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META-ANALYSIS

Probiotics in *Helicobacter pylori* eradication therapy: A systematic review and meta-analysis

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Abstract

AIM: To summarize the evidence from randomized controlled trials (RCTs) regarding the effect of probiotics by using a meta-analytic approach.

METHODS: In July 2013, we searched PubMed, EMBASE, Ovid, the Cochrane Library, and three Chinese databases (Chinese Biomedical Literature Database, Chinese Medical Current Content, and Chinese Scientific Journals database) to identify relevant RCTs. We included RCTs investigating the effect of a combination of probiotics and standard therapy (probiotics group) with standard therapy alone (control group). Risk ratios (RRs) were used to measure the effect of probiotics plus standard therapy on *Helicobacter pylori* (*H. pylori*) eradication rates, adverse events, and patient compliance using a random-effect model.

RESULTS: We included data on 6997 participants from 45 RCTs, the overall eradication rates of the probiotic group and the control group were 82.31% and 72.08%, respectively. We noted that the use of probiotics plus standard therapy was associated with an increased eradication rate by per-protocol set analysis (RR = 1.11; 95%CI: 1.08-1.15; $P < 0.001$) or intention-to-treat analysis (RR = 1.13; 95%CI: 1.10-1.16; $P < 0.001$). Furthermore, the incidence of adverse events was 21.44% in the probiotics group and 36.27% in the control group, and it was found that the probiotics plus standard therapy significantly reduced the risk of adverse events (RR = 0.59; 95%CI: 0.48-0.71; $P < 0.001$), which demonstrated a favorable effect of probiotics in reducing adverse events associated with *H. pylori* eradication therapy. The specific reduction in adverse events ranged from 30% to 59%, and this reduction was statistically significant. Finally, probiotics plus standard therapy had little or no effect on patient compliance (RR = 0.98; 95%CI: 0.68-1.39; $P = 0.889$).

CONCLUSION: The use of probiotics plus standard therapy was associated with an increase in the *H. pylori* eradication rate, and a reduction in adverse events resulting from treatment in the general population. However, this therapy did not improve patient compliance.

Key words: Probiotics; *Helicobacter pylori*; Eradication;

Systematic review; Meta-analysis

Core tip: Probiotics have a positive effect on *Helicobacter pylori* (*H. pylori*) eradication since these compounds also induce anti-inflammatory and anti-oxidative mechanisms that regulate intestinal microbiota. The benefits of probiotics supplementation in the treatment of antibiotic resistant *H. pylori* are still unclear due to the lack of supporting evidence. In this meta-analysis of 45 randomized controlled trials involving nearly 6997 individuals, we found that the use of probiotics plus standard therapy was associated with an increase in the *H. pylori* eradication rate, and a reduction in adverse events resulting from treatment in the general population. However, this therapy did not improve patient compliance.

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INTRODUCTION

Since its identification in 1982 by Barry Marshall and Robin Warren, *Helicobacter pylori* (*H. pylori*) has been studied for more than 30 years. The infection rate of this single dominant pathogen in the stomach varies between 1.2% and 95% according to age, geographic area, socioeconomic status, and other factors[1-5]. Infection with this organism results in a chronic effect by causing duodenal or gastric ulcers[6,7], gastric cancer[8,9], and gastric mucosa-associated lymphoid-tissue lymphoma[6,10]. The therapy used for the eradication of *H. pylori* also prevents the development of the diseases mentioned above in patients who are at high risk[8,11-13]. The success rate of standard therapy ranges from 60% to 90% using first-line treatment, and around 70% with second-line treatment[14-16]. Furthermore, the disruption of coevolved human and *H. pylori* genomes might play an important role in the high incidence of gastric disease[17,18]. Hence, the development of improved strategies is still under investigation to increase the efficiency of eradication or to increase patient compliance, which may contribute to a greater clinical value because of the prevalence of *H. pylori* infection in large populations[19]. Probiotics have a positive effect on *H. pylori* eradication since these compounds also induce anti-inflammatory and anti-oxidative mechanisms that regulate intestinal microbiota[20-23].

Although several meta-analyses[24-27] have assessed the efficacy and safety of probiotics plus standard therapy, most of these studies have investigated these effects with respect to specific strains or certain formulations of probiotics[24-26]. Tong *et al*[27] demonstrated that the administration of probiotics can both improve the eradication rate and reduce adverse events, but their study did not examine the effect of probiotics on patient compliance. The benefits of probiotics supplementation in the treatment of antibiotic resistant *H. pylori* are still unclear due to the lack of supporting evidence[28]. In this study, we performed a meta-analysis of available randomized controlled trials (RCTs) to evaluate the effect of probiotics on *H. pylori* eradication, adverse events, and patient compliance.

MATERIALS AND METHODS

Data sources, search strategy, and selection criteria

This review was conducted and reported according to the requirements outlined in Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement, 2009 (Checklist S1)[29]. RCTs of probiotics plus standard therapy compared with standard therapy were included in our study, regardless of the publication status, *i.e.*, published, in press, or in progress, and the effect of probiotic supplementation on *H. pylori* eradication, adverse events, and compliance were examined. Relevant trials were identified using the following procedure: (1) electronic searches: we searched PubMed, EMBASE, Ovid, The Cochrane Library, and three Chinese databases (Chinese Biomedical Literature Database, Chinese Medical Current Content, and Chinese Scientific Journals database) for articles published through July 2013. Both medical subject headings and free-language terms of *H. pylori* and probiotic, yeast, *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Saccharomyces*, *Enterococcus*, and *Bacillus* were used as search terms; and (2) other sources: meeting abstracts, references of meta-analyses or reviews already published on related topics, and the clinicaltrials.gov website were also screened for completed or on-going studies. Authors were contacted for essential information regarding publications that were not available in full. Medical subject headings, methods, patient population, interventions, and outcome variables of these studies were used to identify relevant trials.

The literature search, data extraction, and quality assessment were independently undertaken by 2 investigators (Qian W and Qin YY) using a standardized approach. Any inconsistencies between these investigators were identified by the primary investigator (Zhou YH) and resolved by consensus. We restricted our study to RCTs that were less likely to be subject to confounding variables or bias than observational studies.

A study was eligible for inclusion in our meta-analysis if the following criteria were met: (1) the study was a RCT; (2) the probiotics were administrated as

adjuvant therapy in combination with the standard eradication therapy used for the treatment of *H. pylori*, including triple therapy, quadruple therapy and sequential therapy; (3) the probiotics group was treated with the standard eradication therapy plus probiotics and the control group received the same eradication regimens with or without a placebo; (4) the trial reported at least one of the following as an outcome: eradication rates, adverse events, or compliance; (5) if there were relevant studies with multiple arms, the data was combined to create a new study group and a new control group with reference to the criteria listed above; and (6) patient age or symptoms at the time of enrolment regardless of publication language were reported.

Finally, the exclusion criteria were as follows: (1) the study was not an RCT; (2) studies with only one group; and (3) studies in which patients were not treated with the standard therapy or in which the control group was treated differently from the group receiving the therapy.

Data collection and quality assessment

All data from included trials were extracted independently by 2 investigators (Qian W and Qin YY) using a standardized protocol. Each data set was reviewed by a third investigator (Zhou YH), and any discrepancies between the 2 investigators' data were resolved by discussion. The data collected from each study included characteristics of the enrolled patients, standard eradication therapy regimens, probiotic strains, dose and duration of probiotics, diagnostic methods of *H. pylori* infection, duration of the therapy and assessment, eradication rates, adverse events, and compliance. If the data of a study were published in more than one article, only the most recent publication was included. Both eradication rates by per-protocol set (PPS) analyses and intention-to-treat (ITT) analyses were collected.

The quality of the trials was assessed according to the recommendations of the Cochrane Collaboration[30], including random sequence generation (selection bias), allocation concealment (selection bias), blinding, intention-to-treat analysis, and completeness of follow-up. Judgments regarding the presence of methodological biases were determine by using the Cochrane criteria guidelines, Quality assessment was also performed independently by 2 researchers (Qian W and Qin YY), and was adjudicated by a third researcher (He J) when there were disagreements.

Statistical analysis

We computed the results of each RCT as dichotomous frequency data. Individual study risk ratios (RRs) and 95%CIs were calculated from event numbers extracted from each trial before data pooling. The overall RR and 95%CIs of eradication rates, adverse events, and compliance were also calculated. Both fixed-effect and random-effect models were used to assess the pooled RR for probiotics plus standard therapy compared with standard therapy. Results from the random-effects model were based on the assumption that the true underlying effect varied among the trials included in our meta-analysis presented here[31,32]. Heterogeneity of the treatment effects between studies was evaluated using the Q statistic, and we considered a P value < 0.10 to indicate significant heterogeneity[33,34].

Subgroup analyses were conducted for eradication rates by ITT analyses on the basis of the participant's age (0-17 years as children; ⩾ 18 years as adults; NM: the study was not mentioned or it contained both children and adults), single or multiple probiotic strains, high dose or low dose of probiotics (divided by the mean intake dosage per day of all included studies), duration of probiotics use longer than 15 d or not, duration of standard therapy longer than 7 d or not, duration between the end of the therapy and assessment longer than 4 wk or not, probiotic strains and types of standard therapy (first-line or second-line). Interaction tests[35] were performed to compare differences between the estimates of the 2 subsets, which were based on the Student t distribution rather than on a normal distribution because the number of inclusive studies was small. We also performed a sensitivity analysis by removing each individual trial from the meta-analysis[36]. Several methods were used to check for potential publication bias. Visual inspection of funnel plots for eradication rates, adverse events, and compliance were conducted. The Egger[37] and Begg test[38] were used to statistically assess publication bias for eradication rates, adverse events, and compliance. All reported P values were two-sided, and P values < 0.05 were considered statistically significant. Statistical analyses were performed using STATA software version 10.0 (Stata Corp., TX, United States).

RESULTS

Based on the literature search strategy, 4531 titles and abstracts were found from the 4 English databases; 102 of them were further searched based on abstracts or full articles, and 38 studies were enrolled. Another 7 studies from Chinese databases were enrolled later. Finally, 45 articles with 6997 participants were included[39-83] (PRISMA Flowchart). The characteristics of the 45 studies are listed in Table 1.

We acquired data relating to 6601 individuals to assess the effect of probiotics plus standard therapy on eradication rates. The pooled eradication rates for the probiotics group and the control group by PPS analysis were 86.23% and 76.60%, respectively. Overall, probiotics plus standard therapy significantly increased the eradication rates (RR = 1.11; 95%CI: 1.08-1.15; P < 0.001; Figure 1). Similarly, in ITT analysis, the pooled eradication rates for the probiotics group and the control group were 82.31% and 72.08%, respectively.

Table 1 Baseline characteristic of studies included in the systematic review and meta-analysis

Study	Patients (*n*)	Age (yr)	Methods of diagnosis	Methods of assessment	Probiotic regimens	Eradication therapy regimens and dosage (mg/d)[1]
Navarro-Rodriguez *et al*[39], 2013	107	Adults	UBT + HA + Giemsa + RUT	UBT + HA + Giemsa + RUT	Lacto + Bifido + Strep	400F + 60La/60M + 1000Te
Ahmad *et al*[40], 2013	66	Children	RUT/HA	HpSA	Lacto + Bifido + Strep	3000A + 360F + 60M
Shavakhi *et al*[41],2013	180	Adults	RUT/HA	UBT	Lacto + Bifido + Strep	2000A + 480B + 1000C + 40M
Kyriakos *et al*[42], 2013	70	Adults	RUT + HA	UBT	Saccha	2000A + 1000C + 40M
Jiang *et al*[43], 2013[2]	80	Adults	RUT + Giemsa	UBT	Bacillus	2000A + 60La + 3000Le
Dajani *et al*[44], 2013[2]	301	Both	UBT/RUT/HA/HpSA	UBT	Bifido	2000A + 1000C/800Me + PPI
Deguchi *et al*[45], 2012	229	Adults	Culture/(HA + RUT)	(UBT + HpSA) + Culture	Lacto	1500A + 400C + 20R
Tolone *et al*[46], 2012	68	Children	UBT + HA	UBT	Lacto + Bifido + Strep	6000A + 1800C + 60M
Mirzaee *et al*[47], 2012[2]	102	Adults	UBT	UBT	NM	2000A + 1000C + 40P
Manfredi *et al*[48], 2012[2]	227	Adults	RUT/HpSA	HpSA	Lacto + Bifido + Strep	2000A + 1000C + 40E + 1000Ti
Du *et al*[49], 2012[2]	234	Adults	UBT/RUT/Giemsa	UBT	Lacto + Bacillus + Strep	2000A + 1000C + 40M
Bekar *et al*[50], 2011	82	Adults	UBT	UBT	Lacto + Bifido	2000A + 1000C + 60La
Yoon *et al*[51], 2011	337	NM	UBT/RUT/HA	UBT	Lacto + Bifido + Strep	2000A + 1000C + 80E
He *et al*[52], 2011	84	Adults	UBT + RUT	UBT + RUT	Lacto + Bifido + Entero	2000A + 1000C + (40-60)R + 1000Ti
Xu *et al*[53], 2010	120	NM	(UBT/RUT) + HA	UBT	Lacto + Bifido + Entero	2000A + (20-40)E + 200F
Yaşar *et al*[54], 2010	76	Adults	HA	UBT	Bifido	2000A + 1000C + 80P
Wen *et al*[55], 2010	200	NM	UBT + RUT	UBT	Lacto + Bifido + Entero	2000A + 40P + 800Ti
Song *et al*[56], 2010[2]	991	Adults	RUT/HA	UBT	Saccha	2000A + 1000C + 40M
Szajewska *et al*[57], 2009	83	Children	2 of (UBT, RUT, HA)	UBT	Lacto	3000A + 1200C + 60M
Hurduc *et al*[58], 2009	90	Children	RUT + HA	RUT + HA	Saccha	3000A + 1800C + 60E/60M
Francavilla *et al*[59], 2008	40	NM	3 of (UBT, RUT, HA, HpSA)	UBT + HpSA	Lacto	2000A + 1000C + 40R + 1000Ti (sequential)
Kim *et al*[60], 2008	347	Adults	UBT/RUT/HA	UBT	Lacto + Bifido + Strep	2000A + 1000C + PPI
Huang *et al*[61], 2008	120	NM	UBT + RUT	UBT	Lacto + Bifido + Entero	1000C + (20-40)E/(20-40)R + 1000Rn
Imase *et al*[62], 20082	19	NM	NM	NM	Clost	1500A + 800C + 60La
Cindoruk *et al*[63], 2007	124	Adults	HA + Giemsa	UBT	Saccha	2000A + 1000C + 60La
Park *et al*[64], 2007	352	Adults	HA	UBT	Bacillus + Strep	2000A + 1000C + 40M
de Bortoli *et al*[65], 2007	206	NM	HA/(UBT + HpSA)	UBT	Lacto + Bifido + Strep	2000A + 1000C + 40E
Sahagún-Flores *et al*[66], 2007	71	Adults	HA	UBT	Lacto	2000A + 1000C + 40M
Lionetti *et al*[67], 2006	40	Children	2 of (UBT, RUT, HA)	UBT	Lacto	3000A + 900C + 60M + 1200Ti (sequential)
Goldman *et al*[68], 2006	65	Children	UBT	UBT	Lacto + Bifido	3000A + 900C + 60M
Sheu *et al*[69], 2006	138	NM	UBT + HA	UBT	Lacto + Bifido + Strep	2000A + 360B + 40M + 1000Me
Ziemniak *et al*[70], 20062	245	Adults	UBT	UBT	Lacto	2000A + 1000C + 80P
Sýkora *et al*[71], 2005	86	Children	2 of (RUT, HA, culture) + HpSA	UBT + HpSA	Lacto	3000A + 900C + (1200-2400)M
Myllyluoma *et al*[72], 2005	47	Adults	UBT + EIA	UBT	Lacto + Bifido + Propionibacterium	2000A + 1000C + 60La
Duman *et al*[73], 2005	389	NM	UBT + HA	NM	Saccha	2000A + 1000C + 40M
Shimbo *et al*[74], 2005	35	NM	RUT + Culture	UBT	Clost	3000A + 800C + 120La
Cao *et al*[75], 2005	128	NM	UBT + RUT	UBT + RUT	Lacto + Bifido + Entero	2000A + 300B + 40M + 800Me
Nista *et al*[76], 2004	106	Adults	UBT	UBT	Bacillus	2000A + 1000C + 40R
Tursi *et al*[77], 2004	70	NM	RUT + HA	UBT	Lacto	3000A + 800B + 40E/40P + 1000Ti
Guo *et al*[78], 2004	97	Adults	RUT + HA	UBT	Clost	1000A + 200F + 40M
Sheu *et al*[79], 2002	160	NM	(RUT/HA) + UBT	UBT/RUT/HA	Lacto + Bifido	2000A + 1000C + 60La
Cremonini *et al*[80], 2002[2]	85	Adults	UBT	UBT	Lacto	1000C + 40R + 1000Ti
Armuzzi *et al*[81], 2001[a]	60	Adults	UBT + EIA	UBT	Lacto	1000C + 40R + 1000Ti
Armuzzi *et al*[82], 2001[b]	120	Adults	UBT + EIA	UBT	Lacto	1000C + 80P + 1000Ti
Canducci *et al*[83], 2000	120	NM	UBT + HA	UBT + HA	Lacto	1500A + 750C + 40R

[1]"400F + 60L + 1000Te" means "Furazolidon 400 mg/d, lansoprazole 60 mg/d, and tetracycline 1000 mg/d". Patient's weight were assumed as 60 kg to calculate the exact dosage if only the dosage per kg were available in the article; [2]These articles were designed with multiple arms, but only relevant groups were combined and included in this meta-analysis. UBT: Urea breath test; RUT: Rapid urease test; HA: Histological assessment; Giemsa: Giemsa staining; HpSA: *H. pylori* stool antigen test; EIA: Enzyme-linked immunosorbent Assay; Culture: Culture test; Lacto: *Lactobacillus*; Bifido: *Bifidobacterium*; Strep: *Streptococcus*; Saccha: *Saccharomyces*; Entero: *Enterococcus*; Clost: *Clostridium*; A: Amoxicillin; B: Bismuth subcitrate; C: Clarithromycin; E: Esomeprazole; F: Furazolidon; La: Lansoprazole; Le: Levofloxacin; M: omeprazole; Me: Metronidazole; P: Pantoprazole; PPI: Proton pump inhibitor; R: Rabeprazole; Rn: Ornidazole; Ti: Tinidazole; Te: Tetracyline; NM: Not mentioned.

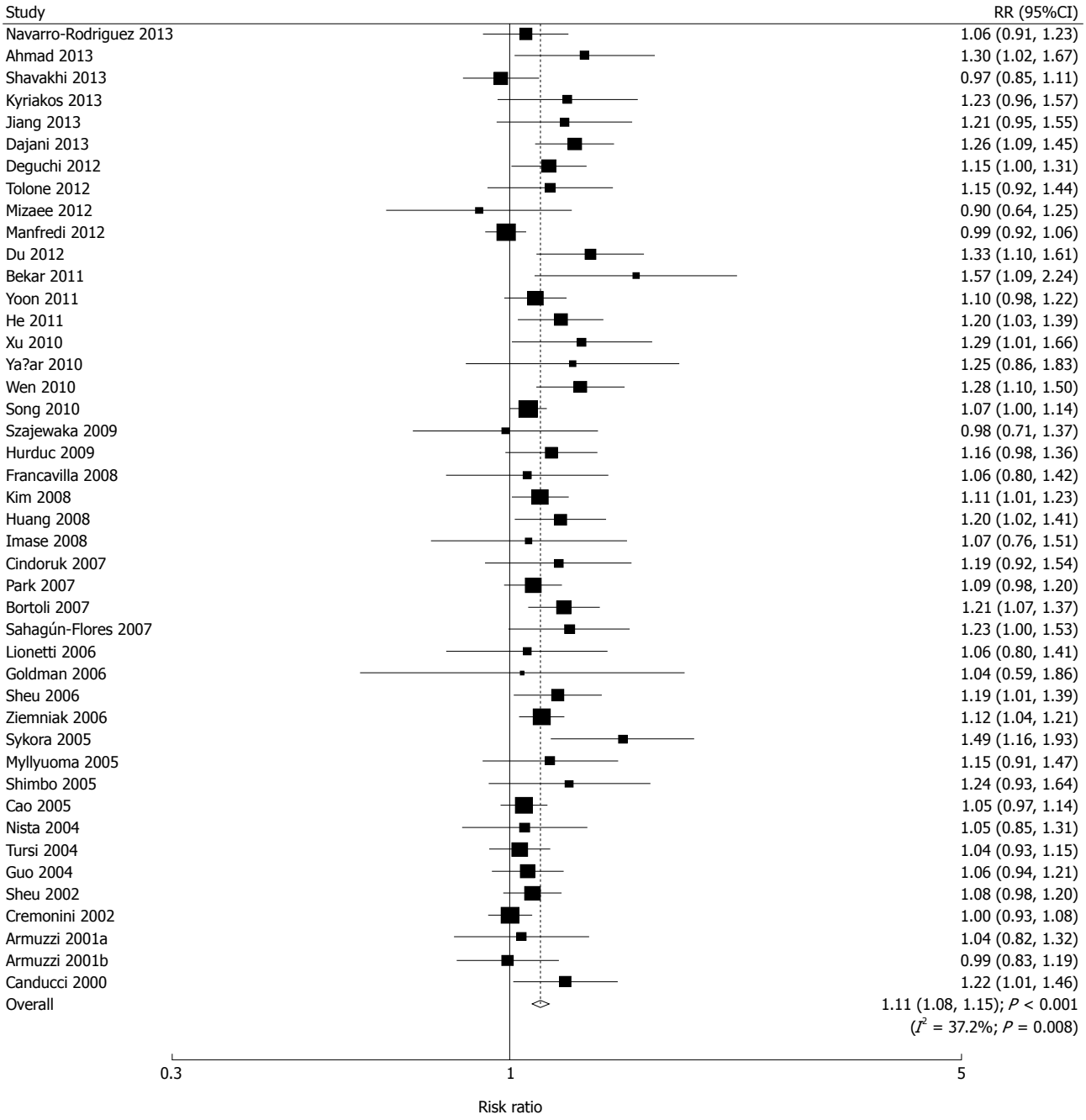

Figure 1 Effects of probiotics plus standard therapy on eradication rate by per-protocol set analysis compared with standard therapy alone. CI: Confidence interval.

Probiotics plus standard therapy significantly increased the eradication rates (RR = 1.13; 95%CI: 1.10-1.16; $P < 0.001$; Figure 2). Although there was significant heterogeneity across the trials by PPS analysis, a sensitivity analysis was conducted and the results suggested that the data were not affected by the sequential exclusion of any particular trial from the pooled analysis.

We acquired data on 5312 individuals to assess the effect of probiotics plus standard therapy on adverse events, and reported 1499 adverse events. We noted that probiotics plus standard therapy significantly reduced the risk of adverse events (RR = 0.59; 95%CI: 0.48-0.71; $P < 0.001$; Figure 3). Substantial heterogeneity was observed in the magnitude of the effect across the trials (I^2 = 81.6%; $P < 0.001$). However, following sequential exclusion of each trial from the pooled analysis, we found that the outcome was not affected by the exclusion of any specific trial. The incidence rates were 21.44% and 36.27% in the probiotics group and the control group, respectively, which demonstrated a favorable effect of probiotics on the reduction of adverse events during *H. pylori* eradication therapy. As presented in Table 2, the combined effects of probiotics were statistically significant for all the listed adverse events, which clarified the protective

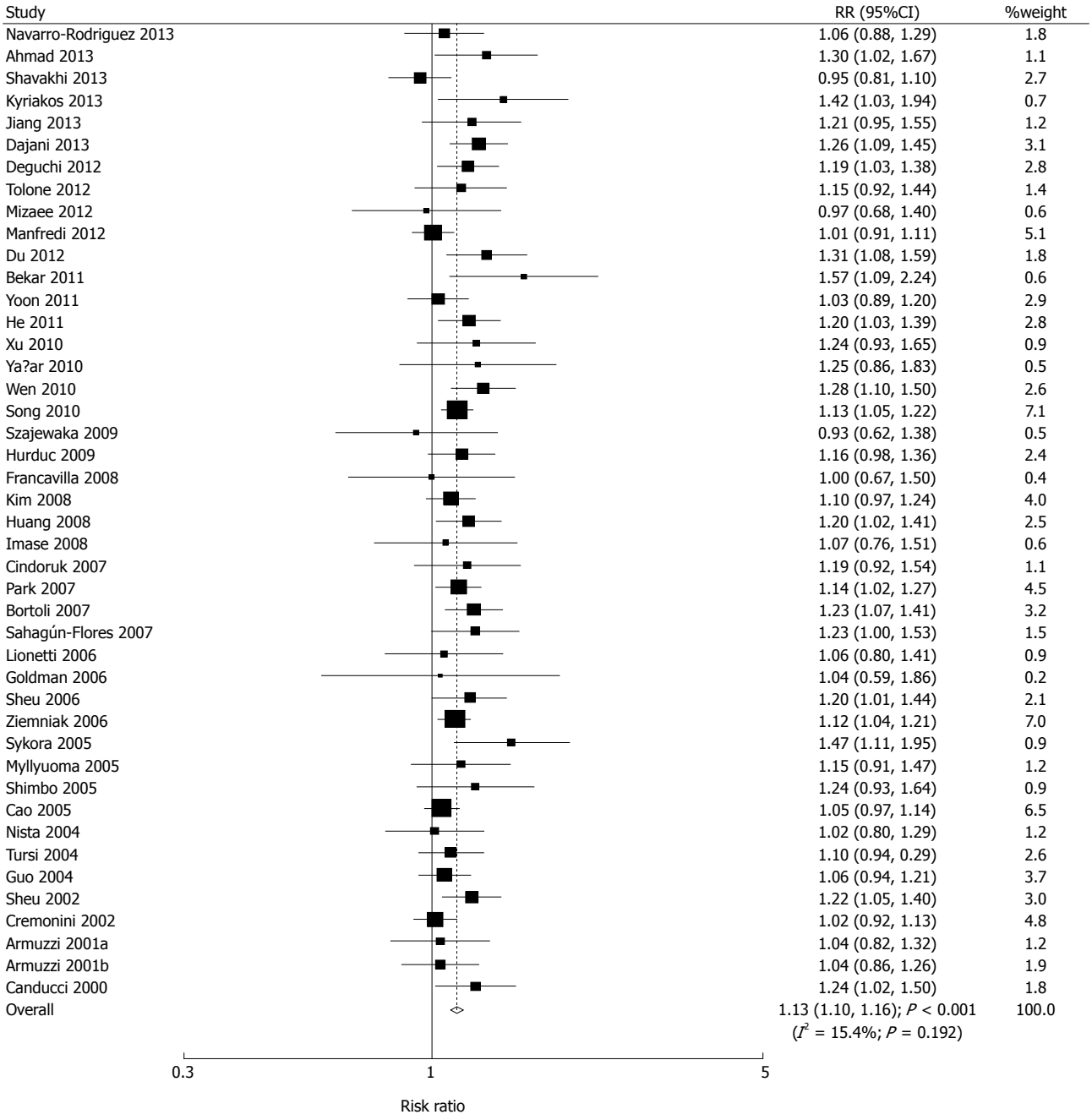

Figure 2 Effects of probiotics plus standard therapy on eradication rate by intention-to-treat analysis compared with standard therapy alone.

effects of probiotics against these adverse events.

We acquired data on 4033 individuals to assess the effect of probiotics plus standard therapy on compliance, and reported 132 events of non-compliance. The inclusion of probiotics in the *H. pylori* eradication treatment regimen did not improve patient compliance according to the results of the pooled analysis (RR = 0.98; 95%CI: 0.68-1.39; *P* = 0.889; without evidence of heterogeneity; Figure 4).

The studies were divided into subgroups based on the age of the patients, single or multiple probiotic strains, dosage of probiotics, duration of probiotics intake, duration of standard eradication therapy, duration between the end of the therapy and assessment, probiotic strains and types of eradication therapy (Table 3). Overall, we noted that *Clostridium* had no significant effect on the eradication rate, and furthermore, probiotics did not affect the eradication rate if patients received a second-line standard therapy. Subgroup analyses based on other factors were associated with a statistically significant increase in the eradication rate.

A review of funnel plots did not exclude the potential for publication bias for the eradication rate, adverse events, and patient compliance. The Egger test[37] results showed potential publication bias for the eradication rate, adverse events, and patient compliance. The Begg test[38] results showed potential

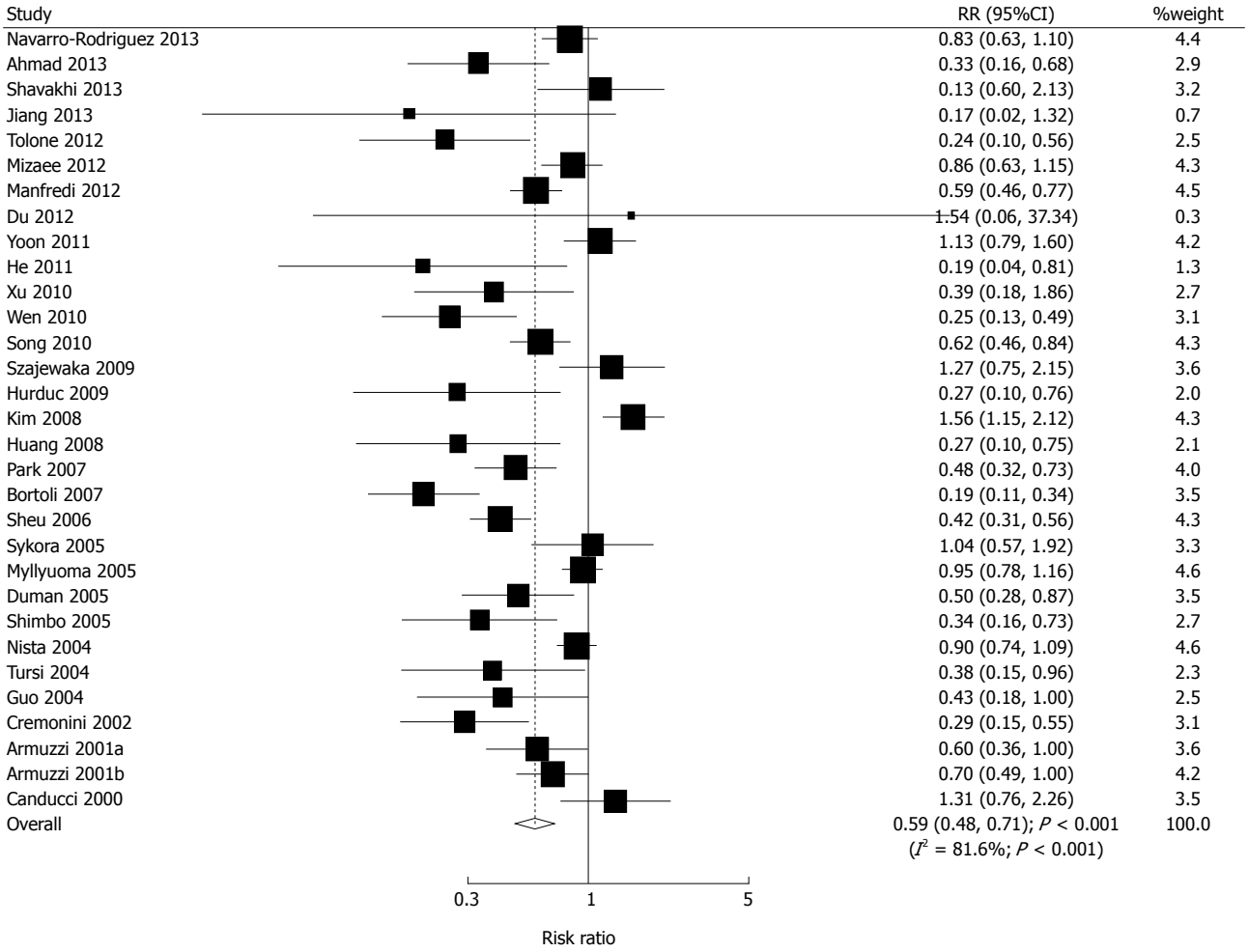

Figure 3 Effects of probiotics plus standard therapy on total adverse events compared with standard therapy alone.

publication bias for patient compliance. The conclusions did not change after adjustment for publication bias by using the trim and fill method[84].

DISCUSSION

Through systematic review and meta-analysis using the results from 45 studies as solid supporting evidence, the effectiveness of the use of probiotics in *H. pylori* eradication therapy is based on 3 criteria: eradication rate, adverse events, and patient compliance. Our results suggest that additional probiotic supplementation significantly increases the eradication rate, and reduces adverse events. However, there is no significant effect on patient compliance.

The eradication rate of *H. pylori* using standard therapy plus probiotics has been significantly improved by about 13% compared with standard therapy alone. The value of RR is small because both the probiotics group and the control group have a relatively large eradication rate. Therefore, an improved eradication rate is the best indicator of the effectiveness of probiotics supplementation. Hence, the addition of probiotics to standard *H. pylori* eradication therapy improves the *H. pylori* eradication success rate within a population.

The duration of antibiotic treatment, different regimens of standard therapy, patient age, dosage of probiotics, different strains of probiotics[4,40,85-87], and different types of standard therapy have been reported to potentially influence the eradication outcome. In our study, there was a statistically significant increase in eradication rates in nearly all the subgroups when these factors were also taken into consideration. These subgroups showed similar outcomes with strong statistical significance, which may be influenced by a large sample size. We consider that probiotics had a comparable effect on the *H. pylori* eradication rate in all these subgroups of more than 500 patients. More studies are needed to assess the outcome in groups with fewer patients, such as groups of children and patients who received second-line therapy.

In addition to the subgroups mentioned above, antibiotic resistance can create a significant problem in *H. pylori* eradication therapy because it can become a major cause of initial eradication failure[19,88-90]. The prevalence of clarithromycin resistance cases treated with clarithromycin-containing triple therapy was reported to be 10%-30%[19,91]. With an increasing number of patients infected with clarithromycin and/

Table 2 Effect of probiotics plus standard therapy *vs* standard therapy on adverse events

Adverse Event	Trials (*n*)	Participants (*n*)	Probiotics group, %	Control group	RR and 95%CI	*P* value	Heterogeneity (*P* value)
Diarrhea	26	4935	5.71%	13.72%	0.41 (0.30-0.57)	< 0.001	58% ($P < 0.001$)
Nausea/vomiting	23	4067	6.95%	12.83%	0.60 (0.48-0.76)	< 0.001	23% ($P = 0.16$)
Epigastric discomfort	8	1806	6.09%	14.13%	0.57 (0.44-0.74)	< 0.001	0% ($P = 0.60$)
Abdominal bloating	13	1516	10.82%	14.51%	0.70 (0.55-0.90)	0.005	0% ($P = 0.53$)
Abdominal pain	10	1373	8.40%	13.05%	0.54 (0.35-0.83)	0.005	31% ($P = 0.16$)
Constipation	13	2021	3.96%	6.73%	0.55 (0.37-0.81)	0.002	0% ($P = 0.77$)
Taste disturbance	19	3611	11.79%	18.76%	0.63 (0.48-0.83)	< 0.001	73% ($P < 0.001$)

RR: Risk ratio.

Table 3 Subgroup analyses comparing the effect of probiotics plus standard therapy *vs* standard therapy on eradication rate based on intention-to-treat

Subgroups	Studies (*n*)	Patients (*n*)	Probiotics group	Control group	RR and 95%CI	*P* value	*P* value for Q statistics
Age							
Adults	23	4116	81.86%	73.23%	1.12 (1.09-1.16)	< 0.001	0.224
Children	7	498	76.89%	64.78%	1.19 (1.07-1.32)	0.002	0.535
Probiotic strains							
Multiple	22	3598	83.29%	73.73%	1.12 (1.08-1.17)	< 0.001	0.046
Single	21	2908	81.60%	70.60%	1.16 (1.11-1.21)	< 0.001	0.724
Dosage of probiotics (CFU/d)							
$\geqslant 5 \times 10^9$	15	2470	82.84%	73.06%	1.13 (1.08-1.18)	< 0.001	0.571
$< 5 \times 10^9$	21	3283	81.49%	70.69%	1.14 (1.09-1.20)	< 0.001	0.046
Duration of probiotic intake							
⩾ 15 d	17	3411	81.15%	71.35%	1.14 (1.10-1.18)	< 0.001	0.976
< 15 d	24	2585	82.30%	71.28%	1.12 (1.06-1.18)	< 0.001	0.022
Duration of standard therapy							
> 7 d	17	2050	81.79%	74.32%	1.11 (1.06-1.17)	< 0.001	0.167
= 7 d	27	4558	82.39%	70.97%	1.16 (1.12-1.20)	< 0.001	0.502
Duration between therapy ending and assessment							
> 4 wk	20	2520	83.86%	73.36%	1.16 (1.11-1.21)	< 0.001	0.282
= 4 wk	22	3984	80.78%	70.91%	1.14 (1.10-1.18)	< 0.001	0.358
Probiotic (containing the following strains)							
Lactobacillus	31	4165	82.67%	73.05%	1.14 (1.10-1.18)	< 0.001	0.088
Bifidobacterium	20	3059	82.66%	71.69%	1.14 (1.10-1.19)	< 0.001	0.058
Streptococcus	11	2262	81.47%	72.65%	1.11 (1.06-1.17)	< 0.001	0.085
Saccharomyces	4	1275	81.14%	69.94%	1.15 (1.08-1.24)	< 0.001	0.594
Bacillus	4	772	80.71%	69.74%	1.17 (1.08-1.28)	< 0.001	0.408
Enterococcus	5	652	87.30%	73.29%	1.17 (1.06-1.30)	0.003	0.046
Clostridium	3	151	93.06%	86.08%	1.08 (0.97-1.21)	0.164	0.456
Therapy regimens							
First-line	16	3474	81.02%	71.00%	1.13 (1.08-1.17)	< 0.001	0.260
Second-line	3	435	88.63%	81.11%	1.08 (1.00-1.17)	0.058	0.185
Not specified	25	2699	82.67%	72.25%	1.18 (1.13-1.23)	< 0.001	0.268

or fluoroquinolone resistant *H. pylori*[92], quadruple therapy with bismuth colloid or sequential therapy has been suggested[92,93]. Probiotic supplementation in this population has rarely been studied before. In this meta-analysis, the studies focusing on antibiotic resistant *H. pylori* were far fewer than expected. Therefore, we have not included a thorough discussion on the topic of antibiotic-resistant strains here. The results from studies conducted so far seem promising and worth pursuing further through the initiation of studies using a larger population of patients.

In addition to improving the eradication rate of infectious organisms, the administration of probiotics can also reduce the incidence of adverse events by preventing or reducing pathogenic adherence, inducing the production of stomach acid, hydrogen peroxide, and bacteriocins to antagonize pathogen growth, and encourage the formation of normal balanced flora[68]. In our study, all the reported adverse events had RRs < 1, which indicated that the use of probiotics effectively protected the gut flora during *H. pylori* eradication. The overall incidence of adverse events was reduced by approximately 41% in the probiotics group. There are also studies confirming that the administration of probiotics can prevent diarrhea[94], abdominal bloating[95], and constipation[96-98].

Since probiotics are effective in the prevention of adverse events, they were also expected to promote patient compliance[22,28]. Non-compliance may drastically affect the *H. pylori* eradication success rate[2]; this

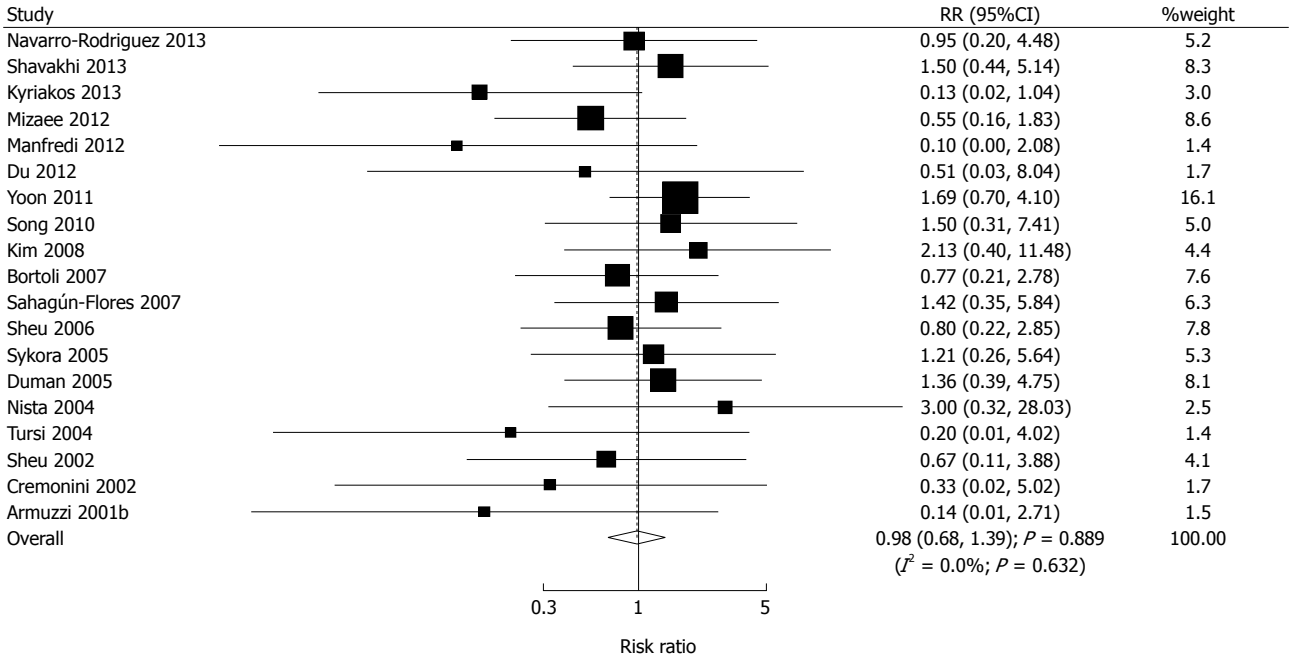

Figure 4 Effects of probiotics plus standard therapy on patients compliance compared with standard therapy alone.

aspect has seldom been studied. Manfredi *et al*[48] reported that the improvement in patient compliance in a study administering lactoferrin and probiotics to treat *H. pylori* infection was not statistically significant. Most studies had no dropouts or minimal losses to follow-up. The non-compliance rate was low and may relate to intrinsic personality traits, which can only be studied using a meta-analysis approach. Unexpectedly, there was no evidence showing a lower rate of non-compliance in the probiotics group. The RR showed a slight tendency for improved patient compliance, but this did not have any practical benefit on eradication success.

In clinical practice, the overall benefit of administering prophylactic probiotics to *H. pylori*-infected patients is not only related to the eradication success or reduced adverse events, but also to medical expenses; the influence of the latter factor in *H. pylori* eradication is still unclear. As *H. pylori* infection is more prevalent in developing countries or areas of lower socioeconomic status[4,99], the cost-effectiveness of taking probiotics may be subtle and difficult to evaluate. Tursi *et al*[77] reported that the extra cost of probiotics may be a limiting factor preventing widespread use. Some researchers report that probiotics were economical[100], but more evidence is required to support this statement.

This study may have the following limitations: (1) some publications may have been neglected to be added to the study because they were not included in any of the databases that were searched, leading to publication bias. Some publications that were unavailable were requested from the corresponding author in order to include their data in this study but only a few requests were answered; (2) there is a limited number of papers that include some subgroups, such as patients infected with antibiotic resistant *H. pylori* who were treated with probiotics. Analysis of these subgroups was not conducted; (3) there may be bias introduced by including studies with multiple arms, and routine means of measuring heterogeneity and publication bias; and (4) probiotics were analyzed by strains instead of by preparations that are available in clinical practice. Furthermore, the eradication therapies were divided into first-line or second-line therapies instead of into specific regimens to account for study number limitations. The correlation of probiotics and standard therapy was not included, and may contribute important information to this study.

In conclusion, the use of probiotics to supplement standard therapy in patients infected with *H. pylori* increased the eradication rate of the organism by about 13% and decreased the overall rate of adverse events by approximately 41%, independent of patient age, genera or dosage of probiotics, time of standard therapy or assessment, and therapy regimen. Unexpectedly, the patient compliance rate did not improve with the addition of probiotics to the therapeutic regimen. An economic evaluation is required to establish the cost-effectiveness of the addition of probiotics to *H. pylori* eradication therapy, and to determine whether the combination of probiotics with a standard therapy would be beneficial in clinical practice.

COMMENTS

Background

Certain studies have reported inconsistent results regarding the efficacy, safety and patient compliance of the use of probiotics in combination with a standard therapy when compared with standard therapy alone for the eradication of

Helicobacter pylori (*H. pylori*).

Research frontiers

The benefits of probiotics supplementation in the treatment of antibiotic resistant *H. pylori* are still unclear due to the lack of supporting evidence. We therefore conducted a meta-analysis to summarize the evidence from randomized controlled trials (RCTs) regarding the effect of probiotics by using a meta-analytic approach.

Innovations and breakthroughs

Several meta-analyses have assessed the efficacy and safety of probiotics plus standard therapy, and most of these studies have investigated these effects with respect to specific strains or certain formulations of probiotics. In this study, we performed a meta-analysis of available RCTs to evaluate the effect of probiotics on *H. pylori* eradication, adverse events, and patient compliance.

Applications

Probiotics supplementing standard therapy in patients infected with *H. pylori* increased the eradication rate and decreased the overall rate of adverse events, independent of patient age, genera or dosage of probiotics, time of standard therapy or assessment, and therapy regimen. This study may represent a future strategy in the treatment of patients with *H. pylori* infection.

Peer-review

In this meta-analysis the articles chosen are sufficient by number and the distribution is worldwide. Addition of probiotics may be an option for low eradication regions. Effect of these live but nonpathogenic bacteria on eradication therapy of *H. pylori* may be by reducing antibiotic related side effects and/or possible antibacterial properties. The studies relating yo cost-effectiveness of this supplementation should be assessed before clinical usage. Also some other measures increasing the compliance of the patient should be taken into account, as appropriate region-based regimens informing the patient.

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