



*Review*

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## THE INHIBITORY EFFECT OF GENUS *LACTOBACILLUS* ON *HELICOBACTER PYLORI* INFECTION

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### ABSTRACT

The triple treatment of *Helicobacter pylori* infection with two antibiotics and PPI has been shown to be the best way to eradicate this bacterium. In the last years the antibiotic resistance is increasing. Meta-analyses on the effects of probiotics on the gastrointestinal diseases have shown positive effects on the prevention and treatment of these disease. Various studies support the hypothesis that probiotics may inhibit *H. pylori* growth. The release of bacteriocins active against *H. pylori* has been studied chiefly in *Lactobacillus*, but probiotic bifidobacteria may also produce them. Probiotics reduce the side effects of *H. pylori* regimens and may slightly increase eradication success. The tradition of yogurt consumption has been related to longevity of some populations living on the Balkans. Probiotics have been claimed to exert anticarcinogenic activities, too. From the 4th Maastricht/Florence Consensus Conference in 2012 about the management of *Helicobacter pylori* infection: "Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects".

**Key words:** *Helicobacter pylori*, *Lactobacillus bulgaricus*, Probiotics, therapy

### INTRODUCTION

*Helicobacter pylori* is the main cause of gastritis, peptic ulcers, and gastric cancer and over 50% of the world population is infected (the majority asymptomatic) by this microorganism. After the eradication of *H.pylori* the severity of gastric mucosal inflammation decrease and the ulcers heal. Treatment of *Helicobacter pylori* infection with antibiotics has been shown to be the best way to eradicate this bacterium but antibiotic resistance is increasing in most countries, and retreatment after eradication failure is difficult. The search for better therapies against *H.pylori* is needed. In clinical studies some probiotic strains eradicate *H. pylori* by themselves in 12–

14% of colonized children and adults. When administered with antibiotics, probiotics decrease their secondary effects; consequently, probiotics are useful in the management of *H. pylori* infection.

### Brief history of *Lactobacillus bulgaricus*

In 1905 the Bulgarian scientist Dr. Stamen Grigorov, discovered a special strain of *Lactobacilli* and it was called *Lactobacillus bulgaricus*. In the microbiological laboratory of Professor Léon Massol in Geneva, Dr. Stamen Grigorov discovered that a certain strain of bacillus is the true cause for the existence of natural yogurt (1). The Russian scientist Ilya Metchnikoff is one of the founders of modern immunology. He has received the Nobel Prize in Medicine in 1908. For the first time he linked the longevity of the Bulgarian people to the consumption of yoghurt, derived mostly in the rural area of Balkan Mountains in Bulgaria, from the villagers themselves. Metchnikoff proposed

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that the lactic acid microbes of fermentation must be antagonistic to the putrefying microbes of the gut. His hypothesis seemed confirmed by the fact that populations that regularly ate yogurt lived a very long time (e.g., Bulgaria, known for longevity). He experimented on himself and reported that his health, which was generally poor, improved with regular ingestion of a sour milk prepared with cultures of the Bulgarian lactic bacillus. Metchnikoff's enthusiasm about yogurt spilled over into the public, and doctors began recommending yogurt/sour milk as a hygienic food. Metchnikoff credited his relatively long life in part to the lactic bacilli in his diet, and hypothesized, "When people have learnt how to cultivate a suitable flora in the intestines of children as soon as they are weaned from the breast, the normal life may extend to twice my 70 years". (2)

#### **In vitro inhibition of *H. pylori* growth by *Lactobacillus***

Various studies support the hypothesis that probiotics may inhibit *H. pylori* growth owing to the production of short-chain fatty acids (SCFAs) and/or bacteriocins. These studies have been carried out mostly in vitro. High lactic acid-producer strains of *Lactobacillus* were shown to decrease *H. pylori* density in the stomach of mice. The release of bacteriocins active against *H. pylori* has been studied chiefly in *Lactobacillus*, but probiotic bifidobacteria may also produce them. The supernatant of a culture of *L. johnsonii* NCC533 was shown to inhibit both the urease activity and growth of *H. pylori* free or adherent to epithelial cells. (3)

*H. pylori* infection induces Smad7 (protein, acts as transcription factor for DNA), NFκB, (nuclear factor kappa-light-chain-enhancer of activated B cells) and IL-8 (interleukin)-production in vitro. Higher doses of *L. acidophilus* pre-treatment reduce *H. pylori*-induced inflammation through the inactivation of the Smad7 and NFκB pathways. Experimentally, *L. acidophilus* decreases the viability of *H. pylori* in vitro independent of pH and lactic acid levels. The data of this study reveals that probiotics contained in yogurt can inhibit Smad7 to diminish *H. pylori* related gastric inflammation. Such probiotics can be quite promising for the improvement of *H. pylori* infection control. Intake of *L. acidophilus*-

containing yogurt may improve gastric inflammation in *H. pylori*-infected patients. (4)

Sgouras et al. has studied the potential inhibitory effect of *Lactobacillus casei* strain Shirota, from the fermented milk product on *Helicobacter pylori*. A significant reduction in the levels of *H. pylori* colonization has been observed in the antrum and body mucosa in vivo in the lactobacillus-treated study group, as assessed by viable cultures, compared to the levels in the *H. pylori*-infected control group. This reduction has been accompanied by a significant decline in the associated chronic and active gastric mucosal inflammation. (5) Probiotics reduce the side effects of *H. pylori* regimens and may slightly increase eradication success. By the authors of another investigation probiotics are often prescribed for 1–3 weeks longer than the duration of antibiotic treatment. They should be taken with food because the increased gastric pH is more favorable for the probiotics. (6)

#### **The potential of probiotics for use in the treatment of *H. pylori* infection**

The authors of another study have performed a literature search of the MEDLINE for the period: 1966–2006 selecting the fully published English-language studies about *H. pylori* and 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. Antibiotics-based *H. pylori* is expensive and causes side effects and antibiotic resistance. Probiotics could approve a low-cost alternative therapy to prevent or inhibit *H. pylori* infection. (7) Probiotics did not improve the effect of clarithromycin monotherapy or omeprazole-amoxicillin bitherapy. 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. The long-term intake of products containing probiotic strains, namely lactobacilli

species, has a favorable effect on *H. pylori* infection in humans. Similarly, there is no clear evidence that the addition of probiotics to *H. pylori* standard tritherapy increases the eradication rates. Regardless of their mechanism of action, probiotics may provide a novel approach to the management of *H. pylori* infection. Numerous animal and human studies have demonstrated a decrease in *H. pylori* density and inflammation following the intake of probiotics. 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. (7) The results of another study have showed that probiotic strain *B. subtilis* 3 exerts antagonistic activity in vitro against *H. pylori* and this activity is due to the production of at least two antibiotics with additive activity, including ampicoumacin A with other properties such as anti-inflammatory and antitumoral activities and is therefore very promising because of its potential for use in the treatment of *H. pylori* infection. (8)

Meta-analyses on the effects of probiotics on the gastrointestinal diseases have shown positive effects on the prevention and treatment of these disease. When choosing to use probiotics in the treatment or prevention of gastrointestinal disease, the type of disease and probiotic species (strain) are the most important factors to take into consideration *Helicobacter pylori*. The primary outcome has been the improvement of *H. pylori* eradication rates reducing side effects with probiotics. (9)

Fujimura S et al confirmed the coccoid conversion of *H. pylori* by DL-lactic acid produced by the *L. gasseri* OLL2716 strain and the suppression of *H. pylori* multiplication. After screening over 200 *Lactobacillus* strains, Kimura found that the *L. gasseri* OLL2716 strain has strong antiacid properties. Furthermore, this strain can compete with *H. pylori* in the human gastric mucus layer and suppresses *H. pylori* infection. This is the first report that showed that the *L. gasseri* OLL2716 strain induces the coccoid conversion of *H. pylori* by using an electron microscope. The incidence of antibiotic-resistant *H. pylori* has increased in recent years. The combination of probiotics using *L. gasseri* OLL2716 and conventional eradication therapy may be effective for the control of these resistant

strains. When they are ingested through yogurt, *L. gasseri* OLL2716 strains which are acid proof to gastric juice will be effective as probiotics against *H. pylori* infection. (10)

Myllyluoma et al have evaluated whether probiotic combination with LGG adheres to the upper gastrointestinal mucosa and modifies *H. pylori* colonisation and *H. pylori* induced inflammation. In conclusion: the decreases in <sup>13</sup>C-urea breath test and gastrin-17 indicate that the probiotic combination exerts a beneficial effect on gastric mucosa in *H. pylori* infected patients. (11) Medouakh et al has tested the inhibitory effect of *Lactobacillus* Sp. from the goat's milk on *H. pylori*. They also concluded that this inhibition is related to lactic acid production by *Lactobacillus* strains. (12)

#### **Fermented milk products (esp. yoghurt with *Lactobacillus bulgaricus*) and *Helicobacter pylori* infection**

The tradition of yoghurt consumption has been related to longevity of some populations living on the Balkans. The main beneficial health effects of *L. delbrueckii subsp. bulgaricus* and *Str. thermophilus* in yogurt is the capability of inhibiting growth of some key oral pathogens like *S. mutans* and *A. Actinomycescomitans*, and *L. delbrueckii subsp. bulgaricus* can induce IL-8 and TNF- $\alpha$  after stimulation of oral epithelial cells in vitro which is strain and concentration dependent. (13) The results of one research of Zhou C et al have indicated that viable *Lactobacillus bulgaricus* (LBG) have prevented *H. pylori* SS1-LPS-activated TLR4 pathway in SGC-7901 cells, leading to its inhibitory effect on IL-8 production stimulated by *H. pylori* SS1-LPS. It was demonstrated that LBG-S had the same inhibitory effect on *H. pylori* SS1-LPS-activated TLR4 signaling transduction as viable LBG. So LBG-S in this experiment probably contained the similar or even same proteins, which could intervene in *H. pylori* SS1-LPS-activated TLR4 signaling through modulating other pathways in SGC-7901 cells (14).

In a study of Bulgaria have been compared two different areas with a different consumption of fermented milk (yoghurt) to the occurrence of gastroduodenal diseases. The areas have been: a town with a lower consumption of yoghurt and a

rural area in front of Balkan mountains with a higher consumption of the same milk product, derived from the villagers themselves. Although the seroprevalence of *H. pylori* was almost identical in the 2 regions, the prevalence of the gastroduodenal diseases has been significantly lower in the Balkan area than in the town: 46 of 151 blood donors have reported peptic ulcer disease in the town vs 10 of 156 donors- in the Balkan area; 100 of 151 have reported symptoms of gastroduodenal diseases in the town vs 58 of 156 - in the Balkan area. From the National Cancer Register, the prevalence of the gastric cancer for the year 1998 was 68.2 per 100,000 in this town vs 42.8 per 100,000 in the Balkan area, and for the year 1999- 77.5 per 100,000 vs 46.7 per 100,000, respectively. One possible interpretation of these results is that repeated consumption of *L. bulgaricus* in traditional yoghurt may lead to a decrease in bacterial cell load in the stomach, which would decrease gastric inflammation and associated diseases. The growth and clinical outcome of *H.pylori* infections could be suppressed by *Lactobacilli* and their fermented products (esp. *L.bulgaricus* in yoghurt) in vivo. (15, 16, 17)

In addition to their antimicrobial activity, probiotics have been claimed to exert anticarcinogenic activities, e.g. inhibition of tumor growth in rodents. A preparation obtained from *Lactobacillus bulgaricus* strain LB51 was especially studied in this respect and has even been used for anti-cancer therapies in humans in Eastern countries (18, 19). This property has been related to the ability of this product to induce TNF $\alpha$  secretion. Perdigon et al. showed that *Lactobacillus casei* could prevent enteric infections and stimulate secretory IgA in malnourished animals. Yogurt could inhibit the growth of chemically induced intestinal carcinoma in mice through increased activity of IgA, T cells, and macrophages. According to their results, they concluded that *L. acidophilus*, *L. casei*, *L. delbrueckii ssp. bulgaricus*, and yogurt induced increased systemic immune response at different levels of stimulation and also that *L. casei* was the most effective. (20,21)

## CONCLUSION

In 2012 at the 4th Maastricht/Florence Consensus Conference 44 experts from 24 countries have examined key clinical aspects of

management of *H.pylori* infection. The results of the individual workshops were submitted to a final consensus voting to all participants. Recommendations are provided on the basis of the best current evidence and plausibility to guide doctors involved in the management of this infection associated with various clinical conditions. One of the statements of this consensus is: "Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects" in the 5 Grade of recommendation: D. (22)

The use of probiotics to enhance intestinal health has been proposed for many years. There is a relatively large volume of literature that supports the use of probiotics to prevent or treat intestinal disorders. The use of probiotics in *H. pylori*-colonized subjects with gastric inflammation is supported by many observations. In association with antibiotic treatments, some probiotics increased eradication rates and decreased adverse effects.

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