

## Meta-analysis of the efficacy of probiotics in *Helicobacter pylori* eradication therapy

Rong Zhu, Kan Chen, Yuan-Yuan Zheng, Hua-Wei Zhang, Jun-Shan Wang, Yu-Jing Xia, Wei-Qi Dai, Fan Wang, Miao Shen, Ping Cheng, Yan Zhang, Cheng-Fen Wang, Jing Yang, Jing-Jing Li, Jie Lu, Ying-Qun Zhou, Chuan-Yong Guo

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Rong Zhu, Department of First Clinical Medical College, Nanjing Medical University, Nanjing 210000, Jiangsu Province, China

**Author contributions:** Zhu R, Chen K and Zheng YY contributed equally to this paper; Zhu R, Chen K, Zheng YY, Zhang HW and Wang JS designed the research; Zhu R, Chen K, Xia YJ, Dai WQ, Wang F, Shen M, Cheng P, Zhang Y and Wang CF performed the research; Yang J and Li JJ contributed new analytic tools; Zhu R, Chen K, Lu J and Zhou YQ analyzed the data; Zhu R, Chen K and Zheng YY wrote the paper; Guo CY accepts full responsibility for this paper.

**Correspondence to:** Chuan-Yong Guo, MD, Professor, Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, No. 301 Yanchang Middle Road, Zhabei District, Shanghai 200072, China. [guochuanyong@hotmail.com](mailto:guochuanyong@hotmail.com)

Telephone: +86-21-66302535 Fax: +86-21-66303983

Received: April 20, 2014 Revised: June 28, 2014

Accepted: July 11, 2014

Published online: December 21, 2014

### Abstract

**AIM:** To evaluate the role of probiotics in the standard triple *Helicobacter pylori* therapy.

**METHODS:** In this meta-analysis, we investigated the efficacy of probiotics in a standard triple *H. pylori* therapy in adults. Searches were mainly conducted in MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. Fourteen studies met our criteria, and the quality of these studies was assessed

using the Jadad scale. We used STATA version 12.0 to extract data and to calculate the odds ratios (ORs), which are presented with the corresponding 95% confidence intervals (CIs). The data are presented as forest plots.

**RESULTS:** The pooled ORs for the eradication rates calculated by intention-to-treat analysis and per-protocol analysis in the probiotic group vs the control group were 1.67 (95%CI: 1.38-2.02) and 1.68 (95%CI: 1.35-2.08), respectively, using the fixed-effects model. The sensitivity of the Asian studies was greater than that of the Caucasian studies (Asian: OR = 1.78, 95%CI: 1.40-2.26; Caucasian: OR = 1.48, 95%CI: 1.06-2.05). The pooled OR for the incidence of total adverse effects was significantly lower in the probiotic group (OR = 0.49, 95%CI: 0.26-0.94), using the random effects model, with significant heterogeneity ( $I^2 = 85.7\%$ ). The incidence of diarrhea was significantly reduced in the probiotic group (OR = 0.21, 95%CI: 0.06-0.74), whereas the incidence of taste disorders, metallic taste, vomiting, nausea, and epigastric pain did not differ significantly between the probiotic group and the control group.

**CONCLUSION:** Supplementary probiotic preparations during standard triple *H. pylori* therapy may improve the eradication rate, particularly in Asian patients, and the incidence of total adverse effects.

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**Key words:** *Helicobacter pylori*; Eradication; Probiotics; Meta-analysis; Adult

**Core tip:** This systematic review and meta-analysis evaluated the role of probiotics in the standard triple *Helicobacter pylori* therapy in adults. Using a rigorous

and rational search strategy, inclusion criteria, and statistical analyses, we found that supplementary probiotic preparations given during standard triple *H. pylori* therapy conferred a higher eradication rate, particularly in Asian patients, and a lower incidence of total adverse effects, particularly diarrhea.

Zhu R, Chen K, Zheng YY, Zhang HW, Wang JS, Xia YJ, Dai WQ, Wang F, Shen M, Cheng P, Zhang Y, Wang CF, Yang J, Li JJ, Lu J, Zhou YQ, Guo CY. Meta-analysis of the efficacy of probiotics in *Helicobacter pylori* eradication therapy. *World J Gastroenterol* 2014; 20(47): 18013-18021 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i47/18013.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i47.18013>

## INTRODUCTION

It has been more than 30 years since Australian scientists Marshall and Warren successfully cultured *Helicobacter pylori* (*H. pylori*) in 1983, and numerous studies have confirmed that *H. pylori* infection is a key risk factor for peptic ulcer, chronic atrophic gastritis, gastric cancer, and other gastrointestinal diseases. *H. pylori* is a gram-negative, microaerophilic bacterium. It is spiral in shape with a flagellum, and colonizes the human gastric mucosa. It has been estimated that 50% of the world's population could be infected with this bacterium, and in some developing countries, this number reaches 80%<sup>[1]</sup>. In most cases, bacterial colonization is present for the whole lifetime and there is a range of clinical manifestations, from asymptomatic subjects to those with serious pathologies<sup>[2,3]</sup>. Therefore, to manage those *H. pylori*-related diseases, it is important to formulate an effective *H. pylori* eradication treatment. In the past few years, the standard triple therapy, which consists of a proton pump inhibitor (PPI) and two antibiotics, is regarded as the first-line treatment<sup>[2]</sup>. The most commonly used antibiotics are tetracycline, amoxicillin, imidazole (metronidazole or tinidazole), and macrolide (clarithromycin or azithromycin). However, antibiotic-associated adverse effects, including diarrhea, nausea, vomiting, abdominal pain, and bloating, limit the use of the eradication treatment, and antibiotic resistance in *H. pylori*, especially clarithromycin resistance, affects the efficacy of the treatment<sup>[3-5]</sup>. In areas with high rates of clarithromycin resistance, the first option is a sequential or concomitant regimen<sup>[6]</sup>. The main reason for the increase in antibiotic resistance is the accumulation of point mutations in the *H. pylori* DNA, which are in most cases associated with the overuse of antibiotics<sup>[7]</sup>. Therefore, the development of a new treatment regimen that not only improves the eradication rate but also reduces the frequency of adverse effects remains the principal challenge.

Probiotics are generally considered safe microorganisms that play a crucial role in stabilizing the intragastric microecological environment. In recent years, probiotics have been used as an anti-*H. pylori* therapy. The most common microorganisms used in probiotic formulations

in clinical practice include species of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and *Streptococcus*, as well as *Enterococcus*<sup>[8]</sup>. These may act in different ways, such as by direct competition with *H. pylori* or by improving the patients' compliance with therapy when the incidence of antibiotic-related adverse effects is reduced<sup>[9]</sup>. The inclusion of a probiotic in an *H. pylori* eradication therapy is thought to increase its efficacy or to reduce the adverse effects of the treatment. However, this remains controversial. A meta-analysis by Tong *et al*<sup>[10]</sup> suggested that supplementation with probiotics could effectively increase the eradication rate of an anti-*H. pylori* therapy and had a positive effect on *H. pylori*-therapy-related adverse effects. However, the studies examined in their meta-analysis included different treatment regimens, and it seems that not all treatment regimens have equally beneficial effects. Therefore, we performed a systematic review and meta-analysis to evaluate the role of probiotics in the standard triple *H. pylori* therapy in adults.

## MATERIALS AND METHODS

### Search strategy

Systematic searches were conducted independently by two investigators (Zhu R and Chen K). The searches were mainly conducted in MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials<sup>[11,12]</sup>. The references cited in the included articles and relevant published reports were also searched manually. The searches were confined to articles written in Chinese or English. No restriction was set on the year of publication. The latest search was updated in 2014. The following strategy was used to find eligible trials, including the keywords: "*Helicobacter pylori*" or "*H. pylori*" and "probiotic", "probiotics", "yeast", "yogurt", "*Lactobacillus*", "*Bifidobacterium*", "*Saccharomyces*", "*Enterococcus*", or "*Streptococcus*". Both free text and MeSH searches for keywords were used.

### Criteria for selection

The criteria for inclusion of studies were: (1) randomized controlled trials (RCTs); (2) comprised of patients aged 18-80 years; (3) compared at least two branches of treatment consisting of a triple regimen (PPI and two antibiotics) with a placebo or no additional intervention, and the same eradication regimen plus a probiotic; and (4) primary outcome was the rate of *H. pylori* eradication, confirmed by any generally accepted method at least four weeks after treatment. The secondary outcome was the frequency of total and specific adverse effects.

### Criteria for exclusion

Studies were excluded from the analysis if the loss rates were more than 20%, or if participants had suffered a chronic decompensated disease, immunological disease, or upper respiratory tract infection, or had used PPIs or H2 blockers in the preceding month. Additionally, publications that were reviews, letters, case reports, editorials, or comments were excluded.

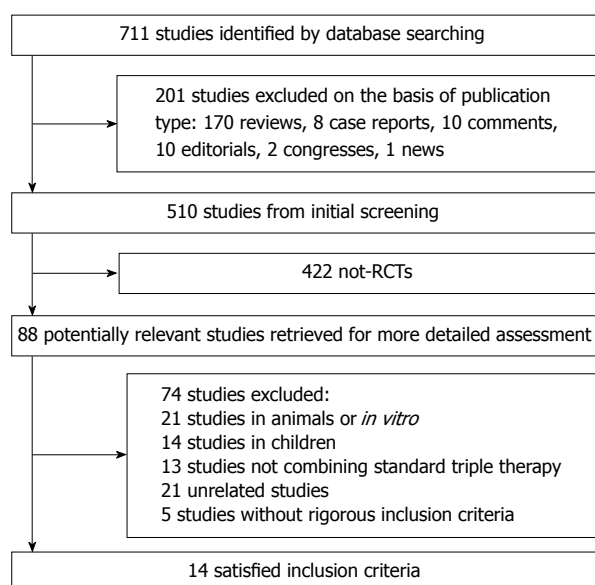


Figure 1 Study selection. RCT: Randomized controlled trial.

### Selection of studies

The titles and abstracts of the studies identified by the search were read thoroughly to confirm the eligibility of the study, and the full texts of potentially eligible studies were then retrieved for further assessment. Doubts between the two investigators were discussed with a third investigator. The authors were contacted for further study details if necessary.

### Assessment of methodological quality

The Jadad scale was selected to evaluate the methodological quality of eligible RCTs<sup>[13]</sup>. This scale is based on three terms: randomization (0-2 points), blinding (0-2 points), and withdrawals and dropouts (0-1 point). A score of 1 is given when randomization or blinding is mentioned, and a further point is given if they are used appropriately. A description of the number of and reasons for withdrawals and dropouts was also accorded a score of 1. The studies were considered to be of low quality when they had scores  $\leq 2$ , and of high quality for scores  $\geq 3$ <sup>[14]</sup>.

### Data extraction

Data were independently extracted from the full-length articles by two investigators (Zhu R and Chen K), using a predesigned form. Disagreements were resolved by discussion. The extracted information included: name of the first author, location of the trial, the number of enrolled subjects, initial/rechecking methods used to assess *H. pylori* infection, strain, the course of the probiotic treatment, the *H. pylori* eradication regimen, follow-up time, and subject loss rate. The primary outcome was the eradication rate and the secondary outcome was the incidence of total adverse effects.

### Statistical analysis

All statistical analyses were performed with STATA version 12.0. Publication bias existed when a *P* value < 0.05

was observed. The *H. pylori* eradication rates and the incidence of adverse effects were treated as dichotomous outcomes and expressed as odds ratios (ORs). The eradication rates were analyzed with intention-to-treat (ITT) and per-protocol (PP) analyses, and the incidence of adverse effects was analyzed with an ITT analysis. Heterogeneity was investigated using the Higgins ( $I^2$ ) estimate. Low heterogeneity was defined as  $I^2 < 25\%$ ; moderate heterogeneity as  $25\% < I^2 < 50\%$ ; and high heterogeneity as  $I^2 > 50\%$ . A fixed effects model was used when no heterogeneity existed and a random effects model was used to collectively analyze the accuracy indicators (Mantel and Haenszel method). The results are presented with the corresponding 95% confidence intervals (CIs) and the significance level was  $\alpha = 0.05$ .

## RESULTS

### Characteristics of the selected studies

A total of 711 studies were identified; 201 articles were excluded because they were unsuitable publication types and 422 non-RCT studies were excluded after the initial screening. Eighty-eight studies were excluded after more detailed assessments were made (21 studies were in animals or *in vitro*, 14 studies were in children, 13 studies did not use a standard triple therapy, 21 were unrelated studies, and 5 studies had no rigorous inclusion criteria), and the remaining 14 studies<sup>[15-28]</sup> were considered suitable for inclusion in the analysis. A flow diagram of the study selection process is shown in Figure 1. The initial and rechecked *H. pylori* assessments, follow-up times, loss rates, and scoring systems used to assess adverse effects are shown in Table 1. The numbers of experimental groups and context groups, the probiotic regimen, and the eradication regimens are shown in Table 2. Fourteen studies involving 2259 patients were included in the meta-analysis; 1124 patients were treated with the standard triple therapy supplemented with probiotics, and 1135 patients were treated with the standard triple therapy only or together with a placebo. The identified studies were published between 2000 and 2014. The ethnicity in five studies was Asian<sup>[17-19,23,26]</sup> and Caucasian in the remaining studies.

### Publication bias

Begg's funnel plots were used to examine the publication bias and are shown in Figure 2. A *P* value of > 0.05 indicated that there was no evidence of substantial publication bias in the 14 studies ( $\bar{z} = 0.44$ ,  $\text{Pr} > |z| = 0.661$ ).

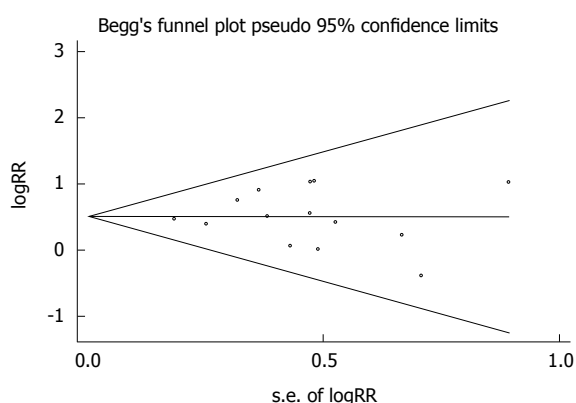
### Eradication rates

Data on the effects of probiotics on the *H. pylori* eradication rates were available from 14 trials (Figure 3). The pooled ORs for the eradication rates in the ITT analysis and in the PP analysis of the probiotic group *vs* the control group were 1.67 (95%CI: 1.38-2.02) and 1.68 (95%CI: 1.35-2.08), respectively, using the fixed effects model. Low heterogeneity was demonstrated between studies in both the ITT ( $I^2 = 0.00\%$ ) and PP analyses ( $I^2 = 0.00\%$ ).

**Table 1** Initial and rechecked *Helicobacter pylori* assessments, follow-up times, loss rates, and scoring systems used to assess adverse effects in the included studies

Ref.	<i>H. pylori</i> assessment		Follow-up time	Loss rate	Side effect scoring system
	Initial	Rechecking			
Emara <i>et al</i> <sup>[15]</sup>	HpSA, RUT, Histology	HpSA, RUT, Histology	4 wk <sup>1</sup> 6 wk <sup>2</sup>	0.00%	Non-Boer
Medeiros <i>et al</i> <sup>[16]</sup>	Culture	UBT	≥ 6 wk	0.00%	Not reported
Song <i>et al</i> <sup>[17]</sup>	RUT, Histology	UBT	4 wk	8.50%	Non-Boer
Du <i>et al</i> <sup>[18]</sup>	RUT, UBT, Pathologic examination	UBT	4 wk	2.60%	Non-Boer
Deguchi <i>et al</i> <sup>[19]</sup>	Culture, Histology, RUT	UBT, HpSA	8 wk	5.20%	Not reported
Mirzaee <i>et al</i> <sup>[20]</sup>	UBT	UBT	4 wk	16.20%	Non-Boer
Canducci <i>et al</i> <sup>[21]</sup>	UBT, Histology	UBT, Histology, Endoscopy	6 wk	2.50%	By de Boer <i>et al</i>
Nista <i>et al</i> <sup>[22]</sup>	UBT	UBT	6 wk	5.70%	By de Boer <i>et al</i>
Sheu <i>et al</i> <sup>[23]</sup>	Histology, RUT	UBT, Histology, RUT	4 wk <sup>1</sup> 8 wk <sup>2</sup>	6.90%	Non-Boer
Myllyluoma <i>et al</i> <sup>[24]</sup>	Rapid whole blood test, UBT, EIA serology	UBT, EIA, serology	4 wk <sup>1</sup> 4 mo <sup>2</sup>	0.00%	By de Boer <i>et al</i>
Yaşar <i>et al</i> <sup>[25]</sup>	Histology	UBT	4 wk	8.90%	Non-Boer
Kim <i>et al</i> <sup>[26]</sup>	RUT, Histology	UBT	4-6 wk	3.00%	Non-Boer
Scaccianoce <i>et al</i> <sup>[27]</sup>	Histology	UBT	4-6 wk	3.00%	Non-Boer
Cindoruk <i>et al</i> <sup>[28]</sup>	Histology	UBT	6 wk	0.00%	By de Boer <i>et al</i>

<sup>1</sup>Probiotic group; <sup>2</sup>Control group. EIA: Enzyme immunoassay; HpSA: *H. pylori* stool antigen test; RUT: Rapid urease test; UBT: C13 or C14 urea breath test.

**Figure 2** Funnel plot of the eradication rates in the included studies.

The overall pooled OR did not change significantly when any single study was excluded, with results ranging from 1.32 to 2.14. The following four criteria were also used to examine the stability of the analysis: (1) The removal of six poor-quality studies (Jadad score  $\leq 2$ ); (2) the removal of two studies that used combined probiotic preparations; (3) patients were divided into two categories according to ethnicity: five studies included Asian patients and nine studies included Caucasian patients; and (4) studies were divided into two categories according to the duration of triple therapy: 10 studies included a 7 d-triple therapy and four studies included triple therapy lasting more than seven days. Our results show that there was no significant difference in the pooled indices of the eight studies with Jadad scores  $\geq 3$ , in the 12 studies that used single probiotic preparations, or when the 14 studies were included. There was also no significant difference between studies that used triple therapy regimens lasting

seven days and those lasting more than seven days. These studies also had overlapping confidence intervals. However, the sensitivity of the Asian studies was greater than that of the Caucasian studies (Asian: OR = 1.78, 95%CI: 1.40-2.26; Caucasian: OR = 1.48, 95%CI: 1.06-2.05).

### Adverse effects

Ten studies provided data on the incidence of total adverse effects. The pooled OR for the incidence of total adverse effects was significantly lower in the probiotic group (OR = 0.49, 95%CI: 0.26-0.94) using the random effects model due to significant heterogeneity ( $I^2 = 85.7\%$ ) (Figure 4A). The studies were then divided into two categories according to the probiotic strains used. Significant heterogeneity was observed in the four studies that included *Lactobacillus* and in another six studies without *Lactobacillus*. Individual adverse effects, such as taste disorders, metallic taste, diarrhea, vomiting, nausea, and epigastric pain, were also analyzed. Probiotic supplementation significantly reduced the incidence of diarrhea (OR = 0.21, 95%CI: 0.06-0.74), whereas the incidence of taste disorders (OR = 0.73, 95%CI: 0.45-1.19), metallic taste (OR = 0.87, 95%CI: 0.20-3.72), vomiting (OR = 0.40, 95%CI: 0.15-1.08), nausea (OR = 0.66, 95%CI: 0.42-1.04), and epigastric pain (OR = 0.55, 95%CI: 0.20-1.57) did not differ significantly between the probiotic group and the control group (Figures 4B, C).

## DISCUSSION

As we know, *H. pylori* is closely associated with peptic ulcers, chronic atrophic gastritis, gastric cancer, and other gastrointestinal diseases. The risk of developing *H. pylori*-associated diseases may increase with increasing levels



**Table 2** Numbers of experimental and context groups, and probiotic and eradication regimens

Ref. (location)	Ethnicity	Total (exp/cont)	Regimen		Jadad scores
			Probiotic	Eradication	
Emara <i>et al</i> <sup>[15]</sup> (Egypt)	Caucasian	70 (35/35)	<i>Lactobacillus reuteri</i> (DSM 17938 and ATCC PTA 6475), $2 \times 10^8$ CFU <i>qd</i> for 4 wk	O: 20 mg A: 1000 mg C 500 mg <i>bid</i> for 14 d	5
Medeiros <i>et al</i> <sup>[16]</sup> (Portugal)	Caucasian	62 (31/31)	<i>Lactobacillus acidophilus</i> (BioSaúde laboratories, Portugal), $15 \times 10^9$ CFU, $10 \times 10^9$ CFU <i>qn</i> for 8 d	E: 20 mg A: 1000 mg C: 500 mg <i>bid</i> for 8 d	2
Song <i>et al</i> <sup>[17]</sup> (Korea)	Asian	661 (330/331)	<i>Saccharomyces boulardii</i> (Bioflor250, Kuhnle Pharmacy, Seoul, Korea), $3 \times 10^{10}$ CFU <i>tid</i> for 4 wk	O: 20 mg A: 1000 mg C: 500 mg <i>bid</i> for 7 d	3
Du <i>et al</i> <sup>[18]</sup> (China)	Asian	156 (77/79)	<i>Lactobacillus acidophilus</i> , 107 CFU, <i>Streptococcus faecalis</i> , $5 \times 10^6$ CFU, <i>Bacillus subtilis</i> , 104 CFU <i>tid</i> for 2 wk	O: 20 mg A: 1000 mg C: 500 mg <i>bid</i> for 7d	3
Deguchi <i>et al</i> <sup>[19]</sup> (Japan)	Asian	229 (115/114)	<i>Lactobacillus gasseri</i> (OLL2716), $\geq 10^9$ CFU <i>bid</i> for 4 wk	R: 10 mg A: 750 mg C: 200 mg <i>bid</i> for 7 d	3
Mirzaee <i>et al</i> <sup>[20]</sup> (Iran)	Caucasian	68 (34/34)	Probiotic yogurt (1.5% fat), 150 mg <i>bid</i> for 7 d	P: 40 mg <i>qd</i> A: 1000 mg <i>bid</i> C: 500 mg <i>bid</i> for 7 d	2
Canducci <i>et al</i> <sup>[21]</sup> (Italy)	Caucasian	120 (60/60)	<i>Lactobacillus acidophilus</i> strain LB, $\geq 5 \times 10^9$ heat-killed organisms <i>tid</i> for 10 d	R: 20 mg <i>bid</i> C: 250 mg <i>tid</i> A: 500 mg <i>tid</i> for 7d	3
Nista <i>et al</i> <sup>[22]</sup> (Italy)	Caucasian	106 (54/52)	<i>Bacillus clausii</i> (Sanofi-Synthelabo OTC, Milan, Italy), $2 \times 10^9$ CFU <i>tid</i> for 14 d	R: 20 mg A: 1000 mg C: 500 mg <i>bid</i> for 7d	4
Sheu <i>et al</i> <sup>[23]</sup> (Taiwan)	Asian	160 (80/80)	<i>Bifidobacterium</i> -containing yogurt, $\geq 5 \times 10^9$ live organisms per bottle <i>bid</i> for 4 wk	L: 30 mg A: 1000 mg C: 500 mg <i>bid</i> for 7 d	2
Myllyluoma <i>et al</i> <sup>[24]</sup> (Finland)	Caucasian	47 (23/24)	Probiotics (Valio Ltd, Helsinki, Finland), $65 \times 10^9$ CFU <i>bid</i> for 1 wk $65 \times 10^9$ CFU <i>qd</i> for 3 wk	L: 30 mg C: 500 mg A: 1000 mg <i>bid</i> for 7d	4
Yaşar <i>et al</i> <sup>[25]</sup> (Turkey)	Caucasian	76 (38/38)	<i>Bifidobacterium</i> (DN-173 010-10), $10^{10}$ CFU <i>qd</i> for 14 d	P: 40 mg A: 1000 mg C: 500 mg <i>bid</i> for 14 d	2
Kim <i>et al</i> <sup>[26]</sup> (Korea)	Asian	347 (168/179)	<i>Lactobacillus acidophilus</i> (HY 2177), $> 15 \times 10^6$ CFU, <i>L. casei</i> (HY 2743), $> 15 \times 10^6$ CFU, <i>B. longum</i> (HY 8001), $> 15 \times 10^7$ CFU, <i>S.</i> <i>thermophilus</i> (B-1), $> 15 \times 10^9$ CFU <i>qd</i> for 3 wk	Standard PPI C: 500 mg A: 1000 mg <i>bid</i> for 7d	2
Scaccianoce <i>et al</i> <sup>[27]</sup> (Italy)	Caucasian	33 (17/16)	<i>Lactobacillus reuteri</i> (ATCC 55730), $10^8$ CFU <i>bid</i> for 7 d	L: 30 mg A: 1000 mg C: 500 mg <i>bid</i> for 7d	1
Cindoruk <i>et al</i> <sup>[28]</sup> (Turkey)	Caucasian	124 (62/62)	<i>Saccharomyces boulardii</i> , 1 gram (250 mg sachets, 500 mg <i>bid</i> Reflor (Sanofi-Synthelabo Ilac A.S., Istanbul, Turkey) <i>bid</i> for 2 wk	L: 30 mg A: 1000 mg C: 500 mg <i>bid</i> for 14 d	4

A: Amoxicillin; C: Clarithromycin; cont: Control; CFU: Colony forming units; E: Esomeprazole; exp: Experimental; L: Lansoprazole; O: Omeprazole; P: Pantoprazole; PPI: Proton pump inhibitor; R: Rabeprazole.

of *H. pylori*<sup>[29,30]</sup>. For the past few years, the standard triple therapy, as recommended by the Maastricht 2-2000 Consensus Report, is regarded as the first-line treatment.

However, the Maastricht 4-2012 Consensus Report recommends sequential or concomitant regimens as the best first-line treatments in areas with high rates of clar-

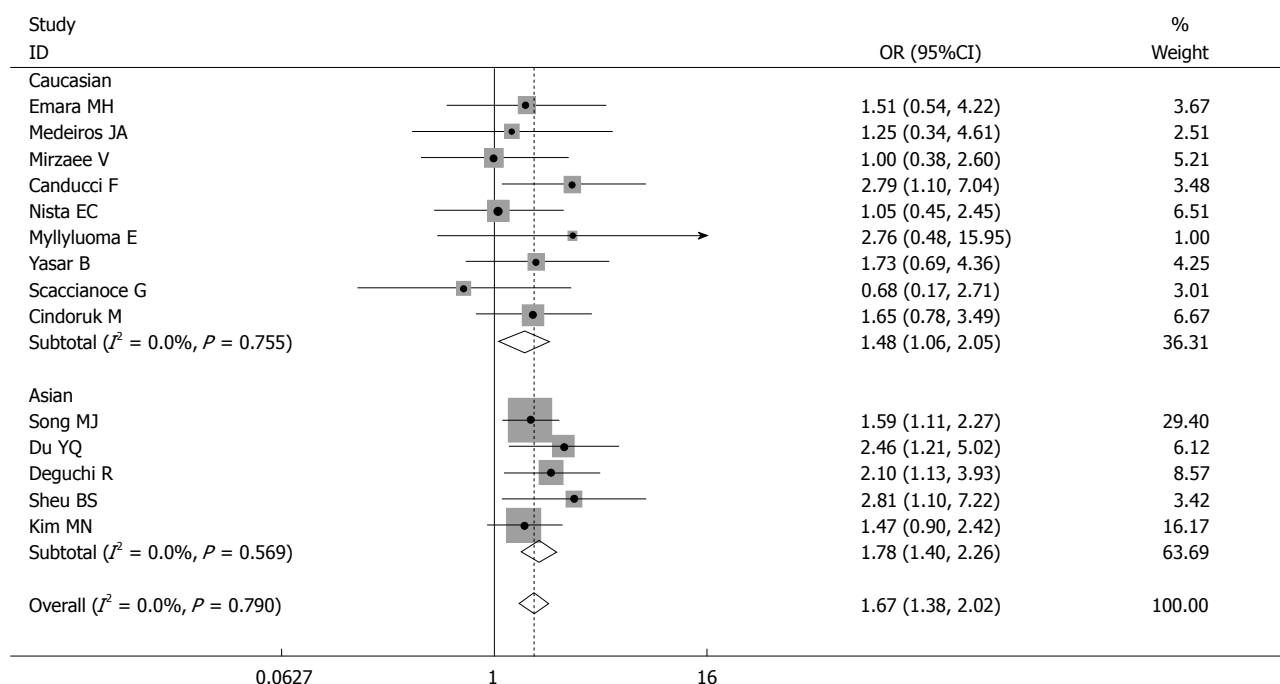


Figure 3 Meta-analysis of studies that evaluated the effects of probiotic supplementation on eradication rates by intention-to-treat.

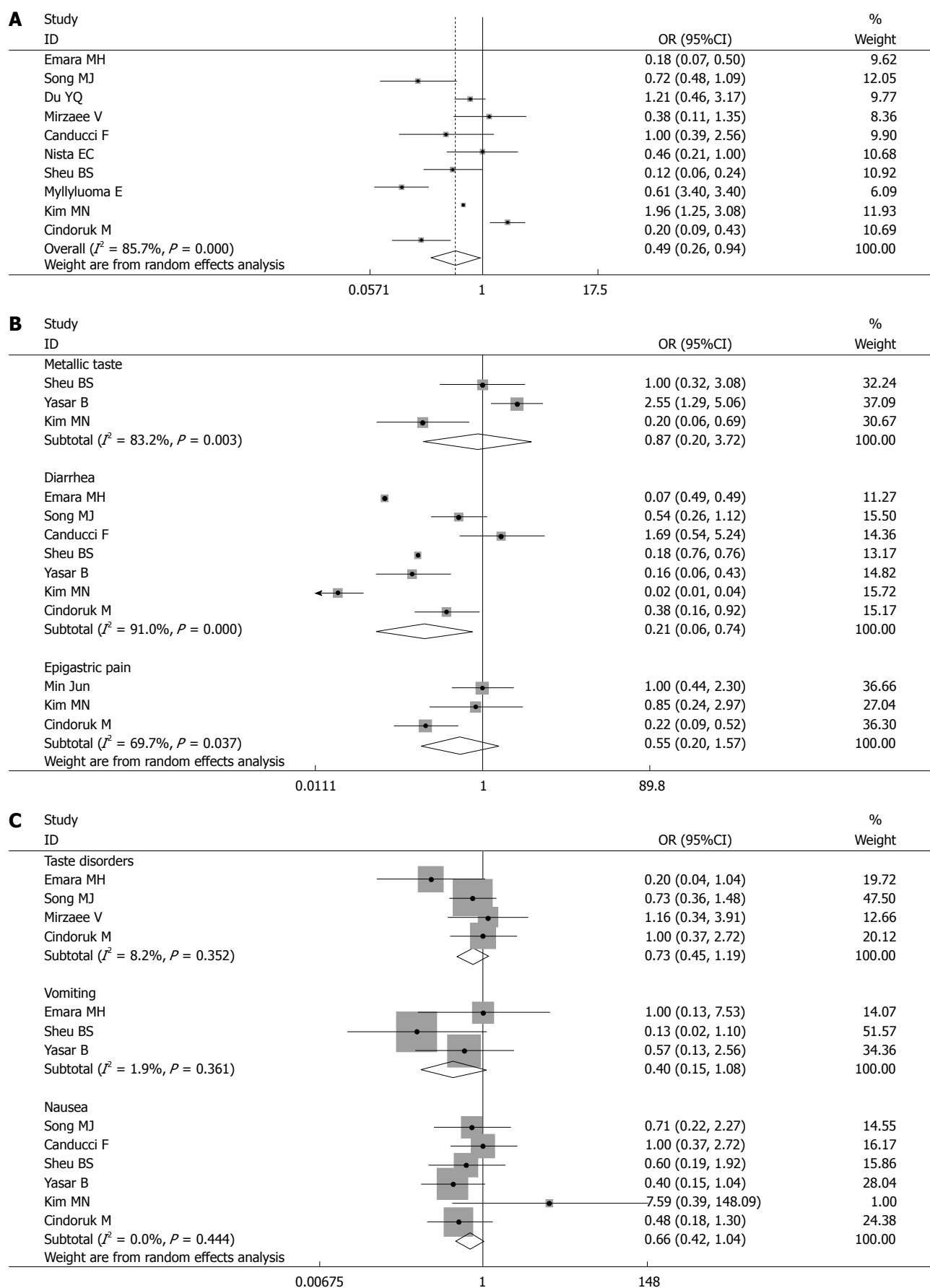
ithromycin resistance. Other treatment regimens include quadruple therapy and miscellaneous therapy. However, unsatisfactory *H. pylori* eradication rates and antibiotic-related adverse effects remain as the two limitations of anti-*H. pylori* therapies.

A probiotic is defined as a living microbial species that may have a positive effect on the bowel microecology and improve health<sup>[31]</sup>. Currently, the most studied probiotics are lactic acid-producing bacteria, particularly *Lactobacillus* species<sup>[32]</sup>. In recent years, the use of probiotics combined with a standard triple therapy has been considered a novel choice. Probiotics may act as surrogate normal microflora after antibiotic therapy until recovery is achieved, although the mechanism is not completely understood<sup>[33]</sup>. Lesbros-Pantoflickova *et al*<sup>[34]</sup> summarized several putative mechanisms by which probiotics can inhibit *H. pylori*, including non-immunological mechanisms, antimicrobial substances, and the *in vitro* inhibitory effects of certain probiotics that are probably related to lactic acid and/or other antibacterial substances yet to be identified. Many clinical trials have suggested that probiotic supplementation is a good strategy to enhance the effectiveness of anti-*H. pylori* therapy and to reduce antibiotic-associated adverse effects, but this remains controversial. Therefore, we conducted this meta-analysis of the evidence in 14 RCTs to provide a quantitative assessment of the efficacy of probiotic supplementation in *H. pylori* eradication.

In our meta-analysis, the results of 14 RCTs pooled with a fixed effects model indicated that probiotic supplementation of a standard triple therapy regimen improved the *H. pylori* eradication rates in both ITT and PP analyses, which is consistent with eradication rates reported in a previous meta-analysis by Tong *et al*<sup>[10]</sup>. However, this result should be interpreted with care because the studies

differed widely in their designs and in the antibiotic and probiotic treatments used. In a subanalysis, the *H. pylori* eradication rate was not related to the quality of the included studies, the probiotic preparations, or the duration of the triple therapy, but was greater in Asian subjects. This may be closely related to the distribution of CY-P2C19 polymorphisms, which affect *H. pylori* eradication rates<sup>[35]</sup>. However, in our meta-analysis, only five studies included Asian patients, whereas nine studies included Caucasian patients, so further clinical studies are required to confirm this speculation.

The effect of probiotic supplementation on antibiotic-associated gastrointestinal adverse effects during anti-*H. pylori* regimens were also examined in our meta-analysis. The results showed that probiotics had a positive effect on the overall *H. pylori*-therapy-related adverse effects, with significant heterogeneity. Several factors may have given rise to this heterogeneity, including patient characteristics and the probiotic regimens used (species, number of colony-forming units given, duration of administration, *etc.*). Therefore, more clinical trials are required to confirm these results. From the perspective of individual adverse effects, probiotic supplementation significantly reduced the incidence of diarrhea. However, it should be noted again that the studies differed with respect to the antibiotic and probiotic treatments used, making the interpretation of the results difficult. Bühlung *et al*<sup>[36]</sup> proposed that the supplementation of a PPI-antibiotic regimen with probiotics corrects antibiotic-induced intestinal dysbiosis. No study has demonstrated the complete eradication of *H. pylori* infection with probiotic treatment<sup>[37]</sup>. However, these probiotic strains can improve patient compliance by reducing antibiotic-associated adverse events, increasing the number of patients who complete



**Figure 4** Meta-analysis of studies that evaluated the effects of probiotic supplementation on the incidence of adverse effects. A: Total adverse effects; B: Individual adverse effects including metallic taste, diarrhea, and epigastric pain; C: Individual adverse effects including taste disorders, vomiting and nausea.

the eradication therapy, and thus improving eradication rate.

In this study, a rigorous and rational search strategy, inclusion criteria, and statistical analyses were used to systematically and comprehensively analyze the effects of probiotics on a standard triple therapy for *H. pylori* in adults. However, this study had many limitations. First, because of the language barrier, non-English and non-Chinese studies could not be evaluated. Second, there was no standardized protocol regarding the species of probiotic, the dose, or the duration of supplementation in these studies, which will inevitably affect the results. It also seems that not all probiotics contribute equal beneficial effects. Third, there have been no trials involving patients from North America or Black individuals.

Finally, our study suggests that probiotic supplementation during *H. pylori* eradication therapy in adults may have beneficial effects on the eradication rate, particularly in Asian patients, and the incidence of total adverse effects, particularly diarrhea. More studies with rigorous designs, large sample sizes, and multiregional cooperation are required to obtain further evidence of the efficacy of probiotics in *H. pylori* eradication therapies.

## COMMENTS

### Background

*Helicobacter pylori* (*H. pylori*) infection is a key risk factor for many gastrointestinal diseases, such as peptic ulcers and chronic atrophic gastritis. Currently, there are no ideal treatments available that provide high eradication rates and few antibiotic-related adverse effects. The inclusion of a probiotic in *H. pylori* eradication therapy is thought to increase the efficacy or to reduce the adverse effects of the treatment. However, this remains controversial.

### Research frontiers

Probiotics are safe microorganisms and stabilize the intragastric microecological environment. Several systematic reviews were recently performed to investigate the role of probiotics in *H. pylori* eradication therapies.

### Innovations and breakthroughs

This meta-analysis confirms that probiotic supplementation during *H. pylori* eradication therapy improves *H. pylori* eradication rates, particularly in Asian patients, and decreases the incidence of total adverse effects.

### Applications

The study results suggest that probiotic supplementation can be used in *H. pylori* eradication therapy in adults, considering the higher eradication rate and lower incidence of adverse effects.

### Peer review

This is a methodologically sound meta-analysis of the probiotic effect on *H. pylori* eradication and side effects of the treatment. The statistical section is correct using updated meta-analytical methods.

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ISSN 1007-9327

