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Dear Editor,

Please find enclosed the manuscript titled “**Evaluation of *Helicobacter pylori* eradication by triple therapy plus *Lactobacillus acidophilus* compared to triple therapy alone**” by Medeiros JAS et al. for consideration for publication in the European Journal of Clinical Microbiology & Infectious Diseases.

The named authors have seen and agreed to the submitted version of the paper. The content is original and has not been published elsewhere, and the manuscript is not currently in submission for publication elsewhere.

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We are looking forward to receiving your answer.

With kind regards,

Jose Augusto da Silva Medeiros, MD, PhD

**EVALUATION OF *HELICOBACTER PYLORI* ERADICATION
BY TRIPLE THERAPY PLUS *LACTOBACILLUS ACIDOPHILUS*
COMPARED TO TRIPLE THERAPY ALONE**

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Abstract

Purpose To evaluate the influence of adding *Lactobacillus acidophilus* to a triple regimen for *H. pylori* eradication, in untreated patients with peptic ulcers or ulcer-scars. **Methods:** Pre-randomized, single-blind, interventional, treatment-efficacy study with active controls and parallel-assignment, set in Coimbra, Portugal, on 62 consecutive *H. pylori*-positive untreated adults with peptic ulcers or ulcer-scars, diagnosed by gastroduodenoscopy, with pre-treatment direct Gram-staining and culture of gastric biopsies. The first 31 patients received esomeprazole 20mg, amoxicillin 1000mg and clarithromycin 500mg (EAC), all b.i.d., for 8 days. The remaining 31 added *L. acidophilus*, 5×10^9 organisms per capsule, 3+2 i.d. for 8 days (EACL). Main outcome measure: ^{13}C urea breath test (UBT), ≥ 6 weeks after completion of therapy. **Results:** Successful eradication (UBT-negativity after treatment), was similar in both groups (EAC=80.6%; EACL=83.9%, $p=0.740$) by both intention-to-treat and per-protocol analysis. The non-eradicated strains were susceptible *in vitro* to both antibiotics. **Conclusion:** Adding *L. acidophilus* to EAC triple therapy did not increase *H. pylori* eradication rate. Considering the cost and the burden of ingesting five extra capsules daily, supplementing the EAC therapy with *L. acidophilus*, at this dose, shows no benefit. Further studies with different dosages and duration, and other probiotics or probiotic combinations are required to improve eradication.

Keywords: *Helicobacter pylori*, *Lactobacillus acidophilus*, triple therapy, eradication, urea breath test, clarithromycin, amoxicillin

The study was presented at the 15th United European Gastroenterology Week (UEGW), 27-31 October 2007, Paris, France. Gut 2007; 56 (Suppl III) A101

INTRODUCTION

H. pylori infection is associated with chronic gastritis and peptic ulcer disease, and is a risk factor for the development of gastric cancer and MALT lymphoma.¹ Successful eradication of the infection by triple associations of antibiotics and proton-pump inhibitors is curative. However, the treatment may fail in 10-35% of all cases due to *H. pylori* resistance, antibiotic side effects and other reasons [1]. Searching for new or additional therapeutic agents is necessary to overcome treatment failures.

There is an ongoing controversy in the literature regarding the usefulness of the addition of probiotics, including *Lactobacillus acidophilus*, to the standard triple therapy for *H. pylori* eradication [2-7]. While the activity of *L. acidophilus*, *L. johnsonii* and *L. casei* subsp. *rhamnosus* strains against *H. pylori* has been demonstrated *in vitro*, the *in vivo* successful *H. pylori* eradication by lactobacilli has been uncommon [2,8,9].

There are relatively few studies using triple regimens supplemented with *L. acidophilus* in humans [5,6,7]. The aim of the study was to evaluate the influence of adding *L. acidophilus* to a triple regimen for *H. pylori* eradication in untreated patients with peptic ulcers or ulcer scars.

PATIENTS AND METHODS

Patients. Eligibility criteria: previously untreated *H. pylori*-positive adults aged 20 years or over who had endoscopically confirmed peptic ulcers or peptic ulcer scars. Exclusion criteria: previous or current treatment with proton pump inhibitors or triple therapy, and neoplastic ulcers. **Design.** Sixty-two consecutive *H. pylori*-positive patients with peptic ulcers or peptic ulcer scars, undergoing upper gastrointestinal endoscopy in an outpatient clinic in Coimbra, Portugal, were enrolled in the study. Patient characteristics are summarized in Table 1. Before treatment of the *H. pylori* infection, eight gastric biopsy specimens were obtained per patient: two specimens from the body and two from the antrum were used for direct Gram staining, and the remaining two specimens from the body and two from the antrum were used for culture. The patients were considered as *H. Pylori*-positive only if the culture was positive [10].

Culture and antibacterial susceptibility testing. The biopsies were frozen in Brucella broth with 25% glycerol and kept at -80° C before being cultured, as previously described [11]. Immediately prior to culture, the biopsies were chopped and spread evenly onto *H. pylori* selective medium (PYL agar, Bio Mérieux, France). The plates were incubated for 3-10 days at 37° C under microaerophilic conditions (CampyGen system, Oxoid, UK).

The suspected colonies were tested with a home-made rapid urease test (personal communication, L Monteiro, Lisboa, Portugal) and subcultured onto *H. pylori* selective medium (Wilkins-Chalgren agar with 10% horse blood, vancomycin 10 mg/L, cefsulodin 5 mg/L, trimethoprim 5 mg/L, and cycloheximide 100 mg/L, Biogerm, Porto, Portugal). The plates were incubated at 37° C for 48 h in a microaerophilic atmosphere (CampyGen). *H. pylori* identification was made by Gram staining and testing for the presence of oxidase, catalase, and urease activity.

The isolated *H. pylori* strains were subcultured. The minimal inhibitory concentrations (MICs) of clarithromycin and amoxicillin were evaluated against 31 strains from the patients in the EACL group and 28 strains from those in the EAC group. Three strains from the EAC group were lost while being subcultured. The strain susceptibility to the antibiotics used in this study was determined by E test, according to the method previously described [11,12]. The plates were incubated for 48 h in a microaerophilic atmosphere and were read according to the supplier's recommendations.

Intervention intended. A pre-randomization design was used [13]. To prevent a selection bias, the first 31 patients were allocated to therapy with esomeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all b.i.d. for eight days (EAC group). The remaining 31 patients were allocated to therapy with esomeprazole, amoxicillin and clarithromycin (as above) plus *L. acidophilus*, 5×10^9 bacteria per capsule, 3 capsules in the morning and 2 capsules at night, for the same period of time (EACL group), (Table 1). The *L. acidophilus* probiotic used was "Lacteol" (BioSaúde laboratories, Portugal). Given the nature of the study, the patients were not blinded to the assigned treatment.

Urea breath test. To detect possible differences in *H. pylori* eradication rates between the patients of EACL group and those of EAC group, a ^{13}C urea breath test (UBT, Helico-Test ^{13}C -Ureia, Isomed S.L. Pharmaceutical Laboratory, Madrid, Spain) was performed six to seven weeks after the end of therapy. The specimen collection was performed immediately before (basal sample) and 30 min after (post-test sample) the ingestion of the marked urea; the $^{13}\text{C}/^{12}\text{C}$ ratio was measured in both specimens, and the result was expressed as the difference between the basal and post-test measurements. The UBT was considered positive when this value was >5 delta over baseline (DOB) per 1,000. This study had a single-blind design, with the technicians administering the UBT and evaluating the outcomes being blinded to patient group assignments.

Statistical analysis. The chi-square test and Fisher's exact test of independence (when appropriate) were used for the statistical analysis. The outcome variable was the presence of

H. pylori eradication (yes vs no) and the exposure variable was *Lactobacillus* supplementation of the triple therapy (yes vs no). A p value of <0.05 was considered statistically significant.

This study was approved by the Ethics Committee of the Social Services of the University of Coimbra (Coimbra, Portugal) with the registration number 36/07. It was registered at ClinicalTrials.gov, of the National Institutes of Health (USA), with the protocol ID "SASUC-36/07". Informed written consent was obtained from all patients.

RESULTS

The MICs of the 31 strains in the EACL group and the 28 strains in the EAC group for amoxicillin were MIC₅₀, <0.016 and <0.016 mg/L, MIC₉₀, 0.023 and 0.023 mg/L, and ranges of <0.016-0.047 and <0.016-0.19 mg/L, respectively. The MICs of the 31 strains in the EACL group and the 28 strains in the EAC group for clarithromycin were MIC₅₀, <0.016 and <0.016 mg/L, MIC₉₀, 0.032 and 0.064 mg/L, and ranges of <0.016- >256 and <0.016-48 mg/L, respectively.

Successful eradication rates, as determined by a negative UBT after treatment, were similar in the patients of EAC group (80.6%, 25 of 31) and in those of EACL group (83.9%, 26 of 31, p=0.740, OR 0.80; 95% CI: 0.22-2.96) by both intention to treat and per protocol analysis. The strains of the 11 non-eradicated patients were *in vitro* susceptible to both clarithromycin and amoxicillin. The MIC ranges against the five strains of EACL group and the six strains of EAC group were <0.016-0.016 and <0.016-0.19 mg/L for clarithromycin, and <0.016-0.047 mg/L and <0.016-0.19 for amoxicillin, respectively.

Safety. There were no reported dropouts from the study due to non-compliance of the patients or side effects from the medications.

DISCUSSION:

Probiotics are live, nonpathogenic microbial feeds or food supplements that have been used to improve the balance of the microflora, primarily in the gastrointestinal tract [14]. Lactobacilli are acid resistant and can persist in the stomach longer than most other bacteria [15]; therefore, they have the potential to inhibit *H. pylori*, both for prophylaxis and for treatment of the infection.

Previous studies have found that the supplementation of standard anti-*H. pylori* regimens with probiotics can reduce the side effects of triple therapy and, therefore, can improve patients' compliance to therapy [14].

Other authors have identified the *in vitro* activity of *L. acidophilus* against *H. pylori*, which has been associated with the secretion of lactic acid, CRL639 autolysins and competition for adhesion [16]. However, most of these properties have been observed only in animal models or *in vitro* data. In addition, the activity of several probiotic species against *H. pylori* has been reported to be strain-dependant [17].

In vivo, the administration of probiotics alone usually does not lead to *H. pylori* eradication [16]. However, in several studies, adding *Lactobacillus* species (e.g., *L. johnsonii* La1 lyophilized + inactivated culture or *L. casei* DN 114001) to a triple therapy of amoxicillin, clarithromycin and a proton pump inhibitor has increased the eradication rate compared to the standard triple regimen alone [14].

In the present study, the addition of 1.5×10^{10} *L. acidophilus* organisms in the morning and 1×10^{10} organisms at night, failed to improve *H. pylori* eradication. Although ^{13}C UBT was performed at least six weeks after the end of therapy, the annual recurrence of *H. pylori* infection has been reported to be low (<1-2.7%) in most developed countries [18]; therefore, UBT-positivity in our sample is most likely due to persistent infection than to reinfection, the latter being unlikely to influence the study outcome.

There are several possible reasons for the absence of effect observed in this study. Firstly, the choice of probiotic to be added to the standard therapy seems to be important. It is still unclear which *Lactobacillus* species and strains are most active against *H. pylori*. So far, the most effective (both *in vitro* and *in vivo*) *Lactobacillus* species have been *L. casei* and *L. johnsonii* La1 [16]. In the relatively few studies on the addition of *L. acidophilus* to the standard eradication regimens, only two sets of data have reported an increase in *H. pylori* eradication rate. However, in one of the successful studies, a probiotic preparation containing both *L. acidophilus* and *L. rhamnosus* had been used [5,7].

In addition, the length (14 days in the study by De Francesco et al. [6], three weeks in the study by Cremonini et al. [19] and 8 days in the present study) and frequency of administration (t.i.d. in the study of Canducci et al.⁵ and b.i.d. in the present study) could also be of importance.

Finally, a combination of probiotics could provide a better effect on *H. pylori* eradication than the use of single species. Several authors [7,20] have obtained an increase in *H. pylori* eradication, compared to the standard therapy with probiotic combinations such as *Lactobacillus*- and *Bifidobacterium*-containing yogurt (AB-Yogurt) or *L. acidophilus* and *L. rhamnosus*. A recent study has demonstrated a significantly higher *H. pylori* eradication rate by a quadruple therapy following pre-treatment with AB-yogurt containing a mixture of *L.*

acidophilus La5, *Bifidobacterium lactis* Bb12, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*, than by the quadruple therapy alone [21].

CONCLUSION

H. pylori eradication rates in the EAC and EACL groups were comparable: adding *L. acidophilus* to the triple therapy used in this study did not increase the eradication rate. Considering both the patients' expenses and the need for the daily ingestion of five extra capsules, the supplementation of the amoxicillin + clarithromycin + esomeprazole therapy with *L. acidophilus*, at a daily dose of 2.5×10^{10} cells, does not benefit the ulcer patient.

Further studies with different posologies or duration of treatment, and with alternative probiotics or probiotic combinations are required to improve the eradication of *H. pylori* infection.

Conflict of interest statement: The authors declare that they have no conflicts of interest, including financial or personal relationships with other people or organisations, that could influence their work.

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quadruple therapy in eradicating residual *Helicobacter pylori* infection after failed triple therapy. Am J Clin Nutr 83:864-869.

Table 1. Patients involved in the study.

Group	Parameter	Patients in the EACL group	Patients in the EAC group
Sex	Men	18 (58.1%)	14 (45.2%)
	Women	13 (41.9%)	17 (54.8%)
Age	Average (years)	50.7	53.8
	Median (years)	52.0	58.5
	Range (years)	22-80	24-78
Diseases	Duodenal ulcer	20 (64.5%)	23 (74.2%)
	Duodenal ulcer scar	10 (32.3%)	5 (16.1%)
	Gastric ulcer	1 (3.2%)	3 (9.7)
Total	All patients	31	31

Abbreviations: EAC group: patients treated by the standard triple therapy – esomeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all b.i.d. for 8 days; EACL group: patients treated by the triple therapy plus *L. acidophilus* – 5×10^9 organisms per capsule, 3 capsules in the morning and 2 capsules at night, for the same period of time.

Table 2. *H. pylori* eradication by adding *Lactobacillus acidophilus* to the eradication regimens of patients with gastroduodenal diseases.

No. of patients treated by standard regimen + probiotic	No. of patients treated by standard regimen	<i>L. acidophilus</i>	Duration of treatment (days)	Regimen	Eradication rate (%) by classic regimen	Eradication rate (%) by probiotic-supplemented regimen	Significant increase in eradication rate	Reference
60	60	<i>L. acidophilus</i> lyophilized and inactivated culture (t.i.d.)	7	RCA	70 (ITT), 72 (PP)	87 (ITT), 88 (PP)	Yes	5
47	37	<i>L. acidophilus</i> LB spent culture supernatant	14	OA	70.3	63.8	No	6
53	192	Lacidofil containing <i>L. acidophilus</i> and <i>L. rhamnosus</i> (two capsules b.i.d.)	10	PPI-AC	85.9	94.3	Yes	7
31	31	<i>L. acidophilus</i> 5x10 ⁹ organisms per capsule, (b.i.d.-3 capsules in the morning and 2	8	EAC	80.6 (ITT and PP)	83.9 (ITT and PP)	No	Present study

capsules
at night)

Abbreviations: ITT: intention to treat analysis., PP: per protocol analysis; RCA: rabeprazole (20 mg b.i.d.), clarithromycin (250 mg t.d.s.) and amoxicillin (500 mg t.d.s.); OA: omeprazole + amoxicillin; EAC: esomeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d. and clarithromycin 500 mg b.i.d., for 8 days; PPI-AC: amoxicillin with clarithromycin and proton pump inhibitor.

Table 1. Patients involved in the study.

Group	Parameter	Patients in the EACL group	Patients in the EAC group
Sex	Men	18 (58.1%)	14 (45.2%)
	Women	13 (41.9%)	17 (54.8%)
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capsules
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