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REGULAR ARTICLE

A randomized, open trial evaluating the effect of *Saccharomyces boulardii* on the eradication rate of *Helicobacter pylori* infection in children

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Abstract

Aim: The failure rate of *Helicobacter pylori* (*H. pylori*) eradication imposes the assessment of new options.

Subjects and methods: A prospective open study was performed in 90 symptomatic children (range 3–18 years) with *H. pylori* infection, randomized in two groups: control (42 patients) and intervention group (48 patients). Both groups were treated with the standard triple eradication therapy (omeprazole/esomeprazole, amoxicillin and clarithromycin) for 7–10 days. The intervention group was also treated with *Saccharomyces boulardii* (*S. boulardii*), 250 mg b.i.d., for 4 weeks. The eradication rate of *H. pylori* was assessed by the same methods (urease test and histology) 4–6 weeks after treatment. Adverse events and compliance were evaluated after 7 and 28 days of treatment. The Chi-square test was used for statistical evaluation ($p < 0.05$).

Results: *H. pylori* infection was identified in 90 of 145 children (62%) and it correlated positively with age ($p < 0.002$) and inversely with socioeconomic status ($p < 0.005$). All infected children had chronic gastritis, with antral nodularity in 76.7%. Overall, *H. pylori* eradication rate was 87.7% (control 80.9%, *S. boulardii* group 93.3%) ($p = 0.750$). The incidence of side effects was reduced in the *S. boulardii* group: 30.9% in the control versus 8.3% in the probiotic group ($p = 0.047$).

Conclusion: The addition of *S. boulardii* to the standard eradication treatment confers a 12% nonsignificant enhanced therapeutic benefit on *H. pylori* eradication and reduces significantly the incidence of side effects.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects almost half of the world's population and its prevalence is strongly associated with the patient's age and socioeconomic conditions (1,2). In 2001, the prevalence of *H. pylori* was estimated to be 80%–90% in developing countries, and 30%–50% in developed countries (3). *H. pylori* is the most prevalent gastric microbial pathogen, is mainly acquired before the age of 5 years and lasts, in general, in the absence of therapy for life (4). *H. pylori* infection is associated with a wide spectrum of gastrointestinal diseases that vary from asymptomatic gastritis to peptic ulceration, gastric carcinoma and mucosa-associated lymphoid tissue lymphoma (MALT) (5). Patients with chronic *H. pylori* infection have an estimated lifetime risk of 10%–20% to develop peptic ulcer disease, and compared with *H. pylori*-negative individuals, a 2- to 6-fold higher relative risk to develop gastric cancer (6). Recent studies have suggested an association between *H. pylori* infection and a miscellany of extragastrointestinal pathologies such as cardiovascular, immunological, hepatobilliary and skin diseases (7).

Although there is still no ideal treatment for *H. pylori* infection, an effective antimicrobial therapy is available, and indications for therapy have been proposed. The optimal treatment protocol for children with *H. pylori* infection has not been defined yet. The eradication rate reached by the standard triple therapies varies between 60 and 80% (8–10).

Probiotics have been tested as a new strategy for the eradication of *H. pylori* in humans (11). Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts (12). There is substantial evidence that probiotic agents may have beneficial effects in many digestive and extraintestinal disorders in humans. The probiotics most commonly used in clinical practice include acid-producing bacteria (*Lactobacillus* and *Bifidobacterium spp*), *Bacillus spp*, *Streptococcus thermophillus* and yeast such as *Saccharomyces boulardii* (*S. boulardii*) (12).

S. boulardii is a nonpathogenic yeast isolated from the skin of lychee fruit and is naturally resistant to antibiotics, gastric acidity and proteolysis (13). *S. boulardii* is a close but distinct relative of *S. cerevisiae*, which has not been genetically modified and has an unusually high optimal growth temperature of around 37°C (14). *S. boulardii* exerts an antimicrobial and anti-inflammatory activity through the inhibition of the nuclear factor-kappa B (NF-κB) translocation into the nucleus and is able to stimulate the local immunity (15,16).

The aim of this trial was to assess the potential benefits of the supplementation of the standard triple therapy with *S. boulardii* in symptomatic children with *H. pylori* infection.

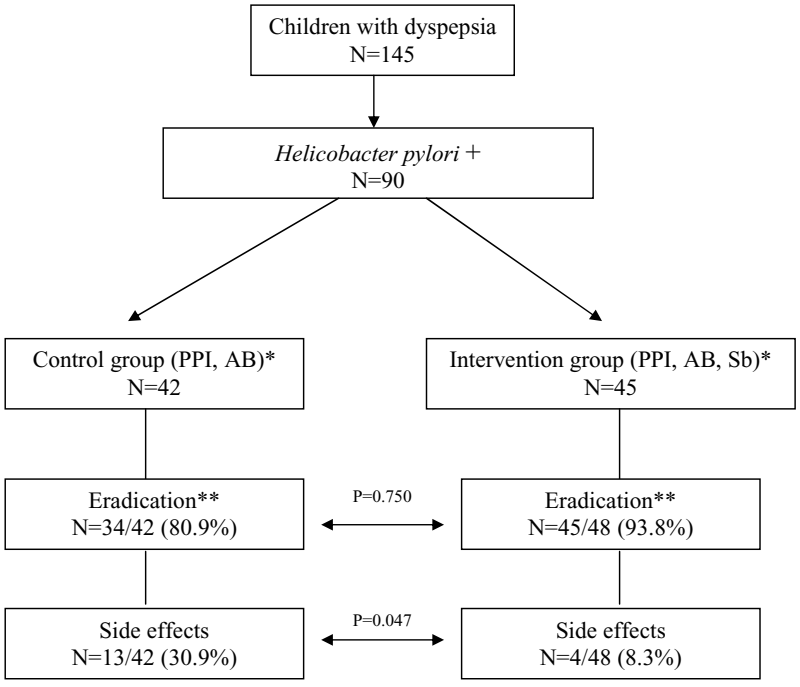
PATIENTS AND METHODS

The study population consisted of 145 consecutive children (81 female, mean age 13.2 years, range 3–18 years) with uninvestigated dyspepsia, with predominantly chronic or recurrent upper abdominal pain, suggesting organic disease requiring an endoscopic evaluation (Patient flow diagram: Fig. 1). This study was conducted over a 1-year period (January 2006–December 2006). All endoscopies were performed by the same gastroenterologist, using a fiber-endoscope Olympus GIF-XP 30 (Olympus, Shinjuku-ku, Tokyo, Japan). All children were sedated with intravenous midazolam. From each child, a minimum of three gastric biopsy specimens were obtained, one for on-site rapid urease testing, and at least two for histopathology (minimum one from the antrum and one from the corpus). In the patients with endoscopically suspected gastric inflammation, biopsy specimens were taken from areas with abnormal-appearing mucosa. The biopsies were embedded in paraffin, sectioned and stained with hematoxylin and eosin to grade inflammatory cells and with the Giemsa staining to grade *H. pylori* density. The grading system used was the Updated Sydney System (17).

H. pylori infection was detected in 90 of 145 (62.1%) children due to a positive histological examination and rapid urease test. All patients with documented *H. pylori* infection had abnormal histological findings and were diagnosed with chronic gastritis, active or inactive, based on the analysis of the inflammatory cells. The exclusion criteria were: children with active upper gastrointestinal bleeding, patients with history of antibiotic, proton pump inhibitors (PPI) or H_2-blockers or probiotic drug treatments during the previous month, known allergy to one of the study treatments and subjects who had a history of gastric surgery or other life-threatening conditions.

The 90 *H. pylori*-infected patients were selected for this randomized clinical trial to evaluate the efficacy and safety of *S. boulardii* as an add-on therapy in the management of *H. pylori* eradication. A detailed questionnaire was administered to the parents and the child to obtain data regarding sociodemographic factors and gastrointestinal and extradigestive symptoms before and during treatment. The standard triple therapy was administered to all *H. pylori*-infected children: PPI (omeprozole or esomeprazole 1 mg/kg/day, b.i.d., for 3 weeks) associated with two antibiotics (amoxicillin, 50 mg/kg/day and clarothromycin 15 mg/kg/day, b.i.d) for 7–10 days. The patients were randomized according to an envelope-drawing system in two groups to receive either only the triple therapy (control group: 42/90 children) or *S. boulardii* (Enterol; Biocodex, Gentilly Cedex, France, 250 mg/day, b.i.d., for 4 weeks) as additional treatment (intervention group: 48/90 children). The questionnaires were analyzed by the same author (DD) who was blinded for the treatment allocation.

As primary endpoint, the eradication rate of *H. pylori* was assessed by the same methods (urease test and histopathology) 4–6 weeks after the end of the treatment. Adverse events, compliance and symptoms were evaluated on day 7 and 28 after the start of the treatment. Only stabilized chronic concomitant treatments that did not interfere with the main investigation variables were allowed.



* PPI: proton pump inhibitor; AB: antibiotic treatment; Sb: *Saccharomyces boulardii*
** Eradication rate: tested 4 to 6 weeks after the end of treatment

Figure 1 Patient flow diagram.

Table 1 Comparison of baseline characteristics of *H. pylori*-infected and -uninfected children undergoing endoscopy because of abdominal complaints

Variable	*H. pylori* status		p-value
	Positive	Negative	
Number	90 (62.1%)	55 (37.9%)	0.023
Mean age	11.2 years (range 3–18 years)	13.2 years (range 3–18 years)	NS
Female/male	51/39	33/22	NS
Family history of digestive diseases	43 (47.8%)	13 (23.6%)	0.07
The mean duration of symptoms	16.9 months	7.8 months	NS
Abdominal pain	83 (92.2%)	46 (83.6%)	NS
Nausea and/or vomiting	46 (51.1%)	27 (43.6%)	NS
Postprandial fullness	36 (40.0%)	25 (45.5%)	NS
Anorexia with/without weight loss	55 (61.1%)	17 (30.9%)	0.05
Antral nodularity	69 (76.7%)	9 (16.4%)	<0.001

The difference between the groups was compared using the Chi-square test. The values of $p < 0.05$ were considered statistically significant differences. The study was conducted according to good clinical practice and was approved by the local ethical committee. Before participation in the study, an informed consent was obtained from at least one parent. A per-protocol and an intention-to-treat analysis were performed. The intention-to-treat analysis included all patients recruited for this trial, and the per-protocol analysis included all patients who completed this study.

RESULTS

Active *H. pylori* infection was documented by a histological examination and rapid urease test in 90 of 145 symptomatic children (62.1%). The baseline demographic and clinical characteristics of all patients examined are reported in Table 1. The family history of digestive disease and the mean duration of symptoms were higher in children with *H. pylori* infection. The symptom characteristics cannot differentiate children with *H. pylori* from uninfected children, except for epigastric pain associated with nocturnal and fasting abdominal pain, which were more frequent in the infected children ($p < 0.01$).

The frequency of *H. pylori* infection increased with age from 12.2% in the 3- to –6-year-old group to 38.9% in the 15- to –18-year-old group. The *H. pylori* prevalence rate was positively correlated with age ($p < 0.002$) and low socioeconomic status ($p < 0.005$). The endoscopic aspect showed an antral predominant gastritis (type B) (59/90 patients, 65.6%) or pangastritis with multifocal atrophic gastritis (31/90, 34.4%). Antral nodularity was the most typical endoscopic sign in *H. pylori*-infected children (69/90 cases, 76.7%) and was associated with more severe gastritis.

All infected patients had histologically proven chronic gastritis: mild chronic gastritis in 8/90 cases (8.9%), or predominantly moderate-to-severe chronic gastritis in 82/90 cases (91.1%). The majority of the children had inactive chronic gastritis (58/90 cases, 64.4%).

All 90 infected patients participated in the trial. All completed the study, were compliant (patients had to return the unused medication) and were seen back by one of the investigators 1 week and 4 weeks after the start of the treatment, and 4–6 weeks after stopping the treatment. At the first two consultations, the data recorded in the questionnaire were checked and discussed. The baseline characteristics in the control group and the *S. boulardii*-supplemented group were comparable (Table 2). Overall, *H. pylori* was eradicated in 79 of 90 patients (87.7%). The eradication rate in the control group was 80.9% (34/42 cases), both in the intention-to-treat analysis and the per-protocol analysis, as there was no dropout (Table 3). The eradication rate in *S. boulardii* group was 93.8% (45/48 cases), also in the intention-to-treat and per-protocol analyses. The difference in the eradication rate was not significant ($p = 0.750$).

The occurrence of side effects was significantly reduced in the *S. boulardii* group. The control group showed more side effects (13/42 cases, 30.9%) compared with the probiotic-supplemented group (4/48 cases, 8.3%; $p = 0.047$). The most common side effects were mild to moderate and self-limiting, such as bloating, taste disturbance, nausea, abdominal pain, diarrhoea, constipation, loss of appetite, fatigue

Table 2 Comparison of baseline characteristics of the two groups of *H. pylori*-infected children

Variable	Control group	*S. boulardii* group	p-value
Number of patients	42	48	NS
Mean age	10.9 years	11.5 years	NS
Female/male	25/17	26/22	NS
The mean duration of symptoms	15.3 months	18.4 months	NS
Abdominal pain	39 (92.9%)	44 (91.7%)	NS
Nausea and/or vomiting	22 (52.4%)	24 (50.0%)	NS
Postprandial fullness	16 (38.1%)	20 (41.7%)	NS

Table 3 Endoscopic and therapeutic findings of the two groups of *H. pylori*-infected children

Variable	Control group	*S. boulardii* group	p-value
Antral predominant gastritis	28 (66.7%)	31 (64.6%)	NS
Antral nodularity	32 (76.2%)	37 (77.1%)	NS
Eradication rate of *H. pylori*	34 (80.9%)	45 (93.3%)	NS
Adverse effects	13 (30.9%)	4 (8.3%)	0.047

and headache. It cannot be excluded that the incidence and interpretation of the side effects is influenced by the fact that this was an open trial.

DISCUSSION

The high prevalence of active *H. pylori* infection in this population of symptomatic children (62.1%) shows that the infection remains a major problem in developing countries, in contrast to the significant decline observed in developed countries (4). The prevalence of *H. pylori* correlates significantly with socioeconomic factors (18). The improvement of the socioeconomic conditions observed in Romania during the last decade is likely to be too recent to cause a similar trend. Also, the population studied does not reflect the country's population at large because this was a study in selected patients. We confirmed the epidemiological data demonstrating that *H. pylori* prevalence is positively correlated with age ($p < 0.002$) and inversely correlated with socioeconomic status ($p < 0.005$). In accordance with previous studies (19,20), our data suggest that *H. pylori* infection is a relatively frequent finding in children presenting with chronic or recurrent abdominal pain, especially if associated with long-lasting abdominal complaints and a familial history of digestive diseases. However, the symptom characteristics cannot differentiate infected from uninfected patients, except for epigastric pain with nocturnal awakening and fasting pain relieved by food, which may represent an indication to screen for *H. pylori* (19,20). Although the author analyzing the questionnaires was blinded for the treatment group to which the patient belonged, treatment allocation was not blinded to the patients, which may have influenced the outcome.

All infected patients had histologically proven chronic gastritis, with predominantly moderate-to-severe forms, with antral nodularity in most cases (77%). Similar to other studies (21), antral nodularity was correlated with *H. pylori* colonization and severity of gastritis.

The standard eradication treatment consists of a triple therapy based on two antibiotics (amoxicillin, clarithromycin or metronidazole) associated with a PPI in a regimen for 7–14 days (10,22). According to the European register evaluating 27 different eradication regimens, an overall eradication rate of 66% is achieved (22). The cure rate for eradication of *H. pylori* with conventional triple therapies appears to be decreasing, especially in childhood. Despite the use of the current standard treatment regimen, approximately 30%–40% of patients may fail to achieve eradication. Therefore, trials have been conducted in the attempt to improve the eradication rate. These alternatives include longer duration therapy, quadruple therapy, sequential therapy, adjuvant therapy or new antimicrobial-based therapies. Among these numerous attempts, some studies show that probiotic microorganisms are effective in reducing and preventing the *H. pylori* infection. In this prospective, randomized study, we could demonstrate that lyophilized *S. boulardii* increased *H. pylori* eradication rate by about 12% in comparison to conventional triple therapy (93% vs. 81%, respectively). This difference is not statistically significant ($p = 0.750$), which might be due to a too small number of patients included. The lack of blinding and the envelope-drawing system may be methodologically weak aspects in this trial, although the primary endpoint 'eradication' of *H. pylori* cannot be influenced by a subjective interpretation. Gotteland and coworkers reported the same eradication rate with *S. boulardii* and inulin in children in Chile (23). Cindoruk et al. reported in 124 infected Turkish adults a nonsignificant increase in the eradication rate of 11% (60% vs. 71%) with *S. boulardii* as an add-on to the standard treatment (amoxicillin, clarithromycin and lansoprazole) (24). It is striking to observe the same trend of improvement of the eradication rate with *S. boulardii* in three independent studies (in Turkey, Romania and Chile), each time with 11%–12%. However, it is still unclear what the efficacy of *S. boulardii* as a unique intervention would be on the eradication of *H. pylori* since no study evaluated this aspect. Similar findings have also been reported with other bacterial probiotics and lactoferrin (25). The regular intake of cranberry juice may be useful in the management of asymptomatic children colonized by *H. pylori* since it eradicates *H. pylori* in 17% (26); however, no synergistic inhibitory effect on *H. pylori* colonization was observed if *Lactobacillus johnsonii* La1 was given in combination with cranberry juice (a 23% eradication) (26). Cranberry products can be used to prevent bacterial attachment to host tissue (27). Clinical studies are important, since probiotic microorganisms with a high efficacy *in vitro* may have no effect *in vivo* (8). A recent meta-analysis concluded that pooled *H. pylori* eradication rates were 84% (95% CI 81%–87%) and 75% (95% CI 71%–79%) for patients with or without probiotics by the intention-to-treat analysis, respectively (28).

The side effects were significantly decreased with *S. boulardii* (8% vs. 31%, $p = 0.047$). The overall tolerability was significantly better in the test group. The same findings were reported in adults (24). This could be due to the possible links between the common side effects of antibiotics (such as bloating, nausea, diarrhea, constipation, loss of appetite and vomiting) and qualitative and quantitative alterations in the intestinal microecology. Thus anti-*H. pylori* standard triple therapies without probiotic supplementation provoke side effects through disruption of the ecological equilibrium of the intestinal microflora. The supplementation of currently used anti-*H. pylori* therapies with a probiotic agent may stabilize or restore the endogenous microflora, and may prevent or minimize the incidence of the most common antibiotic-related side effects (29). The result of our study concerning the decrease of side effects in the probiotic-supplemented group confirms several other reports (8,9,23,24). According to the meta-analysis, the occurrence of side effects is 25% (95% CI 20%–30%) and 39% (95% CI 33%–44%) in groups with or without probiotics, especially for diarrhoea. The global odds ratio (OR) was 0.44 (95% CI 0.30–0.66) (28).

The findings of this study suggest that the addition of *S. boulardii* to the standard triple therapy confers a 12% nonsignificant increased eradication rate of *H. pylori* in children

and reduces significantly the incidence of side effects such as the antibiotic-associated diarrhoea. Our data confirm that *S. boulardii* is a 'possible' tool in the management of *H. pylori* infection and add evidence to the hypothesis that supplementation with probiotics could be effective in increasing the eradication rates of *H. pylori* and could be considered helpful for patients with eradication failure. Furthermore, probiotics such as *S. boulardii* show a positive impact on *H. pylori* therapy-related side effects.

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