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REVIEW ARTICLE

Probiotics and *Helicobacter pylori* infection

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Received: October 2012. Accepted: October 2012

KEYWORDS
Probiotics, Helicobacter pylori, recolonization, Italy.

Abstract
Approximately 50% of the world population is infected with *Helicobacter pylori* (*H. pylori*), with the highest prevalence rates in developing countries. The current guidelines suggest the use of triple therapy as first choice treatment of *H. pylori* infection, although the eradication failure rate is more than 30%. Current interest in probiotics as therapeutic agents against *H. pylori* is stimulated by the increasing resistance of pathogenic bacteria to antibiotics, thus the interest for alternative therapies is a real actual topic. Available data in children indicate that probiotics seems to be efficacious for the prevention of antibiotic associated side-effects, and might be helpful for the prevention of *H. pylori* complications by decreasing *H. pylori* density, gastritis, and for the prevention of *H. pylori* colonization or re-infection by inhibiting adhesion to gastric epithelial cells. There is no clear evidence that probiotics may increase the *H. pylori* eradication rate.

PALABRAS CLAVE
Probióticos, Helicobacter pylori, recolonización, Italia.

Probióticos e infección por Helicobacter pylori

Resumen
Aproximadamente un 50% de la población mundial está infectada con Helicobacter pylori (H. pylori), con una tasa de prevalencia muy elevada en los países en desarrollo. Los lineamientos actuales sugieren el uso de la terapia triple como primer tratamiento de elección, para tratar la infección por H. pylori. Aunque la tasa de falla en erradicarla es más de un 30%. El actual interés en los probióticos como un agente terapéutico contra H. pylori es incentivada por el incremento en la resistencia de

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esta bacteria patógena a los antibióticos. Por lo tanto, el incremento en el interés en terapias alternativas es un tópico actual. Los datos disponibles en niños indican que los probióticos parecen ser eficaces en la prevención de los efectos colaterales de los antibióticos. También pueden ser de ayuda en la prevención de las complicaciones del H. pylori, al disminuír su densidad y gastritis, además de prevenir la colonización o reinfección de la misma al inhibir la adhesión a las celulas epiteliales gástricas. No hay una clara evidencia que los probióticos puedan incrementar la tasa de erradicación del H. pylori.

Introduction

Probiotics have recently been defined by FAO/WHO as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host".[1] Several controlled clinical trials have shown beneficial outcomes in children for the use of probiotics in some different conditions as rotavirus infections, antibiotic-associated diarrhea, irritable bowel syndrome.[2-4]

Most of commonly used microorganism in clinical practice are lactic acid-producing bacteria such as *Lactobacillus* spp, and microrganisms belonging to genus *Bifidobacterium* and *Bacillus*. Other less commonly used probiotic microorganisms are strains of *Streptococcus*, *Escherichia coli*, and *Saccharomyces*.[3] Different biological effects have been described for probiotics, including the synthesis of antimicrobial substances as lactic acid, hydrogen peroxide and bacteriocins, the competitive interaction with pathogens for microbial adhesion sites, and finally the modulation of the host immune response.[5,6] Research efforts into the clinical effects of probiotics in man are rapidly increasing. A field in which particular interest is arising represents the *Helicobacter pylori* (*H. pylori*) infection.

Helicobacter pylori

The Gram-negative, spiral-shaped bacterium *H. pylori* is a common human pathogen and a public health problem that causes gastritis and peptic ulcers both in adults[7] and children[8] and it is considered an important cofactor in the development of gastric cancer.[9] It is well known that childhood is an important period for acquisition of *H. pylori* infection although several recent articles have reported a decline in the prevalence of *H. pylori* infection in children over the last 10 years.[10] Intrafamiliar transmission of the infection, especially from mother to child, has been hypothesized as the major mode of dissemination.[11] Poor socioeconomic conditions remain a significant risk factor for infection, while exclusive breast-feeding (longer than four months) and higher socioeconomic status have been reported as protective factors against the infection.[8]

Recent evidence-based guidelines from ESPGHAN and NASPGHAN recommend, as first choice treatment, a triple therapy using a proton pump inhibitor (PPI) with amoxicillin and clarythromycin or imidazole given twice daily for 7-14 days.[12] These regimens have the disadvantages of being expensive, risking poor compliance, causing side-effects and in particular encouraging resistance emergence, both in *H. pylori* and commensal organisms exposed gratuitously.[13] Moreover, as most of the colonized children remain asymptomatic, the administration of antibiotic treatments is not ethically acceptable. Other factors limiting the administration of such treatments in developing countries are their high cost for the families from the low socio-economic stratum (the most affected by the infections) and the relative inefficiency of the antibiotics due to the fact that, when treated, children tend to be rapidly re-colonized.[8]

Therefore, recent review studies report eradication rates of standard triple therapy in children below 75%.[14,15] It has been recently shown that a novel 10 day sequential regimen, characterized by the sequential administration of three antibiotics, is highly efficacious in eradicating *H. pylori* infection both in adults and children.[16,17] Our group recorded in children an eradication rate significantly higher than that achieved by the standard triple therapy,[18,19] even in *H. pylori* clarithromycin resistant strain.[19] This treatment is now considered a good option for *H. pylori* infection accordingly to ESPGHAN and NASPGHAN guidelines.[12]

Nowadays, there is considerable interest in alternative therapies (e.g. targeting urease, a known virulence factor) or adjunctive treatment against *Helicobacter pylori*[20] to reduce some of the drawbacks associated with the antibiotic consumption. To these aims, probiotics have been included as "possible" tools for management of the infection[21] and a considerable amount of reports have currently been carried out on their possible role in the treatment and prophylaxis of *H. pylori* infection.

Material and methods

Several *in vitro* studies have shown that various lactobacilli can inhibit *H. pylori* growth. Strains with this ability include *Lactobacillus acidophilus*: *L. acidophilus* strain

CRL 639,[22] *L. acidophilus* in a liophilized culture (Lactisyn),[23] *L. acidophilus* LB,[24] *L. acidophilus* strain NAS and DDS-1;[25] *L. casei rhamnosus* dairy starter;[26] *L. johnsonii* La1;[27] *L. salivarius* WB 1004.[28] Lactobacilli are known to produce by catabolism relatively large amounts of lactate, and this has been considered as the inhibitory and/or the bactericidal factor by some authors.[26,29] Indeed, lactic acid could inhibit the *H. pylori* urease[30] and in addition could exert its antimicrobial effect resulting from the lowering of the pH. Other authors have clearly shown that for some strains a substance other than lactate also contributes to the antibacterial effects. [22,24,27,31-33]

Some probiotic strains such as *L. reuteri*[34] or *Weissellaconfusa*[35] can inhibit *H. pylori* growth by competing with adhesion sites. A probiotic that shares glycolipid-binding specificity with *H. pylori* may compete with pathogens for the receptor site making it possible to hypothesize a future application as anti-adhesion drugs.[36] We have recently shown that, two years after *H. pylori* eradication, 30% of children became re-infected[37] therefore the possibility to reduce this phenomenon by the simple administration of a probiotic is fascinating.

In vitro studies have shown that *L. plantarumstrain* 299v and *L. rhamnosus* GG increase the expression of MUC2 and MUC3 genes[38] and the subsequent extracellular secretion of mucin by colon cell cultures.[39] This property can mediate the ability of these strains to restore the mucosal permeability of gastric mucosa or inhibit the adherence of pathogenic bacteria, including *H. pylori*.[30]

Probiotics could also modify the host immune response.[30] *L. salivarius* WB 1004 has shown *in vitro* to reduce IL-8 secretion by gastric epithelial cells[29] and in animal studies certain lactic acid bacteria (*L. casei, L. acidophilus, L. rhamnosus, L. delbrueckiisubsp. bulgaricus, L. plantarum, Lactococcuslactis* and *Streptococcus thermophilus*) have been able to increase the number of IgA producing cells associated to the lamina propria of small intestine.[40] However, the specific interaction of probiotics with the immune system and the mechanism by which they can exert a beneficial effect are still unclear. Moreover, the immunoadjuvant capacity observed would be a property of the strain assayed and cannot be generalized to genus or species.

Recent studies have defined potentially new probiotic strains of *L. reuteri*, a small minority of which showed strong anti-inflammatory combined with anti-pathogen effects. *L. reuteri* ATCC PTA 6475 produces and exports substances that can interfere with TNFα production in human macrophages[41] and suppresses NF-KB activation affecting apoptosis[42] whilst still retaining its basic anti-pathogen activity during both planktonic and biofilm growth.[43]

Results

Probiotics and *H. pylori* loads: $_{13}$C-urea breath test

In most human studies, the effect of probiotic treatment on the level of *H. pylori* infection has been estimated indirectly by the $_{13}$*C-urea breath test* ($_{13}$C-UBT) delta over baseline value, a well-known semi quantitative measurement of the bacterial load.[44]

In children two studies have been performed (by the same investigators) to evaluate the ability of probiotics to interfere with the intra-gastric bacterial load. First, Cruchet et al. performed a randomized, double blind, controlled study on asymptomatic children screened for *H. pylori* by the $_{13}$C-UBT;[45] *H. pylori*-colonized subjects were distributed into five groups to receive a product containing live *L. johnsonii* La1 or *L. paracasei* ST11, heat-killed La1 or *L. paracasei* ST11, or just vehicle every day for four weeks. A second $_{13}$C-UBT was carried out at the end of this period. The authors detected a moderate but significant difference in $_{13}$C-UBT values in children receiving live La1, whereas no differences were observed in the other groups. Subsequently, in a randomized open trial, Gotteland et al.[46] randomized asymptomatic *H. pylori*-positive children to receive either 7-day triple therapy, or *Saccharomyces boulardii* as a symbiotic simultaneously with inulin or *L. acidophilus* LB daily for eight weeks. An additional group of asymptomatic *H. pylori*-positive children was followed for eight weeks without any treatment. A significant decrease in $_{13}$C-UBT values (repeated after eight weeks) was observed in the antibiotic group and in the *Saccharomyces boulardii* group but not in the *L. acidophilus* LB group. No changes in $_{13}$C-UBT values were observed in untreated children. These results suggest that anti-*H. pylori* activity is species and strain specific, with some probiotics, such as *Saccharomyces boulardii* and *L. johnsonii* La1, interfering with *H. pylori in vivo* more actively than others (*L. acidophilus* LB, *L. paracasei* ST11). This ability of some probiotics strains may represent an interesting alternative to modulate *H. pylori* colonization in children infected by this pathogen through a regular ingestion of the beneficial microorganisms.

Probiotics alone and *H. pylori* eradication rate

Table 1 summarizes the clinical trials performed in children on the effect of probiotics on *H. pylori* eradication rates alone or as an adjuvant to eradicating regimens. In children, two studies evaluated whether probiotics may eradicate alone the *H. pylori* infection. Gotteland et al. showed that *H. pylori* eradication was successful in 66% of children treated with antibiotic, in 12% of the *Saccharomyces boulardii* plus inulin and in 6.5% of *L. acidophilus* LB group; no spontaneous clearance was observed in children without treatment.[46] The fact that the $_{13}$C-UBT was carried out immediately after treatment (in the case of probiotic supplementation) limits the conclusion on a real eradication of the bacterium. A further multicentre randomized, controlled, double-blind trial has been recently carried out in asymptomatic *H. pylori* positive children.[50] Subjects have been allocated into four groups to receive one of the following dietary daily treatments for three weeks: cranberry juice and La1 (CB/La1), placebo juice and La1 (La1), cranberry juice and heat-killed

La1 (CB), or placebo juice and heat-killed La1 (control). After treatment, *H. pylori* eradication rates significantly differed in the four groups: 1.5% in the control group compared with 14.9%, 16.9%, and 22.9% in the La1, CB, and CB/La1 groups, respectively; the latter group showed the highest eradication rate. However, a third $_{13}$C-UBT performed after a one month washout showed a recrudescence of the infection in 80% of those children who had resulted negative, suggesting just a temporary inhibition of *H. pylori* that disappeared once the administration of the inhibiting factors was interrupted.[50] In a recent study *Lactobacillus gasseri* OLL2716 (LG21) was administered in cheese to pre-school children for one year.[53] As a result, 24 of 82 subjects who completed the study (29.3%) were considered to be cured after treatment according to the HpSA test, whereas no eradication was observed in the six subjects in the placebo group consuming ordinary cheese. Spontaneous eradication was found in one of 18 children (5.6%) who represented the control group. The difference in the rate of eradication between the active and control groups was statistically significant. However, HpSA test was repeated in 12 of 24 subjects who were HpSA-negative after undergoing the LG21 treatment, but found that five of those 12 (41.7%) had reversed to be HpSA-positive. Therefore, a final eradication rate was around 17%.[53]

Probiotics plus antibiotic treatment and *H. pylori* eradication rate

It has been suggested that the use of probiotics as an adjuvant to eradicating regimens could improve the success of *H. pylori* eradication. Several clinical trials have been carried out both in adults and children, providing conflicting results. **Table 1** summarizes the clinical trials performed in children on the effect of probiotics on *H. pylori* eradication rates. Sykora et al. supplemented a standard triple therapy with fermented milk containing *L. casei* DN-114 001 for 14 days in *H. pylori* positive patients and showed a significantly higher eradication rate in the probiotic as compared to the placebo group.[47]

Hurduc et al. demonstrated that the addition of *Saccharomyces boulardii* to a standard triple therapy in symptomatic children confers a 12% non-significant enhanced therapeutic benefit on *H. pylori* eradication.[51]

In contrast, Goldman et al. tested the efficacy of a commercial yogurt containing *B. animalis* and *L. casei* as an adjuvant to triple therapy and found no difference in *H. pylori* eradication rates between probiotic and placebo group.[48] In a study of our group, aimed to evaluate the efficacy of probiotics to reduce antibiotic side effects, we found no differences in the eradication rates according to the presence/absence of the probiotic *L. reuteri* ATCC 55730 (SD2112).[49]

Table 1. Summary of clinical trials of probiotics in *Helicobacter pylori* infection in children: effects on eradication rates.

Reference and type of study	Eradication therapy	Probiotic regimen	Eradication rate in probiotics group	Eradication rate in control group
Gotteland et al. 2005[46] O, R, C	None	*Saccharomyces boulardii* plus inulin or *L. Acidophilus* for 8 weeks	6/51 and 3/46 (12% and 6.5%)*	0/71 (0%)
Sykora et al. 2005[47] DB, R, P	Omeprazole, amoxicillin, clarithromycin for 1 week	*L. casei* DN-114 001 for 14 days	33/39 (84.6%)*	27/47 (57.4%)
Goldman et al. 2006[48] DB, R, P	Omeprazole, amoxicillin, clarithromycin for 1 week	*B. animalis + L. casei for 3 months*	15/33 (45.4%)	12/32 (37.5%)
Lionetti et al. 2006[49] DB, R, P	Omeprazole, amoxicillin, clarithromycin, tinidazole (sequential therapy) for 10 days	*L. reuteri* ATCC 55730 for 20 days	17/20 (85%)	16/20 (80%)
Gotteland et al. 2008[50] DB, R, P	None	*L. jonsonii* La1 plus cranberry juice or *L. jonshonii* La plus placebo juice *or* cranberry juice plus heat-killed La1 for 3 weeks	16/70, 10/67, 11/65 (22.9%,14.9%,16.9%)*	1/69 (1.5%)
Hurduc et al. 2009[51] O, R, P	Omeprazole, amoxicillin, clarithromycin for 1 week	*Saccharomyces boulardi for 4 weeks*	45/48 (93.7%)	34/42 (80.9%)
Szajewska et al. 2009[52] DB, R, P	Omeprazole, amoxicillin, clarithromycin for 1 week	*L. rhamnosus* GG for 1 week	23/34 (67.6%)	22/32 (68.7%)
Boonyaricaikij et al. 2009[53] SB, C	None	*L. gasseri* OLL2716 for 1 year	24/82 (29.3%)*	1/18 (6.6%)

(): open; R: randomized; C: controlled; DB: double-blind; P: placebo controlled; SB: single-blinded.
*Statistically significant (p<0.05) *vs* controls.

Recently, in a double-blind placebo-controlled randomized clinical trial no difference was found with respect to *H. pylori* eradication rates between children receiving standard triple therapy supplemented with *L. rhamnosus* GG or placebo.[52]

These data do not represent convincing evidence to support the use of probiotics as an adjunct with the aim of increasing the *H. pylori* eradication rate in children. Nevertheless, further studies are needed to clarify their role in this particular issue. The major limit to establish whether a probiotic is able to significantly increase the eradication rate is represented by the power of the study. Indeed, due to the high eradication rates that we mostly achieve with standard antibiotic treatment, to detect a 10% increase in eradication (secondary to the use of a probiotic strain), given a power of al least 80% and an alpha error level of 5%, 150 patients in each arm are needed to be enrolled.

Probiotics and antibiotic-associated gastrointestinal side effects during *H. pylori* eradication therapy

Bacterial resistance and antibiotic' side-effects represent the most frequent cause for anti-*H. pylori* treatment failure in clinical practice.[13]

Several studies evaluated whether probiotic supplementation might help to prevent or reduce drug-related side effects during *H. pylori* eradication therapy.

The rationale of coupling a probiotic to any antibiotic treatment stem from the result of a recent study showing that daily supplementation with viable probiotic bacteria during and post antibiotic therapy reduces the extent of disruption of the intestinal microbiota as well as the incidence and total numbers of antibiotic-resistant strains in the re-growth population, suggesting that a probiotic should be always associated to an antibiotic.[54]

Our group has performed the first trial in children to determine whether adding probiotics to an anti-*H. pylori* regimen could be of help to prevent or minimize the gastrointestinal side-effects burden.[49] Forty *H. pylori*-positive children were consecutively treated with 10-day sequential therapy, and were blindly randomized to receive either *L. reuteri* ATCC 55730 (SD2112) or placebo (maltodextrin) for 20 days starting from the first day of the anti-*H. pylori* regimen. Overall, in all probiotic-supplemented children as compared to those receiving placebo, there was a significant reduction in the gastrointestinal symptom rating scale score during eradication therapy, which became markedly evident at the end of follow-up. In detail, children receiving *L. reuteri* complained of epigastric pain less frequently during eradicating treatment as well as abdominal distension, belching, disorders of defecation and halitosis thereafter.

In a randomized open trial performed in symptomatic *H. pylori* positive children the occurrence of antibiotic associated side effects was significantly reduced by the addition of *Saccharomyces boulardii* compared with the placebo-supplemented group.[51] However, the authors concluded that it could not be excluded that the incidence and interpretation of side effects was influenced by the fact that it was an open trial.

Finally, in a double-blind placebo-controlled randomized clinical trial preformed by Szayeska et al. the supplementation of standard triple therapy with *L. rhamnosus* GG did not significantly alter the incidence of antibiotic associated side-effects.[52]

Given the results from these studies, probiotic treatment seems to be able to reduce *H. pylori* therapy associated side-effects; however, it is evident that not all probiotics are created equal, that the beneficial effects are strain specific, and each strain must be evaluated individually.

Probiotics and *H. pylori* infection prevention

Many preliminary studies have been done concerning therapeutic or prophylactic vaccination against *H. pylori* with a promising effect,[55] but the translation to a human vaccine remains difficult, in part because the immunology of the stomach is still poorly understood. Considering that primary *H. pylori* infection occurs predominantly in early childhood, prophylaxis of the infection will be almost accomplished by administering probiotics to children for a couple of years while at risk for the primary infection. A pilot study for primary prevention has been recently performed:[53] 308 *H. pylori*-negative children have been randomized to receive LG21 containing cheese or ordinary cheese. In the per-protocol analysis, the rates of *H. pylori* infection were 4.1% and 8.1% in the active and placebo groups, respectively. There was no statistically significant difference between those two groups, although the incidence of the infection was reduced by approximately 50% by the LG21-cheese treatment.[53]

Discussion

Probiotics seem to represent a novel approach to the management of *H. pylori* infection. Despite the fact that there is no clear evidence that the addition of probiotics to the eradicating therapy increases the eradication rates in children, it seems to be efficacious for the prevention of antibiotic associated side effects. Results so far are encouraging and further clinical trials are called for. The design of such studies should be such as to clarify which probiotic strains are suitable, in what form, in what dose and for how long. Another important issue will be to address the cost-effectiveness of using probiotics in different clinical conditions.

As a perspective the persistent strains specific ability, although weak in some cases, of some probiotics to decrease *H. pylori* density and gastritis could be of help in reducing the risk of *H. pylori*-associated complication later in life by attenuating level of infection;[56] further studies are needed to evaluate whether this effect is sustained over time. It is also fascinating the hypothesis of using probiotics to inhibiting *H. pylori* adhesion to gastric epithelial cells thus preventing *H. pylori* colonization especially in young children or *H. pylori* re-infection in

high-risk patients. Finally, clinical studies on a combination of the anti-inflammatory effects of some probiotics strains with the earlier known anti-*H. pylori* effect are claimed for clinical application.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial disclosure

No financial support was received in relation to this article.

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