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

Li-Jun Du, Bin-Rui Chen, John J Kim, Sarah Kim, Jin-Hua Shen, Ning Dai

Li-Jun Du, Bin-Rui Chen, John J Kim, Sarah Kim, Jin-Hua Shen, Ning Dai, Department of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310020, Zhejiang Province, China

John J Kim, Division of Gastroenterology, Loma Linda University, Loma Linda, CA 92354, United States

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Correspondence to: Ning Dai, MD, Professor, Department of Gastroenterology, Sir Run Run Shaw Hospital, Zhejiang University, No. 3 East Qingchun Road, Hangzhou 310020, Zhejiang Province, China. ndaicn@yahoo.com
Telephone: +86-571-86006144
Fax: +86-571-86044817

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Abstract

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

METHODS: Randomized controlled trials (RCTs) investigating the efficacy and safety of H. pylori eradication therapy 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 a pooled risk ratio (RR) or a standard mean difference (SMD). All data were analyzed with 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 therapy for symptom improvement; the pooled RR was 1.23 (95%CI: 1.12-1.36, \( P < 0.0001 \)). H. pylori eradication therapy demonstrated symptom improvement during long-term follow-up at \( \geq 1 \) year (RR = 1.24; 95%CI: 1.12-1.37, \( P < 0.0001 \)) but not during short-term follow-up at < 1 year (RR = 1.26; 95%CI: 0.83-1.92, \( P = 0.27 \)). Seven studies showed no benefit of H. pylori eradication therapy on quality of life with an 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 no benefit of H. pylori eradication therapy compared to no eradication therapy (RR = 2.02; 95%CI: 1.12-3.65, \( P = 0.02 \)). Ten studies demonstrated that patients who received H. pylori eradication therapy were more likely to obtain histologic resolution of chronic gastritis compared to those who did not receive 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 therapy 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 disorder and affects as many 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 the patient’s quality of life. FD is diagnosed by Rome III criteria, which are 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 is 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 therapy in FD are inconsistent in previously published randomized trials and meta-analyses.

Previous meta-analyses mainly focused on symptom improvement after *H. pylori* eradication therapy; their findings (whether or not to eradicate) were not consistent because of variable study designs and follow-up durations\(^{(11-13)}\). 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 therapy for symptom relief, but also to discuss the effects on the quality of life, adverse events, and the 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 therapy in this population.

### MATERIALS AND METHODS

#### Search strategy

A standard protocol, based on current PRISMA guidelines, was implemented for study inclusion, data extraction, and data 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 (\(^{13}C\) breath test, histology, or rapid urease test); (3) *H. pylori* eradication regimens (dual, triple, quadruple, and sequential therapies) 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 studies, case reports, or if 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 studies. 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% 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 quality of life (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 studies were homogeneous ($I^2 < 50\%$), the fixed-effects model was used; otherwise ($I^2 > 50\%$), the random-effects model was chosen. Intervention was considered statistically significant when a $P$-value was $< 0.05$. If the studies were heterogeneous, a sensitivity analysis was performed. Publication bias was assessed by the funnel plot. All data were analyzed with 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. Out of 97 full-text studies that were reviewed, 66 did not meet the inclusion criteria. Twenty-five RCTs with a total of 5555 people which met the inclusion criteria were included in this systematic review (Figure 1). 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 therapy on symptom improvement**

Twenty-three of 25 studies reported information on treatment success. Eradication therapy 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 therapy 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 therapy 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 outcomes demonstrated significant heterogeneity (I² = 64%). The forest plot and sensitivity analysis are shown in Figures 4 and 5, respectively.

Benefits of H. pylori eradication therapy 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 (I² = 0%) was performed on all seven studies. Overall, H. pylori eradication therapy had no significant benefit on quality of life, with an
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 therapy 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 compared to no eradication therapy reduced the development of peptic ulcer disease (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 therapy 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 therapy 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 therapy and control groups**

One study provided outcome data on the cost of interventions such as medication, diagnostic tests, and physician consultation and did not demonstrate a difference between eradication therapy and the 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 therapy were more likely to obtain histologic resolution of chronic gastritis compared to control (RR = 7.13; 95%CI: 3.68-13.81, \(P < 0.00001\)).

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### Table: Study effects comparing \(H. \) pylori eradication therapy vs control on symptom relief

| Study of subgroup | Eradication Events | Control Events | Risk ratio M-H, random, 95%CI | Risk ratio M-H, random, 95%CI |
|-------------------|-------------------|----------------|-------------------------------|-------------------------------|
| **1.1.1 Long-term effect** | | | | |
| Ang 2006 | 22 | 71 | 14 | 59 | 2.4% | 1.31 (0.74, 2.32) |
| Blum 1998 | 45 | 164 | 34 | 164 | 4.2% | 1.32 (0.90, 1.95) |
| Chiba 2002 | 72 | 145 | 54 | 149 | 6.5% | 1.37 (1.05, 1.79) |
| Dhali 1999 | 26 | 32 | 10 | 30 | 2.7% | 2.44 (1.43, 4.15) |
| Froblich 2001 | 15 | 74 | 13 | 70 | 1.9% | 1.09 (0.56, 2.13) |
| Gisbert 2004 | 21 | 34 | 8 | 16 | 2.5% | 1.24 (0.71, 2.16) |
| Gwee 2009 | 10 | 41 | 3 | 41 | 0.6% | 3.33 (0.99, 11.24) |
| Hsu 2001 | 47 | 81 | 44 | 80 | 6.4% | 1.05 (0.80, 1.38) |
| Koskenpato 2001 | 16 | 77 | 11 | 74 | 1.7% | 1.40 (0.70, 2.81) |
| Mallertheiner 2003 | 196 | 534 | 89 | 266 | 8.2% | 1.10 (0.90, 1.34) |
| Mazzoleni 2006 | 16 | 46 | 9 | 43 | 1.7% | 1.66 (0.82, 3.36) |
| Mazzenoli 2011 | 94 | 201 | 72 | 203 | 7.2% | 1.32 (1.04, 1.67) |
| McColl 1998 | 33 | 154 | 11 | 154 | 2.0% | 3.00 (1.57, 5.72) |
| Sodhi 2013 | 95 | 217 | 72 | 195 | 7.2% | 1.19 (0.94, 1.50) |
| Talley 1999 | 69 | 150 | 71 | 143 | 7.2% | 0.93 (0.73, 1.18) |
| Talley 1999 (ORCHID) | 32 | 133 | 31 | 142 | 3.7% | 1.10 (0.71, 1.70) |
| Varannes 2001 | 55 | 129 | 38 | 124 | 5.2% | 1.39 (1.00, 1.94) |
| Xu 2013 | 157 | 262 | 68 | 134 | 8.4% | 1.18 (0.97, 1.43) |
| Zanten 2003 | 44 | 75 | 46 | 82 | 6.5% | 1.05 (0.80, 1.37) |
| **Subtotal (95%CI)** | 2620 | 5269 | 2169 | 86.2% | 1.24 (1.12, 1.37) |
| **Total events** | 1065 | 698 |
| Heterogeneity: \(\tau^2 = 0.02; \chi^2 = 28.66, \text{df} = 18 (P = 0.05); \ I^2 = 37\%\) Test for overall effect: \(Z = 4.14 (P < 0.00001)\)

| **1.1.2 Short-term effect** | | | | |
| Koeltz 2003 | 55 | 89 | 61 | 92 | 7.7% | 0.93 (0.75, 1.16) |
| Lan 2011 | 36 | 98 | 19 | 97 | 3.2% | 1.88 (1.16, 3.03) |
| Miwa 2000 | 15 | 48 | 9 | 37 | 1.7% | 1.28 (0.63, 2.60) |
| Naenei 2002 | 12 | 84 | 8 | 73 | 1.3% | 1.30 (0.56, 3.01) |
| **Subtotal (95%CI)** | 319 | 299 | 13.8% | 1.26 (0.83, 1.92) |
| **Total (95%CI)** | 2939 | 2468 | 100.00% | 1.23 (1.12, 1.36) |
| **Total events** | 1183 | 795 |
| Heterogeneity: \(\tau^2 = 0.11; \chi^2 = 8.25, \text{df} = 3 (P = 0.04); \ I^2 = 64\%\) Test for overall effect: \(Z = 1.09 (P = 0.27)\)

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

Our meta-analysis based on well-designed RCTs demonstrated that the effect size of symptom relief from *H. pylori* eradication therapy 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 therapy compared to controls. However, *H. pylori* eradication therapy did not improve the quality of life for patients with FD compared to 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 than in Western countries with high prevalence observed in China and South Korea[40]. Eradication therapy appears to be more effective in Asian populations as shown by the meta-analysis conducted by Jin and Li[13] on the Chinese population. Their study showed that *H. pylori* eradication therapy 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 therapy compared to no eradication therapy was beneficial for improvement of dyspepsia in European (OR = 1.49; 95 CI% 1.10-2.02) and American populations (OR = 1.43; 95%CI: 1.12-1.83).

*H. pylori* is strongly associated with many diseases, including functional dyspepsia, gastric or duodenal ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue 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 experience variable clinical symptoms depending on bacteria, host, and environmental factors. Whether *H. pylori* infection delays 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. First, eradication therapy may be preferable among patients with risk factors for peptic ulcer disease or gastric cancer. Our study showed long-term benefits such as reduction in incidence of future peptic ulcer disease and resolution of gastritis, which are associated with gastric cancer [50,51]. Second, because of apparent adverse effects associated with 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
du LJ et al. *Helicobacter pylori* eradication therapy for FD

| Study of subgroup | Eradication Events | Control Events | Total Events | Total Weight | M-H, random, 95% CI | Risk ratio M-H, random, 95% CI |
|---|---|---|---|---|---|---|
| Blum 1998 | 123 | 164 | 5 | 164 | 15.00% | 24.60 [10.33, 58.58] |
| Dhalli 1999 | 22 | 30 | 8 | 26 | 17.20% | 2.38 [1.29, 4.41] |
| Mazzeolani 2006 | 34 | 46 | 3 | 43 | 12.90% | 10.59 [3.51, 31.98] |
| Siddi 2013 | 132 | 174 | 11 | 180 | 17.50% | 12.41 [5.96, 22.14] |
| Talley 1999 | 74 | 110 | 21 | 114 | 18.80% | 3.65 [2.43, 5.49] |
| Talley 1999 (ORCHID) | 108 | 133 | 18 | 142 | 18.60% | 6.41 [4.13, 9.94] |

Total (95%CI) 657 | 669 | 100.00% | 7.13 [3.68, 13.81] |

| Total events | 493 | 66 |
| Heterogeneity: Tau$^2$ = 0.56; $y^2 = 36.73$, df = 5 ($P < 0.00001$); $I^2 = 86\%$ |
| Test for overall effect: $Z^2 = 5.82$ ($P < 0.00001$) |

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

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

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**COMMENTS**

**Background**

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

**Research frontiers**

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

**Innovations and breakthroughs**

Compared to previous studies, the current meta-analysis included additional clinical outcomes on the benefits of *H. pylori* eradication therapy 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 therapy should be considered after individual assessment. The authors have highlighted that *H. pylori* eradication therapy was significantly beneficial for symptom relief and reduced the risk of development of peptic ulceration in patients with functional dyspepsia. However, *H. pylori* eradication therapy 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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