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TOPIC HIGHLIGHT

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Use of probiotics in the fight against *Helicobacter pylori*

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Abstract

After the discovery of *Helicobacter pylori* (*H. pylori*), and the evidence of its relationship with gastric diseases, antibiotic-based therapies were developed, which efficacy was however limited by antibiotic resistance and lack of patient compliance. A vaccine would overcome these drawbacks, but currently there is not any *H. pylori* vaccine licensed. In the frame of the studies aimed at finding alternative therapies or at increasing the efficacy of the current ones and/or reducing their side effects, the investigation on the use of probiotics plays an interesting role. *In vitro* and preclinical studies have shown the feasibility of this approach. Several clinical trials indicated that administration of probiotics can reduce the side effects of *H. pylori* eradication treatment, increasing tolerability, and often increases the overall efficacy. The results of these trials vary, likely reflecting the variety of probiotics assessed and that of the eradication treatment, as well as the differences in the geographic area that imply different *H. pylori* strains distribution, host susceptibility, and therapy efficacy. In conclusion, the use of probiotics appears promising as an adjuvant for the current *H. pylori* eradication treatment, though it still requires optimization.

Key words: *Helicobacter pylori*; Treatment; Probiotics; *Lactobacilli*; *Bifidobacteria*

Core tip: *Helicobacter pylori* (*H. pylori*) is the only bacterium that has been linked to cancer to date. The efficacy of antibiotic-based eradication treatment is hampered by antibiotic resistance and side effects that may reduce patient compliance. No vaccine is currently licensed. Thus, administration of alternative compounds that may increase the efficacy of the treatment and/or reduce side effects is of particular interest. Administration of probiotics has been proposed to increase tolerability and efficacy of the *H. pylori* eradication treatment. The results of the most recent clinical trials seem to confirm these hypotheses.

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INTRODUCTION

The gastric mucosa of more than 50% of human population is estimated to be colonized by *Helicobacter pylori* (*H. pylori*), a curved or spiral-shaped, flagellated, microaerophilic, Gram-negative bacillus. *H. pylori* was isolated and cultured from human gastric biopsies only at the beginning of 1980s[1] and classified a few years later[2], although bacteria in mammalian stomach had been already observed at the end of 19th century. Prevalence of *H. pylori* infection is much higher in developing than in developed countries[3,4], most probably as a consequence of different hygiene and living conditions.

H. pylori colonization is mostly asymptomatic, but a subset of the *H. pylori*-infected population develops chronic gastritis, peptic ulcer, or gastric mucosa-associated lymphoid tissue (MALT) lymphoma[5-7]. Moreover, *H. pylori* infection increases the risk of developing gastric cancer, thus WHO has included this pathogen among the category 1 carcinogens[8-10]. Both direct bacterial action and host

response originate chronic inflammation of the stomach and the pathological outcome in the presence of *H. pylori* infection. To make inoffensive the strong host immune response, *H. pylori* activates escaping strategies and exerts on the host immune system immunomodulatory action, through various mechanisms, including the ability of eliciting T regulatory cells and of driving T helper type 1 (Th1) and Th17 response[11-14], but establishing in the majority of the cases a relatively harmless coexistence. Nevertheless, the concomitance of certain host genetic backgrounds (such as particular polymorphisms of inflammatory cytokines[15-18]), or particular susceptibility to develop gastric autoimmunity through the activation of CD4+ Th1 cells specific for *H. pylori* peptides cross-reactive with H+, K+-ATPase[19] and factors that make *H. pylori* particularly virulent (such as CagA, the product of cytotoxin-associated gene A[20,21]), can alter this equilibrium and lead to pathological outcomes including malignant lesions.

Diagnosis of *H. pylori* infection in symptomatic subjects is generally followed by the eradication therapy. The eradication causes regression of *H. pylori*-induced peptic ulcer and MALT lymphoma[10,22], and would represent a tool for reduction of gastric cancer incidence in risk populations[23]. Current standard therapies against *H. pylori* are based on the use of one proton pump inhibitor plus two or more antibiotics for one-two weeks[24], with several variants also according to the geographic area[25-27]. The efficacy of the treatments has decreased below 80%[28], mainly due to the increase of antibiotic resistance but also to side effects (such as nausea, vomiting, diarrhea, constipation, fever, headache, *etc.*[29]), which, although generally mild, may cause poor patient compliance and discontinuing of the treatment. Thus, modifications in the combination, sequence, and duration of drug administration are continuously under investigation[24,29].

Vaccination would represent a valid alternative approach to overcome the existing problems with the antibiotic therapy. A large number of preclinical efficacy studies for vaccine candidates against *H. pylori* have been published, which however were followed by a limited number of clinical trials[30]: unfortunately, the trials that included efficacy studies failed. Presently, there is not any licensed anti-*H. pylori* vaccine.

Probiotics include several microorganisms, mostly within *Lactobacillus* or *Bifidobacterium* genus, which can be grouped under the current definition living microorganisms, which, upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition[31,32]. The beneficial effects of probiotics on gastrointestinal diseases, including antibiotic-associate diarrhea, have been widely described[33-37]. Thus, due to the gastric localization of *H. pylori* colonization and its relationships with gastric diseases, it is not surprising that several studies were carried out on the effects of probiotics on *H. pylori*. Numerous *in vitro* studies, demonstrating bacterial killing or inhibition[38], were followed by preclinical and clinical studies[38-40]. These studies indicated only partial efficacy of probiotics against *H. pylori* when administered alone, but increase of efficacy and/or reduction of side effects when probiotics were administered together with the eradication treatment[39,40].

The present review is aimed at summarizing the results of the clinical trials reported in the last two years, which assessed the efficacy of probiotics administration as an adjuvant for *H. pylori* eradication treatment. The efficacy against *H. pylori* of probiotics administered alone will be not discussed.

META-ANALYSES

Three meta-analyses on probiotics supplementation of *H. pylori* eradication therapy were published in 2013. All three meta-analyses concluded, in agreement each other, that overall probiotics exerted beneficial effects on eradication treatment, with eradication rates significantly increased. Two of these meta-analyses observed significant decrease of side effects when probiotics were added to the eradication treatment, while one of them did not observe any variation. The variety of *H. pylori* eradication treatments and of the probiotics used makes impossible a direct comparison of the results of the single studies each other; nevertheless, the overall results may provide valuable information about the possible efficacy of probiotics.

The first analysis, by Wang *et al*[41] included 10 trials (9 in adults, 1 in children), corresponding to 1469 patients overall. Of these, incidence of side effects was reported in 6 trials corresponding to 978 patients. The analysis considered only parallel controlled trials, with confirmation of eradication outcome by urea breath test or rapid urea test, and comparing at least 2 branches of treatment consisting of control group (proton pump inhibitor plus 2 antibiotics with placebo or no additional intervention) and experimental groups (the same eradication regimen plus *Lactobacillus*-containing and *Bifidobacterium*-containing probiotic compound preparation). Eradication was observed in 82.63% (535 patients eradicated/708 treated) (intention-to-treat analysis, ITT) or 87.42% (535/612) (per-protocol analysis, PP) of the subjects receiving eradication therapy supplemented by probiotics, *vs* 67.85% (517/762, ITT) or 76.43 (496/649, PP) in the control group receiving eradication therapy alone. Side effects were observed in 15.37% (71/462, ITT) of the probiotics + therapy group, *vs* 31.01% (160/516, ITT) of the control group.

The second analysis, by Zheng *et al*[42] included 9 trials (6 in adults, 3 in children), corresponding to 1163 patients. Five of these trials, corresponding to 739 patients, reported the incidence of side effects. The analysis considered only randomized controlled trials that compared the efficacy of probiotic preparations, administered together with triple or sequential therapy, with that of placebo (or blank control) in *H. pylori*-positive participants. *H. pylori* positivity was assessed by ^{13}C-urea breath test, and/or histology, and/or stool antigen test. Eradication rate increased from 68.54% (414/604, ITT) of the control group to the 78.18% (437/559, ITT) of the

probiotics+therapy group (receiving a single *Lactobacillus* species or multi-strain compounds including *Lactobacilli*). Side effects did not show variations overall, being observed in 31.21% (108/346, ITT) of probiotics + therapy group, *vs* 34.86% (137/393, ITT) of the controls. Remarkably, significant differences were found when examining separately the subgroup of five trials in which a single *Lactobacillus* species was administered; in this case, significant increase of eradication rate was accompanied by decrease of side effects as compared to control group.

The third analysis, by Li *et al*[43] included 7 pediatric randomized controlled trials, corresponding to 508 patients. Five of them, corresponding to 393 subjects, reported the incidence of side effects. The studies included in this meta-analysis compared at least two treatment groups: one receiving triple regimen (proton pump inhibitor and two antibiotics) with placebo or no extra intervention, and one receiving the same triple regimen plus probiotics. Eradication was confirmed by urea breath test or stool antigen test or histology or rapid urea test. Probiotic preparations consisted of multi-strain compounds including *Lactobacillus* and *Bifidobacterium* species, and *S. thermophilus*; one study used *S. boulardii*. Eradication was observed in 78.13% (200/256, ITT) or 82.30% (200/243, PP) of the probiotics + therapy group *vs* 66.67% (168/252, ITT) or 69.42% (168/242, PP) of the controls; the probiotics + therapy resulted efficacious in reducing side effects to 21.72% (43/198) from 42.56% (83/195) observed in control group.

RECENT CLINICAL TRIALS

The trials reported in 2012-2013, in which *H. pylori* eradication treatments with or without probiotics administration were compared, are summarized in Table 1[44-53]. All were randomized clinical trials that included at least one *H. pylori* eradication treatment group and one group that received the same eradication treatment plus probiotic compounds.

Evidence of the ability of probiotics treatment to both significantly increase the efficacy of *H. pylori* treatment and decrease the side effects was provided in 3 out of 10 studies. Efficacy only in reducing side effects was observed in 3 out of the 9 studies for which the side effects description was available; in 1 out of these 9 studies, the efficacy on *H. pylori* eradication only was observed. In 2 out of 10 studies, inefficacy of probiotics was observed, both in increasing eradication and in decreasing side effects. In summary, efficacy against *H. pylori* was reported in 5 out of 10 studies, while in 6 out of 9 studies reduction of side effects was observed; overall, efficacy against *H. pylori* and/or reduction of side effects was observed in 8 out of 10 studies.

Interestingly, in 3 out of the 5 studies in which probiotics were ineffective to increase eradication rates, the eradication rates achieved with the treatment without probiotics were already relatively high (> 80%). Conversely, in the 5 studies in which inclusion of probiotics significant increased efficacy, the treatment in the absence probiotics gave relatively low eradication rates (< 70%).

In one of these studies[45], one group received probiotics plus lactoferrin, based on a previous study[54] which hypothesized that lactoferrin could contribute to increase eradication efficacy. No differences of eradication rates were observed between the group that received and the group that did not receive lactoferrin; however, eradication rates in all groups of this study were near 90%, thus possible improvements were difficult to observe. Moreover, lactoferrin did not influence the rate of side effects[45].

POSSIBLE MECHANISMS FOR THE EFFICACY OF PROBIOTICS IN REDUCING SIDE-EFFECTS AND/OR INCREASE EFFICACY OF *H. PYLORI* ERADICATION TREATMENT

Antibiotic-associated diarrhea is a frequent phenomenon[35]. Interestingly, diarrhea is the most common side-effect of *H. pylori* eradication therapy that results to decrease upon probiotics administration (Table 1). Antibiotics are known to induce diarrhea because they alter intestinal microflora, leading to a proliferation of resistant bacterial strains, and to impairment of the fermentation processes carried out by intestinal microorganisms[35]. Some authors have already demonstrated significant reduction of antibiotic-associated diarrhea, as well as of acute diarrhea, by using probiotic compounds[34,35,37]. The action of probiotics can be ascribed to their ability to stimulate mucosal immune mechanisms (*e.g.*, activation of local macrophages to increase antigen presentation, and modulation of cytokine profiles). For instance, administration of probiotics-containing yogurt to *H. pylori*-infected children was shown able to restore the normal *Bifidobacterium* spp./*E. coli* ratio, increment serum IgA, and reduce serum interleukin 6 (*IL-6*)[55]. Probiotics action may also be exerted via non-immune mechanisms through antagonism and competition with potential pathogens; in particular, probiotics are able to produce antioxidants and antimicrobial substances, alter local pH, stimulate mucin production, enhance intestinal barrier functions, modify pathogen-derived toxins, and may affect colonization by competing with pathogens for nutrients and for the binding to the host cell surface[37,56]. Finally, microbiota, through the gut-brain connection, have been suggested to be involved in the pathophysiology of mood and anxiety disorders, and possible role of probiotics in modulating abdominal pain has been proposed, based on studies in rats[36,57].

All these general actions of probiotics have been proposed to contribute to their efficacy in increasing *H. pylori* eradication and decreasing side effects when used together with eradication therapy[58,59]. A limited number of *in vitro* or non-clinical studies have been described in

Table 1 Summary of trials using probiotics with *Helicobacer pylori* eradication treatment (2012 to date)

Treatment (oral administration)	Probiotic(s) (oral administration)	Region	Eradication rates		% side effects	Probiotic(s) efficacy	Ref.
			Intention to treat	Per protocol			
Esomeprazole 20 mg, levofloxacin 500 mg, amoxicillin 1 g, all *bid*, 7 d	10^8 CFU *Lactobacillus reuteri*, during therapy + further 7 d	Italy	80% (36/45)	80% (36/45)	66.7	Significant increase of eradication rates and reduction of side effects (nausea and diarrhea)	[44]
	Control		62.2% (28/45)	62.2% (28/45)	100.0		
Esomeprazole 20 mg and amoxicillin 1 g, both *bid*, 5 d; then esomeoprazole 20 mg, clarithromycin 500 mg, tinidazole 500 mg, all *bid*, 5 d (sequential therapy)	10^9 CFU *L. Acidophilus*, 10^9 CFU *L. bulgaricus*, 5×10^8 CFU *Bifidobacterium bifidum*, 10^9 CFU *Streptococcus thermophilus*, *bid*, during therapy	Italy	89% (65/73)	92.9% (65/70)	39.7	Eradication rates unaffected; significant decrease of side effects (metallic taste, abdominal/epigastric pain, diarrhea). Addition of lactoferrin did not influence the results achieved with probiotics	[45]
	Probiotics as above + 200 mg lactoferrin		88.5% (69/78)	93.2% (69/74)	38.5		
	Control		88.2% (67/76)	94.4% (67/71)	65.8		
Omeprazole 1 mg/kg *sid*, amoxicillin 50 mg/kg *bid*, clarithromycin 15 mg/kg *bid*, 7 d	5×10^9 CFU *L. plantarum*, 2×10^9 CFU *L. reuterii*, 2×10^9 CFU *L. casei subsp. rhamnosus*, 2×10^9 CFU *B. infantis* and *B. longum*, 10^9 CFU *L. salivarius*, 10^9 CFU *L. acidophilus*, 5×10^9 CFU *S. thermophilus*, 10^9 CFU *L. sporogenes*, *sid*., during therapy	Italy	88.2% (30/34)	88.2% (30/34)	14.5	Non-significant increase of eradication rates; significant reduction of side effects (epigastric pain, nausea, vomiting, diarrhea)	[46]
	Control		76.4% (26/34)	76.4% (26/34)	61.5		
Omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1 g, all *bid*, 7 d	*L. acidophilus* 14 d after therapy	China	79.2% (61/77)	82.4% (61/74)	89.2	Significant increase of eradication rates; no influence on side effects	[47]
	3×10^7 *L. acidophilus* 14 d before therapy		79.5% (62/78)	81.6% (62/76)	85.5		
	Control		60.8% (48/79)	61.5% (48/78)	87.2		
Omeprazole 20 mg, bismuth subcitrate 240 mg, amoxicillin 1 g, clarithromycin 500 mg, all *bid*, 14 d (quadruple therapy)	*L. casei*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *B. breve*, *B. longum*, *S. thermophilus*, total viable count 10^8 CFU, *bid*, during therapy	Iran	76.6% (69/90)	82.1% (69/84)	18.8	No significant differences in efficacy and overall side effects (decrease of diarrhea but increase of abdominal pain)	[48]
	Control		81.1% (73/90)	84.8% (73/86)	16.6		
Standard triple therapy (details not disclosed)	3×10^9 CFU *B. infantis*, *bid*, during therapy	United Arab Emirates	83% (83/100)		3.0	Significant increase of eradication rates, and reduction of incidence of antibiotic-induced side effects (diarrhea, loose bowel motion)	[49]
	3×10^9 CFU *B. infantis*, *bid*, 14 d before therapy, then during therapy		90.5% (86/95)		2.1		
	Control		68.9% (73/106)		14.2		
Sequential therapy (details not disclosed), 10 d	3×10^9 CFU *B. infantis*, *bid*, during therapy		90.8% (69/76)		1.3		
Amoxicillin 50 mg/kg, furazolidone 6 mg/kg, both *bid*, 7 d, plus omeprazole 1 mg/kg *sid* 28 d	*L. casei*, *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *B. infantis*, *B. breve*, *S. thermophilus*, total viable count 10^9 CFU, *sid*, during therapy	Iran	90.1% (30/33)		21.2	Significant increase of eradication rates, and reduction of side effects (nausea, vomiting, diarrhea)	[50]
	Control		69.7% (23/33)		63.6		
Furazolidone 200 mg, tetracycline 500 mg, lansoprazole 30 mg, *bid*, 7 d	*L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *S. faecium*, 1.25×10^9 CFU each, *sid*,during therapy and further 23 d	Brazil	81.8% (45/55)	89.8% (44/49)	59.3/44.9	Non-significant increase of eradication rates and non-significant reduction of side effects (at 7 and 30 d)	[51]
	control		76.9% (40/52)	85.1% (41/48)	71.2/60.4		
Standard triple therapy	*L. acidophilus*, *B. bifidum* during and after therapy	China	83.7% (36/43)			Increase of eradication rates	[52]
	Control		64.4% (29/45)				
Omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, all *bid*, 14 d	2×10^8 CFU *L. reuteri*, *sid*, during therapy and further 14 d	Egypt	74.3% (26/35)	74.3% (26/35)	28.6%	Non-significant increase of eradication rates; significant decrease of side effects (taste disorders, diarrhea)	[53]
	Control		65.7% (23/35)	65.7% (23/35)	68.6%		

CFU: Colony forming unit; Control: Group that received the eradication treatment without probiotics or with placebo; the term "significant" was used when $P < 0.05$ was reported in the corresponding paper.

the literature that can help to understand possible direct and specific activity of probiotics against *H. pylori*. The most recent studies are described below.

H. pylori urease catalyzes the conversion of urea to carbon dioxide and ammonia; ammonia in turn forms ammonium hydroxide, which neutralizes the local acidity in favor of *H. pylori* survival. Some studies reported the ability of *Lactobacillus casei* (*L. casei*) to inhibit *H. pylori* ure-

ase[60,61]; the specific effect on urease was suggested by the fact that such inhibition was observed under experimental conditions that did not influence the bacterial growth. This activity may be due to the activity of lactic acid[60]. More in general, anti *H. pylori* activity exerted by lactic acid bacteria has been proposed to be due to organic acids produced by these bacteria[56,60,62].

Recently, some *Lactobacillus* strains (*L. gasseri* Chen and *L. plantarum*) have been reported to be able to inhibit *H. pylori* adherence to gastric epithelial cells[63]. Similar results were described for some *Lactobacillus* strains (including *L. acidophilus*, *L. johnsonii*, and *L. salivarius* subsp. *salicinius*) that were able to reduce *H. pylori* adhesion to the human gastric adenocarcinoma cell line AGS, and also its intracellular growth; generally, this activity was more evident using culture supernatants of *Lactobacilli* rather than using bacterial cells[64]. *L. salivarius* was also able to counteract the increase of IL-8 production induced by *H. pylori* in AGS cells[64]. Administration of *L. johnsonii* or *L. salivarius* to rats infected by *H. pylori* revealed a reduction of bacterial load, of local IL-8 production, and of gastric inflammation[64]. Moreover, *L. johnsonii* La1 culture supernatant was found able to reduce *H. pylori* motility and its adherence to the human gastric epithelial cell line MKN74, providing a possible explanation of the ability of *L. johnsonii* La1 to reduce gastric colonization in *H. pylori*-infected Mongolian gerbils[65]. In the same animal model, long-term administration of yogurt supplemented with probiotics (*L. acidophilus, L. bulgaricus, B. lactis, S. thermophilus)* was found to reduce *H. pylori* colonization, TNF-α expression, gastric inflammation and intestinal metaplasia as compared with infected controls not receiving probiotics[66].

Probiotics may also interfere with the activation of specific host pathways by *H. pylori*. *L. acidophilus* produces conjugated linoleic acids (CLA) that have been shown by some studies able to interfere with inflammatory outcomes of *H. pylori* infection[67]. This interference targets nuclear factor-κB pathway[67,68], which is known to be induced by *H. pylori*. Consistently with these observations, CLA from *L. acidophilus* or *L. plantarum* was also shown to suppress the *H. pylori*-induced IL-8 and TNF-α expression by the AGS cell line[69].

Further studies showed that *L. acidophilus* can also interfere with the Smad7 activation, also in this case resulting in reduced inflammatory events[68]. Conditioned media from *L. salivarius*, *L. rhamnosus*, and *L. plantarum* were found to suppress the *H. pylori*-induced Il-8 expression and NFκB activation in AGS cells, without inhibiting *H. pylori* growth; *L. plantarum* was also able to suppress the activation of *c-jun* (which is one of the proto-oncogenes activated by *H. pylori* CagA[70]) *in vitro*, and to attenuate gastric inflammation in a rat model of *H. pylori* infection[71].

CONCLUSION

Probiotics are generally considered safe to administer to humans, and several strains have already received indication for use in specific disorders[37]. Probiotics treatment as an adjuvant of eradication treatment showed in the recent trials efficacy against *H. pylori* and/or decreased side effects of the treatment in most of the studies - but not in all. This confirms the previously reported results. It must be remarked that the efficacy of probiotics treatment in increasing eradication can be evaluated only when eradication rates in the controls that did not receive probiotics are low enough; on the other hand, the efficacy in reducing side effects can be observed when side effects are present, *i.e.,* in almost all studies. To date, it does not appear clear whether probiotics may be more effective in particular subgroups, and if predictive factors for treatment success can be identified. The meta-analysis by Zheng *et al*[42] suggested that using single *Lactobacillus* species could achieve better results than administering multi-strain compounds; however, this was not highlighted by other meta-analyses, and remains a point to be further clarified. Possible influence of age, lifestyle (dietary habit in particular), grade of infection, type of gastroduodenal symptoms, and other similar factors could be analyzed in wider meta-analyses, as this information is provided at least in part in the reports of the clinical trials. Conversely, the possible influence on probiotics efficacy of essential factors such as for instance the *H. pylori* infecting strain, the host genetic background, and the host microbiome, could be assessed only by studies specifically designed to investigate the relevance of these factors.

It is known that *H. pylori* isolates are different according to the geographic areas, and that the susceptibility to *H. pylori* infection and the outcome of the infection vary according to both *H. pylori* and/or host genetic background, that may result in combinations much more harmful than others[17,18,21], and may also influence the eradication rates achievable. Thus, it is not unexpected that some studies, in disagreement with others, did not find beneficial effects of probiotics adjunctive treatment: having more information of *H. pylori* isolates and on genetic background of the hosts would strongly help to understand the reasons of success or of failure of probiotics.

Possible specific activity of probiotics against defined *H. pylori* factors is still largely to be understood. Indeed, the decrease of inflammatory cytokines, restoration of IL-10, suppression of NFκB activation, *etc.*, in the majority of the cases may be indirect effects, *i.e.,* related to the ability of probiotics to reduce *H. pylori* adhesion (*in vitro* studies) or colonization (*in vivo* studies). To date, the only proposed possible specific *H. pylori* target for probiotics has been urease[60,61]. It would be interesting to experimentally assess the possible interference of probiotics or probiotics factors with the *in vitro* and/or *in vivo* activities of other well-characterized *H. pylori* factors such as for instance CagA and VacA, besides urease. However, it must be said that probiotics may have low chance of entering in direct and massive contact with *H. pylori* as the latter resides under the mucus layer of the gastric mucosa, in large part adherent to the epithelial cells, where probiotics are unlikely to arrive in significant amount. In fact, the optimal conditions for probiotics colonization are present

in the large intestine, where the highest concentration of probiotics is found, while scarce concentration of probiotics is usually found in the stomach[72]. Thus, at least for therapeutic use, it seems more likely that probiotics exert indirect and non-specific rather than direct and specific anti-*H. pylori* activity.

In conclusion, administration of safe probiotics as an adjuvant for the current *H. pylori* eradication treatment appears promising, though it still requires optimization; even in the cases in which the treatments achieve high eradication rates, probiotics may reduce side effects. Further investigation on the mechanisms behind the direct and indirect effects of probiotics on *H. pylori* could help not only to better refine the type of treatment, but also may contribute to better understand some aspects of *H. pylori* pathogenesis.

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