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## BRIEF COMMUNICATION

# Clinical application of probiotics in the treatment of *Helicobacter pylori* infection—A brief review



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Received 5 December 2012; received in revised form 6 March 2013; accepted 28 March 2013  
Available online 10 June 2013

**KEYWORDS**

Eradication treatment;  
Gastritis;  
*Helicobacter pylori*;  
Interleukin-6;  
*Lactobacillus*;  
Stomach cancer

The role of probiotics in the treatment of gastrointestinal infections is increasingly being documented as an alternative or complement to antibiotics, with the potential to decrease the use of antibiotics or reduce their side effects. Although antibiotics-based *Helicobacter pylori* eradication treatment is 90% effective, it is expensive and causes antibiotic resistance associated with other adverse effects. Probiotics have an *in vitro* inhibitory effect on *H. pylori*. Animal studies demonstrated that probiotic treatment is effective in reducing *H. pylori*-associated gastric inflammation. About 12 human studies investigated the efficacy of combinations of antibiotics and probiotics, whereas 16 studies used probiotic alone as an alternative to antibiotics for the treatment of *H. pylori* infection. Most of the studies showed an improvement of *H. pylori* gastritis and decrease in *H. pylori* colonization after administration of probiotics. However, no study could demonstrate complete eradication of *H. pylori* infection by probiotic treatment. Probiotic combinations can reduce adverse effects induced by *H. pylori* eradication treatment and, thus, have beneficial effects in *H. pylori*-infected individuals. Long-term intakes of products containing probiotic strains may have a favorable effect on *H. pylori* infection in humans, particularly by reducing the risk of developing disorders associated with high degrees of gastric inflammation.

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## Introduction

For a long time, ulcers were considered to be a result of stress and improper diet. The important discovery that ulcers are caused by a bacterial infection (*Helicobacter pylori*), which was rewarded with the 2005 Nobel Prize in Medicine, has changed gastroenterological practice worldwide. After its discovery, many gastroduodenal diseases became curable infectious diseases. *H. pylori* is a highly prevalent pathogen associated with chronic gastritis and peptic ulcer, and is a risk factor for gastric malignancies. The prevalence rate of *H. pylori* infection in the adult population of industrialized countries is estimated to be at 20–50% and in developing countries, the rate is as high as 80%.<sup>1</sup> *H. pylori* colonizes the stomach and induces chronic gastritis, a long-lasting inflammation of the stomach. The bacterium persists in the stomach for decades in many cases. However, most infected people may never experience clinical symptoms despite having chronic gastritis; 10–20% of those colonized by *H. pylori* may ultimately develop peptic ulcers.<sup>2</sup> *H. pylori* infection is also associated with 1–2% lifetime risk of stomach cancer and a less than 1% risk of gastric mucosa-associated lymphoid tissue (MALT) lymphoma. This pathogen was designated as a class-I carcinogen for stomach cancer in 1994, after epidemiological investigation by the International Agency for Research on Cancer (IARC), a subordinate organization of the World Health Organization.<sup>3</sup> The infection is generally acquired during childhood and can persist indefinitely, if not treated systematically.<sup>4</sup> It has been suggested that *H. pylori* infection rates vary with age, ethnicity, socioeconomic status, sanitary environments, and lifestyle.<sup>5</sup>

None of the antimicrobials is effective enough to eliminate *H. pylori* when given as a monotherapy; only a combination of these can wipe out *H. pylori* effectively.<sup>4</sup> According to Malfertheiner et al,<sup>6</sup> the first-line recommended eradication treatment of *H. pylori* consists of a combination of two antimicrobials and an acid-suppressive drug. This triple therapy used for the treatment of *H. pylori* has several adverse effects, such as diarrhea, nausea, bloating, and taste disturbance, possibly leading to discontinuation of the treatment, and limited efficacy principally because of antimicrobial resistance of the pathogen.<sup>7</sup>

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, synergistically, in combination with antimicrobials, resulting in a more effective anti-*H. pylori* therapy or an alternative way of controlling *H. pylori* infection, have been investigated in depth by several researchers.<sup>2</sup> It is believed that these novel therapies can potentially cut down the costs related to the treatment of *H. pylori*-associated diseases. One of the potential therapies involves an application of probiotic cultures; promising results have been observed in initial studies with numerous probiotic strains. Nevertheless, many questions remain unanswered. As defined by the Food and Agriculture Organization (FAO)/World Health Organization (WHO),<sup>8</sup> probiotics are live microorganisms that may confer a health benefit on the host. The most commonly used probiotic bacteria belong to the genera *Lactobacillus* and

*Bifidobacterium*, and these also include several yeasts such as *Saccharomyces boulardii*.<sup>9</sup>

In the current article, the possible mechanisms of action of probiotics on *H. pylori* infection, as reported by *in vitro* cell line and animal studies, are narrated, followed by the outcomes of the available *in vivo* evidences for the effect of probiotics on *H. pylori* infection in humans. The effect of the addition of probiotics to the standard *H. pylori* eradication therapy is also discussed.

## Mechanisms of probiotic action on *H. pylori*

A number of mechanisms have been anticipated or hypothesized from *in vitro* studies of host intestinal epithelial or immune cell responses to probiotic strains. In that context, probiotic bacteria can inhibit *H. pylori* by either immunological or nonimmunological mechanisms. According to Haller et al,<sup>10</sup> distinct probiotic strains may generate divergent immune responses depending on the host's immune status.

Animal studies suggested that the immunomodulatory effects of probiotic bacteria may be mediated through immune regulation, particularly through controlling the balance of proinflammatory and anti-inflammatory cytokines and chemokines, which in turn would reduce gastric activity and inflammation.<sup>11</sup> Probiotic bacteria can bind to recognition receptors, such as Toll like receptors (TLRs) expressed on the surface of epithelial cells, and thus trigger a cascade of immunological defense mechanisms.<sup>9</sup> In that TLR4 can recognize lipopolysaccharide of Gram-negative bacteria, whereas TLR2 can recognize a variety of microbial components, such as peptidoglycan and teichoic acids, present in Gram-positive bacteria.<sup>12</sup> The cytokine response is initially manifested by the release of interleukin (IL)-8, which leads to the migration of neutrophils and monocytes to the mucosa.<sup>13</sup> These activated monocytes and dendritic cells stimulate production of various cytokines together with IL-4, IL-5, IL-6, and interferon- $\gamma$ . According to Gill,<sup>14</sup> probiotics can modify the immunologic response of the host by interacting with epithelial cells and modulating the secretion of anti-inflammatory cytokines, resulting in a reduction of gastric activity and inflammation. In one of the earlier studies, Kabir et al<sup>15</sup> demonstrated that *Lactobacillus salivarius* inhibits *H. pylori*-stimulated secretion of IL-8 by gastric epithelial cells. During several animal studies, a decrease in specific IgG antibodies to *H. pylori* infection, parallel to a fall in gastric inflammation, was observed following a probiotic intake.<sup>16,17</sup> Also, enhancement of secretory IgA production in the intestinal epithelium may have a role in pathogen defense through strengthening of the mucosal barrier.<sup>13,18</sup> It was also established that *H. pylori* infection induces production of Smad7, nuclear factor (NF)- $\kappa$ B, IL-8, and tumor necrosis factor- $\alpha$  *in vitro*. In a recent investigation, Yang et al<sup>19</sup> observed that pretreatment of *Lactobacillus acidophilus* at higher doses reduced *H. pylori*-induced inflammation through the inhibition of *H. pylori*-induced Smad7 transcription, by inactivating the Jak1 and Stat1 pathways, and subsequently reduced nuclear NF- $\kappa$ B production.

Nonimmunological mechanisms of probiotics include strengthening of mucosal barrier by producing

antimicrobial substances, coaggregation with pathogens, competing with *H. pylori* for adhesion receptors, stimulating mucin production, and stabilization of the gut mucosal barrier. Generally, probiotics such as lactic acid bacteria (LAB) and bifidobacteria are able to produce organic acids, hydrogen peroxide, carbon dioxide, and some other antimicrobial compounds to inhibit potential pathogens.<sup>20</sup> Adhesion of pathogens can also be inhibited by steric hindrance, where a large number of beneficial bacteria may cover receptor sites in a non-specific manner, or by competing for specific carbohydrate receptors that would otherwise be available to pathogens. Several probiotic species have shown growth inhibition or antiadhesion ability against *H. pylori* in a gastric epithelial cell model.<sup>16,21</sup> Mucins, secreted by epithelial cells, may also bind to pathogens, thereby inhibiting their adherence to epithelial cells. Probiotics can interfere with the actions of *H. pylori*, since several strains such as *Lactobacillus plantarum* 299V and *Lactobacillus rhamnosus* GG have been shown to induce mucin gene expression.<sup>22,23</sup> Furthermore, some *Bifidobacterium* strains have been found to release heat-stable proteinaceous antimicrobial compounds against *H. pylori* *in vitro*.<sup>24</sup>

### Probiotics and *H. pylori* infection

In the majority of studies dealing with either animal models or humans, the most frequently used strains were *Lactobacillus johnsonii* La1 and *L. rhamnosus* GG, either in a fermented milk preparation containing live bacteria<sup>25–27</sup> or as a cell-free culture supernatant,<sup>28</sup> followed by other probiotics such as *Lactobacillus casei*, *L. acidophilus*, *Lactobacillus brevis* and *Lactobacillus gasserii* OLL2716, *Lactobacillus reuteri*, *Bifidobacterium lactis*, *Bifidobacterium animalis*, *Bifidobacterium breve*, *Propionibacterium freudenreichii* and probiotic yeast *S. boulardii*. The effect of probiotics on *H. pylori* gastritis is commonly measured by the rapid urease tests, urea breath test (UBT), serological assays, stool antigen test, and histological examination of gastric biopsies.<sup>2,3,17,25–27</sup>

The outcomes of various *in vitro* and *in vivo* clinical studies are discussed in the following sections. They have been categorized as studies in experimental animals and cell lines; and human studies, for better understanding the effect of individual probiotic strain or combination of thereof on *H. pylori* infection.

### Clinical studies using experimental animals and cell lines

Various probiotics have shown favorable effects in animal models of *H. pylori* infection (Table 1). In a few preliminary studies, oral administrations of *L. salivarius* to *H. pylori*-infected gnotobiotic BALB/c mice showed a highly protective and therapeutic effect.<sup>15,17</sup> Similarly, Coconnier et al<sup>29</sup> reported that *L. acidophilus* strain LB was able to protect against *H. pylori* infection in conventional mice. In a C57BL/6 mice model of infection, a probiotic combination containing *L. acidophilus* R0052 and *L. rhamnosus* R0011 was found to reduce the effects of *H. pylori* infection

**Table 1** Probiotics applied for the treatment of *Helicobacter pylori* infection in experimental animal models

Model	Probiotic strain	Product, dose, time	Results	Reference
Gnotobiotic BALB/c mice	<i>Lactobacillus salivarius</i> (WB 1004)	10 <sup>9</sup> CFU once for 1 wk prior to or 4 wk after <i>Helicobacter pylori</i> infection	Only <i>L. salivarius</i> effective, anti- <i>H. pylori</i> IgG titers ↓, <i>H. pylori</i> colonization ↓	Kabir et al <sup>15</sup>
Gnotobiotic BALB/c mice	<i>L. salivarius</i> (WB1004)	10 <sup>9</sup> CFU, 1 <sup>st</sup> week 3 times, then once per wk for 3 wk	Only <i>L. salivarius</i> effective, anti- <i>H. pylori</i> IgG titers ↓	Aiba et al <sup>17</sup>
Conventional BALB/c mice	<i>Lactobacillus acidophilus</i> (ATCC 393)			
	<i>Lactobacillus casei</i> (ATCC 4356)			
	<i>L. acidophilus</i> strain LB	5 × 10 <sup>8</sup> CFU for 7 d	<i>Helicobacter felis</i> colonization ↓, gastric inflammation ↓	Coconnier et al <sup>29</sup>
Gnotobiotic BALB/c mice	<i>Lactobacillus gasserii</i> OLL2716	10 <sup>9</sup> CFU once per week, 4 wk	<i>H. pylori</i> colonization ↓	Ushiyama et al <sup>30</sup>
C57BL/6 mice	<i>L. acidophilus</i> R0052 and <i>Lactobacillus rhamnosus</i> R0011	10 <sup>9</sup> CFU/mL ( <i>ad libitum</i> ), 7 d prior to and 49 d after <i>H. pylori</i> infection	<i>H. pylori</i> growth ↓, gastric inflammation ↓, apoptosis ↔	Johnson-Henry et al <sup>31</sup>
C57BL/6 mice	<i>L. casei</i> strain Shirata	10 <sup>8</sup> CFU/mL ( <i>ad libitum</i> ), 9 mo	Chronic gastritis ↓, anti- <i>H. pylori</i> IgG titers ↓, <i>H. pylori</i> colonization ↔	Sgouras et al <sup>16</sup>
C57BL/6 mice	<i>Lactobacillus johnsonii</i> La1	1.5 × 10 <sup>8</sup> CFU/d, 3 mo	Chronic gastritis ↓, anti- <i>H. pylori</i> IgG titers ↓, <i>H. pylori</i> colonization ↔	Sgouras et al <sup>32</sup>
	<i>Lactobacillus amylovorus</i> CDE 471	2.1 × 10 <sup>8</sup> CFU/d, 3 mo		
	<i>L. acidophilus</i> IBB 801	4.6 × 10 <sup>8</sup> CFU/d, 3 mo		
Mongolian gerbil	<i>L. acidophilus</i> R0052 and <i>L. rhamnosus</i> R0011	2 × 10 <sup>9</sup> CFU 4 h prior to <i>H. pylori</i> infection and daily for 2 wk	Chronic gastritis ↓, gastric acid output ↔, gastrin ↓	Brzozowski et al <sup>33</sup>

CFU = colony forming units; IgG = immunoglobulin G; ↑ = increase; ↓ = decrease; ↔ = no effect.

through reducing *H. pylori* colonization and alleviating *H. pylori*-induced inflammation of the stomach.<sup>31</sup> In a Mongolian gerbil model of *H. pylori* infection, the same probiotic preparation was proved effective via its attenuating effect on *H. pylori* colonization, mucosal inflammation, and impairment of the gastrin–somatostatin link.<sup>33</sup> Studies by Sgouras and coworkers<sup>16,32</sup> in a C57BL/6 mice model demonstrated that *L. casei* strain *Shirota* and *L. johnsonii* La1, both administered in drinking water, attenuated *H. pylori* infection-induced gastric mucosa inflammation. However, only *L. casei* strain *Shirota* was able to down-regulate the colonization of *H. pylori* to gastric mucosa. In another study, *L. gasseri* was found to decrease colonization of clarithromycin-resistant *H. pylori*.<sup>30</sup>

The potential of recombinant *Lactobacillus* or any other probiotics to be used as antigen-delivery vehicles to induce protective immune responses has rarely been studied. A recombinant *L. plantarum* strain producing *H. pylori* urease B subunit was found to induce successfully a partial mucosal protection against the pathogenic strain.<sup>34</sup> By contrast, in the study carried out by Lee et al,<sup>35</sup> *Lactococcus lactis*-producing cytoplasmic urease B was shown to be unable to induce protection against *H. pylori* in a mouse model.

Recently, Chen et al<sup>36</sup> assessed the antagonistic activities of *Lactobacillus* strains against *H. pylori* growth in a co-culture system and its infection in human gastric epithelial cells. Results showed that the *Lactobacillus* strains had significant anti-*H. pylori* activity, which can be attributed to the cell-free supernatants of lactobacilli and live *Lactobacillus* strains *in vitro*.

## Clinical studies on humans

Numerous clinical trials in humans for the treatment of *H. pylori* infection have been documented (Table 2).<sup>25,37–47</sup> The role of probiotics in the treatment of *H. pylori* infection is acknowledged either as a complement or as an alternative to antibiotics, having the potential to decrease the use of antibiotics. However, occurrence of side effects is one of the major drawbacks of antibiotic treatment. Gastrointestinal manifestations may be related to alterations in the intestinal microflora. Probiotics can prevent or reduce antibiotic-associated side effects and have an inhibitory effect on *H. pylori*.<sup>2</sup>

In 2000, the first study on humans was conducted by Canducci and coworkers,<sup>37</sup> which provided evidence that *L. acidophilus* LB improved the rate of *H. pylori* eradication significantly in the probiotic group. However, the supplementation did not alleviate the side effects of the anti-*Helicobacter* treatment. In that connection, two separate double-blind studies reported that *L. rhamnosus* GG was able to reduce the occurrence of adverse effects including diarrhea, nausea, and bloating, unlike the outcomes of the previous study.<sup>38,39</sup> Based on the results of an open and uncontrolled clinical trial, Sheu et al<sup>40</sup> reported that a yoghurt containing *L. acidophilus* La5 and *B. lactis* Bb12 was able to increase the eradication rate and also decrease some side effects of the triple therapy. In another study, Cremonini et al<sup>41</sup> observed that the administration of *L. rhamnosus* GG, probiotic yeast *S. boulardii*, or a

combination of *L. acidophilus* and *B. lactis* for 2 weeks also decreased adverse events during the triple treatment. The effects of a probiotic supplementation seemed to be independent of the probiotic species used. In a 10-day quadruple anti-*Helicobacter* therapy with *L. casei* ssp. *casei* DG, the supplementation improved significantly the eradication rate in patients after failure of the first-line eradication treatment.<sup>42</sup> Similarly, in patients with *H. pylori* resistance, *L. acidophilus* La5 combined with *B. lactis* Bb12 improved the second-line rescue therapy.<sup>45</sup> Myllyluoma et al,<sup>25</sup> in a randomized double-blind study, used a combination of several probiotics and observed a decrease in gastritis and *H. pylori* colonization in 118 individuals.

To date, only two studies have been conducted in dyspeptic children. In the earliest study, fermented milk products containing *L. casei* DN-114 001 were found to increase the eradication rate of standard triple treatment efficiently.<sup>43</sup> The second study was carried out by Lionetti et al,<sup>44</sup> where *L. reuteri* was found to alleviate eradication treatment, with associated adverse effects. In a recent study of Ojetti et al<sup>47</sup> conducted in *H. pylori*-positive patients, *L. reuteri* supplementation increased the eradication rate, at the same time decreasing the incidence of the most common side effects associated with antibiotic therapy in the second-line treatment.

Studies concerning the attenuation of microbiota disturbances with probiotics following an anti-*Helicobacter* triple treatment are limited. Madden and coworkers<sup>48</sup> found that a probiotic combination, which included two strains of *L. acidophilus* (CLT60 and CUL21) and two strains of *B. bifidum* (CUL17 and *B. bifidum* Rhodia), stabilized the number of facultative anaerobes. Later, Plummer et al<sup>49</sup> reported that the same probiotic preparation was able to diminish the amount of antibiotic resistance among enterococci and reduce disruption of the enterobacterial component in the regrowth population.

Probiotics as an alternative to antimicrobials have also been the focus of several studies (Table 3).<sup>27,28,50–63</sup> Initially, Mrda and coworkers<sup>50</sup> studied the effect of acidophilus milk containing live probiotic bacteria on 14 individuals and observed a decrease in *H. pylori* colonization, with a simultaneous increase in the eradication rate. Administration of a culture supernatant or fermented milk containing the strain of *L. acidophilus* La1 was found to decrease *H. pylori* urease activity, as measured by <sup>13</sup>C-UBT values in adults<sup>28</sup> and children<sup>54</sup>; similar results were observed in two other trials, as confirmed by histological analysis.<sup>2,55</sup> In the latter two studies, a decrease in *H. pylori* infection-associated inflammation was evident. However, none of the studies reported that regular intake of *L. acidophilus* (*johnsonii*) La1 eradicated *H. pylori*. In a study conducted by Sakamoto et al<sup>51</sup> in 31 patients with *H. pylori* infection, it was indicated that *L. gasseri* OLL2716 was effective in suppressing *H. pylori* and reducing gastric mucosal inflammation, as measured by <sup>13</sup>C-UBT values and assays of serum pepsinogen I. Similar results were obtained by Shimizu et al,<sup>53</sup> using *L. gasseri* OLL2716 in 12 children. In another study, *L. casei* was also shown to inhibit *H. pylori* growth, as reflected by a reduction in <sup>13</sup>C-UBT values.<sup>56</sup> Similar effects on the growth of *H. pylori* were reported by Wang et al<sup>58</sup> in a study of 59 human volunteers who consumed yoghurt containing *L. acidophilus* La5 and

**Table 2** Clinical trials using probiotics as a complement during *Helicobacter pylori* eradication treatment

Patient group	Study design	Eradication therapy	Probiotic strain	Product, dose, time	Results	Reference
120 dyspeptic adults	O, R	CA + rabeprazole	<i>Lactobacillus acidophilus</i> LB	Capsule, inactivated bacteria, $1.5 \times 10^{10}$ CFU/d, 10 d	Eradication rate ↑, side effects ↔	Canducci et al <sup>37</sup>
60 asymptomatic adults	O, R	CT + pantoprazole	<i>Lactobacillus rhamnosus</i> GG	Freeze-dried powder, $1.2 \times 10^{10}$ CFU/d, 14 d	Eradication rate ↔, side effects ↓	Armuzzi et al <sup>38</sup>
120 asymptomatic adults	DBPC, R	CT + pantoprazole	<i>L. rhamnosus</i> GG	Freeze-dried powder, $1.2 \times 10^{10}$ CFU/d, 14 d	Eradication rate ↔, adverse effects ↑	Armuzzi et al <sup>39</sup>
160 dyspeptic adults	O, R	CA + lansoprazole	<i>L. acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12	Yoghurt, $1 \times 10^{10}$ CFU/d, 4 wk	Eradication rate ↑, adverse effects ↓	Sheu et al <sup>40</sup>
85 asymptomatic adults	DBPC, R	CT + rabeprazole	<i>L. rhamnosus</i> GG, <i>Saccharomyces boulardii</i> , <i>L. acidophilus</i> La5, and <i>B. lactis</i> Bb12	Freeze-dried powder, $1-1.5 \times 10^{10}$ CFU/d, 2 wk	Eradication rate ↔, adverse effects ↓ by all probiotics	Cremonini et al <sup>41</sup>
70 dyspeptic adults with resistant <i>Helicobacter pylori</i>	R	AT + ranitidine bismuth citrate + esomeprazole or pantoprazole	<i>L. casei</i> ssp. <i>casei</i> DG	Capsule, $1.6 \times 10^{10}$ CFU/d, 10 d	Eradication rate ↔, adverse effects ↓	Tursi et al <sup>42</sup>
86 dyspeptic children	DBPC, R	CA + omeprazole	<i>L. casei</i> DN-114 001	Fermented milk, $1 \times 10^{10}$ CFU/d, 2 wk	Eradication rate ↑, adverse effects ↔	Sykora et al <sup>43</sup>
40 dyspeptic children	DBPC, R	A + omeprazole 5 d following CT + omeprazole 5 d	<i>Lactobacillus reuteri</i> ATCC 55730	Capsule, $1 \times 10^8$ CFU/d, 20 d	Eradication rate ↔, adverse effects ↓	Lionetti et al <sup>44</sup>
138 dyspeptic adults with resistant <i>H. pylori</i>	O, R	AM + bismuth citrate + omeprazole	<i>L. acidophilus</i> La5 and <i>B. lactis</i> Bb12	Yoghurt, $4 \times 10^{10}$ CFU/d, 4 wk prior to eradication treatment	Urease activity ↓ during pretreatment, eradication rate ↑, side effects ↓	Sheu et al <sup>45</sup>
65 children	R	CA + omeprazole	<i>Bifidobacterium animalis</i> , <i>L. casei</i>	250 mL yoghurt ( $10^7$ CFU/mL)	Eradication rates ↑	Goldman et al <sup>46</sup>
118 individuals	R, DBPC	CA + omeprazole	LGG + <i>L. rhamnosus</i> LC + <i>Propionibacterium freudenreichii</i> + <i>B. breve</i>	Milk-based drink, $1 \times 10^9$ CFU/mL, twice a day for 4 wk followed by once a day for 6 wk	Eradication ↔, urease activity ↓, gastritis and <i>H. pylori</i> colonization ↓	Myllyluoma et al <sup>25</sup>
90 individuals		A + esomeprazole + levofloxacin	<i>L. reuteri</i>		Eradication rates ↑	Ojetti et al <sup>47</sup>

A = amoxicillin; C = clarithromycin; CFU = colony forming units; DBPC = double-blind placebo controlled; M = metronidazole; O = open; R = randomized; T = tinidazole; ↑ = increase; ↓ = decrease; ↔ = no effect.

**Table 3** Clinical trials using probiotics in the treatment of *Helicobacter pylori* infection

Patient group	Study design	Probiotic strain	Product, dose, time	Results	Reference
14 patients	O	<i>Lactobacillus acidophilus</i>	Acidophilus milk (3 × 250 mL/d) 4 × 10 <sup>9</sup> × 10 <sup>10</sup> live	Eradication rate ↑, <i>Helicobacter pylori</i> colonization ↓	Mrda et al <sup>50</sup>
20 asymptomatic adults	R, DB, PC	<i>L. acidophilus (johnsonii)</i> La1	Culture supernatant + omeprazole, dose NA, 14 d	Eradication ↔, urease activity ↓, <i>H. pylori</i> colonization ↔, inflammation and gastritis ↔	Michetti et al <sup>28</sup>
52 asymptomatic adults	R, DB, PC	<i>L. acidophilus (johnsonii)</i> La1	Acidified milk + clarithromycin, dose NA, 3 wk	Eradication ↔, urease activity ↓, <i>H. pylori</i> colonization ↓, inflammation and gastritis ↓	Felley et al <sup>27</sup>
31 asymptomatic adults	PC	<i>Lactobacillus gasseri</i> OLL2716	Yoghurt, 1.8–2.5 × 10 <sup>9</sup> CFU/d, 8 wk	Serum pepsinogen I/II ratio ↑, serum pepsinogen s ↓, urease activity ↓	Sakamoto et al <sup>51</sup>
27 asymptomatic adults	O	<i>Lactobacillus casei</i> 03, <i>L. acidophilus</i> 2412, and <i>L. acidophilus</i> ACD1	Yoghurt, 2.8 × 10 <sup>11</sup> CFU/d, 30 d	Urease activity ↔	Wendakoon et al <sup>52</sup>
12 children	O	<i>L. gasseri</i> OLL 2716 (LG21)	Yoghurt 120 g twice daily, 8 wk	UBT ↓, serum pepsinogen I/II ratio ↑, HpSA level ↓	Shimizu et al <sup>53</sup>
236 asymptomatic children	R, DB, PC	Living and heat-killed <i>L. acidophilus</i> La1 or <i>Lactobacillus paracasei</i> ST1	Fermented milk products, 1 × 10 <sup>10</sup> CFU/d, 4 wk	Eradication ↔, urease activity ↓ by live La1	Cruchet et al <sup>54</sup>
50 asymptomatic adults	R, DB, PC	<i>L. acidophilus (johnsonii)</i> La1	Acidified milk, 1.25 × 10 <sup>9–10</sup> CFU/d 16 weeks	Eradication ↔, <i>H. pylori</i> colonization ↓, inflammation ↓, and gastritis ↔	Pantoflickova et al <sup>55</sup>
20 asymptomatic adults, six adults in control group	O, C	<i>L. casei</i> Shirota	Milk-based drink, 1.95 × 10 <sup>10</sup> CFU/day, 3 weeks	Eradication ↔, urease activity tended to ↓	Cats et al <sup>56</sup>
22 individuals	R, DB, PC	<i>L. brevis</i> CD2	Lyophilized bacteria in tablets 3 wk	Decrease in UBT, gastritis and <i>H. pylori</i> colonization ↓	Linsalata et al <sup>57</sup>
70 dyspeptic adults, endoscopy for 14 individuals	O, C	<i>L. acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12	Yoghurt, 1 × 10 <sup>10</sup> CFU/d, 4 wk	Eradication ↔, urease activity ↓, gastritis and <i>H. pylori</i> colonization ↓	Wang et al <sup>58</sup>
254 asymptomatic children	O, R	<i>L. acidophilus</i> LB or <i>Saccharomyces boulardii</i> with inulin	Capsule or sachet, LB 1 × 10 <sup>10</sup> CFU/d, <i>S. boulardii</i> 500 mg + 10 g inulin/d, 8 wk	Eradication ↓, <i>S. boulardii</i> with inulin more effective than <i>L. acidophilus</i> LB	Gotteland et al <sup>26</sup>
295 asymptomatic children (6–16 y)	R, DB, PC	<i>L. johnsonii</i> La1	Cranberry juice (200 mL) and La1 product (80 mL) daily for 3 wk	Eradication rate ↑ when cranberry juice and La1 given alone	Gotteland et al <sup>59</sup>
79 individuals	R, DB, PC	<i>Bifidobacterium bifium</i>	Beverage BF-1, 1 × 10 <sup>7</sup> 12 wk	Eradication rate ↑, ΔUBT ↓, PG I level ↓	Miki et al <sup>61</sup>
33 patients and 40 asymptomatic volunteers	R, DB, PC	<i>Lactobacillus reuteri</i> SD2112	Tablets Reuterina	Lower UBT, urease activity ↓, <i>H. pylori</i> density ↓	Imase et al <sup>62</sup>
40 individuals	R, DB, PC	<i>L. reuteri</i> ATCC 55730	Once a day for 4 wk	Suppresses <i>H. pylori</i> infection	Francavilla et al <sup>63</sup>

CFU = colony forming units; DB = double blind; NA = not available; O = open; PC = placebo controlled; R = randomized; UBT = urea breath test; ↑ = increase; ↓ = decrease; ↔ = no effect.

*B. lactis* Bb12 for 6 weeks. A randomized, double-blind, placebo-controlled study conducted by Imase et al<sup>62</sup> in 33 patients and 40 asymptomatic volunteers showed a significant decrease in UBT values, which can be attributed to the suppression of *H. pylori* urease activity and cell density by *L. reuteri*. In 2008, Francavilla et al<sup>63</sup> carried out a double-blind study in 40 individuals, in which *L. reuteri* was found to inhibit the growth of *H. pylori*.

Nevertheless, not all clinical trials have shown effectiveness. In one open study, 27 *H. pylori*-infected volunteers received yoghurt containing three *Lactobacillus* spp. and one commercial starter culture for 1 month, and, at the end of the trial, <sup>13</sup>C-UBT values remained positive in 26 of the participants.<sup>52</sup>

Studies on the effect of synbiotics on *H. pylori* infection remained very scarce. A randomized, open study investigated the effects of *L. acidophilus* LB in comparison with antibiotics and the synbiotic combination of probiotic yeast *S. boulardii* with inulin.<sup>26</sup> The eradication rate was slightly better in the study group using *S. boulardii* combined with inulin. In another study, Gotteland et al<sup>59</sup> recorded similar results with *L. johnsonii* La1, in 295 asymptomatic children, using a mixture of cranberry juice (200 mL) and La1 product (80 mL) as a synbiotic preparation.

## Safety aspects

Even though LAB have been generally recognized as safe (GRAS) status by the WHO, each probiotic strain requires a safety assessment. Different strains of probiotics have different safety profiles, which should be taken into account, and generalizations concerning all probiotics should be avoided.<sup>60</sup> Lactobacilli and bifidobacteria are part of normal gastrointestinal microbiota, and systemic infections with these bacteria may thus occur naturally, unrelated to the ingestion of probiotics. Data on the safety of probiotics suggest that probiotic therapy is generally considered safe.<sup>60,64</sup> A lethal dose (LD<sub>50</sub>) of LAB, as measured for mice when administered orally, was found to be >10<sup>11</sup> CFU/kg, depending on the strain.<sup>65</sup>

Bifidobacteria have been found to be even safer because no cases of sepsis related to probiotic ingestions have been reported. The safety of two *Bifidobacterium longum* strains of human origin was evaluated in healthy adult volunteers; no side effects were reported and even the immune parameters measured remained stable, without any undesirable changes.<sup>66</sup> Propionibacteria are also regarded as safe, mainly because of their long history of safe use in Emmental cheese manufacturing. *Propionibacterium freudenreichii* ssp. *shermanii* has consequently been proposed to be granted "Qualified Presumption of Safety" status by the European Food Safety Authority.<sup>67</sup>

Safety considerations regarding antimicrobial resistance are also taken into account while using probiotics. There are questions about the possibility of resistance transfer both from probiotics to pathogenic bacteria and from commensal microbiota to probiotics. Probiotic strains are generally susceptible to the majority of antibiotics, although several studies have indicated that they can survive gastrointestinal transit reasonably well during antibiotic treatment.<sup>68</sup> However, this did not lead to the transfer

of resistance genes from original microbiota to the ingested probiotics.

In conclusion, the majority of the compiled studies propose that consumption of certain strains of probiotics may be useful in combating *H. pylori* infection as a complement to the first- or second-line eradication therapy. These probiotic strains are able to improve patient compliance by reducing antibiotic-associated adverse events, increasing the number of patients completing the eradication therapy and resulting in an improved eradication rate. Complete eradication of *H. pylori* without an anti-*Helicobacter* therapy has not succeeded; however, regular consumption of probiotic products with specific strains as an alternative to antibiotics may have some potential in the suppression of *H. pylori* infection. In order to further evaluate the potential efficacy of this probiotic combination against *H. pylori* infection, studies comprising a larger number of patients are necessary. It should be possible to eradicate *H. pylori* infection with optimal efficacy and tolerability to avoid excess use of antibiotics and to offer alternative ways of controlling *H. pylori* infection if eradication treatment is not recommended.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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