Complementary Therapies in Medicine 43 (2019) 36–43

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The effect of synbiotics in improving *Helicobacter pylori* eradication: A systematic review and meta-analysis

Makan Pourmasoumi[a,b], Ameneh Najafgholizadeh[a], Amir Hadi[c], Fariborz Mansour-Ghanaei[a,b,*], Farahnaz Joukar[a,b,**]

[a] Gastrointestinal & Liver Diseases Research Center (GLDRC), Guilan University of Medical Sciences (GUMS), Rasht, Iran
[b] Caspian Digestive Diseases Research Center, Guilan University of Medical Sciences (GUMS), Rasht, Iran
[c] Halal Research Center of IRI, FDA, Tehran, Iran

ARTICLE INFO

Keywords:
Synbiotics
Beneficial microbes
Helicobacter pylori
Meta-analysis

ABSTRACT

Background: *Helicobacter pylori* is a common human infection, presenting in half of the world's population. The failure of the *Helicobacter pylori* eradication rate necessitates the assessment of new options. The aim of the present meta-analysis was therefore to assess the role of synbiotics in *Helicobacter pylori* eradication therapy.
Methods: A comprehensive literature search was conducted using PubMed, Google Scholar, Scopus, and Web of Knowledge up to June 2018 to identify all randomized controlled trials assessing the effect of synbiotics on the treatment of *Helicobacter pylori.* A random-effects model was applied for pooling analysis to compensate for the heterogeneity of included studies. The Cochrane Risk of Bias Tool was applied to assess potential bias risks.
Results: A total of 6 randomized controlled trials were found which assessed the effect of synbiotics on *Helicobacter pylori* eradication rate. The pooled effect size of the intention-to-treat showed that synbiotics can improve eradication rate (RR: 1.28; 95% CI: 1.15–1.43; I^2 = 0%). Also, common adverse events resulting from antibiotics therapy were significantly reduced by adding synbiotics to conventional antibiotics treatments (RR: 0.47; 95% CI: 0.25–0.90; I^2 = 36%). However, no difference in eradication rate was observed from per-protocol treatment between intervention and control groups (RR: 0.90; 95% CI: 0.69–1.16; I^2 = 88%).
Conclusion: The present systematic review and meta-analysis suggested synbiotics might improve *Helicobacter pylori* eradication rates, and reduce adverse effects. However, these findings assessed a low number of studies, and further high-quality studies are needed to confirm these results.

1. Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic and spiral bacterium that affects more than half of the world's population.[1] Infection with *H. pylori* is associated with a variety of clinical presentations, from asymptomatic to serious diseases.[2] *H. pylori* colonization can lead to the development of several upper gastrointestinal conditions, including chronic gastritis, increased risks of peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.[3,4] Due to complications in *H. pylori* management, its eradication from the gastric mucosa is required. Today, a combination of antibiotics is a common treatment for *H. pylori*. Although several pharmacological therapeutic methods have been proposed, the ideal scheme to manage *H. pylori* remains unresolved.[5] A standard triple therapy, based on a proton pump inhibitor, amoxicillin and clarithromycin, was the first-line treatment until a few years ago.[6] Due to mutations of the *H. pylori* genome and the consequent spread of antibiotic resistance,[7] the success of triple therapy in *H. pylori* eradication has declined over time, and alternative first-line regimens, including sequential, concomitant, quadruple with and without bismuth have been proposed.[8] However, the current guidelines still have several limitations, and cannot be considered ideal treatments.[9] The main problem in *H. pylori* treatment with standard antibiotic regimens is related to low patient compliance, due to antibiotic-associated adverse events such as diarrhea, nausea, vomiting and abdominal pain.[10] In this regard, many researchers are aiming to find a new strategy which can improve the eradication rate, as well as alleviate the frequency of adverse effects.

Synbiotics are defined as combination of probiotics ("live microorganisms that, when administered in adequate amounts, confer a health benefit on the host")[11] and prebiotics ("indigestible foods that

* Corresponding author at: Gastrointestinal and Liver Disease Research Center, Razi Hospital, Sardar-e-Jangal Avenue, Guilan, PO Box: 95655 - 41448, Rasht, Iran.
** Corresponding author at: Caspian Digestive Diseases Research Center, Guilan University of Medical Sciences (GUMS), Rasht, PO Box: 95655 - 41448, Iran.
E-mail addresses: ghanaie@yahoo.com, ghanaei@gums.ac.ir (F. Mansour-Ghanaei), farajov@gmail.com (F. Joukar).

https://doi.org/10.1016/j.ctim.2019.01.005
Received 16 October 2018; Received in revised form 6 January 2019; Accepted 8 January 2019
Available online 09 January 2019

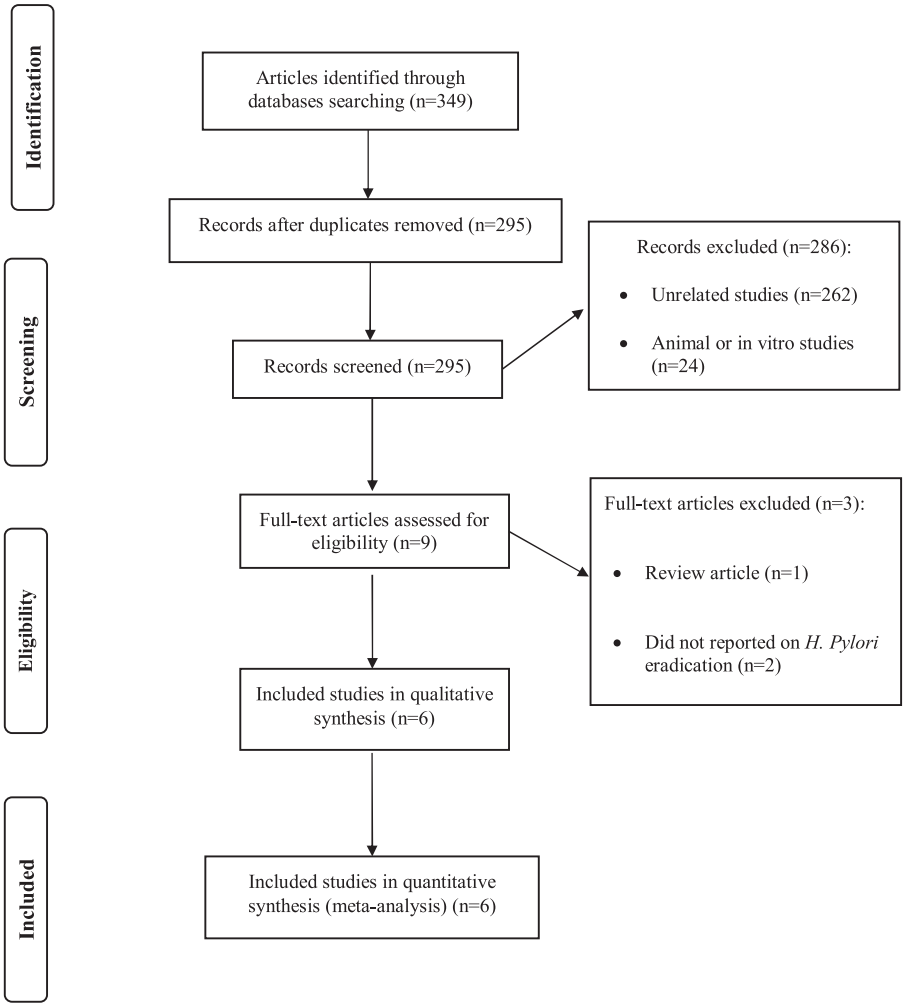

Fig. 1. Flow chart of the process of the study selection.

lead to enhancement of probiotic bacteria colonization in the gut"),[12] which can act synergistically. Several documents have shown that some probiotic lactobacilli have anti-*H. pylori* activity and inhibit *H. pylori* colonization in gastric cell lines.[13,14] In this line, the role of probiotics alone, and in addition to conventional pharmacological therapy, has been well-documented.[15–17] As synbiotics and probiotics are different in nature, and can lead to different results in health outcomes, researchers have also investigated the possible effect of synbiotic addition to *H. pylori* eradication treatments.[18–20] However, these results have been controversial, and remain inconclusive.[21–23] Therefore, the present meta-analysis was conducted to summarize the clinical evidence and to assess the role of synbiotics in *H. pylori* eradication therapy.

2. Methods

To improve the quality of the meta-analyses, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24] was followed as a standard guideline.

2.1. Search strategy

A comprehensive literature search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://scholar.google.com), Scopus (http://www.scopus.com) and Web of Knowledge (http://www.webofscience.com) was carried out up to June 2018 to identify randomized clinical trials (RCTs) evaluating the effects of synbiotics supplementation on *H. pylori* eradication. The following keywords in combination with the wild-card '*' and Medical Subject Heading (MeSH) terms were used: 'synbiotic', 'symbiotic', '*H. pylori*', 'Helicobacter pylori', and '*Campylobacter* Pylori'. No language restrictions were imposed. Additionally, the reference lists of relevant publications were also checked manually to detect extra eligible studies that might have been missed.

2.2. Study selection

Two reviewers (AH and MP) independently assessed publications by title/abstract to select studies which were potentially relevant. Next, the full-texts were screened by two reviewers in blinded fashion to detect eligible papers. Any disagreement was resolved by discussion. All RCTs examining the effect of synbiotics on *H. pylori* eradication were included. Studies were excluded if participants had major gastrointestinal surgery or did not describe study inclusion/exclusion criteria.

2.3. Data extraction and risk of bias assessment

Eligible studies were reviewed by two researchers (AN and AH) independently, and the following data were abstracted: first author's last name, year of publication, study location, sample size, mean age of subjects, diagnostic and recheck method, duration of study, comparison groups, type of intervention and main outcome. Any disagreement was resolved by a third author (MP). Furthermore, unclear information in the included studies was queried by email with the relevant corresponding authors.

The Cochrane Risk of Bias Tool was applied to assess potential risks of bias in the included RCTs.[25] This scale is based on several items to assess the adequacy of random sequence generation, allocation concealment, and blinding, as well as detecting incomplete outcome data, selective outcome reporting, and other potential sources of bias. Based on the recommendations of the Cochrane Handbook, the judgment of each item appears categorized as "Low", "High" and "Unclear" risk of bias.

2.4. Statistical analysis

The meta-analysis was performed by using the Cochrane Program Review Manager Version 5.3 (The Cochrane Collaboration, 2011, The Nordic Cochrane Centre, Copenhagen) and STATA version 11. In all included studies, relative risk (RR) and 95% CI was calculated for the incidence of *H. pylori* eradication and medication side effects. The random-effects model was applied for pooling analysis to compensate for the heterogeneity of included studies.[25,26] Inter-study heterogeneity was explored quantitatively by using Cochran's Q and I^2 statistics. In this regard, $I^2 \geq 50\%$ or $P < 0.05$ was considered as indicating the presence of significant heterogeneity.[27] Number needed-to-treat (NNT) was also assessed, on the basis of the pooled risk ratio and the baseline risk.[28] Potential publication bias was detected using Egger's weighted regression test and Begg's rank-correlation methods.[29,30] Statistical significance was accepted at the level of P-values < 0.05.

3. Results

The study selection process and the reason for excluding studies at each step are reported in detail in Fig. 1. The comprehensive literature search identified unduplicated 295 records, of which 286 publications were excluded due to irrelevant title/abstract. 9 studies remained for full-text assessment. Of those, 3 RTCs were discarded because synbiotics were not reported in terms of *H. pylori* eradication, and/or they were review articles. Finally, 6 RTCs were deemed eligible and included in quantitative analysis.

4. Studies' characteristics

Table 1 shows the main characteristics of the included RCTs. In brief, data were pooled from 6 studies comprising 525 *H. Pylori*-infected patients. 3 studies enrolled patients under 18 years old, and rest of them included participants aged between 18 and 85. All studies had parallel design and recruited both genders as subjects. 4 RTCs [18,19,22,23] reported outcomes as both per-protocol (PP) and intention-to-treat (ITT), whilst one study[21] analyzed data just as PP. Also, one study[20] did not have any drop-out rate, and was included as ITT. 4 RCTs[18,20,22,23] provided information for adverse effects in each active and control group. In 4 studies,[18,20,22,23] participants in the intervention group were given triple therapy plus synbiotics, one study[19] administered quadruple therapy plus synbiotics, and one RTC[21] supplied solely synbiotics in the active group. Endoscopy and biopsies, as well as the urea breath test, were the most frequent tests for confirmation of *H. pylori* infection at the beginning of the study, and for re-checking infection at the end of the study, respectively. The studies were conducted in Turkey [18,20,22,23] Chile[21] and Iran,[19] and published between 2013 and 2017.

5. Risk of bias assessment

Random sequence generation information was appropriately referenced in all included studies. However, only 2[21,23] provided sufficient data for allocation concealment. 2 studies[19,23] described the blinding methodology. All RCTs had low risk of bias in attrition and reporting bias items. The reviewers' judgements regarding each Cochrane risk of bias item are presented in Supplement 1.

6. Systematic review

Shafaghi et al[19] did not provide overall adverse effects results for quadruple therapy, and presented data as a systematic review. This study demonstrated that except for anxiety, which was lower in quadruple plus synbiotics, adding synbiotics did not lead to any changes in quadruple therapy side effects.

7. Effects of synbiotics on *H. pylori* eradication rates (PP treatment)

Risk ratios regarding the effects of synbiotic supplementation on *H. pylori* eradication rates were available for PP analysis in 5 trials. Pooled RR revealed no differences in eradication rates between intervention and control groups (RR: 0.90; 95% CI: 0.69–1.16; $I^2 = 88\%$) (Fig. 2A). When studies were categorized based on type of intervention, synbiotic supplementation did not show significant improvement in *H. pylori* eradication when added to triple therapy (RR: 1.04; 95% CI: 0.88–1.23) or quadruple therapy (RR: 0.93; 95% CI: 0.83–1.04). However, in a subgroup in which synbiotics were solely intervened in comparison with triple therapy, the eradication rate was significantly lower in the intervention than the control group (RR: 0.18; 95% CI: 0.08–0.38). In addition, no difference was noted for the outcomes by subgroup analysis according to age of participants and type of antibiotic regimen in the comparison group (Table 2).

8. Effects of Synbiotics on *H. pylori* eradication rates (ITT)

The pooled ITT eradication rates suggested synbiotics improve *H. pylori* eradication rates, in comparison with control groups, with no inter-study heterogeneity (RR: 1.28; 95% CI: 1.15–1.43; $I^2 = 0\%$) with a NNT of 5.2 (Fig. 2B). Subgroup analysis by mean patient age and type of antibiotic regimen did not reveal any significant differences in elevating eradication rates [≥18 years old (RR: 1.30; 95% CI: 1.13, 1.50) vs < 18 years old (RR: 1.25; 95% CI: 1.05, 1.48), and in terms of quadruple therapy (RR: 1.46; 95% CI: 1.12, 1.89) vs triple therapy (RR: 1.25; 95% CI: 1.11, 1.40)]. (Table 2).

9. Adverse events

Data regarding the overall incidence of adverse events were reported in 4 RCTs. The incidence of adverse events was significantly lower in the synbiotic supplementation plus triple therapy than in the control group (RR: 0.47; 95% CI: 0.25–0.90). No significant inter-study heterogeneity was detected ($I^2 = 36\%$; $P = 0.20$) (Fig. 2C). Subgroup analysis based on mean age did not indicate any significant difference in adverse event incidence between intervention and control groups in both < 18 (RR: 0.97; 95% CI: 0.14–6.71) and ≥18 (RR: 0.43; 95% CI: 0.18–1.04) subgroups (Table 2).

10. Publication bias

No evidence of publication bias was observed by Egger's linear regression and Begg's rank correlation test in estimating the effects of synbiotics on *H. pylori* eradication as PP (Begg's test P = 0.32; Egger's test P = 0.73), ITT (Begg's test P = 0.32; Egger's test P = 0.17), and in terms of assessing adverse events synbiotic addition to treatment with antibiotics (Begg's test P = 0.49; Egger's test P = 0.22).

11. Discussion

To the best of the authors' knowledge, the present systematic review and meta-analysis is the first study assessing the effect of synbiotics on *H. pylori* eradication. These findings indicate that the addition of synbiotics supplementation to antibiotic regimens might increase *H. pylori* eradication rate and reduce adverse events resulting from antibiotic

Table 1
Main characteristics of the studies included in the meta-analysis.

First author (publication year)	Country	Number and gender (M/F)	Mean age	Clinical Trial design /randomized/ Blinding	Duration (Days)	Initial methods for conformation H. pylori infection	Methods for rechecking H. pylori	Antibiotic and drug treatments	Comparison group	Intervention group
Ustundag et al (2017)	Turkey	Intervention:35 Control :34 Both gender	Range: 6–16 Intervention: 11.2 ± 2.9 Control: 11.2 ± 3.1	Parallel/ Randomized /Double blind	14	Endoscopy and biopsies	Urea breath test	Amoxicillin, Clarithromycin, Omeprazole	Triple therapy	Triple therapy Plus synbiotic (*Bifidobacterium lactis* B94 (5×10^9 CFU/dose) plus 900 mg of inulin)
Şirvan et al (2017)	Turkey	Intervention :50 Control :50 Both gender	Range: 5-17 Intervention: 12.7 ± 3.3 Control: 11.4 ± 3.5	Parallel/ Randomized / –	14	Endoscopy and biopsies	Fecal *H. pylori* test	Amoxicillin, Clarithromycin, Lansoprazole	Triple therapy	Triple therapy plus synbiotic (B. lactis sachet)
Gotteland et al (2005)	Chile	Intervention: 51 Control: 45 Both gender	Range: 6–16 Intervention: 8.3 ± 1.5 Control: 8.4 ± 1.7	Parallel/ Randomized/ –	56	Urea breath test	Urea breath test	Lansoprazole, Amoxicillin, Clarythromycin	Triple therapy	Synbiotic (Sachet 250 mg of lyophilized *Saccharomyces boulardii* 5 g inulin)
Shafaghi et al (2016)	Iran	Intervention :38 Control :38 Both gender	Range: - Intervention: 43.75 ± 13.32 Control: 43.35 ± 12.29	Parallel Randomized / Double blind	14	Biopsy specimen and rapid urease test	Urea breath test	Bismuth Subcitrate, Amoxicillin, Clarithromycin, Omeprazole	Quadruple therapy plus placebo	Quadruple therapy plus synbiotic (Lactobacillus casei, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, Lactobacillus acidophilus, *Bifidobacterium longum*, *Lactobacillus bulgaricus*, (TVC: 200 million CFU TVC: 2×10^8 CFU))
Islek et al (2015)	Turkey	Intervention :47 Control :46 Both gender	Range: 18-85	Parallel/ Randomized/ –	17	–	–	Lansoprazole, Amoxicillin, Clarithromycin	Triple therapy plus placebo	Triple therapy plus synbiotic (B. lactis B94 (5 × 109 CFU/dose) plus inulin (900 mg)) twice daily
Şahin et al[18]	Turkey	Intervention :43 Control :48 Both gender	Range: 18-85	Parallel/ Randomized/ –	14	Endoscopic biopsy	Urea breath test	Rabeprozol, Amoksisilin, Clarithromycin	Triple therapy	Triple therapy plus synbiotic twice daily

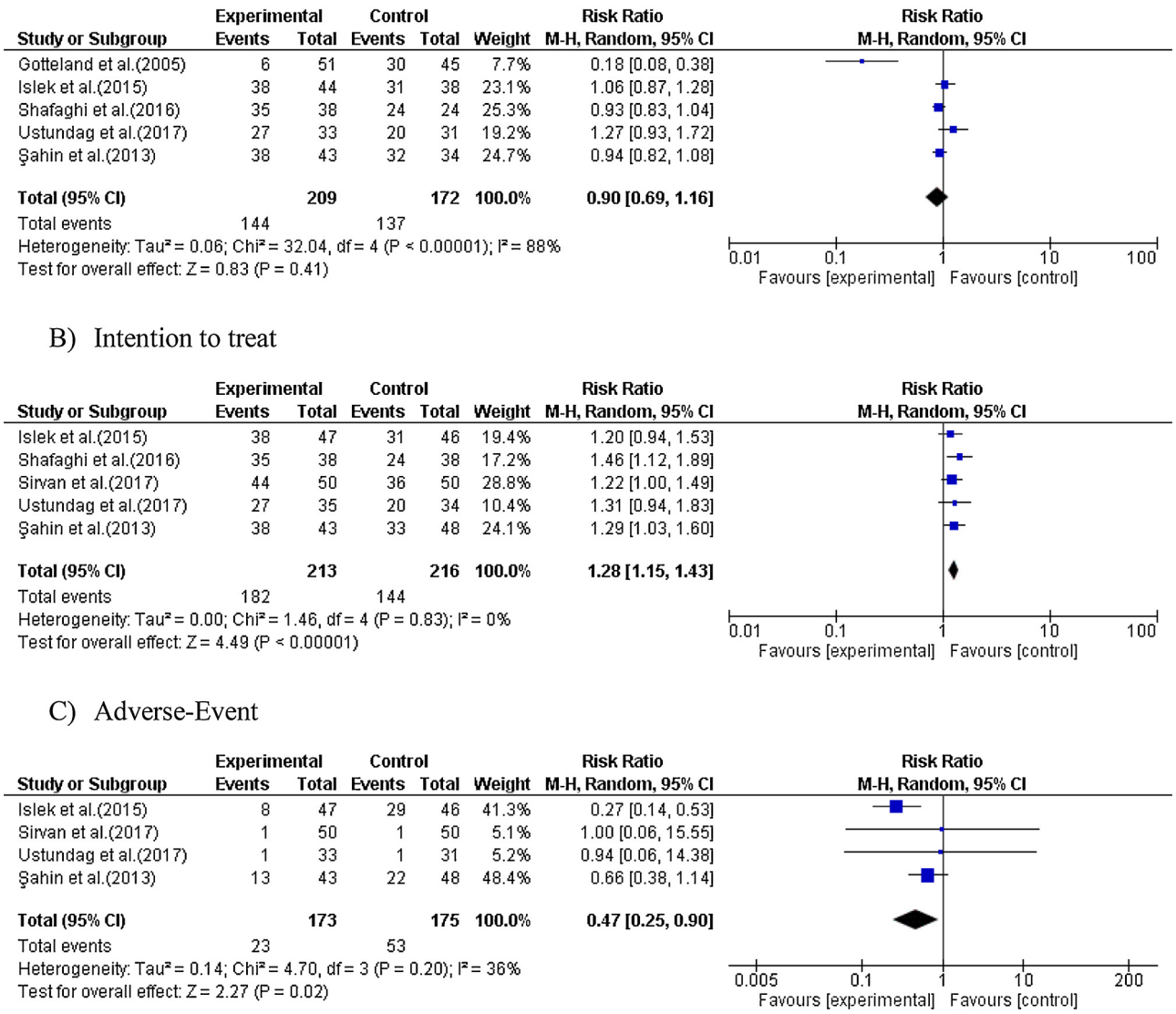

Fig. 2. The effect of symbiotic on H. pylori eradication.

treatment. In this regard, several meta-analyses have reported the favorable effects of probiotics on treating patients suffering from *H. pylori* infections,[31–34] which is consistent with the present result. Although the pooled effect size from PP reports did not show any significant role of synbiotics on the treatment of *H. pylori* infections, the results from ITT analysis revealed that synbiotic can significantly improve the efficacy of conventional pharmacological therapy on the *H. pylori* eradication rate. One possible reason for the differences between the two analysis models might be due to the number of patients who were withdrawn from the control group due to adverse effects from pharmacological therapy. For example, in Shafaghi et al[19], 14 patients in the control group were excluded during the follow-up period, while all participants in the intervention group completed the study. It seems that synbiotics, by increasing the tolerability of common pharmacological therapies, enhance patient adherence, as well as improving the eradication rate of the conventional drug regimen.

One included study[21] investigated the effects of synbiotics in comparison with triple therapy. It showed that synbiotic administration can reduce *H. pylori* bacteria load and was in agreement with previous studies which had reported the efficacy of probiotics on *H. pylori* infection.[35–38] However, this favorable effect was significantly lower than in triple therapy, and that indicated complete eradication was not solely obtained from synbiotic administration.

The effect of quadruple therapy plus synbiotics on *H. pylori* eradication was investigated in one study.[19] It showed that synbiotics plus quadruple therapy could increase the eradication rate and that, except for anxiety, the side effects were similar in both the quadruple therapy and quadruple plus synbiotic therapy groups. There are limited studies that have examined the possible efficacy of probiotics with quadruple therapy, which have suggested that probiotics cannot improve the efficacy or the tolerability of the therapy.[39,40] The reason underlying the differences between the effects of synbiotics/probiotics on the adverse effects of triple and quadruple therapy might be due to different tolerability levels.[41] However, more studies are needed to determine the effect of synbiotics/probiotics (with different strains) on quadruple therapy tolerability (in different line treatments).

The most common antibiotic side effects are nausea, vomiting, diarrhea, and epigastric pain, which have been reported in previous studies.[42,43] The present results revealed that adding synbiotics to antibiotic therapy can reduce common adverse effects, which has been deemed to be the most common reason for low levels of medication compliance, and thus this addition can enhance medication tolerability.

Table 2
subgroup analysis based on age, type of intervention and comparison.

Outcomes	Subgroups		References	Results	Heterogeneity
Per-protocol	Age	≥18	Islek et al[22] Shafaghi et al[19] Şahin et al[18]	0.95 [0.88, 1.03]	I^2 = 0%
		< 18	Gotteland et al[21] Ustundag et al[23]	0.48 [0.05, 5.16]	I^2 = 97%
	Type of intervention	Synbiotic	Gotteland et al[21]	0.18 [0.08, 0.38]	–
		Quadruple therapy plus synbiotic	Shafaghi et al[19]	0.93 [0.83, 1.04]	–
		Triple therapy plus synbiotic	Islek et al[22] Ustundag et al Şahin et al[18]	1.04 [0.88, 1.23]	I^2 = 53%
	Type of antibiotic regimen in comparison group	Quadruple therapy	Shafaghi et al[19]	0.93 [0.83, 1.04]	–
		Triple therapy	Gotteland et al[21] Islek et al[22] Ustundag et al[23] Şahin et al[18]	0.82 [0.55, 1.24]	I^2 = 91%
Intention- to- treat	Age	≥18	Islek et al[22] Shafaghi et al[19] Şahin et al[18]	1.30 [1.13, 1.50]	I^2 = 0%
		< 18	Ustundag et al[23] Sirvan et al[20]	1.25 [1.05, 1.48]	I^2 = 0%
	Type of antibiotic regimen	Quadruple therapy	Shafaghi et al[19]	1.46 [1.12, 1.89]	–
		Triple therapy	Islek et al[22] Ustundag et al[23] Sirvan et al[20] Şahin et al[18]	1.25 [1.11, 1.40]	I^2 = 0%
Adverse events	Age	≥18	Islek et al[22] Şahin et al[18]	0.43 [0.18, 1.04]	I^2 = 76%
		< 18	Sirvan et al[20] Ustundag et al[23]	0.97 [0.14, 6.71]	I^2 = 0%

This finding was consistent with a previous meta-analysis[44] which examined the effect of probiotics on H. pylori eradication, and indicated that the addition of probiotics to first-line therapy could elevate the eradication rate directly by reducing bacteria colonization, and indirectly by enhancing medication efficiency through increasing adherence and reducing pharmacological adverse effects. Although the results suggested that the addition of synbiotics to conventional antibiotics regimens could be a promising finding in enhancing the eradication rate of *H. pylori* and reducing pharmacological adverse effects, it should be interpreted cautiously. Due to the forms of data collection used with different strains of bacteria, along with various antibiotic regimens, the present meta-analysis may be misleading and should be consider as a primary finding.

As synbiotics include probiotics and prebiotics in combination, they can provide synergistic effects by alternating the form and/or function of the gut microbiota. In this regard, one study has showed that synbiotics are more effective on the eradication rate of *H. pylori* in comparison with probiotics.[21] The mechanism underlying the anti-*H. pylori* activity of synbiotics seems to be similar to probiotics. Probiotics can suppress *H. pylori* colonization and growth via the production of mucin, autolysins, organic acids and bacteriocins.[45–48] Furthermore, synbiotics can improve systemic antioxidative activity caused by *H. pylori* infection, through inducing infiltration of the subepithelial gastric lamina propria, and consequently producing excessive amounts of reactive species responsible for oxidative damage.[49] It might modify proinflammatory cytokines and regulate immune responses, as well as preventing *H. pylori* bacteria growth.[50–52] It also stimulates mucin secretion from the gastric epithelium, which is reduced in *H. pylori* infections.[53]

Synbiotics are basically safe, and are widely used by the general population as supplements to enhance health-related outcomes.[54] The association between gut microbiota and many diseases, such as non-alcoholic fatty liver,[55] cardiovascular[56] and type 2 diabetes,[57] have been well documented. In this case, the beneficial role of synbiotics and probiotics in changing gut microbiota populations and modifying metabolic markers, including lipid profiles,[58] inflammation[59,60] and glycemic status-related markers[61] have been previously demonstrated. However, many issues regarding the optimal dosage of probiotics, the treatment duration, and the efficacy of specific strains in specific diseases remain unclear.[62,63] Although studies have suggested minor side effects, especially bloating or diarrhea, by manipulating the microbiome with probiotic and synbiotic supplementation in healthy adults,[64] the safety of their use is only under question in critical diseases, very weak infants, post-operative patients, and weakened immune systems.[65–68] Furthermore, the information around all kind of probiotic strains is different.[69] Current probiotics knowledge is mostly related to lactobacilli and bifidobacteria, however, there are several other probiotic bacteria strains with various influences on metabolic parameters.[69–71] As many studies (similar to the included studies in the present meta-analysis) have used multi-strain probiotics/synbiotics, there is a need to determine the effects of individual probiotic/synbiotic strains, or even genus, as treatment agents. Due to these unclear issues, there is a long way to go before suggesting probiotics as treatment methods in various diseases.

The current study has several limitations, which should be considered when being interpreted. Firstly, there were few eligible trials, and the sample size was relatively small, which prevented multiple subgroup analysis to detect possible effects of other variables. Secondly, the amount and strain of probiotic bacteria as part of synbiotic supplementation was not reported in 2 studies. Lastly, there are concerns about the heterogeneity of the included studies in terms of participant demographics, dosage and strain of bacteria, and study duration, which may have affected the efficacy of the results.

12. Conclusion

In conclusion, the present systematic review and meta-analysis suggested a primary therapeutic effect of synbiotics being the increase of *H. pylori* eradication rates in combination with conventional therapy. It also suggested the reduction of adverse effects of antibiotics treatments. However, the low number of available trials led to limitations in drawing evidence-based conclusions, and this promising effect should

be considered with caution. On the other hand, there is a lack of evidence regarding the effect of various strains of probiotics, and the possible efficacy of synbiotics, on different pharmacological regimens, especially non-bismuth quadruple therapies. This means that there is a necessity for more robust and consistent evidence before recommending it as clinical practice. Further high-quality studies with various strains are needed to confirm these results.

Authorship

MP and AH carried out the concept, design and drafting of this study. AN, AH, and MP searched databases, screened articles and extracted data. MP performed the acquisition, analysis, and interpretation of data. FM-G and FJ critically revised the manuscript. All authors approved the final version of the manuscript. FM-G and FJ are the guarantors of this study.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Funding

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.01.005.

References

1. Wang Y-C. Medicinal plant activity on Helicobacter pylori related diseases. *World J Gastroenterol: WJG.* 2014;20(30):10368.
2. Gunji T, Matsuhashi N, Sato H, et al. Helicobacter pylori infection significantly increases insulin resistance in the asymptomatic Japanese population. *Helicobacter.* 2009;14(5):496–502.
3. Sonnenberg A, Lash RH, Genta RM. A national study of Helicobactor pylori infection in gastric biopsy specimens. *Gastroenterology.* 2010;139(6):1894–1901 e1892.
4. Raghunath A, Hungin APS, Wooff D, Childs S. Prevalence of Helicobacter pylori in patients with gastro-oesophageal reflux disease: systematic review. *Bmj.* 2003;326(7392):737.
5. Georgopoulos SD, Papastergiou V, Karatapanis S. Current options for the treatment of Helicobacter pylori. *Expert Opin Pharmacother.* 2013;14(2):211–223.
6. Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. *Helicobacter.* 2009;14(2):109–118.
7. Ierardi E, Giorgio F, Iannone A, et al. Noninvasive molecular analysis of Helicobacter pylori: is it time for tailored first-line therapy? *World J Gastroenterol.* 2017;23(14):2453.
8. Yakut M, Cinar K, Seven G, Bahar K, Özden A. Sequential therapy for Helicobacter pylori eradication. *Turk J Gastroenterol.* 2010;21(3):206–211.
9. Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change Helicobacter pylori treatment: a matter of geography? *World J Gastroenterol: WJG.* 2013;19(45):8168.
10. Losurdo G, Cubisino R, Barone M, et al. Probiotic monotherapy and Helicobacter pylori eradication: a systematic review with pooled-data analysis. *World J Gastroenterol.* 2018;24(1):139.
11. Hill C, Guarner F, Reid G, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506.
12. Roberfroid M. Prebiotics: the concept revisited. *J Nutr.* 2007;137(3):830S–837S.
13. Coconnier M-H, Lievin V, Hemery E, Servin AL. Antagonistic activity against Helicobacter infection in vitro and in vivo by the human Lactobacillus acidophilus strain LB. *Appl Environ Microbiol.* 1998;64(11):4573–4580.
14. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of Helicobacter pylori infection-The Maastricht III Consensus Report. *Gut.* 2006.
15. Kafshdooz T, Akbarzadeh A, Seghinsara AM, Nasrabadi HT, Milani M. Role of probiotics in managing of Helicobacter pylori infection: a review. *Drug Res.* 2017;11(02):88–93.
16. Wang F, Feng J, Chen P, et al. Probiotics in Helicobacter pylori eradication therapy: systematic review and network meta-analysis. *Clin Res Hepatol Gastroenterol.* 2017;41(4):466–475.
17. Feng J-R, Wang F, Qiu X, et al. Efficacy and safety of probiotic-supplemented triple therapy for eradication of Helicobacter pylori in children: a systematic review and network meta-analysis. *Eur J Clin Pharmacol.* 2017;73(10):1199–1208.
18. Şahin Ö, Yeşil A, Şenateş E, et al. Synbiotic therapy increases eradication rate in Helicobacter pylori eradica-tion. *Acta Medica Cordoba.* 2013;29:569.
19. Shafaghi A, Pourkazemi A, Khosravani M, et al. The effect of probiotic plus prebiotic supplementation on the tolerance and efficacy of Helicobacter pylori eradication quadruple therapy: a randomized prospective double blind controlled trial. *Middle East J Dig Dis.* 2016;8(3):179.
20. Şirvan BN, Usta MK, Kizilkan NU, Urganci N. Are synbiotics added to the standard therapy to eradicate Helicobacter pylori in children beneficial? A randomized controlled study. *Euroasian J Hepato-gastroenterology.* 2017;7(1):17.
21. Gotteland M, Poliak L, Cruchet S, Brunser O. Effect of regular ingestion of Saccharomyces boulardii plus inulin or Lactobacillus acidophilus LB in children colonized by Helicobacter pylori. *Acta Paediatr.* 2005;94(12):1747–1751.
22. Islek A, Sayar E, Yilmaz A, Artan R. Bifidobacterium lactis B94 plus inulin for treatment of Helicobacter pylori infection in children: does it increase eradication rate and patient compliance? *Acta Gastroenterol Belg.* 2015;78(3):282–286.
23. Ustundag GH, Altuntas H, Soysal YD, Kokturk F. The effects of synbiotic "Bifidobacterium lactis B94 plus Inulin" addition on standard triple therapy of Helicobacter pylori eradication in children. *Can J Gastroenterol Hepatol.* 2017;2017.
24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.
25. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions.* John Wiley & Sons; 2011.
26. Dersimonian R, Laird N. Meta-analysis in clinical trials. *ControlClin Trials.* 1986;7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2.
27. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011 [cited 2012 April 11]. Available from: www.cochrane-handbookorb.
28. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med.* 1998;17(8):873–890.
29. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;315(7109):629–634.
30. Sterne J, Bradburn M. Meta-analysis in stata. In: Egger M, Smith G, Altman D, eds. *Systematic reviews in health care 2.* editors London: BMJ Publishing Group; 2001:347–372.
31. Lau CS, Ward A, Chamberlain RS. Probiotics improve the efficacy of standard triple therapy in the eradication of Helicobacter pylori: a meta-analysis. *Infect Drug Resist.* 2016;9:275–289.
32. Lu M, Yu S, Deng J, et al. Efficacy of probiotic supplementation therapy for Helicobacter pylori eradication: a meta-analysis of randomized controlled trials. *PLoS One.* 2016;11(10):e0163743.
33. Lv Z, Wang B, Zhou X, et al. Efficacy and safety of probiotics as adjuvant agents for Helicobacter pylori infection: a meta-analysis. *Exp Ther Med.* 2015;9(3):707–716.
34. Zhu R, Chen K, Zheng YY, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. *World J Gastroenterol.* 2014;20(47):18013–18021.
35. Hsieh PS, Tsai YC, Chen YC, Teh SF, Ou CM, King VAE. Eradication of Helicobacter pylori Infection by the probiotic strains Lactobacillus johnsonii MH-68 and L. salivarius ssp. salicinius AP-32. *Helicobacter.* 2012;17(6):466–477.
36. Holz C, Busjahn A, Mehling H, et al. Significant reduction in Helicobacter pylori load in humans with non-viable Lactobacillus reuteri DSM17648: a pilot study. *Probiotics Antimicrob Proteins.* 2015;7(2):91–100.
37. Francavilla R, Polimeno L, Demichina A, et al. Lactobacillus reuteri strain combination in Helicobacter pylori infection: a randomized, double-blind, placebo-controlled study. *J Clin Gastroenterol.* 2014;48(5):407–413.
38. Linsalata M, Russo F, Berloco P, et al. The influence of Lactobacillus brevis on ornithine decarboxylase activity and polyamine profiles in Helicobacter pylori-infected gastric mucosa. *Helicobacter.* 2004;9(2):165–172.
39. McNicholl AG, Molina-Infante J, Lucendo AJ, et al. Probiotic supplementation with Lactobacillus plantarum and Pediococcus acidilactici for Helicobacter pylori therapy: a randomized, double-blind, placebo-controlled trial. *Helicobacter.* 2018;23(5):e12529.
40. Zagari RM, Romiti A, Ierardi E, et al. The "three-in-one" formulation of bismuth quadruple therapy for Helicobacter pylori eradication with or without probiotics supplementation: efficacy and safety in daily clinical practice. *Helicobacter.* 2018;23(4):e12502.
41. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent helicobacter pylori infection: a meta-analysis. *Am J Gastroenterol.* 2006;101:488.
42. Huang J, Zhou L, Geng L, et al. Randomised controlled trial: sequential vs. standard triple therapy for Helicobacter pylori infection in Chinese children–a multicentre, open-labelled study. *Aliment Pharmacol Ther.* 2013;38(10):1230–1235.
43. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *Jama.* 2012;307(18):1959–1969.
44. Lau CS, Ward A, Chamberlain RS. Probiotics improve the efficacy of standard triple therapy in the eradication of Helicobacter pylori: a meta-analysis. *Infect Drug Resist.* 2016;9:275.
45. Bhatia SJ, Kochar N, Abraham P, Nair NG, Mehta AP. Lactobacillus acidophilus inhibits growth of Campylobacter pylori in vitro. *J Clin Microbiol.* 1989;27(10):2328–2330.
46. Lorca GL, Wadström T, De Valdez GF, Ljungh Å. Lactobacillus acidophilus autolysins inhibit Helicobacter pylori in vitro. *Curr Microbiol.* 2001;42(1):39–44.
47. Hütt P, Shchepetova J, Loivukene K, Kullisaar T, Mikelsaar M. Antagonistic activity of probiotic lactobacilli and bifidobacteria against entero-and uropathogens. *J Appl Microbiol.* 2006;100(6):1324–1332.

48. Gomi A, Harima-Mizusawa N, Shibahara-Sone H, Kano M, Miyazaki K, Ishikawa F. Effect of Bifidobacterium bifidum BF-1 on gastric protection and mucin production in an acute gastric injury rat model. *J Dairy Sci.* 2013;96(2):832–837.
49. Hütt P, Andreson H, Kullisaar T, et al. Effects of a synbiotic product on blood antioxidative activity in subjects colonized with Helicobacter pylori. *Lett Appl Microbiol.* 2009;48(6):797–800.
50. Ruggiero P. Use of probiotics in the fight against Helicobacter pylori. *World J Gastrointest Pathophysiol.* 2014;5(4):384.
51. Rohde CL, Bartolini V, Jones N. The use of probiotics in the prevention and treatment of antibiotic-associated diarrhea with special interest in Clostridium difficile–associated diarrhea. *Nutr Clin Pract.* 2009;24(1):33–40.
52. Jones SE, Versalovic J. Probiotic Lactobacillus reuteri biofilms produce antimicrobial and anti-inflammatory factors. *BMC Microbiol.* 2009;9(1):35.
53. Dooley CP, Cohen H, Fitzgibbons PL, et al. Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. *N Engl J Med.* 1989;321(23):1562–1566.
54. Khalesi S, Bellissimo N, Vandelanotte C, Williams S, Stanley D, Irwin C. A review of probiotic supplementation in healthy adults: helpful or hype? *Eur J Clin Nutr.* 2018 epub ahead of print.
55. Yang YJ, Ni YH. Gut microbiota and pediatric obesity/non-alcoholic fatty liver disease. *J Formos Med Assoc.* 2018 epub ahead of print.
56. Velasquez MT, Centron P, Barrows I, Dwivedi R, Raj DS. Gut microbiota and cardiovascular uremic toxicities. *Toxins.* 2018;10(7).
57. He J, Zhang F, Han Y. Effect of probiotics on lipid profiles and blood pressure in patients with type 2 diabetes: a meta-analysis of RCTs. *Medicine.* 2017;96(51):e9166.
58. Wu Y, Zhang Q, Ren Y, Ruan Z. Effect of probiotic Lactobacillus on lipid profile: a systematic review and meta-analysis of randomized, controlled trials. *PLoS One.* 2017;12(6):e0178868.
59. Park C, Brietzke E, Rosenblat JD, et al. Probiotics for the treatment of depressive symptoms: an anti-inflammatory mechanism? *Brain Behav Immun.* 2018;73:115–124.
60. Dang D, Zhou W, Lun ZJ, Mu X, Wang DX, Wu H. Meta-analysis of probiotics and/or prebiotics for the prevention of eczema. *J Int Med Res.* 2013;41(5):1426–1436.
61. Tabrizi R, Moosazadeh M, Lankarani KB, et al. The effects of synbiotic supplementation on glucose metabolism and lipid profiles in patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Probiotics Antimicrob Proteins.* 2018;10(2):329–342.
62. Verna EC, Lucak S. Use of probiotics in gastrointestinal disorders: what to recommend? *Therap Adv Gastroenterol.* 2010;3(5):307–319.
63. Liu Y, Alookaran JJ, Rhoads JM. Probiotics in autoimmune and inflammatory disorders. *Nutrients.* 2018;10(10).
64. Williams NT. Probiotics. *Am J Health-Syst Pharm: AJHP.* 2010;67(6):449–458.
65. Zawistowska-Rojek A, Tyski S. Are probiotic really safe for humans? *Pol J Microbiol.* 2018;67(3):251–258.
66. Lherm T, Monet C, Nougiere B, et al. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Med.* 2002;28(6):797–801.
67. Ledoux D, Labombardi VJ, Karter D. Lactobacillus acidophilus bacteraemia after use of a probiotic in a patient with AIDS and Hodgkin's disease. *Int J STD AIDS.* 2006;17(4):280–282.
68. Jorgenson MR, Descourouez JL, Siodlak M, Tjugum S, Rice JP, Fernandez LA. Efficacy and safety of probiotics and synbiotics in liver transplantation. *Pharmacotherapy.* 2018.
69. Ozdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol.* 2010;160(3):295–304.
70. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. *Int J Environ Res Public Health.* 2014;11(5):4745–4767.
71. Ciorba MA. A gastroenterologist's guide to probiotics. *Clin Gastroenterol Hepatol.* 2012;10(9):960–968.