



Is *Helicobacter pylori* Associated Functional Dyspepsia Correlated With Dysbiosis?

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Background/Aims

To assess the long-term effect of *Helicobacter pylori* eradication on symptomatic improvement according to the type of antibiotic and the duration of treatment in *H. pylori*-associated functional dyspepsia.

Methods

We searched Pubmed, Embase, CINAHL, and the Cochrane library databases for randomized controlled trials written in English and undertaken up to August 2016 that met our eligibility criteria. The search methodology used combinations of the following keywords: *Helicobacter pylori* OR *H. pylori* OR HP; dyspepsia OR functional dyspepsia OR non-ulcer dyspepsia; eradication OR cure OR treatment. The study outcome was the summary odds ratio (OR) for symptomatic improvement in *H. pylori*-associated functional dyspepsia with successful eradication therapy. Subgroup analyses were performed based on the type of antibiotic, and the duration of treatment, whether or not patients had symptoms of irritable bowel syndrome, and on race.

Results

Sixteen randomized controlled trials met the inclusion criteria. The summary OR for symptomatic improvement in patients in our eradication group was 1.33 (95% confidence interval [CI], 1.16-1.54; $P < 0.01$). In a subgroup analysis on type of antibiotic, symptomatic improvement with metronidazole-containing regimen (OR, 1.87; 95% CI, 1.26-2.77) was better than treatment with clarithromycin (OR, 1.29; 95% CI, 1.11-1.50). *H. pylori* eradication therapy given for 10-14 days was the more effective for symptom improvement than 7-day therapy. When the studies excluding irritable bowel syndrome cases were analyzed, there were no therapeutic effects of *H. pylori* eradication on symptomatic improvement.

Conclusions

In the clinical setting, the most effective *H. pylori* eradication regimen for functional dyspepsia to provide relief of symptoms is a metronidazole-based treatment regimen for at least 10 days. The explanation for this is that *H. pylori*-associated functional dyspepsia could be associated with dysbiosis.

(J Neurogastroenterol Motil 2017;23:504-516)

Key Words

Eradication; Functional dyspepsia; *Helicobacter pylori*

Received: May 22, 2017 Revised: July 15, 2017 Accepted: September 5, 2017

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Introduction

Functional dyspepsia (FD) is a common functional gastrointestinal disorder with reported prevalence rates of between 11% and 29.2%.¹ Its symptoms are characterized by multifunctional disorders of the upper gastrointestinal (GI) tract mediated by altered GI motility,² abnormal acid secretion,³ visceral hypersensitivity,⁴ an imbalance of the autonomic nervous system,⁵ psychological factors, and *Helicobacter pylori* infection.⁶ The role of *H. pylori* infection in functional dyspepsia is not fully elucidated, and the therapeutic gains and symptomatic improvements following *H. pylori* eradication have been matters of debate.

In the literature, the main mechanisms of symptom development in *H. pylori*-associated functional dyspepsia reported were altered GI motility and mucosal inflammation.⁶⁻¹² Increasing eosinophils of the duodenum secondary to the exposure of gastric acid or food allergens to the duodenum might correlate with FD, and it has been suggested that there is a correlation between eosinophils and low-grade inflammation.^{13,14} Furthermore, it has been shown that the patients with microscopic duodenitis achieve greater symptomatic responses to *H. pylori* eradication than those without microscopic duodenitis.¹⁵ In addition to a direct inflammatory response of the GI tract mucosa, decreased gastric acid secretions are common in patients with *H. pylori*-associated FD.^{7,8} This could be closely related to dysbiosis of gut microbiota. Recently, sequencing analysis of gut microbiota showed that *H. pylori* was not alone in the stomach and the interaction of *H. pylori* with those microorganisms might play a role in *H. pylori*-associated functional dyspepsia.^{16,17} In this study, we hypothesize that *H. pylori* infected patients diagnosed as FD might have dysbiosis of the gut microbiota. Most

of them would also have irritable bowel syndrome (IBS).

Previous meta-analyses reported that eradication therapy produced marginal therapeutic gain and relief of symptoms in *H. pylori*-associated FD, although results differed depending on trial design and study selection criteria and quality.^{10-12,18-20} However, there has been no systemic review of the differences in efficacy according to the eradication regimen. We hypothesized that we would find different therapeutic effects for different eradication regimens. Broad spectrum antibiotics and longer treatment durations that had a sufficient effect on gut microbial imbalance would result in better symptomatic improvements after *H. pylori* eradication. The aim of this study was to evaluate whether the therapeutic gain would be different in patients with *H. pylori*-associated FD according to the type of antibiotic and duration of treatment. When FD studies excluding IBS cases were analyzed, we compared the therapeutic effects of *H. pylori* eradication on symptomatic improvement. We also compared the therapeutic effects in Asian and non-Asian populations, because there is considerable heterogeneity of symptoms and pathophysiology based on ethnic differences.

Materials and Methods

Search Strategy

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.²¹ The following procedure was used to collect clinical randomized controlled trials (RCTs) written in English undertaken up to August 2016 from the Pubmed, Embase, Cochrane library and CINAHL digital dissertation databases (undertaken by N.J.K., Medical Library, The Catholic University of Korea, Seoul,

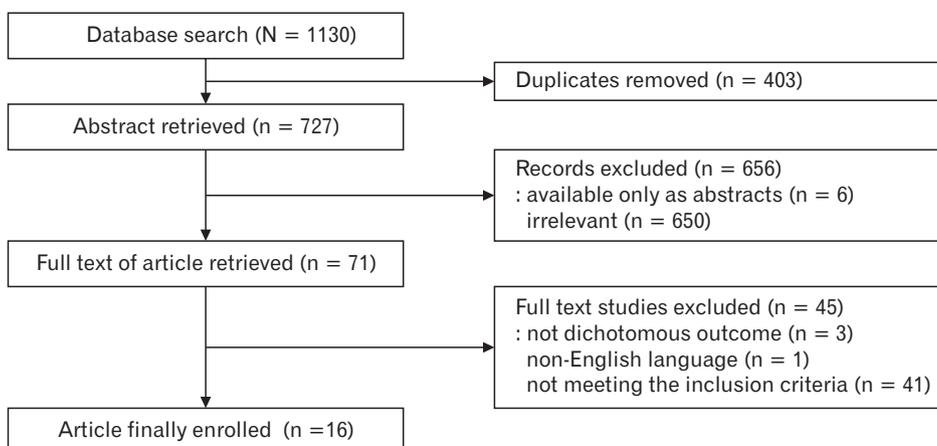


Figure 1. Flow diagram of the study.

Table 1. The Baseline Characteristics of the Enrolled Studies

Studies	Country	HP eradication rate		Age		Sex		Smoking		Drinking	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Ang et al, ²² 2006	Singapore	73.2%	0%	38.6	38.4	35.2%	37.3%	18.3%	16.5%	28.0%	25.6%
Blum et al, ²³ 1998	Multicenter	79%	2%	47	47	39.6%	43.3%	18.3%	16.5%	28.0%	25.6%
Froehlich et al, ²⁵ 2001	Switzerland	75%	4%	43.6 ± 12.4	45.6 ± 14.2	49%	40%	33%	36%	17.9%	27.8%
Gisbert et al, ²⁶ 2004	Spain	76%	4.9%	42	41	30%	28%	30%	36%	7.2%	4.9%
Gwee et al, ²⁷ 2009	Singapore	68.3%	0%	44.7 ± 11.4	36.1 ± 12.1	43.9%	46.3%	30.7%	26.7%	17.9%	27.8%
Hsu et al, ²⁸ 2001	China	78%	0%	50.3 ± 15.1	51.6 ± 16.4	49.4%	47.6%	15.7%	14.6%	7.2%	4.9%
Koskenpato et al, ²⁹ 2001	Finland	82%	1%	51.5 ± 9.5	51.8 ± 11.8	30%	39%	54%	59%	15.4%	14.3%
Mazzoleni et al, ³¹ 2011	Brazil	88.6%	7.4%	46.1 ± 12.4	46.0 ± 12.2	23.4%	19.2%	45.3%	39.4%	15.4%	14.3%
Mazzoleni et al, ³⁰ 2006	Brazil	91.3%	0%	43.2 ± 11.9	39.2 ± 13.8	19.6%	25.6%	17.4%	11.6%	13.0%	16.3%
McColl et al, ³² 1998	UK	88%	5%	42 ± 12	42.2 ± 13	51%	47%	34%	33%	38%	36%
Sodhi et al, ³³ 2013	India	66.6%	6.6%	46	43	29.3%	35.7%	33%	20%	38%	36%
Talley et al, ³⁴ 1999	Australia	85%	4%	51 ± 14	49 ± 13	38%	33%	20%	27.5%	41%	41%
Talley et al, ³⁵ 1999	Australia	90%	2%	46.3	46.5	43%	48%	27%	26%	20.6%	23.2%
Veldhuyzen van Zanten et al, ³⁶ 2003	Canada	82%	6%	47 ± 13	49 ± 13	41.3%	50.0%	34.7%	26.8%	28%	30%
Bruley Des Varannes et al, ²⁴ 2001	France	69%	18%	50 ± 16	52 ± 14	43%	46%	26%	27%	28%	30%
Yazdanbod et al, ³⁷ 2015	Iran	80.3%	4.9%								

HP, *Helicobacter pylori*.

Korea). We used the following Medical Subject Heading (MeSH) terms and/or text words: *H. pylori* OR *Helicobacter pylori* OR HP AND dyspepsia OR functional dyspepsia OR non-ulcer dyspepsia OR FD AND eradication OR treatment OR cure. Two persons (Y.J.K. and W.C.C.) independently reviewed all potentially relevant material to determine whether or not it met the inclusion criteria.

Inclusion and Exclusion Criteria

To be included in our meta-analysis studies had to meet following criteria; (1) RCTs with at least a 12-month follow-up period, (2) study population of patients with dyspepsia (symptom-based Rome I, II, or III classification), (3) symptoms of dyspepsia defined as an outcome measurement of the study, (4) *H. pylori* infection verified by rapid urease test, ¹³C breath test, or histologic examination, (5) treatment group received triple or quadruple therapy for 7-14 days, and (6) control group who only received placebo as intervention and were not treated with any other antibiotics or bismuth.

Studies were excluded if they were available only as an abstract, a review study, a case report, a study without raw data available for retrieval, a duplicate publication or if they were not written in English. When the patients of enrolled studies complained of reflux-like symptoms only, those studies were excluded.

Study Outcomes

The primary outcome of this study was the weighted summary odds ratio (OR) of symptomatic improvement in patients with and without *H. pylori* eradication with 95% CI. All of these analyses were planned a priori. Additional post hoc analyses were performed based the type of antibiotic, duration of therapy, and racial differences. The secondary outcomes were to analyze and compare the

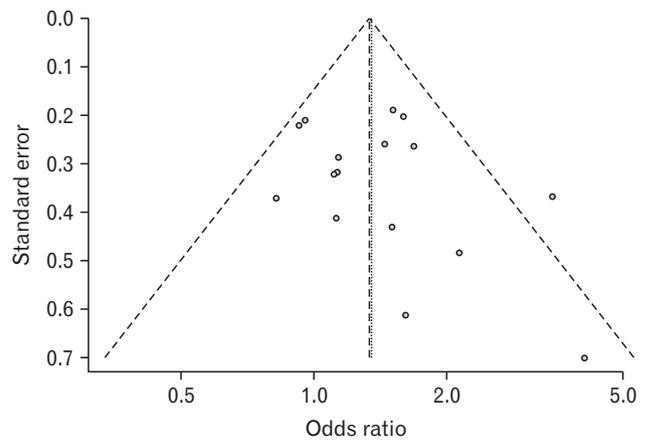


Figure 2. Funnel plot. $P = 0.338$.

OR for each eradication antibiotic and duration of treatment (1 week vs longer than 10 days). Racial differences were compared by comparing Asian and non-Asian study populations. To evaluate the association of *H. pylori*-associated FD and IBS, we tried to find out

whether IBS was included in methods of the articles. Since it was not clear if that IBS included the all studies, we reviewed the articles which mentioned IBS exclusion definitely studies using criteria of Rome II/III and explicit mentioned studies of IBS exclusion.

Table 2. The Results of Meta-analysis for the Effects of *Helicobacter pylori* Eradication on Functional Dyspepsia

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Ang et al, ²² 2006	45	71	0.634	40	59	0.678	0.822	0.397	1.704	3.8	
Blum et al, ²³ 1998	45	164	0.274	34	164	0.207	1.446	0.868	2.408	7.8	
Froehlich et al, ²⁵ 2001	15	92	0.163	13	88	0.148	1.124	0.501	2.521	3.1	
Gisbert et al, ²⁶ 2004	21	34	0.618	8	16	0.500	1.615	0.487	5.361	1.4	
Gwee et al, ²⁷ 2009	10	41	0.244	3	41	0.073	4.086	1.034	16.155	1.1	
Hsu et al, ²⁸ 2001	47	81	0.580	44	80	0.550	1.131	0.606	2.110	5.2	
Koskenpato et al, ²⁹ 2001	16	77	0.208	11	74	0.149	1.502	0.646	3.496	2.8	
Mazzoleni et al, ³¹ 2011	94	201	0.468	72	203	0.355	1.598	1.072	2.383	12.7	
Mazzoleni et al, ³⁰ 2006	16	46	0.348	9	45	0.200	2.133	0.825	5.514	2.2	
McCull et al, ³² 1998	33	160	0.206	11	158	0.070	3.472	1.686	7.152	3.9	
Sodhi et al, ³³ 2013	95	259	0.367	72	260	0.277	1.513	1.044	2.192	14.7	
Talley et al, ³⁴ 1999	32	133	0.241	31	142	0.218	1.135	0.646	1.991	6.4	
Talley et al, ³⁵ 1999	69	170	0.406	71	167	0.425	0.924	0.599	1.425	10.7	
Veldhuyzen van Zanten et al, ³⁶ 2003	44	75	0.587	46	82	0.561	1.111	0.590	2.093	5.0	
Bruley Des Varannes et al, ²⁴ 2001	55	129	0.426	38	124	0.306	1.682	1.003	2.821	7.5	
Yazdanbod et al, ³⁷ 2015	87	186	0.468	83	173	0.480	0.953	0.630	1.443	11.7	
Total (Fixed effect model)							1.334	1.157	1.537	100.0	< 0.01

P-value of test of heterogeneity among studies = 0.152; Higgins' I² = 27.0% (0.0%, 60.0%).

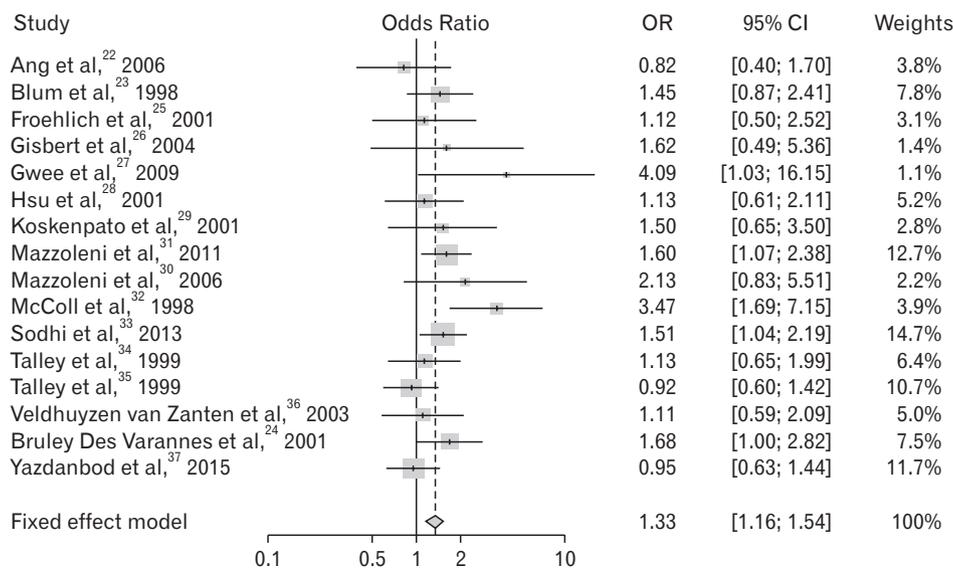


Figure 3. Forest plot for the effects of *Helicobacter pylori* eradication on the symptom relief in patients with functional dyspepsia.

Study Selection and Data Extraction

Two investigators (Y.J.K. and W.C.C.) independently assessed the titles and abstracts of all retrieved papers and assessed their eligibility for inclusion in our meta-analysis. Full articles were scrutinized if the title and abstract were ambiguous. The reviewers used a standardized approach to conduct the literature search, data extraction, and quality assessment. The data sought included the study population, baseline characteristics of the participants, details related to the protocol, year of publication, therapy regimen of *H.*

pylori eradications, definition of symptom relief and study outcome. When the results were combined and any disagreement occurred, this was resolved by the investigators.

Statistical Methods

The R language meta-package version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for the meta-analysis. The summary OR with 95% CI was evaluated for quantitative analyses. Heterogeneity among the studies was measured using Higgin's I^2 statistics and 95% CIs were calculated. When there was

Table 3. Meta-analysis on Symptomatic Improvement Following *Helicobacter pylori* Eradication by the Regimen Including Nitroimidazole Antimicrobial (Metronidazole and Tinidazole)

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Gwee et al, ²⁷ 2009	10	41	0.244	3	41	0.073	4.086	1.034	16.155	8.2	
Hsu et al, ²⁸ 2001	47	81	0.580	44	80	0.550	1.131	0.606	2.110	40.1	
Koskenpato et al, ²⁹ 2001	16	77	0.208	11	74	0.149	1.502	0.646	3.496	21.8	
McCull et al, ³² 1998	33	160	0.206	11	158	0.070	3.472	1.686	7.152	29.8	
Total (Fixed effect model)							1.870	1.260	2.774	100.0	< 0.01

P-value of test of heterogeneity among studies = 0.223; Higgins' I^2 = 56.0% (0.0%, 85.4%).

Table 4. Meta-analysis on Symptomatic Improvement Following *Helicobacter pylori* Eradication by the Regimen Including Clarithromycin

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Ang et al, ²² 2006	45	71	0.634	40	59	0.678	0.822	0.397	1.704	4.3	
Blum et al, ²³ 1998	45	164	0.274	34	164	0.207	1.446	0.868	2.408	8.8	
Froehlich et al, ²⁵ 2001	15	92	0.163	13	88	0.148	1.124	0.501	2.521	3.5	
Gisbert et al, ²⁶ 2004	21	34	0.618	8	16	0.500	1.615	0.487	5.361	1.6	
Gwee et al, ²⁷ 2009	10	41	0.244	3	41	0.073	4.086	1.034	16.155	1.2	
Mazzoleni et al, ³¹ 2011	94	201	0.468	72	203	0.355	1.598	1.072	2.383	14.4	
Mazzoleni et al, ³⁰ 2006	16	46	0.348	9	45	0.200	2.133	0.825	5.514	2.5	
Sodhi et al, ³³ 2013	95	259	0.367	72	260	0.277	1.513	1.044	2.192	16.6	
Talley et al, ³⁴ 1999	32	133	0.241	31	142	0.218	1.135	0.646	1.991	7.2	
Talley et al, ³⁵ 1999	69	170	0.406	71	167	0.425	0.924	0.599	1.425	12.2	
Veldhuyzen van Zanten et al, ³⁶ 2003	44	75	0.587	46	82	0.561	1.111	0.590	2.093	5.7	
Bruley Des Varannes et al, ²⁴ 2001	55	129	0.426	38	124	0.306	1.682	1.003	2.821	8.6	
Yazdanbod et al, ³⁷ 2015	87	186	0.468	83	173	0.480	0.953	0.630	1.443	13.3	
Total (Fixed effect model)							1.286	1.106	1.497	100.0	0.001

P-value of test of heterogeneity among studies = 0.351; Higgins' I^2 = 9.5% [0.0%, 47.9%]

substantial heterogeneity ($I^2 > 50\%$), all analyses were based on the random-effect model (DerSimonian-Laird method); otherwise ($I^2 < 50\%$), the fixed effect model (inverse variance method) was used. To test for publication bias, we used a test for asymmetry of the funnel plot. A P -value of less than 0.05 was considered statistically significant. Meta-analysis of variance (ANOVA) was used for subgroup analysis based on type of antibiotic and duration of treatment regimen. All the statistical methods of this study were performed by S.H.K. and J.H.Y. from Bio-Age, Medical Development Institute, Seoul, Korea.

Results

Study Characteristics

The initial search strategy identified 1130 articles. After removal of duplicates, the 727 remaining articles were screened. After reviewing the title and abstracts, 6 trials were available only as abstracts and 650 trials were irrelevant, leaving 71 potentially relevant studies. In the remaining articles, 1 study was excluded because the manuscript was not written in English, 3 trials did not use dichotomous outcomes, and 41 trials did not meet the eligibility criteria. Reviewing the full manuscripts, we identified 16 RCTs with a total of 1920 subjects that met the inclusion criteria (Table 1 and Fig. 1).²²⁻³⁷

Reviewing the full manuscripts, we identified 16 RCTs with a total of 1920 subjects that met the inclusion criteria (Table 1 and Fig. 1).²²⁻³⁷

Study Result

The cumulative eradication rate of *H. pylori* in the treatment group was 80.3% (Table 1). In the meta-analysis of all 16 RCTs, 13 trials reported successful symptom relief results. Figure 2 shows the existence of publication bias according to the test for the asymmetry of the funnel plot ($P = 0.338$). Because there was no significant heterogeneity (Higgins' $I^2 = 27.0\%$), we summarized OR using a fixed effect model. The summary OR was 1.33 (95% CI, 1.16-1.54; $P < 0.01$), indicating that the patients with *H. pylori*-associated FD had a greater than 1.33-fold increased probability of symptom relief after eradication. (Table 2 and Fig. 3)

We analyzed symptom improvement according to the antibiotic type. The meta-ANOVA analysis showed more significant improvements with metronidazole (OR, 1.87; 95% CI, 1.26-2.77; $P < 0.01$) compared to clarithromycin (OR, 1.29; 95% CI, 1.11-1.50; $P < 0.01$) in the eradication group. Tinidazole was included

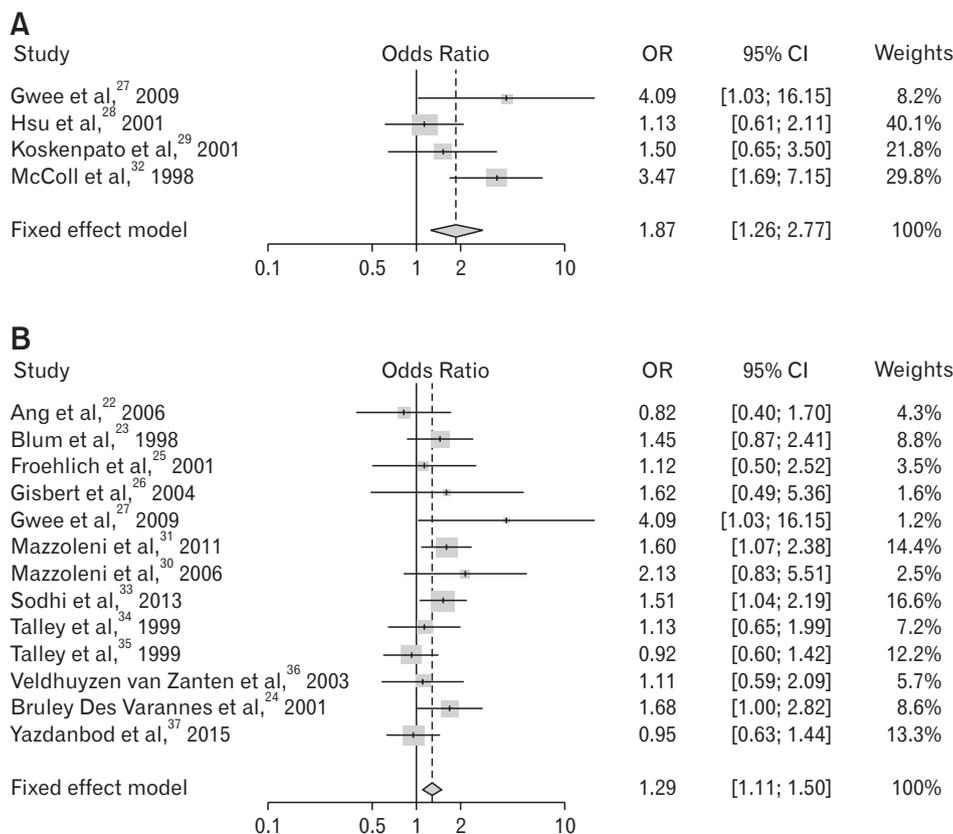


Figure 4. Forest plots for the effects of *Helicobacter pylori* eradication on the symptom relief in patients with functional dyspepsia according to antibiotic use. (A) Metronidazole containing regimen. (B) Clarithromycin containing regimen.

in the metronidazole group as antibiotics of the same drug class, nitroimidazole antimicrobial. The metronidazole-based regimen produced more therapeutic gain than the clarithromycin-based regimen in *H. pylori*-associated FD (Table 3 and 4 and Fig. 4).

The selected studies used different treatment regimen durations (7, 10, or 14 day regimen). We divided the trials into 2 subgroups according to the duration of treatment regimen. Eight trials used a 7-day regimen and the remaining 8 trials administered a regimen of 10 days or more. Subgroup analysis confirmed that a regimen of 10 days or more yielded superior relief of symptoms (OR, 1.45; 95% CI, 1.09-1.93; $P = 0.011$). There was a significant difference between the 2 groups (Table 5 and Fig. 5).

When exclusive diagnostic criteria for FD (excluding IBS) were adopted in the study enrollment, 8 studies were sub-analyzed - studies using criteria of Rome II/III^{24,30,31,34} and explicit mentioned studies of IBS exclusion.^{22,25,27,28} The summary OR was statistically insignificant (OR, 1.12; 95% CI, 0.99-1.26; $P = 0.263$) (Fig. 6). Thirteen studies that were performed on non-Asian populations showed statistically significant benefits for dyspeptic symptom relief, whereas the 3 trials performed on Asian populations revealed insignificant results (Table 6 and Fig. 7).

Table 5. Meta-analysis on Symptomatic Improvement Following *Helicobacter pylori* Eradication According to Duration
(A) 7-day regimen

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Ang et al, ²² 2006	45	71	0.634	40	59	0.678	0.822	0.397	1.704	9.5	
Blum et al, ²³ 1998	45	164	0.274	34	164	0.207	1.446	0.868	2.408	19.5	
Froehlich et al, ²⁵ 2001	15	92	0.163	13	88	0.148	1.124	0.501	2.521	7.8	
Gwee et al, ²⁷ 2009	10	41	0.244	3	41	0.073	4.086	1.034	16.155	2.7	
Hsu et al, ²⁸ 2001	47	81	0.580	44	80	0.550	1.131	0.606	2.110	13.0	
Talley et al, ³⁴ 1999	32	133	0.241	31	142	0.218	1.135	0.646	1.991	16.0	
Veldhuyzen van Zanten et al, ³⁶ 2003	44	75	0.587	46	82	0.561	1.111	0.590	2.093	12.6	
Bruley Des Varannes et al, ²⁴ 2001	55	129	0.426	38	124	0.306	1.682	1.003	2.821	18.9	
Total (Fixed effect model)							1.281	1.023	1.605	100.0	0.031

P -value of test of heterogeneity among studies = 0.532; Higgins' $I^2 = 0.0\%$ (0.0%, 62.6%).

(B) 10-day or more regimen

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Gisbert et al, ²⁶ 2004	21	34	0.618	8	16	0.500	1.615	0.487	5.361	4.7	
Koskenpato et al, ²⁹ 2001	16	77	0.208	11	74	0.149	1.502	0.646	3.496	8.1	
Mazzoleni et al, ³¹ 2011	94	201	0.468	72	203	0.355	1.598	1.072	2.383	17.8	
Mazzoleni et al, ³⁰ 2006	16	46	0.348	9	45	0.200	2.133	0.825	5.514	6.8	
McCull et al, ³² 1998	33	160	0.206	11	158	0.070	3.472	1.686	7.152	9.9	
Sodhi et al, ³³ 2013	95	259	0.367	72	260	0.277	1.513	1.044	2.192	18.7	
Talley et al, ³⁵ 1999	69	170	0.406	71	167	0.425	0.924	0.599	1.425	16.8	
Yazdanbod et al, ³⁷ 2015	87	186	0.468	83	173	0.480	0.953	0.630	1.443	17.3	
Total (random effect model)							1.447	1.088	1.925	100.0	0.011

P -value of test of heterogeneity among studies = 0.046; Higgins' $I^2 = 51.0\%$ (0.0%, 78.1%).

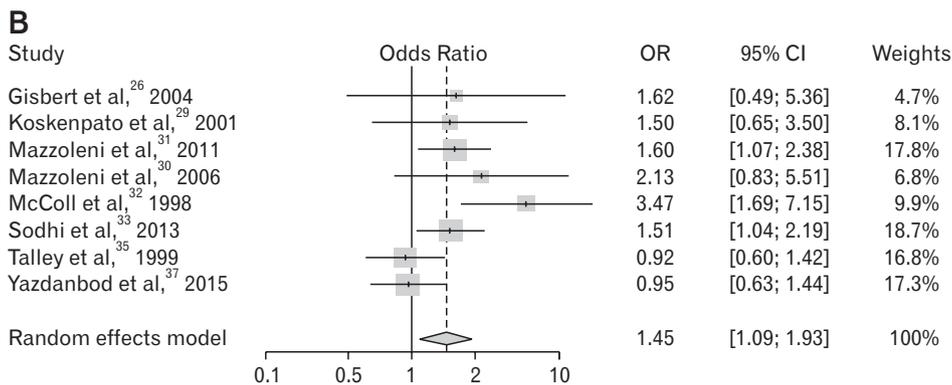
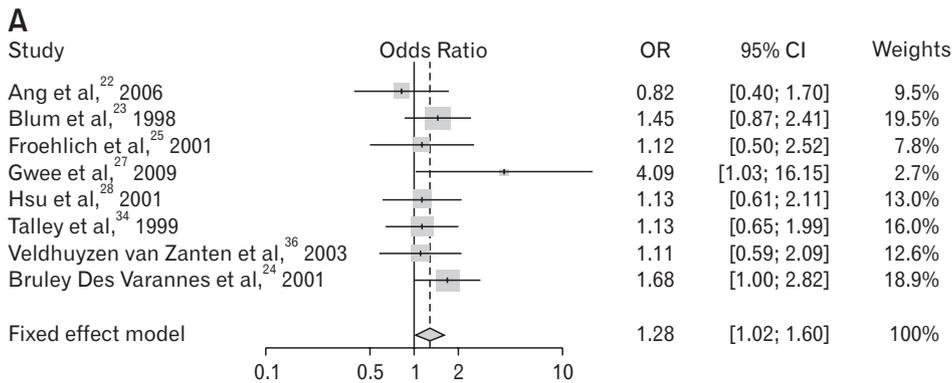


Figure 5. Forest plots for the effects of *Helicobacter pylori* eradication on the symptom relief in patients with functional dyspepsia according to duration of regimen. (A) Treatment period: 1 week. (B) Treatment period: longer than 1 week.

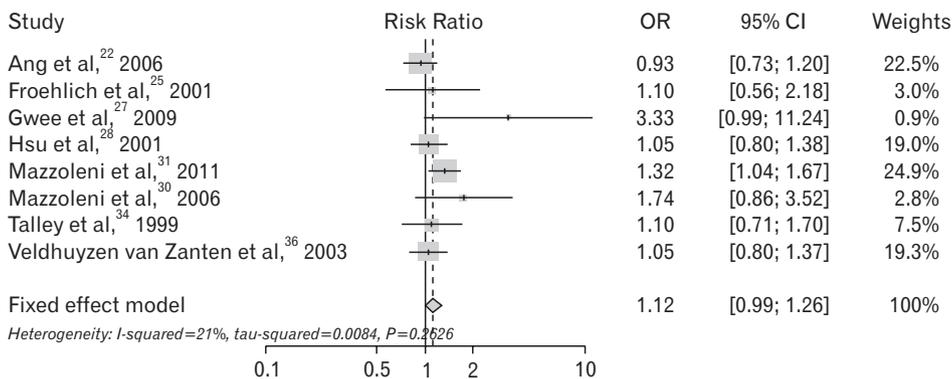


Figure 6. Forest plots for the effect of *Helicobacter pylori* eradication on the symptom relief in patients with functional dyspepsia - its diagnostic criteria excluding irritable bowel syndrome was adopted.

Discussion

It is still unclear whether *H. pylori* infection causes dyspeptic symptoms. Our meta-analysis is a comprehensive study focusing on a comparison of efficacy based on antibiotic type used and the duration of the eradication regimen on symptomatic improvements after *H. pylori* eradication. The strength of this meta-analysis was that it includes more recent trials and subgroup analysis according to *H. pylori* eradication regimens. Multiple complex factors are thought to be involved in the pathophysiology of FD such as gastro-duode-

nal inflammation by intestinal microbiota; our results support such a theory.

Several studies on *H. pylori*-associated FD have focused on changes in the intestinal environment.^{15-17,38} Intestinal microbiota play an important role in the maintenance of host health by providing energy, nutrients, and immunological protection and its imbalance can provoke various GI symptoms and disease.³⁹ Because *H. pylori*-associated FD and intestinal dysbiosis could be shared with common pathogenesis such as impaired motility, there is a close relationship.¹⁴ Another possible pathogenesis is based on the decreased secretion of gastric acid by long-term infection of *H. pylori*.

Table 6. Meta-analysis on Symptomatic Improvement Following *Helicobacter pylori* Eradication by Ethnic Difference**(A) Asian**

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Ang et al, ²² 2006	45	71	0.634	40	59	0.678	0.822	0.397	1.704	37.8	
Gwee et al, ²⁷ 2009	10	41	0.244	3	41	0.073	4.086	1.034	16.155	10.6	
Hsu et al, ²⁸ 2001	47	81	0.580	44	80	0.550	1.131	0.606	2.110	51.6	
Total (Fixed effect model)							1.149	0.734	1.799	100.0	0.542

P-value of test of heterogeneity among studies = 0.152; Higgins' I^2 = 27.0% (0.0%, 60.0%).

(B) Non-Asian

Studies	Treatment			Control			OR	95% lower CI	95% upper CI	Weights	P-value
	Improved patients (n)	Total (n)	Proportion	Improved patients (n)	Total (n)	Proportion					
Blum et al, ²³ 1998	45	164	0.274	34	164	0.207	1.446	0.868	2.408	8.6	
Froehlich et al, ²⁵ 2001	15	92	0.163	13	88	0.148	1.124	0.501	2.521	3.4	
Gisbert et al, ²⁶ 2004	21	34	0.618	8	16	0.500	1.615	0.487	5.361	1.6	
Koskenpato et al, ²⁹ 2001	16	77	0.208	11	74	0.149	1.502	0.646	3.496	3.1	
Mazzoleni et al, ³¹ 2011	94	201	0.468	72	203	0.355	1.598	1.072	2.383	14.1	
Mazzoleni et al, ³⁰ 2006	16	46	0.348	9	45	0.200	2.133	0.825	5.514	2.5	
McCull et al, ³² 1998	33	160	0.206	11	158	0.070	3.472	1.686	7.152	4.3	
Sodhi et al, ³³ 2013	95	259	0.367	72	260	0.277	1.513	1.044	2.192	16.3	
Talley et al, ³⁴ 1999	32	133	0.241	31	142	0.218	1.135	0.646	1.991	7.1	
Talley et al, ³⁵ 1999	69	170	0.406	71	167	0.425	0.924	0.599	1.425	11.9	
Veldhuyzen van Zanten et al, ³⁶ 2003	44	75	0.587	46	82	0.561	1.111	0.590	2.093	5.6	
Bruley Des Varannes et al, ²⁴ 2001	55	129	0.426	38	124	0.306	1.682	1.003	2.821	8.4	
Yazdanbod et al, ³⁷ 2015	87	186	0.468	83	173	0.480	0.953	0.630	1.443	13.1	
Total (fixed effect model)							1.356	1.167	1.575	100.0	< 0.001

P-value of test of heterogeneity among studies = 0.191; Higgins' I^2 = 25.0% (0.0 %, 61.0%).

In patients with severe atrophy induced by *H. pylori* infection, acid secretion would be compromised and subsequently it results in bacterial overgrowth in the intestine. Previously, it has been demonstrated that patients who complained of dyspeptic symptoms would have an increased risk of intestinal dysbiosis.^{14,38,40} Further prospective evaluations are necessary to investigate whether patients with severe atrophic change would benefit on symptomatic improvement from *H. pylori* eradication.

Altered gut microbiota have been considered as a main pathophysiology of IBS and manipulation of gut microbiota represents a new strategy for the treatment of IBS. In the overlap syndrome consisting of FD and IBS, intestinal dysbiosis might be a common

etiologic and dominant pathogenesis. Recent clinical data revealed that intestinal dysbiosis was diagnosed in FD patients with refractory symptoms.³⁸ Another study on *H. pylori*-negative Asian FD patients without IBS-overlap showed that 2-week therapy with rifaximin was efficient in a randomized placebo-controlled trial.⁴¹ This evidence suggested that low-level inflammation of the intestine caused by imbalance of intestinal microbiome might be one of mechanisms of functional dyspepsia. In the near future, new classification of functional GI disorder should be categorized according to the state of small intestinal microbiome. In addition, the concept of "colo-gastric reflex" is another pathophysiology of IBS. In recent human data, gastric accommodation regularly affects lower GI tract

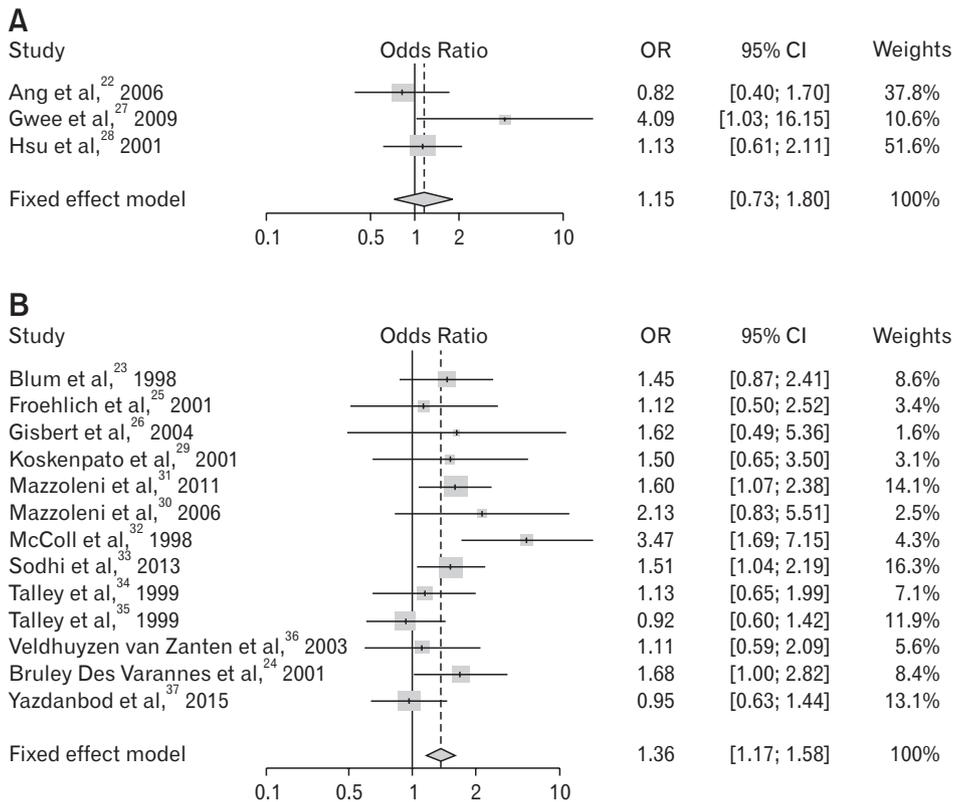


Figure 7. Forest plots for the effects of *Helicobacter pylori* eradication on the symptom relief in patients with functional dyspepsia according to ethnics. (A) Asian. (B) Non-Asian.

function and colonic gaseous distension or constipation decrease gastric accommodation or gastric emptying. It was called as the “colo-gastric reflex.”⁴² In other words, the relationship between dyspepsia and the colonic distension could be even more important.

We hypothesized that many patients with *H. pylori*-associated FD might have FD-IBS overlap and this concept was first applied. When all patients with IBS criteria were excluded, there was no statistical significance of symptomatic improvement after *H. pylori* eradication. However, it was insufficient to make a concrete conclusion because the different types of Rome criteria applied to the different studies and the diagnostic criteria of FD and IBS were mutually exclusive. It was not until recently that overlap syndrome was paid attention. In this point of view, *H. pylori*-associated FD could be a new disease category. Previous reports revealed that responders at 3 months and *H. pylori* eradicated status were associated with improvement of dyspeptic symptoms at 1 year, regardless of the overlapped IBS.⁴³ Gastric mucosal inflammation induced by *H. pylori* infection was a crucial role in symptom generation, and the control of inflammation resulted in symptom improvement. Therefore, the Kyoto Global Consensus report insisted that *H. pylori*-associated dyspepsia was not as a FD, but a kind of infectious disease.⁴⁴

Several antibiotics with various spectra of activity have been used for *H. pylori* eradication therapy. Clarithromycin is a representative of the macrolide antibiotics and these provide coverage of gram-positive bacteria, whereas metronidazole is the drug of choice for the treatment of anaerobic infection and the representative treatment drug for intestinal dysbiosis.⁴⁵ Metronidazole-combined with these antibiotics are thought to be combinations that can cover broader antibacterial spectrum including anaerobes. Our results revealed that metronidazole-containing regimens were significantly more effective for symptom relief compared to clarithromycin-containing regimens. This was because the use of metronidazole in the treatment of *H. pylori* eradication brought about the secondary therapeutic effect of modifying the gut microbiota.

In FD, mucosal inflammation could play an important role and it was demonstrated that increased mast cells or eosinophils in the gastroduodenal mucosa were associated with symptom generation.^{46,47} However, it was questionable whether inflammatory cells were eliminated or lymphoid follicles healed completely after *H. pylori* eradication. Moreover, the influence of antibiotics on the intestinal flora could be temporary, and it would return to previous state after antibiotic therapy.⁴⁸ Previously, several researchers insisted that at least 6 to 12 months of observation period should be re-

quired to judge the outcome of dyspeptic symptoms after successful eradication. Gastric mucosal inflammation activity and physiologic functions including acid secretion could recover or stabilize after 6 months.⁴⁴ The restoration of gastric physiologic functions would have a possibility to modify intestinal dysbiosis.

In 13 studies performed on a non-Asian population, there were statistically significant benefits for dyspeptic symptom relief, whereas the 3 trials performed on Asian populations revealed insignificant results. These differences in race-to-race efficacy are contrary to the predicted results. In Asia, *H. pylori* infection is common at a younger age, and it is more likely that atrophic gastritis has progressed over a longer period of time. In general, more advanced hypo-secretory stomach due to long-term *H. pylori* infection and atrophy of the gastric mucosa is known as a risk factor of dysbiosis. Therefore, Asian *H. pylori*-infected patients are more likely to have a more advanced hypo-secretory stomach. As a result, dysbiosis is more likely to be more prominent in Asian *H. pylori*-infected patients, and the potential for efficacy with antibiotic treatment may increase. However, in the all trials on Asian populations, the 7-day regimen was adopted, and there was a possibility of insufficient dose of antibiotic treatment. In addition, small sample size and a wide confidence interval limits the interpretation of the results. Brain-gut interaction was one of the important mechanisms of functional dyspepsia and it was unlikely that the Rome criteria completely reflect the various symptoms, especially in Asian patients with FD. Large-scale prospective studies should be needed in Asia, particularly in China and Korea which are well known areas of high prevalence of *H. pylori*.

There were potential limitations in this study. First, our literature search was restricted to English-language reports because of translation limitations, which could have introduced some bias. The relatively small number of studies on Asian populations is thought to have resulted in reduced reliability. Second, this study was not a direct pharmaceutical comparison, but a relative comparison via OR. However, based on Monson's experience, an OR of 1.87 is highly effective for symptomatic improvement⁴⁹; therefore, we do not think our comparison of the results was insufficient for our research purpose. Third, differences in enrollment criteria may have created heterogeneous *H. pylori*-associated FD populations in several clinical trials.

In conclusion, *H. pylori* eradication for FD could be an effective treatment strategy. When clinicians choose an eradication regimen for *H. pylori*-associated FD, administering metronidazole for 10 days or more would provide a great benefit for symptom improvement. In the future, more prospective RCTs are necessary for

direct comparison of metronidazole and other antibiotic regimens for treating this disorder.

Financial support: None.

Conflicts of interest: None.

Author contributions: Woo Chul Chung was responsible for the conception of the review question and final approval of manuscript; Na Jin Kim was responsible for the acquisition; Soo Hwan Kim analyzed the data and interpreting data; Yeon-Ji Kim and Woo Chul Chung was responsible for the study selection, data extraction, and drafting the manuscript; Byung Wook Kim, Sung Soo Kim, and Jin Il Kim assisted in review design, interpretation and revision, and drafting of the manuscript; and Yeon-Ji Kim and Woo Chul Chung contributed to the revision of the manuscript.

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