PyloBalance (*L. reuteri* DSM 17648) as an adjunct therapy in the treatment of *H. pylori* infections

Professor Dr Christine Lang
Microbiologist and Bioeconomic Consultant
Chairwoman of Bioeconomic Council of Germany

Angel Chong
B.Sc (Hons) in Nutrition, UKM
"*H. pylori* infection is the strongest risk factor for developing gastric cancer. We need a natural way to help manage the presence of *H. pylori* in the stomach. PyloBalance offers the solution."

Introduction

All Helicobacters are urease-positive, able to convert amino acids and urea into ammonia to neutralize stomach acid, and highly mobile – characteristics that help them invade the mucosal layer to evade the body's immune response. *Helicobacter pylori* (*H. pylori)* is linked to peptic ulcer disease, chronic gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and early gastric cancer. The infection rate of *H. pylori* is over 80% in developing countries and 20–50% in industrialized nations, with over 4.4 billion people testing positive for the bacteria in 2015.[1,2]

Current therapy is limited by a growing problem of antibiotic resistance

The American College of Gastroenterology (ACG) recommends 14 days of clarithromycin-based triple therapy, using a proton pump inhibitor (PPI), clarithromycin and amoxicillin, or bismuth quadruple therapy as the antibiotic therapy of choice for *H. pylori* infection. Treatment efficacy can be measured via ^{13}C-urea breath test (^{13}C-UBT), faecal antigen test, or endoscopic tests 4 weeks after the completion of an antibiotic regimen, with the patient having been off PPIs for at least 2 weeks. However, increasing antibiotic resistance is a concern, with infection eradication rates falling from 90% in clarithromycin-sensitive strains to as low as 20% in clarithromycin-resistant strains.[3]

Additionally, pharmacological agents are associated with a number of side effects. Antibiotics can cause gastrointestinal (GI) symptoms such as nausea and vomiting, allergic reactions and dysbiosis. PPIs can cause headache, nausea, increased risk of osteoporosis-related fractures, and hypomagnesemia. Consequently, these side effects may lead to treatment discontinuation and failure.[4-6] Currently, there are no recommendations available on the prophylactic treatment of *H. pylori* infections.

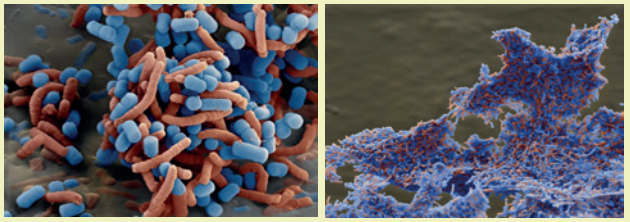
Probiotics as an adjuvant first-line therapy against *H. pylori* infection

A meta-analysis of 10 clinical trials on adjuvant probiotic strains in patients with *H. pylori* receiving standard antibiotic therapy has demonstrated higher cure rates with probiotic supplementation.[3] Among these, *Lactobacillus reuteri* (*L. reuteri*) has shown effectiveness against GI infections, including those caused by *H. pylori*, via the production of antimicrobial compounds (reuterin, lactic acid, acetic acid) and pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-8, TNF-α), inhibition of urease activity, and prevention of gastric mucosa binding.[7,8] The addition of probiotics to standard triple therapy improved eradication rates by 13.8%, thus showing their potential as an adjuvant first-line therapy.[9]

PyloBalance is a probiotic containing *L. reuteri* DSM 17648 strain that is used as an adjuvant first-line therapy against *H. pylori* infection. It binds *H. pylori* in the stomach at pH of 2–8 through a coaggregation process and prevents its mucosal adhesion. The aggregated lump is then "flushed out" of the stomach (**Figure 1**). The screened and filtered specific *L. reuteri* strain is able to work in the stomach environment, and it interacts specifically with *H. pylori* without binding to normal gut microbiota. Importantly, it is safe for consumption as it is a stable and nonviable entity.[10]

Figure 1. PyloBalance and *H. pylori* coaggregates seen under the microscope

PyloBalance = blue | *H. pylori* = red

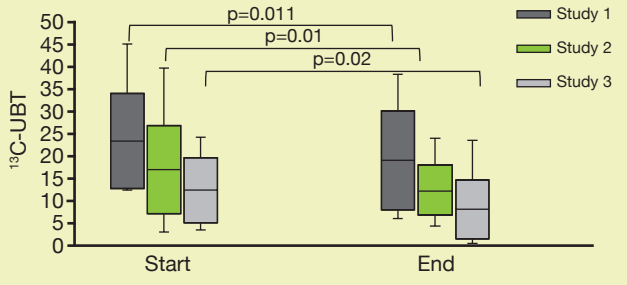


Magnification = 11,000X | Magnification = 1,800X

Probiotic adjuvant therapy is increasingly supported by clinical evidence

According to the Maastricht V/Florence Consensus Report, only specific probiotic strains have an inhibitory effect on *H. pylori*.[6] The supplementation of the *L. reuteri* DSM17648 strain resulted in an absolute reduction of ^{13}C-UBT values. In three separate studies by Mehling H (Study 1), Holz C (Study 2), and Bordin DS (Study 3), the use of *L. reuteri* DSM17468 reduced *H. pylori* load in vivo (**Figure 2**).[11-13]

Figure 2. Average absolute ^{13}C-UBT values before and after the initiation of *L. reuteri* DSM 17648

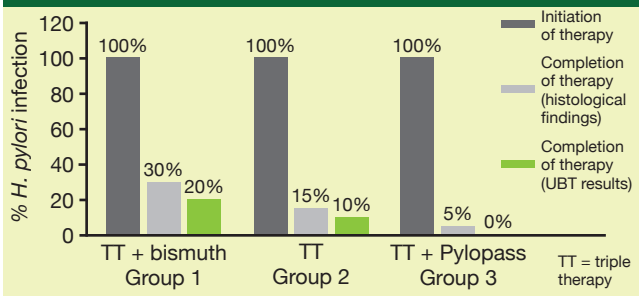


In a placebo-controlled, single-blind Irish study, *H. pylori*-positive adults with mild dyspepsia were given 100 mg of *L. reuteri* DSM 17648 twice daily for 4 weeks. In those receiving *L. reuteri* DSM 17648, 62.5% of subjects showed a reduction in ^{13}C-UBT values and a 4.6% decrease in GI symptoms – measured by the Gastrointestinal Symptom Rating Scale (GSRS) – at the end of treatment.[14]

L. reuteri DSM17648 supplementation improves the efficacy of *H. pylori* eradication. Uspenskiy et al. showed that supplementation with *L. reuteri* DSM 17648 improved the efficacy of *H. pylori* eradication by 10% (**Figure 3**). In the study, patients were split into three groups, with each receiving: *L. reuteri* DSM 17648 200 mg twice daily in addition to triple therapy for 4 weeks, triple therapy for 10 days, or triple therapy with bismuth for 10 days.

At the end of treatment duration, the *L. reuteri* DSM17648 group reported positive clinical outcomes and abdominal pain relief.[15] Separately, Emara MH et al. also showed that *L. reuteri* improved *H. pylori* eradication rates (74.3% vs 65.7% in placebo), lowered GSRS scores, and reduced the side effects experienced by patients receiving triple therapy – particularly diarrhoea – which in turn improved treatment adherence.[16]

Figure 3. Supplementation with *L. reuteri* DSM 17648 improved *H. pylori* eradication rate by 10%



Additionally, *L. reuteri* DSM17648 can be used for the treatment of *H. pylori*-associated gastritis in children. In a double blind, randomized study involving 103 children with gastritis that was conducted by the Gastroenterology Department of St Petersburg Children's City Hospital, subjects were split into three groups: *L. reuteri* DSM17648 monotherapy, quadruple therapy, and quadruple therapy with *L. reuteri* DSM17648 supplementation. Children receiving quadruple therapy, supplemented with *L. reuteri* DSM17648, had the highest eradication rate at 77.8%.[17]

A randomized open label study in Pakistan explored the potential role of probiotic supplementation as a monotherapy option in *H. pylori* treatment. In the study, treatment-naive patients receiving *L. reuteri* DSM17648 100 mg twice daily as a monotherapy had a 76% infection eradication rate, compared with 86% among those receiving *L. reuteri* DSM17648 on top of triple therapy. While symptom relief was significant in both groups, it was greater in the monotherapy group.[18] On the other hand, Dore et al. showed that an *L. reuteri* strain as a monotherapy only achieved a *H. pylori* eradication rate of 14%, which despite being significantly higher than placebo, may not be clinically relevant. Nevertheless, probiotic supplementation was still effective in reducing bacterial load as seen in the reduction of ^{13}C-UBT scores.[19]

Interestingly, Baryshnikova et al. reported that the usage of probiotics containing lactic acid bacteria in *H. pylori*-associated gastritis resulted in significantly higher eradication rates compared with placebo, and that probiotics as a monotherapy may be considered in special patient groups (ie, those who are allergic to antibiotics, have subclinical infections, or intend to use it as prophylaxis treatment). Although probiotic treatment alone may not be as efficacious as standard therapy, it is still beneficial in terms of reducing the incidence of side effects experienced by patients.[20]

While *H. pylori* eradication rates were lower with just *L. reuteri* plus PPI as a combination regime compared with standard therapy, the use of these probiotic strains as an adjuvant therapy can still be expected to enhance eradication rates by 10–14%.[21] Available evidence has clearly shown that specific probiotics enhance *H. pylori* eradication rates when used as an adjuvant therapy; however, more research is needed to explore their potential as a viable monotherapy option.

Key takeaways

Statement 10 of the Maastricht Report states: Certain probiotic strains may have a beneficial effect on *H. pylori* eradication. Existing evidence shows that *L. reuteri* DSM17648 is not only beneficial as an adjunctive component in the eradication of *H. pylori*, but it also reduces the impact of GI side effects from conventional pharmacological therapy.

Q&A with Professor Dr Christine Lang

Q1 How is the *H. pylori* infection transmitted and can reinfection occur?

H. pylori is transmitted orally, most commonly via an infected household member through the contact with saliva or the sharing of utensils. Individuals who are susceptible to the bacteria can be reinfected after a successful eradication treatment, underlying the need for probiotics as a potential prophylactic option.

Q2 What kind of patient profile would benefit from PyloBalance?

PyloBalance could be used prior to the initiation of antibiotic therapy, and patients are monitored for signs of improvement. Adjuvant antibiotic therapy could be introduced subsequently depending on the patients' response to the initial probiotic treatment.

References: 1. Kusters JG, et al. *Clin Microbiol Rev* 2006;19(3):449-490. **2.** Hooi JKY, et al. *Gastroenterology* 2017;153:420-429. **3.** Chey WD, et al. *Am J Gastroenterol* 2017;112:212–238. **4.** NHS. Side Effects – Antibiotics. Available at: https://www.nhs.uk/conditions/antibiotics/side-effects/. Accessed 20 May 2019. **5.** MedicineNet. Proton Pump Inhibitors (PPIs) side effects, list of names, and uses. Available at: https://www.medicinenet.com/proton-pump_inhibitors/article.htm. Accessed 20 May 2019. **6.** Malfertheiner P, et al. *Gut* 2017;66:6-30. **7.** Homan M, et al. *World J Gastroenterol* 2015;21(37):10644-10653. **8.** Mu Q, et al. *Front Microbiol* 2018;9:757. **9.** Lau CSM, et al. *Dovepress* 2016;9:275-289. **10.** YSP. PyloBalance Capsule product information- Date of issue: Oct 2018. **11.** Mehling H, et al. *Nutrients* 2013;5(8):3062-3073. **12.** Holz C, et al. *Probiotics Antimicrob Proteins* 2015;7:91-100. **13.** Bordin DS, et al. *Medical Journal* 2016. **14.** Buckley M, et al. *BMC Nutrition* 2018:4(48). **15.** Uspenskyi et al. 2016. **16.** Emara MH, et al. *Therap Adv Gastroenterol* 2014;7(1):4-13. **17.** Data on file reference - Kornienko et al, Lactobacillus reuteri DSM 17648 in children. **18.** Lang C. (Microbiologist and Bioeconomic Consultant, Bioeconomy Council Germany). [personal communication]. **19.** Dore MP, et al. *Intern Emerg Med*. 2014; 9(6):649-54. **20.** Baryshnikova NV, et al. *J Clin Gastroenterol Treat* 2016;2(1). **21.** Dore MP, et al. *Can J Infect Dis Med Microbiol*. 2019.