Helicobacter pylori and Probiotics

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Abstract

Helicobacter pylori infection, a highly prevalent pathogen, is a major cause of chronic gastritis and peptic ulcer and a risk factor for gastric malignancies. Antibiotics-based H. pylori eradication treatment is 90% effective. However, it is expensive and causes side effects and antibiotic resistance. Probiotics could present a low-cost, large-scale alternative solution to prevent or decrease H. pylori colonization. A literature search of the MEDLINE database (1966–2006) has been performed selecting all in vitro, animal, and human fully published English-language studies dealing with H. pylori and probiotics. Probiotics had an in vitro inhibitory effect on H. pylori. Animal studies demonstrated that probiotic treatment is effective in reducing H. pylori-associated gastric inflammation. Seven of 9 human studies showed an improvement of H. pylori gastritis and decrease in H. pylori density after administration of probiotics. The addition of probiotics to standard antibiotic treatment improved H. pylori eradication rates (81% vs. 71%, with combination treatment vs. H. pylori-eradication treatment alone; \( \chi^2 \) test: \( P = 0.03 \). Probiotic treatment reduced H. pylori therapy-associated side effects (incidence of side effects: 23% vs. 46%, with combination therapy vs. H. pylori-eradication treatment alone; \( \chi^2 \) test: \( P = 0.04 \)). No study could demonstrate the eradication of H. pylori infection by probiotic treatment. So long-term intake of products containing probiotic strains of probiotics 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. J. Nutr. 137: 812S–818S, 2007.

Long-term Helicobacter pylori infection invariably leads to chronic gastritis (1); it is a major cause of peptic ulcer (2) and a risk factor for gastric malignancies (3). At present, combination therapy consisting of 2 antibiotics and a proton pump inhibitor (PPI)\(^6\) is regarded as a treatment of choice to eradicate H. pylori infection (4). Although this regimen is \(~90\%\) effective, it has the disadvantages of being expensive and causing side effects and antibiotic resistance (5). For this reason, triple therapy is not recommended in most infected subjects, i.e., in “healthy” asymptomatic carriers and in dyspeptic subjects without ulcers (4).

A probiotic is defined as a living microbial species that, on administration, may have a positive effect on bowel microecology and improve health conditions (6). At present, the most studied probiotics are lactic acid-producing bacteria, particularly Lactobacillus species (7). Probiotics have been proven to be useful in the treatment of several gastrointestinal diseases such as acute infectious diarrhea or pouchitis (8). The intake of probiotics can be beneficial in H. pylori–infected subjects for several reasons.

First, although the H. pylori infection rate is still high in developing countries (9), it is falling in industrialized countries (10). As a consequence, the spectrum of upper gastrointestinal disorders has changed. On the one hand, peptic ulcer and gastric cancer have decreased continuously over the past 30 y (11). On the other hand, gastroesophageal reflux and esophageal carcinoma have increased continuously in the same time period (11). It is therefore possible that H. pylori infection may be of benefit, for example, by protecting the host from the reflux esophagitis and its complications (12). Thus, dietary approaches that would keep H. pylori density and infection-mediated inflammation on a low level may, at least in some patients, be desirable alternatives to eradication treatment.

Second, the clinical outcome of H. pylori infection is determined by several factors, including the type of H. pylori strain, the extent of inflammation, and the density of H. pylori colonization (13). It has been reported that the risk of the development of peptic ulcer disease and gastric cancer increases with an increasing level of infection (14,15). Therefore, permanent or long-term suppression of H. pylori could decrease the risk of developing H. pylori-related diseases (16).

There is thus a considerable interest in developing low-cost, large-scale alternative solutions to prevent or decrease H. pylori infection.
colony. In this respect, probiotics may close the therapeutic gap.

**Probiotics and H. pylori**

We have conducted several clinical studies that have shown the favorable effect of *Lactobacillus johnsonii* La1 on *H. pylori* gastritis (17–19). We have aimed to corroborate the results of these studies in the present review. For this purpose, we performed a literature search on studies dealing with *H. pylori* and probiotics. All published English-language studies were identified by an electronic search of the MEDLINE database (1966–2006) using the key words “probiotics,” “lactobacilli,” and “lactic acid bacteria” in connection with “*H. pylori.*” Abstracts and studies not yet published in full were excluded.

In the present article we first discuss the possible mechanisms of action of probiotics on *H. pylori* infection, as reported by in vitro and animal studies. Then we provide the available evidence of the effect of probiotics on *H. pylori* gastritis, which comes from the results of in vivo animal and human studies. Finally, the effect of the addition of probiotics to standard *H. pylori* eradication therapy is discussed.

**Mechanism of action.** This section summarizes the several putative mechanisms by which probiotic bacteria can inhibit *H. pylori.*

**Nonimmunological mechanisms.** Nonimmunological barriers such as the acidity of the stomach and the gastric mucosal barrier represent a first line of defense against pathogenic bacteria. It has been suggested that the intake of probiotics strengthens this barrier by producing antimicrobial substances, competing with *H. pylori* for adhesion receptors, stimulating mucin production, and stabilizing the gut mucosal barrier.

**Antimicrobial substances.** Probiotics may inhibit *H. pylori* growth by secreting antibacterial substances. Certain lactobacilli synthesize antimicrobial compounds related to the bacteriocin family (20,21). Other known substances secreted by these bacteria are the endproducts of lactic acid fermentation, such as lactic and acetate acids, and hydrogen peroxide (22).

The production of relatively large amounts of lactate by lactobacilli has been implicated as an inhibitory factor of *H. pylori* by some authors (23–25) (Table 1). 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. For example, *L. johnsonii* La10 does not inhibit *H. pylori* although it produces as much lactic acid as *L. johnsonii* La1 (17). On the other hand, it has been shown that other strains (*L. acidophilus* LB, *L. casei*, *L. johnsonii* La1, and *L. lactis*) exert an inhibitory effect on *H. pylori* by a lactic acid- and pH-independent mechanism (26–28) (Table 1). The involvement of proteinaceous compounds in this inhibitory effect has been demonstrated by several authors (17,26–29). However, the exact nature of antimicrobial substances secreted by these strains remains to be determined. Other probiotic bacteria, such as *Weissella confusa* (30), *L. lactis* (31), and *Bacillus subtilis* (32), were shown to secrete bacteriocins able to inhibit *H. pylori* growth in vitro. In the case of *B. subtilis*, these substances were similar to animocumacins, belonging to the isocoumarin group of antibiotics (32).

In conclusion, the in vitro inhibitory effect of certain probiotic bacteria is probably related to lactic acid and/or to other antimicrobial substances yet to be identified.

**Competition for adhesion.** The adhesion of *H. pylori* to epithelial cells is important in determining the outcome in *H. pylori*-associated diseases (33). In the gastric mucosa, *H. pylori* possibly interacts with epithelial cells through secretory components or as a result of adherence (34). In vitro studies showed that *L. johnsonii* La1, *L. salivarius*, *L. acidophilus*, and *W. confusa* inhibit the attachment of *H. pylori* to intestinal HT29 cells (17,28) or to MKN 45 gastric cell lines (30,35).

There are several possible mechanisms by which probiotic bacteria can inhibit the adhesion of *H. pylori*. Certain lactobacilli such as *L. johnsonii* La1 (17) or *L. acidophilus* LB (28) can exert their antiadhesion activity by secreting antimicrobial substances (Table 1). In addition, strains such as *L. reuteri* (36) or *W. confusa* (30) can inhibit *H. pylori* growth by competing with adhesion sites. For example, it has been demonstrated that *L. reuteri* inhibits the binding of *H. pylori* to specific glycolipid receptors asialo-GMI and sulfatide (36). However, a nonspecific rather than a specific blockage of receptor sites is the most likely mechanism because lactobacilli can inhibit adhesion of large varieties of pathogenic bacteria, although each adheres to its particular receptor on the cells (37).

Animal studies demonstrated that previous colonization by probiotics prevented (35) or reduced *H. pylori* infection in germ-free mice (38). Thus, regardless of the mechanisms involved in the inhibition of the adherence of *H. pylori* to epithelial cells, probiotics could prevent *H. pylori* colonization of the gastric mucosa by inhibiting its adhesion to epithelial cells.

**Mucosal barrier.** Reduced mucus secretion in a damaged or proliferating epithelium is a frequent finding in *H. pylori*-associated gastritis. *H. pylori* is known to suppress MUC1 and MUC5A gene expression in a human gastric cell line (39). It has been shown in vitro that *L. plantarum* and *L. rhamnosus* increase the expression of MUC2 and MUC3 genes (40) and the subsequent extracellular secretion of mucin by colon cell cultures (41). This property can mediate the ability of these strains to restore the mucosal permeability of gastric mucosa (42) or inhibit the adherence of pathogenic bacteria, including *H. pylori* (40,41).

**Immunologic mechanisms.** The inflammatory response to gastric *H. pylori* infection is characterized by the release of various inflammatory mediators such as chemokines and cytokines. The cytokine response is initially manifested by the release of interleukin 8 (IL-8), which leads to the migration of neutrophils and monocytes to the mucosa (43). Activated

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**Table 1**

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Probiotic</th>
<th>Mechanism of inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiba et al. (23)</td>
<td><em>L. acidophilus</em> 4356</td>
<td>Lactic acid</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em> 393</td>
<td>Lactic acid</td>
</tr>
<tr>
<td></td>
<td><em>L. salivarius</em> WB1040</td>
<td>Lactic acid</td>
</tr>
<tr>
<td>Cats et al. (27)</td>
<td><em>L. casei</em> strain Shirota</td>
<td>Heat-labile substance</td>
</tr>
<tr>
<td>Coconnier et al. (28)</td>
<td><em>L. acidophilus</em> LB</td>
<td>Heat-stable protein</td>
</tr>
<tr>
<td>Kim et al. (31)</td>
<td><em>L. lactis</em> BH5</td>
<td>Bacteriocin</td>
</tr>
<tr>
<td>Lorca et al. (29)</td>
<td><em>L. acidophilus</em></td>
<td>CR1639 autolysins</td>
</tr>
<tr>
<td>Namb et al. (30)</td>
<td><em>W. confusa</em> PL0001</td>
<td>Class II bacteriocin</td>
</tr>
<tr>
<td>Michetti et al. (17)</td>
<td><em>L. johnsonii</em> La1</td>
<td>Heat-stable substance</td>
</tr>
<tr>
<td>Midolo et al. (24)</td>
<td><em>L. acidophilus</em></td>
<td>Lactic acid</td>
</tr>
<tr>
<td>Nam et al. (30)</td>
<td><em>L. casei</em> subsp. Rhamnosus</td>
<td>Lactic acid</td>
</tr>
<tr>
<td>Mukai et al. (36)</td>
<td><em>L. reuteri</em> TM 105</td>
<td>Glycolipid-binding proteins</td>
</tr>
<tr>
<td>Pinchuk et al. (32)</td>
<td><em>B. subtilis</em> 3</td>
<td>Anticoumacin A, B, C</td>
</tr>
<tr>
<td>Sgouras et al. (25)</td>
<td><em>L. casei</em> strain Shirota</td>
<td>Lactic acid</td>
</tr>
</tbody>
</table>

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*H. pylori* and probiotics 813S
monocytes and dendritic cells in the lamina propria produce tumor necrosis factor α (TNF-α) as well as IL-1 and IL-6 (44). IL-1 and IL-6 stimulate CD4+ T cells (type 1), and these produce a variety of cytokines including IL-4, -5, IL-6, and interferon-γ (45). This response is unable to clear the infection and sustains inflammation.

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 (46). In vitro studies demonstrated the inhibition of the H. pylori–stimulated secretion of IL-8 by gastric epithelial cells by L. salivarius (35). Animal studies showed that the probiotic effects of lactic acid bacteria may be mediated through immune regulation, particularly through controlling the balance of proinflammatory and antiinflammatory cytokines, which would then result in a reduction of gastric activity and inflammation (47,48). A decrease in specific IgG antibodies to H. pylori infection, following probiotic intake, parallel to a reduction in gastric inflammation was observed in several animal studies (23,25,35). Finally, probiotic intake has been shown to strengthen the mucosal barrier by stimulating local IgA responses, thus leading to a mucosa-stabilizing effect (49).

However, the effect of probiotics on the immune response is difficult to generalize. Distinct probiotics strains may generate divergent immune responses, which, in turn, depend on the host’s immune status (50).

Probiotics and H. pylori gastritis

Animal studies. Several studies using murine models have shown that treatment with different Lactobacillus strains reduced H. pylori or H. felis colonization and decreased Helicobacter-induced gastric inflammation (23,25,28,35,38,51). In conventional mice, oral treatment with the culture-spent supernatant of the human L. acidophilus strain LB decreased H. felis density, reduced H. felis urease activity, and healed H. felis–associated mucosal inflammation (28). Reduction of H. pylori density and gastric inflammation was also observed in specific germ-free mice treated with L. casei strain Shirōta (25). It has been suggested that the degree of suppression of H. pylori or H. felis depends on the probiotic strain used (23,51). For example, L. salivarius suppressed H. pylori and reduced the inflammatory response in gnotobiotic mice more efficiently than L. acidophilus or L. casei (23).

Thus, it has been shown in animal studies that probiotic treatment, although it is unable to clear H. pylori, is effective in reducing H. pylori–associated gastric inflammation.

Human studies. Certain lactobacilli are resistant to the low pH of the stomach and may adhere to and transiently reside in the human stomach (52,53). 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.

Nine fully published trials investigated the effect of probiotics on H. pylori gastritis (17–19,27,54–58) (Tables 2, 3). The most frequently used strain was L. johnsonii La1, either in a fermented milk preparation containing live bacteria (18,19,54) or as a free-cell culture supernatant (17). Other probiotics used were L. casei (27), L. brevis (55), and L. gasseri OLL2716 (57); 2 studies used yogurts containing mixtures of live probiotic bacteria (56,58). Seven of the 9 studies showed a statistically significant effect of probiotic treatment on H. pylori gastritis (17–19,54–57). No study reported the eradication of H. pylori infection by probiotics.

In most studies, the effect of probiotic treatment on the level of H. pylori infection was estimated indirectly by the urea breath test (UBT) (Table 2) (17,27,54–58). Of these 7 studies, 2 reported no effect of probiotics on H. pylori infection (27,58) (Table 2). However, both studies were uncontrolled. In the remaining 5 studies, the administration of probiotics led to a decrease in the H. pylori bacterial load (17,54–57). In the first study, the administration of the free-cell supernatant from L. johnsonii La1 cultures led to the suppression of H. pylori urease activity in asymptomatic volunteers (17). This effect was maintained 6 wk after cessation of treatment and was acid independent, as it was not enhanced by the coadministration of omeprazole (17). In the 4 other studies performed with subjects treated either with L. johnsonii La1 yogurt (54), L. brevis lyophilized bacteria (55), or yogurts containing L. acidophilus and B. lactis (56) or L. gasseri (57), a decrease in UBT values reflected a decrease in the H. pylori bacterial load. In addition, the markers of gastric inflammation such as progestagen I/II ratio (57) or ornithine decarboxylase activity (55) also decreased in the active treatment group compared with the control group.

Of the 3 studies directly assessing the effect of the administration of probiotics on H. pylori gastritis by the histological examination of gastric biopsies (18,19,56), 2 were performed in our laboratory (18,19) (Table 3). In our first study with H. pylori–positive subjects treated with clarithromycin monotherapy, coadministration of L. johnsonii La1–containing milk (LC-1) was associated with an additional reduction in the activity of H. pylori–associated gastritis and H. pylori density (18). These effects persisted for several weeks after the LC-1 intake was stopped (18). Our subsequent study confirmed this favorable effect. In this study, 16-wk treatment with LC-1 without the addition of antibiotics decreased the activity of H. pylori–associated gastritis and H. pylori density, particularly in the antrum. This effect was achieved after 3 wk and was maintained during long-term LC-1 ingestion (19). In addition, a less severe mucus depletion was observed in H. pylori–positive subjects receiving LC-1 treatment (19). This finding seems to confirm the in vitro studies mentioned above that have shown that L. johnsonii La1 may prevent H. pylori adherence by increasing mucus expression (40,41), which is usually down-regulated in H. pylori infection (39).

In conclusion, animal and human studies show that the administration of probiotics improves H. pylori gastritis and diminishes H. pylori density. This effect is statistically significant but weak. On the other hand, any study could demonstrate the eradication of H. pylori infection by probiotic treatment.

Probiotics and H. pylori eradication

Probiotics and H. pylori eradication rates. As discussed in the previous section, the administration of probiotics alone does not lead to the eradication of H. pylori (Tables 2, 3). It has been suggested that coadministration of probiotics with antibiotics–PPI treatment would improve H. pylori eradication rates. It has been hypothesized that, in addition to the mechanisms mentioned above, lactic acid or other potentially antimicrobial substances secreted by probiotic bacteria (see above) can increase the potential of antibiotic therapy to have an antimicrobial effect. In addition, better compliance, as a result of reduced side effects (see below), may play a role.

As shown in Table 4, 9 studies assessed the effect of the coadministration of probiotics with antibiotics on H. pylori eradication rates (18,59–66). Overall, probiotics improved H. pylori eradication rates (81% vs. 71%, with combination treatment vs. H. pylori eradication treatment alone; χ² test: P = 0.03).
However, this result should be interpreted with care because the studies differ widely with respect to study design and the antibiotic and probiotic treatments used.

Probiotics did not improve the effect of clarithromycin monotherapy (18) or omeprazole-amoxicillin bitherapy (62). The results of 7 studies evaluating the effect of probiotics added to conventional tritherapy are inconsistent. Three studies reported better eradication rates with probiotics (60,64,65), whereas the other 4 studies observed no effect (59,61,63,65). Limitations likely to account for the discrepant results include the lack of placebo controls (60,62,64,66) and the short duration of probiotic treatment (59,60,62,65,66) (Table 4). Finally, the role of milk components should not be omitted in studies not using placebo milk products (60,62,64,66). It has been shown that certain constituents of milk (bovine lactoferrin and glycoconjugates, human κ-casein) have an inhibitory effect on H. pylori in in vitro and animal studies (67,68).

In conclusion, clinical trials provide conflicting evidence on the beneficial effect of addition of probiotics to antibiotic treatment with respect to the eradication of H. pylori infection. Further, large, long-term, and placebo-controlled studies are needed to prove this effect.

**Probiotics and side effects of H. pylori eradication treatment.** It has been postulated that the coadministration of probiotics with the PPI-antibiotic regimen would lead to the correction of antibiotic-induced intestinal dysbiosis (69) and consequently a reduction in diarrhea. However, this remains unproven because no study in Table 4 has evaluated the composition of intestinal microflora.

To date, 7 studies have evaluated the effect of probiotic coadministration on the side effects of standard tritherapy (59–61,63–66). In 4 studies, the frequency of side effects was significantly decreased by the administration of probiotics (59,61,64,66), and 3 studies found no effect (60,63,65). Three studies reported a decreased incidence of diarrhea and taste disturbance (59,61,64), and reduction in vomiting and nausea was observed in 2 studies (64,66).

Overall, probiotic treatment seems to reduce H. pylori therapy-associated side effects (incidence of side effects: 23% vs. 47%, with combination therapy vs. H. pylori-eradication treatment alone; χ² test: P = 0.04) (Table 4). However, it should be noted again that studies differ with respect to the antibiotic and probiotic treatment used, making the interpretation of the results difficult.

Thus, the administration of probiotics can decrease the frequency of diarrhea, a frequent side effect of traditional anti-H. pylori tritherapy. There is no logical explanation for how probiotics can reduce the nausea, vomiting, and taste disturbance.

In summary, long-term intake of products containing probiotic strains, namely lactobacilli species, has a favorable effect on H. pylori infection in humans. On the other hand, the administration of probiotics alone does not lead to the eradication of H. pylori. Similarly, there is no clear evidence that the addition of probiotics to H. pylori standard tritherapy increases the eradication rates.

It could not be decided, at present, which strain of probiotic bacteria is most effective in suppressing H. pylori infection. Strains with proven efficacy in vitro and in vivo include L. casei (24,27,59,61,65,66) and L. johnsonii L1 (17–19,54,60) (Tables 1, 4). On the other hand, the in vivo inhibitory effect of L. acidophilus LB (28) was not reproduced in an uncontrolled clinical trial using the L. acidophilus LB spent culture supernatant (62). However, it could not be ruled out that methodological flaws account for this lack of efficacy. Other strains with potential anti-H. pylori efficacy include L. brevis (55), L. gasseri (57), L. lactis (31,61), L. reuteri (36), B. subtilis (32), and W. confusa (30).

Several mechanisms by which probiotics might contribute to a decreased H. pylori density and inflammation were discussed.

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**TABLE 2** The effect of probiotics on H. pylori gastritis

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Treatment</th>
<th>Duration</th>
<th>R</th>
<th>DB</th>
<th>P</th>
<th>N</th>
<th>Study design¹</th>
<th>Decrease in UBT (n/N, δ)</th>
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</thead>
<tbody>
<tr>
<td>Cats et al. (27)</td>
<td>L. casei strain Shirota fermented milk</td>
<td>3 wk</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>20</td>
<td>9/14 *(7.0)</td>
<td>2/6 (9.0)</td>
</tr>
<tr>
<td>Gotteland and Cruchet (54)</td>
<td>L. johnsonii La1 yogurt</td>
<td>2 wk</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>11</td>
<td>9/11 (20)**</td>
<td>—</td>
</tr>
<tr>
<td>Linsalata et al. (55)</td>
<td>L. brevis CD2 lophalized bacteria in tablets</td>
<td>3 wk</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>22</td>
<td>NA (11.2°)</td>
<td>NA (−1.5)</td>
</tr>
<tr>
<td>Michetti et al. (17)</td>
<td>L. johnsonii La1 supernatant fraction + OME vs. L. johnsonii La1 supernatant fraction + PLA</td>
<td>2 wk</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>20</td>
<td>9/10 (16.5°)</td>
<td>0/10 (10.3)</td>
</tr>
<tr>
<td>Wang et al. (56)</td>
<td>L. acidophilus La5 + B. lactis Bb12</td>
<td>4 wk</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>70</td>
<td>NA (6.1**)</td>
<td>NA</td>
</tr>
<tr>
<td>Sakamoto et al. (57)</td>
<td>L. gasseri OLL 2716 yogurt</td>
<td>8 wk</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>31</td>
<td>18/29 (5.7°)</td>
<td>13/29 (−0.4)</td>
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<td>Wendumoon et al. (58)</td>
<td>L. acidophilus La5 fermented milk 16 wk</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>50</td>
<td>Decreased*</td>
<td>Decreased*</td>
<td></td>
</tr>
<tr>
<td>Felley et al. (18)</td>
<td>L. johnsonii La1 fermented milk + CLA vs. CLA + PLA</td>
<td>4 wk</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>52</td>
<td>Decreased*</td>
<td>Decreased*</td>
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<tr>
<td>Pantoflickova et al. (19)</td>
<td>L. johnsonii La1 fermented milk</td>
<td>16 wk</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>50</td>
<td>Decreased*</td>
<td>Decreased*</td>
</tr>
<tr>
<td>Wang et al. (56)</td>
<td>L. acidophilus La5 + B. lactis Bb12</td>
<td>6 wk</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>27</td>
<td>1/27 (NA)</td>
<td>—</td>
</tr>
</tbody>
</table>

¹ Abbreviations: R, randomized; DB, double blind; P, placebo controlled; N, study size; *statistically significant (P < 0.05) vs. controls; **statistically significant (P < 0.05) vs. pretreatment; δ, difference in pretreatment and posttreatment values.

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**TABLE 3** The effect of probiotics on H. pylori gastritis

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Treatment</th>
<th>Duration</th>
<th>R</th>
<th>DB</th>
<th>P</th>
<th>N</th>
<th>Hp gastritis activity</th>
<th>Hp density</th>
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<tr>
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<td>4 wk</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>52</td>
<td>Decreased*</td>
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<td>16 wk</td>
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<td>yes</td>
<td>yes</td>
<td>50</td>
<td>Decreased*</td>
<td>Decreased*</td>
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<tr>
<td>Wang et al. (56)</td>
<td>L. acidophilus La5 + B. lactis Bb12</td>
<td>6 wk</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>14</td>
<td>Decreased*</td>
<td>Decreased*</td>
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</table>

¹ Abbreviations: R, randomized, DB, double blind; P, placebo controlled; N, study size; *statistically significant (P < 0.05).
TABLE 4 Probiotics and H. pylori eradication

<table>
<thead>
<tr>
<th>Probiotic treatment</th>
<th>Treatment</th>
<th>Study design</th>
<th>Assessment of H. pylori eradication</th>
<th>Results</th>
<th>Side effects</th>
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<td></td>
<td>H. pylori eradication treatment</td>
<td>Duration</td>
<td>Bacteria</td>
<td>Probiotic + H. pylori eradication treatment</td>
<td>Probiotic + H. pylori eradication treatment</td>
</tr>
<tr>
<td>Armuzzi et al. (59)</td>
<td>CLA + TIN + RAB</td>
<td>1 wk</td>
<td>LGG freeze-dried powder with viable bacteria</td>
<td>2 wk yes yes yes 60 UBT</td>
<td>25/30</td>
</tr>
<tr>
<td>Canducci et al. (60)</td>
<td>CLA + AMO + RAB</td>
<td>1 wk</td>
<td>L. johnsonii La1 lyophilized + inactivated culture</td>
<td>10 d no no no 120 UBT + gastric biopsies</td>
<td>52/60*</td>
</tr>
<tr>
<td>Cremonini et al. (61)</td>
<td>CLA + TIN + RAB</td>
<td>1 wk</td>
<td>L. acidophilus + B. lactis</td>
<td>3 wk yes yes yes 85 UBT</td>
<td>51/62</td>
</tr>
<tr>
<td>De Francesco et al. (62)</td>
<td>AMO + OME</td>
<td>2 wk</td>
<td>L. acidophilus LB spent culture supernatant</td>
<td>2 wk no no no 84 gastric biopsies</td>
<td>30/47</td>
</tr>
<tr>
<td>Felley et al. (18)</td>
<td>CLA</td>
<td>2 wk</td>
<td>L. johnsonii La1 milk</td>
<td>4 wk yes yes yes 52 gastric biopsies</td>
<td>8/25</td>
</tr>
<tr>
<td>Myllyluoma et al. (63)</td>
<td>CLA + AMO + LAN</td>
<td>1 wk</td>
<td>L. rhamnosus LC + P. freudenreichii + B. breve</td>
<td>4 wk yes yes yes 47 UBT + serology</td>
<td>21/23</td>
</tr>
<tr>
<td>Sheu et al. (64)</td>
<td>CLA + AMO + LAN</td>
<td>1 wk</td>
<td>Lactobacillus + &quot;Bifidobacterium&quot; containing yogurt</td>
<td>5 wk no no no 160 UBT + gastric biopsies</td>
<td>73/80*</td>
</tr>
<tr>
<td>Sykora et al. (65)</td>
<td>CLA + AMO + OME</td>
<td>1 wk</td>
<td>L. casei DN 114001</td>
<td>2 wk yes yes yes 86 UBT + Hp stool antigen test</td>
<td>33/35*</td>
</tr>
<tr>
<td>Tursi et al. (66)</td>
<td>RBC + AMO + 10 d TIN + PAN or ESD</td>
<td>10 d</td>
<td>L. casei subsp. casei</td>
<td>10 d no no no 70 UBT + gastric biopsies</td>
<td>33/35</td>
</tr>
<tr>
<td>Summary rate</td>
<td></td>
<td></td>
<td></td>
<td>326/401*</td>
<td>54/36</td>
</tr>
</tbody>
</table>

Abbreviations: AMO, amoxicillin; CLA, clarithromycin; ESO, esomeprazole; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole; RAB, ranitidine-bismuth citrate; TIN, tinidazole; LGG, L. casei; DB, double blind; R, randomized; P, placebo controlled; *statistically significant (P < 0.05) vs. controls.

These include the strengthening of the nonimmunological defenses of the gastric mucosa and the enhancement of nonspecific and specific immune response. The observation from human studies that the beneficial effect of probiotics on H. pylori infection persisted when probiotics intake was stopped (17,18), together with the fact that certain lactobacilli such as L. johnsonii La1 do not colonize the stomach (I. Corthe`sy, unpublished observation, 2001), speak in favor of an immunological mechanism.

Regardless of their mechanism of action, probiotics may provide a novel approach to the management of H. pylori infection. The risk of developing H. pylori-associated diseases may increase with an increasing level of H. pylori density (14,15). Numerous animal and human studies have demonstrated a decrease in H. pylori density and inflammation following the intake of probiotics (18,19). It can be argued that the effects of lactobacilli on inflammation and H. pylori density are weak. However, the modesty of these effects does not exclude clinical relevance. It is known from other areas that small changes in disturbed functions have major clinical effects. For example, studies conducted in the pre-PPI era showed that small changes in acid secretion produced by antacids had a major effect on ulcer disease (70,71). In any equilibrium between aggression and defense, minor changes are sufficient to prevent or precipitate disease. It can be suggested that the weak but persistent effect of lactobacilli on H. pylori gastritis could prevent diseases such as gastric cancer or peptic ulcer. On the other hand, an attenuated H. pylori infection might be better for the host than no infection at all. H. pylori may be of benefit, for example, by protecting the host from reflux esophagitis and its complications (12). This hypothesis should be evaluated in future well-designed large studies.

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