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***Helicobacter pylori* eradication for functional dyspepsia: Systematic review and meta-analysis**

DuLJ *et al. Helicobacter pylori* eradication for FD

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**Abstract**

**AIM:** To evaluate whether *Helicobacter pylori* (*H. pylori*) eradication benefits patients with functional dyspepsia (FD).

**METHODS:** Randomized controlled trials (RCTs) investigating the efficacy and safety of *H. pylori* eradication for patients with functional dyspepsia published in English (up to May 2015) were identified by searching PubMed, EMBASE, and The Cochrane Library. Pooled estimates were measured using the fixed or random effect model. Overall effect was expressed as pooled risk ratio (RR) or standard mean difference (SMD). All data were analyzed by Review Manager 5.3 and Stata 12.0.

**RESULTS:** This systematic review included 25 RCTs with a total of 5555 patients with FD. Twenty-three of these studies were used to evaluate the benefits of *H. pylori* eradication on symptom improvement; the pooled RR was 1.23 (95%CI: 1.12-1.36, *P <* 0.0001). *H. pylori* eradication demonstrated symptom improvement during long-term follow-up at > 1 year (RR = 1.24; 95%CI: 1.12-1.37, *P <* 0.0001) but not during short-term at < 1 year (RR = 1.26; 95%CI: 0.83-1.92, *P =* 0.27). Seven studies showed no benefits of *H. pylori* eradication on quality of life with a SMD of -0.01 (95%CI: -0.11 to 0.08, *P =* 0.80). Six studies demonstrated that *H. pylori* eradication therapy reduced the development of peptic ulcer disease compared to no eradication therapy (RR = 0.35; 95%CI: 0.18-0.68, *P =* 0.002). Eight studies showed that *H. pylori* eradication increased the likelihood of treatment-related side effects compared to no eradication therapy (RR = 2.02; 95%CI: 1.12-3.65, *P =* 0.02). Ten studies demonstrated that patients who received treatment aimed at *H. pylori* eradication were more likely to obtain histologic resolution of chronic gastritis compared to no eradication therapy (RR = 7.13; 95%CI: 3.68-13.81, *P <* 0.00001).

**CONCLUSION:** The decision to eradicate *H. pylori* in patients with functional dyspepsia requires individual assessment.

**Key words:** Functional dyspepsia; *Helicobacter pylori* eradication; Symptom improvement; Quality of life; Peptic ulceration; Meta-analysis

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**Core tip:** The decision to eradicate *Helicobacter pylori* (*H. pylori*) in patients with functional dyspepsia requires individual assessment. This meta-analysis suggests that *H. pylori* eradication is beneficial for symptom relief, reduces the development of peptic ulceration, and leads to histologic resolution of chronic gastritis but does not improve the quality of life and may even result in adverse events*.* Otherwise, other validated treatment such as acid suppression, prokinetics, and psychiatric treatment should also be considered.

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**INTRODUCTION**

Functional dyspepsia (FD) is a common gastrointestinal disease and affects as high as 21%[1] of the population worldwide and 2%-24%[2,3] of the Chinese population. Characterized by epigastric pain, postprandial fullness, and early satiation without organic causes, FD adversely impacts people’s quality of life and is hard to cure. FD is diagnosed by Rome III, which is a symptom-based criteria[4]. Although the pathophysiology is not well established, gastro-duodenal motility dysfunction[5,6], visceral hypersensitivity[7,8], and psychological disturbance[9] may play a role in the pathogenesis of FD. *Helicobacter pylori* (*H. pylori*)infection has also been found to be more common in patients with dyspepsia (OR = 2.3; 95%CI: 1.9-2.7) in comparison to healthy controls[10]. However, the effects of *H. pylori* eradication on FD are inconsistent in previously published randomized trials and meta-analyses.

Previous meta-analyses mainly focused on symptom improvement after *H. pylori* eradication; their findings (whether or not to eradicate) were not consistent because of variable study designs and follow-up duration[11-13]. One meta-analysis conducted by Moayyedi *et al*[14] provided an economic evaluation and suggested that *H. pylori* eradication therapy is the most cost-effective treatment method. We carried out this meta-analysis not only to evaluate benefits of *H. pylori* eradication for symptom relief, but also to discuss the effects on the quality of life, adverse events, and risk of subsequent peptic ulcer disease. We performed a more comprehensive meta-analysis than previous studies in order to assess the overall clinical impact of *H. pylori* eradication in this population

**MATERIALS AND METHODS**

***Search strategy***

A standard protocol, based on current PRISMA guidance, was implemented for inclusion, data extraction, and analysis. PubMed, EMBASE, and The Cochrane Library were searched for published randomized controlled trials (RCTs) in English from 1988 to 2015. The main search strategies were as follows: “*Helicobacter pylori* OR *Campylobacter* OR *Campylobacter pylori* OR *C. pylori* OR *Helicobacter* infection” AND “treat OR eradication OR eradicating OR therapy OR anti-“ AND “dyspepsia OR functional gastrointestinal disorder OR non-ulcer dyspepsia OR functional dyspepsia”.

***Inclusion and exclusion criteria***

Studies were considered eligible if they met the following criteria: (1) RCTs; (2) study population of patients with dyspepsia (symptom based criteria including ROME I, II, or III) and *H. pylori* infection (13C breath test, histology, and/or rapid urease teat); (3) *H. pylori* eradication regimens (dual, triple, quadruple, and sequential therapy) as intervention for treatment group and placebo or other drugs known not to eradicate *H. pylori* (no antibiotics or bismuth) as intervention for control groups; and (4) age above 17 years old. Studies were excluded if they were available only as abstracts, review articles, case reports, or predefined outcome data required for analyses were lacking.

***Data extraction and quality evaluation***

Two investigators (Du LJ, Chen BR) reviewed all the titles and abstracts independently. Data was extracted from eligible full-text. The data included study population, demographical characteristics, year of publication, country, age, gender, *H. pylori* eradication regimens, duration of follow-up, *H. pylori* eradication rate, and study outcomes. The individual study quality was assessed according to the Cochrane collaboration’s tool for risk of bias, which contains random sequence generation, allocation concealment, blindness, incomplete outcome data, selective outcome reporting, and other biases. Any disagreement was resolved by a third investigator (Dai N).

***Study endpoints***

The primary outcome for this study was the pooled risk ratio (RR) of successful treatment (presence of no more than mild pain or discomfort after treatment) with a 95% confidence Interval (CI). The secondary outcomes were the pooled RR of improvement of dyspepsia at short-term (< 1 year) and long-term (> 1 year) follow-up, standard mean difference (SMD) of improvement in life’s quality (SF-36), pooled RR of incidence of peptic ulceration during follow-up, pooled RR of development of treatment-related adverse events, and pooled RR of histologic resolution of chronic gastritis. If the articles were homogeneous (*I*2 < 50%), the fixed effect model was used. Otherwise (*I*2 > 50%), the random effect model was chosen. Intervention was considered statistically significant when *P* valuewas < 0.05. Sensitivity analysis was performed when the heterogeneity was significant. Publication bias was assessed by the funnel plot. All data was analyzed by RevMan 5.3 and Stata 12.0. The statistical methods of this study were reviewed by professor Yun-Xian Yu from Department of Epidemiology and Health Statistics of Zhejiang University.

**RESULTS**

***Literature search and description of included studies***

According to the search strategy, 2355 citations were identified from three databases. After removing the duplicates (*n =* 1076), two reviewers screened the titles and abstracts of potentially relevant studies (*n =* 1279) independently. 97 full-text papers were reviewed from which 66 papers did not meet the inclusion criteria. Twenty-five RCTs with a total of 5555 people who met the inclusion criteria were included in this systematic review (Figure 1)[15-39]. The assessment on the quality of the individual study is shown in Figure 2. The demographic data, eradication regimens, and eradication rates are listed in Table 1.

***Benefits of H. pylori eradication on symptom improvement***

Twenty-three of 25 studies reported information on treatment success. Eradication groups were treated with antibiotics, proton pump inhibitors, and bismuth, while control groups were treated with placebo, prokinetics, and/or proton pump inhibitors. Primary analysis demonstrated that 1183 (40%) of 2939 patients in the eradication group and 795 (32%) of 2468 in the control groups had no or mild symptoms during the last follow-up visit (pooled RR = 1.23; 95%CI: 1.12-1.36, *P <* 0.0001). Although there was no significant heterogeneity (*I*2 = 42%) among the selected studies, the asymmetry in the funnel plot (Figure 3) indicated existing publication bias. *H. pylori* eradication demonstrated symptom improvement at long-term (> 1 year) (RR = 1.24; 95%CI: 1.12-1.37, *P <* 0.0001) but not at short-term (< 1 year) (RR = 1.26; 95%CI: 0.83-1.92, *P =* 0.27) follow-up. The studies that reported short-term outcome demonstrated significant heterogeneity (*I*2 = 64%). The forest plot and sensitivity analysis are shown in Figures 4 and 5, respectively.

***Benefits of H. pylori eradication on quality of life***

Seven studies reported data on quality of life both at baseline and at the last visit required for the meta-analysis. Five trials used the SF-36, one used the general well-being index, and one used QoL-PEI. A fixed effect model (*I*2 = 0%) was performed on all seven articles. Overall, *H. pylori* eradication therapy had no significant benefits on quality of life, with a SMD of -0.01 (95%CI: -0.11 to 0.08, *P =* 0.80). Detailed information is shown in Figure 6.

***Benefits of H. pylori eradication on long-term peptic ulceration***

Six studies reported endoscopic data at the last visit to evaluate for the development of peptic ulcer disease. *H. pylori* eradication therapy reduced the development of peptic ulcer disease compared to no eradication therapy (RR = 0.35; 95%CI: 0.18-0.68, *P =* 0.002). There was no significant study heterogeneity (*I*2 = 0%). Detailed information is shown in Figure 7.

***H. pylori eradication on the development of adverse events***

Eight studies provided data on development of common side effects associated with the intervention. Patients who received *H. pylori* eradication were more likely to have side effects compared to controls (RR = 2.02; 95%CI: 1.12-3.65, *P =* 0.02). The random effect model was used because significant study heterogeneity (*I*2 = 94%) was detected. The forest plot and sensitivity analysis are shown in Figures 8 and 9.

***Other outcomes comparing H. pylori eradication and control groups***

One study that provided outcome data on the cost of intervention including medication, diagnostic tests, and physician consultation did not demonstrate a difference between eradication therapy *vs* control[38]. However, the cost of intervention from this study was derived from utilization of healthcare services rather than the actual cost. Ten studies reported histological outcomes following intervention (Figure 10). Patients who received *H. pylori* eradication were more likely to obtain histologic resolution of chronic gastritis compared to control (RR = 7.13; 95%CI: 3.68-13.81, *P <* 0.00001).

**DISCUSSION**

Our meta-analysis based on well-designed RCTs demonstrated that the effect size of symptom relief from *H. pylori* eradication in patients with FD was small (RR = 1.23; 95%CI: 1.12-1.36, *P <* 0.0001) with an undetectable short-term benefit. Eradication therapy was nearly three times more likely to reduce the development of peptic ulcer disease compared with no eradication therapy*.* Furthermore, histologic findings of chronic gastritis were more likely to resolve after *H. pylori* eradication compared to controls.However, *H. pylori* eradication therapy did not improve the quality of life of patients with FD compared to treatment with anti-acids, prokinetics, or placebo therapy. Eradication therapy was also more likely to be associated with side effects (RR = 2.02; 95%CI: 1.12-3.65, *P =* 0.02) compared to control.

*H. pylori* infection is more prevalent in Asia compared to Western countries with high prevalence observed in China and Korea[40]. Eradication therapy appears to be more effective in Asian population as shown by the meta-analysis conducted by Jin and Li[13] on Chinese population. Their study showed that *H. pylori* eradication compared to controls increased the likelihood of improvement in dyspeptic symptoms by 3.6-fold. Another meta-analysis performed by Zhao *et al*[12] found that *H. pylori* eradication compared to no eradication was beneficial for improvement of dyspepsia in European (OR = 1.49; 95 CI% 1.10-2.02) and American population (OR = 1.43; 95%CI: 1.12-1.83).

*H. pylori* is strongly associated with many diseases, including functional dyspepsia, gastric or duodenal ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[41,42]. However, *H. pylori-*induced gastritis is the most important risk factor for development of peptic ulcer disease[43]. Most patients with *H. pylori* infection have asymptomatic gastritis, and patients experience variable clinical symptoms depending on bacteria, host, and environmental factors. Whether *H. pylori* infectiondelays gastric emptying is unclear[44,45], but *H. pylori* appears to alter gastric acid production by changing gastrin and somatostatin secretion[46]. Abnormal gastric acid secretion causes mainly dysmotility-like, dyspeptic symptoms[47]. Duodenal acid exposure indirectly induces fullness, bloating, and epigastric pain by suppressing antral contractions, which may contribute to delayed gastric emptying[48,49].

According to the results of this meta-analysis, decision to eradicate *H. pylori* may be influenced by several key points. Firstly, eradication may be preferable among patients with risk factors for peptic ulcer or gastric cancer. Our study showed benefit for other long-term outcomes such as reduction in incidence of future peptic ulcer disease and resolution of gastritis, which are associated with gastric cancer[50,51]. Secondly, because of apparent adverse effects associated eradication therapy, alternative validated therapy for FD such as acid suppression, prokinetics, or lifestyle changes for mild dyspeptic symptoms should also be considered. A large study of 1425 patients showed that *H. pylori* infection was a significant risk factor for dyspepsia. However, other factors such as NSAIDs use, unemployment, and heavy smoking demonstrated larger magnitude of association compared to *H pylori* infection[52]. Furthermore, rising prevalence of antibiotics resistance[53] and *H. pylori* reinfection[54] can not be ignored. Thirdly, it has been well established that the presence of psychiatric disorders, such as anxiety disorder, is more common in patients with functional disease compared to the general population[55,56]. Psychiatric treatment with antidepressants is helpful in the reduction of dyspeptic symptoms[57]. Anxiety and depression are considered to be the best predictors of quality of life[58]. Cognitive-behavioral therapy (CBT), psychotherapy, anxiolytics, and antidepressants can also be taken into consideration to relieve dyspeptic symptoms[59,60].

The strength of this meta-analysis includes analysis of high-quality studies and comprehensive analysis that evaluated various outcomes of FD other than only symptom improvement. There are some limitations to this meta-analysis. Firstly, some well-designed studies were excluded because they were published in non-English language. Secondly, the random effect model was chosen to evaluate the short-term symptom improvement and development of adverse events in the presence of significant study heterogeneity resulting from different study designs and methods. Thirdly, there is a possibility of publication bias as we excluded some RCTs that did not have sufficient data for meta-analysis or were not published in manuscript form at the time of submission.

In conclusion**,** *H. pylori* eradication compared to no eradication has a statistically significant but a small magnitude of benefit for symptom relief and also reduced the development of peptic ulcer disease. However, *H. pylori* eradication was associated with higher incidence of adverse events during the treatment, and eradication therapy failed to demonstrate any effect on improvement in quality of life. In addition to *H. pylori* eradication, alternative therapy such as acid-suppression, prokinetics, psychotherapy, and anxiolytics should also be considered after an individualized assessment.

**ACKNOWLEDGMENTS**

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**COMMENTS**

***Background***

Functional dyspepsia (FD) is a common gastrointestinal disease and affecting as many as 21% of population worldwide. *Helicobacter pylori* (*H. pylori*) is one of the most important factors for development of dyspeptic symptoms.

***Research frontiers***

Benefits of *H. pylori* eradication in patients with FD patients are not consistent. Relying on antibiotics may lead to increased rate of drug resistance, which may consequently lead to increased rate of eradication failure.

***Innovations and breakthroughs***

Compared to previous studies, current meta-analysis included additional clinical outcomes on the benefits of *H. pylori* eradication other than symptom relief such as quality of life, adverse events, and development of peptic ulceration.

***Applications***

According to the current meta-analysis, *H. pylori* eradication should be considered after individual assessment. We have highlighted that *H. pylori* eradication was significantly beneficial for symptom relief and reduced the risk of development of peptic ulceration in patients with functional dyspepsia. However, *H. pylori* eradication failed to improve the quality of life and was associated with higher likelihood of treatment-related adverse effects. Otherwise, alternative validated therapies such as acid suppression, prokinetics, and psychiatric treatment should also be considered.

***Peer-review***

The conclusions are warranted by the results, and it is a useful meta-analysis.

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**P-Reviewer:** Ananthakrishnan N, Kurtoglu E, Lember M, Otegbayo JA

**S-Editor:** Yu J **L-Editor:** **E-Editor:**

Records identified through database searching  
(*n* = 2355)

## Identification

Records after duplicates removed  
(*n* = 1279)

Records excluded  
(*n* = 1182)

1. Review (*n* = 117)
2. Irrelevant (*n* = 1065)

Records screened  
(*n* = 1279)

## Screening

Full-text articles excluded, with reasons  
(*n* = 72)

1. Not meeting the inclusion criteria (*n* = 66)
2. The same population (*n* = 6)

Full-text articles assessed for eligibility  
(*n* = 97)

## Eligibility

Studies included in qualitative synthesis  
(*n* = 25)

## Included

Studies included in quantitative synthesis (meta-analysis)  
(*n* = 25)

**Figure 1 Study flow diagram.**

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**Figur****e 2 Risk of bias graph.** The Cochrane collaboration’s tool was used to evaluate risk of bias.

****

**Figure 3 Funnel plot of included studies for potential publication bias.** The funnel plot appeared not absolutely symmetric.

****

**Figure 4 Forest plot of the effects comparing *Helicobacter pylori* eradication *vs* control on symptom relief.** Twenty-three articles were included. The random effect model (Mantel-Haenszel method) was applied.

****

**Figure 5 Sensitivity analysis of the effects comparing *Helicobacter pylori* eradication *vs* control on symptom relief.**

****

**Figure 6 Forest plot of the effects comparing *Helicobacter pylori* eradication *vs* control on quality of life.** Seven articles were included. The fixed effect model (Inverse Variance method) was applied.

****

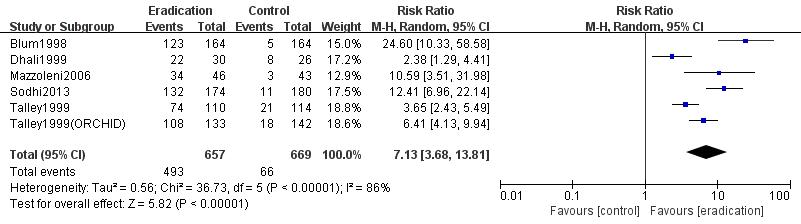
**Figure 7 Forest plot of the effects compared *Helicobacter pylori* eradication *vs* control on long-term peptic ulceration.** Six articles were included. The fixed effect (Inverse Variance method) model was applied.

****

**Figure 8 Forest plot of the effects comparing *Helicobacter pylori* eradication *vs* control on adverse events.** Eightarticles were included. The random effect model (Mantel-Haenszel method) was applied.

****

**Figure 9 Sensitivity analysis of the effects compared *Helicobacter pylori* eradication *vs* control on adverse events.**

****

**Figure 10 Forest plot of the effects comparing *Helicobacter pylori* eradication *vs* control on histologic resolution of chronic gastritis.** Sixarticles were included. The random effect model (Mantel-Haenszel method) was applied.

**Table 1 Characteristics of studies included in the meta-analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Sample (M/F)** | **Age, mean** | **Country** | **Last visit (mo)** | **Intervention** | ***Helicobacter pylori* eradication** |
| Ang, 2006 | 130 (47/83) | 38 | Singapore | 12 | LAC | 73.2% |
| Blum, 1998 | 328 (136/192) | 47 | Global | 12 | OAC | 79% |
| Chiba, 2002 | 394 (148/246) | 49.5 | Canada | 12 | OMC | 75% |
| Dhali, 1999 | 62 (44/18) | 32.5 | India | 12 | BMTe | 87.5% |
| Froehlich, 2001 | 144 (64/80) | 44.6 | Switzerland | 12 | LAC | 75% |
| Gisbert, 2004 | 50 (15/35) | 41.5 | Spain | 12 | OAC | 76% |
| Greenberg, 1999 | 100 (31/69) | 46.5 | United States | 12 | OC | 70.5% |
| Gwee, 2009 | 82 (38/44) | 40.4 | Singapore | 12 | OCT | 68.3% |
| Hsu, 2001 | 161 (78/83) | 50.9 | China | 12 | LMTe | 78% |
| Koelz, 2003 | 181 (74/107) | 47.5 | Switzerland | 6 | AO | 51.7% |
| Koskenpato, 2001 | 151 (52/99) | 51.7 | Finland | 12 | AMO | 82% |
| Lan, 2011 | 195 (89/106) | 47.4 | China | 3 | RAC | 85.7% |
| Malfertheiner, 2003 | 800 (380/420) | 46.2 | Germany | 12 | LAC | 63.9% |
| Mazzoleni, 2006 | 89 (20/69) | 41.3 | Brazil | 12 | LAC | 91.3% |
| Mazzoleni, 2011 | 404 (86/318) | 46 | Brazil | 12 | OAC | 88.6% |
| McColl, 1998 | 318 (155/163) | 42.1 | United Kingdom | 12 | AMO | 88% |
| Miwa, 2000 | 85 (40/45) | 51.5 | Japan | 3 | OAC | 85.4% |
| Naeeni, 2002 | 157 (47/110) | 32.5 | Iran | 9 | ABM | 52.6% |
| Sodhi, 2013 | 519 (169/350) | 44.5 | India | 12 | OAC | 69.9% |
| Talley, 1999 | 293 (133/160) | 46.4 | United States | 12 | LCA | 80% |
| Talley, 1999 (ORCHID) | 275 (98/177) | 50 | Australia | 12 | OAC | 85% |
| Varannes, 2001 | 253 (112/141) | 51 | France | 12 | RaAC | 69% |
| Varasa, 2008 | 48 (21/27) | 37 | Spain | 12 | RA | 81.4% |
| Xu, 2013 | 396 (135/261) | 40 | China | 12 | ACE | 76.36% |
| Zanten, 2003 | 157 (72/81) | 48 | Canada | 12 | LCA | 82% |
| A: Amoxillin; B: Bismuth salt; C: Clarithromycin; E: Esoprazole; F: Furazolidone; L: Lansoprazole; M: Metronidizole; O: Omeprazole; R: Rabeprazole; Ra: Ranitidine; T: Tinidazole; Te: Tetracycline. | | | | | | |