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

Zhu R *et al*. Probiotics and *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

**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**, Department of Gastroenterology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai 200072, China

**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 take 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, 301 Yanchang Middle Road, Zhabei District, Shanghai 200072, China. guochuanyong@hotmail.com.

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

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**Abstract**

**AIM:** To evaluate the role of probiotics in the standard triple *Helicobacter pylori* (*H. 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 qualitiy 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 versus the control group were 1.67 (95%CI: 1.38-2.02) and 1.68 (95%CI: 1.35-2.08), respectively, on 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), on the random modle, with significant heterogeneity (*I2* =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 in adults may have beneﬁcial eﬀects on the eradication rate, particularly in Asian patients, and on the incidence of total adverse eﬀects.

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

**Core tip:** This is a systematic review and meta-analysis evaluated the role of probiotics in the standard triple *Helicobacter pylori* (*H. pylori*) therapy in adult. 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 in adults conferred a higher eradication rate, particularly in Asian patients, and 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; In press

**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%[1]. 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[2,3]. 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[2]. The most commonly used antibiotics are tetracycline, amoxicillin, imidazole (metronidazole or tinidazol), 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[3-5], and in areas with high rates of clarithromycin resistance, the first options is a sequential or concomitant regimen[6]. The main reason for the increase in antibiotic resistance is point mutations that accumulate in the *H. pylori* DNA, which are in most cases associated with the overuse of antibiotics[7]. 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*[8]. These may act in different ways: by direct competition with *H. pylori* or by improving the patients’ compliance with therapy when the incidence of antibiotic-related adverse effects is reduced[9]. The inclusion of a probiotic in a *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*[10] suggested that supplementation with probiotics could effectively increase the eradication rate of an anti-*H. pylori* therapy and has 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 adult.

**MATERIALS AND METHODS**

***Search strategy***

Systematic searches were conducted independently by two investigators (Rong Zhu and Kan Chen). The searches were mainly conducted in MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials[11,12]. 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***

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

***Criteria for exclusion***

(1) Studies with loss rates of more than 20%; (2) 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; and (3) Studies that were published as reviews, letters, case reports, editorials, or comments.

***Selection of studies***

The titles and abstracts of the studies found with the search were read thoroughly to confirm the eligibility of the study, and the full text of potentially eligible studies was then retrieved for further assessment. Doubts 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[13]. 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 ≤ 2 and of high quality with scores ≥ 3[14].

***Data extraction***

Data were extracted from the full-length articles independently by two investigators (Rong Zhu and Kan Chen), 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 (*I²*) estimate. Low heterogeneity was defined as *I²* < 25%; moderate heterogeneity as 25% < *I²* < 50%; and high heterogeneity as 50% < *I²*. A fixed effects model was used when no heterogeneity existed and a random effects model was used to collectively analyze the accuracy indicators. The results are presented with the corresponding 95% confidence intervals (CIs) and the significance level was α = 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 five studies had no rigorous inclusion criteria), and the remaining 14 studies[15-28] 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 regimen are shown in Table 2. As shown in Table 2, 14 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[17-19,23,26] and was 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 (Begg test, *z* = 0.44, 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; Figure 3) and 1.68 (95%CI: 1.35-2.08), respectively, on the fixed-effects model (Mantel and Haenszel method) (Figure 3). Low heterogeneity was demonstrated between studies in both the ITT analysis (*I2* = 0.00%; Figure 3) and PP analysis (*I2* = 0.00%). 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, according to their Jadad scores (Jadad score ≤ 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 ≥ 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; Figure 3).

***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) on the random model (Mantel and Haenszel method), with significant heterogeneity observed (*I2* = 85.7%; Figure 4A). The studies were than divided into two categories according to the probiotic strains used. Significant heterogeneity was observed in 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 and C).

**DISCUSSION**

As we know, *H. pylori* is closely associated with peptic ulcer, chronic atrophic gastritis, gastric cancer, and other gastrointestinal diseases. The risk of developing *H. pylori*-associated diseases may increase with increasing levels of *H. pylori*[29,30]. In 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 Maastricht4-2012 Consensus Report recommends sequential or concomitant regimens as the best first-line treatments in areas with high rates of clarithromycin resistances. Other treatment regimens include quadruple therapy, and miscellaneous therapy. However, unsatisfactory *H. pylori* eradication rates and antibiotic-related adverse effects remain 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[31]. Currently, the most studied probiotics are lactic-acid-producing bacteria, particularly *Lactobacillus* species[32]. 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[33]. Drahoslava *et al*[34] summarized several putative mechanisms by which probiotics can inhibit *H. pylori*, including nonimmunological 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 (OR = 1.67, 95%CI: 1.38-2.02) and PP analyses (OR = 1.68, 95%CI: 1.35-2.08). In a previous meta-analysis, Tong *et al*[10] calculated a pooled OR of 1.72 (95%CI: 1.20-2.47) for the eradication rates in the adult subgroup. Our finding is consistent with this analysis. 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 or the probiotic preparations (single or combined), or the duration of the triple therapy (7-d therapy or therapy for more than 7 d), but was greater in Asian subjects. This may be closely related to the distribution of CYP2C19 polymorphisms, which affect *H. pylori* eradication rates[35]. 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 speculate.

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 patients characteristics and the probiotics regimen 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 effect, 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. Buhling *et al*[36] proposed that the supplementation of a PPI-antibiotic regimen with probiotics corrects antibiotic-induced intestinal dysbiosis.

However, no study demonstrated the complete eradication of *H. pylori* infection with probiotic treatment[37]. However, these probiotic strains can improve patient compliance by reducing antibiotic-associated adverse events, increasing the number of patients who complete 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 negroid 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 ulcer and chronic atrophic gastritis. But up to now, there are still no ideal methods to eradicate *H. pylori* with 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 role of probiotics in *H. pylori* eradication therapies

***Innovations and breakthroughs***

Our meta-analysis conﬁmed that probiotic supplementation during *H. pylori* eradication therapy improved *H. pylori* eradication rates, particularly in Asian patients, and decreased incidence of total adverse effects.

***Applications***

The study results suggest that probiotic supplementation could be used in *H. pylori* eradication therapy in adults, in consideration of higher eradication rate and fewer incidence of adverse effects.

***Peer review***

This is a methologically 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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**P- Reviewers: Buzas GM, Ierardi E, Nath G**

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

**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**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **References** | ***H. pylori* assessment (initial)** | ***H. pylori* assessment (rechecking)** | **Follow-up time** | **Loss-up rate** | **Score system for assessing side effects** |
| Emara MH[15] | HpSA; RUT; Histology | HpSA; RUT; Histology | 4 wk1; 6 wk2 | 0% | Non-Boer |
| Medeiros JA[16] | Culture | UBT | ≥ 6 wk | 0% | Not reported |
| Song MJ[17] | RUT; Histology | UBT | 4 wk | 8.50% | Non-Boer |
| Du YQ[18] | RUT; UBT; Pathologic examination | UBT | 4 wk | 2.60% | Non-Boer |
| Deguchi R[19] | Culture; Histology; RUT | UBT; HpSA | 8 wk | 5.20% | Not reported |
| Mirzaee V[20] | UBT | UBT | 4 wk | 16.20% | Non-Boer |
| Canducci F[21] | UBT; Histology | UBT; Histology; Endoscopy | 6 wk | 2.50% | By de Boer *et al* |
| Nista EC[22] | UBT | UBT | 6 wk | 5.70% | By de Boer *et al* |
| Sheu BS[23] | Histology; RUT | UBT; Histology; RUT | 4 wk1; 8 wk2 | 6.90% | Non-Boer |
| Myllyluoma E[24] | Rapid whole blood test; UBT; EIA serology | UBT; EIA serology | 4 wk1; 4 mo2 | 0% | By de Boer *et al* |
| Yaşar B[25] | Histology | UBT | 4 wk | 8.90% | Non-Boer |
| Kim MN[26] | RUT; Histology | UBT | 4-6 wk | 3.00% | Non-Boer |
| Scaccianoce G[27] | Histology | UBT | 4-6 wk | 3.00% | Non-Boer |
| Cindoruk M[28] | Histology | UBT | 6 wk | 0% | By de Boer *et al* |

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

**Table 2 Numbers of experimental groups and context groups, probiotic regimens, and eradication regimens in the included studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **References and location** | **Ethnicity** | **Total (Exp/Cont)** | **Probiotic** | **Eradication regimen** | **Jadad scores** |
| Emara MH[15] (Egypt) | Caucasian | 70 (35/35) | Lactobacillus reuteri (DSM 17938 and ATCC PTA 6475), 2 × 108 CFU, *qd*, for 4 wk | O 20 mg A 1000 mg C 500 mg, *bid*, 14 d | 5 |
| Medeiros JA[16] (Portugal) | Caucasian | 62 (31/31) | Lactobacillus acidophilus (BioSaúde laboratories, Portugal), 15 × 109 bacteria am, 10 × 109 bacteria *qn*, for 8 d | E 20 mg A 1000 mg C 500 mg, *bid*, 8 d | 2 |
| Song MJ[17] (Korea) | Asian | 661 (330/331) | Saccharomyces boulardii (Bioﬂor250, Kuhnil Pharmacy, Seoul, Korea), 3 × 1010 cfu, *tid*, for 4 wk | O 20 mg A 1000 mg C 500 mg, *bid*, 7 d | 3 |
| Du YQ[18]  (China) | Asian | 156 (77/79) | Lactobacillus acidophilus, 107 cfu, Streptococcus faecalis, 5 × 106 cfu, Bacillus subtilis, 104 cfu, *tid*, for 2 wk | O 20 mg A 1000 mg C 500 mg, *bid*, 7d | 3 |
| Deguchi R[19] (Japan) | Asian | 229 (115/114) | Lactobacillus gasseri (OLL2716), ≥ 109 cfu, *bid*, for 4 wk | R 10 mg A 750 mg C 200 mg, *bid*, 7 d | 3 |
| Mirzaee V[20] (Iran) | Caucasian | 68 (34/34) | Probiotic yogurt (1.5% fat), 150 mg, *bid*, for 7 d | P 40 mg, *qd* A 1000 mg, *bid* C 500 mg, *bid*, 7 d | 2 |
| Canducci F[21] (Italy) | Caucasian | 120 (60/60) | Lactobacillus acidophilus strain LB, ≥ 5 × 109 heat-killed organisms, *tid*, for 10 d | R 20 mg, *bid* C 250 mg, *tid*  A 500 mg, *tid*, 7d | 3 |
| Nista EC[22] (Italy) | Caucasian | 106 (54/52) | Bacillus clausii (Sanoﬁ-Synthelabo OTC, Milan, Italy), 2 × 109 cfu, *tid*, for 14 d | R 20 mg A 1000 mg C 500 mg, *bid*, 7d | 4 |
| Sheu BS[23] (Taiwan) | Asian | 160 (80/80) | Biﬁdobacterium-containing yogurt, ≥ 5 × 109 live organisms per bottle, *bid*, for 4 wk | L 30 mg A 1000 mg C 500 mg, *bid*, 7 d | 2 |
| Myllyluoma E[24] (Finland) | Caucasian | 47 (23/24) | Probiotics (Valio Ltd, Helsinki, Finland), 65 × 109 cfu, *bid*, for 1 wk, 65 × 109 cfu, *qd*, for 3 wk | L 30 mg C 500 mg A 1000 mg, *bid*, 7d | 4 |
| Yaşar B[25] (Turkey) | Caucasian | 76 (38/38) | Bifidobacterium (DN-173 010-10), 1010 cfu, *qd*, for 14 d | P 40 mg A 1000 mg C 500 mg, *bid*, 14 d | 2 |
| Kim MN[26] (Korea) | Asian | 347 (168/179) | Lactobacillus acidophilus HY 2177, > 15 × 106 cfu, L. casei HY 2743, > 15 × 106 cfu, B. longum HY 8001, > 15 × 107 cfu, S. thermophilus B-1, > 15 × 109 cfu, *qd*, for 3 wk | Standard PPI C 500 mg A 1000 mg, *bid*, 7d | 2 |
| Scaccianoce G[27] (Italy) | Caucasian | 33 (17/16) | *Lactobacillus reuteri* (ATCC 55730), 108 cfu, *bid*, for 7 d | L 30 mg A 1000 mg C 500 mg, *bid*, 7d | 1 |
| Cindoruk M[28] (Turkey) | Caucasian | 124 (62/62) | Saccharomyces boulardii, 1 gram (250 mg sachets, 500 mg *bid*, Reﬂor; Sanoﬁ-Synthelabo Ilac A.S., Istanbul, Turkey), *bid*, for 2 wk | L 30 mg A 1000 mg C 500 mg, *bid*, 14 d | 4 |

L: Lansoprazole; T: Tetracycline; F: Furazolidone; P: Pantoprazole; E: Esomeprazole; O: Omeprazole.

fig.2.tif

**Figure 1 Study selection.** RCT: Randomized controlled trial.



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

fig3.tif

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

**A**

fig4.tif

**B**

fig5.tif

**C**

fig6.tif

**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, vomiting, and epigastric pain; C: Individual adverse effects including taste disorders, vomiting and nausea.