Probiotics for the treatment of *Helicobacter pylori* infection in children

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**Abstract**

The combination of a proton pump inhibitor and two antibiotics (clarithromycin plus amoxicillin or metronidazole) has been the recommended first-line therapy since the first guidelines for *Helicobacter pylori* (*H. pylori*) infection in children were published. In recent years, the success of eradication therapies has declined, in part due to the development of *H. pylori* resistant strains. Alternative anti-*H. pylori* treatments are currently becoming more popular than the traditional eradication methods. Components that may be used either as a monotherapy or, in combination with anti-microbials, resulting in a more effective anti-*H. pylori* therapy have been investigated in depth by several researchers. One of the potential therapies is probiotic cultures; promising results have been observed in initial studies with numerous probiotic strains. Nevertheless, many questions remain unanswered. In this article, we comprehensively review the possible mechanisms of action of probiotics on *H. pylori* infection, and present the results of published studies using probiotics as possible agents to control *H. pylori* infection in children. The effect of the addition of probiotics to the standard *H. pylori* eradication therapy for the prevention of antibiotic associated side-effects is also discussed.

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**Key words:** *Helicobacter pylori*; Children; Probiotics; Eradication treatment; Prevention

**Core tip:** Because of the decrease in the *Helicobacter pylori* (*H. pylori*) eradication rate after standard triple therapy with a proton pump inhibitor and two antibiotics, alternative therapies have recently received attention. In this article, we comprehensively review the possible mechanisms of action of probiotics on *H. pylori* infection, and present the results of the published studies using probiotics as possible agents to control *H. pylori* growth in children. The effect of the addition of probiotics to the standard *H. pylori* eradication therapy for the prevention of antibiotic associated side-effects is also discussed.
INTRODUCTION

*Helicobacter pylori* (H. pylori) is a highly prevalent, serious and chronic infection that has been associated causally with a diverse spectrum of gastrointestinal disorders including chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma. In both developed and developing countries, H. pylori is most frequently acquired during childhood, and is associated with family size, clustering in families, low socioeconomic status and low level of education. It is commonly thought that once the H. pylori infection is acquired, it evolves toward persistent chronic infection and that spontaneous clearance is relatively rare. However, in a study of children in which prevalence by age was reported in intervals of 1 year, no increase in prevalence by age was observed. This suggests that transient H. pylori infection is not uncommon in children. In 6-24-mo old children in Mexico, Texas, researchers found 80% spontaneous reversion of the infection. In a very recent study involving 718 schoolchildren in Mexico City, Duque et al found that the majority of them maintained their initial status of H. pylori infection throughout the follow-up, while 11.7% showed changes in their infection status. Variables related to health status and infection transmission, such as iron status and number of siblings, were shown to be important for the incidence of H. pylori and the spontaneous clearance of infection.

The combination of a proton pump inhibitor (PPI) and two antibiotics (clarithromycin plus amoxicillin or metronidazole) has been the recommended first-line therapy since the first guidelines for H. pylori infection in children were published. In recent years, the success of eradication therapies has declined, in part due to the development of H. pylori resistant strains. Several studies have documented high resistance rates to clarithromycin and metronidazole in paediatric and adult populations. In Europe, Koletzko et al showed that primary resistance to clarithromycin and metronidazole was present in 20% and 23% of H. pylori strains respectively, while secondary resistance was found in 42% and 35% of the strains recovered after at least one failed treatment for H. pylori. The use of clarithromycin for other indications, mainly for respiratory tract infections, seemed to be the major risk factor for development of primary resistance to this drug. On the other hand, the only risk factor for primary metronidazole resistance was immigration from a non-European country. In fact, the authors showed that children born in Asia, Africa or the Middle East had a 2.4 times higher risk for primary metronidazole resistance than patients of the same age and gender born in Europe. Iterative metronidazole treatments for parasitic or diarrhoeal diseases in children originating from Africa and Asia may be incriminated in the increased primary resistance rates of metronidazole recorded in these paediatric populations. A prospective United States multicentre study in adults and children also documented similar high clarithromycin resistance rates. Declining eradication rates with standard triple regimens have led to the development of alternate treatment options.

Recently, ESPGHAN and NASPGHAN jointly renewed clinical guidelines for H. pylori infection in children using a standardised evidence based approach. Bismuth-based triple therapy or sequential therapy was recommended as alternate first-line regimens. Quadruple therapy with PPI, metronidazole, amoxicillin, and bismuth was also suggested as second line therapy or salvage therapy in the absence of primary culture and sensitivity testing. These regimens have the disadvantages of being expensive, risking poor compliance, causing side-effects and encouraging the emergence of resistance. 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 is their high cost for families from low socio-economic strata (those most affected by the infection) and the relative inefficiency of the antibiotics due to the fact that children tend to be rapidly re-colonized. Alternative anti-H. pylori treatments are currently becoming more popular than the traditional eradication methods. Components that may be used either as a monotherapy or, in combination with antimicrobials, resulting in a more effective anti-H. pylori therapy have been investigated by several researchers. One of the potential therapies involves probiotic cultures; promising results have been observed in initial studies with numerous probiotic strains. Nevertheless, many questions remain unanswered. In this article, we comprehensively review the possible mechanisms of action of probiotics on H. pylori infection, followed by the outcomes of the published studies using probiotics as possible agents to control H. pylori growth in children. The effect of the addition of probiotics to the standard H. pylori eradication therapy for the prevention of antibiotic associated side-effects is also discussed.

DEFINITION

**Probiotic**

An oral supplement or a food product that contains a sufficient number of viable micro-organisms to alter the microflora of the host and has the potential for beneficial health effects.

Probiotic micro-organisms are typically members of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. These bacteria are fermentive, obligatory, or facultative anaerobic organisms, which are typically non-motile and of varying shapes. Typically they produce lactic acid. Their inherent biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract. It is currently hypothesized that these microbes generate small molecular metabolic byproducts that exert beneficial regulatory influence on host biological functions, including short-chain fatty acids such as butyrate. These metabolic effects and encouraging the emergence of resistance.
byproducts are sometimes referred to as “postbiotics” and may function biologically as modulators of immune function[34]. The most studied probiotic bacteria to date belong to the genera Lactobacillus and Bifidobacterium. Some yeasts and yeast byproducts have also been studied and have been used as probiotic agents, for example the yeast Saccharomyces boulardii.

**MECHANISMS OF ACTION**

Several probiotic strains, especially lactobacilli, have exhibited antagonistic properties against H. pylori in vitro[35]. There are several putative mechanisms for probiotic efficacy against H. pylori. Lactobacilli species are commensal in the human alimentary tract and their concentrations in the normal stomach vary between 0 and 10^7/mL fluid[29]. Being acid resistant, they persist in the stomach longer than other bacteria. The possible role of the local microbiota in the protection against gastric lesions is suggested by the study of Elliott et al[32] who found that the level of total aerobes in the stomach of healthy rats ranged from 10^4 to 10^7 CFU/g of tissue, with Gram-negative micro-organisms representing only 5% of the population; autochthonous gastric lactobacilli were present in all rats. However, one day after the induction of gastric ulcers the total aerobe count peaked at 10^7-10^8 CFU/g and remained high for 1 wk. At this time, Gram-negative bacteria were the majority of the total aerobes while the lactobacilli population disappeared. Colonization by Gram-negative bacteria occurred preferentially at the site of ulcer. These findings suggest that the gastroduodenal microbiota, though low numerically, could represent a first line of defense against pathogenic bacteria. Thus, the intake of exogenous lactic acid bacteria, in particular those with probiotic properties, may reinforce these protective functions in the stomach by maintaining local microbiological homeostasis, interfering with H. pylori and/or decreasing inflammatory processes[35].

Non-immunological barriers such as the acidity of the stomach and the gastric mucosal barrier also represent a first line of defense against pathogenic bacteria. Two main types of substances have been implicated in the inhibition of H. pylori by lactic acid bacteria: short chain fatty acids (SCFAs) and bacteriocins. SCFAs such as acetic, propionic, butyric, and lactic acids are produced during the metabolism of carbohydrates by probiotics and have an important role in decreasing pH[33]. Bhatia et al[34] were the first to observe an antagonistic effect of a lactobacillus strain against H. pylori and to implicate SCFAs in this effect. A dose-dependent inhibition of H. pylori growth has been observed with acetic and lactic acid, the latter demonstrating the most intense effect[33]. Lactic acid, in addition to its antimicrobial effect resulting from the lowering of the pH, could inhibit the H. pylori urease. However, the inhibitory effects of lactobacilli on H. pylori differ from strain to strain[28]. Certain lactobacilli synthesize antimicrobial compounds related to the bacteriocin family[36,37]. Bacteriocins are compounds with potential anti-H. pylori activity. They are small, heat-resistant and dialysable peptidic structures with antimicrobial activities, which are synthesized by several bacterial species including lactic acid bacteria[33].

Other possible mechanisms of protection induced by probiotics include inhibition of the adhesion of H. pylori. The adhesion of H. pylori to epithelial cells is important in determining the outcome in H. pylori-associated diseases[38]. Certain lactobacilli can exert their antiadhesion activity by secreting antimicrobial substances[23]. However, strains such as lactobacilli rutenii (L. rutenii) can inhibit H. pylori growth by competing with adhesion receptors[39]. A nonspecific rather than a specific blockage of receptor sites is the most likely mechanism because lactobacilli can inhibit adhesion of a large variety of pathogenic bacteria, although each adheres to its particular receptor on the cells[40].

It has been suggested that intake of probiotics strengthens the mucosal barrier by stimulating mucin production. Reduced mucus secretion in a damaged epithelium is a frequent finding in H. pylori-associated gastritis. H. pylori is known to suppress MUC1 and MUC2A gene expression in a human gastric cell line[41]. It has been shown in vitro that lactobacilli plantarum and lactobacilli rhamnous increase the expression of MUC2 and MUC3 genes[42]. This property can mediate the ability of these strains to restore the mucosal permeability of gastric mucosa[43] or inhibit the adherence of pathogenic bacteria, including H. pylori[44].

Finally, modulation of immune response to pathogens should also be taken into account as a potential mechanism of probiotic efficacy. The inflammatory response to gastric H. pylori infection is characterized by the release of various inflammatory mediators such as chemokines and cytokines[13]. Probiotics could modify the immunologic response of the host by interacting with epithelial cells and modulating the secretion of antiinflammatory cytokines, which would result in a reduction of gastric activity and inflammation[44]. However, the effect of probiotics on the immune response is difficult to generalize. Distinct probiotics strains may generate different immune responses, which, in turn, depend on the host’s immune status[45].

**PROBIOTICS AND H. PYLORI INFECTION**

Several studies using murine models have shown that probiotic treatment, although it is unable to clear H. pylori, is effective in reducing bacterial colonization and decreasing gastric inflammation in H. pylori-infected mice[46-48]. It has been postulated, on the basis of the results of *in vitro* and animal studies, that probiotics could possibly compete with and down-regulate H. pylori infection in humans[23]. Though utilization of probiotics alone does not lead to the eradication of H. pylori[31,33], a growing body of recent evidence suggests that regular intake of probiotics suppresses H. pylori infection in humans, maintaining lower levels of this pathogen in the stomach[25].
Utilization of probiotics in association with antibiotics in the treatment of H. pylori

The clinical trials performed in children on the effect of probiotics on H. pylori eradication rates as an adjuvant to eradication regimens are summarized in Table 1 and Figure 1. In the earliest study, Sýkora et al. found that the addition of lactobacilli (L. casei) DN-114001 to a standard triple therapy improved the rate of H. pylori eradication. Intention-to-treat based eradication rates for the triple therapy group supplemented with L. casei were 84.6% (95% CI: 71.2%-95.5%), and 91.6% (95% CI: 76.9%-98.2%) by per-protocol analysis. Eradication in the placebo group was 57.5% (95% CI: 42.2%-72.3%) in the intention-to-treat analysis and 61.3% (95% CI: 44.4%-75.0%) in the per protocol analysis. Reported adverse effects were infrequent and self-limiting after therapy cessation in both groups.

In a randomized, double-blind, controlled trial conducted in Italy, symptomatic children with H. pylori infection were treated with 10-d sequential therapy and randomized to receive either L. reuteri ATCC 55730 or placebo for 20 d. All children (or family member) also attended an interview to recall history of gastrointestinal symptoms and the 15-item Gastrointestinal Symptom Rating Scale (GSRS) was used to assess severity and frequency of symptoms. The following symptoms were specifically investigated: epigastric burning and/or pain, abdominal pain, acid regurgitation, heartburn, sucking sensation in the epigastrum, nausea, vomiting, bloating, abdominal distension, eructation, increased flatus, disorders of defecation, inappetence, heartburn, sucking frequency of symptoms. The symptoms and the 15-item Gastrointestinal Symptom Rating Scale (GSRS) was used to assess severity and frequency of symptoms. The symptoms were scored by the child (or family member) on a four-point scale: mild (non-interfering with daily activities), moderate (slightly interfering with daily activities), severe (interfering with daily activities), very severe (continuous and if on therapy, producing treatment interruption). Stool consistency was graded from hard (0) to watery (4). Data were collected before (1 wk before intervention), during (5th and 10th day) and after completion of eradication therapy (15th and 20th day) and patients were invited to return their diaries immediately after the intervention period. No significant difference in H. pylori eradication rates between the treated group and the control group were found. However, in all probiotic supplemented children when compared with those receiving placebo there was a significant reduction in GSRS score during eradication therapy which became markedly evident at the end of follow-up (Table 1). Children receiving L. reuteri reported less side-effects than those receiving placebo.

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 significant difference in H. pylori eradication rates at 1 and 3 mo between probiotic and placebo group. Side effects were not assessed. Similarly, in a randomized, double-blind, controlled trial conducted in Poland, no difference was found with respect to H. pylori eradication rates between children who received triple therapy supplemented with Lactobacillus GC and the control group. Also, the incidence of adverse effects was not reduced. In a randomized, open trial conducted in Romania, children with dyspepsia and H. pylori infection were treated with eradication triple therapy and randomized to receive either Streptococcus boulardii (S. boulardii) (for 4 wk) or placebo. No significant difference in H. pylori eradication rates between the treated group and the control group were found. However, the incidence of side effects was reduced in the S. boulardii group.

Recently, Tolone et al. supplemented a standard triple...
| Study design | Therapy | Probiotic strain (product; dose; time) | Patients | Diagnosis | No. of treated patients | Eradication n (%); P value | Side effects n (%); P value | Test for confirming eradication (time after completion of therapy) |
|--------------|---------|---------------------------------------|----------|-----------|-------------------------|-----------------------------|-----------------------------|---------------------------------------------------------------|
| R, P, DB, PC  | A (25 mg/kg twice daily), C (7.5 mg/kg twice daily), and O (10 or 20 mg twice daily) 1 wk + probiotic vs same eradication therapy + placebo | L. casei DN-114 001 10⁶ CFU in 100 mL of fermented milk (actimel, Danone); 2 wk | 86 (aged 9-15 yr) symptomatic children and adolescents | EGDS (histopathology, culture, and RUT) and HpSA | 39⁶ 36⁷ vs 47⁸ 44⁹ | 33 (84.6)⁶ 33 (91.6)⁷ vs 27 (57.5)⁸ 0.0045 | 27 (61.3)⁸ 0.0019 | HpSA and ¹³C-UBT (4 wk) (nausea, headache, abdominal pain, recurrent vomiting, diarrhoea) |
| O, R          | A (50 mg/kg tid), C (15 mg/kg bid), and L (1 mg/kg bid) 8 d vs Probiotic vs Symbiotic | Lactobacillus acidophilus LB; capsule containing 10⁹ heat-killed and lyophilized LB (Lacteol Forte, Laboratoire du Dr. Boucard, Paris, France); b.i.d. for 8 wk, and Saccharomyces boulardii plus inulin (SHI); sachet containing 250 mg of lyophilized Sb (Perenteryl, Merck Química Chilena, Santiago, Chile); bid for 8 wk | 141 (aged 5-12 yr) asymptomatic children. 81 children were observed without any treatment | ¹³C-UBT | 45⁴ 46⁵ vs 50⁶ | 30 (66)⁴ vs 3 (6.5)⁵ vs 6 (12); 0.001 | No spontaneous clearance was observed in children without treatment | ¹³C-UBT (1 d) |
| R, DB, PC     | A (50 mg/kg per day), (20 mg/kg per day b.i.d), and O (1 mg/kg per day) 1-wk + probiotic vs same eradication therapy + placebo | Bifidobacterium animalis and Lactobacillus casei (10⁸ CFU/mL) in 250 mL of a commercial yogurt; once daily for 3 mo | 65 (aged 5-15 yr) symptomatic children and adolescents | EGDS and ¹³C-UBT (histological data NA) | 33¹² vs 32¹² | 15 (45.5)¹² vs 12 (37.5)¹²; 0.345 at 1 mo | 14 (42.4)¹² vs 13 (40.6)¹²; 0.542 at 3 mo | ¹³C-UBT (1 and 3 mo) |
| R, DB, PC     | O (1 mg/kg/die) plus A (50 mg/kg/die) for 5 d followed by O (1 mg/kg/die) plus C (15 mg/kg/die) and T (20 mg/kg/die) for the next 5 d + probiotic vs same eradication therapy + placebo | L. reuteri [pill containing 10⁸ CFU of L. reuteri ATCC 55730 (SD2112), Reuterin, Nòos]; one pill once daily for a period of 20 d | 40 (aged 3.3-18 yr) symptomatic children and adolescents | EGDS (histopathology and RUT) (pangastritis (27); antral gastritis, mild (20); antral gastritis, moderate (6); antral gastritis, severe (10)) | 20¹² vs 20¹² | 17 (85)¹² vs 16 (80)¹²; NS | Reduction of GSRS score during eradication therapy [4.1 ± 2 (95%CI: 2.9-5.9) vs 6.2 ± 3 (95%CI: 5.2-8.3); P < 0.01] and at the end of follow-up [3.2 ± 2 (95%CI: 2.4-4) vs 5.8 ± 3.4 (95%CI: 4.8-6.9); P < 0.009]; Epigastric pain (15% vs 45%; P < 0.04); Abdominal distension (0% vs 25%; P < 0.02); Eructation (5% vs 35%; P < 0.04); Disorders of defecation (15% vs 45%; P < 0.04); Halitosis (5% vs 35%; P < 0.04) | ¹³C-UBT (8 wk) |
| Study | Design | Probiotic | Baseline | Treatment | Comparator | Outcomes |
|-------|--------|-----------|----------|-----------|------------|----------|
| Hurduc et al. | O, R | A (50 mg/kg per day, bid) and C (15 mg/kg per day, bid) | 90 (aged 3-18 yr) children and adolescents with dyspepsia | EGDS (histopathology and RUT) | 48\(^2\) vs 42\(^2\), 45 (93.3)\(^2\) vs 34 (80.9)\(^2\), 4 (8.3) vs 13 (30.9), P = 0.047 (bloating, taste disturbance, nausea, abdominal pain, diarrhoea, constipation, loss of appetite, fatigue) | EGDS (4-6 wk) (histopathology and RUT) |
| Szajewska et al. | R, DB, PC | A (50 mg/kg per day bid), C (20 mg/kg per day bid), and O (1 mg/kg per day) | 83 (aged 5-17 yr) symptomatic children and adolescents. Excluded from the analysis were 17 children for lack of diary and/or \(^13\)C-UBT | EGDS (2 of 3 tests), \(^13\)C-UBT, histopathology or RUT [histological data NA] | 34\(^2\) vs 32\(^2\), 23 (69)\(^2\) vs 22 (68), RR = 0.98 (95% CI: 0.71-1.4) | Therapy-related diarrhoea: 2 (6) vs 6 (20), P = NS Total side effects: 18 (51.4) vs 13 (40.6), P = NS Abdominal pain: 0 vs 0 Nausea: 4 (11.4) vs 3 (9.4), P = NS Vomiting: 2 (5.7) vs 1 (3.1), P = NS Constipation: 2 (6.7) vs 2 (6.2), P = NS Flatulence: 3 (8.6) vs 3 (8.1), P = NS Taste disturbance: 4 (11.4) vs 5 (15.6), P = NS Loss of appetite: 3 (8.6) vs 3 (3.1), P = NS Need for discontinuation of therapy: 0 vs 0 Epigastric pain: 2 (5.8) vs 6 (17.6), P < 0.05 Nausea: 1 (2.9) vs 3 (8.8), P < 0.05 Vomiting: 0 vs 2 (5.8), P < 0.05 Diarrhoea: 0 vs 8 (23.5), P < 0.05 |
| Tolone et al. | R | A (50 mg/kg per day bid), C (15 mg/kg per day bid), and O (1 mg/kg per day) | 68 (mean age, 8.3 yr) children with heartburn, dyspepsia, nausea and epigastric pain | EGDS (histopathology) [histological data: NA] | 34\(^2\) vs 34\(^2\), 30 (88.2)\(^2\) vs 26 (76.4)\(^2\), 0.1 | \(^13\)C-UBT (4 wk) |
| Ahmad et al. | R, DB, PC | A (50 mg/kg per day bid) and F (6 mg/kg per day bid) | 66 (aged 3-14 yr) children with chronic abdominal pain, gastrointestinal bleeding, unexplained frequent vomiting and unexplained iron deficiency anemia | EGDS (positive RUT or histopathology) | 33\(^2\) vs 33\(^2\), 30 (90.1)\(^2\) vs 25 (69.7)\(^2\), 0.04 | Constipation: 2 (5.8) vs 2 (5.8), P = NS Nausea/vomiting: 2 (6.1) vs 9 (27.3), P = 0.02 Diarrhoea: 2 (8.3) vs 8 (24.2), P = 0.04 Abdominal bloating: 3 (9.1) vs 4 (12.3), P = 1 |

1. Intention-to-treat analysis; 2. Per-protocol analysis; O: Open; R: Randomized; DB: Double-blind; SB: Single-blind; PC: Placebo controlled; P: Prospective; A: Amoxicillin; C: Clarithromycin; F: Furazolidone; M: Metronidazole; T: Tinidazole; O: Omeprazole; E: Esomeprazole; L: Lansoprazole; CFU: Colony forming units; RUT: Rapid urease test; UBT: Urea breath test; H. Pylori: Helicobacter pylori; HpSA: H. Pylori stool antigens; GSRS: Gastrointestinal symptom rating scale; NA: Not available; L. johnsonii: Lactobacillus johnsonii; L. paracasei: Lactobacilli paracasei.
therapy with a commercial probiotic for 7 d and showed that there was no improvement in the rate of *H. pylori* eradication in the probiotic group. However, the addition of probiotic to triple therapy significantly decreased the frequency of epigastric pain, nausea, vomiting, and diarrhea. In a more recent double-blind randomized placebo-controlled study, 10 subjects treated with a triple drug treatment protocol and randomly allocated to receive either probiotic or placebo. *H. pylori* was eradicated in 90.09% of patients receiving probiotic and in 69.69% of those receiving placebo (*P* = 0.04). In probiotic supplemented children there was a lower rate of nausea/vomiting and diarrhea.

In summary, seven of the eight studies listed in Table 1 compare eradication rates for groups treated with antibiotics with those treated with antibiotics plus probiotics. The odds ratios for these seven studies are shown in the forest plot in Figure 1. Six of these seven have estimated odds ratios greater than 1.0 implying an estimated benefit for the addition of probiotics, but only two are statistically significant. The antibiotics used in the studies differ as do the treatment regimens. Similarly, the probiotics used and diagnostic techniques differ between studies. With such heterogeneity of design, even though the statistical test of the heterogeneity is not significant ($\chi^2 = 6.5; P = 0.37$), a meta-analysis of these studies would not be appropriate.

**Utilization of probiotics alone**

The clinical trials performed in children on the effect of probiotics on *H. pylori* eradication rates alone are summarized in Table 2. In a double-blind, randomized, controlled clinical trial Cruchet et al. 13 evaluated the efficacy of *lactobacilli johnsonii* (L. johnsonii) La1 or *lactobacilli paracasei* (L. paracasei) ST11 as a unique intervention on *H. pylori* eradication in 252 asymptomatic school children screened for *H. pylori* by 13C-Urea breath test (UBT). Subjects were distributed into five groups to produce a product containing live L. johnsonii La1 or L. paracasei ST11, heat-killed L. johnsonii La1 or L. paracasei ST11, or just vehicle everyday for 4 wk. There was a moderate but significant difference in 13C-UBT values in children receiving live L. johnsonii La1, whereas no differences were observed in the other groups. The authors conclude that regular ingestion of a probiotic strain such as L. johnsonii La1 may interfere with *H. pylori* colonization in asymptomatic children and may be an effective alternative to modulate *H. pylori* infection and its associated gastritis in pediatric populations with high prevalences of infection by this pathogen.

In a randomized open trial, Gotteland et al. 17 randomized asymptomatic *H. pylori*-positive children to receive either 7-d triple therapy, or *Saccharomyces boulardii* as a symbiotic simultaneously with inulin or *L. acidophilus* LB daily for 8 wk. An additional group of asymptomatic *H. pylori*-positive children was followed for 8 wk without any treatment. A significant decrease in 13C-UBT, performed after 8 wk, was observed in the antibiotic group and in the *S. boulardii* group but not in the *L. acidophilus* LB group. No changes in 13C-UBT values were observed in untreated children. The results of this study suggest that the suppressive effect on *H. pylori* colonization in children depends on the probiotic strain used.

In a multicentric, randomized, controlled, double-blind trial carried out in 271 asymptomatic children who tested positive for *H. pylori* by 13C-UBT, Gotteland et al. 31 evaluated whether cranberry juice and the probiotic L. johnsonii La1 could act additively or synergistically to suppress *H. pylori*. Subjects were allocated in four groups: cranberry juice/L. johnsonii La1, placebo juice/L. johnsonii La1, cranberry juice/heat-killed L. johnsonii La1, and placebo juice/heat-killed L. johnsonii La1 (control), given for 3 wk, after which a second UBT was carried out. A third 13C-UBT was done after one-month washout in those children who tested negative in the second 13C-UBT. *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 placebo juice/L. johnsonii La1, cranberry juice/heat-killed L. johnsonii La1, and cranberry juice/L. johnsonii La1, respectively; the latter group showed a slight but not significant increase when compared with the other treated groups. The third 13C-UBT was carried out only in 19 of the 38 children who tested negative in the second 13C-UBT and *H. pylori* was detected in 80% of them, suggesting just a temporary inhibition of the organism that disappeared once the administration of the inhibiting factors was interrupted.

In a recent study L. gaseri OLL2716 was administered in cheese to pre-school children to evaluate whether its long time administration (for one year) can eradicate *H. pylori* and/or prevent *H. pylori* infection 66. A total of 440 children were screened by the *H. pylori* stool antigen (HpSA) test. Thereafter, 132 *H. pylori*-positive and 308 *H. pylori*-negative children were recruited to eradication and randomized prevention arms, respectively. Of the 132 *H. pylori*-positive children, 28 withdrew in the beginning because they did not like the cheese. However, 18 of the 28 subjects agreed to undergo an HpSA test again 1 year later, and were designated as the control group. Eighty-two of the remaining *H. pylori*-positive subjects completed the eradication arm, of which 24 (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 1 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 *L. gaseri* treatment, but found that 5 of those 12 (41.7%) had reversed to be HpSA-positive. Therefore, a final eradication rate was around 17%. In the randomized prevention arm, 123 of 156 (79.0%) and 99 of 122 (81.0%) completed active and placebo arms, respectively, of which 4.1% and 8.1% were HpSA positive at 12 mo based on a per-protocol analysis (*P* = 0.21).
**Table 2** Clinical trials using probiotics in the treatment of *Helicobacter pylori* infection in children

| Ref. | Study design | Probiotic strain (product; dose; time) | Patients | Diagnosis | Eradication (n (%); P value) | Test for confirming eradication (time after completion of therapy) | Comments |
|------|--------------|---------------------------------------|----------|-----------|-----------------------------|---------------------------------------------------------------|----------|
| Cruchet et al. | DB, R | Lactobacillus johnsonii (La1), living or heat-killed, 30 mL/die, (> 10^9 CFU/mL) | 252 (aged 6-17 yr) asymptomatic children and adolescents: Living La1/LH, n = 51; Heat-killed La1/LH, n = 50; Living ST11/LH, n = 50; Heat-killed ST11/LH, n = 51; LH, n = 50 | C-UBT | A moderate but significant difference in C-UBT values was detected in children receiving live La1, whereas no differences were observed in the other groups | C-UBT (at the end of treatment) | |
| Gotteland et al. | R, DB, PC | Lactobacillus johnsonii La1, living or heat-killed, 30 mL/die, (> 10^9 CFU/mL) for 3 wk (Chamyto, Nestlé) with or without cranberry juice (CB) (200 mL) | 271 (aged 6-16 yr) asymptomatic children and adolescents: CB/La1, n = 70; Placebo juice/La1, n = 67; Placebo juice/heat-killed La1, n = 65; CB/heat-killed La1, n = 65; Placebo juice/heat-killed La1 (control), n = 69 | C-UBT | 13 | C-UBT (a second C-UBT at the end of treatment and a third C-UBT after 1 mo) | The third UBT was carried out in 19 of the 38 children found to be H. Pylori-negative in the second UBT: 12, 2, and 5 subjects from the CB/La1, placebo juice/La1, and CB/heat-killed La1 groups, respectively. Only four children (21) remained negative after 1 mo without treatment: two from the placebo juice/La1 group and two from the CB/La1 group. A total of 440 asymptomatic children were screened by the HpSA test. Thereafter 132 H. Pylori positive and 308 H. Pylori negative children were recruited to eradication and randomized prevention arms, respectively. Eradication was defined as reversion by HpSA at 12 mo; prevention as persistently HpSA negative at 12 mo. |
| Boonyaritichaijik et al. | SR, PC | Lactobacillus casei OLL2716 (LG23), pieces of cheese weighing 1.6-2.0 g, approximately 5 x 10^6 CFU/g for 1 yr | 86 (aged 3-7 yr) asymptomatic children and adolescents completed the eradication arm: LG23, n = 82; ordinary cheese, n = 67; while 222 completed the prevention arm: LG23, n = 123; Ordinary cheese, n = 99 | HpSA | 24 (29.3) vs 0. In the randomized prevention arm: 5 (4.3) vs 8 (8.3); P = 0.21 were HpSA positive at 12 mo. | HpSA (1 yr) | |

1^Per-protocol analysis. R: Randomized; DB: Double-Blind; SR: Single Blind; PC: Placebo Controlled; CFU: Colony Forming Units; C-UBT: Urea Breath Test; H. Pylori: *Helicobacter pylori*; HpSA: *H. Pylori* stool antigens.

**CONCLUSION**

So far, there has been no convincing evidence on the beneficial effect of supplementation of probiotics to triple therapy for eradicating *H. pylori* infection in children. The very few trials performed in children on the effect of probiotics alone suggest just a temporary inhibition of *H. pylori* that disappears once the administration of the inhibiting factors is interrupted. Nonetheless, the majority of these studies were based on relatively small samples and, therefore, they may lack the statistical power necessary to detect an important effect of the probiotics. Finally, in most studies, the effect of probiotic treatment on *H. pylori* infection in children has been estimated indirectly by C-UBT. On the other hand, probiotic treatment seems to be able to reduce *H. pylori* therapy associated side effects and indirectly may help to improve the eradication rate; however it seems that the beneficial effects are strain specific. We conclude that standardized multicenter, placebo-controlled studies in larger series of children are needed to demonstrate any benefit of probiotics in the management of *H. pylori* infection in children, including its effect on the severity of *H. pylori* gastritis. Additional work is necessary to determine the strain, dose and administration to be used. Long-term studies are also needed in children to prove whether the persistent suppressive effect of probiotics on *H. pylori* and its associated gastritis could prevent diseases such as gastric cancer or peptic ulcer.
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