Efficacy and Safety of *Saccharomyces boulardii* in the 14-day Triple Anti-*Helicobacter pylori* Therapy: A Prospective Randomized Placebo-Controlled Double-Blind Study

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Abstract

Background: Recent studies indicate a potential role of *Saccharomyces boulardii* in the prevention of *Helicobacter pylori* treatment-related side-effects and also in improvement of eradication rate. Our aim is to investigate the efficacy and safety of *S. boulardii* in the prevention of side-effects related to *H. pylori* eradication. The secondary aim of the study was to define the effect of *S. boulardii* on the eradication success of anti-*H. pylori* therapy.

Materials and methods: One hundred and twenty-four patients with *H. pylori* infection (male/female: 44/80, mean age: 48 ± 14.25 year) receiving 14 days of triple therapy (clarithromycin 500 mg b.i.d., amoxicillin 1000 mg b.i.d., and lansoprazole 30 mg b.i.d.) were randomly assigned to *S. boulardii* or placebo. Dyspeptic symptoms were recorded by using modified Glasgow Dyspepsia Questionnaire (GDQ). Side-effect profile and tolerability were assessed using a symptom-based questionnaire. *H. pylori* status was rechecked after 6 weeks after completion of eradication therapy.

Results: *H. pylori* eradication rate, although higher in the treatment group, was statistically similar in treatment and control groups: 71% (44/62) versus 59.7% (37/62), respectively ($p > .05$). Nine (14.5%) patients in the treatment group and 19 (30.6%) patients in the placebo group experienced diarrhea ($p < .05$). Epigastric discomfort was more frequent in the control group [9 (14.5%) versus 27 (43.5%), respectively ($p < .01$)]. Diffuse abdominal pain, abdominal gas, taste disturbance, urticaria, nausea symptoms were similar in both groups. GDQ scores after treatment were significantly better for treatment group (mean ± SD, range: 1.38 ± 1.25 (0–5) vs. 2.22 ± 1.44 (0–6), respectively; $p < .01$).

Conclusion: *S. boulardii* improved anti-*H. pylori* antibiotherapy-associated diarrhea, epigastric discomfort, and treatment tolerability. In addition, *S. boulardii* supplement decreased post-treatment dyspepsia symptoms independent of *H. pylori* status. However, *S. boulardii* had no significant affect on the rate of *H. pylori* eradication.

Introduction

Helicobacter pylori is a gram-negative bacteria that colonize the gastric mucosa and is the important etiologic agent for gastric ulcer and carcinomas [1]. However, it has been reported that long-term persistent *H. pylori* infection leads to atrophic gastritis, which increases the risk of gastric adenocarcinomas [2]. The rate of peptic ulcer in *H. pylori*-infected population is approximately 3% in USA and 25% in Japan [3]. The rate of *H. pylori* infection is 50% in worldwide [4]. The *H. pylori* prevalence varies according to the socioeconomic status. The prevalence of *H. pylori* is approximately 67.6–81.3% in Turkey [5]. For developing clinical disease, host genetics, host immune response, and bacterial virulence factors appear to play critical roles [6].

There are several treatment options to cure *H. pylori* and many are still under investigation. Currently, 1 to 2 weeks of therapy with clarithromycin, amoxicillin, and a proton pump inhibitor, is regarded as the reference standard on anti-*H. pylori* schemes. However, side-effects of this eradication therapy limit the overall therapeutic value of the treatment.

Almost all antibiotic treatments may disturb the colonization resistance of gastrointestinal flora and cause a range of clinical symptoms, most notably diarrhea. *Clostridium difficile*-associated diarrhea, however, which is among the most serious of the adverse events related to antibiotic-associated diarrhea (AAD), occurs most often in older, immunocompromised adults who have been admitted to hospital [7]. In the general population, AAD varies in incidence from 5% to 62%, and in timing, from at the initiation of therapy to as long as 2 months after the end of treatment [7–9].

Probiotics are live microbial food ingredients that alter the enteric flora and have a favorable effect on health [10,11]. It has been suggested that nonpathogenic yeast, *Saccharomyces boulardii*, may be effective in the treatment and prevention of AAD, as well as in the prevention of relapses of *C. difficile*-associated diarrhea [12,13]. In addition, probiotics are effective against colonization of *H. pylori* in many experimental studies [14]. Experiments using the mouse model have successfully demonstrated the therapeutic application of *Lactobacillus salivarius* WB 1004 [15,16], *Lactobacillus gasseri* OLL2716 [17], *Lactobacillus casei* strain Shirota [18], *Lactobacillus rhamnosus*, and *Lactobacillus acidophilus* [19] against *H. pylori* infection, and of *L. acidophilus* LB [20] against *Helicobacter felis* infection. The most common effects achieved were decreased *H. pylori* colonization [16–20], decreased gastric inflammation [16,18,19], and prevention of bacterial gastric colonization of infected mice [15].

In this study, we aimed to investigate the efficacy and safety of *S. boulardii* in the prevention of side-effects related to antibiotherapy in outpatients receiving *H. pylori* eradication. The secondary aim of the study was to define the effect of *S. boulardii* on the eradication success of anti-*H. pylori* therapy.

Methods

This is a prospective, randomized placebo-controlled study. One hundred and twenty-four patients with *H. pylori* infection were enrolled (male/female: 44/80, mean age: 48 ± 14.25 years). Patients receiving 14 days of triple therapy consisting of clarithromycin 500 mg b.i.d., amoxicillin 1000 mg b.i.d., and lansoprazole 30 mg b.i.d. before meals were randomly assigned to receive *S. boulardii* (treatment group, n = 62) or placebo (control group, n = 62). Randomization was done using computer-based random numbers. The manufacturer medical company gave placebo sachets. Placebo was administered in the same amount of sachets of probiotic schemes (250 mg, b.i.d.). Boxes containing active study treatments and placebo were identical in shape and color, and contained the same number of sachets. No trademark identifications were present, either on the probiotic or on the placebo sachets.

The treatment group received 1 gram *S. boulardii* (250 mg sachets, 500 mg b.i.d., Reflor; Sanofi-Synthelabo Ilac A.S., Istanbul, Turkey) per day for 2 weeks. All patients were followed for an additional 6 weeks after cessation of therapies and patients were checked for *H. pylori* clearance. After enrollment, patients were examined and interviewed weekly during the study period.

Inclusion criterion was: presence of *H. pylori* infection in biopsy specimens obtained during upper gastrointestinal endoscopy with an indication of dyspepsia in adult patients.

Exclusion criteria were: presence of malignancy, gastrointestinal bleeding, and diarrhea as a result of other causes such as functional–anatomical disturbances of the gastrointestinal tract (irritable bowel syndrome, prior gastrectomy, bowel resection, diabetes mellitus, inflammatory bowel disease, etc.), and history of *H. pylori* eradication.

Dyspeptic symptoms were recorded before initiation of therapy and at the end of follow-up period (week 6) using modified Glasgow Dyspepsia Questionnaire (GDQ) [21]. It has been shown to be a well-validated, reproducible, and easy-to-use questionnaire in the assessment of dyspepsia. The dyspepsia score ranged from 0 to 12. It was designed to reflect a wide range of symptom severity, any nocturnal disturbance, and behavioral response to symptoms sustained. While the questionnaire was performed, both the assessor and the subjects were blind to the treatment arm.

A written informed consent was collected for each patient before the initiation of the study and local ethics committee approved the study protocol.

Side-Effects and Treatment Tolerability Evaluation

During follow-up period, we have assessed side-effect profile and tolerability using a previously reported questionnaire proposed by De Boer et al. and modified by Armuzzi et al. [22]. In order to obtain the highest compliance in registering any possible treatment-related side-effects, subjects received careful instruction and training on filling-in questionnaires (verbal explanations and printed instructions were both given). Subjects were asked to report any side-effect during and thereafter therapy such as taste disturbance, nausea, vomiting, epigastric pain, bloating, diarrhea, and skin rash, and they were asked to grade each side-effect according to severity: mild (effect observed, but could be disregarded), moderate (effect sometimes interfered with daily activities), or severe (effect continuously interfered with daily activities). The side-effect questionnaire was filled-in four times (during the first and second weeks of therapy and first and second weeks after the treatment period) (Fig. 1).

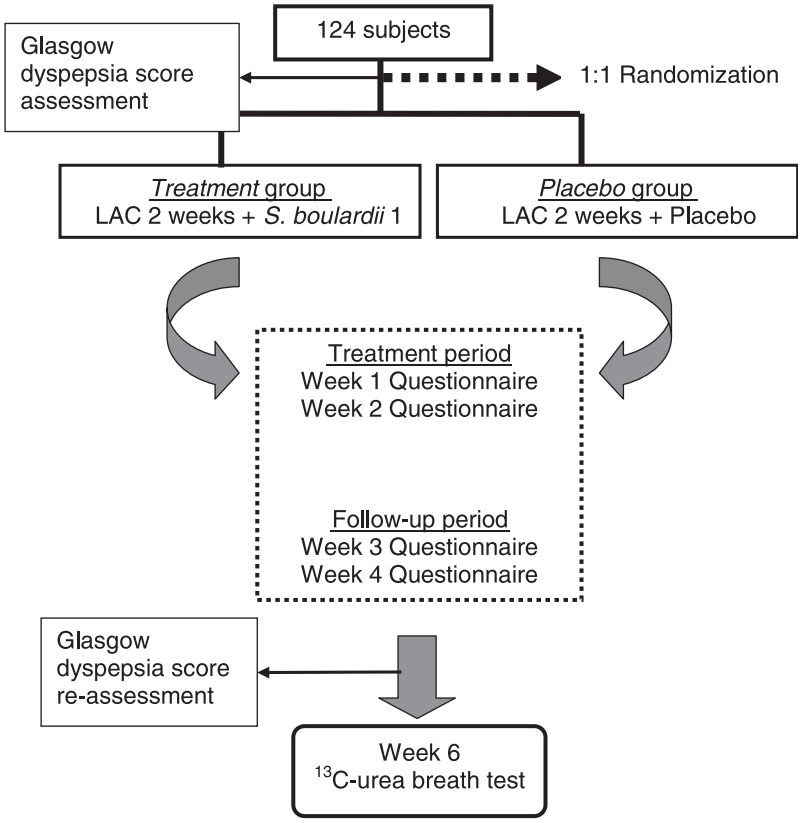

Figure 1 Outline of study profile. LAC: lansoprazole 30 mg b.i.d., amoxyxillin 1 g b.i.d., clarithromycin 500 mg b.i.d.

The effect of side-effects on the treatment compliance was assessed by an overall judgment of tolerability using a five-point scale: (1: no side-effects, 2: slight discomfort, 3: moderate discomfort, sometimes interfering with daily activities, 4: severe discomfort, patient was able to complete treatment however, daily activities were not possible, and 5: severe discomfort, patient forced to discontinue treatment) [22].

Finally, protocol adherence was verified through a tablet count in medication containers returned by the patients the day after finishing therapy and by direct asking the subject about therapy completion. Patients were considered noncompliant if they consumed less than 80% of their medication.

Endoscopy and Diagnosis of *H. pylori* Infection

Endoscopy was performed after an overnight fasting, and two specimens were taken from intact mucosa in the gastric antrum and corpus. The specimens were stained with hematoxylin and eosin and Giemsa to demonstrate *H. pylori*. Gastritis was described according to modified Sydney Classification [23].

H. pylori status was rechecked 6 weeks after completion of eradication therapy using ^{13}C-urea breath test.

Statistical Analysis

The study was designed to allow minimum number of subjects (70) to give a 90% statistical power to detect an increase in eradication rates, from 50% to 80%, between groups. Also, a sample size of 80 patients was calculated as appropriate to detect a difference of 20% in symptom occurrence for any side-effect between treatment and placebo groups (two-sided alpha value: 0.05).

A comparison of continuous data between the two study groups was carried out using the Student's *t*-test. Discontinuous variables were compared by the Wilcoxon rank test. For multiplicity of significance testing in the main analysis, the homogeneity of the two groups was tested by the χ^2 test. Differences in eradication rates between treatment and control groups were tested with the Fisher exact test. The confidence interval (CI) was calculated as 95% (two-tailed). The significance level used was 5%. All calculations were determined by SPSS version 15.0 for Windows XP (SPSS Inc., Chicago, IL, USA) software.

Table 1 Characteristics of patients in the treatment and control groups

	Treatment group (n = 62)	Control group (n = 62)	*p*-value
Gender			
Male	26 (41.9%)	18 (29%)	NS
Female	36 (58.1%)	44 (71%)	NS
Age (years)			
Mean ± SD	45.82 ± 13.35	47.56 ± 13.53	NS
Median (range)	44.5 (18–73)	48 (18–76)	NS
Previous history of AAD [n (%)]	7 (11.2%)	4 (6.4%)	NS
Baseline GDQ [Median (range)]	5 (1–10)	5 (2–10)	NS

GDQ, Modified Glasgow Dyspepsia Questionnaire; AAD, antibiotic-associated diarrhea; SD, standard deviation; NS, not significant.

Table 2 Endoscopic and histologic findings of patients in treatment and control groups[a]

	Treatment group n = 62	Control group n = 62	*p*-value
Endoscopy [n (%)]			
Gastritis	30 (48.30)	28 (45.16)	NS
Duodenal ulcer	2 (3.20)	3 (4.83)	NS
Gastric ulcer	1 (1.61)	1 (1.61)	NS
Esophagitis	12 (19.35)	7 (11.29)	NS
Normal	17 (27.41)	23 (37.09)	NS
Histology[b]			
H. pylori density			
Antrum	5.00 ± 0.74	3.71 ± 0.66	NS
Corpus	3.91 ± 0.56	3.94 ± 0.34	NS
Activity of gastritis			
Antrum	3.90 ± 0.11	4.66 ± 0.56	NS
Corpus	1.33 ± 0.22	2.54 ± 0.29	NS
Gastric Inflammation			
Antrum	5.89 ± 0.34	4.98 ± 0.86	NS
Corpus	4.75 ± 0.87	3.61 ± 0.49	NS

[a]All values are mean ± standard error.

[b]Gastritis was graded according to modified Sydney system [22]. Biopsies were performed twice at each site. Each value is the sum of the grades of the two biopsies.

Results

No major side-effects leading to treatment discontinuation were observed. Compliance was optimal in both groups. All patients completed the 14 days of treatment. For this reason, the eradication rates were calculated by PP analysis. Patient characteristics and endoscopic findings were presented in Tables 1 and 2.

During the study period, nine (14.5%) patients in the treatment group and 19 (30.6%) patients in the placebo group experienced diarrhea ($p < .05$). Diarrhea was mild (less than four times a day, without blood or mucus), self-limited, and lasted for a mean of 3 range: 1–6) days after cessation of therapy. No pathogenic growth was detected in stool cultures. The *C. difficile* toxin was measured in six patients in the treatment group and in eight patients in the control group. These patients had mild abdominal pain and longer duration (mean value of 5.6 days, average number of daily bowel movements: 3) of diarrhea than other patients. However, none of these patients had positive *C. difficile* toxin in their stool samples.

Epigastric discomfort was reported by 9 (14.5%) versus 27 (43.5%) patients in the treatment and control groups, respectively ($p < .01$). Diffuse abdominal pain, abdominal gas, taste disturbance, urticaria, and nausea symptoms were similar in treatment and control groups (Table 3).

Baseline GDQ scores were similar in both groups [mean ± SD, range: 4.69 ± 2.37 (1–10) vs. 4.69 ± 2.35 (2–10), respectively]. However, GDQ scores after treatment were significantly better for treatment group than control group [mean ± SD, range: 1.38 ± 1.25 (0–5) vs. 2.22 ± 1.44 (0–6), respectively; $p < .01$, Wilcoxon rank test].

The overall judgment of tolerability based on a five-point scale was significantly superior in the treatment group ($p < .001$, Table 4). Treatment tolerability was not correlated with age, gender, endoscopic diagnosis, and degree of gastritis according to modified Sydney Classification. However, patients who had reported severe side-effect burden had higher baseline GDQ scores than other patients (mean ± SD; 8.43 ± 2.32 vs. 4.28 ± 1.67, $p = .0078$).

H. pylori eradication rate was 71% (44/62) versus 59.7% (37/62) in treatment and control groups, respectively. Although eradication rate was increased in treatment group, the difference was not significant.

Discussion

Saccharomyces boulardii is nonpathogenic yeast widely prescribed in a lyophilized form in many countries of the

Table 3 Side-effect frequencies during treatment and follow-up periods

	Treatment group (n = 62)			Control group (n = 62)			
Period (n,%)	Treatment	Follow up	Overall	Treatment	Follow up	Overall	*p*-value
Diarrhea	7 (11.2)	2 (3.2)	9 (14.5)*	16 (25.8)	3 (4.8)	19* (30.6)	0.02
Nausea	6 (9.6)	1 (1.6)	7 (11.2)	11 (17.7)	2 (3.2)	13 (20.9)	NS
Epigastric discomfort	8 (12.9)	1 (1.6)	9 (14.5)**	20 (32.2)	7 (11.2)	27 (43.5)**	0.01
Taste disturbance	4 (6.4)	5 (8.0)	9 (14.5)	6 (9.6)	3 (4.8)	9 (14.5)	NS
Urticaria	2 (3.2)	0	2 (3.2)	2 (3.2)	0	2 (3.2)	NS
Abdominal gas	10 (16.1)	4 (6.4)	14 (22.5)	12 (19.3)	3 (4.8)	15 (24.1)	NS

*,**: $p < .05$ according to comparison between overall values for both groups.
NS, not significant.

Table 4 Assessment of treatment tolerability*

Side-effect burden	Treatment group (n,%)	Control group (n,%)
None	48 (77.4)	25 (40.3)
Mild	4 (6.4)	12 (19.3)
Moderate	8 (12.8)	11 (17.7)
Severe	2 (3.2)	14 (22.5)
Forced discontinuation	0	0

*Treatment versus control group, $p = .0023$.

world and used in adults and children as a biotherapeutic agent [24,25]

In this randomized, placebo-controlled study, *S. boulardii* supplemented anti-*H. pylori* regimen showed lower side-effects and higher treatment tolerability. However, *S. boulardii* supplementation had no effect on the eradication rate of the therapy.

In a multicenter study from Turkey, 389 patients were randomized to receive clarithromycin, amoxicillin, and omeprazole with or without *S. boulardii* supplementation. Diarrhea developed in 5.9% of patients in the treatment group versus 11.5% of patients in the control group ($p = .049$). Authors concluded that *S. boulardii* is effective and safe in prevention of AAD when given concomitantly with *H. pylori* eradication [26]. However, this study lacks an assessment of treatment tolerability and questionnaires including dyspepsia and side-effects. Also the study is not a placebo-controlled study.

Lionetti et al. consecutively treated 40 children with omeprazole + amoxicillin for 5 days, and omeprazole + clarithromycin + tinidazole for other 5 days [27]. These children were randomized to receive either *L. reuteri* ATCC 55730 (108 CFU) or placebo. All of the probiotic-supplemented children when compared with those receiving placebo had significant reduction of symptom score during eradication therapy (4.1 ± 2 vs. 6.2 ± 3; $p < .01$). The main limitation of this study is the small number of participants leading to an unpowered study design.

Sheu BS et al. randomized 138 patients to a quadruple anti-*H. pylori* therapy with or without a 4-week pretreatment with AB-yogurt (*Lactobacillus*- and *Bifidobacterium*-containing yogurt, 400 mL/day). The yogurt-plus-quadruple therapy group had a higher *H. pylori* eradication rate than did the quadruple therapy-only group (intention-to-treat [ITT] analysis: 85% compared with 71.1%, $p < .05$; per-protocol [PP] analysis: 90.8% compared with 76.6%, $p < 0.05$) [28].

Nista EC et al. reported *Bacillus clausii* as an adjuvant therapy with anti-*H. pylori* treatment [29]. One hundred and twenty *H. pylori*-positive patients were randomly screened to receive: 1, a standard 7-day triple therapy with rabeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d. and *B. clausii* t.d.s. (each preparation containing 2×10^9 spores) for 14 days starting from the first day of treatment; and 2, the same 7-day triple therapy and placebo t.d.s. for 14 days starting from the first day of treatment. The incidences of nausea, diarrhea, and epigastric pain in patients treated with *B. clausii* were significantly lower than in placebo group, in both PP and ITT analysis. Equally, intensity of nausea and diarrhea in patients treated with B. clausii was significantly lower than in placebo group. There were no differences in adherence to treatment and *H. pylori* eradication rates between groups.

Cremonini et al. randomized 85 *H. pylori*-positive, asymptomatic patients in four groups to receive probiotic or placebo both during and for 7 days after a 1-week triple-therapy scheme (rabeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d., and tinidazole 500 mg b.i.d.). Group I (n = 21) received *Lactobacillus* GG; group II (n = 22), *S. boulardii*; group III (n = 21), a combination of *Lactobacillus* spp. and bifidobacteria; and group IV (n = 21), placebo. In all probiotic-supplemented groups, there was a significantly lower incidence of diarrhea and taste disturbance during

the eradication week with respect to the placebo group. Overall assessment of tolerability was significantly better in the actively treated patients than in the placebo group. No differences in the incidence of side-effects between the probiotic groups were observed. The *H. pylori* eradication rate was almost identical between the probiotic and placebo groups [30].

Three prospective, randomized, placebo-controlled clinical studies have confirmed the efficacy of *S boulardii* for preventing AAD [31]. In a first study, conducted in 180 hospitalized patients [32], *S. boulardii* was given at the dose of 1 g/day during the period of antibiotherapy up to 2 weeks after discontinuation of antibiotics. The occurrence of AAD was 21.8% in the placebo group versus 9.5% in the treated group ($p = .038$). In a second two-center study of 193 hospitalized patients receiving a β-lactam in combination with another antibiotic or not [33], *S. boulardii* was administered at the dose of 1 g/day and was continued during 3 days after discontinuation of antibiotics. Occurrence of AAD was 14.6% in the placebo group versus 7.2% in the group treated with *S. boulardii* ($p = .03$). These data confirm those recorded in a preliminary study conducted in 388 ambulatory patients [34]. Treatment with *S. boulardii* at the dose of 200 mg/day during the antibiotherapy (β-lactams or cyclines) decreased the percentage of AAD from 17.5% to 4.5% [34].

In our study, we have observed higher rates of AAD, both in the treatment (14.5%) and in the control groups (30.6%), than previously published studies. This discrepancy might be the result of prolonged (14 days) anti-*H. pylori* regimen used in our study. It was shown that occurrence of AAD is also correlated with the duration of antibiotic therapy [9,10]. For this reason, higher rates of AAD in our study might be related with the longer duration of antibiotic therapy in our study protocol.

We have observed decreased frequency of diarrhea and epigastric discomfort in treatment arm. This effect is important in countries where anti-*H. pylori* regimens are applied for a longer period of time (14 days). In many European countries, anti-*H. pylori* treatments are limited to 7 days. Fewer occurrences of side-effects and increased treatment tolerability are expected with this short regimen. As mentioned in the recent Maastricht III Consensus Report, 14-day treatment is superior to 7-day treatment duration (by 12% 95% CI 7–17%), and 7 days of treatment may be acceptable where local studies show that it is very effective [35]. However, due to higher clarithromycin resistance rates and probably higher incidence of virulent species of *H. pylori*, developing countries (such as Turkey) prefer long-term regimens (14 days). This increased duration of antibiotherapy possesses the burden of increased side-effects. For this reason, adjuvant therapies minimizing side-effects and increasing treatment tolerability are much more needed with long-term eradication regimens.

The eradication rates in both groups are very low (71% and 59%). The main factor for the treatment failure seems to be clarithromycin resistance, which is approximately 28% in Turkey [36]. A previous study from our center indicated a clarithromycin resistance rate of 16.9% by using DNA sequencing [37], however, this resistance rate have increased in our daily practice.

Many of the published studies regarding the protective role of probiotics in anti-*H. pylori* regimens are reported with short-term treatment regimens (7–10 days) [27–30]. However, the risk of AAD is increased with longer duration of antibiotherapy [31]. For this reason, the protective effect of *S. boulardii* and other probiotics might be underestimated in short-term anti-*H. pylori* treatments.

Sykora et al. investigated the efficacy of triple therapy supplemented with a specially designed fermented milk product containing specific probiotic *L. casei* DN –114 001 strain on *H. pylori* eradication in children [38]. Eradication success was higher in the probiotic-supplemented group. Primary resistance for clarithromycin could be determined in 21.2%.

Although we have noticed a significant improvement in GDQ scores in both groups after treatment, *S. boulardii*-supplemented group achieved better GDQ scores than placebo group at the end of 6 weeks of follow up [mean ± SD, range: 1.38 ± 1.25 (0–5) vs. 2.22 ± 1.44 (0–6), respectively; $p < .01$, Wilcoxon rank test]. This is an interesting finding since the *H. pylori* eradication rates are similar in both groups. Gotteland *et al*. evaluated with ^{13}C-urea breath test of *S. boulardii* plus inulin and heat-killed *L. acidophilus* LB in comparison with triple therapy in colonized schoolchildren [39]. The probiotics were administered twice daily for 2 months. Triple therapy eradicated the microorganism in 66% of the children compared with 12% in those receiving *S. boulardii* and 6.5% of those receiving *L. acidophilus* LB. In our study, the positive effect of *S. boulardii* on the post-treatment symptom scores may be due to decreased gastric inflammation and density of *H. pylori* in the gastric mucosa. Further studies are needed to clarify this issue.

In a recent meta-analysis considering the effects of probiotic supplementation on anti-*H. pylori* regimens, 14 eligible studies were analyzed [40]. Pooled *H. pylori* eradication rates were 83.6% (95% CI = 80.5–86.7%) and 74.8% (95% CI = 71.1–78.5%) for patients with or without probiotics by ITT analysis, respectively, the odds ratio (OR) was 1.84 (95% CI = 1.34–2.54); the occurrence of total side-effects were 24.7% (95% CI = 20.0–29.4%) and 38.5% (95% CI = 33.0–44.1%) for groups with or without probiotics, especially for diarrhea, the summary OR was 0.44 (95% CI = 0.30–0.66).

In the control group, patients who had reported severe side-effect burden also had higher baseline GDQ scores than the rest of the control patients (mean ± SD; 8.43 ± 2.32 vs. 4.28 ± 1.67, $p = .0078$). This is a novel finding since, it may be logical to initiate probiotic supplementation to these patients to decrease side-effects associated with anti-*H. pylori* therapy.

In conclusion, *S. boulardii* improved anti-*H. pylori* antibiotherapy-associated diarrhea, epigastric discomfort, and treatment tolerability. In addition, *S. boulardii* supplement decreased post-treatment dyspepsia symptoms independent of *H. pylori* status. Addition of *S. boulardii* did not affect the rate of *H. pylori* eradication.

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