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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

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

Lucia Pacifico, John Frederick Osborn, Enea Bonci, Sara Romaggioli, Rossella Baldini, Claudio Chiesa

Lucia Pacifico, Sara Romaggioli, Department of Pediatrics and Child Neuropsychiatry, Sapienza University of Rome, 324 00161 Rome, Italy
John Frederick Osborn, Department of Health Sciences and Infectious Diseases, Sapienza University of Rome, 324 00161 Rome, Italy
Enea Bonci, Department of Experimental Medicine, Sapienza University of Rome, 324 00161 Rome, Italy
Rossella Baldini, Department of Human Anatomy, Sapienza University of Rome, 324 00161 Rome, Italy
Claudio Chiesa, Institute of Translational Pharmacology, National Research Council, 100 00133 Rome, Italy
Author contributions: Pacifico L, Osborn JF, Bonci E and Chiesa C designed the study, analyzed the data and wrote the manuscript; Romaggioli S and Baldini R collected the data; all the authors participated in the critical review and in the final approval of the manuscript.
Correspondence to: Lucia Pacifico, MD, Department of Pediatrics and Child Neuropsychiatry, Sapienza University of Rome, Viale Regina Elena, 324 00161 Rome, Italy. lucia.pacifico@uniroma1.it
Telephone: +39-6-49979215 Fax: +39-6-49979216
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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 antimicrobials, 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.

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.

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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[1]. 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[2-5]. It is commonly thought that once the *H. pylori* infection is acquired, it evolves toward persistent chronic infection[6] and that spontaneous clearance is relatively rare[6-8]. 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[9]. This suggests that transient *H. pylori* infection is not uncommon in children[6,10,11]. In 6-24-mo old children in Mexico, and Texas, researchers found 80% spontaneous reversion of the infection[10,11]. In a very recent study involving 718 schoolchildren in Mexico City, Duque *et al*[12] 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[12].

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[13-15]. In recent years, the success of eradication therapies has declined, in part due to the development of *H. pylori* resistant strains[16]. Several studies have documented high resistance rates to clarithromycin and metronidazole in paediatric and adult populations[17-19]. In Europe, Koletzko *et al*[17] 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[18]. Declining eradication rates with standard triple regimens have led to the development of alternate treatment options[20,21].

Recently, ESPGHAN and NASPGHAN jointly renewed clinical guidelines for *H. pylori* infection in children using a standardised evidence based approach[22]. 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[20,22]. 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[23]. One of the potential therapies involves probiotic cultures; promising results have been observed in initial studies with numerous probiotic strains[24-26]. 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[27,28].

Probiotic micro-organisms are typically members of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*[27-29]. 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

byproducts are sometimes referred to as "postbiotics" and may function biologically as modulators of immune function[30]. 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*[31]. 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 10^3/mL fluid[25]. 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 10^3 to 10^4 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 10^9-10^{10} 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[31].

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[35]. 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[23]. 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[23].

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 reuteri* (*L. reuteri*) 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 varieties 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 MUCI and *MUC5A* gene expression in a human gastric cell line[41]. It has been shown *in vitro* that *lactobacilli plantarum* and *lactobacilli rhamnosus* 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*[42].

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[23]. 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[46-50]. 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*[51-55], 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].

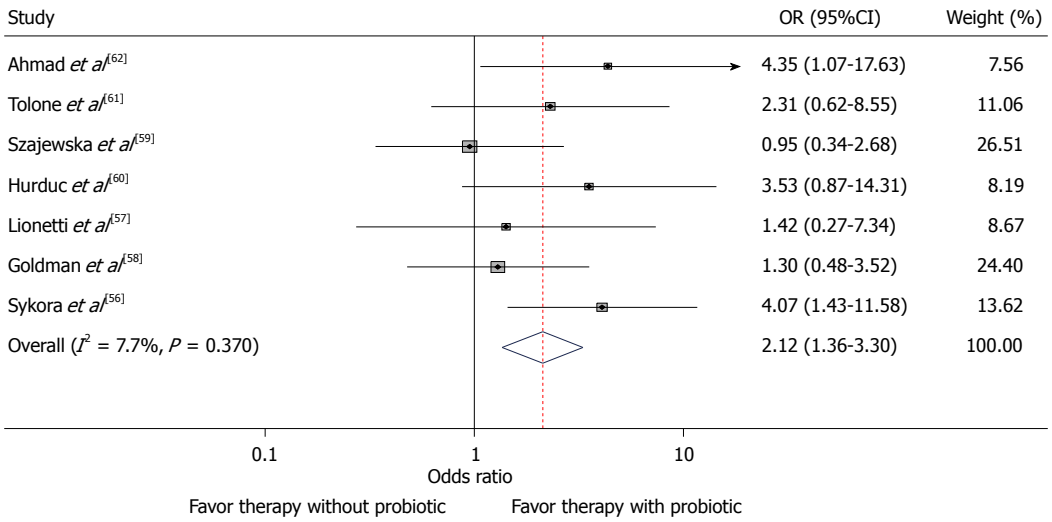

Figure 1 Forest plot showing odds ratios obtained from seven trials comparing an antibiotic therapy with the same therapy plus a probiotic. The antibiotic therapies and the probiotics are not the same in all trials.

Few clinical trials evaluating the use of different probiotic strains have been reported. In some of these studies, probiotics were used alone while in others they were used as adjunctive agents in the classical treatment of *H. pylori* infection.

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 eradicating regimens are summarized in Table 1 and Figure 1. In the earliest study, Sýkora *et al*[56] found that the addition of *lactobacilli casei* (*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[56].

In a randomized, double-blind, controlled trial conducted in Italy[57], 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 epigastrium, nausea, vomiting, bloating, abdominal distension, eructation, increased flatus, disorders of defecation, inappetence, halitosis, taste disturbance and urticaria. 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 eradicating 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[57].

Goldman *et al*[58] 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[59], 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[60], 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*[61] supplemented a standard triple

Table 1 Clinical trials in children using probiotics as a complement during *Helicobacter pylori* eradication treatment

Ref.	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)
Sýkora *et al*[56]	P, R, 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 10^{10} 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	39[1] 36[2] *vs* 47[1] 44[2]	33 (84.6)[1] 33 (91.6)[2] *vs* 27 (57.5)[1]; 0.0045 27 (61.3)[2]; 0.0019	9 (23.1) *vs* 10 (21.2); NS (nausea, headache, abdominal pain, recurrent vomiting, diarrhoea)	HpSA and ^{13}C-UBT (4 wk)
Gotteland *et al*[64]	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* (LB); capsule containing 10^9 heat-killed and lyophilized LB (Lacteol Forte, Laboratoire du Dr. Boucard, Paris, France); b.i.d. for 8 wk, and *Saccharomyces boulardii* plus inulin (Sbl); sachet containing 250 mg of lyophilized Sb (Perenteryl, Merck Quìmica Chilena, Santiago, Chile); bid for 8 wk	141 (aged 5-12 yr) asymptomatic children. 81 children were observed without any treatment	^{13}C-UBT	45[2] *vs* 46[2] *vs* 50[2]	30 (66)[2] *vs* 3 (6.5)[2] *vs* 6 (12)[2]; < 0.001 No spontaneous clearance was observed in children without treatment	NA	^{13}C-UBT (1 d)
Goldman *et al*[58]	R, DB, PC	A (50 mg/kg per day), C (20 mg/kg per day bid), and O (1 mg/kg per day) 1-wk + probiotic *vs* same eradication therapy + placebo	*Bifidobacterium animalis* and *Lactobacillus casei* (10^7 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 ^{13}C-UBT (histological data NA)	33[1,2] *vs* 32[1,2]	15 (45.5)[1,2] *vs* 12 (37.5)[1,2]; 0.345 at 1 mo 14 (42.4)[1,2] *vs* 13 (40.6)[1,2]; 0.542 at 3 mo	NA	^{13}C-UBT (1 and 3 mo)
Lionetti *et al*[57]	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 10^8 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 (14); antral gastritis, severe (10)]	20[1,2] *vs* 20[1,2]	17 (85)[1,2] *vs* 16 (80)[1,2]; 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%; $P < 0.04$)	^{13}C-UBT (8 wk)

Hurduc *et al*[60]	O, R	A (50 mg/kg per day, bid) and C (15 mg/kg per day, bid) 7-10 d; O or E (1 mg/kg per day, bid) 3-wk + probiotic *vs* same eradication therapy + placebo	*Saccharomyces boulardii*, Enterol, Biocodex, Gentilly Cedex; 250 mg bid; 4-wk	90 (aged 3-18 yr) children and adolescents with dyspepsia	EGDS (histopathology and RUT) [chronic gastritis: mild (8); moderate-to-severe (82); active (32); inactive (58)]	48[1,2] *vs* 42[1,2]	45 (93.3)[1,2] *vs* 34 (80.9)[1,2]; NS	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*[59]	R, DB, PC	A (50 mg/kg per day bid), C (20 mg/kg per day bid), and O (1 mg/kg per day) 1-wk + probiotic *vs* same eradication therapy + placebo	*Lactobacillus* GG 1 × 10^9 CFU; 7 d	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: 0.7-1.4)[2]	Therapy-related diarrhea: 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 (5.7) *vs* 2 (6.2); P = NS Flatulence: 3 (8.6) *vs* 1 (3.1); P = NS Taste disturbance: 4 (11.4) *vs* 5 (15.6); P = NS Loss of appetite: 3 (8.6) *vs* (3.1); P = NS Need for discontinuation of therapy: 0 *vs* 0	^{13}C-UBT (4 wk)
Tolone *et al*[61]	R	A (50 mg/kg per day bid), C (15 mg/kg per day bid), and O (1mg/kg per day) 1-wk + probiotic *vs* same eradication therapy + placebo	*Lactobacillus Plantarum* 5 × 10^9, *L. reuterii* 2 × 10^9, *L. casei subsp. Rhamnosus* 2 × 10^9, *Bifidobacterium infantis* and *B. longum* 2 × 10^9, *L. salivarius* 1 × 10^9, *L. acidoPhilus* 1 × 10^9, *Streptococcus termophilus* 5 × 10^9, and *L. sporogenes* 1 × 10^9 + inuline as a prebiotic (5 g/dayose q.d., Probinul , Cadigroup); 7 d	68 (mean age, 8.3 yr) children with heartburn, dyspepsia, nausea and epigastric pain	EGDS (histopathology) [histological data: NA]	34[1,2] *vs* 34[1,2]	30 (88.2)[1,2] *vs* 26 (76.4)[1,2]; 0.1	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); $P < 0.05$ Diarrhea: 0 *vs* 8 (23.5); $P < 0.05$	^{13}C-UBT (4 wk)
Ahmad *et al*[62]	R, DB, PC	A (50 mg/kg per day bid) and F (6 mg/kg per day bid) 1-wk; O (1 mg/kg per day) 4-wk + probiotic *vs* same eradication therapy + placebo	*Lactobacillus acidophilus, L. rhamnosus, L. bulgaricus, L. casei, Streptococcus thermophilus, Bifidobacterium infantis, B. breve*; 1 × 10^9 CFU/1 sachet, Protexin Co; 4 wk	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) [Antral nodularity (57); Gastric erythema (16); Duodenal ulcer (14); Gastric ulcer (1)]	33[1,2] *vs* 33[1,2]	30 (90.1)[1,2] *vs* 23 (69.7)[1,2]; 0.04	ConstiPation: 2 (5.8) *vs* 2 (5.8); P = NS Nausea/vomiting: 2 (6.1) *vs* 9 (27.3); $P = 0.02$ Diarrea: 2 (6.1) *vs* 8 (24.2); $P = 0.04$ Abdominal bloating: 3 (9.1) *vs* 4 (12.1); $P = 1$	HpSA (4-8 wk)

[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*: *Lactobacilli 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[62], *H. pylori*-positive children were 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 heterogeinity 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*[63] 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 ^{13}C-Urea breath test (UBT). Subjects were distributed into five groups to receive 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 ^{13}C-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*[64] 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 ^{13}C-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 ^{13}C-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 ^{13}C-UBT, Gotteland[65] 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 ^{13}C-UBT was done after one-month washout in those children who tested negative in the second ^{13}C-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 ^{13}C-UBT was carried out only in 19 of the 38 children who tested negative in the second ^{13}C-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. gasseri* 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. gasseri* 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*[63]	DB, R	*Lactobacillus johnsonii* (La1), living or heat-killed, 80 mL/die, (> 10^7 CFU/mL) (Chamyto, Nestlé) and *L. helveticus* (LH) for 4 wk; *Lactobacilli paracasei* ST11, living or heat-killed, (> 10^7 CFU/mL) and LH for 4 wk	252 (aged 6-17 yr) asymptomatic children and adolescents: Living La1/LH, $n = 51^1$; Heat-killed La1/LH, $n = 50^1$; Living ST11/LH, $n = 50^1$; Heat-killed ST11/LH, $n = 51^1$; LH, $n = 50^1$	^{13}C-UBT	A moderate but significant difference in ^{13}C-UBT values was detected in children receiving live La1, whereas no differences were observed in the other groups	^{13}C-UBT (at the end of treatment)	
Gotteland *et al*[65]	R, DB, PC	*Lactobacillus johnsonii* La1, living or heat-killed, 80 mL/die, (> 10^7 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, $n = 70^1$; Placebo juice/La1, $n = 67^1$; CB/heat-killed La1, $n = 65^1$; Placebo juice/heat-killed La1 (control), $n = 69^1$	^{13}C-UBT	16 (22.9)[1] 11 (16.9)[1] 10 (14.9)[1] *vs* 1 (1.5)[1]; $P < 0.01$	^{13}C-UBT (a second ^{13}C-UBT at the end of treatment and a third ^{13}C-UBT after 1 mo)	The third UBT was carried out in only 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
Boonyaritichaikij *et al*[66]	SB, PC	*Lactobacillus gasseri* OLL2716 (LG21), pieces of cheese weighing 1.6-2.0 g, approximately 5 × 10^8 CFU/g for 1 yr	88 (aged 3-7 yr) asymptomatic children and adolescents completed the eradication arm: LG21, $n = 82^1$; ordinary cheese, $n = 6^1$ while 222 completed the prevention arm: LG21, $n = 123^1$; Ordinary cheese, $n = 99^1$	HpSA	24 (29.3)[1] *vs* 0. In the randomized prevention arm: 5 (4.1) *vs* 8 (8.1); $P = 0.21$ were HpSA positive at 12 mo	HpSA (1 yr)	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

[1]Per-protocol analysis. R: Randomized; DB: Double-Blind; SB: Single Blind; PC: Placebo Controlled; CFU: Colony Forming Units; ^{13}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 are 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 ^{13}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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