Efficacy and safety of *Saccharomyces boulardii* in prevention of antibiotic-associated diarrhoea due to *Helicobacter pylori* eradication

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Background and aim **Antibiotic-associated diarrhoea may develop during or following *Helicobacter pylori* eradication. We aimed to evaluate the efficacy and safety of *Saccharomyces boulardii* in preventing antibiotic-associated diarrhoea in patients receiving antibiotics for *H. pylori* eradication.**

Methods **In a multicentre prospective clinical trial, patients with peptic ulcer disease or non-ulcer dyspepsia were enrolled to receive clarithromycin, amoxicillin and omeprazole for *H. pylori* eradication for 14 days. These patients were then randomized to receive either *S. boulardii* 500 mg twice daily (treatment group) or no treatment (control group). The primary outcome measure was the development of diarrhoea during (treatment period) or within 4 weeks after treatment (follow-up period).**

Results **Of the 389 patients that were enrolled, 376 completed the study. Within the treatment period, diarrhoea developed in 5.9% of patients in the treatment group and in 11.5% of patients in the control group ($P=0.049$); and in the follow-up period, diarrhoea developed in 1.0% of patients in the treatment group and in 3.8% of patients in the control group ($P=0.09$). Overall diarrhoea rates throughout the whole study period were 6.9% in the treatment group and 15.6% in the control group ($P=0.007$). No significant difference was observed between the treatment and control groups in terms of adverse events.**

Conclusion ***S. boulardii*** **is an effective and safe treatment for prevention of antibiotic-associated diarrhoea when given concomitantly to patients receiving *H. pylori* eradication. *Eur J Gastroenterol Hepatol* 17:1357–1361**

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Introduction

Antibiotic-associated diarrhoea (AAD) is a common complication of treatment with broad-spectrum antibiotics. Although almost all classes of antibiotics have been implicated in aetiology, higher rates have been associated with cephalosporins, penicillin and clindamycin [1]. AAD rates vary from 5 to 25% depending on the specific type of antibiotic [1]. The outcome of AAD may range from uncomplicated diarrhoea to severe diarrhoea with complications including electrolyte imbalance, dehydration, pseudomembranous colitis, toxic megacolon and even death. The most common cause of AAD is *Clostridium difficile*, which is responsible for 26–50% of cases [2], followed by *Salmonella*, *Candida albicans* and enterotoxigenic *Clostridium perfringens*. In the majority of AAD cases, however, the inciting cause is unclear. Neither the dose nor the route of administration of the antibiotic is predictive for AAD, but the type and the duration of antibiotic therapy may be important in defining the risks for AAD [2].

Treatment modalities for mild AAD are limited except discontinuing the inciting antibiotic and supportive care [3]. Severe cases of AAD, particularly those related to *C. difficile*, may require specific antibiotic therapy such as oral metronidazole or vancomycin [3]. However, 20% of the patients with AAD may develop subsequent recurrences [2]. Recent evidence has suggested beneficial

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therapeutic effects with the administration of probiotics [1]. It has been suggested that a non-pathogenic 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 diarrhoea [4]. Results from in-vivo studies have shown that *S. boulardii* reaches high, steady-state levels in the stool (10^7–10^8 viable yeast cells per gram of faeces) within 3–5 days and is no longer detectable 2–6 days after discontinuation [5].

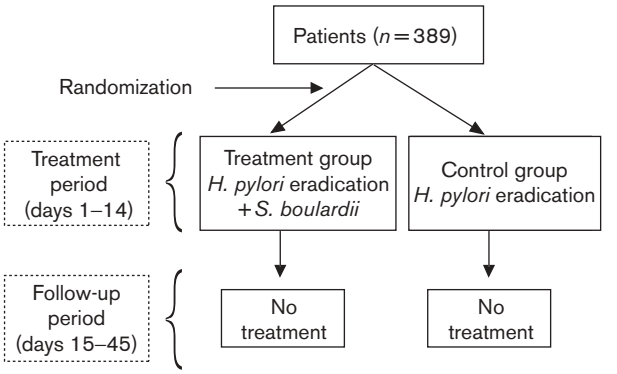
Patients receiving antibiotics for *Helicobacter pylori* eradication are at increased risk to develop AAD and they constitute a distinct homogeneous group as they receive an identical antibiotic regimen. The aim of this study is to evaluate the efficacy and safety of *S. boulardii* in preventing the AAD in outpatients receiving *H. pylori* eradication. The primary outcome measure was the incidence of diarrhoea during and following the antibiotic treatment. Secondary outcome measures were the duration of diarrhoea and frequency of bowel movements during a diarrhoea episode. A secondary aim of the study was to define the prevalence of AAD due to *H. pylori* eradication in otherwise healthy outpatients in Turkey.

Patients and methods

This is a multicentre, prospective, open label and randomized study. It was conducted in nine hospitals throughout Turkey between 2001 and 2003. Patients receiving 14 days of triple therapy consisting of clarithromycin 500 mg twice daily, amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily for *H. pylori* eradication (treatment period) were randomly assigned to receive *S. boulardii* (treatment group) or no treatment (control group). The treatment group received 1 g *S. boulardii* (250 mg capsules, 500 mg twice daily, Reflor; Sanofi-Synthelabo Ilac A.S., Istanbul, Turkey) per day in two divided doses for 2 weeks during the entire treatment period. All patients were followed for an additional 4 weeks after cessation of the antibiotics and *S. boulardii* (follow-up period) (Fig. 1). Following enrolment, patients were examined and interviewed on the 15th and 45th days of the study protocol.

Indications for *H. pylori* eradication were peptic ulcer disease or non-ulcer dyspepsia. Non-ulcer dyspepsia was defined as the presence of dyspeptic complaints in the face of a normal upper gastrointestinal endoscopy or positive *H. pylori* on a ^{13}C-urea breath test in those patients without an endoscopic examination. Peptic ulcer disease was diagnosed by detection of gastric or duodenal ulcers or erosions in endoscopic examination. Patients who had diarrhoea due to causes other than antibiotics such as functional or anatomical gastrointestinal tract disorders and diabetes mellitus were not enrolled into the study.

Fig. 1



Flow of the study protocol.

Patients were instructed to contact a member of the study team immediately in the case of diarrhoea or any other adverse event. Diarrhoea was defined as a change in bowel habits with at least three semi-solid or watery bowel movements per day for at least two consecutive days. Severity of the diarrhoea was defined according to the frequency of bowel movements, the consistency of the stool (watery, semi-solid), the presence or absence of abdominal pain and tenesmus on the basis of the patient's description. Patients with diarrhoea were followed without any treatment unless signs of clinical deterioration such as hypotension, dehydration and tachycardia developed. Compliance with the study drug was verified by the number of tablets/capsules returned at the end of the treatment period.

Microbiology

In the case of diarrhoea, direct microscopic examination of the stool for leucocytes, erythrocytes, ova and parasites was performed and a stool culture was obtained. The stool was tested for the presence of *C. difficile* toxin A and B by a commercial enzyme immunoassay kit (Premier A & B 96 T; Meridian Bioscience Inc., Nice Cedex, France).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The local ethics committee at each centre approved the study protocol and written informed consent was obtained from each patient.

Statistical analysis

Statistical analysis was performed with SPSS 11.5 for Windows. Proportional differences were analysed by the chi-square test and Fisher's exact test, and the differences between the treatment groups were evaluated by Student's *t*-test or the Mann–Whitney *U* test, depending on the normalcy of the data. The mean time to diarrhoea

was compared by the Mann–Whitney *U* test for patients who developed diarrhoea. The cumulative diarrhoea rate as a function of time was calculated by Kaplan–Meier survival analysis and groups were compared by the log-rank test. A *P* value less than 0.05 was considered significant.

Results

A total of 389 patients were enrolled in the study. Of those, 204 patients received *H. pylori* eradication plus *S. boulardii* and 185 patients were given the *H. pylori* eradication regimen only. Patient characteristics and endoscopic findings are presented in Tables 1 and 2. Non-ulcer dyspepsia was present in 95 patients (46.6%) in the treatment group and 101 patients (54.6%) in the control group, while peptic ulcer disease was observed in 109 patients (53.4%) in the treatment group and 84 patients (45.4%) in the control group. Overall, 376 patients (96.7%) completed the study. Thirteen patients, five (1.3%) in the control group and eight (2.0%) in the treatment group, did not complete the study. The number of drop-outs was not different between the groups ($P > 0.05$, chi-square test). The reasons for not completing the study were as follows: eight patients (three in the control group, five in the treatment group) were not compliant with the study protocol, two patients (one in each group) stopped taking their medications because of adverse events and three patients were lost to follow-up. The reported adverse events, which resulted in discontinuation of all the medications, were skin reaction in one patient in the treatment group and palpitation in the control group patient. Compliance with the study drug was complete in the rest of the patients of the treatment group. The data were missing in four patients during the treatment and the follow-up periods. Diarrhoea duration could not be assessed in six patients during the treatment period due to missing records.

During the whole study period, 6.9% ($n = 14$) of the patients in the treatment group and 15.6% ($n = 28$) of patients in the control group developed diarrhoea ($P = 0.007$, chi-square test) (Fig. 2). Considering the AAD development day by day throughout the whole study, the diarrhoea rate was significantly higher in the control group than the treatment group ($P = 0.0027$) (Fig. 3). The severity of diarrhoea was not significantly different between the two groups both in the treatment and follow-up phases of the study in terms of number of

Table 1 **Characteristics of the patients in the treatment and control groups**

	Treatment group ($n=204$)	Control group ($n=185$)	*P* value
Gender			0.682
Male [*n* (%)]	102 (50%)	88 (47.5%)	
Female [*n* (%)]	102 (50%)	97 (52.5%)	
Age (years)			0.455
Mean ± SD	45.68 ± 12.7	44.65 ± 13.9	
Median (range)	45 (17–82)	42 (17–79)	
Previous history of AAD [*n* (%)]	18 (8.8%)	10 (5.4%)	0.21

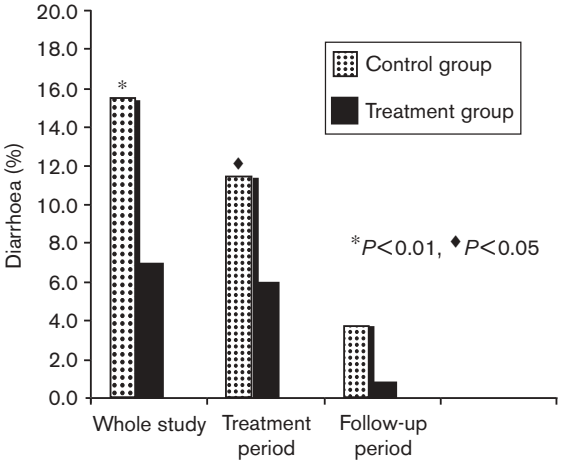
AAD, antibiotic-associated diarrhoea.

Table 2 **Endoscopic findings of patients**

	Control group ($n=185$)	Treatment group ($n=204$)
Gastric ulcer	13 (7%)	16 (7.8%)
Duodenal ulcer	71 (38.4%)	93 (45.6%)
Gastritis	81 (43.8%)	82 (40.2%)
Endoscopy normal	9 (4.9%)	6 (2.9%)
Endoscopy not performed	11 (5.9%)	7 (3.4%)

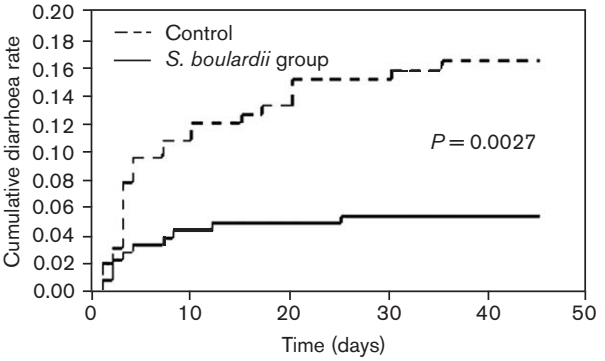
Data presented as the number (%) of patients.

Fig. 2



Prevalence of diarrhoea in the whole study and during treatment and follow-up periods.

Fig. 3



Diarrhoea development over time (days) in the whole study was significantly higher in the control group (dashed line) compared to the treatment group (solid line) given *S. boulardii* (15.6%, SE = 2.7% vs. 6.4, SE = 1.9%, respectively; log-rank test; $P = 0.0027$).

daily bowel movements, presence of abdominal pain or tenesmus (data not shown).

Diarrhoea during the treatment period (Fig. 2)

In the first 15 days, the diarrhoea rates in the treatment and control groups were 5.9% ($n = 12$) and 11.5% ($n = 21$), respectively ($P = 0.049$). Time to the onset of diarrhoea was 4.2 ± 3.6 (1–12) days in the treatment group and 3.7 ± 2.6 (1–10) days in the control group ($P > 0.05$, Student's *t*-test). The duration of diarrhoea and the number of patients with watery diarrhoea were not different between the treatment and control groups. The number of patients with mucus in the stool was significantly fewer in treatment group compared with the control group [one patient (8.3%) versus nine patients (42.9%), respectively; $P = 0.038$ by chi-square test]. No patient developed bloody diarrhoea during the treatment period.

Diarrhoea in the follow-up period (Fig. 2)

Between day 15 and day 45, diarrhoea developed in two patients (1.0%) in the treatment group and seven patients (3.8%) in the control group ($P = 0.09$). Time to the onset of diarrhoea was 35.0 ± 14.1 (25–45)days in the treatment group and 22.4 ± 7.3 (15–35) days in the control group ($P > 0.05$). There was no difference between the treatment and control groups with respect to the duration of diarrhoea and consistency of the stool during a diarrhoea episode. None of the patients had mucus or blood in the stool in the follow-up period (data not shown).

No pathogenic growth was detected in stool cultures. The *C. difficile* toxin test was tested in the stool in 16 patients with diarrhoea (11 in the control group and five in the treatment group) and it was positive only in one patient in the control group. Direct examination of the stool for diarrhoea revealed the presence of leucocytes in five patients in the control group and two patients in the treatment group. No patient required specific treatment for diarrhoea.

There was no serious adverse event in the study populations and the frequency of minor adverse events was similar in the two groups. Within the treatment group, one patient experienced a dry mouth, one patient a metallic taste and one patient a non-specific skin reaction. In the control group, one patient reported an aphthous lesion in the mouth, one patient noted blurred vision and skin reaction, and one patient had palpitations.

Discussion

H. pylori is a common and significant public health problem. Widespread use of broad-spectrum antibiotics for the treatment of this infection carries risk for the development of AAD. We found that *S. boulardii* supplementation reduced the AAD frequency from 15.6 to 6.9% in an ambulatory outpatient group. Remarkably, the cumulative diarrhoea rate day by day in the whole study period was also significantly lower in patients receiving *S. boulardii* compared with controls.

In this study, AAD rates in patients receiving *H. pylori* eradication were 11.5% during the treatment period and 3.8% in the 4 weeks after cessation of antibiotics. This is the first report of AAD incidence due to *H. pylori* eradication treatment in a large population in Turkey. An Italian study showed that 7 days of triple therapy for *H. pylori* eradication (pantoprazole, clarithromycin and tinidazole) is associated with an AAD rate of 23.3% among health care workers [6]. The higher AAD rates observed in this study may be due to the fact that the diarrhoea was classified in a semiquantitative manner from mild to severe rather than using the number of daily bowel movements, thus resulting in higher numbers of patients with diarrhoea.

The frequency of AAD is expected to be lower in outpatients compared with hospitalized patients. Earlier studies have shown AAD rates of 22% [7] and 14.6% [8] among hospitalized patients. The latter figure of relatively lower AAD rate was suggested by the authors to be due to the decreased third-generation cephalosporins use in the centres participating in the study [8]. The AAD rate due to various antibiotics during treatment period was reported in 17.5% of outpatients in a recent study [9], and it was 11.5% in our study.

The onset of AAD may be rapid while the patient is still receiving antibiotic treatment or may be delayed up to 6 weeks after the end of antibiotic therapy [2]. In a study evaluating the β-lactam-associated diarrhoea frequency, most of the diarrhoeal episodes (62%) developed during antibiotic treatment, and only 38% of patients developed AAD after antibiotics had been discontinued [8]. Our study shows that *S. boulardii* is effective in preventing AAD only during the treatment phase of the study, which is also the period when AAD is most commonly encountered. This observation suggests that administration of *S. boulardii* should be considered concomitantly with the antibiotic treatment. Although the efficacy of *S. boulardii* in the prevention of AAD was not specifically mentioned to the patients, the potential placebo effect cannot be excluded in the absence of a placebo arm in our study. In fact, a placebo-controlled earlier study confirmed that *S. boulardii* reduced the AAD development as also reflected in our study [7]. *S. boulardii*, in combination with vancomycin or metronidazole, was shown to be effective also in treating recurrent *C. difficile* disease [10,11]. We observed only a single patient with *C. difficile* toxin in the stool.

The combination regimen of omeprazole, amoxicillin and clarithromycin used in this study is the first-line regimen recommended in the Maastricht consensus report [12] and in the Guidelines of the American College of Gastroenterology [13]. Recently, at least more than 10 days of antibiotic administration was shown to be more effective in *H. pylori* eradication, although this duration was initially advocated as 7 days [13–16]. We therefore administered *H. pylori* eradication for 14 days.

Several mechanisms have been postulated to explain the efficacy of *S. boulardii* in AAD [17]. *S. boulardii* has a direct antagonistic effect on the growth of pathogens like *Candida albicans*, *Escherichia coli*, *Shigella*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and on the actions of cytotoxins of *Vibrio cholerae*, enterotoxic *E. coli* and *Clostridium difficile* [4,18]. It also shows immunoprotective effect via stimulation of secretory components of immunoglobulins in rats [19]. In an experimental model of AAD induced by clindamycin in proximal porcine colon, addition of *Saccharomyces boulardii* resulted in compensation of disturbed short-chain fatty acids that are essential for sodium and water uptake of colonocytes [20]. In humans, *S. boulardii* activates the alternative pathway of the complement system and increases the disaccharidase activity [21]. Another mechanism for the prevention of AAD may be the counteracting effect of *S. boulardii* on prokinetic action of macrolides [22]. This last mechanism of action together with the avoidance of an imbalance of the gut intestinal flora may account for the role of *S. boulardii* in preventing the *H. pylori* eradication-induced diarrhoea.

In conclusion, our study suggests that *S. boulardii* is effective and safe in prevention of AAD when given concomitantly with *H. pylori* eradication. Further studies addressing the quality-of-life gains and cost–utility analysis are needed before reaching definitive conclusions for recommendation of *S. boulardii* to patients receiving *H. pylori* eradication.

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Conflict of interest

None declared.

Authors' contributions

D.G. Duman and C. Kalaycı took part in data collection, data analysis and manuscript preparation. The other authors conducted the study according to the study protocol and provided the crude data.

References

1 Bergogne-Berezin E. Treatment and prevention of antibiotic associated diarrhea. *Int J Antimicrob Agents* 2000; **16**:521–526.
2 McFarland LV. Epidemiology, risk factors, and treatments for antibiotic-associated diarrhea. *Dig Dis* 1998; **16**:292–307.
3 Dodson AP, Borriello SP. *Clostridium difficile* infection of the gut. *J Clin Pathol* 1996; **49**:529–532.
4 Vandenplas Y. Bacteria and yeasts in the treatment of acute and chronic infectious diarrhea. Part I. Yeasts. *Clin Microbiol Infect* 1999; **5**:389–395.
5 Blehaut H, Massot J, Elmer GW, Levy RH. Disposition kinetics of *Saccharomyces boulardii* in man and rat. *Biopharm Drug Dispos* 1989; **10**:353–364.
6 Armuzzi A, Cremonini F, Ojetti V, Bartolozzi F, Canducci F, Candelli M, *et al.* Effects of *Lactobacillus* GG supplementation on antibiotic-associated gastrointestinal side effects during *Helicobacter pylori* eradication therapy: a pilot study. *Digestion* 2001; **63**:1–7.
7 Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, vanBelle G. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: a prospective study. *Gastroenterology* 1989; **96**:981–988.
8 McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Moyer KA, Melcher SA, *et al.* Prevention of β-lactam-associated diarrhea by *Saccharomyces boulardii* compared with placebo. *Am J Gastroenterol* 1995; **90**:439–448.
9 Beaugerie L, Flahault A, Barbut F, Atlan P, Lalande V, Cousin P, *et al.* Antibiotic-associated diarrhoea and *Clostridium difficile* in the community. *Aliment Pharmacol Ther* 2003; **17**:905–912.
10 Surawicz CM, McFarland LV, Elmer G, Chinn J. Treatment of recurrent *Clostridium difficile* colitis with vancomycin and *Saccharomyces boulardii*. *Am J Gastroenterol* 1989; **84**:1285–1287.
11 McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, *et al.* A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *J Am Med Assoc* 1994; **271**:1913–1918.
12 The European *Helicobacter pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. *Gut* 1997; **41**:8–13.
13 Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**:2330–2338.
14 Maconi G, Parente F, Russo A, Vago L, Imbesi V, Porro GB. Do some patients with *Helicobacter pylori* infection benefit from an extension to 2 weeks of a proton pump inhibitor-based triple eradication therapy? *Am J Gastroenterol* 2001; **96**:359–366.
15 Bhasin DK, Sharma BC, Ray P, Pathak CM, Singh K. Comparison of seven and fourteen days of lansoprazole, clarithromycin, and amoxicillin therapy for eradication of *Helicobacter pylori*: a report from India. *Helicobacter* 2000; **5**:84–87.
16 Miehlke S, Bayerdorffer E, Garaham DY. Treatment of *Helicobacter pylori* infection. *Semin Gastrointest Dis* 2001; **12**:167–179.
17 McFarland LV, Bernasconi P. *Saccharomyces boulardii*: a review of an innovative biotherapeutic agent. *Microbial Ecol Health Dis* 1993; **6**: 157–171.
18 Pothoulakis C, Kelly CP, Joshi MA, Gao N, O'Keane CJ, Castagliuolo I, *et al.* *Saccharomyces boulardii* inhibits *Clostridium difficile* toxin A binding and enterotoxicity in rat ileum. *Gastroenterology* 1993; **104**:1108–1115.
19 Buts JP, Bernasconi P, Vaerman JP, Dive C. Stimulation of secretory IgA and secretory component of immunoglobulins in small intestine of rats treated with *Saccharomyces boulardii*. *Dig Dis Sci* 1990; **35**:251–256.
20 Breves G, Faul K, Schröder B, Holst H, Caspary WF, Stein J. Application of the colon-stimulation technique for studying the effects of *Saccharomyces boulardii* on basic parameters of porcine cecal microbial metabolism disturbed by clindamycin. *Digestion* 2000; **61**:193–200.
21 Buts JP, Bernasconi P, Craynest MPV, Maldague P, DeMeyer R. Response of human and rat small intestinal mucosa to oral administration of *Saccharomyces boulardii*. *Pediatr Res* 1986; **20**:192–196.
22 Bortolotti M, Brunelli F, Sarti P, Mari C, Miglioli M. Effects of oral clarithromycin and amoxycillin on interdigestive gastrointestinal motility of patients with functional dyspepsia and *Helicobacter pylori* gastritis. *Aliment Pharmacol Ther* 1998; **12**:1021–1025.