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Probiotics and autoprobiotics in treatment of *Helicobacter pylori* infection

Baryshnikova NV *et al.* Probiotics and autoprobiotics in *Helicobacter pylori*

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Abstract

The article discusses various approaches for probiotic treatment of *Helicobacter pylori* (*H. pylori*) infection: Probiotics as an adjuvant treatment in the standard eradication therapy; probiotic strains as a monotherapy; and autoprobiotics as a monotherapy. Autoprobiotics refer to indigenous bifidobacteria, lactobacilli, or enterococci isolated from a specific individual, intended to restore their microbiota and improve their health. The potential mechanisms of probiotic action against *H. pylori* include correction of gut microbiota, immunological effects (enhancement of humoral and cellular immunity, reduction of oxidative stress), direct antagonistic effects against *H. pylori* (such as colonization resistance and bacteriocin synthesis), and stimulation of local immunological protection (strengthening of the mucous protective barrier and reduction of gastric mucosa inflammation). The incorporation of probiotics into comprehensive eradication therapy shows promise in optimizing the treatment of *H. pylori* infection. Probiotics can enhance eradication rates, reduce the occurrence and severity of side effects, and improve patient compliance. Probiotic or autoprobiotic monotherapy can be considered as an alternative treatment approach in cases of allergic reactions and insufficient effectiveness of antibiotics. We recommend including probiotics as adjunctive medications in anti-*H. pylori* regimens. However, further randomized multicenter studies are necessary to

investigate the effects of probiotics and autoprobiotics against *H. pylori*, in order to gain a better understanding of their mechanisms of action.

Key Words: *Helicobacter pylori*; Probiotic; Autoprobiotic; Eradication; Microbiota; Gut; Immunity

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Core Tip: The usage of probiotics in complex eradication therapy holds promise for optimizing the treatment of *Helicobacter pylori* (*H. pylori*) infection. Probiotics have the potential to enhance the eradication rate, reduce the frequency and severity of side effects, and improve patient compliance. Probiotic and autoprobiotic monotherapy are viable alternatives in cases of allergic reactions or adverse effects caused by antibiotics, owing to their direct antagonistic effect on *H. pylori*. However, conducting new randomized multicenter studies is necessary to investigate the intricate effects of probiotics and autoprobiotics against *H. pylori* infection, with the aim of gaining a better understanding of their mechanisms of action.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is one of the most prevalent and extensively studied bacterial infections worldwide. This microorganism serves as a trigger for various conditions, including peptic ulcer disease, chronic gastritis, gastric MALT lymphoma, gastric cancer, and non-gastroenterological issues like iron deficiency anemia. Over the past 35 years, scientists and clinicians in different countries have been striving to identify the most effective regimen for eradicating *H. pylori*. However, there are several challenges associated with standard eradication regimens, such as antibiotic resistance, low patient compliance due to complex regimens or individual factors, high bacterial density within

the stomach, and bacterial internalization. The use of antibiotics in standard *H. pylori* eradication therapy disrupts the gastrointestinal microbiota, particularly the gut microbiota^[1-5]. Therefore, it is crucial to explore *H. pylori* treatment alternatives that enhance therapy safety and effectiveness while minimizing the negative impact on the gut microbiota. Probiotics represent a potential approach to optimize the management of *H. pylori*-associated diseases^[6,7]. The mention of this treatment method is also found in the Maastricht VI statement, which states that "certain probiotics have demonstrated efficacy in reducing gastrointestinal side effects caused by *H. pylori* eradication therapies"^[8]. However, according to the Toronto consensus, the routine addition of probiotics to eradication therapy to reduce adverse events and improve eradication rates is not recommended due to the very low quality of evidence available^[9].

What are probiotics? According to the guidelines of the World Gastroenterology Organization, "Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"^[10]. Medications aimed at correcting the gut microbiota can be categorized into several groups: Real probiotics (containing live microorganisms), metabiotics (containing the byproducts of gut normobiota metabolism), prebiotics (containing substances that serve as nutrients for microorganisms), synbiotics (a combination of probiotics and prebiotics), and symbiotics (a combination of different probiotics). Metabiotics, also known as postbiotics, refer to bacterial metabolites and structural components derived from probiotic microorganisms that have the ability to optimize regulatory, metabolic, and/or behavioral responses associated with the activity of the host organism's native microbiota^[11,12]. This article focuses on the use of probiotics and symbiotics (medications containing live microorganisms exclusively) in eradication regimens.

The benefit of the addition of probiotics in anti-*H. pylori* regimens could restore the alterations of gastrointestinal microbiota induced by antibiotics or proton pump inhibitors in the regimens. Multiple studies have investigated the effects of probiotics on gastric^[13-15], gastrointestinal^[16] and gut^[17-20] microbiota. Well-known probiotic microorganisms include various species of *Bifidobacterium* (*B. bifidum*, *B. infantis*, *B.*

longum, *B. breve*, *B. adolescents*), *Lactobacillus* (*L. acidophilus*, *L. plantarum*, *L. casei*, *L. bulgaricus*, *L. lactis*, *L. reuteri*, *L. rhamnosus*, *L. fermentum*, *L. johnsonii*, *L. gassed*), non-pathogenic strains of *Enterococcus* (*E. faecium*, *E. salivarius*), certain non-pathogenic species of *Escherichia coli*, non-pathogenic *Bacillus* spp. (*Bacillus subtilis*), lactic acid streptococci (*S. thermophilus*), yeast fungi such as *Saccharomyces boulardii*, and newer variants like probiotic products containing *Clostridium butyricum* or *Akkermansia muciniphila*^[10]. Lactic acid bacteria, particularly *Lactobacillus* spp., are commonly used as adjunct agents in anti-*H. pylori* therapy among probiotics^[21]. The use of lactobacilli or bifidobacteria as additional medications in eradication therapy is promising because these microorganisms secrete bacteriocins that can inhibit the growth of *H. pylori* and disrupt its adhesion to the stomach's epithelial cells^[22]. Furthermore, the supplemental use of probiotic strains of *Bacillus* spp. and *Enterococcus faecium* in triple eradication therapy enhances compliance, reduces the frequency and severity of side effects, and increases microbial eradication efficacy^[23]. However, the use of these microorganisms may potentiate certain side effects (such as constipation, bloating, etc.), and their safety has not been definitively established^[24,25]. Therefore, further studies are necessary to investigate their efficacy and safety, particularly for *E. faecium*, which poses challenges due to antibiotic resistance and potential pathogenicity in certain cases^[26].

Medications with probiotic properties not only correct gut microbiota disorders but also offer several additional beneficial effects. These include metabolic benefits, such as a positive impact on metabolic processes and normalization of lipid profiles and blood sugar levels. Furthermore, they contribute to immunological improvements, including enhancements in humoral and cellular immunity and reduction of oxidative stress. Additionally, probiotic medications exert an effect on *H. pylori* in the stomach through their direct antagonistic action and stimulation of local immune protection, which involves strengthening the protective mucous barrier and reducing the severity of gastric mucosa inflammation^[27,28]. Therefore, it is appropriate to consider the overall positive impact of probiotic medications^[29,30].

PROBIOTICS ACTION AGAINST *H. PYLORI*: MYTH OR REALITY?

Probiotics in the complex eradication therapy

The efficacy of probiotics in complex eradication therapy has been extensively investigated in numerous scientific studies and analyzed in several meta-analyses.

Several meta-analyses confirm the effectiveness of probiotics as an adjuvant component of eradication therapy in significantly improving the rate of *H. pylori* eradication and preventing adverse reactions and antibiotic-associated diarrhea^[31-33].

In a meta-analysis conducted by Wang *et al*^[34] (2017), which included 140 studies (44 English and 96 Chinese) with 20215 patients, it was found that the eradication rate was 84.1% and the incidence of adverse events was 14.4% in the probiotic group, compared to 70.5% and 30.1% respectively in the placebo group. *Lactobacillus acidophilus* was slightly more effective, while *Saccharomyces boulardii* was more suitable for 10-d triple therapy.

In another meta-analysis by Feng *et al*^[35] (2017), which included 29 trials ($n = 3122$), the efficacy of 17 different probiotics was studied. Compared to placebo, probiotic-supplemented triple therapy significantly increased *H. pylori* eradication rates [relative ratio (RR) = 1.19, 95%CI: 1.13-1.25] and reduced the incidence of total side effects (RR = 0.49, 95%CI: 0.38-0.65). *Lactobacillus casei* was identified as the most effective for *H. pylori* eradication rates (P score = 0.84), and a multi-strain combination of *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* was effective for reducing total side effects (P score = 0.93).

According to the data from our prospective open-label study, the additional use of probiotics containing *Lactobacillus spp.* and *Bifidobacterium spp.* increases the effectiveness of eradication therapy by 20%-25%^[36].

While the effects of probiotics in reducing the frequency of side effects in eradication therapy are widely accepted, the mechanisms by which probiotics increase the effectiveness of treatment are not yet fully understood. It is hypothesized that this may be due to improved compliance resulting from a decrease in the occurrence of side effects,

although other mechanisms of probiotic action are also under discussion. The possible mechanisms of probiotic action against *H. pylori* are illustrated in Figure 1.

In light of the possible mechanisms of action of probiotics against *H. pylori*, the question arises: Can we attempt to eradicate *H. pylori* using probiotics? Research in this area is progressing in two directions.

The first approach involves incorporating probiotics into eradication therapy as an adjuvant treatment. The co-administration of probiotics with anti-*Helicobacter* drugs has been shown to increase the success rate of eradication and reduce the frequency of side effects associated with eradication therapy. Consequently, this approach improves patient compliance with the treatment^[37-41]. Another strategy is the administration of probiotics prior to eradication. For instance, the consumption of yogurt containing probiotic strains before starting eradication therapy has demonstrated beneficial effects on the eradication outcome and patient tolerance^[42].

The second way studies the effect of probiotic monotherapy in *H. pylori* eradication. This was recommended to patients who have allergic reactions to antibiotics used in anti-helicobacter therapy regimens and to people who have *H. pylori* infection without clinical manifestations, for example, *H. pylori*-positive family members of patients with diseases associated with *H. pylori*.

METHODOLOGY

For assessment of anti-*H. pylori* efficacy of adjuvant probiotic treatment, we search randomized controlled trials about probiotics action against *H. pylori* in PUBMED for the last 10 years (from 2012 to 2022) with keywords: probiotics and *H. pylori*. In common there are 438 scientific articles with these key words from which 56 were clinical trials, 20 -- systematic reviews, 23 - meta-analyses, 50 - randomized controlled trials, 174 - reviews. From 50 articles with results of randomized controlled trials 23 articles estimated eradication rate of eradication therapy with probiotics/symbiotics treatment with verified probiotic strains. These articles were included in our analysis. For assessment of anti-*H. pylori* efficacy of probiotic monotherapy, we search articles about probiotics action

against *H. pylori* in PubMed for the last 10 years (from 2012 to 2022) with keywords: probiotics, monotherapy and *H. pylori*. In common there are 10 scientific articles with these key words from which 3 were clinical trials or randomized controlled trials, 2 -- systematic reviews and meta-analyses, 5 - reviews. All of these articles were included in our analysis.

ERADICATION RATE ASSESSMENT OF ERADICATION THERAPY WITH/WITHOUT PROBIOTICS

To review the anti-*H. pylori* efficacy of adjuvant probiotic treatment, we selected 23 out of the 56 articles that analyzed the eradication rate when probiotics were used in the treatment of *H. pylori* (Tables 1-4). The majority of the articles demonstrated that the addition of probiotics increased the eradication rate. Several papers showed that probiotics did not significantly increase the eradication rate but effectively reduced the side effects of antibiotic therapy. However, one study found that the addition of *S. boulardii* probiotic to triple antibiotic therapy for *H. pylori* infection did not increase the eradication rate nor reduce the occurrence of adverse events^[43]. These findings highlight the importance of specific strains included in probiotic formulations.

According to the information presented in these tables, it is evident that the most commonly used single-strain probiotics are *Saccharomyces boulardii* and *Lactobacillus reuteri* strains. As for multi-strain probiotics (symbiotics), the combination of *Lactobacillus* spp. and *Bifidobacterium* spp. is widely utilized. Additionally, the inclusion of probiotics in proton pump inhibitor-antibiotics-bismuth regimens has been shown to enhance the safety of anti-*H. pylori* treatment. Furthermore, due to their multifaceted positive effects, probiotics can contribute to higher eradication rates.

PROBIOTIC MONOTHERAPY

Several studies have confirmed the efficacy of probiotics as monotherapy for *H. pylori* eradication^[27,38,66,67]. For instance, one study reported that a probiotic containing *L. acidophilus* led to eradication in 6 out of 14 patients^[38]. Dore *et al*^[68] (2014) assessed the

7 efficacy of *Lactobacillus reuteri* (DSM 17938) 108 CFU in combination with pantoprazole 20 mg twice a day for 8 wk in *H. pylori* eradication. The study defined eradication as a negative result in the (13)C-UBT test 4-6 wk after therapy. The results showed that *L. reuteri* plus pantoprazole achieved eradication in 13.6% of patients by intention-to-treat analysis and 14.2% by per protocol analysis. Another study combining *L. reuteri* with pantoprazole for 4 wk achieved eradication in 12.5% of patients^[69]. Several studies have demonstrated that *L. reuteri* can inhibit *H. pylori* growth and decrease bacterial load^[59,70,71,72]. This antimicrobial activity may be attributed to the production of compounds such as reuterin, reuteritsin 6, reutetsiklin, and metabolites that inhibit bacterial growth. These compounds can reduce *H. pylori* adhesion to gastric epithelial cells and inhibit microbial growth, leading to a significant reduction in *H. pylori* contamination and gastric mucosal inflammation severity^[72].

In another study, 40 *H. pylori* patients were treated with a mixture of 8 species of probiotics for 10 days, while 40 *H. pylori*-positive subjects received a placebo for 1 mo. The eradication rate was 32.5% in the probiotic group and 0% in the placebo group^[73]. Probiotics containing *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* have been shown to reduce the bacterial load of *H. pylori* according to the 13C-urea breath test^[17]. The 10 *Limosilactobacillus reuteri* strain 2892 (*L. reuteri* 2892) of isolated from camel's milk demonstrated the protective effects against *H. pylori*-induced gastritis in the gastric mucosa in animal models due to significantly downregulated the virulence factor *cagA* gene expression^[74]. The 4 combination of fermented milk containing *Lactobacillus paracasei* and *Glycyrrhiza glabra* reduced *H. pylori* density and improved histologic inflammation^[75]. Monotherapy with *Clostridium butyricum*, *Bacillus coagulans*, and a combination of *C. butyricum* and *B. coagulans* showed efficacy for *H. pylori* eradication in 18%, 20%, and 26% of cases, respectively^[76]. However, another study demonstrated no 5 inhibitory activity of a combination of *L. acidophilus*, *L. rhamnosus*, and *L. sporogenes* on *H. pylori*^[77]. *S. boulardii* monotherapy for 2 wk led to *H. pylori* eradication in 28.0% of patients based on intent-to-treat criteria^[78]. In prospective studies, probiotic monotherapy effectively decreased *H. pylori* density (based on the 13C-urease breath test data) by 2.0% to 64.0%^[79]. Initial

studies in children have shown promising results for *H. pylori* eradication with various probiotic strains^[80].

Meta-analysis of 11 studies demonstrated that probiotics eradicated *H. pylori* in 14% (95%CI: 2%-25%, $P = 0.02$). Specifically, lactobacilli were effective in achieving eradication in 16% (95%CI: 1%-31%), *Saccharomyces boulardii* in 12% (95%CI: 0%-29%), and multi-strain combinations in 14% (95%CI: 0%-43%). Although probiotic monotherapy had a minimal effect on *H. pylori* eradication, the successful eradication suggests a possible direct effect of probiotics against *H. pylori*^[81]. A systematic review of 11 high-quality studies concluded that probiotic monotherapy does not significantly affect the eradication rates of *H. pylori* infection. However, when used in combination with eradication therapy, probiotics can increase the eradication rates and significantly reduce side effects associated with antibiotics^[82].

In an *in vitro* study conducted by our team, it was observed that the ²inhibition of *H. pylori* growth occurred in 50% of cases in contact with a probiotic based on *Bacillus subtilis*, 78.6% of cases in contact with *Enterococcus faecium* strain L-3, and 64% of cases in contact with a combination of *Bifidobacterium longum* and *Enterococcus faecium*^[83]. In an *in vivo* study, monotherapy with *Enterococcus faecium* strain L-3 in patients with chronic gastritis associated with *H. pylori* showed an eradication effectiveness of 39%^[84].

Probiotic monotherapy can be considered as an alternative therapy in cases of polyvalent allergic reactions to antibiotics, as the eradication rate of this treatment is significantly lower compared to standard regimens. Additionally, probiotic monotherapy may be preferred in pediatric practice for children under 10 years of age. Among the different monotherapy options, the most promising results were observed with multi-strain probiotics (32.5%), *S. boulardii* (28%), a complex of *C. butyricum* and *B. coagulans* (26%), and *L. reuteri* (14.2%). Our data on the efficacy of *E. faecium* L3 showed a 39% eradication rate, but further multicenter clinical trials are needed to confirm these findings.

WHAT IS AUTOPROBIOTICS?

The benefits of probiotics arise from the interaction of probiotic strains or strain compositions with the host microbiota. However, probiotic therapy has certain limitations, including the risk of strain colonization failure and the need for a prolonged administration course (1 mo or more). Additionally, selecting the most appropriate probiotic for a specific patient from the vast range of options available today remains unclear.

A novel and innovative approach to enhance the effectiveness of correcting gut microbiota disorders and personalized therapy is the development of autoprobiotics (the term proposed by the authors who obtained a patent for the invention)^[85].

Autoprobiotics are strains of indigenous microbiota that are isolated from a specific individual and intended to restore their gas-trointestinal tract microecology. Autoprobiotics can be prepared by culturing individual clones of indigenous bacteria (such as bifidobacteria, lactobacilli, or enterococci) on nutrient cultural media outside the body, or by culturing a complex of indigenous bacteria under anaerobic conditions^[86]. Initially, the selection of autoprobiotic strains involved the addition of blood serum^[87], but later it was replaced by molecular genetic testing of the strains of interest^[88,89].

The advantages of autoprobiotics are: (1) Individual composition: Each autoprobiotic is unique and tailored to the specific beneficial bacteria isolated from an individual's biomaterial; (2) High survival rate: Since the body has been exposed to its own bacteria throughout life, the "survival rate" of auto-probiotics tends to be close to 100%; (3) Safety: Autoprobiotics consist of two main components - the actual indigenous bacteria and special nutrients to support bacterial viability. The body develops immunological tolerance towards the indigenous bacteria included in the autoprobiotic from early years, and they do not enter into conflict with other resident representatives of the human microbiota; and (4) Extended duration in the gut: Compared to probiotics, autoprobiotics have a longer duration in the gut, allowing for shorter treatment courses (as short as 10 days).

Experimental studies utilizing autoprobiotics have demonstrated that in rats with antibiotic-associated dysbiosis, the administration of different indigenous strains of

bacteria (such as bifidobacteria, enterococci, or a bacterial mixture) resulted in a rapid restoration of the microbiota compared to untreated animals^[86,90]. Several clinical studies have already shown the effectiveness of autoprobiotics based on indigenous strains of *Lactobacillus* spp. in restoring and stabilizing the levels of key representatives of the normal intestinal microbiota (such as *Bifidobacterium* spp., *Lactobacillus* spp., and *E. coli*) in dysbiotic disorders caused by anti-biotic usage^[91-93], as well as in infection and inflammatory diseases^[86,90,94]. The efficacy of monotherapy using auto-probiotics based on indigenous non-pathogenic enterococci has been demonstrated in the treatment of chronic gastritis associated with *H. pylori*: The eradication rate was 80%, and there was 100% relief of symptoms after a 20-d autoprobiotic treatment^[95].

The high efficacy of autoprobiotics in *H. pylori* eradication can be attributed to their personalized effect on the host gastrointestinal microbiota. It can be hypothesized that the use of indigenous microorganisms holds greater potential compared to the administration of commercial probiotics.

DISCUSSION

The addition of probiotics to standard triple or quadruple therapy has shown significant improvement in *H. pylori* eradication efficacy and reduction in adverse reactions associated with anti-*H. pylori* antibiotics, such as diarrhea and nausea. However, some studies have indicated that probiotics do not have a significant positive influence on the eradication rate and/or the frequency of adverse reactions, which may depend on the specific microbial strain(s) included in the product. Therefore, further randomized multicenter studies are necessary to investigate the effects of probiotics against *H. pylori*, focusing on strains with specific anti-*H. pylori* activity.

Probiotic monotherapy has demonstrated successful eradication rates of up to 39% for *H. pylori*, which is significantly higher than the percentage of spontaneous eradication (3%-5%). Probiotic monotherapy can be considered as an alternative method of treating *H. pylori*-associated diseases, particularly when standard anti-helicobacter therapy with antibiotics is not effective.

There are several interesting and controversial points to consider regarding the use of probiotics as an additional treatment for *H. pylori* infection: Probiotics can be administered for a longer duration: Unlike aggressive eradication therapy, which lasts 10-14 days, the duration of probiotic therapy is not strictly regulated. It is important to determine the optimal duration for each probiotic strain to achieve the best therapeutic outcomes and predict clinical effects.

Probiotics are generally safer than antibiotics but may still have side effects. Further studies are needed to identify possible side effects associated with different probiotic strains, in order to choose the safest and most effective options.

Possible approaches to prescribing probiotic therapy for patients with *H. pylori*-associated diseases include: Pre-eradication probiotic therapy: Prescribing probiotics 3-4 wk before eradication therapy to realize the immunomodulatory effects and enhance the predictability of positive eradication outcomes.

Co-eradication probiotic therapy: Prescribing probiotics simultaneously with eradication therapy (10-14 days) to increase eradication effectiveness and reduce the risk of side effects); post-eradication probiotic therapy: Prescribed for a period of 3-4 wk after eradication (to restore the gut microbiota and reduce the risk of *H. pylori* reinvention (recolonization).

Probiotic monotherapy may be prescribed to patients with a history of allergic reactions to antibiotics included in eradication regimens, or if the patient categorically refuses to take antibiotics, or for asymptomatic young children. In such cases, probiotics should be administered for a minimum of one month. However, it is important to note that this type of therapy exhibits lower efficacy compared to standard regimens, which significantly limits its application.

Autoprobiotics represent a novel type of probiotics with promising results in terms of anti-*H. pylori* efficacy. However, randomized placebo-controlled multicenter studies are necessary to confirm their efficacy and safety.

These considerations highlight the potential benefits and challenges associated with probiotic therapy in the context of *H. pylori* infection and suggest various strategies for optimizing its use.

CONCLUSION

The incorporation of probiotics into complex eradication therapy holds promise for optimizing the treatment of *H. pylori* infection. Probiotic strains, through their correction of gastric and gut microbiota, immunomodulatory effects, and direct antagonistic activity against *H. pylori* (*via* bacteriocins and other factors such as bacterial synthesized acids and hydrogen peroxide), can improve eradication rates, reduce the frequency and severity of side effects, and enhance patient compliance and treatment outcomes (Figure 1).

While probiotics alone cannot surpass antibiotics in the eradication of *H. pylori*, they play an important role as an additional component to triple or quadruple therapy, particularly in cases of antibiotic resistance. Therefore, it is recommended to include probiotics as adjunctive medicines in anti-*H. pylori* regimens. Probiotic or autoprobiotic monotherapy can be used as an alternative treatment method for individuals with allergic reactions to antibiotics. Furthermore, identifying the optimal probiotic/autoprobiotic strain or combination of strains for each patient is crucial for achieving the best clinical results and eradication rates. This represents an important objective for future investigations.

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