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MINIREVIEWS

Are probiotics useful in *Helicobacter pylori* eradication?

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Abstract

Helicobacter pylori (*H. pylori*) is considered an etiologic factor for the development of peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma. Therapeutic schemes to eradicate the bacteria are based on double antibiotic therapy and proton pump inhibitor. Despite many therapeutic improvements in *H. pylori* eradication treatment, it is still associated with high infection rate also in developed countries. Bacterial resistance and adverse events occurrence are among most frequent causes for anti- *H. pylori* treatment failure. Several studies have reported that certain probiotic strains can exhibit inhibitory activity against *H. pylori* bacteria. In addition, some probiotic strains can reduce the occurrence of side effects due to antibiotic therapy and consequently increase the *H. pylori* eradication rate. The results of the prospective double-blind placebo-controlled studies suggest that specific probiotics, such as *S. boulardii* and *L. johnsonni* La1 probably can diminish the bacterial load, but not completely eradicate the *H. pylori* bacteria. Furthermore, it seems that supplementation with *S. boulardii* is a useful concomitant therapy in the standard *H. pylori* eradication treatment protocol and most probably increases eradication rate. *L. reuteri* is equally effective, but more positive studies are needed. Finally, probiotic strains, such as *S. boulardii*, *L. reuteri* and *L. GG*, decrease gastrointestinal antibiotic associated adverse effects.

Key words: *Helicobacter pylori*; Probiotics; Eradication therapy; Adverse effects; Strain

Core tip: Poor eradication rates in *Helicobacter pylori* (*H. pylori*) infected patients have been reported, which was mostly explained by the increased rates of bacterial resistance to antibiotics and a low compliance for those drugs. This situation needs the development of alternative treatment options for the *H. pylori* infection in patients. The results of recent studies suggest that certain probiotic strains supplemented to standard eradication therapy diminish the frequency of gastrointestinal adverse effects and consequently also increase the eradication rates.

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HELICOBACTER PYLORI

Helicobacter pylori (*H. pylori*) is a Gram-negative micro-organism. From the original discovery of genus *Helicobacter*, more than 20 species have now been formally defined[1]. The gastric mucosa is well protected against bacterial infection. After ingestion *H. pylori* must survive the bactericidal activity of the gastric lumen and enter the mucus layer. *H. pylori* is highly adapted to special conditions in the stomach. It possess flagella, which enable colonization of the gastric epithelium[2]. Moreover, the bacteria produce enzyme urease, which hydrolyzes urea into carbon dioxide and ammonia and elevates pH in the surroundings of the bacteria. The enzyme activity is highest at low pH[3]. The *H. pylori* bacteria usually causes chronic infection due to a complex balance between host factors and virulence bacterial factors. Among several bacterial factors one of the main factors, which drive Th17 inflammation, represents the secreted peptidyl prolyl cis, trans-isomerase[4]. In the colonization and chronic infection the adherence of the bacteria to the gastric epithelium is also very important. Lipopolysaccharide is a component of bacterial wall consisted of an O-specific polysaccharide chain, oligosaccharide, and the lipid A. The Lewis-like antigens (Le^x, Le^y, Le^a, Le^b) of *H. pylori* lipopolysaccharide are also expressed in the epithelial cells of gastric mucosa, therefore they probably play an important role in adherence to gastric cells[5]. Around 5% of the *H. pylori* genome encodes outer membrane proteins (OMP). OMP are adhesins on the surface of the bacteria, which promote binding to the epithelial cells in the stomach. The major OMP is the blood group antigen-binding adhesion A (BabA), which mediates the binding of *H. pylori* to the fucosylated Le^b blood group antigen. It also mediates binding to salivary mucin MUC5B, a proline-rich glycoprotein, and to the glycoprotein gp-340[6]. The second most important OMP is the sialic acid-binding adhesion (SabA)[7]. SabA mediates the binding of the bacteria to the sialyl-dimeric-Le^x, to salivary mucin MUC5B, and to salivary glycoproteins like MUC7 and zinc-glycoprotein[8]. In gastric colonisation are also involved other OMPs like AlpA, AlpB, HopZ and HomB. Tight binding of bacteria to gastric epithelial cells is enabled therefore also with BabA2 and Saba adhesins. The *H. pylori* is very closely associated with extracellular MUC5AC and epithelial cells that produce MUC5AC, therefore MUC5AC plays a role in the adherence of *H. pylori* to the gastric mucosa. The important receptor for bacteria is the Le^b structure present in the normal gastric tissue and MUC5AC is the most important carrier of Le^b, with the attachment being made through BabA[9].

H. pylori infection is still one of the most common bacterial infections all over the world. *H. pylori* infection is very common in Eastern Europe, Africa and most Asian countries[10]. In developed parts of the world the prevalence has lowered and is below 10% in children and below 30% in adults[11].

Twenty percent of infected individuals develop symptomatic gastritis, gastric or duodenal ulcer, gastric adenocarcinoma, and non-Hodgkin's gastric lymphoma[12]. *H. pylori* is also associated with iron-deficiency anemia, idiopathic thrombocytopenic purpura and vitamin B_{12} deficiency[13]. Several bacterial, host and environmental factors have been studied to determine clinical outcome of *H. pylori* infection. Among bacterial factors, virulence genes are most important, and the severity of *H. pylori* related disease correlates with the presence of *cagA, vacA s1m1* and *babA2* genotypes[14,15]. Chronic active gastritis can proceed to precancerous lesions such as gastric mucosal atrophy and intestinal metaplasia, and finally to the development of gastric adenocarcinoma. The results of recent studies support the beneficial effect of *H. pylori* eradication on preventing gastric cancer as well as on the regression of mucosal atrophy and intestinal metaplasia of the gastric mucosa[16]. Therefore, precancerous gastric lesions demand rapid detection of *H. pylori* and eradication of bacteria.

H. pylori is suggested to have also beneficial properties. Several studies and meta- analysis showed an inverse relationship between *H. pylori* infection and asthma occurrence[17,18]. The association was stronger for children than adults, but more prospective studies are needed to confirm the above mention relationship. In addition, *H. pylori* infection probably decreases the prevalence of obesity in children[19]. The association between *H. pylori* infection and gastroesophageal reflux disease is still unclear. Although it has previously been suggested that *H. pylori* eradication may cause reflux disease, the existence of such association was not confirmed recently[20].

The standard eradication therapy consists of two antibiotics and a proton pump inhibitor lasting for 7-14 d. The percentage of treatment failures is rising and major cause for this is bacterial resistance to frequently prescribed antibiotics. The frequent use of clarithromycin for respiratory tract infections has led to high *H. pylori* clarithromycin resistance rates[21]. Resistance to metronidazole has less clinical impact. Metronidazole resistance can be partially overcome by increasing the dose and treatment duration. The resistance of *H. pylori* to metronidazole has been reported between 30% and 40%[22]. The eradication levels using standard triple therapy is between 60% and 80%, the last being regarded as the minimal acceptable level according to the Maastricht guidelines[23]. Therefore, there is a great interest of developing new alternatives to eradication therapy, such as quadruple therapy or sequential therapy. Another possibility is to add the additional

drug to standard therapy protocol. Several studies have examined the potential influence of probiotics as adjuncts to standard therapy on *H. pylori* eradication rate.

In addition, probiotics were studied to lower the frequency of side effects, because adverse events relating to *H. pylori* therapy are an important factor that influences compliance. The overall rate of adverse events was 53.3% in a multicentre study[24]. The most common adverse events reported are diarrhoea, nausea and vomiting, which have significant physical and social impacts, and it has been shown that side effects were significantly associated with decreased compliance and treatment failure[25].

PROBIOTICS

The FAO/WHO definition of probiotics is that probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host[26]. The most commonly used probiotics in humans are microorganisms belonging to genera *Bififobacterium, Lactobacillus, Saccharomyces* and *Bacillus*[27]. They are used as single species or multispecies preparation. The beneficial effects of probiotics seem to be strain-specific and dose-dependent. Clinical studies of probiotics in human are rapidly increasing. The beneficial effect of probiotics is already confirmed in diseases such as acute diarrhoea, antibiotic- associated diarrhoea, functional gastrointestinal disorders, inflammatory bowel disease, *etc*[28]. *H. pylori* infection is also a field in which particular interest in using probiotics is arising.

GASTRIC MICROBIOTA

Lactobacillus species are acid resistant and they are normally present in healthy gastric microbiota. Some strains can even adhere to gastric epithelial cells so they can stay longer than other bacteria in the stomach[29]. These has been confirmed in a study where it was possible to detect *L. reuteri* 55730 adhering to gastric epithelial cells of healthy volunteers a few hours after oral administration[30]. Elliott *et al*[31] has observed that in a rat with active gastric ulcer the local microbiota changed toward Gram-negative bacteria including *E. coli* while the *Lactobacullus* species almost disappeared. In the process of gastric mucosa healing the *Lactobacillus* population reappeared again and these process was accelerated by the oral lactulose administration. This study suggests that normal gastric microbiota participate in maintaining healthy mucosa. In addition, the oral intake of probiotics may reinforce protective functions in the stomach.

DIFFERENT MECHANISMS OF PROBIOTICS ANTIBACTERIAL ACTION

Probiotics can inhibit *H. pylori* by several immunological and non-immunological mechanisms.

Probiotics are capable of modifying immunologic response of the host. Neutrophils, lymphocytes, plasma cells, and macrophages are involved in the inflammatory response to *H. pylori*. The consequences are increased levels of pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8 and tumor necrosis factor α in the gastric mucosa[32]. Probiotics like *L. salivarius* WB 1004 have *in vitro* reduced IL-8 secretion by gastric epithelial cells[33]. It looks like that at least in vitro *L. acidophilus* can improve *H. pylori*-induced gastric inflammation by inactivating the Smad7 and NFκB pathways[34]. Furthermore, Zhou *et al*[35] demonstrated that *L. bulgaricus* inhibited the activation of the TLR4 signaling pathway and IL-8 production induced by *H. pylori* lipopolysaccharide in SGC-7901 cells. The gastric inflammation can be controlled to some level by different strains of *Lactobacilli* through inactivating JAK2 through JAK– STAT pathways and through higher expression of SOCS protein family[36]. *H. pylori* also induce humoral response of gastric mucosa, which may contribute to gastric mucosal damage. *Lactobacilli* were able to increase the local IgA concentration and decrease specific anti *H. pylori* IgG antibodies in animal models[37,38].

Among non-immunological mechanisms probiotics are capable to influence on bacterial growth by secreting antibacterial substances such as lactic acid, short chain fatty acids, hydrogen peroxide and bactericins. The metabolites can diminish the number of spiral bacteria[39]. Lactic acid has probably an additional effect on *H. pylori* by lowering the pH and inhibiting the urease[40]. *L. acidophilus* CRL 639 secret an autolysin, a proteinaceous compound released after cell lysis, which has some antibacterial activity[41]. Substances, similar to isocoumarin antibiotics, are produced by *B. subtilis* and those can also kill *H. pylori* bacteria[42]. *L. reuteri* ATCC 55730 produce unique substance called reuterina which suppress growth of spiral bacteria[43].

Mucins are high-molecular-weight glycoproteins that protect the gastric epithelium. The gastric surface-type mucin is decreased in infected patients, because *H. pylori* suppresses the expression of MUC5AC and MUC1 genes[44]. It has been shown that *L. plantarum* strain 299v increases the expression of MUC2 gene and that *L. rhamnosus* GG stimulates the expression of MUC3 gene and the subsequent extracellular secretion of mucin by colon cell cultures[45,46]. Therefore, the ability of some probiotic strains to increase mucin production can protect the gastric mucosal barrier against the adherence of pathogenic bacteria such as *H. pylori*.

Adherence of *H. pylori* to the host tissue is of vital importance for colonization the gastric mucosa[47]. There are several proposed mechanisms of anti-adherence activity of probiotics. *L. reuteri* and *W. confusa* are capable of competing with *H. pylori* strains for adhesion sites. For example, *L. reuteri* strains, JCM 1081 and TM

105, inhibit the binding of spiral bacteria to glycolipid receptors asialo-GMI and sulfatide[48]. In addition, Sakarya *et al*[49] demonstrated that *S. boulardii* contains neuraminidase activity, which removes surface α(2-3)-linked sialic acid, the ligand for the sialic acid-binding *H. pylori* adhesion.

POSSIBLE ROLE OF PROBIOTICS IN *H. PYLORI* TREATMENT

Eradication failure rate of more than 20% and high percentage of adverse effects of antibiotic therapy are main problems in standard eradication therapy protocols. Furthermore, lover compliance due to adverse events results in higher antibiotic resistance of bacterial strains. Studies published to date suggest that probiotics can have dual role in fighting against *H. pylori* infection. They diminish the frequency of gastrointestinal adverse events caused by antibiotic therapy and increase the eradication rate. The probiotics have been experimentally used as single therapy in eradication protocols or as therapeutic agent used concomitantly with standard eradication therapy.

Probiotics as single therapy in H. pylori treatment

The first *in vitro* positive results were published in 1989[50]. Bhatia *et al*[50] discovered that *H. pylori* growth *in vitro* was inhibited, if *L. acidophilus* was present in the culture. Michetti *et al*[51] studied for the first time the effect of probiotics [*L. acidophilus* (La1)] on the *H. pylori* colonisation in humans. The study showed that the density of bacterial load diminishes in the probiotic group of asymptomatic patients, whereas complete eradication of *H. pylori* was not successful. Similarly, Wang *et al*[52] revealed that after intake of *B. lactis* Bb12 and *L. acidophilus* La5 in *H. pylori* infected adults a decrease in urea breath test values was detected. The bacterial load was evaluated by the semi-quantitative ^{13}C-urea breath test in subjects treated with *L. johnsonii* La1[53], *L. brevis* CD2 lyophilized bacteria[54], *B. bifidum* BF-1[55], *L. reuteri* ATCC 55730[43], *L. gasseri* OLL 2716[56], and with multispecies probiotics such as a combination of *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6457[57] or combination of *L. rhamnosus* GG, *L. rhamnosus* LC705, *P. Freudenreichii* JS and *B. lactis* Bb12[58]. Regardless of the used probiotics the authors reported significant decrease in ^{13}C-urea breath test values in the probiotic group of studied patients.

Gotteland *et al*[59] included 182 asymptomatic children infected with *H. pylori* and they were divided into four groups: standard triple therapy group, *S. boulardii* and inulin synbiotic group, *L. acidophilus* LB probiotic group, or control group without any therapy. Statistically significant decreases of urea breath test values were detected in two groups: the standard triple group and the *S. boulardii* inulin synbiotic group of children. The authors concluded that *S. boulardii* can lower the bacterial load in the gastric mucosa of children infected with *H. pylori* bacteria. Surprisingly, in 12% of children in the second group treated with *S. boulardii* and inulin *H. pylori* even the eradication was successful. The same author carried out randomized, double-blind study in 295 asymptomatic children infected with *H. pylori*[60]. The study compared eradication rates after 3 wk of therapy with (1) placebo juice/*L. johnsonii* La1; (2) cranberry juice /*L. johnsonii* La1; (3) placebo juice/heat-killed *L. johnsonii* La1; and (4) cranberry juice/heat-killed *L. johnsonii* La1. Except for the placebo group the eradication rates were above 14% in all tested groups, but didn't statistically significantly differ between each other. Cruchet *et al*[61] included 326 infected children in a similar study. The children were divided into five groups. They were treated for one month either with live or heat-killed *L. johnsonii* La1 or either with live or inactivated *L. paracasei* ST11. The fifth group was the control group. Statistically significant changes in ^{13}C-urea breath test were observed only in the group of pediatric patients treated with live *L. johnsonii* La1 probiotics.

In conclusion, there are only a few studies evaluating the effect of probiotics as monotherapy on *H. pylori* eradication rate. The results of the studies suggest that specific probiotics, such as *S. boulardii* and *L. johnsonni* La1 probably diminish the bacterial load, but not completely eradicate the *H. pylori* bacteria.

Probiotics as adjuvant therapy in standard eradication protocols

Several systematic reviews and meta-analyses regarding effect of probiotics as adjuvant therapy to standard treatment of *H. pylori* infection have been published[62,63]. The authors suggested that probiotics supplementation in general probably increase the eradication rate and reduce the frequency of adverse effects due to double antibiotic therapy. However, the beneficial effects of probiotics seem to be strain-specific, thus, collecting data on different strains in meta-analysis may result in misleading conclusions. Regarding this, a better approach is to pool the data on single probiotics strain and perform a meta-analysis. Szajewska *et al*[64] recently published a systematic review to evaluate the effects of supplementations with *S. boulardii* to standard triple therapy protocol on *H. pylori* eradication rate. Five randomized controlled trials of good methodological quality involving 1307 patients were identified. Among them only 90 children were included. The daily dose of *S. boulardii* ranged from 500 mg to 1000 mg and the duration of the therapy was from 2-4 wk. From four trials the complete data on the eradication rates were available. In 80% of the included patients treated with *S. boulardii* along with triple therapy the eradication was confirmed by standard diagnostic tools. In the control group 9% lover absolute eradication rate

was detected (71%, 324 of the 455 patients). The authors concluded that compared with placebo or no intervention, *S. boulardii* given along with triple therapy significantly increased the eradication rate [relative risk (RR) = 1.13, 95%CI: 1.05-1.21]. The secondary endpoints of the same meta-analysis were also to determine the effect of *S. boulardii* on therapy-related adverse effects. About 24.3% of patients experienced adverse effects in control group treated with triple therapy, compared to 12.9% of patients in probiotic group. Thus, the significant difference was found between the *S. boulardi* group and the control group with respect to the risk of overall adverse effects (five randomised control trials, *n* = 1305, RR = 0.46, 95%CI: 0.3-0.7). The authors analyse also the data of specific adverse effects. With regard to epigastric pain, taste disturbance/dry mouth, nausea or abdominal gas/bloating no significant difference was found between the studied groups. On the other hand, the risk of therapy related diarrhoea was statistically significantly lower in the probiotic group compared with the control group treated only with antibiotics and proton pump inhibitor (5.6% *vs* 12.2%, RR = 0.47, 95%CI: 0.32-0.69). The conclusions of the meta-analysis were that the concomitant use of *S. boulardii* with triple therapy moderately increases *H. pylori* eradication rates and decreases antibiotic related adverse effects, especially diarrhoea.

However, more recent studies published by Song *et al*[65] and Zojaji *et al*[66] didn't confirm positive impact of *S. boulardii* on eradication rate. In Song's study 991 *H. pylori* infected patients were recruited. Patients in group A were treated only with two antibiotics and proton pump inhibitor, in group B *S. boulardii* was added for one month, and in group C the same regimen was used and in addition mucoprotective agent DA-9601 derived from *Artemisia asiatica* was concomitantly prescribed. Interestingly, the eradication rate was significantly higher in group B and C compared to group A only if intention to treat analysis was performed (*P* = 0.003), whereas the eradication rate difference of per protocol patients analysis was not significant. The conclusion was that supplementation with *S. boulardi* could be effective for improving eradication rates by reducing adverse effects thus helping completion of eradication therapy. Zojaji *et al*[66] included 160 adult patients. In the study protocol the probiotic *S. boulardii* was added to clarithromycin, amoxicillin and omeprazole for two weeks. The study showed that probiotics decrease the frequency of adverse events due to antibiotic therapy, but didn't increase the eradication rate of *H. pylori*.

Tong *et al*[62] systematically evaluated the effectiveness of supplementation with different probiotics in increasing *H. pylori* eradication rates. In the publication they also made sub-analysis for different probiotics preparations. In eight of fourteen reported randomized trials single probiotics strain was used. In tree trials, *Lactobacillus species* was administered to the standard eradication therapy[67-69]. However, increased *H. pylori* eradication rate in *Lactobacillus* group was reported in only two studies published by Sýkora *et al*[69] and Canducci *et al*[67]. Overall in the tree studies the eradication rates were 70% in control group and 84% in probiotic supplemented group, which is a statistically significant difference (RR = 2.09, 95%CI: 1.28-3.41). In addition, this meta-analysis revealed that adding probiotics to standard eradication protocols reduces adverse effects during treatment (25% *vs* 39%, RR = 0.44, 95%CI: 0.30-0.66). The positive impact on diarrhoea and taste disturbance was most prominent.

The effectiveness of *L.* GG in children with *H. pylori* infection was studied in a trial from Poland[70]. Of the 83 children tested, 34 children in a probiotics group received *L.* GG 10^9 twice daily for one week concomitantly with triple therapy. No significant difference in *H. pylori* eradication rates between the probiotic and the control group were found (RR = 0.98, 95%CI: 0.7-1.4). This result is in accordance with trials in adult population. Armuzzi *et al*[68] included 60 infected asymptomatic patients in a prospective study in which patients were treated with rabeprazole, clarithromycin tinidazole and *L. GG* or with the same triple therapy and placebo. Diarrhoea, nausea and taste disturbance were significantly reduced in the *L. GG* supplemented group (relative risk = 0.1, 95%CI: 0.1 ± 0.9; relative risk = 0.3, 95%CI: 0.1 ± 0.9; relative risk = 0.5, 95%CI: 0.2 ± 0.9, respectively). In another Italian study 85 asymptomatic adults were included, and the conclusion of the study was that *L. GG* supplementation to standard therapy beneficially affects treatment related adverse effects[71]. However, it seems that *L.* GG has no effect on eradication rates.

Demonstration that *L. reuteri* ATCC 55730 is able to colonize the stomach and duodenum prompted studies regarding the effect of this strain on *H. pylori* eradication rates and the frequency of side effects[30]. In a recent study conducted in Italy, Ojetti *et al*[72] recruited 90 patients in their study. *L. reuteri* supplementation was concomitantly used for 14 d with second line therapy receiving esomeprazole, levofloxacin and amoxicillin in patients infected with *H. pylori*. Probiotic supplementation increased the eradication rate in treated patients (group 1: 36/45, 80%; group 2: 28/45 62%; *P* < 0.05). In addition, the incidence of side effects associated with antibiotic therapy was also significantly lower in the probiotic group. This is in agreement with a trial that also evaluated the impact of *L. reuteri* ATCC 55730 (10^8 CFU for twenty days) as an adjuvant to 10-d sequential therapy in a group of 40 *H. pylori* infected children[73]. The Gastrointestinal Symptom Rating Score was lower in the group of children treated with *L. reuteri* (3.2 *vs* 5.8, *P* < 0.009). However, the use of *L. reuteri* as an adjunct to the sequential eradication therapy had no effect on eradication rates (17/20 *vs* 16/20). In 2009,

Francavilla *et al*[43] compared the eradication rates and antibiotic adverse effects in 40 *H. pylori* positive subjects who were receiving for a month placebo or *L. reuteri* (10^8 CFU) once a day. At the end of the trial patients received standard 10-d sequential eradication therapy. Four week supplementation with *L. reuteri* was effective in lowering gastrointestinal adverse effects and also in reducing bacterial load, whereas no statistical significant difference in eradication rates was observed (88% *vs* 82%). Recently, the same group published results of the double-blind placebo-controlled randomized study using a combination of two *L. reuteri* strains (*L. reuteri* DSM 17938 and *L. reuteri* ATCC 55730) as an adjunct to triple eradication therapy[57]. *L. reuteri* DSM 17938 is a safe daughter strain of previously used *L. reuteri* ATCC 55730 in which two plasmids coding antibiotic resistance were removed. The new *L. reuteri* ATCC 55730 strain seems to have strong anti-inflammatory properties. A combination of two *L. reuteri* strains or placebo was given for two months concomitantly with one-week triple eradication therapy in a second part of the study. A significant reduction of adverse effects was shown in the group treated with eradication therapy and the combination of two *L. reuteri* strains, whereas *H. pylori* eradication rate was only slightly but not significantly increased in the same group of patients. In another study published by Emara *et al*[74] triple therapy supplemented with *L. reuteri* increased eradication rate by 8.6% and reduced the frequency of side effects. *L. reuteri* has a positive influence on gastrointestinal side effects especially diarrhoea, but conflicting reports regarding the impact of *L. reuteri* on *H. pylori* eradication rates demand further studies, especially because new strain combination was developed.

The use of commercial yogurt containing *B. animalis* and *L. casei* combined with conventional triple therapy was investigated in two studies. Sheu *et al*[75] tested the efficacy of this yogurt as adjuvant to triple treatment. The difference in eradication rates of *H. pylori* infection in two groups was statistically significant in favour of probiotic group (73/80 *vs* 63/80, $P < 0.05$). Only patients supplemented with yogurt showed restoration of the percentage of *Bifidobacterium* in the stools at the end of the study to the level in the stools on enrolment. Goldman *et al*[76] was not able to confirm the important role of yogurt supplementation to standard triple therapy in a pediatric study. Contrary to Sheu study protocol, in which yogurt was administrated for five weeks, they continued with the probiotics treatment for three months. In spite of prolonged therapy they found no difference in *H. pylori* eradication rates among the yogurt and the placebo groups of patients (14/33 *vs* 13/32, *P* value is not significant).

Effect of pre-treatment with *L. gasseri* OLL2716 on first-line eradication therapy was studied in a trial published by Deguchi *et al*[77]. About 229 infected patients were randomized into two groups, either one-week triple therapy (rabeprazole, clarithromycin, amoxicillin) or the same therapy with addition of probiotics. Overall eradication was significantly better in the studied probiotic group [intention to treat ($P = 0.018$)/per protocol ($P = 0.041$)], but more prospective studies are needed to evaluate the role of *L. gasseri* OLL2716 in the treatment in *H. pylori* infection.

Beneficial effects of adding fermented milk product containing *L. casei* DN-114 001 to the triple therapy on the eradication rate of *H. pylori* infection in children were showed in a multicentre study from the Check Republic[67]. Eighty-six symptomatic children infected with *H. pylori* were randomized either to receive the omeprazole, amoxicillin, clarithromycin or the same regimen with addition of probiotic for 7 d. Eradication rate was statistically significantly higher in the probiotic group ($P = 0.0045$). *B. claussi* have also been studied as a possible adjunct to standard therapy for *H. pylori* eradication, but the positive effect on eradication rate was not confirmed[78]. The characteristics of important studies where probiotics were used as adjuvant therapy to eradication treatment are presented in Table 1.

CONCLUSION

Chronic infection with *H. pylori* is a well-described risk factor for ulcer disease, gastric adenocarcinoma and MALT lymphoma. Therefore, eradication of *H. pylori* is a primary goal in symptomatic patients. The eradication rates achieved by classic triple therapy consisted from proton pump inhibitor and double antibiotic therapy are quite low and range from 60% to 80%, due to resistance to antibiotics and to moderate patient compliance. Antibiotic-associated gastrointestinal adverse events are the major cause for lower compliance. Therefore, probiotics were proposed as a useful adjunct to improve eradication rate and to decrease the frequency of adverse effects.

So far, mostly different types of *Lactobacillus* and *S. boulardii* were tested. The above-mentioned probiotics most probably decrease the bacterial load but don't eradicate *H. pylori* completely in the gastric mucosa, if they are used as monotherapy. On the contrary, some probiotics when added to classical triple therapy may increase eradication rates. A reasonable amount of evidence exists that supplementation with *S. boulardii* is a useful concomitant therapy in the standard *H. pylori* eradication treatment protocol and most probably increases the eradication rate. *L. reuteri* is also a good candidate for adjunctive therapy, but more positive studies are needed. The effect of other probiotics strains is less well described.

Side effects, caused by double antibiotic therapy, can be lowered with probiotics. Probiotic strains, such as *S. boulardii*, *L. reuteri* and *L. GG*, decrease gastrointestinal antibiotic associated adverse effects, especially diarrhoea. The Maastricht IV/Florence Consensus Report suggests that certain probiotics

Table 1 Probiotics as adjuvant therapy in *Helicobacter pylori* eradication protocols

Ref.	Therapy		Study		Eradication rate		Adverse effects	
	Eradication therapy (d)	Probiotic therapy (d)	No. pts	Reass. of *H. pylori*	*H. pylori* + probiotic therapy	*H. pylori* therapy	*H. pylori* + probiotic therapy	*H. pylori* therapy
Cindoruk *et al*[79]	PPI + AC (14)	*S. boulardii* (14)	124	UBT	44/62[1]	37/62	14/62[1]	37/62
Cremonini *et al*[71]	PPI + CT (7)	*S. boulardii* (14)	43	UBT	17/20	16/20	3/21[1]	12/20
Duman *et al*[80]	PPI + AC (14)	*S. boulardii* (14)	389	-	-	-	17/204[1]	31/185
Hurduc *et al*[81]	PPI + AC (10)	*S. boulardii* (28)	90	UBT, hist.	45/48	34/42	4/48[1]	13/42
Song *et al*[65]	PPI + AC (7)	*S. boulardii* (28)	661	UBT	264/330	237/331	48/330[1]	63/331
Zojaji *et al*[66]	PPI + AC (14)	*S. boulardii* (14)	160	UBT	75/80	65/80	14/80[1]	29/80
Canducci *et al*[67]	PPI + AC (7)	*L. acidophilus* (7)	120	UBT	42/60[1]	52/60	-	-
Sýkora *et al*[69]	PPI + AC (7)	*L. casei* (14)	86	UBT	33/39[1]	27/47	7/39	9/47
Armuzzi *et al*[68]	PPI + CT (7)	*L. GG* (14)	60	UBT	25/30	24/30	12/30[1]	20/30
Szajewska *et al*[70]	PPI + AC (7)	*L. GG* (14)	83	UBT, hist., RUT	23/34	22/32	18/35	13/32
Cremonini *et al*[71]	PPI + CT (7)	*L. GG* (14)	85	UBT	16/21	16/20	3/20[1]	12/20
Ojetti *et al*[72]	PPI + AL	*L. reuteri* (14)	90	UBT	36/45[1]	27/45	10/45[1]	26/45
Lionetti *et al*[73]	PPI + ACT (10)	*L. reuteri* (20)	42	UBT	17/20	16/20	3/20[1]	9/20
Francavilla *et al*[57]	PPI + (7)	*L. reuteri* (2 strains) (60)	100	UBT				
Emara *et al*[74]	PPI + AC (14)	*L. reuteri* (28)	70	hist., RUT	26/35	23/35	10/35[1]	24/35
Sheu *et al*[75]	PPI + AC (7)	*B. animalis*, *L. casei* (35)	160	hist., RUT, UBT	73/80[1]	63/80	15/80[1]	53/80
Goldman *et al*[76]	PPI + AC (7)	*B. animalis*, *L. casei* (90)	65	UBT	14/33	13/32	-	-
Deguchi *et al*[77]	PPI + AC (7)	*L. gasseri* (28)	229	UBT	95/111[1]	79/106	-	-
Nista *et al*[78]	PPI + AC (7)	*B. clausii* (14)	120	UBT	39/50	37/50	21/50[1]	30/50

[1]Statistically significant ($P < 0.05$). -: Data are not available; p: Pediatric study; Pts.: Patients; Reass.: Reassessment; PPI: Proton pump inhibitor: UBT: Urea breath test; Hist.: Histology; RUT: Rapid urease test; A: Amoxicillin; C: Clarithromycin; T: Tinidazole; L: Levofloxacin.

and prebiotics show promising results as an adjuvant treatment in reducing side effects[13].

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