Gastric microbiota and probiotic opportunities in Helicobacter pylori eradication in children

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Abstract: Probiotics can have a direct antagonistic effect on H. pylori. The study was conducted from 2015–2017 St. Petersburg Children's City Clinical Hospital No. 5, Russian Federation. In 103 children with histologically confirmed H. pylori-associated chronic gastritis a double-blind, randomized, placebo-controlled study of the effectiveness of L. reuteri DSMZ17648 was performed both as monotherapy and an adjuvant to eradication therapy (omeprazole + amoxicillin + metronidazole + bismuth-OAMB for 10 days).

Materials and Methods. In the study were included children who had been admitted for upper endoscopy because of symptoms of dyspepsia (recurrent pain and discomfort in the upper abdomen). Following upper endoscopy and verification of H. pylori status, 104 children (55 boys and 49 girls) aged between 9 to 17 years with histologically confirmed H. pylori-associated chronic gastritis were randomized into three groups according to the treatment regimen used. (Figure 1)

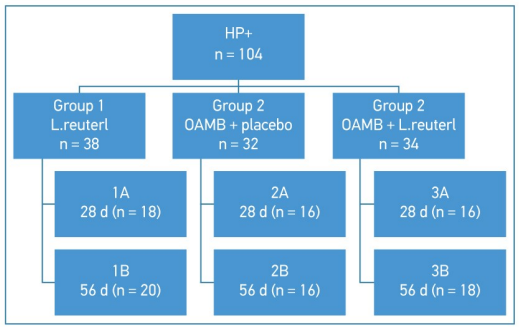

Figure 1. Research design. Patient distribution to groups.

Group 1 (n = 38): L. reuteri DSMZ17648 monotherapy of 1 capsule (200 mg) twice a day with meals.
Group 2 (n = 32): omeprazole + amoxicillin + metronidazole + three potassium bismuth di citrate (OAMB) regimen for 10 days. The medication was administered at average age-appropriate dosage according to ESPGHAN recommendations. From the first day of treatment, patients received a placebo in similar capsules that did not contain a probiotic, 1 capsule twice a day during meals.
Group 3 (n = 34): omeprazole + amoxicillin + metronidazole + three potassium bismuth di citrate (OAMB) regimen lasting 10 days, in average age doses. From the first day of this standard treatment, patients received *L. reuteri* DSMZ17648 in 1 capsule (200 mg) twice a day with meals. **The L. reuteri course in subgroups A lasted for 28 days and in subgroups B for 56 days.** Neither the patients, nor the investigators knew which capsules—probiotic or placebo—the patients received; this information was recovered just after the study finished. The groups were comparable in gender and age composition and did not have statistically significant differences. Table 1.

The control was performed by endoscopy, histology, AMA rapid urease test (AMA RUT), HELIC ammonia breath test (HELIC ABT), H. pylori count in the biopsy, inflammatory, and atrophic indices (Fig.2.)

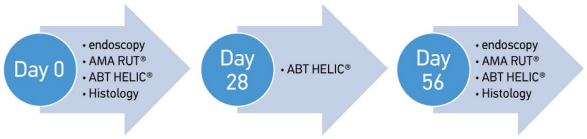

Figure 2. Research design. Research methods and points.

Table 1. Characteristics of patients in groups 1B, 2B, and 3B.

Indicator	Group 1B	Group 2B	Group 3B	All participants	Comparison of Group 3B and Group 2B (p)	Comparison of Group 1B and Group 2B (p)
Qualitative indicators, n (%)						
Number of patients	20 (37.0)	16 (29.6)	18 (33.3)	54 (100.0)	–	–
Gender Male Female	 10 (50.0) 10 (50.0)	 7 (43.8.0) 9 (56.3)	 9 (50.0) 9 (50.0)	 26 (48.1) 28 (51.9)	 0.744	 0.749
Quantitative indicators, Me (Q1; Q3)						
Age, years	14.0 (13.0; 16.0)	15.0 (13.0; 16.0)	15.0 (13.8; 16.3)	15.0 (13.0; 16.0)	0.430	0.540

To study the gastric microbiota composition we determined the bacterial metagenome of the biopsy specimens of the gastric mucosa in eight H. pylori (+) and eight H. pylori (-) children. We found that changes in the gastric microbiome were more prominent the longer H. pylori infection persisted and correlated with the severity of inflammation and atrophy. The dominant stomach bacterial phyla in children with chronic gastritis were Proteobacteria, Bacteroidetes, and Firmicutes, whereas Actinobacteria, Cyanobacteria, and Fusobacteria were represented to a lesser extent. In H. pylori (+) patients, H. pylori averaged 64.1% of the total microbiome, and Proteobacteria reached 75–99% (Figure 3). In five of the eight H. pylori (+) patients (samples 1_1, 1_2, 7_1, 10_1, 13_1), H. pylori significantly dominated both among all microbes and among Proteobacteria.

In children with a small amount of H. pylori, the surrounding microbiota maintained diversity because of the short history of disease, which was similar to the H. pylori (-) children. The dominated orders were Actinomycetales, Bacteroidales, Bifidobacteriales, and Sphingobacteriales.

The highest percentage of H. pylori eradication was achieved in patients who received a 10-day eradication regimen (OAMV) in combination with the L. reuteri DSMZ17648 probiotic for 56 days (Table 2) - 77.8%. The efficiency of the combination of the traditional regimen of eradication therapy with the placebo, irrespective of the treatment duration (28 or 56 days), was 68.8%. Long-term L. reuteri DSMZ17648 probiotic therapy (56 days) had an efficiency almost similar to standard quadrotherapy with two antibiotics and bismuth (60% and 68.8% H. pylori eradication, respectively), and the L. reuteri DSMZ17648 supplemented with traditional therapy increased its efficiency by 9% (from 68.8% to 77.8%). The H. pylori eradication rate correlated to the duration of the probiotic monotherapy: 50% after 28 days, and 60% after 56 days of treatment

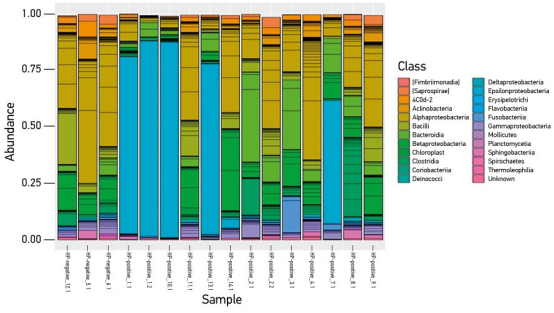

Figure 3. Taxonomic composition of the gastric microbiota in children with chronic gastritis (n = 16) at the class level.

Tabl.2. The effectiveness of the therapy regimens for H. pylori infection.

Group	Therapy Regimen	Duration of Treatment (days)	Number of patients (n)	Eradication Efficiency (%)
1A	*L. reuteri* DSMZ17648	28	18	50
1B	*L. reuteri* DSMZ17648	56	20	60
2A	Eradication therapy (O + A + M + B) + placebo	10 28	16	68,8
2B	Eradication therapy (O + A + M + B) + placebo	10 56	16	68,8
3A	Eradication therapy (O + A + M + B) + *L. reuteri* DSMZ17648	10 28	16	60
3B	Eradication therapy (O + A + M + B) + *L. reuteri* DSMZ17648	10 56	18	77,8

We believe that in children with chronic H. pylori-associated gastritis, L. reuteri DSMZ17648 monotherapy has advantages over standard triple therapy as it better cures clinical manifestation and gastric mucosa inflammation, which is most likely due to the correction of the state of gastric microbiota as a whole.

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