous outcomes. We expressed the results as the odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). We pooled data using both fixed-effect and random-effects models. We reported only the results of the fixed-effect model when both models led to the same conclusion. Otherwise we reported the results from fixed-effect and random-effects models.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis based on the participants with or without oral*H. pylori* infection, regardless of the type and the duration of eradication therapy and antibiotics.

We also carried out subgroup analysis based on the different durations of periodontal therapy.

1. During eradication therapy only.
2. Continued until testing the result of eradication therapy was complete.
3. Continued for longer.

If data had been sufficient, we would also have performed subgroup analyses on the basis of different levels of economic development (developed countries or developing countries) and whether or not the participants were diagnosed with periodontitis and prescribed periodontal therapy.

Sensitivity analysis

We conducted a sensitivity analysis by removing trials where investigators did not perform ITT analysis to check how robust the results were. We also performed sensitivity analysis according to relevant clinical features and to determine whether the pooled results changed when we excluded low quality studies from this meta-analysis. We assessed the quality of included studies by modified Jadad scale and defined the studies with less than four points as low quality.

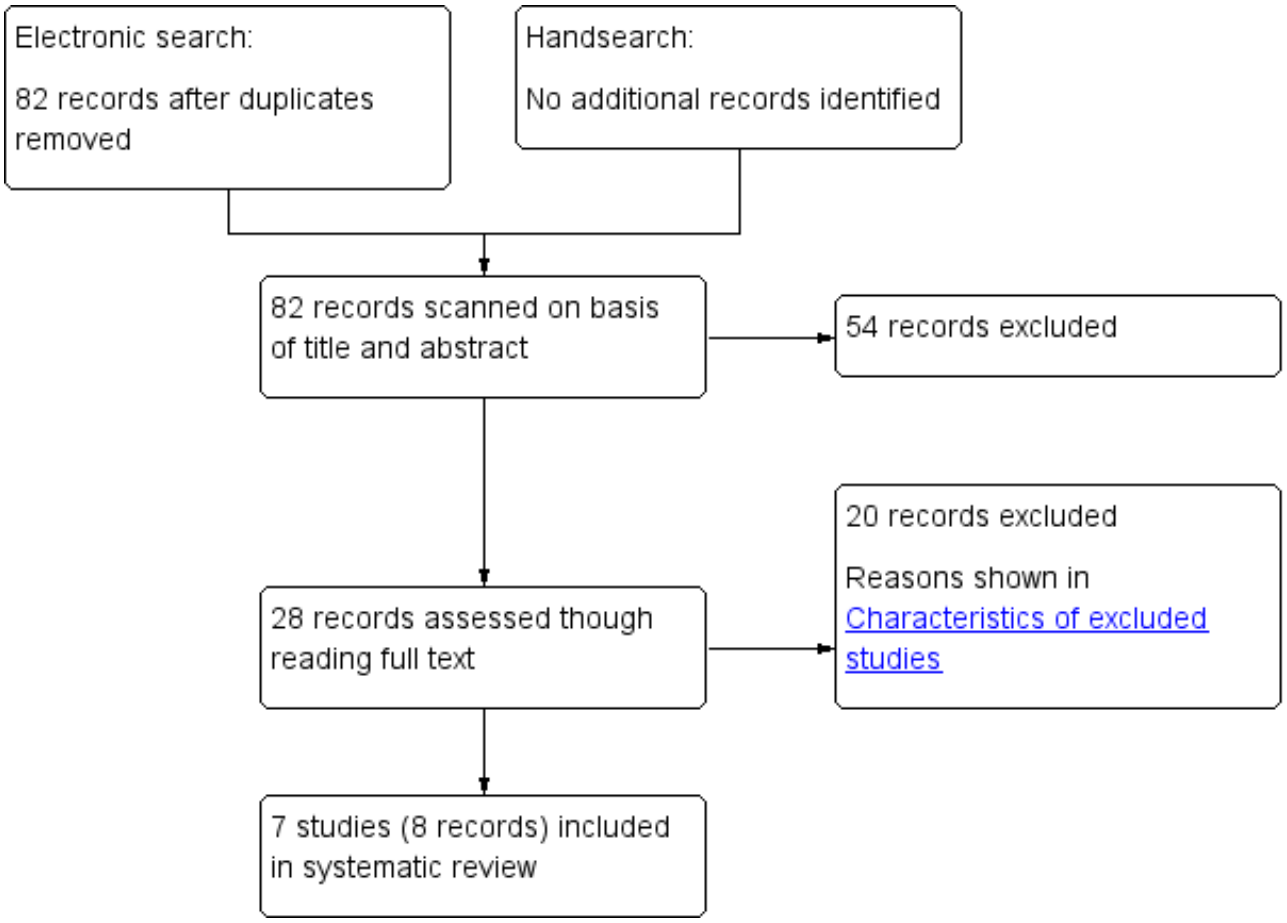
RESULTS

Description of studies

Results of the search

Examining the results of the electronic searches from CENTRAL, MEDLINE, EMBASE, and the CBM in November 2010 and the updated search in August 2015, we identified a total of 82 records after excluding duplicates. We did not find any additional relevant trials by handsearching the reference lists of included trials. The search flow chart is shown in Figure 1. After reading titles and abstracts, we excluded 54 irrelevant references. We evaluated the full text of 28 other records, excluding 20 records for the reasons described in the Characteristics of excluded studies table. Finally, we included seven small RCTs (described in eight reports) that met all of the eligibility criteria for this review.

Figure 1. Search flow diagram



Included studies

Overall, we included seven small RCTs from eight reports involving 691 participants. One included study took place in the Clinical Center Zveadara in Belgrade, Serbia (Zaric 2009), while the others were Chinese (Jia 2009a; Jin 2003; Jin 2007; Liu 2012; Lv 2006; Wang 2014). Six RCTs assessed the effects of periodontal therapy plus eradication treatment for gastric *H. pylori*. Three RCTs observed the role of periodontal therapy on recurrence rate of gastric *H. pylori*. The periodontal therapy in these studies included oral hygiene education, toothbrushing, mouthwash with or without special agents, dental plaque control (ultrasonic scaling and subgingival scaling). The aim of these meta-analyses is to assess the effect of periodontal treatment on gastric *H. pylori*, regardless of which professional interventions the trials used. We regrouped the participants of Jia 2009a into two groups: eradication therapy alone and eradication treatment plus oral dental plaque control, with or without professional care. In Wang 2014, we only extracted data from the two groups that met the inclusion criteria.

The criteria for entering the study were similar in all seven studies. Three RCTs recruited 194 participants positive for both gastric *H. pylori* and periodontitis, including chronic gastritis and peptic ulcer participants (Jin 2003; Jin 2007; Zaric 2009). In the four other studies, participants had gastric diseases associated with *H. pylori* but did not have a diagnosis for periodontitis (Jia 2009a; Liu 2012; Lv 2006; Wang 2014). The infection of *H. pylori* was confirmed by ^{13}C or ^{14}C urea breath test, RUT, histology, or PCR, and some studies also detected the presence of oral *H. pylori* using PCR, urease test, or *H. pylori* flagellin test (Lv 2006; Zaric 2009; Wang 2014). After completion of treatment, all trials except Zaric 2009 used the urea breath test to assess whether participants were infected with primary *H. pylori*. The age of the individuals in six of the included studies varied between 17 and 78 years, but Lv 2006 did not report the details of baseline data, such as mean age and sex ratio. In all studies, baseline data appeared similar across the intervention and control groups. For more details about included studies see Characteristics of included studies.

Excluded studies

We excluded 20 studies after reading the full text. Please see Characteristics of excluded studies.

Four of these trials met all the inclusion criteria except randomization. The most remarkable of these is Jia 2009b, a controlled clinical trial that elucidated the relationship between dental plaque control and *H. pylori* infection of gastric mucosa. That study divided a total of 110 participants with gastritis or peptic ulcer into two groups according to participant preferences and adherence instead of randomization. All participants received systemic gastric *H. pylori* eradication treatment, then 59 participants in the intervention group received periodontal therapy, including toothbrushing, mouthrinse, scaling, root planing and polishing, whereas the individuals in the control group used only their routine daily oral care procedures without

any special dental plaque control. Six months after eradication treatment, investigators used the ^{13}C urea breath test to detect the prevalence of gastric *H. pylori*. The result showed that the eradication rate was 76.3% in the intervention group according to an intention-to-treat analysis, compared with 15.7% in the control group; investigators concluded that long-term professional dental plaque control is beneficial to gastric *H. pylori* eradication and prevention of *H. pylori* reinfection.

In Hou 2002, the authors divided participants into three groups based on the depth of the periodontal pocket instead of randomization. Participants with periodontal pockets less than 4 mm received eradication therapy only. Further, all participants with periodontal pockets deeper than 4 mm received eradication therapy, with or without periodontal therapy; however, the trial reports failed to explicitly mention random allocation. Likewise, Ye 2012 did not report a random grouping design. We therefore classified these trials as controlled clinical trials, and the results indicated that periodontal therapy including scaling and mouthwash could increase the eradication rate of gastric *H. pylori* infection when combined with triple eradication treatment. The other noteworthy trial is Tarullo 2001, which recruited participants with periodontitis and concomitant gastric disturbances who tested positive for *H. pylori* after two cycles of antibiotic polytherapy. The study randomized participants into placebo (10 participants) and treatment groups (14 participants), with treated participants receiving ablation of dental plaques, toilette of periodontal pockets with special agents for prevention against bacteria, and mouthwash. The placebo group received the same procedure but without the special agents. All participants were followed up for 24 months to detect gastric symptoms and the presence of *H. pylori*. However, this trial failed to describe many details, such as the use of eradication treatment during the process of oral therapy, the presence of *H. pylori* in the control group after two years, and so on. We tried to contact the authors to get more details, but the trial paper did not provide any email or mailing address. Therefore, there were not enough details to decide whether or not the trial used triple therapy in both groups.

Risk of bias in included studies

Two authors independently undertook the quality evaluation of every eligible study, assessing methods of randomization, allocation concealment, blinding, strategy for addressing incomplete outcome data, selective reporting and other possible sources of bias. We present the summary of the 'Risk of bias' assessment in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

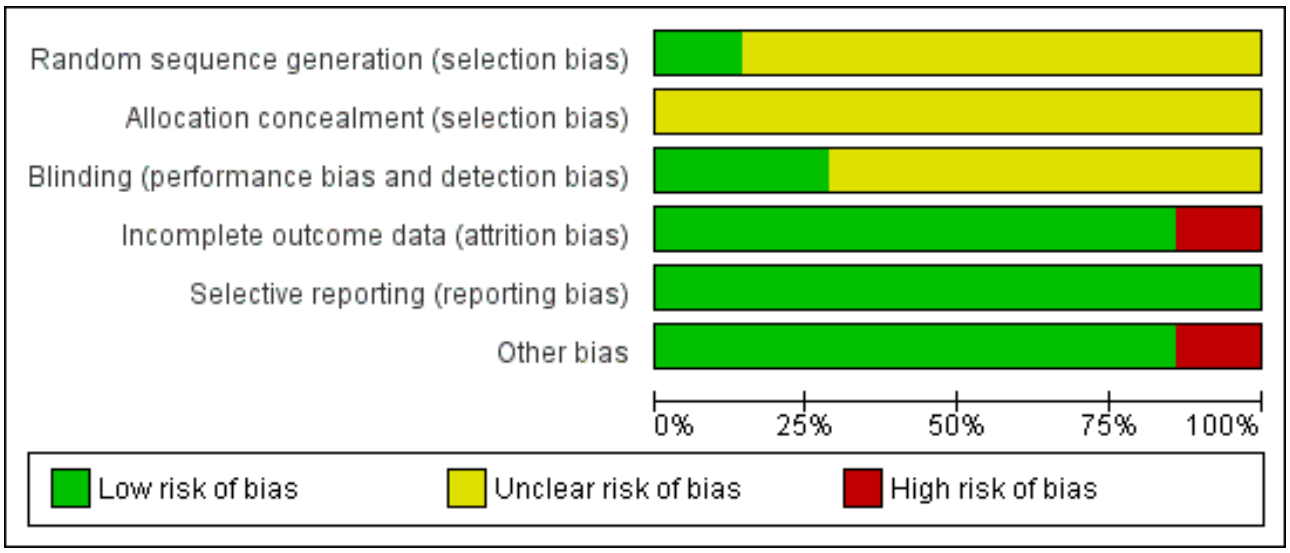
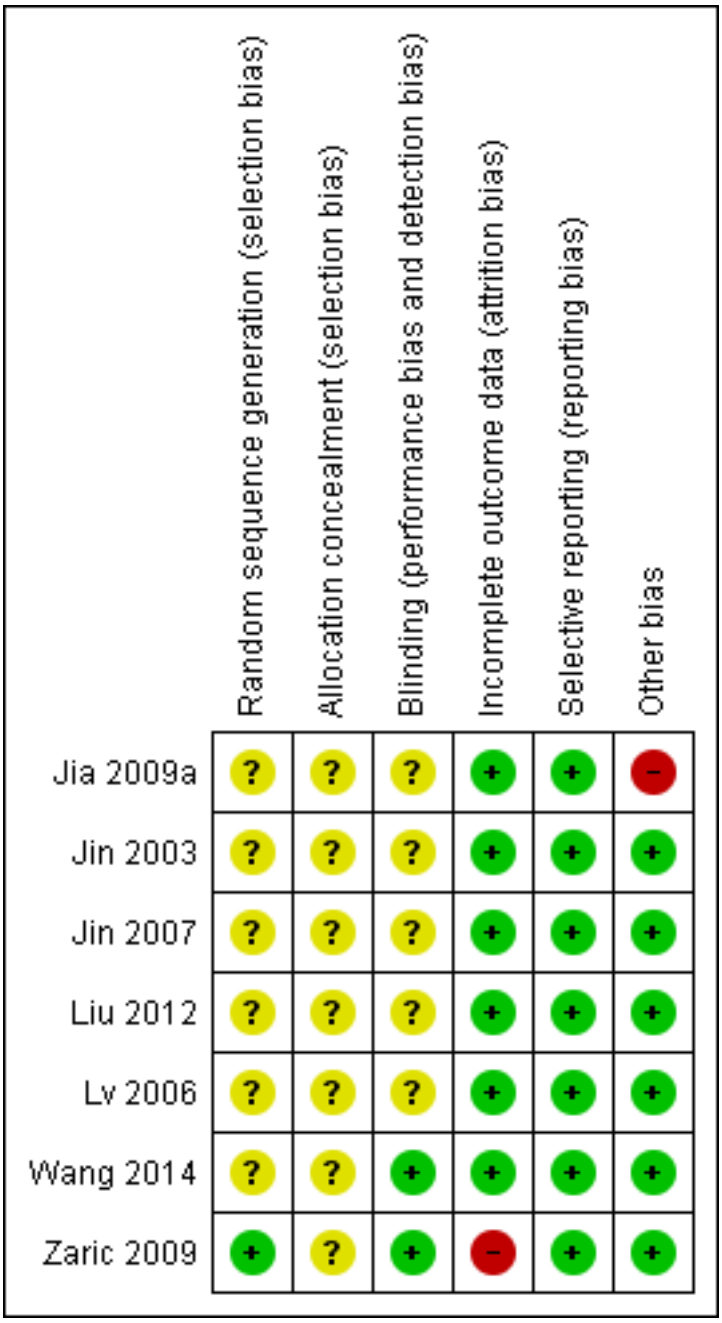


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

None of the trials reported on the generation of random sequence or allocation concealment. After contacting authors of each trial, we obtained further information on Zaric 2009, which used a block randomization method for group allocations. We deemed the risk of allocation bias in the other studies to be unclear.

Blinding

The aim of this meta-analysis was to assess the effect of periodontal therapy on eradication of gastric *H. pylori*, so it is difficult to blind the operators, such as dentists carrying out treatments, and the participants who received oral hygiene education and professional oral care in clinical practice. However, the outcome of interest was the presence of *H. pylori,* which is an objective result. For this reason, we judged that blinding of the outcome assessor was sufficient to prevent knowledge of group allocation in terms of *H. pylori* detection. The examiners of Zaric 2009 who detected the presence of gastric *H. pylori* were blinded, whereas Wang 2014 was double blind (participants and outcome assessors). We judged both of these trials to be at low risk in this domain. The remaining five studies did not describe whether blinding was used (Jia 2009a; Jin 2003; Jin 2007; Liu 2012; Lv 2006), so we considered them to carry an unclear risk.

Incomplete outcome data

Jia 2009a excluded five cases in intervention group 1 because the participants discontinued use of mouthwash, along with eight cases in intervention group 2 because participants did not adhere to strict dental plaque control. Investigators used the intention-to-treat analysis to minimize bias in this analysis, so we considered it to be at low risk. We also judged Liu 2012 to be at low risk, because even though it lost 16 cases to follow-up, authors undertook both intention-to-treat and per-protocol analyses. Authors of Zaric 2009 confirmed through correspondence that some participants from both groups did not complete the study. However, their paper did not report the exact number or the reasons, and so we judged the trial to be at high risk in this domain. In the remaining four trials, there were no drop-outs after randomization (Jin 2003; Jin 2007; Lv 2006; Wang 2014), and we assigned the trials a low risk for this domain.

Selective reporting

All trials were free from bias due to selective reporting (Jia 2009a; Jin 2003; Jin 2007; Liu 2012; Lv 2006; Zaric 2009; Wang 2014).

Other potential sources of bias

Jia 2009a reported that all participants were negative for gastric *H. pylori* infection by ^{13}C urea breath test after *H. pylori* eradication treatment, considering the efficacy rate of eradication therapy to be 100%. Since studies have suggested that the eradication rate of anti-*H. pylori* treatment is historically low (Vakil 2009), we considered that there could be some participants with treatment failure who were not reported. The remaining six trials were free from bias due to other potential sources (Jin 2003; Jin 2007; Liu 2012; Lv 2006; Zaric 2009; Wang 2014).

Effects of interventions

See: **Summary of findings for the main comparison** Eradication therapy combined with periodontal therapy versus eradication therapy alone for gastric Helicobacter pylori infection

Eradication rate of gastric H. pylori

Six RCTs reported eradication rates after evaluating 543 participants from China and Serbia at one to three months (Jin 2003; Jin 2007; Liu 2012; Lv 2006; Wang 2014; Zaric 2009). Combining the results of all of the studies, eradication rates of gastric *H. pylori* were 75.5% (206/273) in participants receiving eradication therapy plus periodontal treatment, and 60.0% (162/270) in participants receiving eradication therapy alone. Compared with only eradication treatment, periodontal therapy given along with eradication treatment significantly increased the eradication rate of gastric *H. pylori* (OR 2.15; 95% CI 1.47 to 3.14; P < 0.0001; test of heterogeneity P = 0.78, I^2 = 0%), see Analysis 1.1. We downgraded the outcome from high to moderate quality due to risk of bias.

Non-recurrence rate of gastric H. pylori

Three trials investigated the recurrence rate after successful gastric *H. pylori* eradication (Jia 2009a; Jin 2003; Jin 2007). A total of 299 participants with gastric *H. pylori* received treatment with eradication therapy; after one month, ^{13}C or ^{14}C urea breath testing confirmed the successful eradication of *H. pylori* in 272 participants. At 6- to 12-month follow-up, the non-recurrence rate of gastric *H. pylori* infection was significantly higher in participants who received adjunctive periodontal therapy compared with those receiving eradication therapy alone (OR 3.60; 95% CI 2.11 to 6.15; P < 0.00001), see Analysis 1.2. The quality of evidence was low due to risk of bias and imprecision.

Subgroup analysis

We conducted the planned subgroup analyses according to oral *H. pylori* status and duration of periodontal therapy. There was no significant difference between any of the subgroups.

OralH. pylori status

Three trials included participants with both gastric and oral *H. pylori* infection to assess the gastric *H. pylori* eradication rate (Liu 2012; Zaric 2009; Wang 2014). Periodontal therapy increased the eradication rate in the meta-analysis (OR 2.42; 95% CI 1.52 to 3.87; P = 0.0002). The other three trials recruited participants with gastric *H. pylori* regardless of oral *H. pylori* status, and there was no significant difference between the intervention and control group (OR 1.70; 95% CI 0.88 to 3.26; P = 0.11); see Analysis 2.1.

Duration of periodontal therapy

Two trials treated participants simultaneously with periodontal therapy and eradication treatment, stopping both treatments at the same time (Lv 2006; Zaric 2009). The eradication rate in the intervention group was higher (OR 2.72; 95% CI 1.20 to 6.14; P = 0.02) than in the control group. In the other four studies, periodontal therapy began with eradication therapy and continued until the time of testing gastric *H. pylori* (Jin 2003; Jin 2007; Liu 2012; Wang 2014). There was a significant decrease in the eradication rate between intervention and control groups (OR 2.02; 95% CI 1.31 to 3.10; P = 0.001).

Two of the trials assessed recurrence after treatment, with data showing that in the intervention group, the non-recurrence rate was significantly higher compared with the control group (OR 3.13; 95% CI 1.60 to 6.10; P = 0.0008). In one trial, participants received periodontal therapy for half a year, that is, five months after testing the eradication rate (Jia 2009a). Compared with eradication treatment alone, periodontal therapy significantly increased the gastric *H. pylori* non-recurrence rate (OR 4.49; 95% CI 1.83 to 11.04; P = 0.001); see Analysis 3.1 and Analysis 3.2.

Sensitivity analysis

Using the modified Jadad scale, we classified five trials as low quality studies, as the score was three points (Jia 2009a; Jin 2003; Jin 2007; Liu 2012; Lv 2006). We excluded these five trials and analyzed the results of Wang 2014 and Zaric 2009. The outcome showed that periodontal therapy increased the efficiency rate of eradication treatment significantly (OR 3.18; 95% CI 1.60 to 6.33; P = 0.001), see Analysis 4.1.

'Summary of Findings' table

We created a 'Summary of findings' table using all the outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook*

for Systematic Reviews of Interventions (Higgins 2011) and used GRADEpro software. We justified all decisions to down- or up-grade the quality of studies using footnotes and made comments to aid the reader's understanding of the review where necessary. We considered whether there was any additional outcome information that was not able to be incorporated into meta-analyses and planned to note this in the comments and state if it supports or contradicts the information from the meta-analyses.

DISCUSSION

Summary of main results

We included seven RCTs in this meta-analysis, which involved 382 participants in the intervention groups and 309 participants in the control groups. Results for the review's primary outcome showed that the use of periodontal therapy could increase the eradication rate of *H. pylori* treatment. Subgroup analysis based on status of oral *H. pylori* found that the result was consistent with the total study meta-analysis for participants with oral *H. pylori.* However, in participants who were not tested for oral *H. pylori*, there was no significant difference in the eradication rate compared with the control group.

Researchers have considered the oral cavity to be a potential reservoir for *H. pylori* (Song 2000b). Becauseeradication therapies have not usually been effective in clearing *H. pylori* from the oral cavity (Gebara 2006), the colonization and growth of oral *H. pylori* could spread to the stomach during deglutition and affect the eradication of gastric *H. pylori*. For this reason, the use of periodontal therapy should have different effects on gastric *H. pylori* eradication depending on participants' oral status. In the subgroup analysis examining this aspect, studies collected data from participants with or without oral*H. pylori* as the same group, which could explain why we found no difference between periodontal therapy plus eradication treatment versus eradication treatment alone. Another subgroup analysis based on the duration of periodontal therapy showed the same results as the overall findings, with no significant difference between any of the subgroups, regardless of the duration of periodontal therapy.

We also conducted a sensitivity analysis, excluding the low quality studies and analyzing data from the two remaining trials (175 participants) to evaluate the eradication rate. There still was a significant increase in the eradication rate in those receiving adjunctive periodontal therapy compared with the control group. However, more high quality studies are needed to draw a reliable conclusion.

The results of our analyses on the secondary outcome showed that the use of periodontal therapy could increase the non-recurrence rate after eradication therapy. The results of the subgroup analysis stratified by different durations of periodontal therapy was consistent with the overall result on non-recurrence rate.

Overall completeness and applicability of evidence

This meta-analysis included participants with gastric *H. pylori*, regardless of oral*H. pylori* infection. However, only a few published RCTs have assessed periodontal therapy as adjunctive treatment for gastric *H. pylori*. More high quality randomized control trials comparing eradication treatment plus periodontal therapy versus eradication treatment alone are required. In addition, RCTs should be conducted based on oral*H. pylori* infection and duration of periodontal therapy. In summary, this review is applicable to people with gastric*H. pylori* infection.

Quality of the evidence

Considering the lack of description regarding methods of the random sequence generation, allocation concealment and blinding, we only judged Wang 2014 and Zaric 2009 to be of high quality. In the other studies, authors just mentioned 'randomization' in text, but did not describe their methods. We considered that there were two possible explanations: one was that authors used the adequate methods for randomization, allocation concealment, and blinding, but did not report these processes accurately or completely; the other possibility was that the trials did not use standard methods during the performance of the trials. If the latter was the case, the trials were not truly randomized controlled trials.

With the exception of Zaric 2009, all of the studies adequately reported follow-up. Investigators followed up all participants in four studies from one month to one year (Jin 2003; Jin 2007; Lv 2006; Wang 2014). The other two trials lost some participants to follow-up or excluded them due to poor adherence (Jia 2009a; Lv 2006). All trials were free from selective reporting. In addition, Jia 2009a reported that all participants were free of gastric*H. pylori* after triple therapy. We considered that potential biases probably exist. Overall, the quality of included trials was not good enough to draw a firm conclusion. Moreover, all seven included trials took place in two developing countries—China and Serbia—where overall health indicators are not as good as they are in developed countries. For this reason, different daily oral hygiene routines may have a differential impact on oral hygiene status in developed versus developing countries, so the significant effect of periodontal therapy for gastric *H. pylori* in developing countries may not be generalizable to developed countries.

Potential biases in the review process

We searched CENTRAL, MEDLINE, EMBASE, the CBM, ClinicalTrials.gov and the WHO ICTRP portal for published, unpublished and ongoing studies. We could not obtain the details of all identified studies from reading the publications or contacting the trial authors. The limited search and the incompleteness of study details could affect the accuracy and objectivity of the results of this systematic review.

Agreements and disagreements with other studies or reviews

There is only one meta-analysis assessing the effects of dental plaque control and periodontal therapy on prevention of gastric *H. pylori* recurrence (Bouziane 2012), and we did not identify any meta-analysis review evaluating the use of periodontal therapy for the gastric *H. pylori* eradication rate. Bouziane 2012 included three trials with 298 participants. One was a controlled clinical trial, and the other two were RCTs that we also included in our review. Reviewers used the absence of recurrence of gastric *H. pylori* as an outcome, calculating the risk ratio (RR) but not the odds ratio (OR) during data analysis. The results showed that in patients with gastric diseases, periodontal therapy as adjunctive treatment significantly decreased the RRs of persistence of gastric *H. pylori*. Another review by Li 2012 found that periodontal therapy could not only kill oral *H. pylori* but also increase the eradication rate of

gastric*H. pylori* and reduce recurrence of this bacterial infection, and the conclusions suggested the use of periodontal therapy to improve the efficiency of gastric *H. pylori*.

AUTHORS' CONCLUSIONS

Implications for practice

In this meta-analysis, periodontal therapy had benefits on the treatment for gastric *H. pylori*. The eradication rate increased in patients who received periodontal therapy plus eradication, particularly in those with both gastric and oral *H. pylori*. After long-term follow-up, patients treated with periodontal therapy had a higher non-recurrence rate compared to those without basic oral therapy. The low quality of the included RCTs and incomplete reporting about methodology introduce some uncertainty with regard to these findings, and there is still a need for more high quality, large-scale, multicenter randomized controlled trials to obtain clear and reliable evidence to recommend using periodontal therapy for patients with gastric diseases associated with *H. pylori*.

Implications for research

In this review, we considered the vast majority of included trials to be of low quality due to the lack of adequate description of randomization method, allocation concealment, and blinding. There is a need for more high quality trials to investigate the effects of adjunctive periodontal therapy on the eradication and recurrence of gastric *H. pylori*. Well-designed, large-scale randomized controlled trials with long-term follow-up should be performed in both developing and developed countries to gain reliable evidence and to understand the applicability of these therapies across different settings and socioeconomic contexts.

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Xia HX, Talley NJ, Keane CT, O'Morain CA. Recurrence of *Helicobacter pylori* infection after successful eradication: nature and possible causes. *Digestive Diseases and Sciences* 1997;**42**(9):1821-34.

Yamaoka 2010

Yamaoka Y. Mechanisms of disease: *Helicobacter pylori* virulence factors. *Nature Reviews. Gatroenterology & Hepatology* 2010;**7**(11):629-41.

Zou 2011

Zou QH, Li RQ. *Helicobacter pylori* in the oral cavity and gastric mucosa: a meta-analysis. *Journal of Oral Pathology & Medicine* 2011;**40**(4):317-24.

References to other published versions of this review

Ren 2011

Ren Q, Yan X, Zhou Y, Li WX. Periodontal therapy as adjunctive treatment for gastric Helicobacter pylori infection. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD009477]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Jia 2009a

Methods	Randomized clinical trial
Participants	Country: China
	Sample size: 148 patients with gastritis and peptic ulcer (group 1, 54; group 2, 55; control 39)
	Sex(M/F): Group 1 (31/23), Group 2 (30/25), Control group (21/18)
	Age: Group 1 (25 to 72 years), Group 2 (26 to 70 years), Control group (23 to 69 years)
	H. pylori testing: ^{13}C urea breath test
	Oral *H. pylori* status: not tested

Jia 2009a *(Continued)*

Interventions	Intervention group 1: *H. pylori* eradication for 6 weeks, followed by daily plaque control for 6 months Intervention group 2: *H. pylori* eradication for 6 weeks, followed by daily plaque control and oral professional intervention for 6 months Control group: *H. pylori* eradication for 6 weeks only *H. pylori* eradication: omeprazole 20 mg, amoxicillin 500 mg and metronidazole 400 mg, twice daily for 2 weeks, followed by ranitidine 300 mg every night and bismuth citrate 110 mg 4 times a day for 4 weeks. Daily plaque control: toothbrushing performed with Bass method half an hour after each meal for at least 3 min. The toothbrush changed every month. 10 mL mouthwash containing chlorhexidine was used for 1 min twice a day. Dental floss or interdental brush was used if needed. Oral professional intervention: oral professional examination and hygiene education were performed every other week. Ultrasonic scaling and subgingival scaling were performed to remove dental plaque (until testing the result of eradication therapy).
Outcomes	Recurrence rate of gastric *H. pylori* (6 months after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were reported, including the excluded participants with non-adherence. The intention-to-treat analytical approach was used.
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	High risk	After *H. pylori* eradication treatment, all patients were confirmed without gastric *H. pylori* infection by ^{13}C urea breath test. We considered whether the efficacy rate of eradication therapy could reach 100%.

Jin 2003

Methods	Randomized clinical trial
Participants	Country: China Sample size: 64 patients with peptic ulcer and periodontitis (intervention, 32: control, 32) Sex (M/F): 41/23

Jin 2003 *(Continued)*

	Age: 19 to 66 years *H. pylori* testing: ^{14}C urea breath test Oral *H. pylori* status: not tested
Interventions	Intervention group: *H. pylori* eradication for 2 weeks plus periodontal treatment for 4 weeks Control group: *H. pylori* eradication for 2 weeks only *H. pylori* eradication: omeprazole 20 mg, once a day, amoxicillin 1.0 g and metronidazole 400 mg, twice a day, for 2 weeks Periodontal treatment: oral hygiene education, ultrasonic scaling and subgingival scaling, and mouth-wash for 1 month with Compound Borax Solution (until testing the result of eradication therapy)
Outcomes	Eradication rate of gastric *H. pylori* (1 month after eradication) Recurrence rate of gastric *H. pylori* (12 months after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up until the end of trial. The intention-to-treat analytical approach was used.
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	—

Jin 2007

Methods	Randomized clinical trial
Participants	Country: China Sample size: 87 patients with peptic ulcer and periodontitis (intervention, 46; control, 41) Sex (M/F): 53/34 Age: 17 to 65 years *H. pylori* testing: ^{14}C urea breath test

Jin 2007 *(Continued)*

	Oral *H. pylori* status: not tested
Interventions	Intervention group: *H. pylori* eradication for 1 week plus periodontal treatment for 4 weeks Control group: *H. pylori* eradication for 1 week only *H. pylori* eradication: omeprazole 20 mg, clarithromycin 0.5 g and amoxicillin 1.0 g, twice a day for 1 week Periodontal treatment: oral hygiene education, ultrasonic scaling and subgingival scaling, and mouth-wash for 1 month with Compound Borax Solution (until testing the result of eradication therapy)
Outcomes	Eradication rate of gastric *H. pylori* (1 month after eradication) Recurrence rate of gastric *H. pylori* (12 months after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up until the end of trial. The intention-to-treat analytical approach was used.
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	—

Liu 2012

Methods	Randomized clinical trial
Participants	Country: China Sample size: 152 patients with peptic ulcer (intervention, 78; control, 74) Sex (M/F): not reported Age: Intervention group (22 to 68 years), Control group (23 to 70 years) *H. pylori* testing: rapid urease test and ^{14}C urea breath test Oral *H. pylori* status: positive
Interventions	Intervention group: *H. pylori* eradication for 2 weeks plus periodontal treatment for 4 weeks

Liu 2012 *(Continued)*

	Control group: *H. pylori* eradication for 2 weeks only *H. pylori* eradication: omeprazole 20 mg, metronidazole 400 mg and amoxicillin 1.0 g, twice a day for 2 weeks Periodontal treatment: oral hygiene education for teaching the Bass brushing method, ultrasonic scaling and subgingival scaling, and mouthwash. Toothbrushing performed half an hour after each meal for at least 3 min. 10 mL mouthwash containing chlorhexidine for 1 min twice a day (until testing the result of eradication therapy)
Outcomes	Eradication rate of gastric *H. pylori* (1 month after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 patients lost to follow-up, but intention-to-treat analytical approach used
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	—

Lv 2006

Methods	Randomized clinical trial.
Participants	Country: China Sample size: 65 patients with peptic ulcer and chronic gastritis (intervention, 35; control, 30) Sex (M/F): not reported Age: not reported *H. pylori* testing: rapid urease test or histology Oral *H. pylori* status: tested, but the results were not used for assessing effect of oral *H. pylori* on eradication of gastric *H. pylori*
Interventions	Intervention group: *H. pylori* eradication and periodontal treatment for 4 weeks Control group: *H. pylori* eradication for 2 weeks only

Lv 2006 *(Continued)*

	H. pylori eradication: bismuth potassium citrate capsules 220 mg and amoxicillin 0.5 g, twice a day, plus metronidazole 0.3 g 3 times per day Periodontal treatment: ultrasonic scaling and subgingival scaling were performed by dentist. Rhizoma Coptidis aerosol used after each meal, 3 times a day for 4 weeks (during triple therapy)
Outcomes	Eradication rate of gastric *H. pylori* (1 month after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described in article
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up until the end of trial. The intention-to-treat analytical approach was used.
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	—

Wang 2014

Methods	Randomized clinical trial
Participants	Country: China Sample size: 277 individuals were recruited in this study, but only 132 adult patients were included for this review. 132 adult patients suffered from both stomach and oral *H. pylori* infections (intervention, 60; control, 72) Sex (M/F): 121/156 Age: 3 to 77 years *H. pylori* testing: ^{13}C urea breath test Oral *H. pylori* status: positive
Interventions	Intervention group: *H. pylori* eradication for 2 weeks plus periodontal treatment for 1 month Control group: *H. pylori* eradication for 2 weeks only *H. pylori* eradication: standard dose PPIs were used twice a day (PPIs include: lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg, and esomperazole 40 mg), and tetracy-

Wang 2014 *(Continued)*

	cline 500 mg, twice a day, plus amoxicillin 1000 mg twice a day (or bismuth subsalicylate 525 mg, once daily, plus metronidazole 250 mg 4 times per day) Periodontal treatment: mouthwash with 20 mL solution was performed twice a day (in the morning and at the night before bed) for 1 month (during triple therapy). The mouthwash solution contained lysine (0.4%) and glycerol monolaurate (0.2%).
Outcomes	Eradication rate of gastric *H. pylori*
Notes	Only participants infected with oral Hp, but without gastric Hp were collected in this study. Mouthwash solution provided a 72.58% effectiveness rate on the oral Hp infection, but traditional drug gastric eradication and teeth cleaning had less than a 10% effectiveness rate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in article
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind (participants and outcome assessors)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up until the end of test.
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported.
Other bias	Low risk	—

Zaric 2009

Methods	Randomized clinical trial
Participants	Country: Serbia Sample size: 66 individuals were selected in this study, but only 43 patients were included for this review. 43 patients with both gastric and oral *H. pylori* infection, all patients with periodontitis (intervention, 21; control, 22). Sex (M/F): 29/37 Age: 19 to 78 years *H. pylori* testing: PCR Oral *H. pylori* status: *H. pylori* positive
Interventions	Intervention group: *H. pylori* eradication and periodontal treatment for 7 days Control group: *H. pylori* eradication for 7 days only

Zaric 2009 *(Continued)*

	H. pylori eradication: amoxicillin 2.0 g, clarithromycin 1.0 g, pantoprazole 80 mg, once a day for 7 days Periodontal treatment: oral hygiene orientation, ultrasonic scaling and root planing for removing plaque and calculus, irrigation of periodontal pockets with 0.12% chlorhexidine-gluconate (during triple therapy)
Outcomes	Eradication rate of gastric *H. pylori* eradication rates (3 months after eradication)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization method was performed for treatment allocations (author correspondence)
Allocation concealment (selection bias)	Unclear risk	Not described in article
Blinding (performance bias and detection bias) All outcomes	Low risk	Single blind (blinding of outcome assessment): the examiner who was responsible for *H. pylori* detection was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	From both groups, a number of patients did not complete the study due to different reasons, but the authors did not report the exact number or the reasons (author correspondence).
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes were reported
Other bias	Low risk	—

ITT: intention-to-treat; **PCR**: polymerase chain reaction; **PPI**: proton pump inhibitor.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Avcu 2001	Not treated with any periodontal therapy Conclusion: *H pylori* positivity in dental plaque was correlated with oral hygiene index (OHI) scores. The patients with poor OHI scores had the most frequent gastric recurrence of *H. pylori,* compared with those with fair OHI scores and good OHI scores.
Bago 2011	Not treated with any periodontal therapy Conclusion: Nearly half of the patients with gastric*H. pylori* harboured *H. pylori* in the oral cavity. The eradication therapy was very effective in the treatment of oral *H. pylori*.
Bai 2014	Failed to extract the details of the trial. There are not enough details to know how long the periodontal therapy lasted. Conclusion: Periodontal therapy combined with triple therapy could increase the eradication rate of gastric *H. pylori*, when compared with triple therapy only.
Hou 2002	Not a randomized clinical trial, though it met other inclusion criteria. The patients were assigned into 3 groups based on the depth of periodontal pocket.

Study	Reason for exclusion
	Conclusion: Periodontal therapy may affect the eradication of gastric *H. pylori*. Periodontal therapy increased eradication rate in patients with both gastric *H. pylori* and periodontitis non-significantly, when combined with triple eradication treatment. For long-term follow-up, the eradication rate was reduced significantly in the intervention group compared with control group after 1 year.
Hou 2003	Not treated with any periodontal therapy Conclusion: the eradication rate of gastric *H. pylori* was correlated with the presence of oral *H. pylori*. The patients with oral *H. pylori* had a low eradication rate compared with those without oral *H. pylori*.
Hou 2004	Gastic *H. pylori* eradication rate was not observed. The aim of this study is to evaluate the role of periodontal therapy on oral *H. pylori* infection.
Ierardi 1998	Not compliant with aim of this meta-analysis. The aim was to investigate the possible relationship between 'objective' halitosis and *H. pylori.* Conclusion: Halitosis was correlated with *H. pylori*, since eradication with triple therapy may resolve the symptom.
Jia 2009b	Not a randomized clinical trial, though complied with other inclusion criteria Conclusion: Long-term (6 months) professional dental plaque control was correlated with less gastric *H. pylori* reinfection. The prevalence of gastric *H. pylori* infection in patients with professional dental plaque control was significantly lower than those in the control group.
Li 2012	A review
Miyabayashi 2000	Not treated with any periodontal therapy Conclusion: The outcome of eradication therapy and the recurrence of gastric*H. pylori* infection were affected by *H. pylori* in oral cavity. The eradication rate in patients with oral *H. pylori* was significantly lower compared with those without oral *H. pylori*. Inversely, recurrence of gastric *H. pylori* was significantly higher in patients with oral *H. pylori 2* years after successful treatment.
Namiot 2001	Not treated with any periodontal therapy. Retrospective review of the relationship between natural teeth status and the efficacy of *H. pylori* eradication. Conclusion: Natural teeth status may influence the outcome of *H. pylori* eradication. The number of teeth was higher and caries index lower in successfully eradicated patients with triple regimen (omeprazole, amoxicillin, tinidazole), compared with those with eradication failure.
Namiot 2004	Not treated with any periodontal therapy. The aim was to assess the effect of salivary secretion on the efficacy of gastric *H. pylori* eradication. Conclusion: Reduced salivary secretion was associated with eradication failure.
Namiot 2007	Not treated with any periodontal therapy. Retrospective review of the relationship between oral health, oral hygiene practices and the efficacy of *H. pylori* eradication. Conclusion: Oral health and oral hygiene practices seem unlikely to increase the efficacy of *H. pylori* eradication from the stomach.
Qian 2014	Patients in intervention group treated with triple eradication and periodontal pocket rinse with sodium chloride solution. Patients in control group treated with triple eradication and periodontal therapy, including supragingival scaling, subgingival scaling, mouthwash with tinidazole, periodontal pocket rinse with sodium chloride solution and hydrogen peroxide. Study did not meet other inclusion criteria.

Study	Reason for exclusion
	Conclusion: Periodontal therapy combined with triple therapy could improve the eradication rate non-significantly in patients with both gastric *H. pylori* and chronic periodontitis. For long-term follow-up, the eradication rate was increased significantly in the intervention group compared with control group, after 3, 6 and 12 months.
Tarullo 2001	Patients in both groups were not treated with triple eradication therapy. Patients in the treatment group received ablation of dental plaques, toilette of periodontal pockets with special agents for prevention against bacteria, and mouthwash. The placebo group received the same procedure except for the presence of the special agents. Conclusion: Based on the 2-year follow-up results, periodontal pockets treatment for patients with gastric *H. pylori* infection led to long-term *H. pylori* eradication.
Xu 2001	Patients treated with dual therapy for eradication of *H. pylori.* The abstract was not consistent with full text. Conclusion: The use of mouthrinse solution containing amoxicillin, metronidazole and chlorhexidine did not increase the eradication rate of gastric *H. pylori* when combined with eradication treatment.
Yang 2013	Failed to extract the details of the trial. There are not enough details to know how long the periodontal therapy lasted. Conclusion: In patients with periodontitis and peptic ulcer, the periodontal treatment in combination with triple therapy could increase the eradication of *H. pylori*.
Ye 2012	Not a randomized clinical trial, though complied with other inclusion criteria. Conclusion: Mouthwash with Chinese herbal medicine plus triple therapy significantly increased eradication of gastric *H. pylori*, when compared with triple therapy alone.
Zhao 2000	Oral surgical treatment was included in periodontal therapy. Conclusion: No significant differences in *H. pylori* eradication rate could be found between the patients with periodontal treatment plus bismuth triple therapy and those with bismuth triple therapy alone. The recurrence rate in the former were significantly lower than in the latter group.
Özdemir 2001	Not treated with any periodontal therapy. The aim was to detect the presence of *H. pylori* in dental plaque and tongue scrapings of patients with chronic gastritis and to investigate the effect of eradication treatment on *H. pylori* in dental plaque, tongue scrapings and gastric mucosa. Conclusion: patients with gastric *H. pylori* infection had higher rates of *H. pylori* colonization in dental plaque and tongue scrapings. Triple eradication therapy failed to respond to *H. pylori* in dental plaque and tongue scrapings.

DATA AND ANALYSES

Comparison 1. Eradication therapy combined with periodontal therapy versus eradication therapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eradication rate of gastric*H.pylori*	6	543	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.47, 3.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Non-recurrence rate of gastric *H.pylori*	3	299	Odds Ratio (M-H, Fixed, 95% CI)	3.60 [2.11, 6.15]

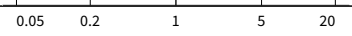
Analysis 1.1. Comparison 1 Eradication therapy combined with periodontal therapy versus eradication therapy alone, Outcome 1 Eradication rate of gastric*H.pylori*.

Study or subgroup	Invention group n/N	Control group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Jin 2003	28/32	26/32		8.84%	1.62[0.41,6.38]
Jin 2007	38/46	32/41		16.01%	1.34[0.46,3.86]
Liu 2012	48/78	34/74		36.51%	1.88[0.99,3.59]
Lv 2006	26/35	17/30		12.81%	2.21[0.78,6.29]
Wang 2014	49/60	43/72		19.5%	3[1.34,6.73]
Zaric 2009	17/22	10/21		6.33%	3.74[1,13.92]
Total (95% CI)	**273**	**270**		**100%**	**2.15[1.47,3.14]**
Total events: 206 (Invention group), 162 (Control group)					
Heterogeneity: Tau^2=0; Chi^2=2.45, df=5(P=0.78); I^2=0%					
Test for overall effect: Z=3.95(P<0.0001)					

Intervention group — Control group

Analysis 1.2. Comparison 1 Eradication therapy combined with periodontal therapy versus eradication therapy alone, Outcome 2 Non-recurrence rate of gastric *H.pylori*.

Study or subgroup	Intervention group n/N	Control group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Jia 2009a	54/109	7/39		34.82%	4.49[1.83,11.04]
Jin 2003	22/32	13/32		27.19%	3.22[1.15,8.99]
Jin 2007	27/46	13/41		38%	3.06[1.27,7.39]
Total (95% CI)	**187**	**112**		**100%**	**3.6[2.11,6.15]**
Total events: 103 (Intervention group), 33 (Control group)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=4.69(P<0.0001)					



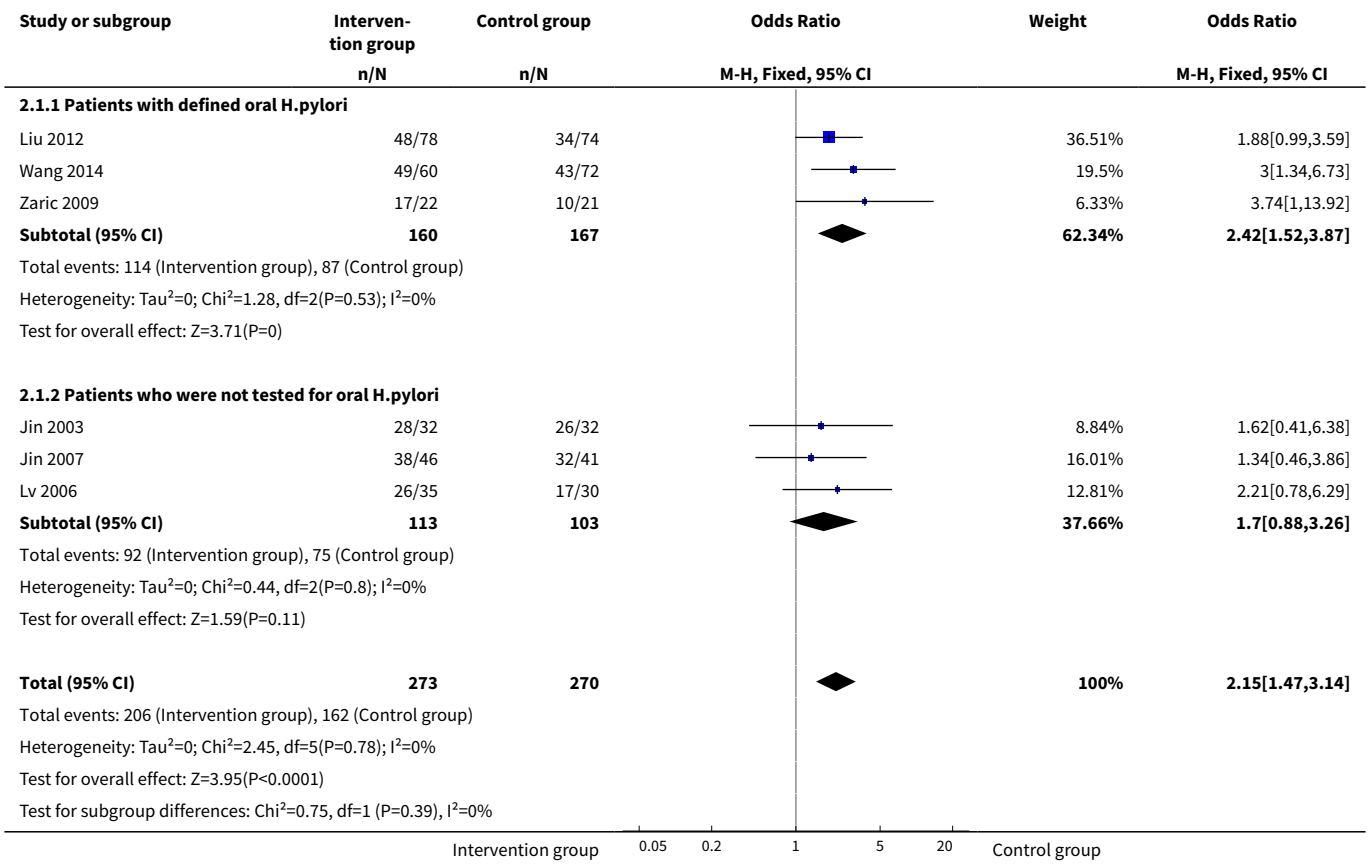
Intervention group — Control group

Comparison 2. Subgroup analysis: Stratified by different oral *H.pylori* status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eradication rate of gastric*H.pylori*	6	543	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.47, 3.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Patients with defined oral *H.pylori*	3	327	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [1.52, 3.87]
1.2 Patients who were not tested for oral *H.pylori*	3	216	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.88, 3.26]

Analysis 2.1. Comparison 2 Subgroup analysis: Stratified by different oral *H.pylori* status, Outcome 1 Eradication rate of gastric*H.pylori*.



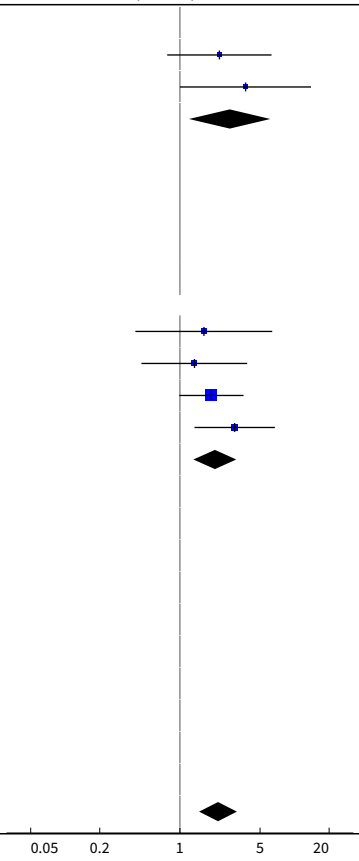
Comparison 3. Subgroup analysis: Stratified by different durations of periodontal therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eradication rate of gastric*H.pylori*	6	543	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [1.47, 3.14]
1.1 Periodontal therapy during eradication therapy	2	108	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [1.20, 6.14]

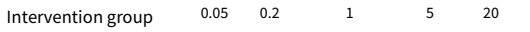
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Periodontal therapy continued until testing the result of eradication therapy	4	435	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.31, 3.10]
1.3 Periodontal therapy continued for longer	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Non-recurrence rate of gastric*H.pylori*	3	299	Odds Ratio (M-H, Fixed, 95% CI)	3.60 [2.11, 6.15]
2.1 Periodontal therapy during eradication therapy	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Periodontal therapy continued until testing the result of eradication therapy	2	151	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [1.60, 6.10]
2.3 Periodontal therapy continued for longer	1	148	Odds Ratio (M-H, Fixed, 95% CI)	4.49 [1.83, 11.04]

Analysis 3.1. Comparison 3 Subgroup analysis: Stratified by different durations of periodontal therapy, Outcome 1 Eradication rate of gastric*H.pylori*.

Study or subgroup	intervention group n/N	Control group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Periodontal therapy during eradication therapy					
Lv 2006	26/35	17/30		12.81%	2.21[0.78,6.29]
Zaric 2009	17/22	10/21		6.33%	3.74[1,13.92]
Subtotal (95% CI)	**57**	**51**		**19.14%**	**2.72[1.2,6.14]**
Total events: 43 (intervention group), 27 (Control group)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=2.4(P=0.02)					
3.1.2 Periodontal therapy continued until testing the result of eradication therapy					
Jin 2003	28/32	26/32		8.84%	1.62[0.41,6.38]
Jin 2007	38/46	32/41		16.01%	1.34[0.46,3.86]
Liu 2012	48/78	34/74		36.51%	1.88[0.99,3.59]
Wang 2014	49/60	43/72		19.5%	3[1.34,6.73]
Subtotal (95% CI)	**216**	**219**		**80.86%**	**2.02[1.31,3.1]**
Total events: 163 (intervention group), 135 (Control group)					
Heterogeneity: Tau^2=0; Chi^2=1.66, df=3(P=0.65); I^2=0%					
Test for overall effect: Z=3.2(P=0)					
3.1.3 Periodontal therapy continued for longer					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (intervention group), 0 (Control group)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**273**	**270**		**100%**	**2.15[1.47,3.14]**

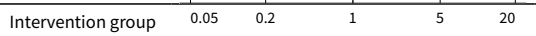


Study or subgroup	intervention group n/N	Control group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 206 (intervention group), 162 (Control group)					
Heterogeneity: Tau²=0; Chi²=2.45, df=5(P=0.78); I²=0%					
Test for overall effect: Z=3.95(P<0.0001)					
Test for subgroup differences: Chi²=0.4, df=1 (P=0.53), I²=0%					



Analysis 3.2. Comparison 3 Subgroup analysis: Stratified by different durations of periodontal therapy, Outcome 2 Non-recurrence rate of gastric*H.pylori*.

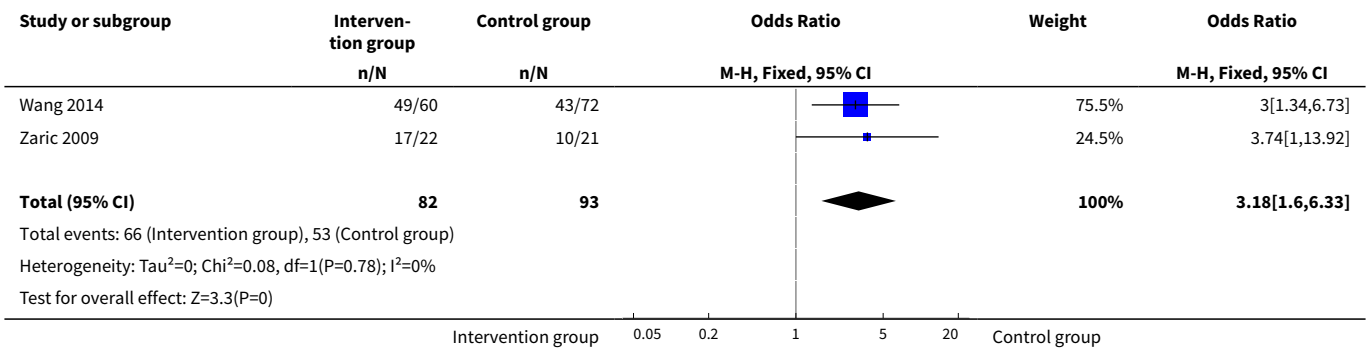
Study or subgroup	intervention group n/N	Control group n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.2.1 Periodontal therapy during eradication therapy					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (intervention group), 0 (Control group)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.2.2 Periodontal therapy continued until testing the result of eradication therapy					
Jin 2003	22/32	13/32		27.19%	3.22[1.15,8.99]
Jin 2007	27/46	13/41		38%	3.06[1.27,7.39]
Subtotal (95% CI)	**78**	**73**		**65.18%**	**3.13[1.6,6.1]**
Total events: 49 (intervention group), 26 (Control group)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%					
Test for overall effect: Z=3.34(P=0)					
3.2.3 Periodontal therapy continued for longer					
Jia 2009a	54/109	7/39		34.82%	4.49[1.83,11.04]
Subtotal (95% CI)	**109**	**39**		**34.82%**	**4.49[1.83,11.04]**
Total events: 54 (intervention group), 7 (Control group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.27(P=0)					
Total (95% CI)	**187**	**112**		**100%**	**3.6[2.11,6.15]**
Total events: 103 (intervention group), 33 (Control group)					
Heterogeneity: Tau²=0; Chi²=0.41, df=2(P=0.82); I²=0%					
Test for overall effect: Z=4.69(P<0.0001)					
Test for subgroup differences: Chi²=0.4, df=1 (P=0.53), I²=0%					



Comparison 4. Subgroup analysis: After removing low-quality studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eradication rate of gastric *H.pylori*	2	175	Odds Ratio (M-H, Fixed, 95% CI)	3.18 [1.60, 6.33]

Analysis 4.1. Comparison 4 Subgroup analysis: After removing low-quality studies, Outcome 1 Eradication rate of gastric *H.pylori*.



APPENDICES

Appendix 1. CENTRAL search strategy

1. h-pylori.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. h-pylori infection.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. Helicobacter pylori.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. Helicobacter pylori infection.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. PPI.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. proton pump inhibitor.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. or/1-6
8. (clarithromycin or 6-o-methylerythromycin or abbott-56268 or biaxin or clarith or klaricid or "te 031").mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9. (amoxicillin or actimoxi or almodan or amix or amopen or amoram or amoxicot or amoxidin or amoxil or amoxymed or amrit or biomox or brl 2333 or clamoxyl or dispermox or flemoxin solutab or galenamox or larotid or moxatag or moxilin or p-hydroxyampicillin or penamox or polymox or respillin or rimoxallin or senox or sumox or trimox or utimox or wymox or zoxycil).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. (2 methyl 5 nitroimidazole 1 ethanol or anabact or bayer 5360 or clont or danizol or edg dentalgel or elyzol or flagyl or gineflavir or metric or metro iv or metrocream or metrodzhil or metrogel or metrolotion or metrolyl or metronizole or metrotop or metrovex or metrozol or metryl or nidazol or noritate or norzol or nydamax or obagi or protostat or rozex or satric or trichopol or tricom or trivazol or vagilen or vaginyl or vandazole or vitazol or zadstat or zidoval).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. (chlorhexidine or acclean or acriflex or avagard or betasept or calgon vesta or chloraprep or chlorhexamed or chlorhexigard or chlorohex 2000 or chlorostat or corsodyl or curasept ads 220 or cx antiseptic dusting or denticare or dyna-hex or eludril or excel or gibitan or habistat or hexidine or hibiclens or hibident or hibiscrub or hibisol or hibitane or mk 412a or novalsan or oris or oro clense or peridex or periochip or periogard or periosep or perisol or phiso-med or pre-scrub ii or rotersept or sebidin a or spectrum-4 or sterexidine or steripod pink or tubulicid or unisept or uriflex c).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. (omeprazole or h 16868 losec or nexium or omesec or prilosec or rapinex or ulcergard or zegerid).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (ranitidine or ah 19065 or azanplus or biotidin or gr 122311x or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zaedoc or zantac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. (tinidazole or bioshik or fasigin or fasigyne or tindamax or tricolam).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. or/8-14
16. (periodontal and (disease$ or therap$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

17. (oral hygiene or buccal cavity or dental hygiene).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. periodontal scaling.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. periodontal root planing.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. subgingival bacterial plaque.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. (gingival and (pocket$ or plaque$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22. or/16-21
23. 7 and 15 and 22

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. helicobacter pylori.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. helicobacter.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. pylori.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. H-pylori.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. or/12-15
17. PPI.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. proton pump inhibitor.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. (amoxicillin or actimoxi or almodan or amix or amopen or amoram or amoxicot or amoxidin or amoxil or amoxymed or amrit or biomox or brl 2333 or clamoxyl or dispermox or flemoxin solutab or galenamox or larotid or moxatag or moxilin or p-hydroxyampicillin or penamox or polymox or respillin or rimoxallin or senox or sumox or trimox or utimox or wymox or zoxycil).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. (clarithromycin or 6-o-methylerythromycin or abbott-56268 or biaxin or clarith or klaricid or "te 031").mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. (2 methyl 5 nitroimidazole 1 ethanol or anabact or bayer 5360 or clont or danizol or edg dentalgel or elyzol or flagyl or gineflavir or metric or metro iv or metrocream or metrodzhil or metrogel or metrolotion or metrolyl or metronizole or metrotop or metrovex or metrozol or metryl or nidazol or noritate or norzol or nydamax or obagi or protostat or rozex or satric or trichopol or tricom or trivazol or vagilen or vaginyl or vandazole or vitazol or zadstat or zidoval).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22. (chlorhexidine or acclean or acriflex or avagard or betasept or calgon vesta or chloraprep or chlorhexamed or chlorhexigard or chlorohex 2000 or chlorostat or corsodyl or curasept ads 220 or cx antiseptic dusting or denticare or dyna-hex or eludril or excel or gibitan or habistat or hexidine or hibiclens or hibident or hibiscrub or hibisol or hibitane or mk 412a or novalsan or oris or oro clense or peridex or periochip or periogard or periosep or perisol or phiso-med or pre-scrub ii or rotersept or sebidin a or spectrum-4 or sterexidine or steripod pink or tubulicid or unisept or uriflex c).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. (omeprazole or h 16868 losec or nexium or omesec or prilosec or rapinex or ulcergard or zegerid).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
24. (ranitidine or ah 19065 or azanplus or biotidin or gr 122311x or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zaedoc or zantac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. (tinidazole or bioshik or fasigin or fasigyne or tindamax or tricolam).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26. or/17-25
27. periodontal therap$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

28. oral hygiene.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
29. (buccal cavity or cavitas oris or mouth or oral cavity or dental hygiene).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30. (periodontal and (disease$ or therap$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
31. periodontal scaling.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
32. periodontal root planing.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
33. ((subgingival or supragingival) adj5 bacterial plaque).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
34. (periodontal adj10 chemotherapeutic agent$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
35. (irrigation adj10 periodontal pocket$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36. gingival pocket.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
37. or/27-36
38. 11 and 16 and 26 and 37

Appendix 3. EMBASE search strategy

1. Clinical trial.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
2. Randomized controlled trial.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
3. Randomization.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
4. Single-blind method.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
5. Double-blind method.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
6. Cross-over studies.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
7. random allocation.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
8. placebo.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
9. randomi?ed controlled trial$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
10. Rct.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
11. Random allocation.tw.
12. randomly allocated.tw.
13. allocated randomly.tw.
14. (allocated adj2 random).tw.
15. single blind$.tw.
16. double blind$.tw.
17. ((treble or triple) adj blind$).tw.
18. placebo$.tw.
19. prospective study.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
20. or/1-19
21. case study.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
22. case report.tw.
23. abstract report/ or letter.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
24. or/21-23
25. 20 not 24

26. H-pylori.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
27. H-pylori infection.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
28. Helicobacter pylori.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
29. helicobacter pylori infection.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
30. or/26-29
31. PPI.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
32. proton pump inhibitor$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
33. (clarithromycin or 6-o-methylerythromycin or abbott-56268 or biaxin or clarith or klaricid or "te 031").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
34. (amoxicillin or actimoxi or almodan or amix or amopen or amoram or amoxicot or amoxidin or amoxil or amoxymed or amrit or biomox or brl 2333 or clamoxyl or dispermox or flemoxin solutab or galenamox or larotid or moxatag or moxilin or p-hydroxyampicillin or penamox or polymox or respillin or rimoxallin or senox or sumox or trimox or utimox or wymox or zoxycil).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
35. (chlorhexidine or acclean or acriflex or avagard or betasept or calgon vesta or chloraprep or chlorhexamed or chlorhexigard or chlorohex 2000 or chlorostat or corsodyl or curasept ads 220 or cx antiseptic dusting or denticare or dyna-hex or eludril or excel or gibitan or habistat or hexidine or hibiclens or hibident or hibiscrub or hibisol or hibitane or mk 412a or novalsan or oris or oro clense or peridex or periochip or periogard or periosep or perisol or phiso-med or pre-scrub ii or rotersept or sebidin a or spectrum-4 or sterexidine or steripod pink or tubulicid or unisept or uriflex c).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
36. (omeprazole or h 16868 losec or nexium or omesec or prilosec or rapinex or ulcergard or zegerid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
37. (ranitidine or ah 19065 or azanplus or biotidin or gr 122311x or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zaedoc or zantac).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
38. (tinidazole or bioshik or fasigin or fasigyne or tindamax or tricolam).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
39. or/31-38
40. (periodontal and (therap$ or disease$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
41. (oral hygiene or buccal cavity or dental hygiene).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
42. periodontal scaling.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
43. oral cavity.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
44. dental plaque$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
45. gingival pocket$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
46. periodontal root planing.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
47. periodontitis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
48. preventive dentistry.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
49. mouth hygiene.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
50. oral hygiene.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
51. subgingival bacterial plaque.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

52.(tooth adj4 (calculus or plaque)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

53.or/40-52

54.25 and 30 and 39 and 53

CONTRIBUTIONS OF AUTHORS

Qian Ren drafted the review protocol and modified it according to the opinions of the editors and peer reviewers. Qian Ren undertook the literature search, extracted and analyzed data, and wrote the review. WeiXin Li performed the literature search, original data extraction, and analysis. Xiang Yan and YongNing Zhou participated in analysing data and interpreting the results. All authors contributed to the completed systematic review.

DECLARATIONS OF INTEREST

QR: none known.

XY: none known.

YNZ: none known.

WXL: none known.

SOURCES OF SUPPORT

Internal sources

- The First Hospital of Lanzhou University, China.

External sources

- The Evidence-Based Medicine Center of Lanzhou University, China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol stage, we planned to include randomized controlled trials comparing periodontal therapy plus triple therapy with triple therapy alone. However, in the review, we actually included patients treated with eradication therapy comprising triple therapy, quadruple therapy, sequential therapy and concomitant therapy, only excluding dual therapy because of the low eradication rate. According to the comments of statistical editor and considering the balance of randomisation, we used 'non-recurrence rate' instead of 'recurrence rate' to evaluate periodontal therapy for gastric *H. pylori* at long-term follow up. Additionally, we searched both ClinicalTrials.gov and the WHO ICTRP portal to reduce potential bias as much as possible.

INDEX TERMS

Medical Subject Headings (MeSH)

*Helicobacter pylori; Helicobacter Infections [prevention & control] [*therapy]; Periodontics; Periodontitis [*therapy]; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention [methods]

MeSH check words

Adolescent; Adult; Aged; Humans; Middle Aged