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Can probiotics improve efficiency and safety profile of triple *Helicobacter pylori* eradication therapy? A prospective randomized study

Mogu li probiotici poboljšati efikasnost i bezbednosni profil trostruke eradikacione terapije za *Helicobacter pylori*? Prospektivna randomizirana studija

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Abstract

Background/Aim. Some studies suggest the benefit of applying different probiotic strains in combination with antibiotics in the eradication of *Helicobacter pylori* (*H. pylori*) infection. The aim of this study was to evaluate the effect of coadministration of multiple probiotic strains with triple *H. pylori* eradication therapy. **Methods.** This prospective study included 167 patients with dyspeptic symptoms and chronic gastritis who were diagnosed with *H. pylori* infection and randomized into two groups. The group I of 77 patients underwent triple eradication therapy, for 7 days, with lansoprazole, 2 × 30 mg half an hour before the meal, amoxicillin 2 × 1.000 mg *per* 12 hours and clarithromycin 2 × 500 mg *per* 12 hours. After the 7th day of the therapy, lansoprazole continued at a dose of 30 mg for half an hour before breakfast for 4 weeks. The group II of 90 patients received the same treatment as the patients of the group I, with the addition of the probiotic cultures in the form of a capsule comprising *Lactobacillus Rosell-52*, *Lactobacillus Rosell-11*, *Bifidobacterium Rosell-1755* and *Saccharomyces boulardii*, since the beginning of eradication for 4 weeks. Eradication of *H. pylori* infection control was performed 8 weeks after the therapy by rapid urease test and histopathologic evaluation of endoscopic biopsies or by stool antigen test for *H. pylori*. **Results.** Eradication of *H. pylori* infection was achieved in 93.3% of the patients who received probiotics with eradication therapy and in 81.8% of patients who were only on eradication therapy without probiotics. The difference in eradication success was statistically significant, ($p < 0.05$). The incidence of adverse effects of eradication therapy was higher in the group of patients who were not on probiotic (28.6%) than in the group that received probiotic (17.7%), but the difference was not statistically significant. **Conclusion.** Multiple probiotic strains addition to triple eradication therapy of *H. pylori* achieves a significantly better eradication success, with fewer side effects of antibiotics.

Key words:
helicobacter pylori; helicobacter infection; disease eradication; clinical protocols; probiotics; treatment outcome.

Apstrakt

Uvod/Cilj. Pojedine studije ukazuju na dobrobit primene različitih probiotskih sojeva u kombinaciji sa antibioticima u eradikaciji infekcije prouzrokovane bakterijom *Helicobacter pylori* (*H. pylori*). Cilj ove studije bio je da se proceni efekat koadministracije multiplih probiotskih sojeva i trostruke eradikacione terapije za *H. pylori*. **Metode.** U ovu prospektivnu studiju bilo je uključeno 167 bolesnika sa dispeptičkim simptomima i hroničnim gastritisom kod kojih je dijagnostikovana *H. pylori* infekcija i koji su randomizirani u dve grupe. Grupa I, od 77 bolesnika, podvrgnuta je trostrukoj eradikacionoj terapiji u trajanju od 7 dana, sa lansoprazolom 2 × 30 mg pola sata pre obroka, amoksicilinom 2 × 1 000 mg na 12 sati i klaritromicinom 2 × 500 mg na 12 sati. Posle 7. dana nastavljena je terapija lansoprazolom u dozi od 30 mg pola sata pre doručka još 4 nedelje. Grupa II, sastavljena od 90 bolesnika, podvrgnuta je istoj terapiji kao i bolesnici grupe I, uz dodatak kulture probiotika u vidu jedne kapsule, koja je sadržala *Lactobacillus Rosell-52*, *Lactobacillus Rosell-11*, *Bifidobacterium Rosell-1755* i *Saccharomyces boulardii*, od početka eradikacione terapije, u trajanju od 4 nedelje. Kontrola eradikacije *H. pylori* infekcije izvršena je 8 nedelja nakon terapije brzim ureaza testom i patohistološkom procenom endoskopskih biopsija ili testom antigena u stolici na *H. pylori*. **Rezultati.** Eradikacija *H. pylori* infekcije postignuta je kod 93,3% bolesnika koji su dobijali probiotik uz eradikacionu terapiju i kod 81,8% bolesnika koji su bili samo na eradikacionoj

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terapiji bez probiotika. Razlika u uspehu eradikacije *H. pylori* bila je statistički značajna, ($p < 0,05$). Učestalost ispoljavanja neželjenih efekata eradikacione terapije bila je veća u grupi I bolesnika koji nisu bili na probiotiku (28,6%), nego u grupi II koja je dobijala probiotik (17,7%), ali razlika nije bila statistički značajna. **Zaključak.** Dodatkom multiplih probiotiskih kultura trostrukoj eradikacionoj terapiji *H. pylori* infekcije postiže se značajno bolji stepen eracikacije sa manje neželjenih efekata primene antibiotika.

Ključne reči:
helicobacter pylori; infekcija, helicobacter; bolest, eradikacija; protokoli, klinički; probiotici; lečenje, ishod.

Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic bacterium that colonizes the gastric mucosa. Since the discovery of *H. pylori* in 1983, numerous studies have shown that this bacterium is a major risk factor in the development of peptic ulcer, chronic gastritis, gastric cancer and mucosa associated lymphoid tissue (MALT) lymphoma. The prevalence of infection in developed countries is 20–50%, while in developing countries it reaches up to 80% [1]. However, the majority of infected people, despite the existence of chronic gastritis has no symptoms, while 10–20% obtain peptic ulcer. In 1–2% of infected persons there is the risk of developing gastric cancer during the lifetime, and in less than 1% the risk of developing gastric lymphoma. Therefore, elimination of infection is a good strategy for the prevention of gastric malignancy. In addition, indications for eradication of *H. pylori* infection are certain extragastric diseases, such as idiopathic thrombocytopenic purpura, vitamin B12 deficiency and unclear iron deficient anemia [2–4].

Standard triple eradication therapy with a proton pump inhibitor (PPI) and two antibiotics (clarithromycin, amoxicillin or metronidazole) is still the most frequent first line therapy. The rising resistance to clarithromycin requires the introduction of sequential or concomitant therapy as the first option, especially for the areas with high resistance to clarithromycin. Levofloxacin in combination with different antibiotics showed a good therapeutic effect as the first, second or third line therapy but arriving problem is the emergence of resistance to fluoroquinolones [5, 6]. In a study from Japan newer fluoroquinolones sitafloxacin, which shows the lowest minimum inhibitory concentration for *H. pylori*, proved to be effective in combination with PPI, amoxicillin and metronidazole as third line therapy [7]. Quadruple therapy with bismuth, like fluoroquinolones, has proved effective as a first line therapy or as rescue therapy. The main reason for the increased resistance to antibiotics is point mutations which accumulate in the *H. pylori* DNA [5].

The main principle of treating *H. pylori* infection is based on the introduction of newer therapeutic regimes which would achieve better therapeutic effects and reduce side effects of antibiotics. A number of studies suggest that lactic acid bacteria, such as *Lactobacillus* and *Bifidobacterium*, increase the effect of eradication of *H. pylori* and reduce side effects when combined with antibiotics. These bacteria inhibit the growth of *H. pylori* by means of the secretion of protein components, or organic acids, reduce the capacity of adherence of *H. pylori* on the gastric epithelial cells, reduce the mucosal inflammation, and stabilize the gastric barrier [8, 9]. Many preparations of probiotics in addition to the strains of *Lactobacillus* and *Bifidobacterium* contain probiotic yeast, such as *Saccharomyces boulardii* [10]. Unlike the studies that support the co-administration of probiotics with the standard therapy, sequential therapy and therapy based on levofloxacin [11, 12], other studies do not support co-administration of probiotics [13, 14]. The literature has evaluated the use of individual probiotic strains (usually *Lactobacillus spp*, *Saccharomyces spp*, *Bifidobacterium spp* and *Bacillus clausii*) and multiple strains. The reason for conflicting results of particular studies is the lack of placebo-controlled trials, a significant heterogeneity in probiotics treatment duration and the time of administration of probiotics with respect to the use of antibiotics and the use of different probiotic strains [2].

The aim of this prospective randomized study was to evaluate the effect of co-administration of multiple probiotic strains (*Lactobacillus spp*, *Bifidobacterium spp* and *Saccharomyces spp*) and triple *H. pylori* eradication therapy.

Methods

This prospective randomized study included a total of 167 patients with endoscopic and histological findings of chronic gastritis (41.3% or 69 males and 98 or 58.7% females), diagnosed with *H. pylori* infection in the period of one year (during 2014). The patients had symptoms of upper dyspepsia (nausea, epigastric pain, postprandial bloating, belching, heartburn), without alarming symptoms (bleeding, anemia, weight loss). The criteria for exclusion of patients from the study were: younger than 18 years, the use of antibiotics, proton pump inhibitors (PPI) and H2 receptor antagonists in the last two weeks (according to Maastricht IV consensus report [4]), allergy to penicillin and any other administered drugs, previous eradication of *H. pylori*, pregnancy, lactation, previous gastric surgery, gastric malignancy, peptic ulcer, peptic pyloric stenosis, reflux esophagitis and significant comorbidity with the presence of malignant disease and/or bad general condition.

Patients were randomized into two groups. The group I of 77 patients (27 or 35.1% males and 50 or 64.9% females), average age 56.2 ± 14.8 years (range 21 to 80 years) were treated with triple eradication therapy of *H. pylori* infection, within 7 days, with a proton pump inhibitor lansoprazole 2 × 30 mg half an hour before a meal, amoxycillin 2 × 1.000 mg at 12 hours and clarithromycin 2 × 500 mg *per* 12 hours. After the 7th day of the therapy, lansoprazole was continued in a dose of 30 mg for half an hour before breakfast for 4 weeks. The group II of 90 patients (42 or 46.7% males and

48 or 53.3% females), average age 56.3 ± 14.8 years (range 20 to 82 years) underwent the same therapy as well as the patients in the group I (lansoprazole, amoxicillin and clarithromycin in the same dose and duration), with the addition of probiotic cultures in the form of a capsule during the lunch, from the beginning of eradication therapy within 4 weeks. One capsule contains 5 billion live probiotic lyophilized microorganisms: *Saccharomyces boulardii*, *Lactobacillus Rosell*-52, *Lactobacillus Rosell*-11 and *Bifidobacterium Rosell*-175. The lyophilization process makes that the viability of probiotic microorganisms in the composition is maintained. Upon release from the capsule microorganisms become active again in the intestine where their effect is required.

The initial diagnosis of *H. pylori* infection was done by biopsy tests during upper gastrointestinal (GI) endoscopy (rapid urease test and histopathological examination). Upper GI endoscopy was performed with videoendoscopy OLYMPUS EXERA CV-165 and OLYMPUS EXERA CLV-180. Standard forceps was used for taking endoscopic biopsies from the antrum and corpus of the stomach. The result of rapid urease test was read after 1 h, 3 h and 24 h. The test was considered positive if the substrate color changed from yellow to red. For identification and semiquantitative assessment of *H. pylori* by histological examination, endoscopic biopsy specimens were fixed in a standard solution of 10% formalin for 24 hours. Subsequently, the tissue was routinely processed, embedded in paraffin, cut at a microtome to the thickness of 4 microns. After dewaxing and processing in graduated alcohol, selected sections were stained with hematoxylin-eosin (HE) and the Giemsa method.

H. pylori infection eradication control was done 8 weeks after the treatment with upper GI endoscopy, rapid urease test, and histopathologic evaluation of staining by Giemsa. Eradication of *H. pylori* infection was considered successful in case of negativity of both tests to *H. pylori* (urease test and histological examination). In a small number of patients who did not agree with the second endoscopy (5 or 6.5% of the patients of the group I, and 13 or 14.4% of the patients of the group II) assessment of the success of eradication was carried out by stool antigen test for *H. pylori*. Stool antigen test is a qualitative immunochromatography test type CER-TEST BIOTEC SL. The test relies on the presence of nitrocellulose membranes coated with mouse monoclonal antibodies against *H. pylori* in the test line, in the field of results, and with rabbit polyclonal antibodies to a specific protein, in the control line. Anti-*H. pylori* antibodies present on the membrane (test line) bind dye conjugate and the red line used to read the results becomes visible.

Statistical analysis of the results was carried out with the help of tests for the arithmetic mean, standard deviation, Student's *t*-test, Fisher's exact test and χ^2 test. Differences between individual parameters were considered significant at *p* values less than 0.05.

Results

Among the groups of patients there were no statistically significant differences found in gender, age, smoking status, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetyl salicylic acid (ASA), as well as in terms of comorbidity (Table 1). Regarding the comorbidity in the group I there was hypertension (14 or 18.2%), diabetes mellitus 3 (3.9%), hypothyroidism (3 or 3.9%), hyperthyroidism (1 or 1.3%) and chronic obstructive pulmonary disease (3 or 3.9%). Within the group II of the patients there was hypertension (22 or 20%), diabetes mellitus (8 or 8.9%), hypothyroidism (2 or 2.2%) and chronic obstructive pulmonary disease (COPD) (1 1.1%).

H. pylori infection eradication was achieved in 63 out of 77 (81.8%) patients of the group I and in 84 out of 90 (93.3%) patients of the group II. The difference in the success of eradication between the groups of patients was statistically significant, $\chi^2 = 5.16 > \chi^2$ (1 and 0.05) $= 3.84$, $p < 0.05$, adds ratio (OR) = 3.1 (1.04 < OR < 9.63), confidence interval (CI) 95%; relative risk (RR) = 1.14 (1.01 < RR < 1.28), CI 95% (Table 2).

Table 1

Basic characteristics of the examined groups of patients

Parameter	Group I (n = 77)	Group II (n = 90)	*p*
Gender (male/female), n (%)	27 (35.1)/50 (64.9)	42 (46.7)/48 (53.3)	ns
Age, $\bar{x}$ ± SD	56.2 ± 14.8	56.3 ± 14.8	ns
Smokers, n (%)	10 (13)	13 (14.4)	ns
NSAID users, n (%)	24 (31.2)	26 (28.9)	ns
Comorbidity, n (%)	24 (31.2)	31 (34.5)	ns

NSAID – non-steroidal anti-inflammatory drugs;
Group I – patients treated with triple eradication therapy of *Helicobacter pylori* infection (lansoprazole, amoxycillin, clarithromycin); Group II – patients treated with the same triple eradication therapy as patients of the Group I + probiotic cultures; n – number of patients; *p* – significance (χ^2–test).

Table 2

Comparison of success of eradication of *Helicobacter pylori* (*H. pylori*) infection between the examined groups of patients

Group	Eradicated, n (%)	Not eradicated, n (%)	Total, n (%)
Group I	63 (81.8)	14 (18.2)	77 (46.1)
Group II	84 (93.3)*	6 (6.7)*	90 (53.9)
Total	147 (88)	20 (12)	167 (100)

For explanations see under Table 1. *$p < 0.05$ (χ^2 test).

Comparing the success of eradication between the genders in the group I, infection eradication was achieved in 23/27 (85.2%) women and in 40/50 (80%) men. The difference in the success of eradication by gender was not statistically significant in the group I of patients, $p < 0.05$, OR = 1.44 (0.35 < OR < 6.21) CI 95%; RR = 1.06 (0.86 < RR < 1.31) 95% CI. In the group II *H. pylori* infection eradication was achieved in 39/42 (92.8%) males and 45/48 (93.7%) women. The difference in the success of eradication of *H. pylori* by gender was not statistically significant in the group II, $p < 0.05$, OR = 0.89 (0.13 < OR < 5.94), CI 95%; RR = 0.99 (0.89 < OR < 1.11), 95% CI.

While taking eradication therapy in the patients of the group I there were nausea (in 9 11.6% the patients), metallic taste in the mouth (5 or 6.5%), headache (3 or 3.9%), diarrhea (3% or 3.9) and epigastric pain (3 or 3.9%). Also, in the patients of the group II during eradication therapy there were nausea (7 or 7.7%), metallic taste in the mouth (2 or 2.2%), headache (2 or 2.2%), diarrhea (1 or 1.1%) and epigastric pain (3 or 3.3%). With individual comparative analysis of the incidence of adverse effects there was no statistically significant difference observed between the group I and the group II. In the total of 22 (28.5%) patients of the group I and in 15 (16.7%) patients of the group II adverse effects of the therapy occurred. The total difference in respect of adverse effects of eradication therapy was also not statistically significant between the groups of patients, $\chi^2 = 3.35 < \chi^2$ (1 and 0.05) = 3.84, $p > 0.05$, OR = 1.99 (0.89 < OR < 4.46), CI 95%, RR = 1.16 (0.98 < RR < 1.37), 95% CI (Table 3). In both groups of the patients adverse effects in any case did not lead to discontinuation of the therapy.

Table 3

Analysis of the incidence of adverse effects in the examined groups of patients

Adverse effect	Group I (n = 77)	Group II (n = 90)	*p*
	n (%)	n (%)	
Nausea	9 (11.7)	7 (7.7)	ns
Metallic taste	5 (6.5)	2 (2.2)	ns
Headache	3 (3.9)	2 (2.2)	ns
Diarrhea	3 (3.9)	1 (1.1)	ns
Epigastric pain	3 (3.9)	3 (3.3)	ns
Total	23 (29.9)	15 (16.7)	ns

For explanations see under Table 1.

We compared the frequency of lagging dyspeptic symptoms after eradication therapy. Dyspeptic symptoms maintained in 19 (24.6%) of the patients of the group I and in 21 (23.3%) of the patients of the group II. The difference was not statistically significant, $\chi^2 = 0.04 < \chi^2$ (1 and 0.05) = 3.84, $p > 0.05$, OR = 0.93 (0.43 < OR < 2.01) CI 95%, RR = 0.95 (0.55 < RR < 1.63), CI 95%.

Discussion

In recent years, many alternative treatments of *H. pylori* infection have been studied because of the phenomena of resistance to antibiotics and occurence of adverse effects of the application of several antibiotics simultaneously, as in case of concomitant therapy. One attempt to solve this problem is the use of probiotic cultures. Certain initial studies had promising results, but many issues remained unresolved. Namely, we do not know the exact mechanism of probiotics' action. Different probiotic strains can cause different host responses, depending on the immune status of the host. Studies on animal models suggest that probiotic bacteria establish immune regulation by controlling the balance of proinflammatory and anti-inflammatory cytokines, which can lead to reduction of the activity of inflammation in the stomach. Previous studies had shown that *Lactobacillus salivarius* inhibits the secretion of gastric epithelial cells stimulated by *H. pylori* over the interleukin-8. It also leads to increased production of secretory IgA in the intestinal epithelium, which enhances the mucosal barrier. The non-immunological mechanisms of probiotics action are the product of antimicrobial substances, competition with *H. pylori* to adhesion receptors, stimulation of mucus production and stabilization of the mucosal barrier. Some strains, such as *Lactobacillus plantarum 299V* and *Lactobacillus rhamnosus GG* induce mucin gene expression. Certain strains of *Bifidobacterium* release antimicrobial protein substances that act against *H. pylori* [15].

Latest studies show that the strain of *Lactobacillus pentosus LPS16* through the production of lactic acid achieves the bactericidal effect against *H. pylori* and that the bactericidal effect is identical to the antibiotics sensitive and resistant strains of *H. pylori*. It has been shown that lactic acid have a higher bactericidal activity than the acetic acid and hydrochloric acid. Therefore, the application of *Lactobacillus pentosus LPS16* proved to be useful in prevention and in the treatment of *H. pylori* infection, especially in cases of *H. pylori* resistance to many antibiotics [9].

In most studies on animal and human models different strains of *Lactobacillus* were tested (*L. Jahnsonii La1*, *L. rhamnosus GG*, *L. casei*, *L. acidophilus*, *L. brevis*, *L. gasseri OLL2716*, *L. reuteri*), *Bifidobacterium* strains (*B. lactis*, *B. animalis*, *B. breve*) and probiotic yeast *Saccharomyces boulardii*. The diagnosis of *H. pylori* infection and the effect of probiotics on *H. pylori* gastritis is usually assessed by serological tests, rapid urease test, urea breath test, stool antigen test and histological examination of gastric biopsies [16, 17].

In our study we examined the effect of probiotic cultures to *H. pylori* infection, which contained *Lactobacillus Rosell-52*, *Lactobacillus Rosell-11*, *Bifidobacterium Rosell-175*

and *Saccharomyces boulardii*. For the initial diagnosis of *H. pylori* infection, we used rapid urease test and histological examination of gastric biopsies. In order to assess the eradication success we used rapid urease test, histological examination of gastric biopsies and stool antigen test for *H. pylori*. Qualitative immunochromatography test antigen in stool, which we used, has high sensitivity, over 94%, and specificity over 99%.

Our study showed a significantly higher success in infection eradication in the group of patients treated with triple eradication therapy combined with probiotic cultures than in the group without probiotics (93.3% *vs* 81.8%), $p < 0.05$. The success of eradication by gender was not statistically significantly different in the examined groups of patients. Despite the fact that in a small number of patients in the group with probiotic there were side effects of eradication therapy manifested (17.8%) compared to the group without probiotics (28.6%), the difference was not statistically significant ($p > 0.05$).

One of the first clinical studies on the effects of probiotics on *H. pylori* eradication is a study by Canducci et al. [18], which shows that *Lactobacillus acidophilus LB* significantly enhances the effect of eradication, but does not diminish the adverse effects of antibiotic therapy. The open and uncontrolled study by Sheu et al. [19] shows that *Lactobacillus acidophilus La5* and *Bifidobacterium lactis Bb12* increase the effect of eradication and decrease adverse effects of triple eradication *H. pylori* therapy. Studies of some authors show that the application of *Lactobacillus acidophilus La5* together with *Bifidobacterium lactis Bb12* before quadruple secondary line therapy after failure of triple eradication therapy enhances the effect of eradication. The benefit of the application of probiotic strains seems not to depend on the type of applied strains [1].

A recent meta-analysis of 14 randomized controlled trials has shown that the addition of probiotics to standard triple therapy improves eradication effect, established by both intention-to-treat (ITT) analysis (OR = 1.67, 95% CI: 1 : 38 to 2 : 02) and per-protocol (PP) analysis (OR = 1.68, 95% CI: 1 : 35 to 2 : 08). Also, most studies have proved a positive effect of probiotic supplementation on the adverse effects of antibiotics. In particular, the frequency of diarrhea caused by antibiotics was reduced with the correction of intestinal dysbiosis by probiotics. However, the authors conclude that the results should be interpreted with caution because the studies are designed differently with different antibiotics and different probiotic strains being used [20]. Padoł et al. [21] suggest that when assessing eradication effect of triple therapy, one should take into account the distribution of CYP2C19 polymorphism, which may be of greater importance in relation to the manner of use of probiotics (single or combined strains) and in relation to the length of triple therapy (7 or more days).

After completing the triple eradication therapy, maintenance of dyspeptic symptoms was slightly more common in the group without probiotics (24.7%) than in the group with probiotics (23.3%) but the difference was not statistically significant. Maintenance of dyspepsia after termination of antibiotic therapy could be linked to the success of eradication but also with the application of probiotics. It would be expected from probiotics to have positive effect on reducing of dyspeptic symptoms, while causing dyspeptic symptoms by probiotics would be less likely. In fact, studies have shown no adverse effects of probiotics, considering that some strains of probiotics such as *Lactobacilli* and *Bifidobacteria* are part of a normal gastrointestinal microbiota [22–24].

Conclusion

Our study shows that triple *H. pylori* eradication therapy achieves a statistically significantly better eradication success combined with probiotic strains *Lactobacillus Rosell-52*, *Lactobacillus Rosell-11*, *Bifidobacterium Rosell-175* and *Saccharomyces Boulardii*. Also, there are fewer adverse effects of antibiotic therapy by using probiotics although the difference is not statistically significant. To come to more accurate conclusions about the effects of probiotic strains in the treatment of *H. pylori* infection further studies and standardization of studies in terms of the type of the applied probiotic strain is required, as well as the number of probiotic strains (single use of a single strain or multiple strains), and the length and time of administration of probiotics in relation to antibiotic therapy.

REFERENCES

1. *Patel A, Shar N, Prajapati JB*. Clinical application of probiotics in the treatment of Helicobacter pylori infection: A breaf review J Microbiol Immunol Infect 2014; 47(5): 429−37.
2. *Papastergiou V, Georgopoulos SD, Karatapanis S*. Treatment of Helicobacter pylori infection: meeting the challenge of antimicrobial resistance. World J Gastroenterol 2014; 20(29): 9898−911.
3. *Shiotani A, Cen P, Graham DY*. Eradication of gastric cancer is now both possible and practical. Semin. Cancer Biol. 2013; 23(6 Pt B): 492−501.
4. *Malfertheiner P, Megraud F, O'morain CA, Atherton J, Axon AT, Bazzoli F*, et al. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. Gut 2012; 61(5): 646−64.
5. *O'Connor A, Vaira D, Gisbert JP, O'Morain C*. Treatment of Helicobacter pylori infection 2014. Helicobacter 2014; 19(Suppl 1): 38−45.
6. *Xiao SP, Gu M, Zhang GX*. Is levofloxacin-based triple therapy an alternative for first-line eradication of Helicobacter pylori?, A systematic review and meta-analysis. Scand J Gastroenterol 2014; 49(5): 528−38.
7. *Furuta T, Sugimoto M, Kodaira C, Nishino M, Yamade M, Uotani T*, et al. Sitafloxacin-based third-line rescue regimens for Helicobacter pylori infection in Japan. J Gastroenterol Hepatol 2014; 29(3): 487−93.
8. *Praitano MM, Iacono S, Francavilla R*. Probiotics and Helicobacter pylori infection. Med Universit 2012;14:217-223.
9. *Zheng PX, Fang HY, Yang HB, Tien NY, Wang MC, Wu JJ*. Lactobacillus pentosus strain LPS16 produces lactic acid, inhibiting multidrug-resistant Helicobacter pylori. J Microbiol Immunol Infect 2014; pii: S1684-1182(14)00079-6. (In Press)

10. *Saxelin M, Tynkkynen S, Mattila-Sandholm T, Vos WM*. Probiotic and other functional microbes: from markets to mechanisms. Curr Opin Biotechnol 2005; 16(2): 204−11.
11. *Du YQ, Su T, Fan JG, Lu YX, Zheng P, Li XH*, et al. Adjuvant probiotics improve the eradication effect of triple therapy for Helicobacter pylori infection. World J Gastroenterol 2012; 18(43): 6302−7.
12. *Efrati C, Nicolini G, Cannaviello C, Sed NP, Valabrega* S. Helicobacter pylori eradication: sequential therapy and Lactobacillus reuteri supplementation. World J Gastroenterol 2012; 18(43): 6250−4.
13. *Manfredi M, Bizzarri B, Sacchero RI, Maccari S, Calabrese L, Fabbian F,* et al. Helicobacter pylori infection in clinical practice: Probiotics and a combination of probiotics + lactoferrin improve compliance, but not eradication, in sequential therapy. Helicobacter 2012; 17(4): 254−63.
14. *Shavakhi A, Tabesh E, Yaghoutkar A, Hashemi H, Tabesh F, Khodadoostan M,* et al. The effects of multistrain probiotic compound on bismuth-containing quadruple therapy for Helicobacter pylori infection: A randomized placebo-controlled triple-blind study. Helicobacter 2013; 18(4): 280−4.
15. *Collado MC, González A, González R, Hernández M, Ferrús MA, Sanz Y*. Antimicrobial peptides are among the antagonistic metabolites produced by Bifidobacterium against Helicobacter pylori. Int J Antimicrob Agents 2005; 25(5): 385−91.
16. *Lesbros-Pantoflickova D, Corthésy-Theulaz I, Blum AL*. Helicobacter pylori and probiotics. J Nutr 2007; 137(3 Suppl 2): 812S−8S.
17. *Myllyluoma E, Veijola L, Ahlroos T, Tynkkynen S, Kankuri E, Vapaatalo H*, et al. Probiotic supplementation improves tolerance to Helicobacter pylori eradication therapy - a placebo-controlled, double-blind randomized pilot study. Aliment Pharmacol Ther 2005; 21(10): 1263−72.
18. *Canducci F, Armuzzi A, Cremonini F, Cammarota G, Bartolozzi F, Pola P,* et al. A lyophilized and inactivated culture of Lactobacillus acidophilus increases Helicobacter pylori eradication rates. Aliment Pharmacol Ther 2000; 14(12): 1625−9.
19. *Sheu BS, Wu JJ, Lo CY, Wu HW, Chen JH, Lin YS,* et al. Impact of supplement with Lactobacillus- and Bifidobacterium-containing yogurt on triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther 2002; 16(9): 1669−75.
20. *Zhu R, Chen K, Zheng Y, Zhang H, Wang J, Xia Y,* et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. World J Gastroenterol 2014; 20(47): 18013−21.
21. *Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH*. The Effect of CYP2C19 Polymorphisms on H. pylori Eradication Rate in Dual and Triple First-Line PPI Therapies: A Meta-analysis. Am J Gastroenterol 2006; 101(7): 1467−75.
22. *Hammerman C, Bin-Nun A, Kaplan M*. Safety of probiotics: comparison of two popular strains. BMJ 2006; 333(7576): 1006−8.
23. *Boyle RJ, Roy MR, Tang ML*. Probiotic use in clinical practice: what are the risks. Am J Clin Nutr 2006; 83: 1256−64.
24. *Mäkeläinen H, Tahvonen R, Salminen S, Ouwehand AC*. In vivo safety assessment of two Bifidobacterium longum strains. Microbiol Immunol 2003; 47(12): 911−4.

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