Probiotics versus Rifaximin as Adjuvant Therapy for *Helicobacter pylori* Eradication

Bahaa Osman Taha [1], Mohammed Ezz-Eldin [2], Tarek Abdelrahman [1]

[1]*Internal Medicine Department, Gastroenterology Unit - Faculty of Medicine, Assiut University, Assiut, Egypt.*

[2]*Tropical and gastroenterology department , Faculty of Medicine, Assiut University, Assiut, Egypt.*

Corresponding Author
Bahaa Osman Taha
Tel. +201015599135
E-mail:
bahaa_osman99@aun.edu.eg

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Background and study aim: Helicobacter pylori infection, affecting over 50% of the global population, is a major cause of peptic ulcers and gastric cancer. Standard triple therapy (proton pump inhibitor [PPI], clarithromycin, amoxicillin) achieves modest eradication rates (~70%) but often causes gastrointestinal (GI) side effects, including diarrhea. Probiotics (e.g., *Bacillus clausii*) and Rifaximin have been proposed as adjuvants to mitigate these effects, though evidence remains conflicting.The aim of this study is to compare the efficacy of *B. clausii* and Rifaximin as adjuvants to triple therapy in reducing GI side effects and improving *H. pylori* eradication rates.

Patients and Methods: In this open-label randomized trial, 225 patients with confirmed H. pylori infection were allocated to three 14-day regimens (n=75 each): C-Triple (standard therapy: pantoprazole, amoxicillin, clarithromycin), R-Triple (standard therapy plus Rifaximin 550 mg BID), and P-Triple (standard therapy plus *B. clausii* 2 billion spores BID). GI symptoms were recorded daily, and eradication was assessed via stool antigen testing 4 weeks post-treatment.

Results: GI Side Effects: Diarrhea incidence was significantly lower in P-Triple (4%) versus R-Triple (17.3%) and C-Triple (20%) (*p=0.023*; P-Triple vs. R-Triple *p=0.037*). No significant differences were observed for abdominal pain, nausea, or vomiting.

Eradication Rates: No significant differences among groups (C-Triple: 72%, P-Triple: 80%, R-Triple: 85.3%; *p=0.15*).

Conclusion: *B. clausii* significantly reduced antibiotic-associated diarrhea but did not improve eradication rates. Rifaximin showed no benefit for either side effects or eradication. These findings support probiotics—but not Rifaximin—as adjuvants to mitigate diarrhea during *H. pylor*i therapy, without impacting eradication success.

INTRODUCTION

Helicobacter pylori (*H. pylori*), a gram-negative bacterium with a global prevalence exceeding 50% [1], is typically asymptomatic. However, it contributes to dyspeptic symptoms, peptic ulcer disease, and is associated with more severe conditions including gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, and extra-gastrointestinal diseases [2,3]. Non-invasive diagnostic techniques, such as the *H. pylori* stool antigen test and urea breath test, offer excellent sensitivity and specificity [4]. Nevertheless, accurate testing requires discontinuation of antibiotics for four weeks and proton pump inhibitors (PPIs) for two weeks prior to testing [5].

Most guidelines recommend a "test-and-treat" strategy for *H. pylori* in specific clinical scenarios [3]. Eradication regimens typically combine antibiotics with acid suppression therapy (PPIs or potassium-competitive acid blockers) for 14 days [6]. Standard triple therapy (double-dose PPI, clarithromycin, and amoxicillin for 14 days) achieves eradication rates exceeding 70% [7].

Triple therapy is often associated with side effects such as nausea, vomiting, abdominal pain, and diarrhea [8]. These symptoms can persist for weeks post-treatment. The pathophysiology of diarrhea likely involves antibiotic-induced alterations in gut microbiota [9]. Probiotics, including *Bacillus clausii*, are commonly used to treat viral diarrhea in children and mitigate antibiotic-associated side effects [10]. *B. clausii* spores withstand gastric pH, germinate in the intestine, adhere to the intestinal wall, and colonize the mucosa [11].

Rifaximin, a Rifamycin-class antibiotic structurally similar to rifampicin, exhibits potent luminal antibacterial activity [12]. It may also reduce bacterial virulence factors, inhibit adhesion, and attenuate mucosal inflammation [13].

Studies evaluating the addition of probiotics or rifaximin to *H. pylori* eradication therapy have yielded conflicting results regarding their impact on side effects and eradication rates [14,15]. Probiotics incorporated into various regimens appear beneficial for reducing gastrointestinal adverse effects, particularly diarrhea, but do not consistently improve eradication rates [16]. Similarly, rifaximin supplementation does not enhance *H. pylori* eradication rates [17], and evidence regarding its efficacy in alleviating therapy-associated gastrointestinal side effects is insufficient [18]. Furthermore, direct head-to-head comparisons of rifaximin and probiotics as adjuvant therapies are lacking.

Aims:

1. Primary: To examine the effects of adding a probiotic (*Bacillus clausii*) or a locally active antibiotic (rifaximin) to standard triple therapy on reported gastrointestinal side effects (diarrhea, abdominal pain, vomiting, nausea).
2. Secondary: To examine the *H. pylori* eradication rate when incorporating either adjuvant into triple therapy.

PATIENTS AND METHODS

This open label, randomized clinical trial was conducted in the outpatient clinic of the Tertiary Hospital for Gastroenterology and Hepatology between April 2024 and April 2025, following approval by the institutional review board (IRB No. 04-2024-300490) in April 2024.

1. Participants: Two hundred and twenty-five patients with dyspeptic symptoms and confirmed *H. pylori* infection (positive stool antigen test) was enrolled. Patients with alarm symptoms, aged over 60 years, or asymptomatic were excluded.
2. Randomization: After obtaining written informed consent, participants were randomized (1:1:1) using a computerized random number generator and sealed opaque envelopes into three groups (n=75)each.
3. Sample Size: Based on a previous study [19],Guarino, Alfredo et al., 2015, a sample size of 180 was calculated to detect a ≥20% difference in diarrhea incidence between the three groups with 80% power and a two-sided 5% significance level. To account for potential dropouts, each group size was increased to 75.
4. Interventions (14 days for all groups):

* C-Triple (Control): Standard triple therapy (pantoprazole 20 mg BID, amoxicillin 1000 mg BID, clarithromycin 500 mg BID.(

* R-Triple (Rifaximin): Standard triple therapy + rifaximin 550 mg BID.

* P-Triple (Probiotic): Standard triple therapy + probiotic (2 billion *Bacillus clausii* spores BID.(

5. Follow-up:

* Side Effects: Participants recorded daily gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea) on provided sheets throughout treatment.

* Eradication Confirmation: Successful eradication was assessed via stool antigen testing 4 weeks after completing antibiotic therapy.

6. Statistical Analysis: Data were analyzed using SPSS Version 21 (SPSS Inc.). Non-normally distributed variables (assessed via normality tests) were analyzed using non-parametric tests. Categorical adverse event data are presented as percentages; associations between groups were assessed using the chi-square test.

RESULTS

Baseline Characteristics and Medical Characteristics of the Studied Groups (Table 1): The three groups (n=75 each) showed no significant differences in baseline demographics or clinical characteristics (age, sex, BMI, smoking status, NSAID use, diabetes, hypertension.(

Gastrointestinal Side Effects During Treatment of the Studied Groups (Table 2): Diarrhea: Incidence was 20% (15/75) in C-Triple, 4% (3/75) in P-Triple, and 17.3% (13/75) in R-Triple. The difference between groups was statistically significant (p=0.023). Pairwise comparison showed a significant difference between P-Triple and R-Triple (p=0.037). Abdominal Pain: Incidence was 14.7% (11/75), 4% (3/75), and 9.3% (7/75) in C-Triple, P-Triple, and R-Triple, respectively (p=0.08, NS). Nausea/Vomiting: No significant differences were observed between groups.

Comparison of Probiotic Vs. Rifaximin as Adjuvant Therapy in Preventing Gastrointestinal Side Effects of the Studied Groups (Table 3): The incidence of gastrointestinal (GI) side effects was compared between the P-triple group (probiotic adjuvant) and the R-triple arm (Rifaximin adjuvant) during treatment. Abdominal pain was reported in 4% (n=3) of the probiotic group vs. 9.3% (n=7) in the Rifaximin group (p=0.16). Nausea occurred in 9.3% (n=7) of the probiotic group compared to 17.3% (n=13) in the Rifaximin group (p=0.22). Vomiting was observed in 5.3% (n=4) of the probiotic group vs. 13.3% (n=10) in the Rifaximin group (p=0.07). Diarrhea was significantly lower in the probiotic group (5.7%, n=4) than in the Rifaximin group (17.3%, n=13) (p=0.037.(

While most GI symptoms showed a trend toward lower incidence with probiotics, only diarrhea reached statistical significance ($p < 0.05$.(

Eradication Rates of Helicobacter pylori of the Studied Groups (Table 4): Eradication rates were 72% (54/75) for C-Triple, 80% (60/75) for P-Triple, and 85.3% (64/75) for R-Triple. The difference was not statistically significant (p=0.15).

Table 1 Baseline clinical and medical characteristics of the studied groups.

	C-triple group N (75)	P-triple group N (75)	R-triple group N (75)	P value
Age Mean ± SD	35± 11	33±9.6	33 ± 8.3	0.38
Sex	39 M /36 F	40 M/ 35 F	38M/37F	0.98
Smoking	20% (N 15)	22.7%(N 17)	(15) 20%	0.93
BMI kg/m2 Mean ± SD	26.3 ± 4.3	26.4 ± 2.9	25.4 ± 3	.16
DM	5.3 % (N 4)	8% (N 6)	6.7% (N 5)	0.8
HTN	8% (N6)	10.7%(N 8)	13.3 %(N10)	0.57
NSAID uses	5 (6.7%)	7(9.3%)	8 (10.7%)	0.76

Note: BMI (body mass index). M (male). F(female). DM (diabetes mellitus). HTN (hypertension). NSAID (non-steroidal anti-inflammatory drugs). N (number) . SD standard deviation

Table 2: Gastrointestinal Side Effects During Treatment of the Studied Groups

	C-triple group	P-triple group	R-triple group	P value
Abdominal pain	11(14.7%)	3 (4%)	7 (9.3%)	.08
Nausea	11(14.7%)	7(9.3%)	13(17.3%)	0.4
Vomiting	7(9.3%)	4(5.3%)	10 (13.3)	.26
Diarrhea	15 (20%)	4(5.7%)	13(17.3%)	**.023**

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Table 3: Comparison of Probiotic Vs. Rifaximin as Adjuvant Therapy in Preventing Gastrointestinal Side Effects of the Studied Groups.

	P-triple group	R-triple arm	P value
Abdominal pain	3 (4%)	7 (9.3%)	0.16
Nausea	7(9.3%)	13(17.3%)	0.22
Vomiting	4(5.3%)	10 (13.3)	0.07
Diarrhea	4(5.7%)	13(17.3%)	**0.037**

Table 4: Eradication rate of Helicobacter pylori in the groups studied.

		C-triple group		P-triple group		R-triple group		P value
		N	% within group	N	% within group	N	% within group	
H. Pylori stool antigen	**negative**	54	72%	60	80.0%	64	85.3%	0.15
	Positive	21	22%	15	20.0%	11	14.7%	

DISCUSSION

This randomized trial demonstrates that neither rifaximin nor *Bacillus clausii* significantly improves the *H. pylori* eradication rate of standard triple therapy. However, *B. clausii* significantly reduced the incidence of diarrhea compared to both standard therapy and Rifaximin supplementation.

Although most *H. pylori* therapy-related gastrointestinal side effects are self-limiting, severe cases can impact treatment adherence. The observed reduction in diarrhea with probiotics aligns with the proposed pathophysiology involving antibiotic-induced gut microbiota alterations. Our findings support previous RCTs, such as Plomer et al. [20], which reported antidiarrheal benefits of *B. clausii* combined with triple therapy. While our study relied on symptom event reporting versus Plomer's symptom-free-day analysis, both found no improvement in eradication rates with probiotics (eradication was not assessed by Plomer et al.).

The literature on probiotics for *H. pylori* eradication remains inconsistent. While some meta-analyses [e.g., Lü Muhan et al. [21]] suggested a positive effect on eradication, others and our study found no significant benefit. This discrepancy may relate to probiotic strain, timing of administration, and regimen type. Wang et al. [22] highlighted significant variations in efficacy between strains and formulations (e.g., Bifidobacterium-Lactobacillus combinations showing superior eradication rates in some analyses). The concurrent administration of probiotics with antibiotics in our study may also explain the lack of eradication benefit.

Rifaximin, despite its luminal antibacterial activity and efficacy in other diarrheal conditions, showed no benefit for either *H. pylori* eradication or prevention of therapy-associated diarrhea in this study. This aligns with a large meta-analysis by Wang et al. [23] concluding Rifaximin offers no role in *H. pylori* eradication regimens. Rifaximin's limited impact on commensal gut microbiota may explain its inferiority to probiotics in preventing diarrhea.

To our knowledge, this is the first head-to-head trial comparing rifaximin and probiotics as adjuvants in *H. pylori* eradication. It highlights their lack of effect on eradication rates and demonstrates the ineffectiveness of adding rifaximin specifically for side effect reduction. This provides evidence against the unnecessary inclusion of rifaximin in such regimens. Limitations include potential *H. pylori* strain variation influencing eradication, lack of gut microbiota analysis, and possible bias in patient-reported symptoms (especially abdominal pain and nausea).

Further randomized, double-blind, multicenter studies are needed to confirm the role of specific probiotics in reducing triple-therapy-associated diarrhea, evaluate optimal strains and administration timing, and correlate effects with gut microbiota changes.

CONCLUSION

The addition of either *Bacillus clausii* or rifaximin to standard triple therapy did not significantly improve *H. pylori* eradication rates. However, *B. clausii* significantly reduced the incidence of diarrhea associated with treatment. Rifaximin provided no significant benefit in alleviating gastrointestinal side effects compared to standard triple therapy alone.

Ethical considerations: This open label, randomized clinical trial was conducted in the outpatient clinic of the Tertiary Hospital for Gastroenterology and Hepatology between April 2024 and April 2025, following approval by the institutional review board (IRB No. 04-2024-300490) in April 2024.

List of abbreviations:

C-Triple Standard therapy: pantoprazole, amoxicillin, clarithromycin

GI Gastrointestinal

H. pylori *Helicobacter pylori*

MALT Mucosa-associated lymphoid tissue

PPI Proton pump inhibitors

P-Triple Standard therapy plus B. clausii 2 billion spores

R-Triple Standard therapy plus Rifaximin

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CRediT authorship contribution statement

Bahaa Osman taha : Conceptualization, Ethical approval procedures, literature search, methodology, and writing the manuscript. Mohammed Ezz-Eldin: literature search, methodology, coding of the data and data presentation & commenting on results, and writing the manuscript. Tarek Abdelrahman: consultation and follow up of the research steps and supervision.

All the authors have read and approved the final manuscript.

The data are available as requested.

HIGHLIGHTS

- *Helicobacter pylori* is an infection that is widely distributed globally and is associated with both gastric and extra-gastric diseases.
- Eradication treatment of *Helicobacter pylori* is usually challenging and depends upon antibiotics and acid suppression agents, such as PPIs. Treatment is usually associated with gastrointestinal side effects, which could affect patient compliance.

- Both rifaximin and probiotics could not increase the eradication rate of *H. pylori*.
- Probiotics might have a beneficial effect by alleviating the associated diarrhoea during triple therapy with *Helicobacter pylori*.

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