

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori***Evidence-based assessment of proton-pump inhibitors in *Helicobacter pylori* eradication: A systematic review**

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recommendations and level of evidence regarding the role of the dose, type of proton-pump inhibitor, and the length of the treatment. The review also discusses the various regimens for second line therapy, sequential therapy and new alternate/adjuvant therapies for *H. pylori* therapy.

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Abstract

Peptic ulcer disease continues to be issue especially due to its high prevalence in the developing world. *Helicobacter pylori* (*H. pylori*) infection associated duodenal ulcers should undergo eradication therapy. There are many regimens offered for *H. pylori* eradication which include triple, quadruple, or sequential therapy regimens. The central aim of this systematic review is to evaluate the evidence for *H. pylori* therapy from a meta-analytical outlook. The consequence of the dose, type of proton-pump inhibitor, and the length of the treatment will be debated. The most important risk factor for eradication failure is resistance to clarithromycin and metronidazole.

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Key words: *Helicobacter pylori*; Peptic ulcer disease; Systematic review; Proton-pump inhibitors

Core tip: This review will discuss the different traits of treatment regimens for *Helicobacter pylori* (*H. pylori*) and will also give an insight about some unconventional and novel treatment strategies from a meta-analytic viewpoint. This review summarizes the

INTRODUCTION

Marshall and Warren^[1] identified and subsequently cultured the *Helicobacter pylori* (*H. pylori*) in 1982. This organism is associated with chronic gastritis^[2], most peptic ulcers^[3], and gastric adenocarcinoma^[4] and lymphoma^[5]. A meta-analysis that included seven controlled trials (all in areas with a high incidence of gastric cancer) found significantly lower rates of gastric cancer (1.1% vs 1.7%) in patients randomized to eradication (OR = 0.65, 95%CI: 0.43-0.98)^[6].

There are numerous regimens recommended for *H. pylori* eradication which include triple, quadruple, or sequential therapy regimens. Currently regimens that use proton-pump inhibitors (PPIs) in combination with several antibiotics such as clarithromycin, amoxicillin and metronidazole have been highly successful for *H. pylori* eradication^[7,8]. Numerous treatments have been evaluated for *H. pylori* therapy in randomized controlled trials^[9-11]. In spite of the numerous studies, the ideal schedule is still controversial. This review will discuss the different traits of treatment regimens for *H. pylori* and will also give an insight about some unconventional and novel treatment

strategies from a meta-analytic viewpoint.

LITERATURE SEARCH

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review^[12]. We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to July 2013. The search terms included “*Helicobacter pylori*, gastric cancer, intestinal metaplasia, gastric atrophy, dysplasia, prevention, treatment, and eradication”. In addition, we identified relevant trials from the reference list of each selected article. Selection criteria were established. To be eligible, the studies have to be systematic reviews or meta-analyses about various eradication regimes and alternate remedies. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

WHAT IS THE ROLE OF THE DIFFERENT PPI DOSES IN *H. PYLORI* ERADICATION THERAPY?

A combination of a double dose of proton pump inhibitor plus two antibiotics is the standard regimen for *H. pylori* infection. A report also suggests that the use of single dose of proton pump inhibitor is similarly efficacious^[13]. Unitat de Malalties Digestives^[13] conducted a MEDLINE search for their meta-analysis comparing single and double dose of a proton pump inhibitor head to head in triple therapy for *H. pylori* eradication. As a result thirteen studies were included (double dose of proton pump inhibitor: 1211 patients, single dose of proton pump inhibitor: 1180 patients). Eradication rates with double doses of proton pump inhibitor (80 mg of pantoprazole, 60 mg of lansoprazole, 40 mg of omeprazole) were greater in both the intention-to-treat analysis and per protocol analysis. To summarize, the use of high-dose (twice a day) PPI increases the effectiveness of triple therapy compared to a single dose PPI (level of evidence 1b, grade of recommendation A)^[14].

DIFFERENT PPIS IN *H. PYLORI* ERADICATION THERAPY

In a systematic review published by Gisbert *et al*^[15] low doses of rabeprazole (10 mg *bid*), reached similar *H. pylori* eradication rates to omeprazole and lansoprazole (Figure 1). A systematic review regarding lansoprazole demonstrates a greater efficacy in eradicating *H. pylori*. 1076 patients were prescribed rabeprazole and 1150 with other PPIs. This efficacy is comparable to that of other

PPIs^[16]. Twelve studies equating pantoprazole and other PPIs were included in a meta-analysis by Gisbert *et al*^[17]. The average *H. pylori* eradication rate for using pantoprazole plus antibiotics was similar in the two cohorts. A sub-analysis was no different statistically which included only studies comparing pantoprazole with omeprazole, or pantoprazole with lansoprazole. The subgroup analysis of six studies administering equivalent doses of all PPIs established statistically homogeneous results with pantoprazole.

Shanghai Institute of Digestive Disease^[18] screened 75 articles and included 11 RCTs (2159 subjects) in their meta-analysis of esomeprazole-based triple therapy. The mean *H. pylori* eradication rates (intention-to-treat, ITT) with esomeprazole + antibiotics were 6% higher than other PPI therapies with a statistically significant odd ratio of 1.38. A subgroup analysis of six selected high-quality studies produced statistically homogeneous results. In 2004, Gisbert *et al*^[19] performed a similar meta-analysis and published analogous results. Vergara *et al*^[20] performed a MEDLINE search for their meta-analysis of fourteen studies that compared the efficacy of different proton-pump inhibitors in triple therapy showed similar results. The effectiveness of different proton-pump inhibitors is comparable in standard triple therapy.

DURATION OF PPI-BASED TRIPLE THERAPIES

An extended period of therapy (2 wk against 1 wk) could be more efficacious in eradicating infection but this is contentious^[21,22]. Fuccio *et al*^[21] performed a meta-analysis with 21 studies. Diarrhea and dysgeusia were the most commonly described side effects (5%). They concluded that prolonging the period of PPI-clarithromycin-containing triple treatment from 7 to 10-14 d increases the eradication rate by about 5%. This is currently equates to level of evidence 1b and grade of recommendation A^[14].

PPI-BASED TRIPLE REGIMENS AS OPPOSED TO QUADRUPLE THERAPY

The University of North Texas Health Science Center performed a meta-analysis with 93 studies (10178 participants)^[23]. For triple therapies, clarithromycin resistance had a larger effect on treatment effectiveness than nitroimidazole resistance. Metronidazole resistance reduced effectiveness by a quarter in triple therapies containing a nitroimidazole, tetracycline and bismuth, while effectiveness was reduced by only 14% when a proton pump inhibitor was added to the regimen. The occurrence of nitroimidazole and clarithromycin resistance has increased considerably; standard triple therapies are inadequate to eradicate *H. pylori*. Quadruple regimens are usually used as second line; they should be considered as first-line, essentially in areas of high drug resistance however, it may not be effective in context of concomitant clarithromycin

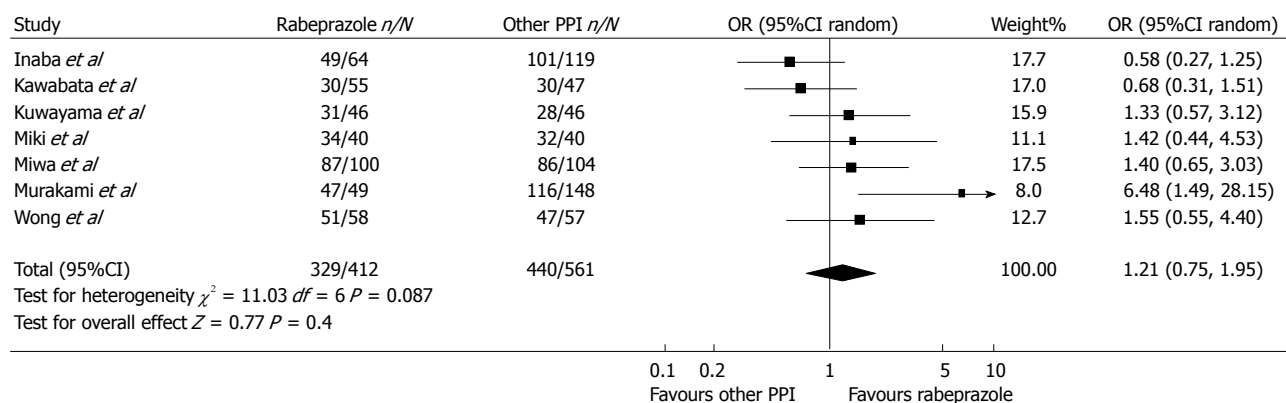


Figure 1 Meta-analysis of studies comparing *Helicobacter pylori* eradication with rabeprazole 10 mg *bid* vs omeprazole 20 mg *bid* or lansoprazole 30 mg *bid* in triple therapies^[15]. PPI: Proton pump inhibitor.

and metronidazole resistance. In regions of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment. However, Bismuth-containing quadruple treatment is also an alternative. (level of evidence 1a, grade of recommendation A)^[14]. In areas of high clarithromycin resistance, bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available a non-bismuth quadruple treatment is recommended (level of evidence 1a, grade of recommendation A)^[14].

SEQUENTIAL THERAPY FOR *HELICOBACTER PYLORI* INFECTION

Multiple randomized trials have demonstrated that sequential therapy and concomitant quadruple therapy are equally effective for eradication of *H. pylori* in treatment-naïve patients. Sequential therapy for 14 d may be more effective in eradicating *H. pylori* as compared with triple therapy in regions where clarithromycin resistance is high and metronidazole resistance is low^[24-27]. This difference in antimicrobial resistance patterns may explain the seemingly contradictory results in two randomized controlled trials conducted in Taiwan and Latin America^[28,29]. In a randomized controlled trial in Taiwan, 900 adults with *H. pylori* were assigned to 14-d triple therapy (lansoprazole, amoxicillin, and clarithromycin) or 14-d sequential therapy (lansoprazole and amoxicillin for seven days followed by lansoprazole, clarithromycin, and metronidazole for seven days) or 10-d sequential therapy (lansoprazole and amoxicillin for five days followed by lansoprazole, clarithromycin, and metronidazole for five days)^[29]. In this study, 14-d sequential therapy was significantly more likely to eradicate *H. pylori* as compared with the 14-d triple therapy. In contrast, in a randomized trial of 1463 *H. pylori* infected patients in Latin America, 14-d triple therapy (lansoprazole, amoxicillin, and clarithromycin) had higher eradication rates than five-day concomitant quadruple therapy (lansoprazole, amoxicillin, clarithromycin, and metronidazole) and 10-d clarithromycin containing sequential therapy (82%, 74% and 77%, respectively)^[28].

However, among 1091 patients in whom *H. pylori* had been successfully eradicated, one-year recurrence rates were not significantly different based on the antibiotic regimen^[30].

Horvath *et al*^[31] ten RCTs involving a total of 857 children. This resulted in a statistically significant relative risk of 1.14 and with a number needed to treat of 15 for the eradication rate for sequential therapy. Sequential therapy had greater efficacy to 7-d standard triple therapy, however failed to statistical significant better results than 10-d or 14-d triple therapy. The risks of adverse effects were similar in the different groups.

In 2008 University of Louisville^[32] concluded that sequential therapy is better than standard triple therapy for eradication of *H. pylori* infection. However, there was clear evidence of publication bias.

Gatta *et al*^[33] included ten RCTs with 3006 adults. The eradication rate for *H. pylori* with sequential therapy (ST) compared with triple therapy (TT) produced a number needed to treat of 6. In patients with clarithromycin resistance, eradication with ST was clearly 10 times more superior to TT. However, the number of studies was small (Figure 2). In regions of high clarithromycin resistance, bismuth-containing quadruple treatments are suggested for first-line empirical treatment if this is unavailable, sequential treatment is the level of evidence 1a and with a grade A recommendation^[14].

PPIS AS OPPOSED TO RANITIDINE BISMUTH CITRATE-BASED REGIMENS

Gisbert *et al*^[9] performed a meta-analysis using randomized controlled trials that compared PPI vs ranitidine bismuth citrate (RBC) plus two antibiotics for 1 wk. The mean *H. pylori* eradication with 7-d RBC-clarithromycin-amoxicillin, RBC-clarithromycin-nitroimidazole, and RBC-amoxicillin-nitroimidazole were 83%, 86%, and 71%, respectively. They concluded the effectiveness of ranitidine bismuth citrate and PPI-based triple regimens were similar. Nonetheless, equating PPI vs RBC plus clarithromycin and a nitroimidazole demonstrated superior cure rates with RBC than with PPI.

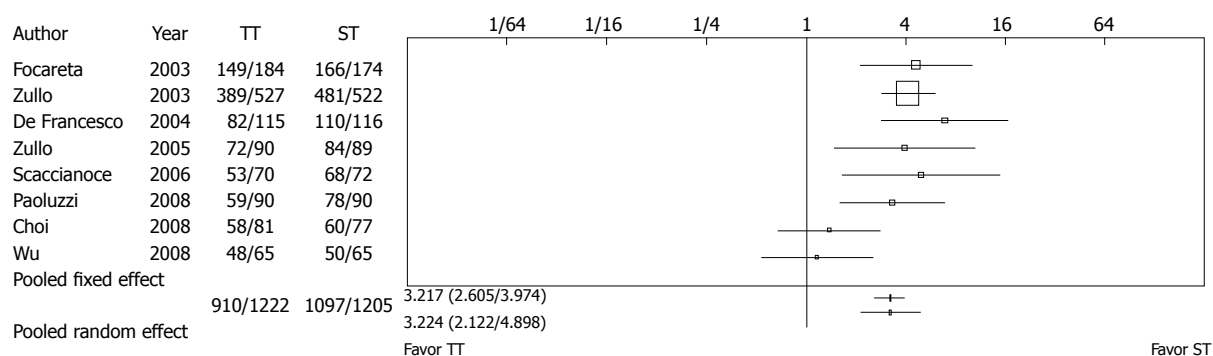


Figure 2 Sequential vs triple therapy lasting 7 d^[33]. ST: Sequential therapy; TT: Triple therapy.

Two other meta-analyses published in *Alimentary Pharmacology and Therapeutics* by the University Medical Centre St^[34] and University Hospital of ‘La Princesa’^[35] proposed similar conclusions. The effectiveness of RBC and PPI-based triple regimens are similar to the clarithromycin-amoxicillin or the amoxicillin-metronidazole combination. Nevertheless, RBC seems to have a greater effectiveness than PPI when clarithromycin and a nitroimidazole are the antibiotics administered.

H. PYLORI ERADICATION WHEN FIRST-LINE THERAPY FAILS: QUINOLONE-BASED RESCUE REGIMENS

Fluoroquinolones are inhibitors of bacterial DNA synthesis by inhibiting DNA gyrase and topoisomerase IV^[36]. The First Affiliated Hospital of Nanjing Medical University^[37] in 2010 conducted a meta-analysis compare the efficacy and safety of clarithromycin and second-generation fluoroquinolone-based triple therapy *vs* bismuth-based quadruple therapy for the treatment of persistent *H. pylori* infection. Thirteen RCTs equated levofloxacin-based triple therapy to bismuth-based quadruple therapy; the eradication rates of the two regimens were similar. However, the eradication rates established greater efficacy for the 10-d levofloxacin-based triple therapy over 7-d bismuth-based quadruple therapy and was better accepted than bismuth-based quadruple therapy with lower incidence of adverse events and lower rates of cessation of therapy due to side effects.

Similar meta-analyses performed by University of Michigan Medical Center^[38] and University Hospital of ‘La Princesa’^[39] concluded that 10-d course Quinolone triple therapy has superior efficacy than 7-d bismuth-based quadruple therapy in the treatment of stubborn *H. pylori* infection. Evidence-Based Medicine Center of Lanzhou University^[40] proved that moxifloxacin-based triple therapy is superior and does not rise the frequency of adverse events equated to clarithromycin-based triple therapy. Fluoroquinolone-based triple therapy is more active and does not increase the incidence of overall side effects compared to clarithromycin-based triple therapy in the treatment of *H. pylori* infection. *H. pylori* resistant to a PPI-clarithromycin containing therapy, either a bis-

muth containing quadruple therapy or levofloxacin containing triple therapy is suggested (level of evidence 1b, grade of recommendation A)^[41]. The first-line regimens for *H. pylori* eradication have been summarized in Table 1.

ADVERSE EFFECTS

The incidence of side effects is up to half of the individuals taking one of the triple therapies^[41,42]. These are typically minor; fewer than 10 percent of individuals halt treatment due to side effects^[42].

The most common adverse effect reported due to metronidazole or clarithromycin is a metallic taste^[43]. Metronidazole can lead to a disulfiram-like reaction, peripheral neuropathy, and seizures^[43]. Clarithromycin can cause taste alteration, nausea, vomiting, abdominal pain, and rarely QT prolongation^[43]. Doxycycline and tetracycline can lead to a photosensitivity reaction and it is contraindicated in pregnant women and young children. Amoxicillin can cause diarrhea or skin rash^[43].

Levofloxacin has been linked with anorexia, nausea, vomiting, and abdominal discomfort^[43]. In institutional settings with outbreaks of the epidemic fluoroquinolone-resistant strain of *Clostridium difficile* (*C. difficile*), use of fluoroquinolones has been a risk factor for development of *C. difficile*-associated diarrhea^[44]. Central nervous system toxicities of levofloxacin including mild headache and dizziness have predominated, followed by insomnia and alterations in mood. Other adverse effects comprise of rashes and other allergic reactions, tendinitis and tendon rupture, QT prolongation, hypoglycemia and hyperglycemia, and hematologic toxicity^[43].

Common side effects of Bismuth subcitrate are blackening of faeces, darkening of teeth and tongue. The infrequent adverse effects are nausea, vomiting, dizziness, headache and diarrhea^[43].

The primary concern with bismuth compounds is bismuth intoxication; this was a problem primarily when bismuth subgallate was used for prolonged periods at high doses. Bismuth absorption varies with the specific form of bismuth; absorption is much greater with colloidal bismuth subcitrate than with bismuth subsalicylate^[45]. Concurrent administration of H2 receptor antagonists increases bismuth absorption from CBS, but not from bismuth subsalicylate^[46]. Nevertheless, significant clinical

Table 1 First-line regimens for *Helicobacter pylori* eradication^[88]

Regimen	Standard dose PPI <i>bid</i> (esomeprazole <i>is qid</i>), clarithromycin 500 mg <i>bid</i> , amoxicillin 1000 mg <i>bid</i> for 10-14 d	Standard dose PPI <i>bid</i> , clarithromycin 500 mg <i>bid</i> metronidazole 500 mg <i>bid</i> for 10-14 d	Bismuth subsalicylate 525 mg <i>po qid</i> metronidazole 250 mg <i>po qid</i> , tetracycline 500 mg <i>po qid</i> , ranitidine 150 mg <i>po bid</i> or standard dose PPI <i>qid</i> to <i>bid</i> for 10-14 d	PPI + amoxicillin 1 g <i>bid</i> 5 d followed by PPI, clarithromycin 500 mg, tinidazole 500 mg <i>bid</i> for 5 d
Note	Consider in nonpenicillin allergic patients who have not previously received a macrolide	Consider in penicillin allergic patients who have not previously received a macrolide or are unable to tolerate bismuth quadruple therapy	Consider in penicillin allergic patients	Requires validation in North America

PPI: Proton-pump inhibitors.

toxicity has not been reported in clinical trials with colloidal bismuth subcitrate or bismuth subsalicylate^[47,48]. Bismuth should be avoided or serum bismuth concentrations monitored in patients with renal failure^[49].

The subsalicylate moiety in bismuth subsalicylate is converted to salicylic acid and absorbed; however, salicylate in the absence of the acetyl group does not inhibit platelet function or appear to share the same high risk of aspirin for gastrointestinal bleeding^[50,51]. However, the salicylate from bismuth subsalicylate will contribute to serum salicylate levels and cause salicylate toxicity, and combination with other salicylate products should therefore be avoided.

Proton pump inhibitors are usually well accepted. Common side effects include headache, nausea, vomiting, diarrhea, abdominal pain, constipation and flatulence. Uncommon adverse effects are rash, itch, dizziness, fatigue, drowsiness, insomnia and dry mouth^[43]. There have been some concerns regarding long term use of proton pump inhibitors.

Recently, a meta-analysis of 42 observational studies that included 313000 patients found that PPI use was linked with an increased risk of both incident and recurrent *C. difficile* infection (OR = 1.7, 95%CI: 1.5-2.9 and 2.5, 95%CI: 1.2-5.4, respectively)^[52]. A meta-analysis of 31 studies found that patients taking PPIs or H2 receptor antagonists were at increased risk for pneumonia, with an odds ratio of 1.27 (95%CI: 1.11-1.46) with PPIs and 1.22 (95%CI: 1.09-1.36) with H2 receptor antagonists^[53]. Hypomagnesemia due to reduced intestinal absorption has been described^[54]. Yu *et al*^[55] included 11 studies to evaluate the relationship between proton pump inhibitor or H2 receptor antagonist use and fractures (1084560 patients with 62210 PPI users, 71339 patients with hip fractures, 161179 patients with any-site fractures, and 5728 patients with spine fractures). The risk of hip fracture was increased among PPI users compared with nonusers (RR = 1.30, 95%CI: 1.19-1.43). There was also an increased risk of spine fracture (RR = 1.56, 95%CI: 1.31-1.85) and any-site fracture (RR = 1.16, 95%CI: 1.02-1.32)^[55].

ALTERNATIVE THERAPIES

Probiotics

The intestinal tract is host to a vast ecology of microbes,

which are necessary for health, but also have the potential to contribute to the development of diseases by a variety of mechanisms. Perturbations in intestinal epithelial barrier function or innate immune bacterial killing, for example, can lead to an inflammatory response caused by increased uptake of bacterial and food antigens that stimulate the mucosal immune system^[56,57]. The maximum understanding has been in the inflammatory bowel diseases, ulcerative colitis^[58], Crohn's disease^[59], and pouchitis^[60-62], although clinical trials are emerging in several other conditions.

Wang *et al*^[63] proposed that regular consumption of yogurt containing *Lactobacillus acidophilus* or *Bifidobacterium lactis* successfully curbed *H. pylori* infection in human beings. The Medical University of Warsaw^[64] identified five RCTs that compared with placebo or no intervention, *Saccharomyces boulardii* given along with triple therapy. When *S. boulardii* was given along with triple therapy a significant increase in eradication rates was observed and lowered the rate of side effects principally of diarrhea.

The Shanghai Institute of Digestive Disease^[65] performed a meta-analysis using 14 randomized trials with 1671 subjects. The pooled *H. pylori* eradication rates improved significantly with an odds ratio of 1.84 the incidence of total side effects was reduced by almost 14% and reduced diarrhea significantly (Figure 3).

Zou *et al*^[66] identified nine randomized trials ($n = 1343$) in their meta-analysis that investigated the role of lactoferrin. The pooled *H. pylori* eradication rates improved significantly with an odds ratio of 2.26 and the rate of total side-effects reduced by half, particularly nausea.

Probiotics have reduced the incidence of total side effect *H. pylori* therapy-related side effects and could be an efficacious strategy in amplifying eradication rates of anti-*H. pylori* therapy and might be useful for patients with eradication failure. (level of evidence 5, grade of recommendation D)^[14].

Chinese herbal therapy

Herbs have been used conventionally for the management of a extensive variety of ailments, including gastrointestinal ailments^[67]. Department of Gastroenterology at Shuguang Hospital^[68] assessed the efficacy of traditional Chinese medicine by performing a systematic review with the help of sixteen trials. Large statistical heterogeneity

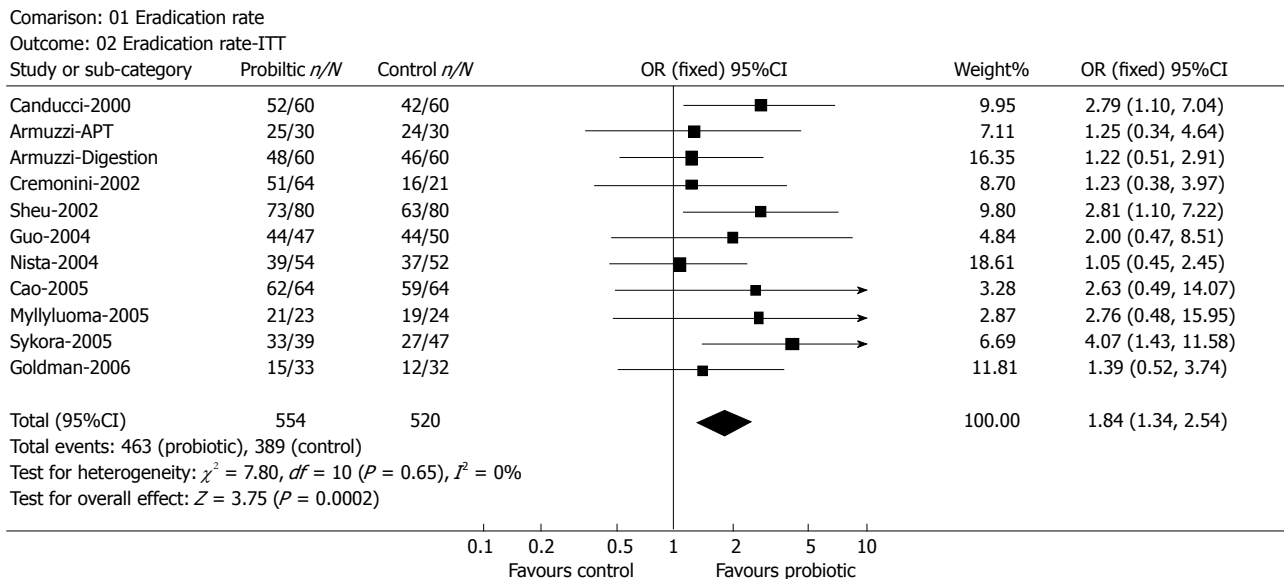


Figure 3 The effect of probiotics supplementation vs without probiotics on eradication rates by intention-to-treat analysis^[65]. n: Number of successful eradication; N: Number of participants; ITT: Intention-to-treat.

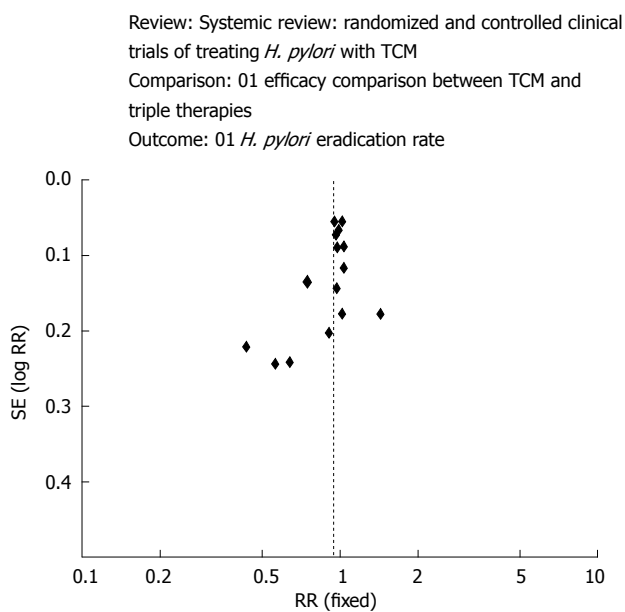


Figure 4 Clinical trials treating *Helicobacter pylori* with traditional Chinese medicine^[68]. *H. pylori*: *Helicobacter pylori*; TCM: Traditional Chinese medicine.

was observed among the trials. The mean eradication rates subsequent traditional Chinese medicine and triple therapy were similar and the incidence of side effects was 15 times lower with Chinese medicine (Figure 4).

Guangzhou University of Chinese Medicine^[69] reported that oral administration with HZJW and ranitidine in rodent experimental models considerably reduced the ulcerative lesion index in a dose-dependent way.

Liu *et al.*^[70] investigated the bactericidal effects of Jinghua Weikang Capsule and its individual herb *Chenopodium ambrosioides* L. against antibiotic-resistant *H. pylori*. *In vitro* they are considered to be active against antibiotic-resistant *H. pylori*.

Many Brazilian medicinal plants like *Davilla elliptica* and *Davilla nitida*^[71], *Alchornea glandulosa*^[72], *Mouririelliptica*^[73], *Calophyllum brasiliense* Camb^[74-76], *Hancornia speciosa*^[77], *Strychnos speciosa*^[78] and many more have been evaluated for their anti-*H. pylori* effect *in vitro*.

Honey

Honey is frequently utilized by numerous individuals with the trust due to its antimicrobial properties, cost effectiveness and accessibility. It is utilized as a wound antiseptic and cough syrup. University of Buea^[79] assessed the antimicrobial potential of honeys (ManukaTM, Capillano[®], Eco- and Mountain) at diverse concentrations against of *H. pylori*, no statistically significant difference was eminent among the honeys at diverse concentrations. The antimicrobial properties of these honeys at diverse concentrations were highly analogous to clarithromycin. A prospective randomized trial would help in deciding its efficacy.

Green tea

Tea extracts for instance catechins deter the growth of *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis*, *Vibrio cholerae* (*V. cholerae*) O1, *V. cholerae non-O1*, *Vibrio parahaemolyticus*, *Vibrio mimicus*, *Campylobacter jejuni* and *Plesiomonas shigelloides in vitro*^[80] and have antimicrobial activity against methicillin-resistant *S. aureus in vitro*^[81].

University of Massachusetts Medical School^[82] assessed the antimicrobial activity of green tea against *Helicobacter felis* and *H. pylori in vitro* and assessed the consequence of green tea on the pathogenesis of *Helicobacter*-induced gastritis in an animal experimental model. This resulted in significant inhibition of *Helicobacter* and averts gastric mucosal inflammation if consumed before being infected with *Helicobacter*.

Similarly an Italian study^[83] proposed that in *H.*

pylori-infected mice, Ethanol-free red wine and green tea mixture considerably reduced gastritis, restricted the localization of bacteria and VacA to the gastric mucosa. Another study from Japan^[84] concluded that *H. pylori* was significantly decreased by Green tea catechins-sucralfate in *Mongolian gerbils*.

Recently, Yonsei University^[85] performed a meta-analysis regarding green tea consumption and stomach cancer risk. A total of 18 studies were incorporated in the publication which demonstrated a statistically significant of 14% reduction in the risk of stomach cancer with high green tea consumption. Some studies have suggested that Green tea has antimicrobial activity^[86,87], which can extend to *H. pylori*. Natural remedies could be used in the future for inhibition and management of Helicobacter-induced gastritis in Homo sapiens however, further studies are required in this field.

CONCLUSION

The advancement of *H. pylori* treatment over the years has been admirable. Bismuth-containing quadruple regimens for 7-14 d are alternative first-line treatment option. Sequential therapy for 10 d has revealed potential. Bismuth quadruple therapy is the most commonly used rescue regimen in patients with persistent *H. pylori*. The first-line regimens for *H. pylori* eradication are listed in Table 1. Current facts propose that a PPI, levofloxacin, and amoxicillin for 10 d is superior to bismuth quadruple therapy for persistent *H. pylori* infection^[88]. The current literature suggests that probiotics^[64] and Chinese herbal therapy^[68] might be beneficial in eradicating *H. pylori*. Further research in the area of alternative medicine might help us achieve higher rates of eradication and reduce side effects.

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