

LACTOBACILLUS REUTERI – AN ALTERNATIVE IN THE FIRST-LINE OF HELICOBACTER PYLORI ERADICATION

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Abstract

In the context of reduced effectiveness of classical antibiotic regimens in eradicating *Helicobacter pylori* infection, it is justified to search for alternative therapies. The present study included 70 patients diagnosed with *Helicobacter pylori* infection by the rapid urease test, randomized into two therapeutic regimens: *Lactobacillus reuteri* DSMZ17648, liquorice and calcium carbonate and classical proton pump inhibitor - amoxicillin - clarithromycin scheme. The eradication efficiency was 54.3% in the *Lactobacillus reuteri* group vs 77.1% in the antibiotic group ($p = 0.042$) but with a significantly lower rate of side effects (2.9% vs 17.1%, $p = 0.037$). Finding new drugs to eradicate *Helicobacter pylori* with increased efficacy, cost-effectiveness ratio and no side effects remains a challenge.

Rezumat

În condițiile reducerii eficacității schemelor clasice cu antibiotice în eradicarea infecției cu *Helicobacter pylori*, este justificată preocuparea pentru terapii noi. Studiul de față a inclus 70 de pacienți diagnosticați prin testul rapid ureazic cu infecție cu *Helicobacter pylori*, randomizați în două regimuri terapeutice: *Lactobacillus reuteri*, extract de lemn dulce și carbonat de calciu și schema clasică cu inhibitor de pompă de protoni – amoxicilină – claritromicină. Eficiența eradicării a fost de 54,3% în grupul tratat cu *Lactobacillus reuteri* comparativ cu 77,1% în grupul tratat cu antibiotice ($p = 0,042$), dar cu o rată semnificativ mai mică de efecte secundare (2,9% vs 17,1%, $p = 0,037$). Găsirea de noi medicamente în eradicarea *Helicobacter pylori* cu eficacitate crescută, cost-eficiente și fără efecte secundare rămâne în continuare un deziderat.

Keywords: *Helicobacter pylori*, eradication, antibiotic resistance, *Lactobacillus reuteri*

Introduction

It is estimated that 50% of the globe population is infected with *Helicobacter pylori* (*H. pylori*) with variations between 20% and 80%, the prevalence being higher in emerging economies compared to those developed [1, 2]. In Romania, the *H. pylori* infection prevalence is about 70% of the adult population [3]. *H. Pylori* is involved in the pathogenesis of numerous digestive disorders and is considered as a risk factor for gastric cancer [4]. Indications for the eradication of *H. pylori* infection include: gastritis, peptic ulcer, MALT lymphoma, *H. pylori* positive dyspepsia, long-term treatment with non-steroidal anti-inflammatory drugs, antiaggregants or anticoagulants, proton pump inhibitors (PPI), iron deficiency anaemia, B12 vitamin deficiency, idiopathic thrombocytopenia (for the last three indications other causes must be excluded first) [5]. *H. pylori* infection eradication is a continuing challenge. Commonly, the eradication regimen includes PPI associated with two antibiotics: clarithromycin and

amoxicillin or metronidazole with a therapy duration of 7, 10, up to 14 days. This regimen known as “legacy therapy”, even though still widely used as first-line therapy, has a low efficiency as a result of global growth of microbial resistance to clarithromycin and metronidazole [6, 7]. Therefore, most current guidelines recommend as first-line of eradication approach the quadruple concomitant therapy or 14-day bismuth quadruple therapy [5, 8, 9]. Prolonged duration and multiple antibiotic treatment is shadowed by intestinal microbiota damage and a series of side effects that often decrease compliance and cause treatment discontinuation. New drugs, with different mechanisms of action, seek their place as first-line therapy or as associate to classic therapy with antibiotics in the *H. pylori* eradication: probiotics, metabiotics, bacteriophages, bacteriocins, in association with the study of microorganism and host genetic particularities [10, 11].

In recent years, evidences have accumulated suggesting that *H. pylori* could be eradicated from the stomach through selective intercellular interactions by some

particular *Lactobacillus* strains [12]. *Lactobacillus reuteri* (*L. reuteri*) strains have been identified as *H. pylori* binding high specificity antagonists. *L. reuteri* has been shown to inhibit through competition *H. pylori* binding to a series of so-called glycolipid receptors. Mukai *et al.* examined the competition of binding of *L. reuteri* and *H. pylori* to gangliosylceramide (asialo-GM1) and sulphatide which are putative glycolipid receptor molecules of *H. pylori*, and identified a possible sulphatide-binding protein of the *L. reuteri* strains [13]. In order to identify a strain of *L. reuteri* with the highest specificity for *H. pylori*, Organobalance GmbH, Berlin, Germany, selected from hundreds of *Lactobacillus* strains, *L. reuteri* DSMZ17648. The study has shown that they are capable of forming a stable co-aggregate with *H. pylori* in an acid environment similar to gastric acid. Co-aggregation occurred within a few seconds after contacting the two strains, flow cytometry indicating that each *L. reuteri* DSMZ17648 cell binds 2-3 *H. pylori* cells [14]. These co-aggregates are subsequently eliminated, reducing the colonization of the gastric mucosa with *H. pylori* without affecting the normal intestinal flora [10]. Moreover, it has been desired to create a biologically inactive strain that retains its aggregation properties without being influenced by the antibiotic treatment, a fact done biotechnologically by spray-dye and lyophilisation [15]. Results of clinical trials using the *L. reuteri* DSMZ 17648 strain in *H. pylori* eradication are still contradictory [16]. In this regard, the association of *L. Reuteri* DSMZ17648 with deglycyrrhizinated liquorice extract and calcium carbonate seems to be a promising tool against *H. pylori*. It has been also proved that the extract of liquorice roots inhibit the adhesion of *H. pylori* to human gastric mucosa [17]. The purpose of our study was to compare the classic eradication scheme (PPI, clarithromycin, amoxicillin) with the association between *L. Reuteri* DSMZ17648, deglycyrrhizinated liquorice extract and calcium carbonate as the first line treatment in eradicating *H. pylori* infection.

Materials and Methods

The prospective randomized study was conducted over one year (2017) in a tertiary gastroenterology centre in Romania. All patients signed the informed consent and the study was approved by the local Ethics Committee.

Inclusion criteria

We enrolled adult treatment-naive patients with dyspeptic symptoms, who underwent upper digestive endoscopy, diagnosed with *H. pylori* infection and had *H. pylori* eradication indication. Diagnosis of *H. pylori* infection was made by rapid urease test, with two biopsies taken: one of the antrum and one of the gastric body.

Exclusion criteria

Patients treated with PPI, bismuth or antibiotics in the last month, patients with upper digestive bleeding, neoplastic disease, pregnancy and breastfeeding, patients with contraindications to any of the drugs used in eradication schemes (e.g: infection with *Clostridium difficile*, known antibiotic allergies) and patients that followed previously any *H. pylori* treatment regimen were excluded.

Patient management

Patients were randomized 1:1 in two groups: group A (STT) received esomeprazole (20 mg bid) - clarithromycin (500 mg bid) - amoxicillin (1000 mg bid) standard triple therapy for 10 days and group B (*L. reuteri*) received esomeprazole 20 mg bid and the association between *L. Reuteri* DSMZ17648, deglycyrrhizinated liquorice extract and calcium carbonate, 1 cps bid for 14 days. All patients were re-evaluated 6 weeks after therapy by *H. pylori* mono-clonal stool antigen test. The registered parameters were: demographic data (age, sex), diagnosis based on upper digestive endoscopy, presence of comorbidities, eradication efficiency and the presence of side effects in the two types of therapies.

Outcome

The primary endpoint was *H. pylori* eradication 6 weeks after completion of therapy. The secondary endpoint was the development of adverse effects to the therapy used.

Statistical analysis

The database was consisted using SPSS 18.0 application. The dispersion analysis of the dependent variable intra and intergroup was performed using ANOVA test. The significant difference between two or more groups depending on the distribution of the series of values for a significance threshold of 95% for the quantitative variables was assessed using: the t-Student test - parametric test which compares the average values registered in two groups with normal distributions and the test χ^2 - nonparametric test which compares 2 or more frequency repartitions coming from the same population, applied when the expected results exclude one another; p-value < 0.05 was considered significant. The ROC curve - draws the balance specificity/sensitiveness as a prognosis factor.

Results and Discussion

The study included 70 patients, aged between 26 and 72, assigned as follows: 35 patients in the STT group and 35 patients in *L. reuteri* group with a slight predominance of female gender (55.71%). The indication for *H. pylori* infection eradication was in the order of frequency: functional dyspepsia (28/70 - 40%), gastritis (26/70 - 37.14%), duodenal ulcer (11/70 - 15.71%) and gastric ulcer (5/70 - 7.14%). 16 patients (22.85%) experienced comorbidities and concomitant treatments for associated conditions: 5 cases of diabetes

mellitus, 4 cases of cardiac pathology, 3 cases of liver pathology, 2 cases of chronic kidney disease, 1 case of rheumatoid arthritis, 1 case of psychiatric pathology. The presence of comorbidities induced an estimated

risk of treatment failure of 1.68 times higher (RR = 1.86; IC95%: 1.01 - 2.95). There were no statistically significant differences between the clinical parameters of the two studied groups (Table I).

Table I

Characteristics of patients in the two studied groups

Characteristics	STT (n = 35)	<i>L. reuteri</i> (n = 35)	p-value
Average age \pm SD (min - max)	48.37 \pm 12.84 (26 - 72)	51.74 \pm 10.85 (27 - 72)	0.240
Age			0.291
< 40, n (%)	9 (25.7%)	4 (11.4%)	
40 - 60, n (%)	20 (57.1%)	23 (65.7%)	
> 60, n (%)	6 (17.1%)	8 (22.9%)	
Male, n (%)	16 (45.7%)	15 (42.9%)	0.810
Female, n (%)	19 (54.3%)	20 (57.1%)	
Functional dyspepsia	13 (37.1%)	15 (42.9%)	0.723
Gastritis	12 (34.3%)	14 (40.0%)	
Gastric ulcer	3 (8.6%)	2 (5.7%)	
Duodenal ulcer	7 (20.0%)	4 (11.4%)	
Comorbidities, n (%)	7 (20.0%)	9 (25.7%)	0.569
Treatment success, n (%)	27 (77.1%)	19 (54.3%)	0.042
Side effects, n (%)	6 (17.1%)	1 (2.9%)	0.037

The success of *H. pylori* eradication was higher in the antibiotic treated group (77.1% intention-to-treat and 81.81% per-protocol) compared to *L. reuteri* treated (54.3%, $p = 0.042$). In contrast, side effects (nausea, abdominal pain, abdominal bloating, diarrhoea) were significantly more common in the STT-treated group (17.1% vs 2.9%, $p = 0.037$), causing discontinuation in 2 cases (both due to diarrhoea). In the *L. reuteri* -

treated group, only one patient reported morning vomiting, during the first days of treatment. The risk of side effects was 1.86 times higher in patients treated with antibiotics (RR = 1.86; IC95%: 1.24 - 2.79). The side effects were associated with an estimated 2.37-fold greater treatment failure rate (RR = 2.37; IC95%: 1.30 - 4.32).

Table II

Treatment success vs failure based on clinical parameters

Characteristics	STT (n = 35)			<i>L. reuteri</i> (n = 35)		
	Success (n = 27)	Failure (n = 8)	p-value	Success (n = 19)	Failure (n = 16)	p-value
Average age \pm SD (min-max)	50.48 \pm 12.81 (28 - 72)	41.25 \pm 10.79 (26 - 53)	0.074	50.37 \pm 9.92 (27 - 69)	53.38 \pm 11.98 (31 - 72)	0.422
Age			0.159			0.511
< 40 year-old, n (%)	6 (22.2%)	3 (37.5%)		2 (10.5)	2 (12.5)	
40 - 60 year-old, n (%)	15 (55.6%)	5 (62.5%)		14 (73.7)	9 (56.3)	
> 60 year-old, n (%)	6 (22.2%)	0 (0.0%)		3 (15.8%)	3 (31.3%)	
Male, n (%)	12 (44.4%)	4 (50.0%)	0.782	7 (36.8%)	8 (50.0%)	0.433
Female, n (%)	15 (55.6%)	4 (50.0%)		12 (63.6%)	8 (50.0%)	
Functional dyspepsia, n (%)	9 (33.3%)	4 (50.0%)	0.397	11 (57.0%)	4 (25.0%)	0.047
Gastritis, n (%)	10 (37.1%)	2 (25.0%)	0.521	7 (36.8%)	7 (43.8%)	0.678
Gastric ulcer, n (%)	2 (7.4%)	1 (12.5%)	0.664	0 (0.0%)	2 (12.5%)	0.070
Duodenal ulcer, n (%)	6 (22.2%)	1 (12.5%)	0.529	1 (5.3%)	3 (18.8%)	0.266
Comorbidities, n (%)	3 (11.1%)	4 (50.0%)	0.024	3 (15.8%)	6 (37.5%)	0.142

Analysing the success rate of treatment in each group we observed that STT treatment failure was statistically associated with the presence of comorbidities, while the best results of *L. reuteri* treatment were recorded in patients with functional dyspepsia (Table II). The ROC curve shows that, compared to antibiotic treatment, the success of *L. reuteri* treatment was influenced in a proportion of 76.6% by the younger age (AUC = 0.766; IC95%: 0.570 - 0.961), 61.3% by the type of associated medical condition (functional dyspepsia) (AUC = 0.613; IC95%: 0.362 - 0.864) and

60.3% by the lack of comorbidities (AUC = 0.603; IC95%: 0.313 - 0.812) (Figure 1). In patients less than 50 years of age with functional dyspepsia and without comorbidities the success of *H. pylori* eradication with *L. reuteri* was 87.5%.

The triple therapy with clarithromycin remains the most prescribed *H. pylori* infection eradication scheme [18]. In our study, *H. pylori* eradication with STT was 77.1%, comparable to other Romanian and European studies [19, 20]. Two other studies published in Romania showed the increase in the effectiveness

of triple PPI-amoxicillin-clarithromycin therapy by using the double dose of PPI or extending the duration of treatment to 14 days [21, 22]. In recent years, there has been an increase in antibiotic resistance, especially in clarithromycin, which leads to a decrease in eradication efficiency below 80% [9, 23]. In our country there is very little data on primary resistance to antibiotics used in the first line to eradicate *H. pylori* infection [21].

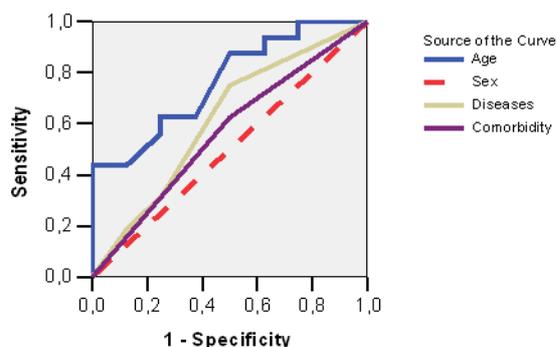


Figure 1.

L. reuteri treatment success rate (ROC curve, balance of clinical data sensitivity/specificity)

In our study we used an association of *L. reuteri* DSMZ17648 100 mg, with extract of deglycyrrhizinated liquorice 75 mg (protects the gastric mucosa from the corrosive action of gastric acid, helps in its regeneration and has an anti *H. pylori* action) and calcium carbonate 80 mg (antacid action). *L. reuteri* DSMZ17648 is technologically processed and stabilized so as to form co-aggregates with *H. pylori* and not to affect other components of the intestinal flora. In the study group, eradication with *L. reuteri* associated with PPI was 54.3%. Our data are consistent with other studies that demonstrated the effectiveness of *L. reuteri* in eradicating *H. pylori* infection. Multiple studies have shown a decrease in ^{13}C UBT values in *H. pylori* positive patients receiving *L. reuteri* DSMZ 17648 compared to placebo [14, 15, 24]. In addition, Borodin's study demonstrated an improvement in clinical symptoms and histology in patients treated with *L. reuteri* DSMZ17648 [24]. Saggioro *et al.* obtained in a randomized placebo-controlled trial on 30 *H. pylori*-positive dyspeptic patients a 60% eradication rate in positive group vs 0% with placebo. The group was treated with 40 mg omeprazole and *L. reuteri* 1.6×10^6 CFU/day, bid, pre-prandial for 30 days [25]. In contrast, Dore *et al.* in an open study on 21 *H. pylori* confirmed patients showed that treatment with *L. reuteri* 2×10^8 CFU and pantoprazole 40 mg/day, for 60 days eradicated *H. pylori* in just 14.2% of patients [26]. The differences between the results obtained in this study and the previous one were considered by the authors generated on the basis of distinct geographic areas with different *H. pylori* strains, possible differences between the *L. reuteri* strains

used, doses, timing and duration of administration. Results similar to our study were also reported in the pediatric population: 50% eradication with *L. reuteri* DSMZ17648 200 mg/day administration vs 68.75% in the antibiotic-treated group [27]. Another promising approach is the addition of *L. reuteri* strains to antibiotic treatment, which leads to increased rates of eradication and side effects minimization [28, 29]. This approach has not been the subject of our study and requires further research. The good results of *H. pylori* eradication in our study could have more explanations. First, *L. reuteri* was given as capsules rather than tablets. The compressive force required to obtain a tablet is very high and there are significant structural alterations of the ingredients of cellular origin [30]. Secondly, unlike other studies with *L. reuteri*, the drug was administered before meals, thus favouring optimal contact between *L. reuteri* and *H. pylori*. Third, the association with extract of deglycyrrhizinated liquorice and calcium carbonate seems to increase the efficacy of *L. reuteri*.

An important issue in the eradication of *H. pylori* is patient compliance, which is largely affected by side effects related to the antibiotic therapy used. In our study, side effects were statistically significantly more present in the STT group (17.1%), leading to premature discontinuation of treatment in 2 cases compared to *L. reuteri* group. The frequency of side effects in the classic eradication scheme is similar to the data published in the literature [5]. There are many other studies in the literature which highlight the good tolerability and lack of side effects in patients treated with *L. reuteri* [14-16, 27-29].

In our study, treatment with *L. reuteri* seems more effective in young patients with functional dyspepsia and without comorbidities (eradication rate more than 80%), regardless of sex, but larger patient trials are needed to confirm this data.

Conclusions

L. reuteri in association with extract of deglycyrrhizinated liquorice and calcium carbonate may be an alternative to the classic antibiotic regimen in eradicating *H. pylori* infection in treatment-naïve patients. *L. reuteri* has been successful in eradicating *H. pylori* in over 50% of patients, with very good tolerability and compliance. Future studies, on larger study groups, are needed in order to include alternative therapies to classic antibiotic regimens in *H. pylori* infection management.

Conflict of interest

The authors declare no conflict of interest.

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